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Original Research Article

Prevalence and Clinical Correlates of Pulmonary Hypertension in Systemic Sclerosis

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Abstract

Introduction*:** Development of pulmonary artery hypertension (PAH) worsens prognosis of systemic sclerosis (SSc) and can be either isolated precapillary PAH or secondary to interstitial lung disease (ILD). Early diagnosis is of crucial importance. There is scarcity of data on PAH in patients with SSc in Bangladesh. Objectives: To determine the Prevalence and clinical correlates of pulmonary hypertension in systemic sclerosis. ***Materials and Methods: The concerned non randomized cross-sectional observational study was conducted at department of Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh. Clinical and functional characteristics of 100 patients of systemic sclerosis were studied and they were evaluated by echocardiography to detect pulmonary artery hypertension. Our objective was to study the prevalence and the clinical correlation of PAH in SSc. ***Results:*** PAH was found in 29% patients on echocardiography. Prevalence tend to increase with age of onset and duration of disease. However, it did not differ significantly between patients with limited cutaneous SSc (lcSSc) and patients with diffuse cutaneous SSc (dcSSc). On binary logistic regression analysis, none of the studied variables had any independent influence on development of PAH. ***Conclusion*:** PAH in SSc occurs in a remarkable proportion (29%) of patients without any ominous signs in early stages. Non-invasive screening of patients with SSc for PAH will help in early diagnosis and appropriate timely therapeutic intervention before significant end-organ damage occurs.

Keywords: Interstitial Lung Disease, Pulmonary Artery Hypertension, Systemic Sclerosis.

INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease and presents with vasculopathy, inflammation, and fibrosis of the skin and internal organs [1]. SSc also presents with heterogeneous organ damages such as pulmonary arterial hypertension (PAH) and interstitial pneumoniae (IP), gastrointestinal dysfunction, cardiac dysfunction, and skin disorder [2]. Scleroderma or systemic sclerosis is a generalized connective tissue disorder characterized by microvascular obliteration & increased deposition of collagen, resulting in widespread fibrotic lesions [3]. SSc involves not only the skin but a host of other organ systems. Cardio Pulmonary involvement is a common feature of systemic sclerosis and one of the principle causes of death in such patients [3]. Cardiovascular disease in patients with SSc may be due to either primary involvement of the heart by sclerosing disease or a secondary involvement from disease of the kidney or lungs. Cardiac involvement is a poor prognostic factor & PAH itself is a sole ominous prognostic sign in SSc. Various risk factors like increasing age, male gender, digital pits, infarcts and black race have been implicated in the development of pulmonary arterial hypertension in scleroderma [4]. Therefore, PAH can coexist with other forms of PH in SSc, including PH related to heart disease, interstitial lung disease/hypoxemia, chronic thromboembolism and pulmonary venous occlusive disease (currently included in group 1PH), which further complicates diagnosis and management.

MATERIALS AND METHODS

The concerned non randomized cross-sectional observational study was conducted from June 2020 to July 2021 on 100 patients, presenting with clinical &

laboratory evidences of SSc at department of Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Bangladesh. Inclusion criteria were based on presence of symmetric sclerosis according to American College of Rheumatology (ACR) criteria.[5] Informed consent was taken from all study subjects. Pregnant females and patients with acute left ventricular failure, valvular heart disease involving mitral valve, atrial fibrillation, chronic liver disease with portal hypertension with porto-pulmonary shunt were carefully excluded from the study.

Subjects were clinically evaluated for involvement of musculoskeletal and other organ systems in a case record format. Immunologic markers studied included: ANA (anti-nuclear antibody), ENA (extractable nuclear antibody) Panels. Chest X-ray PA view & 12 lead ECG and HRCT-thorax in selected cases. Echocardiography (2D, M-Mode and color Doppler) were evaluated in all the cases. Confirmation of PAH in borderline cases was done by right heart catheterization & showing a mean pulmonary artery pressure >25 mm of Hg during rest &>30 mm Hg during exercise. Methods of estimating pulmonary artery pressure were based on American Society of Echocardiography guidelines. Estimated pulmonary artery systolic pressure more than 40 mmHg by echocardiography, or, peak tricuspid regurgitation (TR) gradient more than 35mmHg, or, estimated mean pulmonary artery pressure (MPAP) more than 25 mmHg was defined as pulmonary arterial hypertension. Pulmonary artery pressure was compared among different demographic variables and correlations with clinical parameters were studied. Compared disease sub-groups were: DcSSc, LcSSc, CREST syndrome and overlap syndrome. Statistical analysis was done using SPSS16 software. Chi-square test and Fischer's exact test was used for dependent categorical variables. For dependent interval and normal variables between multiple independent groups ANOVA test was used to find out level of significance. Correlation coefficient was calculated for interval and normal variables to find out degree of correlation. Binary logistic regression analysis was done to find out any independent predictors of PAH.

