Clinical Profile, Immediate- and Short-term Outcome of Patients with Intermediate-risk Acute Pulmonary Thromboembolism

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ABSTRACT

Background: Long-term outcomes of acute pulmonary thromboembolism (PTE) have been reported. However, the immediate- and short-term outcomes have not been reported adequately.

Objectives: Primary objective was to determine the patient characteristics, and immediate- and short-term outcomes of intermediate-risk PTE, and the secondary objective was to evaluate the benefit of thrombolysis in normotensive PTE patients.

Material and methods: This study included patients diagnosed with acute intermediate PTE. Patient's electrocardiography (ECG) parameters along with echocardiography (echo), etc., conducted at the time of admission, during their stay in hospital, at the time of discharge, and during follow-up were recorded. The patients were treated using thrombolysis or anticoagulants depending on hemodynamic decompensation. During follow-up, they were reassessed for echo parameters–right ventricular (RV) function and pulmonary arterial hypertension (PAH).

Results: Among 55 patients, 29 (52.73%) were diagnosed with intermediate high-risk PTE and 26 (47.27%) with intermediate low-risk PTE. They were normotensive and most of them had a simplified pulmonary embolism severity index (sPESI) score <2. Typical ECG pattern S1Q3T3 along with echo patterns and elevated cardiac troponin levels were observed in most of the patients. Patients treated with thrombolytic agents showed a reduction in hemodynamic decompensation as opposed to patients treated with anticoagulants who had clinical signs of right heart failure (RHF) on follow-up after 3 months.

Conclusion: This study contributes to the existing literature on outcomes of intermediate-risk PTE and the effect of thrombolysis on patients with hemodynamic stability. Thrombolysis reduced the incidence and progression of RHF in patients with hemodynamic instability.

Keywords: Anticoagulants, Hemodynamics, Intermediate-risk pulmonary thromboembolism, Outcome, Thrombolysis.

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HIGHLIGHTS

- Patients with intermediate-risk PTE are normotensive with a sPESI score <2, with other predominant characteristics, including typical ECG pattern of S1Q3T3 and elevated cardiac troponin levels.
- Short-term outcomes included reduced hemodynamic decompensation after thrombolysis.
- Thrombolysis reduced the incidence and progression of RHF in patients with hemodynamic compromise.

INTRODUCTION

Pulmonary thromboembolism is a life-threatening disease, which is reported to be the third most common cause of cardiovascular death after coronary heart disease and stroke.[1] In India, PTE is reported to have an incidence of 17.46 per 10,000 admissions.[2] Risk factors associated with PTE could be inherited hypercoagulable states like deficiencies of antithrombin III, Protein S and Protein C, prothrombin gene mutation, antiphospholipid syndrome, or acquired, like trauma due to surgery, prolonged immobilization, active malignancy, etc. The predisposition is identified by Virchow's triad consisting of obstruction of blood flow, vascular endothelial damage, and hypercoagulability, which leads to thrombosis.[1] According to European Society of Cardiology (ESC) guidelines on acute pulmonary embolism, the presence of elevated cardiac troponin, RV dysfunction on computed tomography pulmonary

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angiography (CTPA), and hemodynamic instability indicates high-risk PTE. An elevated cardiac troponin level with RV dysfunction on CTPA and without hemodynamic instability indicates intermediate high-risk PTE. Intermediate low-risk PTE is indicated by either RV dysfunction or elevated cardiac troponin levels without hemodynamic instability.[3] Echocardiography determines RV dysfunction in acute PTE, as well as right heart hemodynamic changes. Other diagnostic methods for PTE included pulmonary

Table 1: Risk stratification in pulmonary thromboembolism

	Indicators of risk		
Risk stratification	Hemodynamic instability	RV dysfunction on CTPA	Elevated cardiac troponin levels
High-risk PTE	+	+	+
Intermediate-risk PTE			
Intermediate-high	–	+	+
Intermediate-low	–	Either one (or none) positive	
Low-risk PTE	–	–	–

