Management of pulmonary embolism at a large academic hospital

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ABSTRACT

The initial management of patients presenting with acute pulmonary embolism (PE) is individualized based on hemodynamic status and other prognostic factors. Patients at low risk of adverse outcomes are treated conservatively with anticoagulation, whereas high-risk and selected intermediate-risk patients should be considered for advanced interventions. Seeking to better understand local practice patterns, we retrospectively reviewed 196 cases of acute PE diagnosed in the emergency department of Baylor University Medical Center over a 12-month period. Given the available data, we classified 86 cases as low risk, 101 as intermediate risk, and 9 as high risk for early mortality. Four patients with high-risk PE and 11 patients with intermediate-risk PE were treated with thrombolytic therapy. Central embolus location, right ventricular dilation on computed tomography, and right ventricular strain on electrocardiogram were associated with the use of thrombolytic therapy in the intermediate-risk group. In total, 9 patients died and 11 suffered major bleeding. Patients with acute PE are a remarkably heterogeneous group with wide variations in workup, treatment, and outcomes.

KEYWORDS Computed tomography; pulmonary embolism; thrombolysis

Pulmonary embolism (PE) is diagnosed in about 12 per 100,000 adults and accounts for nearly 40,000 in-hospital deaths annually,¹ although the true burden is unknown because many cases may be undiagnosed or are diagnosed only after death. Cases of acute PE may be classified by the probability of early adverse outcome as low risk (hemodynamically stable and with normal right ventricular [RV] function), intermediate risk or sub-massive (hemodynamically stable with radiographic, echocardiographic, electrographic, and/or biochemical evidence of RV dysfunction), and high risk or massive (having sustained hypotension, pulselessness, or need for inotropic support). Though patients with low-risk PE can be safely managed with anticoagulation alone, the management of patients with intermediate- and high-risk PE is more complex and may include a combination of anticoagulation, systemic or catheter-directed thrombolysis, and mechanical thrombectomy. Thrombolysis is recommended in all patients with high-risk PE and may be considered in selected patients with intermediate-risk PE, but guidelines have evolved in recent years

and consensus recommendations on which patients should receive thrombolysis are lacking.^{2–4} A growing trend is the institution of a multidisciplinary pulmonary embolism response team (PERT) to coordinate and streamline care for patients with intermediate- and high-risk pulmonary embolism.⁵ In this study, we explored local practice patterns in the stratification and management of acute PE.

METHODS

We conducted a retrospective cohort study based on review of electronic health records of all patients diagnosed with acute PE by computed tomography (CT) angiography in the emergency department (ED) of Baylor University Medical Center, a 914-bed tertiary care hospital in Dallas, Texas, over a 12-month period from July 1, 2016, to June 30, 2017. We excluded inpatients diagnosed with PE and those diagnosed by other modalities (e.g., high-probability ventilation-perfusion scan or identification of deep venous thrombosis by duplex ultrasound in patients with a high

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pretest probability) in order to produce a relatively homogeneous study population in which diagnosis, risk stratification, and management decisions occur over a short period with a minimum of confounding variables. For each case we abstracted patient demographics, initial vital signs, troponin I and B-type natriuretic peptide (BNP) levels, radiographic characteristics (location of most proximal embolus and number of lobes involved), and evidence of RV dysfunction on CT, echocardiogram, and electrocardiogram (ECG). Biomarkers, echocardiograms, and ECGs were considered only if obtained within 24 hours of diagnosis. For each patient we calculated a simplified PE severity index (sPESI), a predictor for 30-day mortality in which points are assigned for age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate ≥ 110 bpm, systolic blood pressure <100 mm Hg, and oxygen saturation <90%.⁶ Evidence of RV dysfunction was defined as troponin >0.05 ng/mL or BNP >100 pg/mL, RV dilation or flattening of the interventricular septum on CT, RV systolic dysfunction or estimated RV systolic pressure >40 mm Hg on echocardiogram, or ECG findings of new complete or incomplete right bundle branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion. CTs and echocardiograms were classified according to the reports of the interpreting radiologists and cardiologists, and all ECGs were reviewed by one of the authors (Z.F.). We classified each case as low, intermediate, or high risk as previously defined.

Other data points included use of thrombolytic therapy and inferior vena cava filters, need for mechanical ventilation, major bleeding, in-hospital mortality, and length of stay. Predictors for the use of thrombolysis in patients with intermediate-risk PE were identified using two-sided Fisher's exact test for categorical variables and binomial logistic regression for ordinal and continuous variables. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using SPSS Version 25.0 (IBM Corp., Armonk, NY).

