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Prevalence and Predictors of Pulmonary Arterial Hypertension in a Sample of Iraqi Patients with Systemic Sclerosis: A Cross-Sectional Study

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Abstract

Background: Pulmonary arterial hypertension (PAH) is now the most frequent cause of death in systemic sclerosis (SSc). **Aims:** The aims of the present study were to evaluate the prevalence of pulmonary arterial hypertension (PAH) and predictors in SSc among Iraqi patients. **Materials and Methods:** A cross-sectional study conducted on 56 patients with SSc diagnosed according to the criteria developed by the American College of Rheumatology. Baseline characteristics [age, sex, body mass index (BMI), duration of SSc, type of SSc, duration of Raynaud's phenomenon, and presence of telangiectasia] were documented. Antiscleroderma 70 (anti-SCL70) and anticentromere antibodies were measured. Doppler echocardiography was done to diagnose PAH. A risk score was obtained from 7 criteria, namely: Anti-Centromere Ab, Limited disease type, short duration of Raynaud's phenomena (<2.5 years), older age group (40+ years), absence of Telangiectasia, female gender, and absence of anti SCL70 Ab. **Results**: We found that PAH was present in 11 (19.6%) SSc patients with a 95% confidence interval of (9.2% to 30.0%). Risk score in addition to anti-centromere antibodies were enough to diagnose PAH with accuracy level of 89.3%. **Conclusions:** PAH in SSc occurs in significant proportion of patients. Risk score and anti-centromere antibodies had high accuracy level in predicting PAH. Screening of patients with SSc for PAH will help in early diagnosis and appropriate timely therapeutic intervention before significant endorgan damage occurs.

Key words Systemic sclerosis. Connective tissue. Pulmonary hypertension

1. Introduction

Systemic sclerosis (SSc)is a rare systemic autoimmune disease characterized by wide spread vasculopathy affecting the small and medium-sized blood vessels, fibroblast activation, and excessive collagen production culminating in fibrosis of the skin and internal organs. [1] Pulmonary complications are relatively common with reports of up to 26% of patients developing pulmonary hypertension (PHT). [2] PHT is a serious complication in patients with SSc with poor prognosis [3] and it is considered one of the leading causes of death in SSc. [4] PAH is an important clinical subgroup that causes PHT in SSc. [5] Other causes are pulmonary fibrosis, [6] diastolic ventricular dysfunction, [7] and primary cardiac involvement. [8] Moreover, PAH may be asymptomatic in the early stages and when symptoms develop, they are usually non-specific so that diagnosis is delayed until the disease is advanced and less responsive to therapy; [5,6] therefore, early detection and screening of at-risk patients may improve clinical outcome with the advent of specific therapies. [7, 8] Treatment of patients who are mildly symptomatic is associated with improved exercise tolerance and pulmonary hemodynamics [9] indices that are strongly indicative of disease progression and clinical worsening in PAH. [10]

Screening programmes for PAH have been established in other countries. [11-13] However, the prevalence of PAH in SSc from these studies varies considerably from 4.9 to 26.7% [14] and there is no universal assessment to allow accurate comparisons between studies. This study was designed to evaluate prevalence of PAH in Iraqi patients with SSc and to assess its predictors if present.

2. Materials and Methods

2.1Study design and sample selection

This cross-sectional study was conducted at the Rheumatology unit, Department of Medicine in Baghdad Teaching Hospital from October 2011 to May 2012. A total of 56 consecutive patients with systemic sclerosis diagnosed according to the criteria developed by the American College of Rheumatology [15] were included in the study. Informed consent was obtained from each participant included in this study according to the declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Baghdad University, College of Medicine, Medical Department. Patients were excluded from the study if they had: severe pulmonary

function impairment (forced vital capacity [FVC], total lung capacity [TLC], or forced expiratory volume in 1 s [FEV1] <60% predicted), those with relevant cardiac disorders (significant valvular defects, left ventricular ejection fraction <50%), or overlapping with other connective tissue diseases like systemic lupus erythematosus, and inflammatory arthritis as rheumatoid arthritis**.**

2.2 Data collection

All patients were asked for ages, duration of SSc, type of SSc, duration of Raynaud's phenomenon, and telangiectasia. Body mass index (BMI) was measured according the equation BMI=weight / height ^{2}. Data entry of patients was done using paper clinical research (CRF) form through interview and questionnaires.

