Original Research Article

Association of risk stratification and mortality outcomes in patients of acute pulmonary embolism

Jit H. Brahmbhatt, Zeeshan H. Mansuri*, Roopesh R. Singhal

Department of Cardiology, Smt. B. K. Shah Medical Institute and Research Center, Vadodara, Gujarat, India

*Correspondence:
Dr. Zeeshan H. Mansuri,
E-mail: zzeeshan2014@gmail.com

ABSTRACT

Background: To study the association of risk stratification and mortality outcomes of patients with high/intermediate risk acute pulmonary embolism who are given the guideline directed therapy after the diagnosis of pulmonary embolism.

Methods: Prospective observational study of demographics, clinical profile, risk stratification, management and outcome of patients presenting with acute pulmonary embolism from October 2019to December 2020. Risk stratification was done as per ESC 2019 guidelines into high and intermediate categories, intermediate category patients were further stratified into intermediate-high and intermediate-low-risks.

Results: 100 patients who were detected to have acute pulmonary thromboembolism with a mean age of 45.08 years with 60% being males were included in the study. There were 31 patients in high-risk group, 59 patients in intermediate-high subgroup, 10 patients in intermediate-low subgroup. Echocardiography was done in all patients. Outcome was relatively grave in these subgroups with overall mortality of 56 patients. 49 patients were thrombolysed with rTPA, 27patients with alteplase, 4 patients with streptokinase, 12patients who had contraindication to systemic thrombolysis were subjected to catheter directed thrombolysis and 8 patients were taken up for surgical embolectomy.

Conclusions: Pulmonary embolism can present with unexplained dyspnea and atypical chest pain among other signs and symptoms. Early diagnosis, risk stratification and guideline directed prompt management can lead to favorable outcomes however; patients with high and intermediate risk at presentation are associated with higher mortality rate despite GDT.

Keywords: Pulmonary embolism, Risk stratification, Mortality

INTRODUCTION

Venous thromboembolism (VTE), clinically presenting as DVT or PE, is globally the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke in some Western countries.[1] In epidemiological studies, annual incidence rates for PE range from 39 to 115 per 100 000 population; for DVT, incidence rates range from 53 to 162 per 100000 population.[2,3] Venous thromboembolism (VTE) is a common and potentially life-threatening condition. It continues to be under diagnosed and undertreated.

Awareness among Indians regarding this potentially life-threatening disease is low. Contrary to earlier belief, the incidence of VTE in Asia and India is comparable to that in Western countries.[4,5] The risk of VTE is especially high in hospitalized patients, in a majority of whom it is clinically silent. It is one of the commonest causes of unplanned readmission and preventable death.[3]

The clinical manifestations of acute pulmonary embolism are highly variable, ranging from pulseless electrical activity to mild dyspnea, which can cloud the diagnosis.[6] Pulmonary embolism should be a part of the differential diagnosis in patients who present with new or worsening

dyspnea, chest pain and/or hypotension. Based on the physician's level of suspicion, the diagnostic workup may include a clinical evaluation, echocardiography, biomarkers (e.g., d-dimer, troponins), and/or imaging modalities such as computed tomography angiography or a ventilation-perfusion scan. Additional evaluations may be performed with B-type natriuretic peptide (BNP) and Pro-BNP. PE is commonly classified as massive (high-risk), submassive (intermediate-risk), and low-risk to help determine the required treatment. Risk stratification scores are used to determine management and the risk of complications and associated mortality. Myocardial infarction and heart failure increase the risk of PE. Conversely, patients with VTE have an increased risk of subsequent myocardial infarction and stroke, or peripheral arterial embolization. There are very few studies from Asian countries especially in India. Current study was conducted in Western Indian considering the need to improve the knowledge about characteristics, clinical profile, management and outcomes of patients with PE.[7-9]

Aim

The aim of this study is to establish relationship between mortality outcomes of patients with high/intermediate risk acute pulmonary embolism and the existing guideline directed therapy for the same categories, so to assess, scopes of future advancements in the treatment strategies.

METHODS

This prospective-observational single center study carried out in the department of cardiology at SBKS MIRC between October 2019 to December 2020. The manuscript is in accordance with the Helsinki Declaration and with ethical guidelines from our studies committee. 100 patients of pulmonary embolism with CTPA showing thrombus in pulmonary arteries fulfilling inclusion and exclusion criteria formed study population. The distribution and sampling was done by stratified random sampling method. Informed consent of all the patients/attendants (relatives) was taken prior to enrolment into the study.

