Original Article

Pulmonary arterial hypertension in Saudi patients with systemic sclerosis: Clinical and hemodynamic characteristics and mortality

Hadil AK. Al Otair, Majdy M. Idrees[1], Sarfraz A. Saleemi[2], Ahmed M. Eltoukhy, Ali A. Alhijji[3], Waleed A. Al Habeeb[4], Mohammed A. Omair[3]

Department of Critical Care, King Saud University, [1]Department of Medicine, Division of Pulmonology, Prince Sultan Military Medical City, [2]Department of Medicine, Division of Pulmonology, King Faisal Specialist Hospital and Research Center, [3]Department of Medicine, Division of Rheumatology, King Saud University, [4]King Fahad Cardiac Centre, King Saud University, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Hadil AK. Al Otair, Department of Critical Care, King Khalid University Hospital, King Saud University, P. O. Box 2925 (38), Riyadh 11461, Kingdom of Saudi Arabia.
E-mail: hadil.alotair@live.com

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Abstract:

BACKGROUND: Pulmonary arterial hypertension (PAH) is a major cause of morbidity and mortality in patients with systemic sclerosis (SSc). The objective of this study is to describe the clinical characteristics, mortality, and predictors of SSc-PAH in Saudi patients.

METHODS: Retrospective chart review study of SSc patients who were followed for at least 1 year in three tertiary care centers in Saudi Arabia was conducted. Clinical information, echocardiographic findings, and right heart catheterization (RHC) results were collected. Descriptive statistics were used for demographic and disease characteristics.

RESULTS: Fifty-seven patients with SSc were reviewed. PAH was confirmed by RHC in 40 patients (87.5%, females). Their mean age was 45.43 ± 13.48 years. The mean pulmonary artery pressure was 42.9 ± 12.7 mmHg, the pulmonary vascular resistance index was 19.4 ± 7.7 woods unit, and cardiac index was 2.43 ± 0.68 min/m². The median time from symptoms to first assessment was 42.8 ± 115.62 months. Most patients (77.5%) presented with functional Class III or IV and more than half (22.55%) were on dual combination therapy. Ten patients (25%) SSc PAH died over a follow up period of 37 ± 7 months. Compared to SSc patients without PAH, SSc-PAH patients had shorter 6-min walk distance (6MWD) (296.1 ± 116.5 vs. 399.59 ± 40.60 m, $P < 0.0001$), higher pro-brain natriuretic peptide (1755.8 ± 2123.4 vs. 69.8 ± 44.3 pg/ml $P = 0.004$), and more frequent Raynaud's phenomenon (RP) (90% vs. 35%, $P < 0.0001$). Logistic regression showed RP (odds ratio [OR] =48.58, 95% confidence interval [CI]; 3.73–633.10) and 6MWD (OR 1.02: 95% CI; 1.01–1.03) were associated with the development of PAH.

CONCLUSION: Our cohort of Saudi SSc-PAH patients has a younger disease onset and a lower mortality than what is described worldwide despite late presentation and requirement of combination therapy. The presence of RP and lower were associated with the development of SSc-PAH.

Keywords:

Mortality, pulmonary arterial hypertension, Saudi Arabia, systemic sclerosis

Pulmonary arterial hypertension (PAH) is a serious complication and a major cause of death in patients with systemic sclerosis (SSc).[1-3] Pulmonary hypertension (PH) is defined as a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg on right heart catheterization (RHC). While PAH is further distinguished by a pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR) >3 wood units, without chronic hypoxemia from interstitial lung disease (ILD).[4]

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PH in SSc is most frequently attributed to Group 1 (PAH) (64%), followed by Group 3 (chronic lung disease) (20%) and Group 2 (left-sided heart involvement) (16%). Approximately 30% of patients with SSc have an elevated right ventricular systolic pressure (≥40 mmHg) on screening echocardiogram. While in prospective studies, the prevalence of PAH in patients undergoing RHC is 7%–12%.[5,6]

