

Clinical Characteristics, Management, and Outcomes of Patients Diagnosed With Acute Pulmonary Embolism in the Emergency Department

Initial Report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry)

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- Objectives** In a large U.S. sample, this study measured the presentation features, testing, treatment strategies, and outcomes of patients diagnosed with pulmonary embolism (PE) in the emergency department (ED).
- Background** No data have quantified the demographics, clinical features, management, and outcomes of outpatients diagnosed with PE in the ED in a large, multicenter U.S. study.
- Methods** Patients of any hemodynamic status were enrolled from the ED after confirmed acute PE or with a high clinical suspicion prompting anticoagulation before imaging for PE. Exclusions were inability to provide informed consent (where required) or unavailability for follow-up.
- Results** A total of 1,880 patients with confirmed acute PE were enrolled from 22 U.S. EDs. Diagnosis of PE was based upon positive results of computerized tomographic pulmonary angiogram in most cases ($n = 1,654$ [88%]). Patients represented both sexes equally, and racial and ethnic composition paralleled the overall U.S. ED population. Most (79%) patients with PE were employed, and one-third were older than age 65 years. The mortality rate directly attributed to PE was 20 in 1,880 (1%; 95% confidence interval [CI]: 0% to 1.6%). Mortality from hemorrhage was 0.2%, and the all-cause 30-day mortality rate was 5.4% (95% CI: 4.4% to 6.6%). Only 3 of 20 patients with major PE that ultimately proved fatal had systemic anticoagulation initiated before diagnostic confirmation, and another 3 of these 20 received a fibrinolytic agent.
- Conclusions** Patients diagnosed with acute PE in U.S. EDs have high functional status, and their mortality rate is low. These registry data suggest that appropriate initial medical management of ED patients with severe PE with anticoagulation is poorly standardized and indicate a need for research to determine the appropriate threshold for empiric treatment when PE is suspected before diagnostic confirmation. (J Am Coll Cardiol 2011;57:700-6) © 2011 by the American College of Cardiology Foundation

Pulmonary embolism (PE) is a common condition that can cause serious morbidity or death. However, few published reports have documented the clinical characteristics, risk stratification methods, and treatments for suspected or

confirmed PE used in U.S. emergency departments (EDs). Only 3 large multicenter registries of patients with acute PE have been published. In aggregate, only 3% of patients in these registries were from the United States. Moreover, no

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previous multicenter registry differentiated between patients presenting acutely to an ED for evaluation of potential PE and hospitalized patients who developed PE during an in-patient stay (1–3).

Several issues suggest the need for a contemporary registry specific to ED patients in the United States. First, approximately one-half of all cases of PE in the U.S. are diagnosed in the ED (4). Second, prior PE registries have not provided data specific to race or ethnicity. Third, data are lacking to compare the availability and contemporaneous use of risk stratification methods, including serum biomarkers, for patients diagnosed with PE. Fourth, no prior data have documented the frequency of use of empiric anticoagulation in the ED, an intervention that may affect outcome (5).

This report represents the first publication from the EMPEROR (Emergency Medicine Pulmonary Embolism in the Real World Registry) study. The objectives of this report were to establish more definitively the presentation symptoms and signs of PE presenting in the ED setting; characterize treatment used by U.S. emergency physicians; and measure use of risk stratification methods, frequencies of empiric anticoagulation use, and rates of major hemorrhage and mortality among patients who present to the ED.

Methods

Study design. EMPEROR was designed as a national, prospective, multicenter, observational registry to characterize the epidemiology, presenting clinical signs and symptoms, ED-utilized diagnostic modalities, ED treatment, and 30-day outcomes of patients diagnosed with PE. Patients were enrolled from 22 community and academic EDs (Online Appendix) by site investigators who were identified on the basis of their published experience with large, multicenter ED-based registries (6,7).

