Original Article

Acute pulmonary thromboembolism: Epidemiology, predictors, and long-term outcome – A single center experience

U.M. Nagamalesh *, V.S. Prakash, K.C. Karthik Naidu, S. Sarthak, Anupama V. Hegde, T. Abhinay

Department of Cardiology, MS Ramaiah Medical College, MS Ramaiah Memorial Hospital, Bangalore, Karnataka, India

ABSTRACT

Introduction: Acute pulmonary thromboembolism (PTE) is a life-threatening disease. Mortality in PTE still remains very high in spite of progress in diagnostic tools. Mortality rate is about 30% in patients with unrecognized acute PTE.

Methods: It is a single center observational study of 31 consecutive patients who were hospitalized in the Department of Cardiology at MS Ramaiah Memorial hospital between January 1, 2010 and June 2015. All the patients confirmed with diagnosis of acute PTE by CT scan (either HRCT or CTPA) were included in the study. Following relevant investigations chosen patients were risk stratified as per standard guidelines into massive, sub massive or low risk and treated accordingly. The included patients were followed up for a period of 1 year with 2D-echocardiogram and other relevant investigations for comparison to assess improvement. Mortality due to either acute PTE or other causes was noted in the study.

Results: Of the 31 patients enrolled in our study, 71% ($n = 22$) of the patients belonged to the age range 20–50 years with those in the age group 31–40 years comprising 39% ($n = 12$) of the total. Elderly people over 65 years of age comprised only 19% ($n = 6$) of the total number of patients. Dyslipidemia, prolonged immobilization, deep vein thrombosis, post-operative state, malignancy and post-partum period were the commonly reported risk factors. We thrombolysed a total of 18 (58%) patients with massive and submassive PTE, of which 12 (39%) received tenecteplase and 6 patients received streptokinase (19%). Three (9%) patients required repeat thrombolysis with streptokinase due to failed thrombolytic therapy with tenecteplase.

Conclusions: Our study reported higher incidence of acute PTE in the middle age group population. Prevalence of dyslipidemia was high in this cohort of patients studied although the exact association of it in APE could not be determined. Thrombolytic therapy can be considered for patients with both massive and submassive pulmonary thromboembolism. Repeat thrombolysis can be considered in case one thrombolytic agent failed to give the desirable results.

1. Introduction

Acute pulmonary embolism (PE) is a common and potentially lethal form of venous thromboembolism (VTE) which is commonly encountered in clinical practice. Most patients die of this fatal condition usually within the first 1 h of the event with mortality rate reaching nearly 10% during this period.[1] Mortality rate of diagnosed and treated pulmonary embolism ranges from 3 to 8%, but increases to about 30% in untreated pulmonary embolism.[1] In the United States, acute pulmonary embolism afflicts 500,000–600,000 persons annually and is either a primary or secondary cause of death in 150,000–200,000 of these individuals.[2] The 1-year mortality rate in the PIOPED study was reported as ≈25%, with 2.5% dying from primary cause as pulmonary embolism itself.[3] Other studies have reported that in patients without preexisting cardiac or pulmonary disease, the 1-year mortality rate ranged from 3% to 9%.[4,5] Mortality in APE is mainly reported to be due the associated comorbid conditions like cancer, infections, cardiovascular diseases, and other pulmonary diseases.[6]

* Corresponding author at: Department of Cardiology, MS Ramaiah Memorial Hospital, MSRIT Post, Bangalore, Karnataka 560054, India.
  E-mail address: nmalesh@yahoo.co.in (U.M. Nagamalesh).

The varied clinical presentation of this condition makes the diagnosis challenging, treatment diverse and results unpredictable with subsequent high morbidity and mortality. The condition is often suspected in patients who present with unexplained dyspnea, tachypnea, or chest pain. Further, a background of high risk predisposing conditions like malignancy, immobilization, recent major surgery, orthopedic surgeries and others warrant an urgent investigation when APE is clinically suspected.

Despite therapeutic and diagnostic advances, the data from developing countries are largely lacking with respect to diagnostic and treatment efficacy and also there is insufficient data of long-term follow-up of those treated.

Our study was conducted to understand the clinical profile of patients with APE and its response to standard guideline based treatment. Further, the patients who were successfully treated were followed up long-term to understand the overall long-term benefit achieved.

2. Methods

It was a single center observational study conducted at MS Ramaiah Memorial hospital. The study began in January 2010 and recruitment of patients concluded on June 2014. However, data collection on long-term follow-up concluded on June 2015, i.e., after 1 year of the last date of recruitment period.