The treatment algorithm of SSc-PAH has dramatically changed due to the introduction of new therapeutic agents used as monotherapy or in combination.[7] Despite these promising advances, the 3-year survival in the modern era is 56%–75%.[2,3]

The effect of background ethnicity on disease phenotype is well documented in the SSc literature. African American patients are more likely to have diffuse disease, digital ulcers, PH, and a younger disease onset than Caucasians,[8,9] while Chinese had a milder disease compared to Caucasians.[10]

Data published on the Saudi population are scant. Reports describing PAH include a small subset of patients with connective tissue disease-related PAH and even a smaller group of SSc-PAH. The objective of this study is to describe the clinical characteristics, hemodynamics, and mortality of Saudi patients with SSc-PAH and to identify clinical parameters associated with the development of PAH.

Methods

This is a retrospective chart review study of SSc patients conducted in the following multicenter: King Khalid University Hospital, King Faisal Hospital and Research Center, and Prince Sultan Military Medical City in Riyadh, Saudi Arabia. A standardized data collection sheet was used to collect patients' information including clinical and demographic information, respiratory parameters, serology results, treatments received, and outcome. Echocardiographic findings and RHC parameters were recorded. Institutional Research Board approval was obtained from the three centers.

Inclusion criteria

1. Diagnosis of SSc based on the 1980 criteria[11]
2. Follow-up period of ≥12 months
3. Availability of screening echocardiogram for at least once
4. Diagnosis of PAH based on RHC.[4]

Exclusion criteria

1. Overlap with systemic lupus erythematosus
2. Significant ILD by high-resolution computed tomography lungs.

Statistical methods

Descriptive statistics were used to describe demographics, disease characteristics, and hemodynamics. Chi-square test and Student's *t*-test were used to compare between patients with and without PAH for normally distributed variables, while Mann–Whitney U-test and Fisher's exact test were used for data with skewed distribution and the median and the range (minimum to maximum) were reported. Binary logistic regression analysis was performed using variables with statistically significant results, to identify predictors for the development of PAH in SSc patients. Statistical analysis was performed using Statistical Package for the Social Sciences version 22.0 software (SPSS Inc., Chicago, IL, USA).

Results

Fifty-seven SSc patients were identified. Forty SSc-PAH patients were diagnosed by RHC. Of those, 35 (87.5%) were females with a mean age was 45.43 ± 13.48 years and 31 patients (77.5%) of PAH patients presented with functional Class III and IV [Table 1]. The median time from symptoms to first assessment in their respective PH centers was 42.8 ± 115.62 months. Over 50% of patients were on dual combination therapy and 15% were receiving triple combination [Table 2].

The mPAP was 42.97 ± 12.744 mmHg and PVR was 10.4167 ± 5.309 wood unit and cardiac index was 2.43 ± 0.68 [Table 3 and Figure 1].

Ten patients (25%) with SSc-PAH died during follow-up period of 37 ± 7 months; seven patients died from right ventricular failure, two patients from sepsis, and one patient from cardiorespiratory arrest. None of SSc patients without PAH died. This was statistically lower than patients with PAH ($P = 0.02$).

Compared to SSc patients without PAH, those with PAH had lower 6-min walk test (6MWT) (399.588 ± 40.60 vs. 296.138 ± 116.55 m, $P < 0.0001$), higher pro-brain natriuretic peptide (Pro-BNP) (69.833 ± 44.37 vs. 1755.843 ± 2123.43, $P = 0.004$), and more frequent Raynaud's phenomenon (RP) (90% vs. 35%, $P < 0.0001$). There were more patients with limited SSc in the SSc-PAH group than without PAH; however, the difference did not reach statistical significance (65% vs. 41%, $P = 0.096$) [Table 1].

PAH patients were more likely to be positive for anti-ribonucleoprotein (anti-RNP) (25.0% vs. 0%, $P = 0.020$), Sjögren's syndrome-related antigen type B (35% vs. 0%, $P = 0.003$), and lower anti-double-stranded DNA (7.1% vs. 45.5%, $P = 0.004$) [Table 4].