Patient aged 18 years and above admitted with clinical features suggestive of acute pulmonary embolism and demonstration of thrombus in pulmonary arteries by echo or CTPA were included in the study. Patients with suspected case of pulmonary embolism and D-dimer positive patients without demonstration of thrombus in pulmonary artery were excluded from the study. Patients underwent detailed evaluation including history, clinical examination and laboratory investigations. Detailed history regarding risk factors of pulmonary embolism is taken in all patients. All patients underwent basic and relevant biochemical investigations. Clinical probability of all patients was assessed by using Wells simplified score and revised Geneva score. Patients with high probability of pulmonary embolism were evaluated with

D-dimer and cardiac biomarkers and 2D Echocardiography was done in all patients to look for RA/RV dilatation, RV dysfunction, RVSP, thrombus in MPA and its branches, left ventricular function and ejection fraction. Chest x-ray was done in all patients to look for other causes of dyspnea. Computed tomographic pulmonary angiography done in all patients to look for thrombus, location, number and RV function. Ultrasonography of the lower limbs was done in all patients. Patients were risk stratified on basis of ESC guidelines 2019 in to intermediate and high risk. Intermediate risk was again stratified into intermediate low and intermediate high risk. rTPA was used in dose of 100 mg over 2 hours (0.6 mg/kg over 15 mins), streptokinase was used in dose of maximum of 1.5 mill IU over 2 hours for systemic thrombolysis. Heparin infusion was continued for 2 days keeping activated thromboplastin time between 50 to 70s. Alteplase was used in low dose regimen (<24 mg) over 24 hours for catheter directed thrombolysis in patients with relative or absolute contraindication for systemic thrombolysis.

Statistical analysis

All statistical studies were carried out using IBM SPSS program vs. 20. Quantitative variables were expressed as the mean±standard deviation and qualitative variables were expressed as percentage (%). Parametric values between two groups were performed using the independent sample test or ANNOVA. Categorical variables were compared using the chi-square test. A nominal significance was taken as a two tailed $p<0.05$.

RESULTS

A total of 100 patients were admitted during the study period with a clinical diagnosis to have pulmonary embolism if there is evidence of thrombus in CT pulmonary angiogram or 2D-Echo. The mean age of the cohort was a 45.08±14.10 year with 60% being males and 40% females. Baseline characteristics and risk factors were showed in (Table 1-2).

The most common finding in ECG is sinus tachycardia (89%) followed by ST-T changes (62%), RAD (49%), Incomplete RBBB (24%) and S1Q3T3 pattern (36%). Chest X-ray was done in all patients. Amongst 100 patients 88 (88%) patients had a normal chest radiograph and remaining 12 patients, 10 (10%) had pleural effusion, 1 (1%) had cardiomegaly and 1 (1%) patient had fibrosis suggestive of old pulmonary Koch's. 2D ECHO was used as a screening tool in all patients in our study. Out of 100 patients 89 (89%) of patients had RV dysfunction which was assessed by TAPSE. RA and RV dilatation was present in 92 (92%) of patients in our study. Mean RVSP was 63 mmHg. Majority of patients in study had Tricuspid regurgitation at presentation. 76 (76%) had moderate TR and 22 (22%) had severe TR. Definitive evidence of thrombus in MPA and its branches were

observed in 54 (54%) patients on 2D Echo screening (Table 3).

Table: 1 Baseline characteristics of patients.

Variables	Mean±SD, n=100
Age	45.08±14.10
BP	92.88±14.27
HR	117.88±26.37
Male, N (%)	60 (60)
Female, N (%)	40 (40)
Dyspnea, N (%)	91 (91)
NYHA class I, N (%)	0 (0)
NYHA class II, N (%)	12 (12)
NYHA class III, N (%)	33 (33)
NYHA class IV, N (%)	65 (65)
Chest pain, N (%)	69 (69)
Anxiety, N (%)	12 (12)
Cough, N (%)	63 (63)
Hemoptysis, N (%)	37 (37)
Syncope, N (%)	13 (13)

Table: 2 Risk factors at presentation (n=100).