North Carolina. Funding was provided by GlaxoSmithKline. Dr. Pollack has served as a consultant and a speaker for Sanofi-Aventis and has received research funding from Sanofi-Aventis and GlaxoSmithKline. Dr. Goldhaber is a consultant for Sanofi-Aventis, Eisai, Bristol-Myers Squibb, Boehringer Ingelheim, and Medscape. Dr. Fanikos has served as a consultant to Sanofi-Aventis and GlaxoSmithKline. Dr. O'Neil is on the Speakers Bureau for GlaxoSmithKline, Sanofi-Aventis, and Bristol-Myers Squibb; and is on the advisory board for HeartScape Technologies. Dr. Hiestand has received research funding from Medtronic Inc., Biosite Inc., Inovise Medical Inc., HeartScape International, Nanosphere Inc., Mitsubishi Medience, and The Medicines Company; and has a medical writing consulting relationship with newMentor Inc. Dr. Pendleton is on the Speakers Bureau for Sanofi-Aventis; and has received research support from Pfizer, Bristol-Myers Squibb, and Boehringer Ingelheim. Dr. Miller has received research support from Siemens, Breathquant Medical LLC, Biosite, Schering-Plough, Johnson and Johnson/Scios Inc., and PDL Biopharma and served as a speaker for Genentech and at CME events sponsored by Sanofi-Aventis and Schering-Plough and as a consultant to Breathquant Medical LLC, the Medicines Company, and Molecular Insight. Dr. Kline has received funding from the National Institutes of Health and has been a clinical investigator on a clinical trial sponsored by Octapharma (octaplex) and a clinical trial sponsored by Pfizer (apixaban) and a primary investigator on an investigator-initiated clinical trial funded by Genentech; he has stock ownership in CP Diagnostics, a privately held LLC in North Carolina. All other authors have reported that they have no relationships to disclose.

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The study protocol was approved by the institutional review board at each site according to local policies and procedures. The principal investigators (C.V.P., J.A.K., and S.Z.G.) were responsible for the study design and protocol. The study was monitored by a steering committee composed of 7 site investigators (C.V.P., J.A.K., D.H.S., D.E.S., B.H., J.F., and B.O.) and one independent consultant (S.Z.G.).

Patient identification. All adult patients age ≥ 18 years who presented to the ED with suspected PE were potentially eligible for inclusion. Two cohorts of patients were identified. One group had confirmed acute PE (diagnostic criteria identified below). The second group consisted of patients with clinically suspected PE who were empirically anticoagulated in the ED (in accordance with American College of Chest Physician guidelines) before completion of diagnostic testing but who subsequently had negative imaging studies, and ultimately PE was not confirmed (8).

Exclusion criteria were inability to obtain informed consent (in those institutions where consent was required by the local institutional review board) or evidence suggesting that the patient would be unavailable for 30-day follow-up (homelessness, incarceration, etc).

Main measurements. Study personnel collected data from the patient and the medical record beginning in the ED, including the hospital stay, and concluded with a review of outcomes at 30 days. Using methodology similar to that previously described, data were recorded on secure Web-based electronic data collection forms (DCFs) designed by 2 authors (J.A.K. and C.V.P.) (8). During the period of study enrollment, the Web site and database were managed by an independent contractor (C.L.J.) who was not affiliated with the study sponsor. The DCF included 264 unique data fields that were defined in advance by a data dictionary that is included in the Online Appendix. Study personnel at each site were allowed to use a paper data collection template, but all data were ultimately entered into the Web-based DCF. The source for all data elements was either directly from the patient or from the medical record. Data elements collected included those necessary to calculate an ED Wells' pretest probability score (9); sites were encouraged and expected to address the criterion "is PE the most likely diagnosis?" prospectively (i.e., before imaging), but this was not verified in every case.

All patients were followed for 30 days to determine clinical outcomes, including death, recurrent venous thromboembolism (VTE), bleeding complications, or rehospital-

Abbreviations and Acronyms

BNP = brain natriuretic protein
CTPA = computerized tomographic pulmonary angiogram
DVT = deep venous thrombosis
ED = emergency department
PE = pulmonary embolism
PESI = Pulmonary Embolism Severity Index
RV = right ventricular
SBP = systolic blood pressure
VQ = ventilation-perfusion
VTE = venous thromboembolism