"+" indicates presence; "–" indicates absence[3]; CTPA, computed tomography pulmonary angiography; PTE, pulmonary thromboembolism, RV, right ventricular

angiogram, magnetic resonance angiogram, and computed tomography.[4] Intermediate-risk PTE accounts for 60% of PTE cases, which is heterogeneous in nature that includes normotensive patients with RV compromise.[5]

The gold standard treatment for PTE is anticoagulation, but thrombolysis is considered for patients with high- and intermediate-risk PTE.[6] The prognosis of patients with PTE varies considerably, depending on severity. While prognosis of low-risk PTE patients includes a <1% chance of mortality, there is a 5–15% increased risk of sudden death in intermediate-risk patients presenting with elevated right ventricular systolic pressure (RVSP) or PAH.[7] Chronic thromboembolic pulmonary hypertension and RHF were found to be long-term outcomes of intermediate-risk PTE.[8] While long-term outcomes have been reported, there is a lacuna of studies for immediate- and short-term outcomes.[4,9]

This study was conducted to determine the clinical characteristics and immediate- and short-term outcomes of patients with acute intermediate-risk PTE and to investigate the benefit of thrombolysis in normotensive patients.

MATERIALS AND METHODS

This prospective study was conducted between January and December 2019 after obtaining Institutional Ethics Committee approval (Project No. 18/372) and written informed consent from all the patients.

The sample population included patients who were diagnosed with acute intermediate-risk PTE with CTPA and further diagnosed as intermediate high-risk PTE defined as those who have acute right ventricular dysfunction and myocardial injury, with high cardiac troponin levels, without hemodynamic compromise and intermediate low-risk PTE with either RV dysfunction or elevated cardiac troponin levels and without hemodynamic instability (Table 1). Geneva scores were calculated for each patient to evaluate the risk (high, intermediate, and low) of PTE. Geneva score is a pretest assessment (before imaging) that confirms or aids in the clinical decision of the presence of PTE. Patients with a score of 0–3 were at low, 4–10 were at intermediate, and >10 were at high probability of having a confirmed diagnosis of PTE.[4] Patients above 18 years were considered for the study, and those with known significant bleeding risk and coagulation disorders, hemodynamically unstable, on thrombolytic agents for the last 4 days, and with normal troponin T/I levels were excluded from the study.

The patient's vitals, namely heart rate (HR), respiratory rate (RR), and blood pressure was recorded, along with ECG, echo parameters like presence of PAH, RV dysfunction, etc., and elevated levels of cardiac troponin-T were recorded at the time of admission, along with treatments underwent which is either thrombolysis or anticoagulation with unfractionated heparin (UFH), low-molecular-weight

heparin (LMWH), Vitamin K antagonists, or novel oral anticoagulants (NOAC). In-hospital conditions, including ventilator support and hemodynamic status, were noted, and immediate outcomes of recovery or worsening of hemodynamic status at discharge were also noted. Patients were reassessed for echo parameters–RV function and PAH, after 3 months.

Statistical Analysis

Data were analyzed using R software version 4.1.2 and Excel. Continuous variables were reported as mean ± standard deviation (SD)/median (min, max). Chi-square test was used to check the dependency between categorical variables, and two-sample t-test was used to compare various patient parameters with thrombolysis. p-value less than or equal to 0.05 was considered to be statistically significant.

RESULTS

A total of 55 patients diagnosed with acute PTE with CTPA, with a mean age of 55.04 ± 18.22 years, were enrolled. The majority of the patients enrolled were males (60%). Among 55 patients, 29 (52.73%) were diagnosed with intermediate high-risk PTE and 26 (47.27%) with intermediate low-risk PTE; 70.91% of patients had predisposing factors, and 30.91% were smokers. On calculating Geneva scores of patients, 7 (12.73%) had low, 39 (70.91%) inter-mediate, and 9 (16.36%) had high Geneva scores (Fig. 1).

Among the parameters assessed at diagnosis, typical ECG pattern S1Q3T3, indicative of RV dysfunction was observed in 45 (81.82%) patients, echo patterns–RA-RV dilation and PAH were observed in 41 (74.55%) and 19 (34.55%) patients, respectively. Right ventricular systolic pressure in patients with PAH was high in 8 (14.55%), mild in 2 (3.64%), and moderate in 9 (16.36%) of them.