6MWT, Pro-BNP, RP, and diffusing capacity of the lungs for carbon monoxide (DLCO) were included in logistic

Table 1: Demographics and clinical characteristics of the study population

	Without PAH (*n*=17), *n* (%)	PAH (*n*=40), *n* (%)	*P*
Gender			
Male	0	5 (12.5)	0.16
Female	17 (100)	35 (87.5)	
Age (years)	41.76±16.46	45.43±13.48	0.38
BMI (kg/m^2)	24.63±5.45	27.91±6.39	0.07
Raynaud	6 (35)	36 (90)	<0.0001
Duration of Raynaud			
Mean±SD (years)	3.10±1.88	4.06±2.01	0.38
Median (minimum-maximum)	3.0 (1–6)	4.0 (2-8)	
Heart block	0	1 (2.5)	0.70
IHD	0	2 (5)	0.49
HTN	0	1 (2.5)	0.70
Pattern involvement			
Limited	7 (41.2)	26 (65)	0.1
Diffuse	10 (58.8)	14 (35)	
NYHA FC			
I-II	14 (82.4)	9 (22.5)	<0.0001
III-IV	3 (17.6)	31 (77.5)	
Pericardia effusion	0	4 (10)	0.23
Pleural effusion	0	1 (2.5)	0.70
Hb (g/dl)	12.45±1.01	12.06±1.89	0.32
Creatinine (mmol/L)			
Mean±SD	63.18±14.93	68.36±26.50	0.84
Median (minimum-maximum)	62.0 (41.0-88.0)	63.0 (41.0-176.0)	
Pro-BNP			
Mean±SD (pg/ml)	69.83±44.37	1755.84±2123.43	0.004
Median (minimum-maximum)(pg/ml)	54.0 (24.0-151)	1048.0 (20.0-9674)	
DLCO (%)			
Mean±SD	71.22±16.04	57.60±17.62	0.012
Median (minimum-maximum)	70 (37.4-99.6)	60.50 (17.6-84)	
FVC (%)	69.60±20.12	64.04±23.01	0.39
6MWT distance (m)	399.5±40.60	296.14±116.55	<0.0001
SO_2 preexercise (%)	97.80±1.94	96.263±3.29	0.075
SO_2 postexercise (%)	94.41±2.88	90.342±6.66	0.003
Desaturation (%)	3.77±3.11	6.40±6.50	0.11

PAH=Pulmonary arterial hypertension, BMI=Body mass index, SD=Standard deviation, IHD=Ischemic heart disease, HTN=Hypertension, 6MWT=6-min walk test, Hb=Hemoglobin, Pro BNP=Brain natriuretic peptide, DLCO=Diffusing capacity of the lungs for carbon monoxide, SO_2=Oxygen saturation, FVC=Forced vital capacity, NYHA FC=*New York Heart Association functional class*

