Acute Pulmonary Thromboembolism: Risk Factors, Clinical Profile, and Management Outcome in a Developing Country

1. Arif Rehman Sheikh, 2. Suhail Mantoo, 3. Sanaullah Shah, 4. Farzana Manzoor

1. Senior Resident, Department of Pulmonary and Internal Medicine, SKIMS, Srinagar, India

2. Assistant Professor, Department of Pulmonary and Internal Medicine, SKIMS, Srinagar, India

3. Professor, Department of Pulmonary and Internal Medicine, SKIMS, Srinagar, India

4. Government Medical College, Srinagar, India

Corresponding Author: Name: Arif Rehman Sheikh

Address: SKIMS campus, Srinagar, Jammu and Kashmir, India

Phone numbers: +91 9622418609

E-mail address: ess.arif53@gmail.com

Abstract

Background: Pulmonary Thromboembolism (PTE) remains a common disease throughout the world with significant morbidity and mortality. There is, however, limited data regarding profile of patients withPTE from India. The aim of our study was to analyse the risk factors, clinical profile and management outcome in our patients with acute PTE.

Materials & Methods: It was a hospital based observational prospective study done over a period of 4 years. Confirmed cases of pulmonary thromboembolism defined as patients with evidence of thrombus on CT pulmonary angiogram (CTPA) were included in this study. All included patients' data, includingthe demographics, risk factors, clinical examination, laboratory investigations, and treatment(s) given were recorded. Hospital outcome in terms of all-cause mortality was noted.

Results: 150 patients were included in the study with a mean age of 52.3 years (±15.56, range 18-85 years). Most common underlying risk factors were immobilization (33.3%), chronic lung disease (22.7%), malignancy (15.3%), and trauma to lower extremities (14.7%). The most common symptom prompting evaluation for PTE in our study patients was dyspnoea (94%), pleuritic chest pain (38%), and cough (33.3%). 50 patients (33.3%) had hemodynamic instability at presentation. Among 150 patients, 14 patients died in the hospital, thus constituting an in hospital mortality of 9.3%.

Conclusion: Clinical characteristics, and hospital outcome ofpatients with acute pulmonary thromboembolismin India is comparable with published international data albeit with some significant departures.

Keywords: Pulmonary Embolism, Clinical Profile

Introduction

Pulmonary thromboembolism (PTE) remains a major cause of morbidity and mortality all over the world. It is the third most common cardiovascular disease of the industrialised world after myocardial infarction and stroke[1]. The annual incidence rate of pulmonary embolism is about104-183 per 100,000 person-years[2]. More than 100,000 deaths annually are attributed to pulmonary embolism in USA[3]. Furthermore, as a cause of sudden death, pulmonary embolism is second only to sudden cardiac death[4].

Despite being so common and fatal, more than half of the patients with acute pulmonary embolism remain undiagnosed as the clinical presentation of acute pulmonary embolism is highly variable[3]. Pulmonary embolism has been called as the great masquerader[5].The classic presentation of acute PTE, i.e., rapid onset of pleuritic chest pain, dyspnoea, and hypoxia, is hardly seen. Rather every patient presenting with respiratory symptoms unexplained by an alternative diagnosis should be evaluated for pulmonary embolism.

Although rapid advances have taken place in the diagnosis and management of pulmonary embolism, it still is an underreported and underdiagnosed entity from the developing countries especially from India. The aim of our study was to evaluate risk factor profile, clinical characteristics, and hospital outcome of Indian patients with acute pulmonary thromboembolism.

Materials and Methods
It was a hospital based observational prospective study, conducted ata leading tertiary care institute in north India. An approval to conduct the study was obtained from the Institutional Review Board of the hospital although the study didn't involve any diagnostic or therapeutic maneuver outside of the routine evaluation of these patients and did not entail any extra costs to them.

The study began in August 2015 and the recruitment of patients concluded in September 2019. Confirmed cases of pulmonary thromboembolism defined as patients with evidence of thrombus on CT pulmonary angiogram (CTPA) were included in this study. Patients with previous history of PTE irrespective of their current treatment status were excluded from this study.