2.3 Measurements

Doppler echocardiography was done for all patients enrolled in the study to diagnose PAH. All echocardiograms were carried out using Standard transthoracic echocardiography (SSD 4000, Aloka, Vivid I, GE Medical, Munich, Germany) by a senior technician and validated by a senior cardiologist. Two-dimensional, M-mode and color Doppler ECHO were used to evaluate cardiac morphology, flow abnormalities and cardiac functional status including ejection fraction (EF).

The limit of normotension using TTE was a maximum tricuspid regurgitant (TR) jet gradient of 30 mmHg. Pulmonary artery systolic pressure was estimated from the TR jet gradient. Patients with TR jet gradient value >30 mmHg were considered to have PAH. [16] Blood samples were obtained for measurements of Anti SCL70 and anticentromere antibodies. Pulmonary function tests (PFT) and high resolution CT scan were done for all patients to detect type of lung involvement.

2.4 Statistical analysis

Statistical analysis was done using SPSS version 20 computer software (Statistical Package for Social Sciences). Frequency distribution for selected variables was done first. The 95% confidence interval for a sample proportion was used to show the expected range for prevalence of PAH in the reference population of SSc cases with 95% certainty.The statistical significance of difference in mean of a normally distributed variable, like age, BMI and duration between 2 groups was assessed using the independent samples Student's t-test. Associations between presence of PAH and selected explanatory dichotomous variables were explored by cross-tabulation. The statistical significance of such associations was assessed by Chi-square (χ^2) test of homogeneity or Fisher's exact test (when the conditions for a valid chi-square test were not met).

Discriminant analysis was used to study the strength of association between risk factors and presence of PAH. It is a good substitute for multiple logistic regression, which needs strict assumptions that cannot be met in the present study sample. ROC analysis was used to assess validity parameters and set optimum cut-off values for quantitative variables when used to predict PAH. P value less than 0.05 was considered statistically significant.

3. Results

The results presented here were based on the analysis of 56 cases with SSc. Their ages ranged between 16 and 61 years old (mean= 40.5 +/- 10.8 years SD). Females were more frequent in the study sample (n=51) and constituted the highest proportion (91.1%), table 1.Limited disease type constituted 58.9% of cases. A positive anti-centromere antibody was observed in 23.2% of cases, and a positive antiSCL70 antibody was observed in 8.9% of cases. A diagnosis of PAH was established in 11 (19.6%) of study sample with a 95% confidence interval of (9.2% to 30.0%), table 1.

As shown in table 2, there were no obvious or statistically significant differences in mean BMI and duration of SSc disease between those with and without PAH. The mean age was significantly higher among cases with PAH (46.6 years of age) compared to those negative for PAH (39 years of age). The mean Duration of Raynaud's phenomena was significantly lower among cases with PAH (1.5 years) compared to those negative for PAH (4.6 years), table 2. A later onset of Raynaud's phenomena as reflected by the shorter duration of this finding is predictive of PHT. ROC analysis was used to calculate the typical cut-off value for age and duration of Raynaud's phenomena to use them as a predictive criterion for PAH. Age was associated with a ROC area of 0.73 (P=0.02), while duration of Raynaud's was associated with a ROC area of 0.81 (P=0.001), when used to predict PAH positive cases differentiating them from SSc cases with no evidence of PAH. The typical cut-off value for age was 40+ years of age and that of Raynaud's duration was <2.5 years, figure 1 and 2.