All the patients with clinically suspected APE were assessed with Well's Criteria. Those with likely APE on Well's criteria were investigated further with D-dimer testing and diagnosis of APE was finally confirmed by CT scan (either HRCT or CTPA). Patients who were admitted in our cardiac intensive care following an established diagnosis were only included for the study as it needed close monitoring of treatment response of these patients. Also it enabled us to study the clinical parameters in greater detail at baseline and further helped to enroll them for long-term follow-up. Patients with diagnosis of APE who had already received treatment before reaching the study center, those with previous diagnosis of Acute PTE irrespective of their current treatment status, patients with suspected diagnosis of APE who died before a diagnosis could be established, those who did not consent for CT imaging and patients with non-availability of baseline data or long-term follow-up data were again excluded.

A total of 38 patients with suspected PTE were identified during the study period. Out of this, two patients did not consent for enrollment. Five patients were critically ill with significant co-morbidities (mainly renal dysfunction) which made them unsuitable for CTPA and were treated on the basis of clinical suspicion only. After satisfying the necessary criteria we were able to recruit 31 patients during the study period. A detailed record of clinical profile of all the patients included in the study was done. Baseline record of following investigations were made in common in all patients: complete hemogram, renal function tests, serum electrolyte assay, liver function tests, fasting lipid profile, thyroid profile, coagulation profile, ECG, 2D-echocardiogram, ultrasonography of abdomen and chest X-ray. Additional investigations were done as deemed necessary for identification of etiology and/or complications in specific group of patients. Chosen patients were risk stratified as per standard guidelines into massive, sub massive or low risk and treated as per current guidelines. The included patients were followed up for a period of 1 year with 2D-echocardiogram and other relevant investigations for comparison to assess improvement. Mortality due to either acute PTE or other causes was noted in the study.

Statistical analysis was done and continuous variables were presented as mean, and ordinal variables as percentages.

Table 1
Age distribution of patients.

Age group	Number of patients	Percentage (%)
20–30	05	16
31–40	12	39
41–50	05	16
51–60	03	10
>60	06	19
Total	31	100

3. Results

Of the 31 patients enrolled in our study, 71% ($n = 22$) of the patients belonged to the age range 20–50 years (Table 1). 39% ($n = 12$) of the total belonged to age range 31–40 years. Elderly over 65 years of age comprised 19% ($n = 6$) of the total. Sex difference was also noticed with APE being observed to be more common among male patients (58%) (Fig. 1).

Dyslipidemia, prolonged immobilization, deep vein thrombosis, post-operative state, malignancy and post-partum period were the commonly reported risk factors in our study population (Fig. 2). Dyslipidemia was identified in 42% ($n = 13$) of our patients although the clinical significance of dyslipidemia as a risk factor is yet to be clearly established. 35% ($n = 11$) of the patients reported prolonged immobilization prior to the event with over 50% ($n = 6$) of them being the elderly over 65 years of age. The reasons for prolonged immobilization were mainly recent long travels, serious illnesses, and musculoskeletal causes with the latter being more commonly reported among the elderly.

Dyspnea was the most common symptom reported at presentation in all the 31 patients. Additionally reported symptoms included palpitations (71%, $n = 22$) syncope (32%, $n = 10$) and chest pain (29%, $n = 9$) (Fig. 3). The most common clinical sign was tachycardia (58%, $n = 18$) and tachypnea (32%, $n = 10$). Patients with dyspnea on clinical assessment had NYHA Class II or more symptoms at presentation. Following treatment when these patients were reassessed for NYHA functional class at the end of
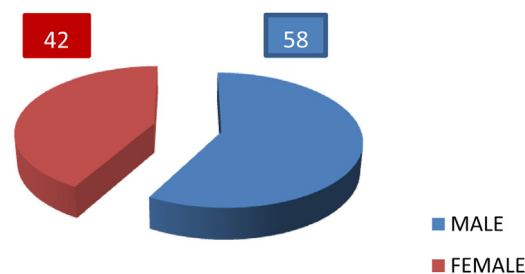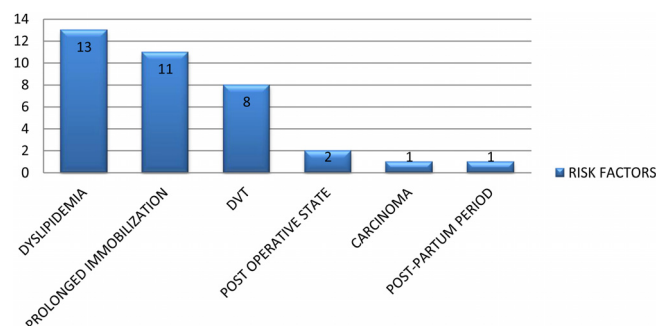

