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Study of clinical profile and management of patients with pulmonary thromboembolism at a tertiary care centre in South Gujarat, India

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ABSTRACT

Background

Pulmonary thromboembolism (PTE) is a major, common and often lethal health problem that causes high mortality and morbidity. The epidemiology of PTE is difficult to determine because it may be asymptomatic, or its diagnosis may be an incidental finding. Delayed diagnosis is a common cause of death in PTE; if the condition is caught early the risk may be temporary and reversible. The clinical manifestations of acute pulmonary embolism are highly variable. The objective of this research was to study patients' clinical profile and the association of risk factors with diagnosis of pulmonary thromboembolism.

Methods

The study was carried out over a period of two years, from August 2016 to July 2018. Patients were enrolled in the study if they met the inclusion criteria: all patients aged 18 years and above admitted at a tertiary care centre, Civil Hospital Ahmedabad, with clinical features suggestive of acute pulmonary embolism and who demonstrated a thrombus in pulmonary arteries by echo or computed tomography pulmonary angiogram (CTPA). All participants underwent detailed evaluation including history, clinical examination and laboratory investigation. Detailed history regarding risk factors of pulmonary embolism was taken from all patients. All patients underwent basic and relevant biochemical investigations: D-dimer and cardiac biomarkers, Chest x-ray, 2D echocardiography, CTPA and ultrasonography of the lower limbs.

Results

The mean age of all the enrolled patients was 48.3 years. The male to female ratio was nearly 3:1. According to the New York Heart Association (NYHA) classification, 6% of the patients fell in class I, 28% in class II, 56% in class III and 10% in class IV. Risk factor stratification shows that 60% patients were smokers, 28% were alcoholic and 28% had chronic lung disease; 14% of patients had a history of immobilization for a minimum of 2 weeks, 8% had history of blood transfusion, 6% had previously suffered a stroke, 6% had undergone major surgery within the last six weeks and 4% had a malignancy.

Conclusion

The clinical presentation and the investigations, including electrocardiography, chest radiography and analysis of arterial blood gases, lack adequate specificity to confirm or rule out pulmonary embolism. Echocardiography, cardiac biomarkers and simplified PESI score are helpful for treatment and prognosis purposes.

Keywords: Pulmonary thromboembolism, Risk factors, Clinical profile

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INTRODUCTION

Pulmonary thromboembolism (PTE) is an occlusion of pulmonary arterial circulation by a blood clot formed elsewhere, usually in the deep veins of the leg; less than 5% of venous thrombosis occurs in other sites. It is a major health concern with high mortality and morbidity. Overall, pulmonary embolism is a major cause of mortality, morbidity and hospitalization in the world. The incidence of PTE is estimated to be approximately 60-70 per 100,000, and that of venous thrombosis 124 per 100,000 of the general population.[2,3] Delayed diagnosis is a common cause of death in PTE, with nearly 10% of untreated PTE proving fatal in the first hour.[1] Mortality rates among diagnosed and treated pulmonary embolism patients range from 3-8% but mortality increases to about 30% in untreated cases.[1]

In the last decade it has been found that PTE is not a disease but a complication of venous thrombo-embolism (VTE).[4] VTE includes PTE and deep vein thrombosis (DVT), which encompasses a single disease category. VTE along with stroke and myocardial infarction rank as three major cardiovascular killers. Pulmonary embolism is seen in 60–80% of patients with DVT but more than half these patients remain asymptomatic.[5] VTE may be lethal in the acute phase or lead to chronic disease and disability but it is also often preventable. The epidemiology of PTE is however difficult to determine because it is often asymptomatic, and its diagnosis may be an incidental finding.[6]