RESULTS

100 patients were studied, which included 92 females & 8 males (Table-1). Most (74%) of the patients belonged to the age group of 20-49. Among 100 patients 66 had a rural background and 34 patients belonged to urban area. There was no statistically significant difference of locality among the different disease groups (P>0.5). 66 patients came from lower socioeconomic strata, 34 were from middle income group and none belonged to the higher socioeconomic strata. Among the 100 patients of SSc, 78 had DcSSc and 18 had LcSSc including CREST variant and rest of the 4 patients had overlap syndrome. Mean duration of disease in the total population was 4.84 ±2.55 years. There was no statistically significant difference of mean duration of disease between different disease groups (P =0.68). Maximum duration of disease was 16 years and minimum duration of disease was 6 months. The most common skin finding was hyperpigmentation which was strikingly high (95%) with predominant diffuse (69%), followed by mottled type (29%). Calcinosis, telengiectasia and digital ulcer was found in 50%, 46% and 48% cases respectively. All of them were found significantly higher in the LcSSc, CREST and overlap syndrome compared to DcSSc group (P<.01). 31% of the patient having digital ulcers developed PAH. 10 patients had borderline pulmonary artery pressure in echocardiography. They underwent right heart catheterization after proper consent. MPAP more than 25 mmHg at resting condition was confirmed in 5 of these patients. In the other five patients PAH was excluded. Mean pulmonary pressure in the patients who underwent right heart catheterization was 31.89 mmHg. There was a weak correlation (p=-0.134) between between sex of patients and PHTN. It was not statistically significant (P=0.225). No significant correlation was found between age of patients, duration of disease in years, skin score, duration of Raynaud's phenomenon in months and mean as well as systolic pulmonary arterial pressure. On binary logistic regression analysis none of the variables like age of the patient, duration of disease in years, duration of Raynaud's in months, disease subtype, skin score, presence of calcinosis, or telangiectasia were found to have any independent predictive effect for the development of PAH. However significant correlation was found between right ventricular internal diameter in diastole and pulmonary artery systolic pressure (p=0.23, P=.036). Significant negative correlation was also found between ejection fraction and right ventricular diastolic dimension (p=-0.336 and P=.002).Systolic and mean pulmonary artery pressure in different patient groups has been shown in (Table-2).

Table 1: Demographic profile and clinical features of study population (N=100)

Variables	N (%)
Mean age of disease presentation	34.99 yrs
% of females	92(92%)
Reynaud's Phenomenon	92(92%)
Hyperpigmentation	95(95%)
Skin thickening	100(100%)
Digital pits/Ulcers	48(48%)

Variables	N (%)
ANA	90(90%)
Dyspnea	42(42%)
PAH	29(29%)
ILD	37(37%)
#Mean PASP	33.5± 11.01 mmHg
$Mean MPAP	20.54 ± 7.21 mm Hg
# mean pulmonary artery systolic pressure, $population mean of mean pulmonary artery pressure	

Table 2: Systolic and mean pulmonary artery pressure in different patient groups (mmhg)

Groups		SSc	DcSSc	LcSSc	CREST	Overlap	Male	Female
MPAP	Mean	20.54±	20.09±	22.87±	20.68±	22.30±	23.46±	20.19±
	St.DEV	7.21	7.19	6.69	8.19	7.56	8.96	6.89
SPAP	Mean	33.46±	33.13±	38.38±	30..54±	32.48±	38.92±	32.99±
	St.DEV	11.6	11.4	13.1	11.71	12.54	17.1	11.13