Fig. 1. Sex disribution.
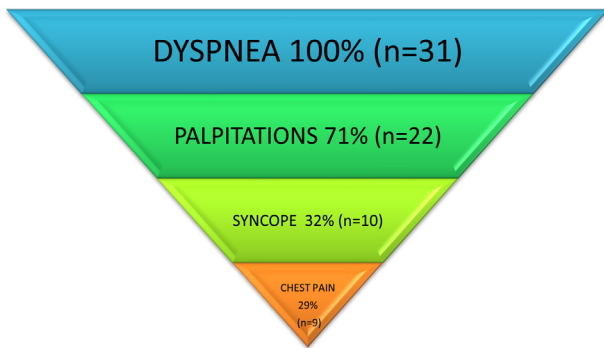

Fig. 2. Risk factors for APE.

Fig. 3. Clinical features at presentation.

Table 3
Complications in ape.

Sl. no.	Complications	Number (n)	Percentage (%)
1	Reversible shock on admission	8	26
2	Mechanical ventilation	3	10
3	Aborted sudden cardiac death	1	3
4	Shock requiring inotropic use	8	26
5	Bleeding	4	13
6	Elevated PA pressure after 1 year	8	26
7	RV dilatation/dysfunction after 1 year	10	32

Fig. 5. Classification of APE.

1 year, 74% ($n = 23$) of the patients showed significant improvement of their functional class to NYHA Class I. Out of the 35% ($n = 11$) patients who were in NYHA Class IV at admission, nearly 81.8% patients ($n = 9$) showed significant improvement of their functional status to NYHA III or less at 1 year (Table 2; Fig. 4).

2D echocardiography was used for assessing the parameters like pulmonary artery pressure and RV dilatation. These parameters were easily available for comparison during future follow-up. During follow-up 26% ($n = 8$) of patients had persistently elevated pulmonary artery pressure and 32% ($n = 10$) patients had RV dilatation even after 1 year of treatment of APE (Table 3). Out of this, three patients had clinical features of progressive right heart failure.

In our study all the patients with suspected APE on initial assessment were subjected to CTPA, Echocardiography and troponin T. Based on the findings patients were classified as massive, sub-massive and low risk groups.

Acute PE with sustained hypotension with SBP <90 mmHg for at least 15 min or requiring inotropic support were considered as massive PTE, which consists of 26% (08) of patients. Submissive PE patients were those with APE without systemic hypotension (SBP ≥90 mmHg) but with either RV dysfunction or myocardial necrosis, which consisted 32% of patients (10). Mild APE formed the remainder group of patients (41%, $n = 13$) (Fig. 5).
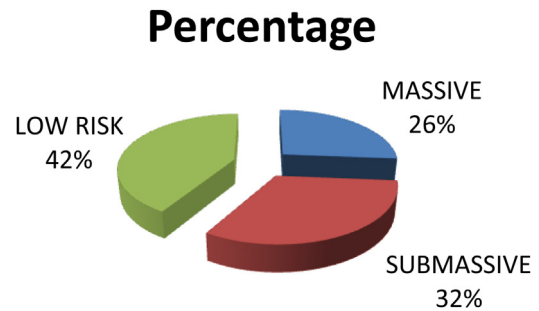
We thrombolysed a total of 18 (58%) patients majority of whom had massive or submassive PTE, of which 12 (39%) received tenecteplase and 6 patients received streptokinase (19%). Three (9%) patients required repeat thrombolysis with streptokinase due to failed thrombolytic therapy with tenecteplase (Table 4).

In view of persistent elevated PA pressure and early RV dysfunction two patients underwent pulmonary endarterectomy after 6 months of index event. They are under follow-up with normal PA pressure and normal RV function. None of them were sent for surgical embolectomy. 16% ($n = 5$) patients were put IVC Filter after careful clinical assessment to prevent recurrent PE (Table 5).

Overall reported mortality rate was 6% ($n = 2$). One patient with massive pulmonary embolism died in hospital after thrombolysis due to persistent hypoxia, bleeding and shock. The second patient died after few weeks at home. He had minor PTE with no DVT and was on oral anticoagulation. The exact cause of death in him could not be reached. Overall 52% ($n = 16$) of the subjects presented with shock at admission or within 48 h following admission. Out this 50% ($n = 8$) required inotropic support to maintain stable hemodynamics (Table 4). The duration of requirement of inotropic support varied from 24 h to 96 h with mean of 48 h. Inotropic

Table 2
NYHA class at admission and at 1-year follow-up.