The clinical manifestations of acute pulmonary embolism are highly variable, ranging from pulse-less electrical activity to mild dyspnoea, new or worsening dyspnoea, chest pain or hypotension. PTE when suspected during a routine diagnostic session includes biomarkers (e.g. D-dimer), and/or imaging modalities, such as computed tomography angiography or a ventilation-perfusion scan. Additional evaluations may be performed with troponins, B-type natriuretic peptide (BNP), Pro-BNP, and/or echocardiography.[7] PTE is commonly classified as massive (high-risk), sub-massive (intermediate-risk), and low-risk to help determine the required treatment. Massive pulmonary embolism accounts for 5-10% of cases[4]. PTE often appears in the presence of a temporary or reversible risk factor such as surgery, trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy within the last 6-12 weeks before diagnosis. Risk stratification scores are used to determine management and the risk of complications and associated mortality.[8]

The reporting of pulmonary thromboembolism is not given much importance in Asian countries in general and in India in particular. The present study was carried out to study the clinical profile and associated risk factors in patients diagnosed with pulmonary thromboembolism in one Indian tertiary care facility.

MATERIALS AND METHODS

The present study was an observational study carried by the Medicine Department, Civil Hospital and B.J. Medical College, Ahmedabad. The study was carried out over a period of two years from Aug 2016 to July 2018. Institutional Human Research Ethics Committee permission was taken before starting the study. Patients were screened for enrollment according to inclusion and exclusion criteria. Inclusion criteria were all patients aged 18 years and above admitted at tertiary care center Civil Hospital Ahmedabad with clinical features suggestive of acute pulmonary embolism and who demonstrated a thrombus in pulmonary arteries by echo or computed tomography pulmonary angiogram (CTPA). Patients with suspected pulmonary embolism and D-dimer positive patients without demonstration of a thrombus in the pulmonary artery were excluded from the study. Patients were included in the study only after taking written informed consent.

Fifty patients fulfilled inclusion criteria and thus formed the study population. Patients underwent detailed evaluation including history, clinical examination and laboratory investigation. Detailed history regarding risk factors of pulmonary embolism was taken in all patients. All patients underwent basic and relevant biochemical investigations. Clinical probability of all patients was assessed by using Wells simplified score, which can rule out (or not) the likelihood of pulmonary embolism.

Patients with a high probability of pulmonary embolism were evaluated with D-dimer and cardiac biomarkers. 2D echocardiography was done in all patients to look for Right Atrial (RA)/ Right Ventricle (RV) dilatation, RV dysfunction, right ventricular systolic pressure (RVSP), thrombus in MPA and its branches, left ventricular function and ejection fraction. Chest x-rays was taken for all patients to look for other causes of dyspnea. CPTA was undertaken in all patients to look for thrombus, location, number and RV function. Ultrasonography of the lower limbs was carried out in all patients. Patients were risk-stratified on basis of ESC guidelines (2014) into low risk, intermediate and high risk[9]. By taking into consideration issues such as cardiac enzymes and simplified PESI score, patients with sub-massive pulmonary embolism were further divided into intermediate high and low risk groups and were managed accordingly. All the patients assessed to be in the high and intermediate risk group, and two patients with intermediate low risk group, received thrombolysis in addition to standard UFH and oral anticoagulant therapy. All low-risk patients were treated with standard heparin therapy followed by oral anticoagulation: 27 patients were given tenecteplase, three were given streptokinase and one was given alteplase as thrombolytic agents.