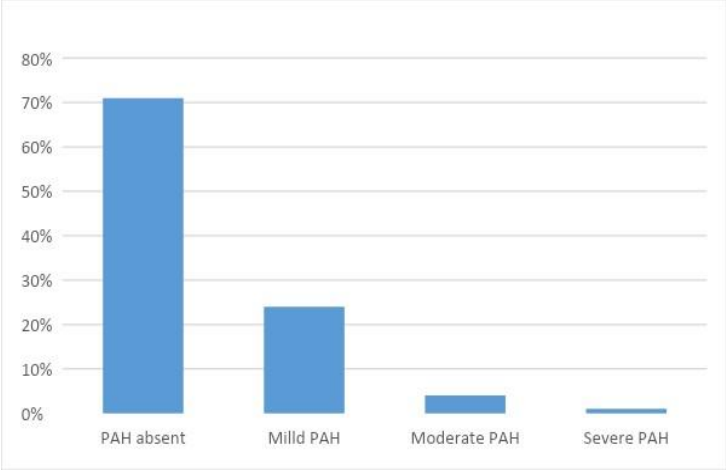

Figure 1: Grading of PAH in SSc patients

PAH was detected in 29 patients. Among them, 24 patients had mild PAH (MPAP 25-35 mmHg) while 4 patients had moderate PAH (MPAP 35-50mmHg) and one patient had severe PAH (MPAP >50mmHg) (Figure 1). Age wise presentation of PAH has been shown in (Fig 2).

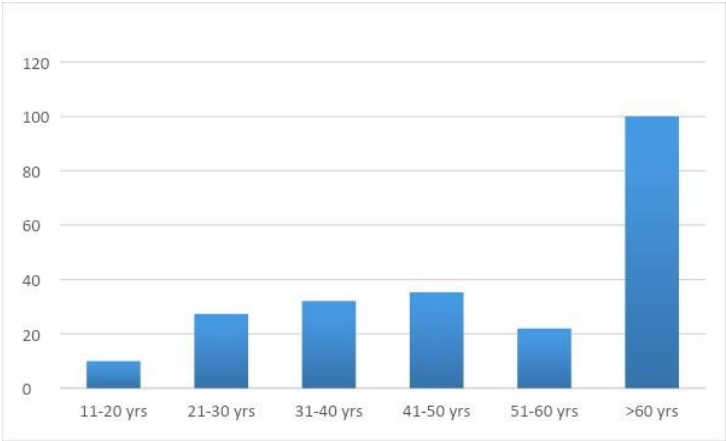

Figure 2: Bar diagram showing Age wise presentation of PAH in the study population

There was increased incidence of PAH among 60-69yr age group compared to other groups, but overall it didn't reach statistical significance (P=0.49). However, 60-69-year age group had significantly higher mean pulmonary artery pressure compared to 10-19,20-29,30-39, age groups (P< 0.01) and 40-49-year age group (P<0.05). About 27.2% of females and 50% of males had pulmonary artery hypertension. There was no significant difference between the two groups in the incidence of PAH, (P=0.225). Percentage of PAH in

different disease groups were: SSc (29%), DcSSc (29.5%), LcSSc (26.7%), CREST (33.3%), Overlap syndrome (25%). ANA staining pattern and their relationship with presence of PAH is shown in (Table 3). It was statistically significant (P = 0.048).

Table 3: ANA pattern and pulmonary hypertension cross-tabulation (N=100)

ANA patterns	PAH Absent (no. of patients)	PAH Present (no. of patients)	Total
Absent	9	1	10
Speckle	42	14	56
Nucleolar	18	7	25
Mixed	1	6	7
Homogenous	1	1	2
Total	71	29	100

The most common pattern observed was speckled (56%), followed by nucleolar (25%) and mixed (speckled/nucleolar, homogenous/nucleolar) (9%). Correlation between disease type and presence of types of ENA was good. AntiScl-70 was found mainly in the diffuse cutaneous scleroderma group whereas LcSSc & CREST group had mainly anti-centromere antibodies. Anti U1rnp was found significantly more in the overlap syndrome patients (P<.0001).Relationship of ENA (extractable nuclear antibody) with presence of PAH is shown in (Table 4).

Table 4: ENA pattern and pulmonary hypertension cross-tabulation (N=100)

ENA	PAH Absent (no. of patients)	PAH Present (no. of patients)	Total
No ENA	46	15	61
Anti Scl-70 ab	11	7	18
Anticentromere ab	12	4	16
AntiU1RNP ab	2	3	5
Total	71	29	100

However, PAH was not influenced significantly by the presence or absence of ENA or by the type of ENA (P = 0.372). ILD was present in 37 patients. Relationship of ILD & PAH is shown in (Table 5).