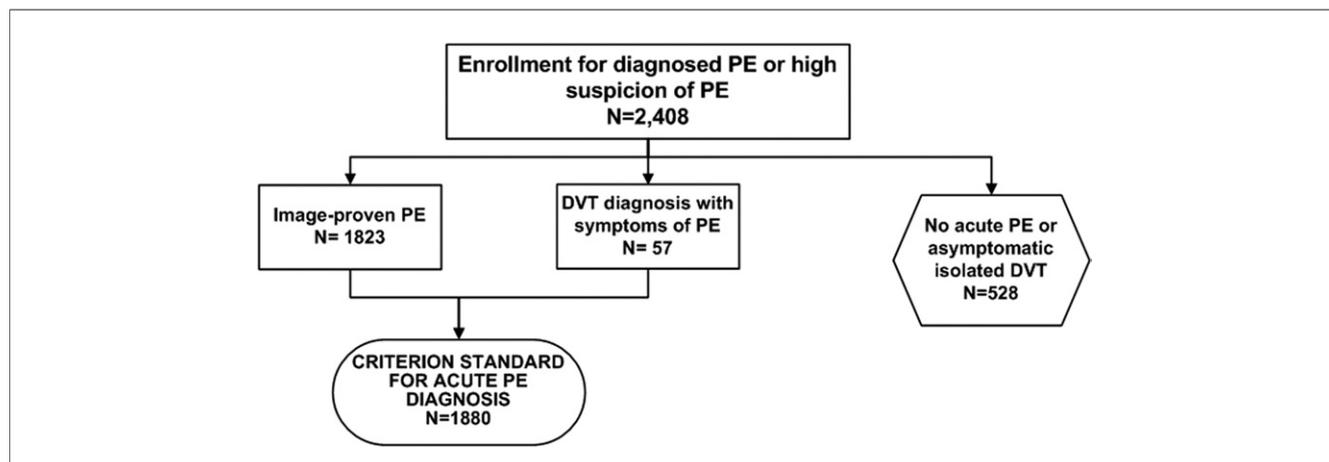


Figure 1 Flow Diagram of Enrolled Patients in the EMPEROR Trial

The flow diagram shows the outcome of all enrolled patients with respect to diagnosis of venous thromboembolism. DVT = deep venous thromboembolism; PE = pulmonary embolism.

ization. Follow-up data were collected by telephone interview or chart review (10). Cause of death was adjudicated by the primary investigator at each participating center, based upon available medical records. All clinical data, including protocols for performing diagnostic imaging studies and the tests used to risk-stratify PE (including troponins, natriuretic peptides, and echocardiography), were evaluated using local standards (11–13).

A Pulmonary Embolism Severity Index (PESI) score was calculated for all patients for whom sufficient data was available. The score assigns points by age, male sex (+10), presence of cancer (+30), heart failure (+10), chronic lung disease (+10), pulse ≥ 110 beats/min (+20), systolic blood pressure (SBP) < 100 mm Hg (+30), respiratory rate ≥ 30 breaths/min, temperature $< 36^\circ\text{C}$, altered mental status (+60), and arterial oxygen saturation $< 90\%$ (+20). Patients with confirmed PE with scores > 85 are reported to have higher rates of mortality (14).

Diagnostic criteria for PE. The diagnostic evaluation for PE was entirely at the discretion of the board-certified or board-eligible attending emergency physician directly responsible for the care of the patient. For purposes of inclusion in the registry, the diagnosis of PE was considered confirmed when any one of the following criteria was met:

- Computerized tomographic pulmonary angiogram (CTPA) interpreted by the attending radiologist as positive for PE, based on accepted radiologic criteria
- High-probability nuclear ventilation-perfusion (VQ) lung scan
- Pulmonary angiogram interpreted as positive for PE
- Pulmonary vascular magnetic resonance angiography interpreted as positive for PE
- Deep venous thrombosis (DVT) on a duplex ultrasound of the lower or upper extremities performed within 30 days before enrollment, in association with chest pain or shortness of breath

Sample size. The sample size was based on pre-planned subgroup analyses and a planned total enrollment of at least 2,250 patients, assuming that 80% would have confirmed PE. We aimed to narrow the 95% confidence interval (CI) around the in-hospital mortality rate to less than $\pm 5\%$ for patients with confirmed PE, which was estimated from existing reports in 2006 to be 10% (15,16). Patients without PE were enrolled only if during their real-time ED evaluation they were deemed to be of sufficiently high clinical risk for PE to initiate empiric full-dose anticoagulation therapy in the ED before pulmonary vascular imaging, which subsequently was negative for PE.