Information about the patient demographics, risk factors, clinical examination, laboratory investigations, and treatment(s) given were recorded on a preformed proforma. Patients with PTE were classified as 'High Risk', if the patient had shock or persistent hypotension (defined as systolic blood pressure less than 90mmHg or a drop at least 40mmHg for at least 15 min); "intermediate risk" if there was evidence of right ventricular dysfunction and/or myocardial injury in absence of hypotension; and "low risk" if the patient was having none of the above features.

The complications of the treatment (if any) were noted. The complications that were considered were intracranial hemorrhage, bleeding from other sites and others like drug related reactions. The primary outcome measure was all-cause mortality during the hospital stay.

Results:
A total of 150 patients were enrolled during the 4-year study period. The mean age of the subjects was 52.3 years (±15.56, range 18-85 years). Females represented 56% of the total patients. In our patients with pulmonary thromboembolism, the most common underlying risk factor was immobilization (33.3%), followed by chronic lung disease (22.7%) and malignancy (15.3%). History of trauma to lower extremity & pelvis within preceding three months was present in 22 patients (14.7%). 35 patients (23.3%), however, had no identified provoking factor at the time of diagnosis (table 1).

Table 1: Prevalence of risk factors among study patients		
Risk Factor	**Frequency**	**Percentage**
Immobilization	50	33.3
Chronic lung disease	34	22.7
Malignancy	23	15.3
Trauma to lower extremity and pelvis during past three months	22	14.7
Surgery within the last three months	19	12.7
Heart failure	19	12.7
Stroke, paresis and paralysis	11	7.3
Pregnancy/post-partum period	5	3.3
Connective tissue disorder	3	2.0
Inflammatory Bowel Disease	2	1.3
Current or past history of thrombophlebitis	1	0.7
Oral contraceptive use	1	0.7
Others	4	2.7
Unprovoked	35	23.3

The most common symptom at the time of diagnosis in our study patients was dyspnea (94%), pleuritic chest pain (38.0%) & cough (33.3%). Other symptoms like palpitations, decreased level of consciousness, hemoptysis, syncope and fever were seen only in fewer patient (table 2).Tachycardia was the most common physical finding seen in our patients with PTE (88%), followed by tachypnea (86.7%). Lower extremity edema was seen in 62.7% of patients. Hypotension was seen in 32.7% of patients (table 3).

Table 2: Prevalence of symptoms in Study Population

Symptoms	Frequency	Percentage
Dyspnoea	141	94.0
Pleuritic chest pain	57	38.0
Cough	50	33.3
Palpitations	24	16.0
Decreased level of consciousness	22	14.7
Syncope	16	10.7
Fever	16	10.7
Hemoptysis	15	10.0
Abdominal pain	2	1.3
Others	11	7.3
No symptom	4	2.7

Table 3: Prevalence of various signs in study patients

Signs	Frequency	Percentage
Tachycardia	132	88.0
Tachypnea	130	86.7
Lower extremity edema	94	62.7
Rales	66	44.0
Hypotension	49	32.7
Fever	18	12.0
Accentuated second heart sound	14	9.3
Cardiac murmur	7	4.7

Diaphoresis	4	2.7
Thrombophelibitis	1	0.7
Others	6	4.0
No Sign	2	1.3

Basic lab tests like CBC & ABG were available in majority of patients at the time of diagnosis. Findings of basic lab investigations are summarized in table4.

Table 4. Lab findings in study patients		
Lab finding	**Frequency**	**Percentage**
Hemoglobin<10 g/dl	33	22.0
Total leucocyte count >11,000/ul	69	46.0
Platelet <150,000/ul	63	42.0
Hypoxemia (po2 <60mmHg)	95	63.3
Hypocapnia (pco2 <35mmHg)	63	42.0
Respiratory alkalosis (pH >7.45 & pCO2 <35 mmHg)	32	21.3

Table 5 shows chest X-ray, ECG and echocardiographic findings in our patients. Abnormal chest radiography was documented in 52% of patients. 88% of patients had abnormal ECG in our study. Of the patients with abnormal ECG, the most common finding was sinus tachycardia (88%). The commonest abnormality found in patients of PTE in our study was dilated right heart chambers (45.3%).