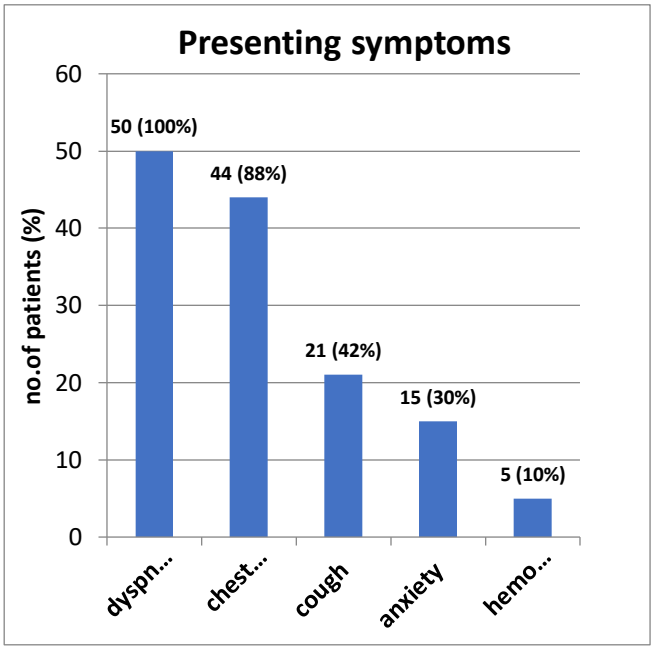

Figure 1: Presenting symptoms

Statistical analysis was carried out using IBM SPSS version 20. Quantitative variables were expressed as the mean ± standard deviation and qualitative variables were expressed as percentage (%). Categorical variables were compared using the chi-square test. A nominal significance was taken as a two tailed p value<0.05.

RESULTS

A total of 50 patients who were newly diagnosed to have acute pulmonary thromboembolism were included in the study. Their mean age was 48.3 years, 38 (76%) were male and 12 (24%) were female. Median blood pressure was 114/72 mm of hg for patients in the study. Median heart rate was 106/min. (Table 1)

As seen in Table 2, all patients were classified according to NYHA classification: 6% were in class I, 28% were in class II, 56% of the patients fell in class III, and 10% in class IV. The most common clinical presentation of patients was dyspnea (100%) followed by chest pain (88%). Other symptoms included cough (42%), anxiety (30%) and haemoptysis (10%) (Fig 1).

Out of the 50 patients, 30 (60%) were smokers, 14 (28%) were alcoholic, 14 (28%) had chronic lung disease, 9 (18%) had a history of congestive heart failure, 7 (14%) had a history of immobilization for a minimum of two weeks, 4 (8%) had a history of blood transfusion, 3 (6%) had previously suffered a stroke, 3 (6%) had undergone major surgery within 6 weeks and 2 (4%) had a malignancy. Half of the patients had two or more risk factors, seven (14%) patients had no risk factor; 18 (36%) had one risk factor, 18 (36%) patients had two risk factors, 6 (12%) patients had three risk factors and 1 (2%) patient had four risk factors (Fig 2).

All recruited patients underwent blood investigations. Mean haemoglobin was 12.79 gm/dl; mean serum creatinine was 1.15mg/dl; mean SGPT 45IU/L, mean troponin -I was 1.52 ng/ml; mean D-dimer value was 5512, mean PT was 20.64 and mean APTT was 46.93. (Table 3) The most common finding in ECG was sinus tachycardia (88%) followed by ST-T changes (44%), Right axis deviation (38%), $S_1Q_3T_3$ pattern (32%) and Incomplete RBBB (30%) (Table 4).

Amongst the 50 patients, 40 (80%) had a normal chest radiograph. Of the remaining 10 (20%) patients, 3 (6%) had pleural effusion, 5 (10%) had cardiomegaly, and 2 (4%) had fibrosis suggestive of an old pulmonary Koch's. 2D ECHO was used as a screening tool in all patients in the study. 34 patients (68%) had RV dysfunction, which was assessed by TAPSE (mean TAPSE 13.78±2.26). RA and RV dilatation was present in 44 (88%) of patients. Mean RVSP was 63.8 mmHG. The majority of patients had tricuspid regurgitation at presentation; 42 (84%) had moderate TR and 5 (10%) had severe TR. Definitive evidence of thrombus in MPA and its branches were observed in 13 (26%) patients on 2D ECHO screening. All 50 patients underwent CTPA of whom 24 (48%) had a dilated main pulmonary artery; 8 (16%) had saddle thrombus; 23 (46%) had right main pulmonary artery partial thrombus; 30 (60%) had left pulmonary artery partial thrombus and 24 (48%) had thrombus seen in segmental and sub-segmental vessels. Lower limb venous ultrasonography was carried out in all patients; 31 (62%) had evidence of deep venous thrombosis; 25 (50%) patients had proximal and 6 (12%) patients had distal vein thrombosis. (Table 5). Risk stratification of patients was based on ESC 2014 guidelines with help of four variables: shock, RV dysfunction, simplified PESI score and cardiac enzymes. Out of all 50 patients, 2 (4%) had high risk, 27 (54%) had intermediate high risk; 7 (14%) had intermediate low risk and 14 (28%) of the patients belonged to the low-risk group (Table 6). 31 (62%) were managed with thrombolysis plus anticoagulation, and 19 (38%) were treated with anticoagulation only. All the patients from high risk (n=2) and intermediate high risk (n=27) group were thrombolysed, while only two out of seven from the intermediate high-risk group, and none in the low-risk group were thrombolysed (Table 6).