Variables	N (%)
Smoker	52 (52)
Malignancy	4 (4)
Immobilization	38 (38)
Stroke	12 (12)
Alcohol	22 (22)
H/o blood transfusion	8 (8)
Major surgery	6 (6)
Chronic lung disease	30 (30)
Congestive heart failure	16 (16)

Among 100 patients who underwent CTPA, 75 (75%) had dilated main pulmonary artery; 32 (32%) had saddle thrombus; 73 (73%) had right main pulmonary artery partial thrombus; 18 (18%) had left pulmonary artery partial thrombus. 91 (91%) patients had thrombus seen in segmental and sub-segmental vessels. Lower limb venous ultrasonography done in all patients. Out of 100 patients 72 (72%) patients had evidence of deep venous thrombosis; 60 patients had proximal and 12 patients had distal vein thrombosis. Risk stratification of patients was done according to ESC 2019 guidelines with help of variables which include shock, RV dysfunction, simplified PESI score and cardiac enzymes.[6]

Out of 100 patients 31 (31%) had high risk, 59 (59%) had intermediate high risk; 10 (10%) patients had intermediate low risk. The purpose of this for better management and outcome of further treatment. sPESI score was 1 in 90% of patients with troponin-I positivity and 10% of patients with troponin negativity with p<0.0001. This is suggestive of troponin is increased in correlation with sPESI. RV dysfunction was present in 96.7% of patients with troponin positive and 62% of

patients with negative troponin had RV dysfunction with p value of 0.0004 suggest that troponin I is a marker of RV dysfunction and help in probability of diagnosis.

Table: 3 Pulmonary embolism diagnostic parameters.

Parameters	N (%)
ECG finding	
Sinus Tachycardia	89 (89)
ST-T changes	62 (62)
RAD	49 (49)
Incomplete RBBB	36 (36)
S1Q3T3	39 (39)
X-ray finding	
Normal	88 (88)
Pleural effusion	10 (10)
Cardiomegaly	1 (1)
Echo finding	
Moderate-severe TR	98 (98)
RV dysfunction	89 (89)
Definite evidence of thrombus in MPA and it branches	54 (54)
Pulmonary arterial hypertension	86 (86)
CTPA finding	
MPA dilated	75 (75)
Saddle thrombus	32 (32)
RPA partial thrombus	73 (73)
LPA partial thrombus	18 (18)
Segmental and sub-segmental occlusion	91 (91)

All patients with high risk and intermediate high risk had troponin I positive as per guidelines. In our study all high risk and intermediate high risk had positive troponin-I. Out of 10 patients with intermediate low risk 3% had troponin positive and 7% had negative with p value of 0.03. Mean hemoglobin was 13.1±1.40gm/dl; mean serum creatinine was 1.11±0.54mg/dl; mean SGPT 119.36±295.66 IU/l, mean troponin-I was 0.32±0.68 ng/ml; mean D-dimer value was 5772.43±2339.19, mean PT was 16.68±8.49 and mean APTT was 38.59±16.34. All blood investigations are relatively high in intermediate high-risk group. Outcome was relatively grave in all subgroups with overall mortality of 56 (56%) and 44 (44%) patients were discharged on oral anticoagulation. As per risk stratification, all massive PE patients required thrombolysis and in submassive PE patients, thrombolysis is to be balanced against risk of death and bleeding and minor PE is to be treated with anticoagulation. By taking into consideration cardiac enzymes and sPESI score, patients with submassive PE were further divided into intermediate high and intermediate low risk and treated accordingly. In this study, all the patients were subjected to thrombolytic therapy or CDT as per the guideline recommendations. High risk patients (31%) who were thrombolysed with rTPA (49%), alteplase (27%) or streptokinase (4%), a few of them showed improvement symptomatically. 12 patients showed improvement in dyspnea and oxygen

saturation within 24 hours of thrombolysis and ionotropic supports were weaned off in 48 hours. No major bleeding was documented in our study group. Intermediate high-risk group (59%), all the patients had sPESI score >1 with positive cardiac enzymes and RV dysfunction and hence were subjected to thrombolytic therapy as per the guidelines. Of all 3 subgroups, 44 patients who survived, 23 patients had shown improved oxygen saturation level (>90%) after 24 hours of our treatment, ionotropic support was tapered off in all 44 patients within 48 hours of admission. RV function was back to normal in 32 patients before discharge. Out of these 44, 38 patients had mild TR after 72 hours of admission. 6 patients had moderate TR and all were discharged on oral anticoagulation and kept in follow up.