As shown in table 3, a positive anti-centromere antibodies was associated with a significantly higher percentage of positive PAH (69.2%) compared to SSc cases with negative antibodies (4.7%). A limited type of SSc was associated with a significantly higher percentage of positive PAH (33.3%) compared to SSc cases of a diffuse type (0%). A short duration (<2.5 years) of Raynaud's phenomena was associated with a significantly higher percentage of positive PAH (40%) compared to those of longer duration (3.2%).Presence of telangiectasia was associated with an obviously lower percentage of positive PAH (0%) compared to SSc cases with no similar findings (22.4%). The association however failed to reach the level of statistical significance (possibly because

of small sample size). A female gender was associated with an obviously higher percentage of positive PAH (21.6%) compared to SSc male cases (0%). The association, however failed to reach the level of statistical significance (possibly because of small sample size).A positive anti-SCL70 antibody was associated with an obviously lower percentage of positive PAH (0%) compared to SSc cases with negative antibody (21.6%). The association however failed to reach the level of statistical significance (possibly because of small sample size).

As shown in table 4, anti-centromere antibody test was associated with the highest accuracy when used to predict PAH positive cases among SSc group. The test was 81.8% sensitive and 91.1% specific. A positive anti-centromere antibody will establish the diagnosis of PAH with 69.2% confidence in a clinical context where the pretest probability (prevalence) of PAH is 19.6%. Ranked second in diagnostic importance for PAH was the short duration of Raynaud's phenomena (<2.5 Years) and having a limited type of SSc which established the diagnosis of PAH with 40% and 33.3% confidence respectively in the current sample of SSc where the prevalence of PHT was 19.6%. An age ≥40 years would establish a diagnosis of PHT with 29.4% confidence. Absences of Telangiectasia, Female Gender and Absence of Anti SCL70 antibody (Ab) were associated with low accuracy levels (32.1%, 21.6% and 21.6 respectively).

It is worthy to notice that criteria with a perfect sensitivity (100%) can exclude a possible diagnosis of PAH with 100% confidence when the pretest probability (prevalence) of PAH is as low as 19.6% among cases with SSc. Therefore, a diffuse type of SSc, presence of telangiectasia, male gender and positive anti-SCL70 Ab are useful in excluding PAH, table 4.

The previously tested 7 criteria for detecting PAH were summed together to yield a risk score. Each risk item is given a score of 1 when positive and zero when absent. The resulting risk score range between zero (no risk item positive) to 7 (all risk items being positive). ROC analysis showed that risk score had very high validity in diagnosing PAH in SSc cases (ROC area = 0.97) as in Table 5, Fig.3.

The typical cut-off value for the resulting risk score was 6+, which was associated with a sensitivity of 90.9% and a specificity of 91.1%. This cut-off value was of high accuracy (91.1%). A risk score of 6+ can predict PAH with 71.9% confidence in a group of SSc cases where the prevalence of PAH is 19.6% only, table 5 and figure 3. Variables eligible for inclusion in discriminant model were risk score, anti-Centromere Ab, limited disease type, short duration of Raynaud's phenomena (<2.5 years), older age group (40+ years), absence of telangiectasia, female gender, and absence of Anti SCL70 Ab.

As shown in table 6, risk score was added to all 7 risk items in a multivariate model to assess its role in differentiating PAH from non-PAH SSc cases. A selection algorithm was used to build a model with smaller number of included predictors and having the best predictive accuracy. It was shown that risk score in addition to anti-centromere antibodies test were enough to calculate a discriminant score that was able to classify SSc subjects into those with and without PAH with 89.3% accuracy. A calculated discriminant score based on the formula provided in table 6 that is higher than 0.84 will predict presence of PAH.

Table 1: Frequency distribution of the study sample by selected parameters.

