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Mortality from Pulmonary Embolism by Clinical Severity

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Abstract

Background: Mortality related to pulmonary embolism varies widely in the reported literature even for the same clinical severity category of PE.
Aim: To report all-cause and PE related short term mortality by clinical severity of PE and to identify any missed opportunities for thrombolysis.
Method: Electronic medical records of all patients presenting to a large tertiary care teaching hospital in London, between October 1, 2018 and January 16, 2020, who had a discharge diagnosis of acute pulmonary embolism were reviewed retrospectively.
Results: There was no PE related mortality in the low-risk PE group. There was one PE related death in the submassive PE group (1.47% mortality at day 14 and day 30). Massive PE was associated with a 29.4% PE related mortality short-term mortality.

Keywords
Pulmonary embolism; thrombolysis; sub-massive pulmonary embolism

Background

Mortality related to pulmonary embolism (PE) has varied considerably in published literature over the years. (1–5) Wide differences exist even for the same clinical severity of PE, among clinical-trial data and data from registries. (2, 3, 6)

In a study of the RIETE database, a multinational registry of patients with PE, 34,390 patients were included and 3.5% had haemodynamic instability. All cause 30-day mortality was 14% for those with haemodynamic instability compared to 5.4% for those without. (2) In the PEITHO trial of patients with moderate-risk PE, 2.4% of those thrombolysed and 3.2% of those treated with anticoagulation alone, died by day 30. (7) The MOPETT (8)and SEATTLE II (9)clinical trials also reported much lower mortality with moderate-risk PE. Mortality from acute massive PE in registry data has been as high as 52%. (10)

The main aim of our paper was to provide contemporary, real world data on mortality from pulmonary embolism by its clinical severity at a large tertiary care teaching hospital in London, where treatment was expected to be largely based on the current management guidelines.

The terms massive, submassive (alternatively called intermediate- or moderate-risk) and low-risk PE are classifications of clinical severity and not of the radiologic burden of the thrombus, which has not been shown to be a predictor of mortality. (11) As current descriptions stand, massive PE refers to acute PE that results in haemodynamic compromise, defined in most guidelines as a systolic blood pressure of less than 90 and in some guidelines additionally, as a drop in systolic blood pressure by 40 mm of Hg or more, compared to the initial or baseline systolic blood pressure. (12)

Submassive PE, also referred to as moderate-risk or intermediate-risk PE, refers to PE not associated with a low blood pressure but associated with evidence of right heart strain, either on imaging (CT scan or

echocardiogram) or in the form of raised troponin or brain natriuretic peptide (BNP) levels. Troponin rise in the context of PE represents right ventricular microinfarction as a result of right ventricular strain from the burden of thrombus. (13)

The American Heart Association (AHA) classifies all other PE as low risk. (14)Existing PE severity scoring systems, such as the Pulmonary Embolism Severity Index (PESI) and Geneva scores are often used to guide decision-making about outpatient versus inpatient management. (15, 16) The broader clinically distinct categories of PE used in our paper, have implications on the choice of initial treatment, specifically, whether or not thrombolysis is appropriate. The National Institute of Clinical Excellence (NICE) and European Society of Cardiology (ESC) 2019 guidelines recommend thrombolytic therapy only when PE is massive, that is, it results in a low blood pressure. Currently, majority of guidelines advice against thrombolysis for submassive PE. (17, 18)

There is evidence to show that thrombolysis in submassive PE results in improved pulmonary arterial pressures and decreased incidence of right ventricular failure. (9) However, a mortality benefit to thrombolysis in submassive PE has not yet been demonstrated. (19) The risk of major bleeding, including intracranial bleeding from thrombolysis has also been reported variably in published literature and has been as high as 9.2% in a meta-analysis. (20, 21)

In the face of relatively low, albeit variably, reported mortality rates in submassive PE, the benefits of thrombolysis are not felt to outweigh the associated risk of major bleeding. Due to the much higher mortality with massive PE, the consensus swings in favour of thrombolysis, with the bleeding risk being outweighed by the afforded mortality benefit.

It should also be noted that clinical trials done so far have been inadequately powered to detect a mortality benefit in either low-dose or full-dose thrombolysis in submassive PE. (22)Exceeding large sample sizes would be needed to adequately power such a study, at the given mortality rates. A secondary goal of our paper was to identify the mortality associated with the clinical severity categories of PE in contemporary practice and add to the existing but variable literature on PE associated mortality.

We also reviewed records of all deaths individually to audit whether there had been any potential opportunities for thrombolysis.

Methods

Institutional audit was registered. Electronic medical records of all patients presenting to a large tertiary care teaching hospital in London, between October 1, 2018 and January 16, 2020, who had a discharge diagnosis of acute pulmonary embolism were reviewed retrospectively. Haemodynamic instability was defined by a systolic blood pressure of less than 90 mm of Hg or by a drop in systolic blood pressure by 40 mm of Hg or more.