At the time of admission, 26 (47.27%) patients had sinus tachycardia, 9 (16.36%) of them had RR >30, and 17 (30.91%) had oxygen saturation level <90% (Table 2).

During the hospital stay (Table 3), a sPESI score was calculated, where 45 (81.82%) had a sPESI score <2 and 10 (18.18%) patients had a high sPESI score >2. Non-invasive ventilation (NIV) was necessary for 11 (20%) patients, while 3 (5.45%) were intubated during their hospital stay. Patients were treated with either UFH (9.09%), LMWH (89.09%), NOAC (47.27%), or acenocoumarol (52.73%) (Fig. 2). A total of 10 patients were administered with thrombolytic agents either at the time of admission or during hospital stay due to worsening of hemodynamic parameters as per the ESC guidelines of management of acute pulmonary embolism.[3] Streptokinase and Tenecteplase were used for thrombolysis in 6 (10.91%) and 4 (7.27%) patients, respectively. A thrombotic workup of the patients showed that 9 (16.36%) were antiphospholipid antibody (aPLA) positive, 4 (7.27%) antinuclear antibody (ANA) positive, 3
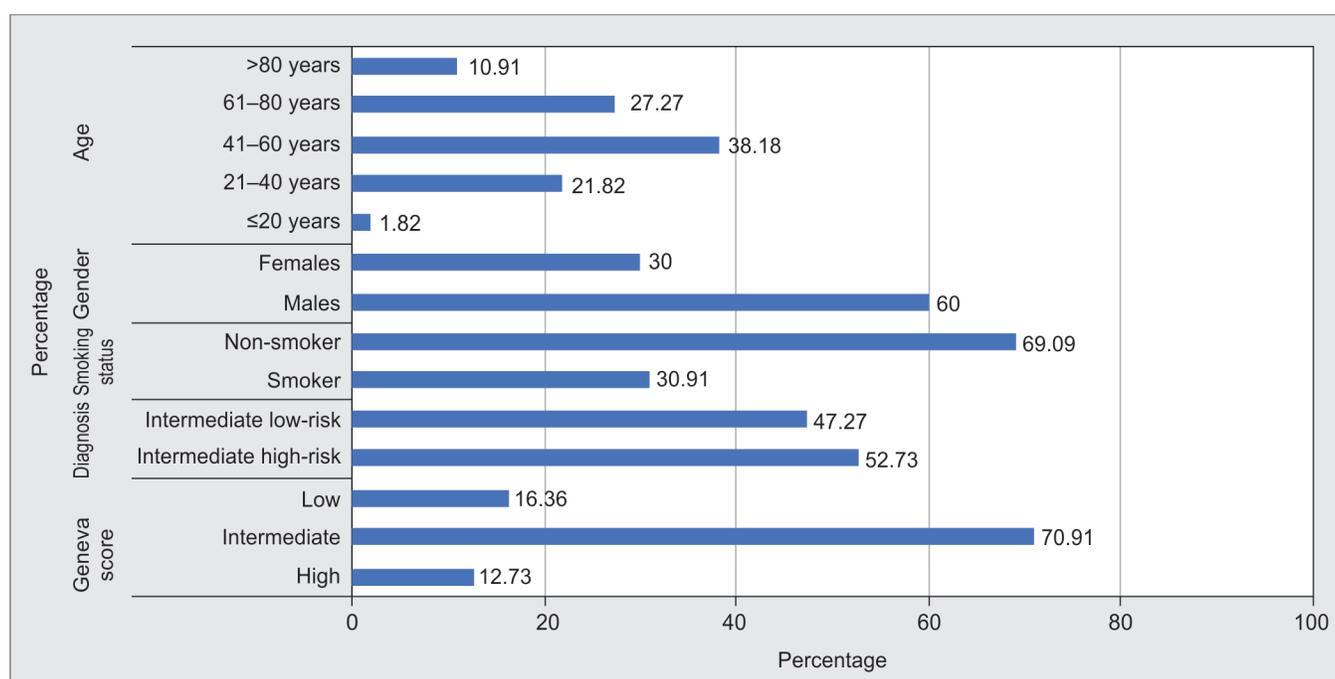
Fig. 1: Demographics and diagnosis of patients