	N	%
Female Gender Compared to male		
Male	5	8.9
Female	51	91.1
Limited type Vs Diffuse		
Diffuse	23	41.1
Limited	33	58.9
Anti-Centromere Ab		
Negative	43	76.8
Positive	13	23.2
Anti SCL70 Ab		
Negative	51	91.1
Positive	5	8.9
PAH		
Negative	45	80.4
Positive	11	19.6
Total	56	100.0

N, number, %, percentile, Ab, antibody, SCL, scleroderma,PAH, pulmonary arterial hypertension

Table 2: The difference in mean of selected parameters between SSc cases with and without PAH.

	PAH Negative (n=45)	Positive (n=11)	P
Age (years)			0.034*
Range	(19-56)	(16-61)	
Mean	39	46.6	
SD	10	12.2	
SE	1.49	3.67	
BMI (Kg/m2)			0.99
Range	(18.6-39)	(15-31.1)	
Mean	24	24	
SD	3.4	4.9	
SE	0.51	1.48	
Duration of the disease in years			0.86
Range	(0.8-20)	(3-20)	
Mean	7.4	7.8	
SD	6	5.5	
SE	0.9	1.67	
Duration of Raynaud's phenomena (years)			0.008*
Range	(1-20)	(1-4)	
Mean	4.6	1.5	
SD	3.7	1	
SE	0.55	0.29	

*, p value significant(<0.05); BMI, body mass index; SD, standard deviation; SE, standard error

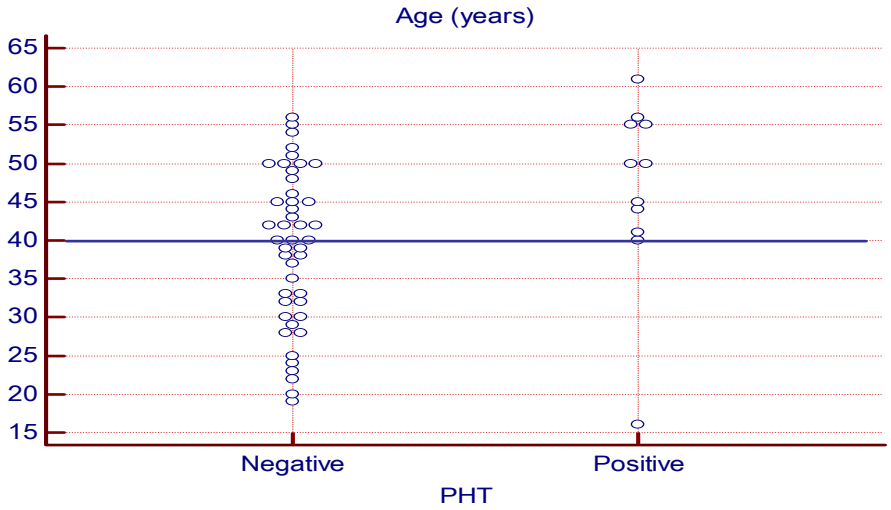

Figure 1: Dot diagram showing the typical cut-off value for age when used to differentiate between PAH positive and negative SSc cases.