Analysis. Frequency data are presented as proportions with associated 95% CI, calculated by the exact binomial method. Continuous data are shown as means with associated SD. We did not report any specific hypothesis-testing p values.

Results

Over 26 months (from January 1, 2005, to December 29, 2008), 2,408 patients were enrolled, including 1,880 (78%) patients with confirmed PE (Fig. 1). This report focuses on these 1,880 patients with acute PE. The diagnosis of PE was based upon positive results of CTPA ($n = 1,654$), diagnostic VQ scan ($n = 82$), formal pulmonary angiography ($n = 91$), DVT with appropriate PE symptoms ($n = 51$), or positive pulmonary magnetic resonance angiography ($n = 2$).

Clinical characteristics. Tables 1 to 3 present the demographic, risk factors, and clinical features of the study populations with and without confirmed PE. Definitions of risk factors are included in the Online Appendix. The mean age was 57 ± 18 years, with a slight majority of women (53%; 95% CI: 50.5% to 55.0%); the majority of patients were Caucasian (68%). The mean vital sign data suggested that the PE population manifested no significant differences

Table 1 Age, Sex, Race, and Ethnicity of Registry Participants

Demographic Feature	Confirmed PE (n = 1,880)	PE Not Confirmed (n = 528)
Mean age, yrs (SD)	56.5 (18.1)	55.9 (18.0)
Age >65 yrs	631 (33.5)	159 (30.1)
Female sex	992 (52.8)	304 (57.6)
Race/ethnicity		
Caucasian	1284 (68.3)	312 (59.1)
African American	482 (25.6)	161 (30.5)
Hispanic	57 (3.0)	29 (5.5)
Asian	11 (0.6)	3 (0.6)
Unknown	17 (0.9)	10 (1.9)
Other	29 (1.5)	13 (2.5)

Values are n (%).
PE = pulmonary embolism.

from the PE-negative group (17). Only 58 (3.0%) patients had SBP <90 mm Hg at presentation. The most common presenting signs and symptoms were dyspnea at rest (50%), pleuritic chest pain (39%), dyspnea with exertion (27%), and extremity swelling suggestive of DVT (24%). Consistent with other studies, only 5% of patients with PE presented with syncope (1–3).

Clinical features and comorbid conditions relevant to medical decision making for the diagnosis and treatment of PE are described in Table 2. The most common comorbidities that could represent potential risk factors for PE were hypertension (46%), obesity (27%), recent hospitalization (24%), and active malignancy (22%). Based on the absence of any of these 28 predefined risk factors for PE (Online Appendix), 312 of the 1,880 (16.5%) patients were considered to have idiopathic PE. In response to the specific criterion of the Wells' PE pre-test probability score (was PE the most likely diagnosis at the time that the evaluation was initiated?), clinicians indicated that they believed that 1,572 of 1,880 (84%) of PE-positive patients had PE as their most likely pre-test diagnosis. The mean Wells' score was 3.0 ± 1.7 (median 2.5). The distribution of scores by low (<2), moderate (2 to 6), and high (>6) pre-test probability values were 40.2%, 54.3%, and 5.5%, respectively.

Risk stratification. A quantitative D-dimer was performed in 543 (29%) and was elevated (per local lab normal range) in the majority (477 of 543 [87%]), with a mean value of 7,162 ± 14,241 ng/ml (median 2,125 ng/ml; 1st to 3rd quartiles 896 to 5,327 ng/ml). Transthoracic echocardiography was performed on 430 of 1,880 patients (23%), revealing right ventricular (RV) hypokinesis in 218 (51% of those imaged). A serum troponin assay was performed in 1,287 (68%) patients, revealing an elevated value (compared with local normal range) in 424 (33% of those tested). A serum brain natriuretic peptide (BNP) or NT-proBNP measurement was obtained in 661 (35%), revealing an elevated value in 207 (31% of those tested). In aggregate, 661 of 1,880 (35%) patients with confirmed PE manifested at least 1 of the following predictors of an adverse outcome

while in the ED: echocardiography (performed in the ED) with RV hypokinesis, elevated troponin level, or elevated BNP or NT-proBNP level. The mean value of the PESI score for patients with confirmed PE was 88 ± 34, with a range from 18 to 215 (17).