Table 1 Demographic features of patients

Sr. No	Demographic features	Mean±SD, n= (%)
1	Age	48.3±14
2	BP	114.12±4.96
3	HR	106±13
4	Male	38 (76%)
5	Female	12 (24%)

Table 2 Classification of all patients according to NYHA class

Symptoms	No. of patients
NYHA class I	3(6%)
NYHA class II	14 (28%)
NYHA class III	28 (56%)
NYHA class IV	5 (10%)

Table 3 Laboratory investigations

Laboratory findings	n=50
Blood glucose	146.58± 49.36
Haemoglobin	12.79±1.35
S.Creatinine	1.15±0.74
SGPT	45±21.1
TROP-I	1.52±1.13
D-Dimer	5512.28±2328.53
PT	20.64±8.44
APTT	46.93±19.01

Table 4 ECG findings among all patients

	ECG Changes	
1	Sinus Tachycardia	44 (88%)
2	ST-T changes	22 (44%)
3	Right axis deviation	19 (38%)
4	Incomplete RBBB	15 (30%)
5	S1Q3T3	16 (32%)

Table 5 Findings on various radiological investigations

Sr. No	Findings on various investigations	No. of patients (%)
Chest x-ray findings		
1	Normal	40 (80%)
2	Pleural effusion	3 (6%)
3	Cardiomegaly	5 (10%)
4	Fibrosis	2 (4%)
2D echo findings		
1	Moderate-severe TR	47 (94%)
2	RV dysfunction	34 (68%)
3	Definite evidence of thrombus in MPA and its branches	13 (26%)
4	Pulmonary arterial hypertension	44 (88%)
5	RA- RV dilatation	44(88%)
CT Pulmonary angiography findings		
1	MPA dilated	24 (48%)
2	Saddle thrombus	8 (16%)
3	RPA partial thrombus	23 (46%)
4	LPA partial thrombus	30 (60%)
5	Segmental and sub-segmental occlusion	24 (48%)
Lower limb Doppler study findings		
1	Proximal venous thrombosis	25 (50%)
2	Distal venous thrombosis	6 (12%)

Table 6 Risk stratification and no. of patients thrombolysed

Category	No. of patients	No. of patients thrombolysed
High risk	2 (4%)	2 (6%)
Intermediate high risk	27 (54%)	27 (87%)
Intermediate low risk	7 (12%)	2 (7%)
Low risk	14 (30%)	0 (0%)

DISCUSSION

Acute pulmonary embolism is associated with a significant mortality rate as high as 30%, if untreated, whereas the death rate of diagnosed and treated pulmonary embolism is 8%. Up to 10% of acute PE patients die suddenly.[10] This prospective observational study gives an insight into the clinical profiles of 50 hospitalized patients with a confirmed diagnosis of acute pulmonary embolism based on CT pulmonary angiography. The mean age of 48.3 years, and greater percentage of males (n=38, 76%) than females (n=12, 24%) is consistent with another study carried out in Chennai.[18] In that study, the mean age of patient population was 52.1 years, and 62.8% were males and 37.2% were females. Another study carried out in Karnataka[11] showed a mean age of the cohort of 47.2 ± 13 years, with considerably more men than women.