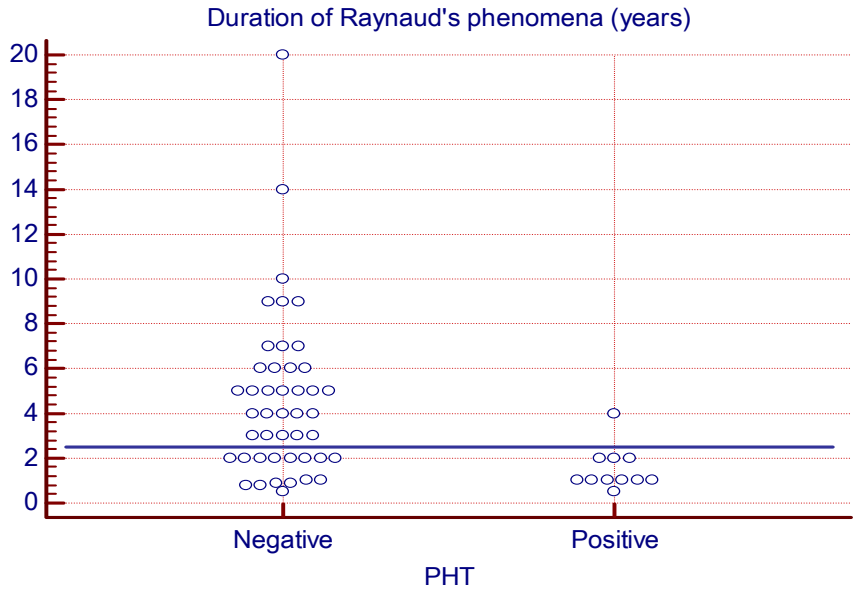

Figure 2: Dot diagram showing the typical cut-off value for duration of Raynaud's phenomena when used to differentiate between PAH positive and negative SSc cases.

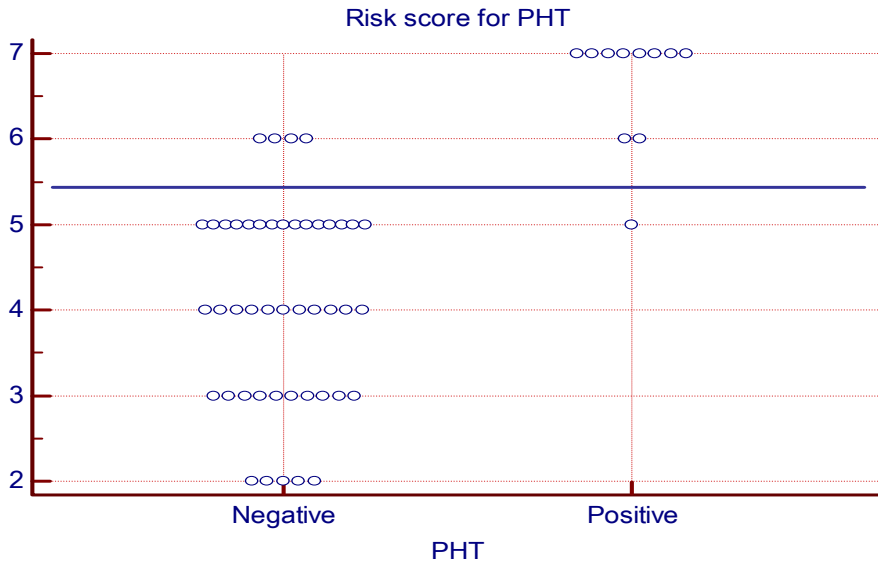

Figure 3: Dot diagram showing the typical cut-off value for risk score when used to differentiate between PAH positive and negative SSc cases.
ROC area for risk score = 0.97 P<0.001

Table 3: The rate of PAH positive SSc cases by selected explanatory variables.

	Total	Having Pulmonary hypertension		
	N	N	%	P
Anti-Centromere Ab				<0.001*
Negative	43	2	4.7	
Positive	13	9	69.2	
Limited type Vs Diffuse				0.002*
Diffuse	23	0	0.0	
Limited	33	11	33.3	
Short duration of Raynaud's phenomena (<2.5 years)				0.001*
Negative	31	1	3.2	
Positive	25	10	40.0	
Older age group (40+ years)				0.036*
Negative	22	1	4.5	
Positive	34	10	29.4	
Telangiectasia				0.32
Negative	49	11	22.4	
Positive	7	0	0.0	
Female Gender Compared to male				0.57
Male	5	0	0.0	
Female	51	11	21.6	
Anti SCL70 Ab				0.57
Negative	51	11	21.6	
Positive	5	0	0.0	

*p<0.05, N, number, %, percentile, Ab, antibody, SCL, scleroderma,PAH, pulmonary arterial hypertension

Table 4: Validity parameters for selected criteria when used as a test to predict PAH among SSc cases.