DISCUSSION

Pulmonary embolism and DVT are separate but related aspects of the same dynamic disease process, now termed VTE.[10,11] Male:female ratio in our study was 1.5:1. This is consistent with study done by Calvin et al from Chennai.[12] In that study mean age of patient population was 52.1 years and 62.8% were males and 37.2% were females. In our study smoking was major risk factor present in 52% of the patients. Studies done by Mitchell et al also showed smoking as the major risk factor for acute pulmonary embolism and was found in 22 (41.5%) of the patients.[13] Landmark study PIOPED II, also depicted smoking was one of the major risk-factor found in approximately 43% of the patients, which is similar to our study findings.[14] Apart from smoking chronic lung disease found to be another important risk factor. In our study chronic lung disease was present in 20% of patients which is comparable to PIOPED II study in which it was observed in 26% of patients.[10]

The most common clinical presentation of patients included in our study is dyspnea (91%) followed by chest pain (69%). The other symptoms being cough (63%) and hemoptysis (37%) and syncope (13%). This is consistent with our studies done in India. Study done by Shukla et al showed most common clinical presentation is dyspnea (100%) followed by chest pain (52%), syncope (30%), and cough (40%) The other symptoms being hemoptysis (10%).[15] Another study done 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 hemoptysis (3.8%).[16] Stein et al author of landmark study PIOPED II demonstrated similar findings.[10] This confirms an important fact that the finding of solitary dyspnea in a patient provides a strong suspicion for pulmonary embolism.

The ECG in addition to clinical symptoms can be essential in directing the physician towards the diagnosis. ECG findings in Calvin et al study was sinus tachycardia (91.4%) followed by RV strain pattern (65.7%), S1Q3T3 pattern (34.2%) and RBBB (20%). Shukla et al also showed ST-T depression in 80% of patients in his study.[15] Other findings were S1Q3T3 IN 30%, RBBB in 13%, and low voltage in 66% of patients with pulmonary embolism.

89% had evidence of RV dysfunction and RA and RV dilatation was present 92% of patients. Majority of patients in study had Tricuspid regurgitation at presentation. 76 (76%) had moderate TR and 22 (22%) had severe TR. Definitive evidence of thrombus in MPA and its branches were observed in 54 (54%) patients on 2D Echo screening. Study done by Mitchell et al from south India showed PAH was main finding present in 85% of patients.[16] Other findings in their study were RV dysfunction in 58% and definite evidence of thrombus in 5.7% of patients. Another study done by Shukla et al depicted moderate to severe TR in 73% of patients and RV dilatation and dysfunction in 86% of patients which is consistent with our study. This implies its use as an important screening tool in suspicion of acute pulmonary embolism, especially if there is no prior cardiopulmonary disease. The abnormality was mainly in the form of a raised pulmonary artery pressure.

In present study CTPA findings; 75 (75%) had dilated main pulmonary artery; 32 (32%) had saddle thrombus; 73 (73%) had right main pulmonary artery partial thrombus; 18 (18%) had left pulmonary artery partial thrombus. 91 (91%) patients had thrombus seen in segmental and subsegmental vessels. Study done by Calvin et al showed 83% patients had thrombus located in the main and lobar arteries. 4 patients in that study (16.7%) had thrombus seen in subsegmental vessels. Another study done by Shukla et al showed MPA thrombus in 40% of patients, thrombus in MPA branches in 40% of patients and 20% of patient had segmental and sub segmental occlusion.[15]

all the patients in the study were given thrombolytic agents rTPA (49%), alteplase (27%), and streptokinase (4%) and those who had contraindication to thrombolysis were given catheter directed thrombolysis (12%) or were subjected to surgical embolectomy (8%).[16] MAPPET-3 study stated in-hospital death or clinical deterioration requiring escalation of treatment is lower with heparin + alteplase than with heparin+placebo (11% vs. 25% respectively, p=0.006) and rate of recurrent PE was low and bleeding incidence similar in both groups.[17] Results of PEIATHO-2 will give a direction for further treatment of intermediate risk patients. PEITHO-2 trial protocol also does not satisfy patients into intermediate risk group. Konstantinides et al show that >95% of patients with acute PE are hemodynamically stable at presentation and are not to be considered at high risk.[18] Hence our study was focused on association of risk stratification and mortality outcomes of the similar subgroups.

Limitations

Although the results of current study have significant statistical values but it is limited by being a single center

experience with a small group of patients. More studies in future are required comprising of a multicenter analysis with a large patient cohort to add to the current knowledge and formulate an effective risk stratification as well as therapy model for sub-massive PE patients. Such a model shall be helpful both regarding improving patient outcomes and early decision-making need for aggressive management strategies.

CONCLUSION

Echocardiography, cardiac biomarkers and sPESI score are helpful for prognosis purpose. Pulmonary embolism can present with unexplained dyspnea and atypical chest pain among other signs and symptoms. Early diagnosis, risk stratification and guideline directed prompt management can lead to favorable outcomes however, patients with intermediate and high risk at the presentation have higher mortality despite guideline directed therapy.

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