The majority of the studies carried out in the Western world show a higher incidence of acute PE among those aged above 60 years. In studies by Goldhaberet al (2010)[12] and Miniati et al (2012)[13] the authors found that the majority of patients with pulmonary embolism were aged above 65 years.

Risk factors for venous thromboembolic disease and pulmonary embolism are well characterized in the literature. Risk factors are present in 96% of patients with confirmed venous thromboembolic disease.[14] In the present study it was found that most of the patients had at least one risk factor for PTE indicating the importance of looking for a risk factor in each and every patient with acute pulmonary embolism. We found smoking to be a major risk factor, present in 60% of the patients. The studies by Mitchell et al (2012)[15] also showed smoking as the major risk factor for acute pulmonary embolism, finding it in 41.5% of the patients. The landmark study PIOPED II[16] also depicted smoking as one of the major risk factors, found in 43% of the patients, which is similar to present study findings. Apart from smoking, chronic lung disease was found to be another important risk factor. In the present study, chronic lung disease was present in 28% of patients, which is comparable to PIOPED II study in which it was observed in 26% of patients.

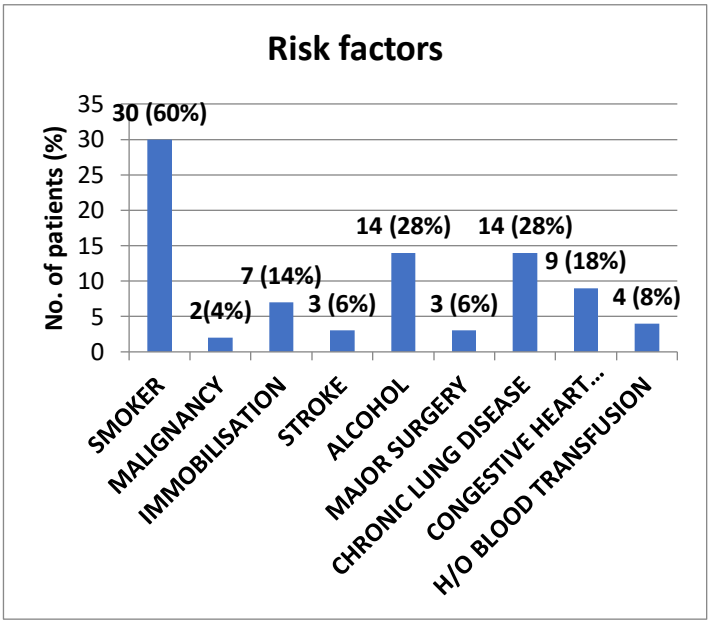

Fig 2 Associated risk factors

The most common clinical presentation of patients included in the present study was dyspnea (100%) followed by chest pain (88%), cough (42%) and haemoptysis (10%). This is consistent with other studies carried out in India.[15] A study by Shukla et al showed the most common clinical presentation is dyspnea (100%), followed by chest pain (52%), syncope (30%) and cough (40%).[17] The study by Mitchell et al also showed dyspnea was the predominant symptom (71.7%), followed by syncope (17.0%), cough (15.1%), chest pain (7.6%) and haemoptysis (3.8%).[15] This suggests that finding solitary dyspnea in a patient provides a strong suspicion for pulmonary embolism.