	Sensitivity	Specificity	Accuracy	PPV	NPV
Positive Anti-Centromere Ab	81.8	91.1	89.3	69.2	95.3
Short duration of Raynaud's phenomena (<2.5 years)	90.9	66.7	71.4	40	96.8
Limited disease type	100	51.1	60.7	33.3	100
Older age group (40+ years)	90.9	46.7	55.4	29.4	95.5
Absence of Telangiectasia	100	15.6	32.1	22.4	100
Female Gender	100	11.1	28.6	21.6	100
Absence of Anti SCL70 Ab	100	11.1	28.6	21.6	100

Table 5: validity parameters of risk score when used as a test to predict PAH among SSc cases.

Risk score for PHT	Sensitivity	Specificity	Accuracy	PPV	NPV
≥5	100.0	57.8	66.1	37.2	100.0
≥6	90.9	91.1	91.1	71.9	97.6
≥7	72.7	100.0	94.6	100.0	93.6

Table 6: Discriminant model for 8 selected parameters when used to predict SSc cases with PAH differentiating them from those negative for PAH.

	Rank according to importance (discriminating power)
Risk score for PAH	1
Anti-Centromere Ab	2

Overall predictive accuracy = 89.3%
Wilks' Lambda=0.445
P (Model) < 0.001

D = -2.899 + (0.538 x Risk score for PAH) + (1.886 x Anti-Centromere Ab)

Cut-off value for D score= 0.84
D score ≥ cut-off value is a predictive of PAH, while a D score < cut-off value is suggestive of negative PAH. Variables eligible for inclusion in discriminant model**:** Risk score, anti-Centromere Ab, limited disease type, short duration of Raynaud's phenomena (<2.5 years), older age group (40+ years), absence of telangiectasia, female Gender, absence of anti SCL70 Ab**.**

4. Discussion

Pulmonary arterial hypertension (PAH) is a major complication of systemic sclerosis (SSc) and a significant cause of morbidity and mortality. [17] Recent advances in treating patients with idiopathic PAH have raised the hopes that early recognition and therapeutic intervention in PAH-SSc may similarly improve prognosis. [18, 19] Additionally, identifying predictors of PAH in SSc may help in targeting specific subgroups of SSc patients who will require frequent screening and perhaps prompt treatment.

This study showed that the prevalence of PAH among Iraqi patients with SSc was 19.6%. Possible mechanism of PAH in SSc patients may be primarily intimal proliferation, medial hyperplasia, and adventitial fibrosis leading to an obliterative vasculopathy. [20]

Similar finding was reported by Chang *et al* [21] in a study of 619 SSC patients who found that prevalence of PAH was 19.2% .Kumar *et al* [22] studied prevalence of PAH in SSc (n=100) and found 32% had PAH on 2D-echocardiography.

Other published data were widely variable ranging from 5-35% in various studies depending upon the different methods and diagnostic criteria used for diagnosis. [23- 26] This difference from our study may be explained by small sample size in our study and variety of methods used to estimate pulmonary artery pressure in those studies. In addition, echocardiography estimates right ventricular systolic pressure (RVSP) and the diagnosis of PAH is based on the increase in mean pulmonary arterial pressure (PAP). [18]

Interestingly, in this study, we found that positive anticentromere antibody was associated with a significantly higher percentage of positive PAH (69.2%) compared to SSc cases with negative antibodies (4.7%) and had the highest accuracy when used to predict PAH. Similar finding was reported by Kampolis *et al* [27] who showed that presence of positive anticentromere Ab was significantly associated with increasing risk of PAH (OR 8.75, CI 1.12-68.38, p = 0.039).