Functional status. The ED clinicians categorized enrolled patients into one of 4 categories of functional status upon presentation, as listed in Table 4. The primary finding was that most (79%) patients diagnosed with PE in the ED were independent and employed.

Treatments and outcomes. Systemic non-vitamin K-dependent anticoagulation was initiated in the ED in 1,593 of 1,880 (84%) patients, with unfractionated heparin (n = 898), enoxaparin (n = 671), fondaparinux (n = 23), or dalteparin (n = 1). However, heparin of any type was administered before the results of diagnostic imaging to only 173 of 1,880 (9%) patients who had confirmed PE. Based upon the Wells' score, the pre-test probabilities were low in 44 (25%), moderate in 111 (65%), and high in 18 (10%). A fibrinolytic agent was administered in the ED to 33 patients (alteplase n = 29 and tenecteplase n = 4), 3

Table 2 Risk Factors for PE and Comorbid Conditions*

Feature	Confirmed PE (n = 1,880)	PE Not Confirmed (n = 528)
Hypertension	857 (45.6)	274 (51.9)
Obesity	505 (26.9)	140 (26.5)
Recent hospitalization	448 (23.8)	97 (18.4)
Malignancy, active	419 (22.3)	96 (18.2)
Current smoker	332 (17.7)	99 (18.8)
Recent surgery	271 (14.4)	38 (7.2)
Prior DVT	224 (11.9)	103 (19.5)
Current DVT	178 (9.5)	36 (6.8)
Prior PE within 3 months	60 (3.2)	50 (9.5)
Immobility	218 (11.6)	31 (5.9)
Prior PE >3 months	172 (9.1)	86 (16.3)
COPD	159 (8.5)	66 (12.5)
Family history of DVT or PE	157 (8.4)	23 (4.4)
History of heart failure	141 (7.5)	61 (11.6)
Coronary artery disease with prior myocardial infarction	128 (6.8)	36 (6.8)
Malignancy, in remission	108 (5.7)	40 (7.6)
Limb immobilization	96 (5.1)	6 (1.1)
In-dwelling venous catheter	91 (4.8)	32 (6.1)
Recent significant trauma	88 (4.7)	11 (2.1)
Oral contraceptives	83 (4.4)	8 (1.5)
Known genetic prothrombotic state	70 (3.7)	21 (4.0)
Neurologic paralysis	53 (2.8)	14 (2.7)
Estrogen replacement therapy	24 (1.3)	5 (0.9)
History of lupus erythematosus	16 (0.9)	12 (2.3)
Postpartum	16 (0.9)	2 (0.4)
Pregnancy	14 (0.7)	4 (0.8)
History of sickle cell disease	12 (0.6)	4 (0.8)
Connective tissue disease	12 (0.6)	2 (0.4)

Values are n (%). *See Online Appendix for definitions.
COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; PE = pulmonary embolism.

Table 3 Signs and Symptoms at Presentation

Feature	Confirmed PE (n = 1,880)	PE Not Confirmed (n = 528)
Vital signs at presentation in ED		
Heart rate, beats/min*	95.7 (20.5)	93.8 (21.8)
Respiratory rate, breaths/min*	20.5 (5.2)	21.2 (7.7)
Systolic blood pressure, mm Hg*	132.3 (24.8)	137.1 (26.7)
Oxygen saturation, %*	95.3 (5.4)	95.7 (5.6)
Symptoms reported by patient		
Dyspnea at rest	942 (50.1)	268 (50.8)
Pleuritic chest pain	740 (39.4)	150 (28.4)
Dyspnea with exertion	507 (27.0)	88 (16.7)
Cough without hemoptysis	430 (22.9)	121 (22.9)
Substernal chest pain	285 (15.2)	90 (17.0)
Dizziness	230 (12.2)	51 (9.7)
Diaphoresis	220 (11.7)	70 (13.3)
Upper abdominal pain	202 (10.7)	39 (7.4)
Fever	182 (9.7)	52 (9.8)
Cough with hemoptysis	143 (7.6)	24 (4.5)
Unilateral extremity pain	110 (5.9)	28 (5.3)
Syncope	103 (5.5)	30 (5.7)
Altered mental status	90 (4.8)	29 (5.5)
Angina	74 (3.9)	20 (3.8)
Physical findings in ED		
Extremity swelling suggestive of DVT	442 (23.5)	97 (18.4)
Respiratory distress	309 (16.4)	71 (13.4)
Rales	158 (8.4)	32 (6.1)
Diaphoresis	133 (7.1)	28 (5.3)
Chest radiograph findings		
Normal	545 (40.1)	161 (40.7)
Westermark sign	5 (0.4)	1 (0.3)
Hampton hump	11 (0.8)	1 (0.3)
Atelectasis	230 (16.9)	61 (15.4)
Infiltrate	184 (13.5)	55 (13.9)
Pleural effusion	220 (16.2)	55 (13.9)
Elevated hemidiaphragm	34 (2.5)	7 (1.8)
Cardiomegaly	162 (11.9)	51 (12.9)
Stable non-PE pathology	197 (14.4)	59 (14.9)