Table 5: Chest X-Ray, ECG and ECHO findings in study patients			
Findings		**Frequency**	**Percentage**
Chest X-Ray	Pleural Effusion	24	16.0
	Parenchymal Infiltrate	35	23.3

	Raised CTR	13	8.7
	Hamptons hump	6	4.0
	Pala's Sign	3	2.0
	Not related to PE	3	2.0
	Normal	72	48.0
ECG	Sinus Tachycardia	132	88.0
	S1Q3T3	26	17.3
	RAD	5	3.3
	RBBB	10	6.7
	Normal	18	12.0
	Others	17	11.3
ECHO	Dilated RA/RV	68	45.3
	RV Hypokinesia	23	15.3
	PAH	58	38.7
	Others	11	7.3
	Normal	54	36.0

Table 6. In hospital mortality as per patient class			
Patient class	**Total number of patients**	**Number of patients who died**	**In hospital mortality**
High risk	50	10	20%
Intermediate risk	35	3	8.5%
Low risk	65	1	1.5%

The mean d dimer of patients was 2178.3 ng/ml. Troponin card test was positive in 46 (30.7%) of patients. 50 patients belonged to high risk group, while as 35 patients belonged to intermediate risk and 65 patients belonged to low risk group.

All the patients received anticoagulation. In addition, 34 patients belonging to high risk group received systemic thrombolysis, with streptokinase being the most common thrombolytic agent used (figure 2). Majority (87.3%) of the patients had no complication from PTE specific treatment; however, 4 patients (2.7%) had major bleed in the form of ICH & 12 other patients (8.0%) had bleeding from other sites like epistaxis, hematuria & bleeding the venipuncture sites. The in hospital all-cause mortality was 9.3% in our study (figure 3).

Figure 1. Thrombolytic agents used in study patients

Figure 2. Hospital outcome of patients
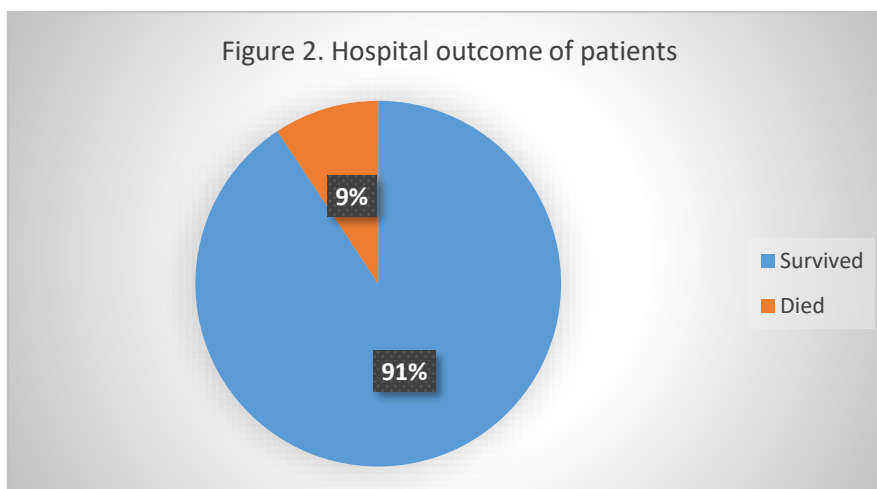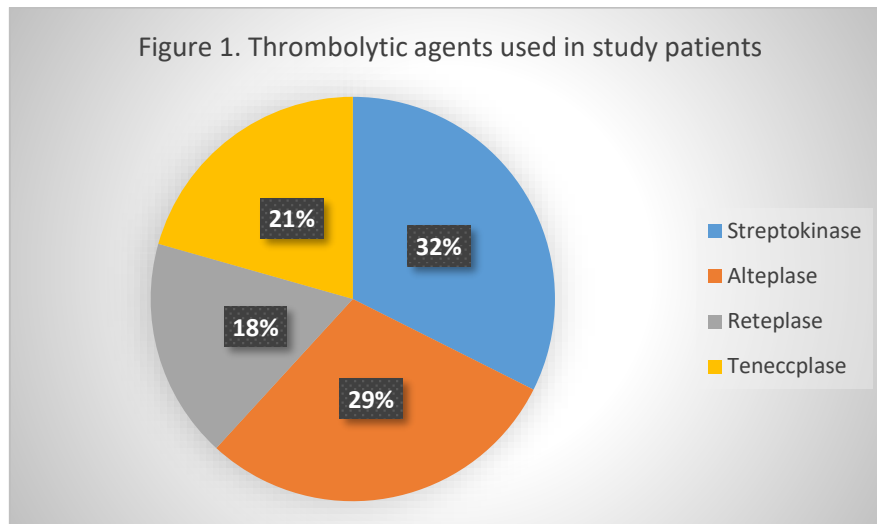
Discussion:

