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ADULT CARDIOLOGY

Frequency of Resolution of Pulmonary Embolism 6-Months Post Diagnosis and Initiation of Treatment

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ABSTRACT

Objective: To determine the frequency of resolution of pulmonary embolism 6 months after diagnosis and treatment using CT pulmonary angiography.
Study Design: Analytical, Cross-sectional study.
Place and Duration of Study: Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi, from Dec 2022 to May 2023.
Methodology: This study was conducted on thirty-one patients with pulmonary embolism, enrolled by consecutive sampling technique. Patients underwent computed tomography pulmonary angiography (CTPA). Pulmonary embolism protocol was used for taking the computed tomography angiography and resolution of embolism was also assessed.
Results: Out of total 31 patients, males were 10(32.3%) and females were 21(67.7%). Mean age was 48.58±9.61 years. Prevalence of PE resolution and no resolution at all was 21(67.7%) and 10(32.3%) respectively. Thrombus in major pulmonary arteries was resolved in 15(68.1%) out of 22, while segmental arteries' thrombus was resolved in 21(67.7%) out of 31 patients and there was significant association with the type of thrombolytic drug used (p<0.05).
Conclusion: The present study found that prevalence of PE complete resolution on CT angiography was 67.7%. Heparin gave comparatively good instant results. Resolution was comparatively low in smokers, diabetic and cancer patients while 0.0% resolution of PE was observed in patients with hypercoagulability.

Keywords: Computed Tomography Pulmonary Angiography, Pulmonary Arteries, Pulmonary Embolism.

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INTRODUCTION

Pulmonary embolism (PE) is an acute disease that affects long-term clinical outcomes and health conditions and its treatment and medical follow-up is limited to 6 months from initial diagnosis.[1] PE contributes as a leading cause to the majority of morbidity and mortality cases.[2] In a study conducted in Pakistan reported 5.4% prevalence of venous thromboembolism (VTE).[3] Risk strati-fication is re-quired for the management and treatment of PE after diagnosis.[4] Catheter directed thrombolysis, surgical embolectomy, anti-coagulation alone, reduced-dose ST, and extracorporeal membrane oxygenation (ECMO) are various treatment options for PE.[5,6]

The growing cases of PE are frequently associated with the introduction of CT pulmonary angiography.[7] CT angiogram during follow-up showing no PE evidence in any artery/vessel was defined as complete angiographic resolution.[8] The thromboembolism resolution degree measurement with perfusion scintigraphy (Q-scan) and found the profusion complete normalization in 40% cases after 6 months of diagnosis. AK *et al.*,[9] reported that initial clot volume showing the complete resolution was found in 72% cases during their follow-up. Prevalence of pulmonary embolism was 2% in a study conducted in South Asia.[10] Regardless of clinical implications, there are limited investigations on PE resolution following anticoagulation treatment specifically in cardiac patients.

The findings of our study may help physicians to identify patients who are at higher risk of developing complications or experiencing recurrent blood clots in the veins. This information can aid in implementing appropriate preventive measures and tailored treatment plans for individual patients. By understanding the effectiveness of different treatment options and identifying key risk factors, physicians can make informed decisions to optimize patient care and improve outcomes for individuals with PE. Therefore, the present study was aimed to determine

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frequency of resolution of pulmonary embolism 6-months post diagnosis after initiation of treatment.

METHODOLOGY

This analytical cross-sectional study was conducted on 31 patients with PE who underwent CT pulmonary angiography in the Cardiology Department of Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi, Pakistan, from Dec 2022 to May 2023. Institutional consent was taken from IERB under the approval letter number (9/2/R&D/2023/249).

The sample size (n=31) was calculated by using WHO sample size calculator as per the prevalence of pulmonary embolism 2%.[7] 95% confidence level and 5% margin of error was kept.

Inclusion Criteria: Patients (20-80 year of age) of either gender having pulmonary embolism, deep venous thrombosis, patients with hyper-coagulability, malignancy, known thrombophilia, recent immobilization, Cerebral Vascular Accident (CVA), major trauma, fracture of lower limb, hip or knee replacement, patients who underwent recent surgery within 3-months, patients on oral contraceptive pills (OCP) or hormone replacement therapy, and cancer patients were enrolled.

Exclusion Criteria: Those patients who were on anticoagulant therapy, having history of hemorrhagic/ ischemic stroke, and patients with impaired renal function (creatinine clearance of <30 mL min^{-1}) were not selected as study participants.