Finally, we compared our institutional practices and outcomes to those from the Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR), a prospective observational study that enrolled patients from 22 community and academic EDs across the United States between 2005 and 2008.⁷

RESULTS

A total of 2639 CT angiograms were performed in our ED during the 12-month period. Of these, 196 (7.4%) were interpreted as compatible with acute PE, 40 (1.5%) as consistent with chronic PE, 32 (1.2%) as indeterminate, and the remaining 2371 (89.8%) as negative. Characteristics of the patients with acute PE are shown in *Table 1*.

An ECG was performed in 184 patients (93.9%) and a formal transthoracic echocardiogram in 94 patients (48.0%) within 24 hours of diagnosis. An additional 8 patients (4.1%) underwent a focused bedside echocardiogram by the emergency medicine physician. Troponin was

Table 1. Patient characteristics ($n = 196$)

Variable	Value
Age (years), mean $\pm$ SD	62.2 $\pm$ 16.7
Sex	
Male	102 (52.0%)
Female	94 (48.0%)
Race/ethnicity	
White	114 (58.2%)
Black	71 (36.2%)
Hispanic	10 (5.1%)
Asian	1 (0.5%)
Cancer	48 (24.5%)
Heart failure	25 (12.8%)
Chronic lung disease	33 (16.8%)
Heart rate (bpm), mean $\pm$ SD	96.1 $\pm$ 21.7
Systolic blood pressure (mm Hg), mean $\pm$ SD	138.9 $\pm$ 29.4
Shock index, ^a mean $\pm$ SD	0.73 $\pm$ 0.26
Oxygen saturation <90%	34 (17.3%)
Altered mental status	17 (8.7%)
Discharged from ED	28 (14.3%)
Admitted	168 (85.7%)
Required mechanical ventilation	15 (7.7%)
Major bleeding	12 (6.1%)
In-hospital mortality	9 (4.6%)
Length of stay (days), mean $\pm$ SD	5.34 $\pm$ 5.96

^aDefined as heart rate divided by systolic blood pressure.
bpm indicates beats per minute; ED, emergency department.

measured in 174 patients (88.8%) and BNP in 114 patients (58.2%); in 113 patients (57.7%), both biomarkers were obtained, and in 21 (10.7%) neither was checked. Given the available data, we classified 86 cases (43.9%) as low risk, 101 (51.5%) as intermediate risk, and 9 (4.6%) as high risk for early mortality.

Fifteen patients received thrombolytic therapy with alteplase, administered as a 10-mg bolus followed by either a 90-mg (full dose) or 40-mg (half dose) infusion over 2 hours. Four of the 9 patients with high-risk PE received full-dose thrombolysis, and the remaining 5 had documented contraindications to thrombolysis. Ten patients with intermediate-risk PE received either full- or half-dose thrombolysis in the ED, and an 11th received full-dose thrombolysis on the third hospital day after suffering hemodynamic decompensation. Though most patients who received thrombolytic therapy had an echocardiogram performed, only 3 had the study performed prior to thrombolysis. Use of thrombolytic therapy among patients with intermediate-risk PE was associated

Table 2. Comparison of patients with intermediate-risk pulmonary embolism who did and did not receive thrombolysis in the ED

Variable	Thrombolysis (n = 10)	No thrombolysis (n = 91)	P value
Age (years), mean ± SD	69.6 ± 16.3	65.6 ± 16.6	0.467
Female	3 (30%)	40 (44%)	0.510
Nonwhite race	3 (30%)	39 (43%)	0.516
Cancer	1 (10%)	19 (21%)	0.682
Heart failure	0	20 (22%)	0.204
Chronic lung disease	1 (10%)	20 (22%)	0.683
Heart rate (bpm), mean ± SD	101.5 ± 18.6	97.0 ± 22.9	0.549
Systolic blood pressure (mm Hg), mean ± SD	133.0 ± 25.7	144.9 ± 30.8	0.243
Shock index, ^a mean ± SD	0.81 ± 0.26	0.71 ± 0.26	0.251
Oxygen saturation <90%	3 (30%)	21 (23%)	0.698
Altered mental status	0	5 (5%)	1.000
Required mechanical ventilation in ED	0	1 (1%)	1.000
Troponin >0.05 ng/mL	7 (70%)	42 (46%)	0.192
BNP >100 pg/mL	4 (40%)	43 (47%)	0.748
Central embolus location ^b	9 (90%)	28 (31%)	<0.001
Multilobar involvement	10 (100%)	72 (79%)	0.201
RV dilation on CT	10 (100%)	47 (52%)	0.004
RV strain on ECG	7 (70%)	28 (31%)	0.030
sPESI, mean ± SD	1.5 ± 1.1	1.5 ± 1.1	0.159

^aDefined as heart rate divided by systolic blood pressure.