This study has provided the first insights into the demographic profile and clinical presentations of patients with pulmonary embolism from India and has afforded a glimpse of the state of overall care of these patients. To our knowledge, this is the largest study on such patients ever conducted in India.

Pulmonary thromboembolism has been described a disease of older age and numerous studies have shown that incidence of first time PTE rises with age. In our study, the mean age of the subjects was 52.3 years (±15.56, range= 18-80 years), which is lower than the reported mean age of patients from western countries[7,8,9]. The low mean age in Indian patients could be attributable to population structure in India, as only 6% of the population is above 65 years as compared to about 13% in western countries.

Common risk factors that have been consistently associated with PTE include prolonged immobility, malignancy, major surgery, polytrauma, chronic lung disease and chronic heart failure. In our study, 76.7% of patients had at least one risk factor of venous thromboembolism which is consistent with that of differentpatient registries[7,8,9].

The most common risk factor associated with PTE in our study was immobilization of more than 72 hours (33.3%). Similar results were found in **ICOPER**[7]**&EMPEROR**[6] studies in 28 & 38.5% of patients respectively. The reasons for prolonged immobilization were mainly serious illnesses, musculoskeletal problems especially in elderly, and sedentary life style.

The prevalence of patients with cancer (15.3%) was lower than the range of 18.3-24.3 % reported in other studies[6,7]. This result may have been influenced partly by selection bias, as costly investigations like CT pulmonary angiography are avoided in patients with advanced malignancies & partly by the prevalence of cancer in the different populations studied.

The most common symptom prompting evaluation for PTE in our study patients was dyspnea (94%), followed by pleuritic chest pain (38%) and cough (33.3%). Other symptoms like syncope and hemoptysis were seen only in fewer patients. Tachycardia was the most common physical finding seen in patients with PTE (88%), followed by tachypnea (86.7%). Lower extremity edema was seen in 62.7% of patients. Hypotension was seen in 32.7% of patients. Similar results were reported in many studies[7,8].Since all these signs and symptoms could be present in a vast number of conditions, our data re-demonstrates the non-specificity and variability in the clinical presentation of PE.

The basic laboratory tests are non-specific for evaluation of patients with acute PTE. ABG is done in majority of patients suspected to have PTE in our hospital and the findings of hypoxemia, hypocapnia & respiratory alkalosis are often looked into. However, in our study, it was found that hypoxemia (paO2<60mmHg) was found in only 63.3% of patients; similarly, hypocapnia was found in 42 % of patients while as respiratory alkalosis was found in 21.3% of patients. These results are consistent with that of **PIOPED**study[17] in which 67% of patients had paO2 of less than 80mmHg, 57% of patients had hypocapnia and 45% of patients with PE had alkalosis. This reaffirms the non-sensitivity of ABG in either confirming or ruling out PTE.

ECG is an important test for evaluation of patients with presentation similar to that of PTE. More than 88% of patients had abnormal ECG in our study. These results are consistent with the study of *Stein et al*[18] who have mentioned an abnormality in 87% of the patients with PTE. Of the patients with abnormal ECG, the most common finding was sinus tachycardia (88%).The classical S1Q3T3 pattern was seen only in 26 patients (17.3%) consistent with study of *Manuel et al*[20] (18%) & *SompradeekulS et al*[21] (14%).