Non-probability consecutive sampling technique was used to gather data. Patient's confidentiality and anonymity was strictly maintained and written informed consent was taken prior to data collection. Pulmonary embolic patients' data was noted on a designed proforma. Detailed history (comorbities, risk factors such as; prolong immobilization, cancer status, hypercoagulability, major trauma, recent surgery and hip or knee replacement) was taken and examination was done followed by vitals monitoring, ECG and Echocardiography. PE protocol was followed for taking the CTPA. The presence of clot in pulmonary arteries (left, main, and right) was assessed. PE is the arterial blood clot and blood flow blocks to the lung. PE usually originates from the thrombus from the lower extremity deep venous system; yet, it can also originate from upper extremity, renal, pelvic area, and heart chambers.[1] Patients with pulmonary embolism were diagnosed on CTPA and images were taken utilizing a 10-, 16-, 40-, or 64-MDCT angiography unit and diagnosis was confirmed on CTPA report (i.e. filling defects within pulmonary vasculature, webs or bands, intimal irregularities, and pouching defects). Patients were treated with heparin, streptokinase or tPA according to their risk factors, clinical status, and CTPA findings. CTPA was done again at 24 hour after thrombolytic therapy. Patients were advised to visit OPD after 06 months. At the end of 06 months, a telephonic reminder was given to patients to revisit for follow-up CTPA, findings were recorded and resolution of thrombus was noted in major pulmonary arteries and segmental branches. Those patients who lost to follow-up were ruled out from study.

Data was entered and analyzed in a software; Statistical Package for Social Sciences (SPSS) version 24:00. Mean and standard deviations were calculated for continuous data variable such as; age. Frequency and percentages were analyzed for qualitative variables such as demographics, comorbids, PE etc. Stratification of PE was done for various risk factors such as DM, smoking, prolonged immobilization, and hypertension to see effect modifiers such as age, CT findings, dose duration, gender, and thrombolytic drugs types. Chi-square test was applied to find the association of study's variables with resolution of PE. *p*-value <0.05 was kept as statistically significant.

RESULTS

Total 31 patients were recruited who underwent CTPA and they were followed-up on 6-months. Among these, frequency of females was higher than males [21(67.7%) vs 10(32.3%)] having PE and mean age was 48.58±9.61 years. Majority of the participants were non-smokers 25(80.6%), non-hypertensive 25(80.6%) and non-diabetics 26(83.9%). Prolong immobilization was occurred in 10(32.3%) patients. 12(38.7%) were cancer patients. Hypercoagulability was present in 4(12.9%), history of major trauma and recent surgery was seen in 3(9.7%) and 9(29.0%) cases respectively. Lower limb fracture/ hip or knee replacement was present in 6(19.4%) patients. For PE resolution heparin, streptokinase and tPA were administered in 16(51.6%), 7(22.6%) and 8(25.8%) patients respectively. Post-treatment PE resolution was seen in 9(29.0%) while on 6-month follow-up, complete resolution was in 12(38.7%). Overall, PE resolution prevalence was 21(67.7%). However, 10(32.2%) patients presented with no resolution at all. It was observed slower in cancer patients such as out of 12-cancer patients; post-treatment resolution was in

only 1(8.3%) patient, on-follow-up complete resolution was in 7(58.3%) patients while 4(33.3%) were presented with no resolution. Among study subjects, there were 4(12.9%) patients who presented with hypercoagulability and their outcome was not good as there was no resolution in all of these patients even on follow-up. It can be seen that there were comparatively good results in patients who were given heparin i.e. complete resolution was in 14(87.5%) patients out of 16-patients (resolution was in 8-cases right after treatment and in 6-cases on follow-up). Streptokinase was found to be slower in action but resolution occurred in 6(85.7%) patients out of 7 (resolution was in 1-case right after treatment and in 5-cases on follow-up). While out of 8-patients, PE was resolute in only single case 1(12.5%), by the administration of tPA (Table-I).

Table-II findings depicted association of thrombolytic drug used with PE resolution and CTPA

Table-I: Pulmonary Embolism Resolution comparison in terms of Demographics, Comorbids and Type of Thrombolytic Drug (n=31)