Table 5: Presence of ILD & PAH cross-tabulation (N=100)

Status of ILD	PAH Absent (no. of patients)	PAH Present (no. of patients)	Total
ILD absent	42	21	63
ILD present	29	8	37
Total	71	29	100

ILD was present in 37 patients (37%) out of 100 patients studied. Those without ILD, 21cases (33.3%) had pulmonary arterial hypertension. 8(21.6%) patients with ILD also had pulmonary artery hypertension. This difference was not statistically significant between the two groups (P=0.3).

DISCUSSION

Our study population had more diffuse cutaneous (78%) and less of limited cutaneous scleroderma (18%) variant compared to previous studies both in India and Western world [5]. Mean age of presentation of 34.99±12.058 years was similar to other Indian studies and lower than the Western literature [6, 7]. There was female preponderance in our study (92/8) similar to other Western studies Maione S *et al*., [8] Mean duration of disease (4.84±2.55years) was much less in our study compared to previous studies by Mukherjee *et al*., Meune *et al*., and Maione S *et al*., but nearly similar to other studies [7-10]. Most common non respiratory symptom, was Raynaud's phenomenon present in 92% of cases similar to the western literature and most of the Indian literature except for one South Indian study where it was reported to be 28.2 [11]. Skin pigmentation in our study population was similar to one study from India and another from Iraq [12]. 31% of cases of the patient having digital ulcers developed PAH similar to other studies [13]. ANA was found positive in 90% of patients almost similar in frequency between the different disease subsets. This result is at par with the results found in previous studies in India but higher than Western studies [14, 15]. Higher incidence of nucleolar pattern than our study was observed by another Indian study [7]. Pulmonary artery hypertension (PASP ≥ 40mmHg or MPAP ≥ 25mmHg) was found in 29 % of cases. Estimates of the prevalence of scleroderma-associated PAH vary widely in the past literature depending on the definition of PAH used and the diagnostic tools used to identify PAH. Using echocardiography as a diagnostic tool, up to 60% of scleroderma patients have been reported to have PAH.

However, using cardiac catheterization as a diagnostic tool to confirm the presence of PAH, a much lower prevalence rate in the range of 8%-12% has been reported. Lower prevalence of PAH was partly due to higher cut off value in our study. However, when 30 mmHg was taken as cut off value the prevalence increased to 56%. Mean pulmonary artery systolic pressure in our study population was33.52±11.01. The cut off value of 35mm Hg for trans tricuspid pressure gradient which we used has sensitivity of 75%, specificity of 66% and positive and negative predictive value of 85% and 50% respectively [16]. Our study more or less confirms the finding of Kumar U *et al*., [17]. In our study, prevalence of PAH didn't differ significantly between those with clinically detectable ILD (37 patients) and without ILD. This suggests poor sensitivity of clinical examination in ILD. Probability of subclinical ILD in the rest of the patients probably has accounted for this result. Incidence of ILD was slightly lower in our study patients compared to other studies probably because HRCT thorax couldn't be done in all cases. However, the finding was similar to that of Gaude G S *et al*., [18]. Strengths of our study were: (1) relatively good sample size, (2) heterogeneity of population, (3) detailed echocardiography examination, (4) Tissue Doppler examination in all cases. However, limitations of the study were: i) relatively smaller number of LcSSc cases, ii) not confirming PAH in all cases by right heart catheterization, iii) not determining severity of DLPD by HRCT fibrosis score or doing DLCO, (iv) lack of prospective follow up of echocardiographic data.

CONCLUSION

Systemic sclerosis involves a multitude of organs with a plethora of complications. Development of pulmonary hypertension is of immense prognostic consequence. However, at the early stages overt clinical features may be absent. Hence early detection of complications is an utmost necessity to relieve patient's sufferings. Noninvasive assessment of PAH in SSc patients enable us to institute early therapeutic intervention to prevent clinical deterioration. Prospective follow up of such patients may confer better understanding of the influence of clinical and demographic variables over the course of disease, behavior of pulmonary artery hypertension over time and its clinical outcome. Better understanding of this dreaded disease and its ominous consequences might assist in the research and development of newer therapies to reduce patient sufferings and to increase their longevity.

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