Table 2: Clinical parameters assessed at the time of admission

Parameters assessed at the time of admission	Subcategory	No. of patients (%)
ECG rhythm	Junctional rhythm	1 (1.82%)
	Sinus bradycardia	2 (3.64%)
	Sinus rhythm	26 (47.27%)
	Sinus tachycardia	26 (47.27%)
S1Q3T3	Absent	45 (81.82%)
	Present	10 (18.18%)
ST-T segment changes	Absent	32 (58.18%)
	Present	23 (41.82%)
ECHO	Absent	14 (25.45%)
Right atrial, right ventricular dilation	Present	41 (74.55%)
Pulmonary hypertension	Absent	36 (65.45%)
	Present	19 (34.55%)
Right ventricular systolic pressure	0	36 (65.45%)
	High	8 (14.55%)
	Mild	2 (3.64%)
	Moderate	9 (16.36%)
Troponin-T	Negative	9 (16.36%)
	Positive	46 (83.64%)
Heart rate	<60	2 (3.64%)
	>100	26 (47.27%)
	60–100	27 (49.09%)
Respiratory rate	>30	9 (16.36%)
	16–20	3 (5.45%)
	20–29	43 (78.18%)
Oxygen saturation	<80	6 (10.91%)
	80–89	11 (20%)
	90–94	25 (45.45%)
	95–100	13 (23.64%)

Table 3: Clinical parameters assessed during the hospital stay

Parameters assessed during hospital stay	Subcategory	No. of patients (%)
Hemodynamic during stay	Improved	49 (89.09%)
	Worsened	6 (10.91%)
Heart rate	<60	1 (1.82%)
	>100	14 (25.45%)
	60–100	40 (72.73%)
Oxygen saturation	80–89	2 (3.64%)
	94–94	36 (65.45%)
	95–100	17 (30.91%)
Respiratory rate	<16	10 (18.18%)
	>30	1 (1.82%)
	16–20	38 (69.09%)
	20–29	6 (10.91%)
Simplified PESI score	0	22 (40%)
	1	23 (41.82%)
	2	9 (16.36%)
	3	1 (1.82%)
Malignancy	No	50 (90.91%)
	Yes	5 (9.09%)

had Protein C, Protein S, and antithrombin III deficiencies each, 20 (36.36%) had high homocysteine, and 5 (9.09%) had underlying malignancy (Fig. 3).

At the time of discharge, all patients improved hemodynamically except one who had a cardiac arrest (Table 4).