Study Variables		Frequency (%) (Total=31)	Resolution of Pulmonary Embolism Frequency (%)		
			PE Resolution (at start of treatment) (Total=9)	PE Resolution (6-month follow-up) (Total=12)	No PE Resolution (6-month follow-up) (Total=10)
Gender	Male	10(32.3)	2(22.2)	2(16.7)	6(60.0)
	Female	21(67.7)	7(77.8)	10(83.3)	4(40.0)
Smoking	Yes	6(19.4)	-	1(8.3)	5(50.0)
	No	25(80.6)	9(100.0)	11(91.7)	5(50.0)
Hypertension	Yes	6(19.4)	-	5(41.6)	1(10.0)
	No	25(80.6)	9(100.0)	7(58.3)	9(90.0)
Diabetes Mellitus	Yes	5(16.1)	-	2(16.7)	3(30.0)
	No	26(83.9)	9(100.0)	10(83.3)	7(70.0)
Prolong Immobilization	Yes	10(32.3)	4(44.4)	4(33.3)	2(20.0)
	No	21(67.7)	5(55.5)	8(66.7)	8(80.0)
Cancer	Yes	12(38.7)	1(11.1)	7(58.3)	4(40.0)
	No	19(61.3)	8(88.9)	5(41.6)	6(60.0)
Hypercoagulability	Yes	4(12.9)	-	-	4(40.0)
	No	27(87.1)	9(100.0)	12(100)	6(60.0)
Major Trauma	Yes	3(9.7)	2(22.2)	1(8.3)	-
	No	28(90.3)	7(77.8)	11(91.7)	10(100.0)
Recent Surgery	Yes	9(29.0)	6(66.7)	3(25)	-
	No	22(71.0)	3(33.3)	9(75)	10(100.0)
Lower limb Fracture/ Hip or Knee Replacement	Yes	6(19.4)	2(22.2)	2(16.7)	2(20.0)
	No	25(80.6)	7(77.8)	10(83.3)	8(80.0)
Type of Thrombolytic drug	Heparin	16(51.6)	8(88.9)	6(50)	2(20.0)
	Streptokinase	7(22.6)	1(11.1)	5(41.6)	1(10.0)
	tPA	8(25.8)	-	1(8.3)	7(70.0)

PE=Pulmonary Embolism; CT=Computed Tomography; tPA=Tissue Plasminogen Activator

Table II: Association of type of Thrombolytic Drug used with Pulmonary Embolism Resolution and Computed Tomography Pulmonary Angioplasty Findings (n=31)

Resolution of Pulmonary Embolism			Frequency (%) Total=31	Type of Thrombolytic Drug Frequency (%)			*p*-value
				Heparin (Total=16)	Strepto-kinase (Total=7)	tPA (Total=8)	
After administration of drug		Yes	9(29.0)	8(50.0)	1(14.3)	-	0.018
		No	22(70.9)	8(50.0)	6(85.7)	8(100.0)	
On 6-month follow-up		Yes	21(67.7)	14(87.5)	6(85.7)	1(12.5)	0.001
		No	10(32.3)	2(12.5)	1(14.3)	7(87.5)	
CTPA Findings (thrombus found in major pulmonary arteries)	Pre-treatment	Yes	22(71.0)	9(56.2)	5(71.43)	8(100.0)	0.028
		No	9(29.0)	7(43.7)	2(28.6)	-	
	On 6-month follow-up	Yes	7(22.6)	1(6.2)	-	6(75.0)	<0.001
		No	24(77.4)	15(93.7)	7(100)	2(25.0)	
CTPA Findings (thrombus found in segmental branches)	Pre-treatment	Yes	31(100.0)	16(100)	7(100)	8(100.0)	-
		No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
	On 6-month follow-up	Yes	10(32.3)	3(18.7)	1(14.3)	6(75.0)	0.015
		No	21(67.7)	13(81.2)	6(85.7)	2(25.0)	

PE=Pulmonary Embolism; CT=Computed Tomography; tPA=Tissue Plasminogen Activator; CTPA=Computed Tomography Pulmonary Angioplasty

findings. It was noted that type of thrombolytic drugs significantly associated with the resolution of PE (p<0.01). PE was resolved completely in 21(67.7%) patients and out of these, in 9-patients PE was resolved right after treatment. When study participants were reported in hospital, their CTPA findings regarding major and segmental pulmonary branches, explored thrombus in 22(71.0%) and 31(100.0%) patients respectively. On 6-month follow-up PE was being resolved in 15(68.1%) patients and 21(67.7%) who had PE in major pulmonary arteries and segmental branches respectively, on presentation. All the findings in relevance to the type of thrombolytic drug used were statistically significant (p<0.05).

DISCUSSION

The present study mainly focused on the resolution of PE and found that the current investigation discovered 67.7% prevalence of PE resolution. However, 32.2% patients showed no resolution at all. Thrombus in major pulmonary arteries was resolved in 15(68.18%) out of 22 while segmental arteries' thrombus was resolved in 21(67.7%) out of 31 patients with significant association with the type of thrombolytic drug used for thrombolysis. Heparin gave comparatively good instant results. Resolution was comparatively low in smokers, diabetic and cancer patients while no resolution of PE was found in patients with hypercoagulability. These findings of current study are comparable with the past studies.