In addition, a limited type of SSc was significantly associated with a higher percentage of positive PAH (33.3%) compared to SSc cases of a diffuse type (0%) and ranked second in diagnostic importance for prediction of PAH with 33.3% confidence and perfect sensitivity. This indicates that diffuse type of SSc exclude PAH. Similar finding was reported by other studies. Chang *et al* [28] assessed risk factors for developing pulmonary hypertension (PHT) in patients with scleroderma (n=1136). They found limited SSc is a risk factor for PAH and had a 27.3% probability of developing severe PAH. Steen [29] reported that isolated PAH was characteristically seen in limited SSC. Cox *et al* [30] evaluated isolated PAH in cohort of scleroderma in systematic review of the clinical course of all patients registered on the South Australian Scleroderma Register, a population-based register of 374 living and 234 deceased patients with scleroderma. The majority of PAH had limited scleroderma.

Notably, short duration of Raynaud's phenomena was significantly associated with PAH and established the diagnosis of PAH with 40% confidence. This indicates that a later onset of Raynaud's phenomena as reflected by the shorter duration of this finding is predictive of PAH. This in accordance with Kumar et al who found onset of Raynaud's phenomenon later in life was associated with a higher PAH(24).Also Walker *et al* [31] have shown that later onset of Raynaud's phenomenon was positively associated with PAH in a total of 3656 SSc patients enrolled in102 centers and 30countries.

The current study showed that older age group (40+ years) was a risk factor for PAH. In scleroderma, aging may promote the development of PAH via several important pathogenic pathways. First, aging tends to reduce endothelial release of nitric oxide and endothelium dependent relaxation by acetylcholine. [32] Second,

spontaneous endothelial injury, possibly as a result of the generation of excess oxygen-derived free radicals and defective in vivo endothelial repair mechanisms, increases in older individuals. [33] Third, changes in immune reactivity with aging (termed immunescence) include aberrant T-cell proliferation and increased production of autoantibodies. [34] These aging related changes in vascular biology may render the pulmonary arterial tree particularly susceptible to the pathophysiologic mechanisms observed in scleroderma. Similarly, in a recent European meta-analysis conducted by Avouac *et al*, [35] precapillary and postcapillary pulmonary hypertensions were significantly associated with advanced age.

Moreover, in the present study, absence of Telangiectasia was associated with low accuracy levels of predicting PAH and had prefect sensitivity. Therefore, presence of telangiectasia may be useful in excluding PAH. In contrast to a recent study performed by Shah *et al* [36] who assessed telangiectasia in consecutive adult patients with scleroderma (n=147) and found that increased numbers of telangiectasia is strongly associate with the presence of pulmonary vascular disease. The association between telangiectasia and PAH in our study failed to reach the level of statistical significance possibly because of small sample size.

Furthermore, we found no significant association between genders, anti-scl 70 Ab and PAH. Similar findings were reported by Plastiras *et al* [37] who evaluated 114 SSc patients with Doppler echocardiography and found gender and autoantibodies were not significantly associated with PAH.

The main limitations of this study were: First; the small number of patients because of the rarity of the disease, and so the findings need to be confirmed in a larger prospective study. Second, we could not confirm our finding with right heart catherization because of ethical reasons.

However, our study had points of strength. First, well defined inclusion criteria of SSc patients without overlapping with other connective tissue diseases or inflammatory arthritis that may affect the results. Second, strict exclusion of patients with severe pulmonary function impairment by pulmonary function tests and high resolution CT of the chest, in addition to excluding relevant cardiac disorders by two-dimensional, M-mode and color doppler ECHO. Finally, we used a selection algorithm to build a model with smaller number of included predictors and having the best predictive accuracy. It was shown that risk score in addition to anti-centromere antibodies test were enough to calculate a discriminant score that was able to classify SSc subjects into those with and without PAH with high accuracy.

In conclusion, PAH in Iraqi patients with SSc was frequent (19.6%). Risk score and anti-centromere antibodies had high accuracy level in predicting PAH. This suggests early detection of PAH patients in SSc by Doppler echocardiography as a non-invasive screening method and some predictors ensure appropriate treatment.

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