Functional class	On admission	Percentage (%)	After 1 year	Percentage (%)
NYHA I	00	00	23	74
NYHA II	08	26	03	9
NYHA III	12	39	05	16
NYHA IV	11	35	00	00

Fig. 4. NYHA class at admission and at 1 year.

Table 4
Thrombolytic therapy.

Thrombolytic drug	Number of patient	Percentage (%)
Streptokinase	06	19
Tenecteplase	12	39
Repeat thrombolysis	03	10

Table 5
Surgical management.

Type of procedure	Number of patients	Percentage (%)
Surgical thrombectomy	–	–
Pulmonary endarterectomy	02	6
IVC filter	05	16

support for maintaining blood pressure was common in patients with massive and sub massive APE ($n = 6$). One patient developed profound irreversible shock and respiratory failure requiring inotropic support and mechanical ventilation. This patient had massive APE and was treated with thrombolytic therapy. Overall, 10% ($n = 3$) of the patients with massive APE required mechanical ventilation with one reported mortality. Bleeding following intravenous thrombolysis was noted in four patients (13%) with one patient having massive bleeding episode requiring blood transfusion.

4. Discussion

The incidence of venous thromboembolism (VTE), which includes PE and deep venous thrombosis (DVT), has remained relatively constant, with age- and sex-adjusted rates of 117 cases per 100,000 person-years.[7,8] VTE incidence rises sharply after age 60 in both men and women, with PE accounting for the majority of the increase.[7,8] Acute pulmonary embolism (APE) is a major cause of death associated with surgery, injury, and medical illnesses. The mortality rate associated with PE is underappreciated; if untreated, acute PE is associated with a significant mortality rate (as high as 30%) with two of three such people dying of APE die within the first 2 h of presentation.[1] Mortality rate is up to 8% among those diagnosed and treated.[1] In nearly 25% of patients with PE, the initial clinical manifestation is sudden death.[7]

Numerous published studies have shown that the incidence of first-time VTE rises exponentially with age. In the patients between 50 and 59 years, Anderson reported the incidence of first time VTE of 62 per 100,000, and Silverstein et al. observed a much higher incidence of 122 per 100,000 among women and 147 per 100,000 among men.[8] Between 70 and 79 years age group Anderson et al. reported 316 cases per 100,000 per year (35% recurrent); Silverstein et al. reported 440 cases per 100,000 per year.[8] Nordström et al. overall estimated the cumulative probability of developing VTE between ages 50 and 80 at 10.7% for Swedish men.[8] In our study, 71% of the patients belonged to age group 20–50 years with remaining 29% being over 50 years of age. In those patients over 50 years the pre-disposing factors leading to APE could be ascertained in most cases. However, the cause remained elusive many a times among the group <50 years of age.

Sex predilections for VTE have shown consistent differences in the incidence of VTE among both the sexes across different subsets of age groups. Anderson et al. found a similar incidence in both sexes.[9,10] Silverstein et al. reported slightly higher incidence rate among younger women, and a modest predilection among older men.[8] Cushman et al. reported similar incidences among men and women except for a 2-fold higher rate in men over age 75.[8] The ICOPER study had male predominance in incidence of pulmonary thromboembolism.[11] Overall our study reported higher incidence of PTE among the male population (58% in males as against 42% in females). However, majority of this difference was due to higher incidence rates of PTE in elderly males. Among the young patient population of our study, there was no significant difference in PTE incidence in either population group.

Risk factors that have been consistently associated with VTE include advanced age, prolonged immobility, malignancy, major surgery, polytrauma, prior VTE, and chronic heart failure. Major risk factors for pulmonary thromboembolism in our study were dyslipidemia 42%, prolonged immobilization 35% and DVT 26%.

Due to lack of direct evidence for dyslipidemia it is difficult to attribute dyslipidemia as risk factor for PTE. However, the effects of circulating lipid molecules on the vascular endothelium, platelet function, and coagulation factors in DVT are yet to be elaborated. Better epidemiologic evidence is required to establish whether dyslipidemia is a risk factor for venous thromboembolism.

The clinical presentation of PE varies widely with dyspnea being most frequent presenting symptom. Symptoms vary from severe dyspnea, cyanosis, or syncope suggesting a massive PE while pleuritic pain, cough, or hemoptysis indicating a smaller peripherally located PE. On physical examination, tachypnea is the most common sign. All the patients in our study with APE presented with dyspnea with NYHA Class II or >. Palpitations (71%), chest pain (29%) and syncope (32%) were the other commonly reported symptoms. Tachycardia (58%, $n = 18$) and tachypnea (32%, $n = 10$) were the common signs noted. The presence of initial presenting symptoms and signs from our study were similar to most of the landmark trials. Following successful therapy, at the end of 1 year study period majority of the patients reported significant improvement in their symptoms with dyspnea improving from NYHA Class II or > to NYHA Class I (74%).