^bDefined as a saddle embolus or embolus in the left or right pulmonary artery.

BNP indicates B-type natriuretic peptide; bpm, beats per minute; CT, computed tomography; ECG, electrocardiogram; ED, emergency department; RV, right ventricular; sPESI, simplified pulmonary embolism severity index.

with central embolus location; that is, a saddle embolus straddling the bifurcation of the main pulmonary artery or one located in one or both pulmonary arteries ($P < 0.001$), presence of RV dilation on CT ($P = 0.004$), and evidence of RV strain on ECG ($P = 0.030$). These findings are summarized in [Table 2](#).

Alteplase was administered through peripheral or central venous catheters in all cases. No patient was treated with catheter-directed thrombolysis, mechanical thrombectomy, or extracorporeal membrane oxygenation during the study period. Fourteen patients (7.1%) received inferior vena cava filters for various reasons including contraindication to anticoagulation and recurrent venous thromboembolism despite anticoagulation.

Twenty-eight patients (14.3%) were discharged from the ED, all of whom had an sPESI score of 0 or 1 and most of whom were prescribed a direct-acting oral anticoagulant. One hundred sixty-eight patients (85.7%) were admitted. The median length of stay was 3 days in the low-risk group, 4 days in the intermediate-risk group, and 17 days in the high-risk group. Among survivors with intermediate-risk PE, there was no significant difference in length of stay between those who received thrombolysis in the ED and those who

did not ($P = 0.555$). Major extracranial bleeding occurred in 12 patients (6.1%), including 2 (13.3%) of those who received thrombolysis. There were no cases of intracranial hemorrhage. Nine patients (4.6%) died in the hospital. Six had high-risk PE, 4 of whom suffered cardiac arrest in the field and/or the ED. Two had intermediate-risk PE but were terminally ill, one with end-stage liver disease and one with metastatic pancreatic cancer. The final death was in a patient with intermediate-risk PE and persistent hypoxemia being treated with unfractionated heparin. On the fourth hospital day, she suffered sudden cardiac death that was attributed to a recurrent PE.

The findings of a comparison between our data and those of the EMPEROR registry are shown in [Table 3](#).

DISCUSSION

Following the diagnosis of acute PE, risk stratification is crucial to identify patients who may benefit from advanced therapies. We found that patients with high-risk PE were quickly recognized and, when possible, treated with thrombolytic therapy. We also observed that patients with no identifiable risk factors generally did not undergo

Table 3. Comparison between local data and data from EMPEROR registry

	Baylor University Medical Center (<i>n</i> = 196)	EMPEROR registry (<i>n</i> = 1880) ^a
Age (years), mean ± SD	62.2 ± 16.7	56.5 ± 18.1
Age >65 years	89 (45.4%)	631 (33.6%)
Female	94 (48.0%)	992 (52.8%)
White	114 (58.2%)	312 (16.6%)
Black	71 (36.2%)	161 (8.6%)
Hispanic	10 (5.1%)	57 (3.0%)
Asian	1 (0.5%)	11 (0.6%)
Intermediate and high risk	110 (56.1%)	661 (35.2%)
Echocardiogram performed	94 (48.0%)	430 (22.9%)
Troponin obtained	174 (88.8%)	1287 (68.5%)
BNP obtained	114 (58.2%)	661 (35.2%)
Thrombolysis in ED	13 (6.6%)	33 (1.8%)
Thrombolysis after admission	2 (1.0%)	12 (0.6%)
In-hospital mortality	9 (4.6%)	63 (3.4%)

^aIncludes patients with PE confirmed by any imaging modality. Eighty-nine percent were diagnosed by CT pulmonary angiography. BNP indicates B-type natriuretic peptide; ED, emergency department; EMPEROR, Emergency Medicine Pulmonary Embolism in the Real World Registry.

unnecessary testing and were often appropriately discharged from the ED. However, the management of hemodynamically stable patients with evidence of RV dysfunction was more varied and deserves closer examination.