Right heart strain was identified by either a diagnosis of the same on a CT pulmonary angiogram (CTPA) or echocardiogram or by an elevated level of cardiac biomarkers (troponin or nt-pro Brain Natriuretic Peptide (BNP). PE associated with haemodynamic instability was classified as massive, while PE without haemodynamic instability, but with right heart strain, was classified as submassive. All other PE were classified as low risk. Major bleeding was defined as (23) (1) fatal bleeding and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in Haemoglobin level of 2 g/dL or more or requiring a transfusion of two or more units of whole blood or red cells.

Mortality data was reviewed on electronic medical records. For in-hospital deaths, the date of death was updated on records by the hospital staff; for out-of-hospital deaths, records were updated by the GP. Records of all patients who died were reviewed for PE related 14 day and 30-day mortality. Mortality attributable to a cause other than PE was not considered PE related mortality but was reported in all-cause mortality. Records were also reviewed to identify patients that would be deemed to have a high-risk of bleeding. (24)This data was used when auditing individual deaths as it would have bearings on decisions surrounding thrombolysis.

Results

There were 229 presentations to our hospital between October 1, 2018 and January 16, 2020 where the

discharge diagnosis was “acute pulmonary embolism”. Attendances that recurred for the same instance of acute pulmonary embolism and attendances where the diagnosis was subsequently disproven on scan were excluded. Also excluded was a patient in whom PE was diagnosed at another hospital two weeks ago and a patient in whom mortality data was unavailable.

There were 171 patients, who had a confirmed discharge diagnosis of acute PE between October 1, 2018 and January 16, 2020. Approximately half of the them were male, thirty percent had a history of cancer and in about 8%, the PE was a recurrence. (Table 1).

All-cause mortality was 4.1 % at day 14 and 5.8 % at day 30. PE related mortality at day 14 and 30 was 2.9 % and 3.5 % respectively. Of the 171 patients, 83 had low-risk PE, 68 had submassive PE, 17 had massive PE and for 3 patients there was not enough data to accurately categorize the PE. There was no PE related mortality recorded in the low-risk PE group. There was one PE related death in the submassive PE group (1.5% mortality at day 14 and day 30). Massive PE was associated with a 29.4% PE related mortality short-term mortality.

Major bleeding occurred in 4 patients (2.3%), three of whom had received thrombolytic therapy. A total of 22 patients were thrombolysed. Ten of these had massive PE and 12 had submassive PE. Most of the seven patients with massive PE who were not thrombolysed had relative contraindications to thrombolysis.

Discussion

Though our sample size was smaller than most registry data, records of each patient were independently reviewed to ensure accuracy of diagnosis and all other data obtained. This is not necessarily the case with registries. For example, the International Cooperative Pulmonary Embolism Registry, ICOPER, accepted without independent review diagnoses provided by participating centres. (6)Mortality rates from PE at our institute were comparable to those reported in the more recent studies and lower than those reported in some registries.

Of the 10 patients who died by day 30 of admission, three had had an out of hospital cardiac arrest with subsequent return of circulation and eventual cardiac arrest again. Of these three, two received thrombolysis. The CT pulmonary angiogram of the patient who had an out-of-hospital cardiac arrest and did not receive thrombolysis reported “subtle bilateral pulmonary emboli with evidence of right heart strain”. The cardio-pulmonary resuscitation (CPR) downtime for this patient was 40 minutes with evidence of ischemic hepatitis and an International normalized ratio (INR) of 3.8. The decision to not offer thrombolysis was documented.

Of the 10 patients who died by day 30 of admission, six had massive PE, two had submassive PE and two had low-risk PE. Both patients with low-risk PE had non-PE related mortality. Of the two who died with submassive PE, one had sickle cell disease with acute kidney injury on a background of chronic kidney disease and severe pulmonary hypertension. A CT pulmonary angiogram had shown segmental pulmonary emboli within the right upper lobe; the cardiac arrest itself was from hyperkalaemia with a serum potassium of 9.1 mmol /L. Thrombolysis, along with anti-hyperkalaemia treatment were instituted at the point of cardiac arrest, with subsequent return of circulation and eventual further deterioration and death the next day in intensive care.

The other patient with submassive PE who died had a sudden cardiac arrest at the point of discharge from the hospital, two days after admission. A CTPA had reported “…major massive central pulmonary embolism with a saddle embolus present across the bifurcation of the main pulmonary artery with associated right ventricular strain”. This patient was treated initially with low-molecular weight heparin and an interim plan was made to offer thrombolysis should the systolic blood pressure dip to less than 100 mm of mercury or should any oxygen requirement develop. This patient remained haemodynamically stable and without supplemental oxygen, until a sudden cardiac arrest, at which point thrombolysis was instituted. There was a brief return of circulation, but death occurred shortly after. This was this patient’s third PE and there was a background of breast cancer under surveillance.