During follow-up, 7 patients lost to follow-up in the anticoagulant group, and among other patients in the anticoagulant group, who followed up 15 (27.27%) had clinical signs of RHF. All
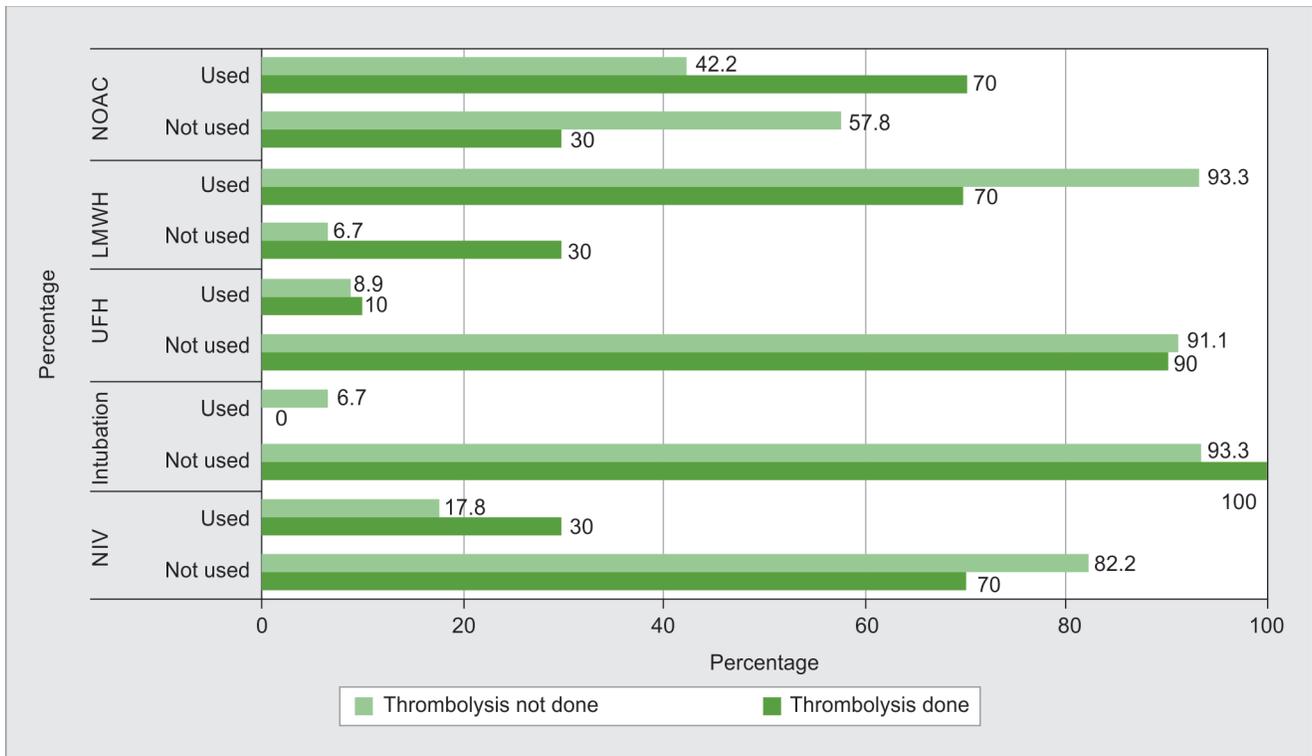
Fig. 2: Anticoagulants and breathing support used on patients treated/not treated with thrombolysis
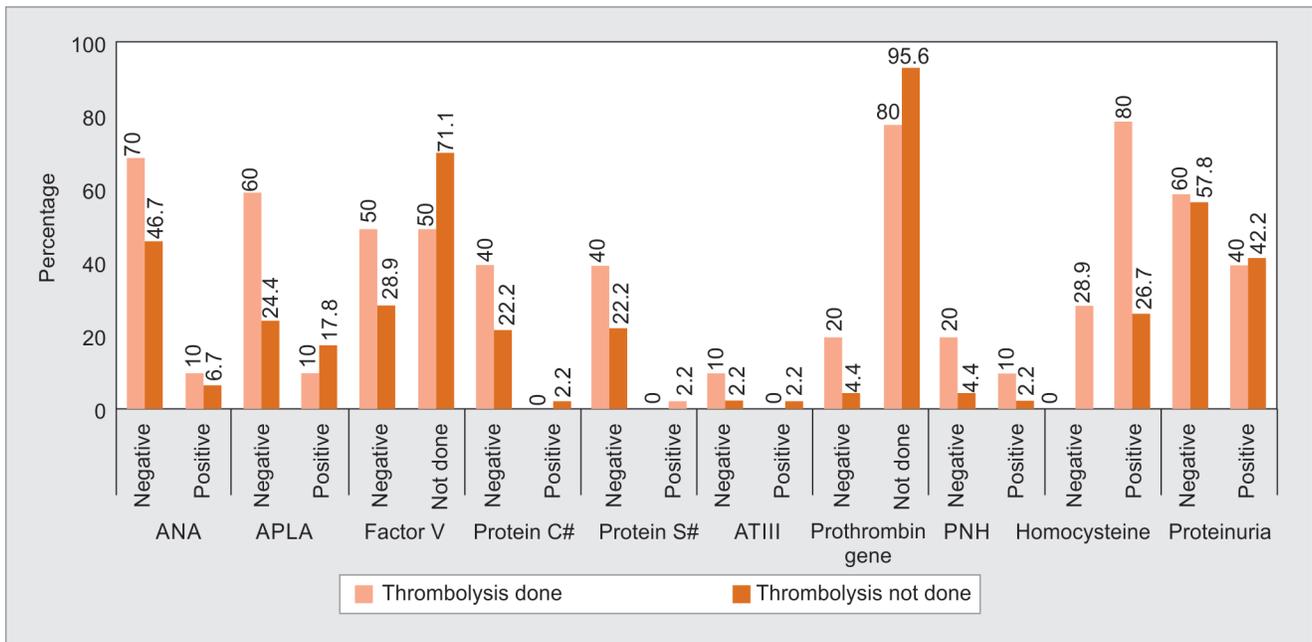
Fig. 3: Summary of thrombotic workup