The use of thrombolytic therapy in patients with intermediate-risk PE is a contentious subject. In the Pulmonary Embolism Thrombolysis trial, the largest of its kind, 1006 normotensive patients with acute PE, RV dysfunction on imaging, and elevated cardiac troponin were randomized to a single intravenous bolus of tenecteplase plus heparin versus placebo plus heparin. Thrombolytic therapy reduced the primary outcome of death or hemodynamic decompensation at 7 days (odds ratio = 0.44; 95% confidence interval, 0.23 to 0.87; *P* = 0.02) at the expense of higher rates of extracranial bleeding (6.3%) and hemorrhagic stroke (2.0%) compared to placebo (1.2% and 0.2%, respectively).⁸ Furthermore, a 24-month follow-up study conducted in a subset of the original participants found no long-term differences in mortality or residual dyspnea, functional limitation, or echocardiographic evidence of pulmonary hypertension and RV dysfunction.⁹ Therefore, routine use of thrombolysis in patients with intermediate-risk PE is not recommended, and criteria to identify those most likely to benefit from thrombolysis remain to be determined. Current guidelines from the European Society of Cardiology and the American College of Chest Physicians recommend thrombolysis only for those with clinical signs of hemodynamic decompensation.^{3,4}

Approximately 10% of our patients with intermediate-risk PE were treated with thrombolytic therapy, and the

selection of these patients was not always clear from the available data. The factors associated with the use of thrombolytic therapy in patients with intermediate-risk PE were central embolus location, RV dilation on CT, and evidence of RV strain on ECG. Though the finding of a large, centrally located embolus might be expected to portend an adverse outcome, one meta-analysis found that large thrombus burden and central embolus location actually did not predict all-cause mortality, whereas increased right-left ventricular diameter ratio did.¹⁰ Surprisingly, tachycardia, relative hypotension, and hypoxia did not appear to drive our physicians to use thrombolytic therapy. Although it did not meet statistical significance, one concerning trend was the higher utilization of thrombolytic therapy in older patients, including some in the ninth and tenth decades of life. A meta-analysis of several trials examining the use of thrombolysis in acute PE found that patients >65 years of age were over 4.5 times more likely to suffer major bleeding than those ≤65 years when treated with thrombolysis (12.9% vs 2.8%).¹¹ Given these data, physicians should take pause before giving thrombolytic therapy to the elderly patient with acute PE who is hemodynamically stable.

The EMPEROR registry was a prospective, observational study enrolling 2408 patients with suspected PE, including 1880 with PE confirmed by any means, from 22 community and academic EDs between 2005 and 2008. Despite the obvious methodologic differences and an interval decade of experience, we attempted to draw some comparisons with our findings. Our all-cause mortality rate was similar despite

our higher mean patient age and a greater proportion of patients in the intermediate- and high-risk groups, and our institution obtained more echocardiograms and cardiac biomarkers than those in the registry. Perhaps the most striking difference was our higher utilization of thrombolysis (7.7% vs 2.4%), which may be partially explained by the greater acuity of our cohort.

The PERT model was developed at Massachusetts General Hospital in 2012 to improve the quality and efficiency of care for patients with intermediate- and high-risk PE. A multidisciplinary team typically includes members of the emergency medicine, pulmonology/critical care, cardiology, hematology, interventional radiology, and vascular or cardiothoracic surgery services. Upon activation, the team convenes virtually to discuss the case, make a consensus treatment recommendation, and mobilize appropriate resources. Adoption of the PERT model is growing, and over 50 institutions have formed a national consortium dedicated to promotion of the model, education of patients and health care providers, and coordination of research efforts.¹² Further analysis is needed to determine whether a PERT would be successful and cost-effective at our institution.

Our study adds to the literature a snapshot of practice patterns at a modern American academic hospital and yields valuable insight into which factors guide the use of thrombolytic therapy in a time when explicit guidelines are lacking. Our study has several limitations. It is inherently biased toward the practice of emergency medicine physicians and may not accurately represent the approach taken by other specialists. It was not powered to detect differences in outcomes such as mortality and major bleeding. Finally, it may fail to capture certain drivers of medical decision making such as resource availability and patient preference.

In summary, we found that hemodynamically stable patients presenting to the ED with acute PE are a large and heterogeneous group with clinical courses ranging from brief observations to long, complicated hospitalizations and even death. Standardization of risk stratification and management is needed and might be improved by formation of a PERT. Finally, our apparent overuse of CT angiography, as evidenced by a positivity rate of only 7.7%, represents an opportunity for further study.

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