As the literature is scarce regarding post-treatment PE resolution prevalence specifically in cardiac patients, limited findings we had found relevant to our study. In a literature, PE resolution was observed on follow-up CTPA and revealed increased frequency of resolution with time after initial diagnosis and treatment. Complete resolution of PE was occurred in 81% patients which is comparable to the existing study's findings i.e. 67.7% prevalence of PE resolution. It was documented that major vessels' thrombus resolves faster than segmental branches. Similarly, current study observed the 68.18% resolution in major pulmonary arteries while 67.7% in segmental branches.[1]

PE patients who are at risk undergo anticoagulant therapy which plays significant role in resolution of emboli.[11-13] Studies done by Goldhaber *et al.*,[14] and Sharma *et al.*,[15] demonstrated prompt reduction of resistance as well as pulmonary artery pressure due to early resolution of PE, results in improved right ventricular function. Follow-up of PE patients showed significantly good results in patients treated with thrombolytic therapy as compared to the patients who were treated with only anticoagulation. Compared to this, following the contraindications (absolute) for thrombolysis such as; ischemic stroke in recent 2-months, active bleeding, and hemorrhagic stroke history while relative contraindications such as; recent major operation (within 10-days), multiple trauma (in recent 2-weeks), ophthalmologic or neuro surgery (in recent 1-month) or similar condition,[16,17] we had used only the thrombolytic drugs to resolve PE embolism and found good results in heparinized patients. The relative contra-indications are in significant association with PE risk. However, for confirmed cases of PE (as a participant of cardiac arrest), thrombolytic treatment is considered to be reasonable and effective during emergency.[18]

According to Aghavev *et al.*, complete remission of PE is significantly faster in patients with PVD (peripheral clots) (Hazard Ratio(HR): 1.78; p=0.032), while slower in subjects of venous thromboembolism history HR: 0.57; p=0.019. In cancer patients, resolution was faster in comparison to non-cancer patients (HR: 1.67; p=0.032) while mortality was significantly higher in cancer patients (p<0.05). In contrast, our study showed slower resolution frequency in cancer patients [1(11.1%), 7(58.3%), 4(40%) resolution post-treatment, on 6-month follow-up and no resolution respectively].[19]

Resolution of PE varied across different literature due to varied sample size such as CTPA findings revealed resolution in 82% of patients (in 28-days) studied by Stein *et al.*,[1] Similarly Lopez-Beret *et al.*,[20] Alonso *et al.*,[21] Aghayev *et al.*,[22] had found 91%, 74% and 68.8%% cases with complete resolution in 30 days, 4.5 months and 3 months respectively. Moreover, Rossum *et al.*,[23] came up with lower proportions i.e. 32% prevalence of PE resolution in 42 days and Es *et al.*,[24] had found 44% prevalence in 21 days. In another study with subjects n=290, 209(72.1%) showed complete resolution on follow-up intervals (7 and 184-days). 66(22.7%) study subjects showed limited resolution (partial) on CTPA fandings. In comparison, our study revealed 21(67.7%) prevalence of complete resolution on 6-month follow-up while 32.2% patients were having no resolution of PE.[19]

In a research study, complete resolution was noted in 77% patients in follow-up intervals with

faster resolution rate in peripheral branches than that of main pulmonary arteries. Complete resolution in major pulmonary vessels was noted in 14/16(42.9%) patients and segmental branches' clot resolution was in 11/16(68.8%) patients in 14-day follow-up period while in 15-28 days' follow-up, it was 6/9(66.7%) and 6/7(85.7%) respectively, in 29-90 days, it was 9/16(56.3%) and 15/15(100%) respectively and in >90 days follow-up; 17/19(89.5%) and 15/15(100%) respectively.[22] Comparatively, current study showed 77.4% (24/31) patients with complete resolution of thrombus in major pulmonary arteries and 67.7%(21/31) patients with thrombus resolution in segmental branches on 6-month follow-up. Variations in findings can be due to small sample size and extended follow-up interval. However, we didn't study the rate of resolution rather our focus was only the prevalence of resolution. Furthermore, sub-segmental branches were not studied and main concern was qualitative aspect. Quantitative analysis of variations in clot volume on small intervals with respect to the sequence of pulmonary arteries is suggested.

LIMITATIONS OF STUDY

Number of limitations were being encountered in our study such as; very small sample size, single center study, and no intermediate follow-up of patients. Resolution rate was also not monitored. Sequelae of PE (chronic) such as; strictures, web, mosaic perfusion, engorged central pulmonary vessels or peripheral pulmonary arteries' pruning) was not studied. However, further follow-up studies based on accurate observation and monitoring to define the resolution rate of diagnosed PE, are needed.

CONCLUSION

The present study found that prevalence of PE complete resolution on CT angiography was 67.7%. Resolution in major vessels is greater than the segmental branches. Heparin gave comparatively good instant results. Resolution was comparatively low in smokers, diabetic and cancer patients while no resolution of PE was in patients with hypercoagulability.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript:

AY & RS: Study concept, study design, drafting the manuscript, approval of the final version to be published.

UA & AZK: Study concept, data acquisition, critical review, approval of the final version to be published.

MM & ZH: Data acquisition, data analysis, data interpretation, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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