Values are n (%). *Data are presented as mean (SD).
ED = emergency department; other abbreviations as in Table 2.

(9.1%) of whom had hypotension upon ED arrival; an additional 12 patients received alteplase after admission.

Table 5 presents the primary outcomes data. The mortality rate directly attributed to PE in the patients with confirmed PE was 1.1% (20 of 1,880; 95% CI: 0% to 1.6%). Twelve of these 20 patients manifested at least 1 high-risk predictor of an adverse outcome while in the ED, including

arterial SBP <90 mm Hg (n = 4), elevated troponin concentration (n = 6), or RV hypokinesis observed on echocardiography (n = 2). Based upon the Wells' score, the pre-test probabilities of these 20 were low in 6 (30%), moderate in 14 (70%), and high in 0 (0%). In these patients, the choice of initial anticoagulant was unfractionated heparin in 12 (60%), enoxaparin in 7 (35%), and fondaparinux in 1 (5%); however, only 3 received acute anticoagulation before imaging, and 3 others received fibrinolytic therapy more than 2 hours after the diagnosis was established. Three patients (0.2%) died from hemorrhage during their initial hospitalization; none of these received fibrinolysis during their hospitalization. The all-cause mortality rate at 30 days was 102 of 1,880 (5.4%; 95% CI: 4.4% to 6.5%) in the PE-confirmed cohort. Of all patients who died from any cause, 87% had PESI scores >84, whereas only 42% of survivors had PESI scores >84.

Discussion

This report presents key findings from the first large multicenter registry specifically designed to quantify clinical characteristics and outcomes of patients with PE diagnosed in an ED setting.

These results quantify a surprisingly low mortality rate for patients diagnosed with PE in the ED setting. In contrast to the 10% to 15% mortality rate that has been found in previous registries, the data from EMPEROR suggest a remarkably low in-hospital mortality rate directly attributable to PE of 1.1% (95% CI: 0.0% to 1.6%) and an all-cause mortality rate at 30 days of only 5.4% (95% CI: 4.4% to 6.5%). The all-cause mortality rate within 14 days after diagnosis of PE (primarily in the in-patient environment) in the ICOPER (International Cooperative Pulmonary Embolism Registry) study was 11.2% (95% CI: 10.0% to 12.5%), and the RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) study reported an approximate 30-day mortality directly attributable to PE (among 6,518 patients with confirmed PE) of 3.3% (95% CI: 2.9% to 3.8%). Importantly, our data are consistent with the 2007 National ED Survey, which reported a 3.3% in-hospital mortality rate for 121,026 ED patients diagnosed with PE (4).

The low mortality rate probably reflects several factors. First, this registry included only outpatients who suffered PE, and the data suggested that this population was younger

Table 4 Functional Status and Comorbid Conditions

Functional Status	All Patients (n = 2,408)	Confirmed PE (n = 1,880)	PE Not Confirmed (n = 528)
Dependent upon caregivers	174 (7.2)	137 (7.3)	37 (7.0)
Dependent upon family	180 (7.4)	134 (7.1)	46 (8.7)
Independent but disabled	174 (7.2)	123 (6.5)	51 (9.7)
Independent employed	1,880 (78.1)	1,486 (79.0)	394 (74.6)

Values are n (%).
PE = pulmonary embolism.