the patients who underwent thrombolysis were alive, while 30% of them had sinus tachycardia, and all of them had normal HR and oxygen saturation levels (Table 5).

To evaluate the clinical benefits of thrombolysis in normotensive patients with acute intermediate-risk PTE, we compared various parameters recorded like demographic, ECG, echo, thrombotic workup, final diagnosis, etc., with thrombolysis, where we observed a significant association with age ($p = 0.027$), diagnosis ($p = 0.002$),

hemodynamic instability ($p < 0.001$), and homocysteine levels ($p = 0.0055$). However, no statistical significance was observed with other variables.

DISCUSSION

Our study enrolled patients diagnosed with acute intermediate high- and low-risk PTE. Among the clinical characteristics observed during admission, the typical S1Q3T3 pattern of ECG was prominent

Table 4: Clinical parameters assessed on discharge

Parameters assessed on discharge	Subcategory	Thrombolysis		Total no. of patients (%)
		Done	Not done	
Hemodynamic at discharge	Improved	10 (100%)	44 (97.78%)	54 (98.18%)
	Worsened	0	1 (2.22%)	1 (1.82%)
Heart rate	>100	2 (20%)	2 (4.44%)	4 (7.27%)
	60–100	8 (80%)	43 (95.55%)	51 (92.72%)
Oxygen saturation	80–89	0	1 (2.22%)	1 (1.82%)
	90–94	2 (20%)	14 (31.11%)	16 (29.09%)
	95–100	8 (80%)	30 (66.67%)	38 (69.09%)
Respiratory rate	<16	2 (20%)	2 (4.44%)	4 (7.27%)
	16–20	6 (60%)	33 (73.33%)	39 (70.90%)
	20–30	2 (20%)	10 (22.22%)	12 (21.82%)

Table 5: Clinical parameters assessed during follow-up after 3 months

Parameters assessed during follow-up	Subcategory	Thrombolysis		Total no. of patients (%)
		Done	Not done	
Clinical right heart failure*	No	7 (70%)	26 (57.78%)	33 (60%)
	Yes	3 (30%)	12 (26.67%)	15 (27.27%)
HR*	<60	0	1 (2.22%)	1 (1.82%)
	>100	3 (30%)	7 (15.56%)	10 (18.18%)
	60–100	7 (70%)	30 (66.67%)	37 (67.27%)
SpO$_2$*	80–89	0	1 (2.22%)	1 (1.82%)
	90–94	1 (10%)	8 (17.78%)	9 (16.36%)
	95–100	9 (90%)	29 (64.44%)	38 (69.09%)
Death*	Alive	10 (100%)	37 (82.22%)	47 (85.45%)
	Death	0	1 (2.22%)	1 (1.82%)