In addition to clinical symptoms, the ECG is essential in directing the physician towards the diagnosis. There is no isolated ECG abnormality that is definitively associated with pulmonary embolism; however, certain constellations of ECG abnormalities have been shown to be reasonably specific. The most common finding in ECG was sinus tachycardia, followed by ST-T changes, RAD, Incomplete RBBB and $S_1Q_3T_3$ pattern. ECG findings in a study by Calvin et al was sinus tachycardia, followed by RV strain pattern, $S_1Q_3T_3$ pattern and RBBB.[18] Another study by Shukla et al also showed ST-T depression in 80% of patients. Other findings were $S_1Q_3T_3$, RBBB and low

voltage in patients with pulmonary embolism.[17] Agarwal et al showed S1Q3T3 pattern with presence of S and Q waves in limb leads 1 and 3, respectively, inversion of T-wave in limb lead 3 in 29% of patients and 12% patients had T-wave inversions in leads V1-4 and R/S>1 in V1.[19]

In the present study 68% of total participants had evidence of Right Ventricular dysfunction and Right Atrium and Right Ventricular dilatation was present in 88% of patients. The majority of patients in the study had tricuspid regurgitation (TR) at presentation. 82% had moderate TR and 10% had severe TR. Definitive evidence of thrombus in MPA and its branches were observed in 26% patients on 2D ECHO screening. Mitchell et al[15] showed Pulmonary Arterial Hypertension as a main finding in 85% of patients in south India. Other findings were RV dysfunction and definite evidence of thrombus in many patients; Shukla et al[17] depicted moderate to severe TR in 73% of patients and RV dilatation and dysfunction in 86% of patients, consistent with present study. This suggests important screening tools in a suspected acute pulmonary embolism, especially if there is no prior cardiopulmonary disease. The abnormality was mainly raised pulmonary artery pressure.

CT Pulmonary Angiography findings show that 48% of patients had a dilated main pulmonary artery; 16% had saddle thrombus; 46% had right main pulmonary artery partial thrombus; 60% had left pulmonary artery partial thrombus; 48% patients had thrombus seen in segmental and sub segmental vessels. Calwin et al[18] showed 83% of patients had thrombus located in the main and lobar arteries while 16.7% had thrombus in sub-segmental vessels.[18] Shukla et al showed MPA thrombus in 40% of patients, thrombus in MPA branches in 40% of patients and 20% of patients had segmental and sub segmental occlusion. It was found that 31 (62%) patients had evidence of DVT in venous Doppler.[17] As per this risk stratification, all massive pulmonary embolism patients required thrombolysis and in sub-massive pulmonary embolism patients, the use of thrombolysis is to be balanced against risk of death and bleeding; minor pulmonary embolism should be treated with anticoagulation. Two out of seven patients in the intermediate low-risk group were given a thrombolytic agent and rest, and were treated conservatively. None of the low risk group patients received thrombolysis in the present study. The number of high-risk patients who were saved with early initiation of treatment, without any major bleeding, demonstrates the importance of clinical suspicion and prompt intervention. High clinical suspicion can help to prevent mortality.

There is no proper consensus about management of the intermediate risk group patient.[20] Thrombolysis in the intermediate risk group is associated with increased bleeding complications and reduced mortality.[21] The intermediate high-risk group were haemodynamically stable but they had RV dysfunction and elevated cardiac enzymes, for which they needed strict monitoring and early intervention to prevent haemodynamic collapse and early mortality. All patients survived in this group in our study and benefited from thrombolysis in terms of prevention of early haemodynamic compromise and reduced 30-day mortality as well as reduced chances of developing recurrent PTE.

Our approach also prevented late complications such as PAH, persistent dyspnoea and moderate TR, leading to improvement in quality of life. All low risk patients were managed with parenteral anti-coagulation and discharged on oral anticoagulation.

CONCLUSION

Pulmonary thromboembolism presents with a wide clinical spectrum, from asymptomatic disease to life-threatening massive PTE that causes hypotension and cardiogenic shock. The clinical presentation and the investigations, including electrocardiography, chest radiography and analysis of arterial blood gases, lack adequate specificity to confirm or rule out pulmonary embolism. Echocardiography, cardiac biomarkers and simplified PESI score were helpful for treatment and prognosis purposes. Risk stratification into high, intermediate and low risk will guide further appropriate treatment of patients and prevent under and over treatment.

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