Abnormal chest radiography was documented in 52% of patients with the commonest finding being parenchymal infiltrates (23.3%) followed by pleural effusion (16.0%) and increased cardiothoracic ratio (8.7%). The findings on chest X-Ray in our study is slightly different as compared to other studies, which have reported the commonest finding in patients of PTE as cardiac enlargement (27%), followed by pleural effusion (23%), elevated hemi diaphragm (20%), and pulmonary artery enlargement (19%)[7]. This difference in our study could be because of observer bias in the interpretation of chest radiograph.

Transthoracic echocardiography is an important investigation in the setting of PTE. It not only helps in diagnosis of massive PTE, but also helps in risk stratification of non-massive PTE. An abnormal echo was found in 64% of patients. The commonest abnormality found in patients of PTE in our study was dilated right heart chambers (45.3)%, followed by pulmonary arterial hypertension (38.7%) and right ventricular hypokinesia (15.3%). *Kurnicka K et al*[22] in a study of 511 patients with PTE found that RV enlargement, RV free wall hypokinesia, and interventricular septal flattening were present in 27.4%, 26.6%, and

18.4% of patients, respectively. Similar findings were found in a study done by *Aggarwal et al*[11], where 83% of the patients with a confirmed diagnosis of acute PTE had echo cardiographic abnormalities.

Risk stratification of patients into different classes is important in management decisions as well as predicting early mortality in patients of pulmonary embolism. Patients with hypotension are classified as 'High Risk'; normotensive patients with presence of RV dysfunction or elevated cardiac laboratory biomarkers are classified as 'Intermediate Risk' whereas patients who do not possess these characters are classified as 'Low Risk'. In our study patients, 33.7% belonged to high risk group, 23.3% belonged to intermediate risk group and 43.3% belonged to low risk group. The percentage of patients belonging to high risk group is slightly higher than that reported in major registries of pulmonary embolism patients: PIOPED[17] (8%), EMEP[12] (19.9%), MAPPET(28%), EMPEROR[6] (3%), & ICOPER[7] (4.2%). The reason for this higher percentage of patients in high risk group in our study could be because of the selection bias as more patients with hypotension undergo CT pulmonary angiography than those without.

All patients in the study received anticoagulation. In addition, 34 patients belonging to high risk group were thrombolysed and streptokinase was the main thrombolytic agent used in our study. 12.7% of patients developed treatment related complications, which included ICH in 4 patients and bleeding from other sites in 12 patients (8.0%). The finding that 33.7% of patients had hypotension in our study group suggests that we may be underdoing thrombolysis in our patients.

In hospital mortality in our study group was 9.3%. This is slightly lower than many of the hospital based observational studies: *Manuel A et al*[20] has reported a hospital mortality rate of 20%, *Agarwal et al*[11] 16.6%, *Shah et al*[23] 16.1% and *Hussain et al*[24] have reported an in-hospital mortality rate of 13%. In hospital mortality was 20% in high risk group, 8.5% in intermediate risk and 1.5% in low risk group. The lower all-cause in hospital mortality in our study could be because of different patient characteristics like slightly younger age, lesser number of patients with malignancies, & lesser number of patients with positive markers of myocyte injury.

Conclusion:

Pulmonary embolism is common in this part of the world also, with the mean age of presentation being low in our patients. Risk profile & clinical characteristics in our patients are comparable with the published literature with some deviations for which we have offered some explanations. The main limitations of our study is relatively small number of patients. This study should instigate better- designed and larger studies on pulmonary embolism to promote awareness among healthcare providers, for early diagnosis and treatment of these patients to improve the outcome.

References:

1. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis:a major contributor to global disease burden. ArteriosclerThrombVasc Biol 2014; 34: 2363–71.
2. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015; 12: 464–74.
3. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: an analysis using multiple-cause mortality data. Arch Intern Med. 2003. 163:1711-7

4. Reference.medscape.com. Pulmonary Embolism: Practice Essentials, Background, Anatomy. [online] (2020) Available at: http://reference.medscape.com/article/300901 [Accessed 5 April. 2020].

5. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The clinical course of pulmonary embolism. NEngl J Med. 1992; 326:1240 –5.

6. Pollack CV, Schreiber D, Goldhaber SZ, Slattery D, Fanikos J, O'Neil BJ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR(Multicenter Emergency Medicine PulmonaryEmbolism in the RealWorld Registry). J Am Coll Cardiol2011;57:700–6

7. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386–9

8. Kasper W, Konstatinides S, Geibel A,Olschewski M, Heinrich F, Grosser KD, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicentre registry. J Am Coll Cardiol. 1997;30:1165-71

9. Nakamura M, Fujioka H, Yamada N, Sakuma M, Okada O, Nakanishi N, et al. Clinical characteristics of acute pulmonary thromboembolism in Japan: results of a multicentre registry in the Japanese Society of Pulmonary Embolism Research. Clin Cardiol. 2001;24:132-8

10. Davidsingh SC, Srinivasan N,Balaji P,Kalaichelvan U, Mullasari AS. Study of clinical profile and management of patients with pulmonary embolism. Indian Heart Journal. 2014;66:197-202

11. Agarwal R, Gulati M, Mittal BR, Jindal SK. Clinical profile, diagnosis and management of patients presenting with symptomatic pulmonary embolism. Indian J Chest Dis Allied Sci. 2006;48:111-5

12. Volschan A, Albuquerque DC, Tura BR, KnibelMde F, Souza PC, Toscano ML. Pulmonary embolism: multicenter registry in tertiary hospitals. Rev Bras Ter Intensiva. 2009; 21:237-46

13. Silverstein MD, HeitJA, Mohr DN, Petterson TM, O'Fallon WM, Melto III LJ . Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch. Intern. Med. (1998) 158, 585–593

14. Anderson Jr FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT study. Arch Intern Med. 1991; 151:933–938.

15. Cushman M, Tsai AW, White RH,Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am. J. Med. 2004; 117:19–25.

16. Lolly M, Patil BB, Eti A, Sujay J, Khan S, Bansal A. Clinical profile of patients presenting with acute pulmonary thromboembolism in a tertiary care hospital in India: A retrospective study. J NTR Univ Health Sci 2017;6:15-8

17. Stein PD, Beemath A, Matta F,Weg JG, Yusen RD, Hales CA, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med.2007;120: 871–9

18. Stein PD, Dalen JE, McIntyre KM,Sasahara AA, Wenger NK, Willis 3rd PW. The electrocardiogram in acute pulmonary embolism. Prog Cardiovasc Dis. 1975; 17:247–57

19. Bajaj N , Bozarth AL , Guillot J,Kojokittah J, Appalaneni SR, Cestero C, et al. Clinical features in patients with pulmonary embolism at a community hospital: analysis of 4 years of data. J Thromb Thrombolysis. 2014;37:287–92

20. Manuel A, Aufico A, Africano R, Peralta T, Salas A, Silva A, et al. Clinical profile, management and outcomes of patients with pulmonary embolism: a retrospective tertiary centre study in Angola. Cardiovasc J Afr 2017; 28:356-61

21. Sompradeekul S, Ittimakin S. Clinical Characteristics and Outcome of Thai Patients with Acute Pulmonary Embolism. J Med Assoc Thai 2007; 90 (Suppl 2): 59-67

22. Kurnicka K, Lichodziejewska B, Goliszek S, Dzikowska-Diduch O, Zdonczyk O, Kozlowska M, et al Echocardiographic Pattern of Acute Pulmonary Embolism: Analysis of 511 Consecutive Patients. J Am Soc Echocardiogr. 2016;29:907-13

23. Shah I, Shahzeb, Faheem M, Khan K, Hafizullah M, Nisar M, et al . Pulmonary Embolism: Clinical Characteristics, Hospital Course and Outcome; Experiences at Lady Reading Hospital Peshawar. Annals 2012:18: 266-76

24. Hussain SJ, ZubairiAB,Fatima K, Irfan M, Atif M, Saeed MA. Clinical characteristics, Management and Outcome of Major Pulmonary Embolism: an experience from a tertiary care center in Pakistan. J Pak Med Assoc 2009:59: 372-5