Table 5 In-Hospital and 30-Day Outcomes

Feature	Confirmed PE (n = 1,880)	PE Not Confirmed (n = 528)
All-cause mortality in-hospital	63 (3.4)	22 (4.2)
Death from PE	20 (1.1)	6 (1.1)
Death from hemorrhage	3 (0.16)	1 (0.19)
Death from other	40 (2.1)	15 (2.8)
All-cause death within 30 days	102 (5.4)	37 (7.0)
Recurrent PE within 30 days	49 (2.6)	10 (1.9)
New DVT within 30 days	11 (0.58)	2 (0.38)

Values are n (%).
 Abbreviations as in Table 2.

and less ill than were populations enrolled in prior registries that included in-patients. For example, the mean patient in the present study was 56.5 years, compared with the mean age of 62 and 66 years in the ICOPER and RIETE registries, respectively. Almost one-third of our sample was non-Caucasian, a predictor of worsened outcome for many acute cardiovascular illnesses. The present study was conducted in the era of CTPA scanning as the primary diagnostic modality, raising the speculative point that diagnosis and treatment may have been faster than when VQ scanning was the primary method of diagnosis. Lastly, the present registry reflected an increased use of low-molecular-weight heparin and pentasaccharide anticoagulants, which may have affected mortality.

Our data do suggest an opportunity for better standardization of treatment. For example, of the 20 patients who died from PE, only 3 received anticoagulation before diagnostic confirmation of PE, even though none of the 20 had a documented contraindication to anticoagulation. Prior work has suggested that delays in anticoagulation are associated with increased short-term adverse events, including recurrence of VTE (18,19). Two independent reports have found an increase in mortality in ED patients with PE who did not receive heparin until after hospital admission, compared with patients who received heparin in the ED (5,18,19). Moreover, Smith *et al.* (5) found that the time to heparin administration was an independent predictor of mortality in a logistic regression equation that was adjusted for the cumulative effect of comorbidities. Furthermore, in the present study, of 20 patients who died of PE, only 3 received fibrinolytic therapy in the ED. The variable application of fibrinolytic therapy in the ED, compared with contemporary, evidence-based guideline recommendations, are both cause for concern and an opportunity for a future randomized, controlled trial of empiric heparin versus no anticoagulation prior to confirmatory imaging (8,20).

Other significant findings included that 79% of ED patients with PE were employed and capable of independent living. Only 11.6% reported generalized immobility, and only one-third were older than 65 years. These observations may be surprising because most published reports suggest that “typical” patients with PE have chronic or

incurable disease, are of advanced age, or are bed-bound. Our findings emphasize the point that emergency physicians should not limit their consideration of the diagnosis to “typical” presentations (1–3).

Idiopathic PE was diagnosed in only 312 (16%), and all but 24 (1.3%) of these patients had tachycardia (heart rate >100 beats/min), had hypoxemia (SaO₂ <95%), or were ≤65 years of age. Thus, the clinician need not be overly concerned that many young ED patients are diagnosed with PE in the presence of no risk factors and normal vital signs.

These data also reported the novel finding that patients diagnosed with PE have an ethnic and racial distribution that closely parallels that of all patients who present to U.S. EDs (21).

Finally, we observed a balanced sex distribution for patients diagnosed with, or empirically treated for, PE. This finding is remarkable because a previous large multicenter U.S.-based study of ED patients found that clinicians evaluated female patients with pulmonary vascular imaging twice as often as male patients (22).

These data should be useful to clinicians and researchers. Clinicians can use these data to inform ED patients that, in general, the prognosis of PE with respect to survival is good. Researchers may find the mortality rate particularly important in designing treatment studies centered in the ED. For example, if a researcher wishes to test the effect of a treatment on mortality in patients presenting with PE in the ED, our data indicated that a large sample size will be needed to produce a statistically significant reduction in mortality rate directly attributable to PE.