Three patients with massive PE had in-hospital deaths. One had bilateral pulmonary emboli with right heart strain and was treated with low-molecular weight heparin. This patient also had evidence of major haemorrhage at the time of admission evidenced as a new drop in haemoglobin from 99 to 69 g/L and necessitating >2 units of packed red cells to be transfused. Subsequent upper GI endoscopy had shown no stigmata of recent bleeding and this patient was awaiting a CT colonogram. Thrombolysis was offered at the point of cardiac arrest. Whilst no blood pressure

Table 1: Characteristicsof patients with confirmed acute pulmonary embolism *

Variable	
Male: Number (%)	86 (50.3%)
Age in years: Mean (SD)	62.4 (17.1)
History of cancer: Number (%)**	52 (30.6%)
Recurrent PE: Number (%)***	14 (8.2%)
Identified as high-risk for bleeding: Number (%)	19 (11.1%)

*Total number of patients= 171
**Data for this variable was missing for 1 patient. Total number= 170.
*** Data for this variable was missing for 1 patient. Total number= 170.

Table 2: Mortalityby PE risk-category

PE risk-category	N	All deaths, any cause, by day 30: Number (%)	PE related deaths, by day 30: Number (%)
Massive (high-risk) PE	17	6 (35.29%)	5 (29.4%)
Submassive (intermediate-risk PE)	68	2 (2.94%)	1 (1.47%)
Low-risk PE	83	2 (2.4%)	0 (0%)
Unclassified*	3	0	0

*Patients for whom enough data was not available to accurately assign PE risk category.

reading was recorded as less than 90 mm of mercury, the drop in systolic blood pressure from her best baseline readings was > 40 mm of Hg. Further, this patient had rapidly progressive hypoxia. This was this patient's third PE and mortality was directly PE related.

Both of the other two patients with massive PE and in-hospital death had been offered thrombolysis.

Notably, individualised 'case-by-case basis thrombolysis' for submassive PE was practiced at our institute. Twelve of the 68 patients with submassive PE were thrombolysed. None of these twelve patients suffered major bleeding and all but one survived. The single death in this group was not PE related.

Our data reaffirms that mortality from submassive and low-risk PE is low. There was no major bleeding observed in our selection of patients with submassive PE who received thrombolysis. Mortality from massive PE continues to approach 30% even today.

References

1. Horlander KT, Mannino DM, Leeper KV. Pulmonary Embolism Mortality in the United States, 1979-1998: An Analysis Using Multiple-Cause Mortality Data. Arch Intern Med. 2003;163(14):1711–1717.
2. Jimenez D, et al. for the RIETE investigators. Epidemiology, patterns of care and mortality for patients with hemodynamically unstable acute symptomatic pulmonary embolism. International Journal of Cardiology. 2018;269:327–333.
3. Lilienfeld DE. Decreasing mortality from pulmonary embolism in the United States, 1979-1996. International Journal of Epidemiology. 2000;29(3):465–469.
4. Alpert JS, et al. Mortality in Patients Treated for Pulmonary Embolism. JAMA. 1976;236(13):1477–1480.
5. Lehnert P, et al. Acute Pulmonary Embolism in a National Danish Cohort: Increasing Incidence and Decreasing Mortality. Thromb Haemost. 2018;118(03):539–546.
6. Goldhaber SZ, et al. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). The Lancet. 1999;353(9162):1386–1389.
7. Meyer G, et al. for the PEITHO investigators. Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism. N Engl J Med. 2014;370:1402–1411.
8. Sharifi M, et al. Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial). The American Journal of Cardiology. 2013;111(2):273–277.

9. Piazza G, et al. for the SEATTLE II investigators. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism. JACC: CARDIO VASCULAR INTERVENTIONS. 2015;8(10).
10. Kucher N, et al. Massive Pulmonary Embolism. Circulation. 2006;113(3):577–582.
11. Morris MF, et al. CT Findings and Long-Term Mortality After Pulmonary Embolism. AJR. 2012;198:1346–1352.
12. Bernal AG, et al. Management of PE. Expert Opinion. American College of Cardiology. 2020;.
13. Kucher N, Goldhaber SZ. Cardiac Biomarkers for Risk Stratification of Patients With Acute Pulmonary Embolism. Circulation. 2003;108(18):2191–2194.
14. Jaff MR, 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;123:1788–1830.
15. Zhou X, Ben S, Chen H, et al. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: a meta-analysis. Respir Res. 2012;13:111.
16. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing Clinical Probability of Pulmonary Embolism in the Emergency Ward. Archives of Internal Medicine. 2001;161(1):92–97.
17. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NICE guideline [NG158]Published date: 26 March; 2020.
18. Konstantinides SV, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Respiratory. 2019;.
19. Marti C, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. European Heart Journal. 2015;36(10):605–614.
20. Daley MJ, Murthy MS, Peterson EJ. Bleeding risk with systemic thrombolytic therapy for pulmonary embolism: scope of the problem. Therapeutic Advances in Drug Safety. 2015;p. 57–66.
21. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage: A Meta-Analysis. JAMA. 2014;311(23):2414–2421.
22. Kucher N, et al. Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism. Circulation. 2014;129:479–486.
23. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. for the Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13:2119–2126.
24. Fugate JE, Rabinstein AA. Absolute and Relative Contraindications to IV rt-PA for Acute Ischemic Stroke. Neurohospitalist. 2015;5(3):110–121.

Conflict of Interest

Authors declare no conflict of interest