RV dysfunction has been shown to predict disease recurrence and mortality. In a randomized controlled trial, Goldhaber et al.[12] found RV function improved at 24 h in 16/18 thrombolysed patients compared with 8/18 treated with heparin.

On admission 26% of patients were classified as massive, 32% were submissive and 41% were low risk. In the ICOPER study, the 90-day mortality rate for patients with acute PE and systolic blood pressure <90 mmHg at presentation (108 patients) was 52.4% (95% confidence interval [CI] 43.3–62.1%).[13] Similarly, in the Germany-based Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) of 1001 patients with acute PE, in-hospital mortality was 8.1% for hemodynamically stable patients versus 25% for those presenting with cardiogenic shock and 65% for those requiring cardiopulmonary resuscitation.[14] In patients with low risk pulmonary embolism short-term mortality approach ≈1%. Risk stratification of the patients with APE helped define the population suitable for thrombolytic therapy. Data from four registries MAPPET, ICOPER, RIETE, and, EMPEROR have suggested a trend toward decrease in all-cause mortality from PE, especially massive PE in those patients treated with fibrinolysis.[15] Konstantinides et al.[15] found a 30 day mortality of 4.7% in 169 patients who received thrombolysis, compared with 11.1% in 550 who were treated with heparin. Recurrence rates were 7.7% and 18.7% respectively.

In our study, both massive and submissive group received thrombolytic therapy and low risk patients received low molecular weight heparin.

Six trials with 481 patients have compared various thrombolytic regimens using rTPA, streptokinase, and urokinase, with rTPA being delivered over 2 h and urokinase and streptokinase delivered over 2–24 h.[15–21] No agent has proved superior.

Among the 18 (58%) patients in our study, 39% received tenecteplase and 19% of patients received Streptokinase. In the tenecteplase group three patients (10%) had failed thrombolysis that was then treated with streptokinase. All those patients were maintaining normal pulmonary artery pressure and functional class at the end of study period. One of the single center study reported failed thrombolysis in 40 patients (8.2%) among the 488 APE patients who underwent thrombolysis.[22] Out of this 14 patients were treated by rescue surgical embolectomy, and 26 were treated by repeat thrombolysis.[22] There was no significant difference in the baseline characteristics of the two groups. However, there was significantly more recurrent PEs (fatal and nonfatal) in the repeat-thrombolysis group (35% versus 0%).[22] The rate of uneventful long-term evolution was the same in the two groups.[22] The questions whether thrombolytic therapy was really successful in our cohort of patients and whether failed thrombolytic therapy can be treated again with repeat thrombolysis with the different agent still remains to be answered. The small sample size of the study made it difficult to address the above issue clearly although clinically a benefit was noted in patients who were managed accordingly.

Two of the patients who received heparin therapy followed by oral anticoagulants for low risk PTE, later developed chronic PTE with severe PAH with exertional dyspnea Class III (NYHA) and RV dysfunction. These patients underwent pulmonary endarterectomy. They now have exertional dyspnea Class I/II (NYHA) and normal PA pressures. In a recent series >91.3% of the patients were in NYHA Functional Class III or IV before procedure and at 1 year after operation, 91.4% of patients were reclassified as NYHA Functional Class I or II.[23] In addition, with the elimination of sustained pressure overload, RV geometry rapidly reverts toward normal.[23]

5. Limitations

The small sample size and single center observation were the main limiting factors of our study. However, successful attempts were made to elaborately discuss most of the clinico-epidemiologic issues concerned with diagnosis and treatment of acute pulmonary thromboembolism. We also tried to address some of the key controversial issues concerned with failed thrombolytic therapy. Also, the role of other surgical and non-surgical interventions also could not be elaborated completely due to small sample size again.

Nevertheless, our study shows the potential for a future large scale multi-center trial in this regard and also gives a basic framework on which it can be further improvised to understand the clinico-epidemiologic aspects of APE.

6. Conclusion

APE which was once a disease of the old and frail is now increasingly becoming common among the young and middle aged. APE still masquerades itself presenting in various clinical settings, and posing a great diagnostic challenge to the physician. A high degree of clinical suspicion with close observation of key clinical signs is needed to identify this entity. Diagnosed cases need to be risk stratified into mild, moderate and massive to plan appropriate treatment strategy. In case of failed thrombolysis a repeat thrombolysis can be considered before subjecting to definitive surgical approach, however, it needs further validation from more large scale studies.

Conflicts of interest

The authors have none to declare.

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