*Seven patients lost to follow-up after 3 months

in the majority (81.82%) of the patients, however, there are studies that report both a decreasing prevalence of RV strain from high- to intermediate- to low-risk PTE, and the S1Q3T3 pattern to be an independent predictor of developing complications in PTE.[10–12] Along with ECG patterns, echo patterns and cardiac biomarkers also provide help in risk stratification of PTE. Recently published studies reported RA RV gradient, RV systolic pressure, and pulmonary arterial systolic pressure along with cardiac troponin levels to be independent predictors of prognosis, including mortality in intermediate-risk PTE patients.[13–15] We observed RA RV dilation in 74.55%, PAH in 34.55%, and elevated cardiac troponin in 83.64% of the patients. Hemodynamic parameters observed in our study (HR, RR, and SpO$_2$ levels) at the time of admission were comparable with the diagnosis of intermediate-risk PTE, which is normal hemodynamic with RV dysfunction, however, intermediate-risk PTE patients being heterogeneous in nature may develop systemic arterial hypotension, cardiogenic shock, and sudden death, without warning.[5,16] While all the patients in our study improved hemodynamically at the time of discharge, one of them died due to cardiac arrest. Consistent with the ESC guidelines for the diagnosis of acute intermediate-risk PTE,[3] most of the patients (81.82%) in our study reported a sPESI score <2. Patients in our study underwent treatment with either anticoagulants or thrombolytics, where the latter was recommended in patients with worsening hemodynamic

parameters as it is reported to reduce recurrence of PTE and clinical deterioration along with decrease in all-cause, 30-day mortality compared with standard treatment of anticoagulant administration.[17] A study that was conducted to evaluate the role of fibrinolytic therapy for intermediate-risk pulmonary embolism reported improved hemodynamic compensation by fibrinolysis, which was similar to that observed in our study. However, they also reported an increase in the risk of stroke and hemorrhage in the long term, which could not be confirmed in our study, as long-term follow-up assessments were not carried out.[18]

To assess the immediate outcome of patients after treatment, we recorded hemodynamic parameters which had improved significantly in all the patients who underwent either anticoagulant or thrombolytic treatment, however, the former group saw a case of cardiac arrest. As discussed above, thrombolysis has been shown to reduce short-term mortality compared to anticoagulants, where the latter is also known to elevate RVSP.[15,19] During follow-up after 3 months, patients who underwent thrombolysis did not show hemodynamic decompensation, except for tachycardia (30%), while 27.27% of those who underwent anticoagulation had RHF, this might hint at thrombolysis being a better treatment option for normotensive patients. A review of data for evaluation and management of PTE reported a reduction in hemodynamic decompensation on thrombolysis, although an increased risk

of major bleeding or stroke was observed within 30-days of treatment.[19] Our study did not report any major bleeding incidences or recurrent PTE following thrombolysis.

We observed a significant association of high homocysteine levels with thrombolysis, which has been reported as an inherited risk factor of PTE.[1] Significant association was found between thrombolysis and intermediate high- or low-risk PTE. A review of studies for advanced management of PTE suggested thrombolysis for hemodynamically stable and RV dysfunction, which is a diagnosing factor of intermediate high-risk PTE.[16] However, in cases of massive acute PTE, with arterial hypotension, catheter-directed therapies become the choice of treatment, with an 86% success rate.[20] We also found a significant association between thrombolysis and the age of the patient. With respect to major complications like bleeding and hemorrhage risk, reduced risk was seen in patients <65 years, and our study included patients with a mean age of 55.04 ± 18.22 years, which could have been the reason why no complications such as bleeding or hemorrhage were observed.[21]

Limitations

To confirm the benefit of thrombolysis on patients with hemodynamic stability, a randomized clinical trial with a larger sample size is necessary.

In this study, we observed the short-term (3 months) outcome of intermediate-risk PTE, however, the risk of bleeding associated with thrombolysis as a long-term outcome was not assessed, as bleeding and hemorrhage have been cited as a short-term effect.[18,21]

Conclusion

This study evaluated the clinical profile and short-term outcome of intermediate-risk PTE along with the benefit of thrombolysis. Thrombolysis was shown to reduce the incidence and progression of RHF in patients with hemodynamic compromise. This could serve as a pilot study to evaluate the effect of thrombolysis on patients with hemodynamic stability and contribute to existing literature on short-term outcomes of intermediate-risk PTE.

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