Study limitations. All registries have some degree of systematic sampling bias. We believe the primary source of bias in this study was related to the lack of certainty that our sample was a truly random or representative sample of PE presenting in the ED. Although the present study enrolled patients regardless of hemodynamic stability, only 58 of 1,880 (3%) patients were hypotensive at presentation. However, given that this is about the same proportion of hypotensive patients with massive PE as was found in ICOPER (2), another, more likely possibility is that the massive PE rate, with “massive” defined as hypotensive PE, is approximately 3%. It should also be noted that we collected only presentation vital signs, without subsequent serial data; patients who became hypotensive only later in the ED or after admission would not be recognized as “hypotensive” in the database.

Conclusions

Patients with acute PE diagnosed in U.S. EDs had a low all-cause mortality rate of 5.4% at 30 days. Acute anticoagulation with a heparinoid was administered relatively late in the care of patients with fatal PE. These data suggested that empiric anticoagulation in patients with suspected PE should be instituted more often in the ED and that timely, therapeutic anticoagulation should be administered after the

diagnosis is confirmed. Future treatment studies of PE conducted in U.S. EDs should focus on accelerating the time frame of administration of systemic anticoagulation and fibrinolysis to patients with evidence of severe PE. The low mortality rate also implied that efficacy aims for treatment studies should probably measure composite end points that include recurrent VTE, complications of anticoagulation including bleeding, and perhaps other patient-oriented end points associated with quality of life.

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REFERENCES

1. Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *J Am Coll Cardiol* 1997;30:1165–71.
2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353:1386–9.
3. 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 Tromboembolica Venosa (RIETE) Registry. *Circulation* 2008;117:1711–6.
4. Healthcare Cost and Utilization Project (HCUP). Nationwide Inpatient Sample (NIS). Available at: <http://www.hcup-us.ahrq.gov/nisoverview.jsp>. Accessed December 1, 2010.
5. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest* 2010;137:1382–90.
6. Blomkalns AL, Lindsell CJ, Chandra A, et al. Can electrocardiographic criteria predict adverse cardiac events and positive cardiac markers? *Acad Emerg Med* 2003;10:205–10.
7. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6:772–80.
8. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest* 2008;133:454S–545S.
9. Kline JA, Johnson CL, Webb WB, Runyon MS. Prospective study of clinician-entered research data in the emergency department using an Internet-based system after the HIPAA Privacy Rule. *BMC Med Inform Decis Mak* 2004;4:17–25.
10. Kline JA, Mitchell AM, Runyon MS, Jones AE, Webb WB. Electronic medical record review as a surrogate to telephone follow-up to establish outcome for diagnostic research studies in the emergency department. *Acad Emerg Med* 2005;12:1127–232.
11. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation* 2007;116:427–33.
12. Kruger S, Merx MW, Graf J. Utility of brain natriuretic peptide to predict right ventricular dysfunction and clinical outcome in patients with acute pulmonary embolism. *Circulation* 2003;108:e94–5.
13. Sanchez O, Trinquart L, Colombet I, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *Eur Heart J* 2008;29:1569–77.
14. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172:1041–6.
15. Kucher N, Rossi E, DeRosa M, Goldhaber SZ. Massive pulmonary embolism. *Circulation* 2006;113:577–82.
16. Arkin CF, Wachtel MS. How many patients are necessary to assess test performance? *JAMA* 1990;263:275–80.
17. Edmonds ZV, Mower WR, Lovato LM, Lomeli R. The reliability of vital sign measurements. *Ann Emerg Med* 2002;39:233–7.
18. Kline JA, Hernandez J, Jones AE, Rose GA, Norton HJ, Camargo CA Jr. Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. *Acad Emerg Med* 2007;14:592–8.
19. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy. The emerging theme of delayed recurrence. *Arch Intern Med* 1997;157:2317–21.
20. Torbicki A, Perrier A, Konstantinides S, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008;29:2276–315.
21. McCaig LF, Burt CW. National hospital ambulatory medical care survey: 2002 emergency department summary. *Advance Data* 2004;1–34:1491–8.
22. Beam DM, Courtney DM, Kabrhel C, Moore CL, Richman PB, Kline JA. Risk of thromboembolism varies, depending on category of immobility in outpatients. *Ann Emerg Med* 2009;54:147–52.

Key Words: anticoagulation ■ epidemiology ■ fibrinolysis ■ pulmonary embolism ■ venous thromboembolism.

▶ APPENDIX:

For participating sites and lists of definitions and exclusions, please see the online version of this article.