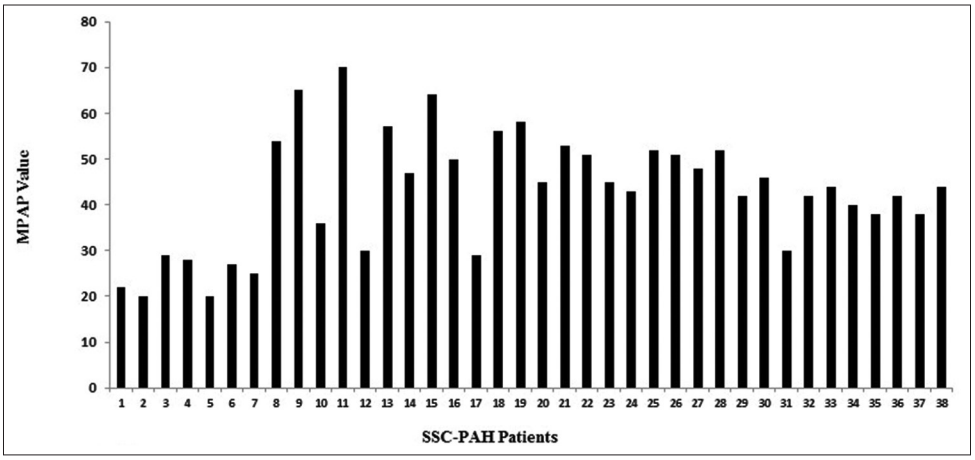

Figure 1: Value of distribution of mean pulmonary artery pressure in patients with systematic sclerosis-associated pulmonary arterial hypertension. SSc-PAH: Systematic sclerosis pulmonary arterial hypertension, MPAP: Mean pulmonary artery pressure

Table 2: Treatment received by the study patients

	Without PAH (*n*=17), *n* (%)	PAH (*n*=40), *n* (%)	*P*
PDE-5	4 (23.5)	35 (87.5)	<0.0001
ERA	2 (11.8)	30 (75)	<0.0001
Prostacycline	0	9 (22.5)	0.03
PDE-5 + ERA + prostacycline	0	6 (15)	0.11
PDE-5 + ERA	1 (5.9)	20 (50)	0.002
PDE-5+ prostacycline	0	2 (5)	0.49
Number of medications			
One	4 (23.5)	12 (30)	0.44
Two	1 (5.8)	22 (55)	0.001
Three	0	6 (15)	0.11
Proton pump inhibitor	15 (88.2)	25 (62.5)	0.05
Nefidipine	4 (23.5)	8 (20)	0.51
Amlodipine	1 (5.9)	2 (5)	0.66
Ranitidine	2 (11.8)	1 (2.5)	0.21
Domperidone	1 (5.9)	14 (35)	0.02
Metoclop	4 (23.5)	2 (5)	0.06
Prednisone	9 (52.9)	24 (60)	0.62
Methotrexate	14 (82.4)	10 (25)	<0.0001
Cyclophiops	15 (88.2)	9 (22.5)	<0.0001
Azathioprine	15 (88.2)	15 (37.5)	<0.0001
Cellcept	15 (88.2)	17 (42.5)	0.001
Penicillamine	15 (88.2)	9 (22.5)	<0.0001

PAH=Pulmonary arterial hypertension, PDE-5=Phosphodiesterase type 5, ERA=Endothelin receptor antagonists

Table 3: Cardiac hemodynamics in systemic sclerosis patients

	Without PAH (*n*=17)	PAH (*n*=40)	*P*
LA diameter (cm)	3.12±0.422	3.09±0.4	0.81
LV diastolic diameter (cm)	4.29±0.46	4.19±0.51	0.14
LV systolic diameter (cm)	2.75±0.44	2.7±0.50	0.18
LV shortening fraction	34.39±14.38	36.83±18.09	0.64
EF (%)	63.89±9.76	62.72±11.49	0.73
SPAP (mmHg)	24.0±4.97	60.58±21.95	0.003
DPAP (mmHg)	10.0±4.16	28.84±9.19	0.002
MPAP (mmHg)	15.75±5.32	42.97±12.74	0.002
PAWP (mmHg)	10.0±4.24	9.95±3.79	0.76
RAP (mmHg)	4.75±2.99	10.5±4.51	0.01
CO (l/min)	5.11±1.61	3.98±1.128	0.12
CI (l/min/m^2)	3.35±1.64	2.43±0.69	0.27
PVR (woods/unit)	1.28±0.65	10.42±5.31	0.003

PAH=Pulmonary arterial hypertension, LA=Left atrium, LV=Left ventricle, EF=Ejection fraction, SPAP=Systolic pulmonary artery pressure, DPAP=Diastolic pulmonary artery pressure, MPAP=Mean pulmonary artery pressure, PAWP=Pulmonary arterial wedge pressure, RAP=Right atrial pressure, CO=Cardiac output, CI=Cardiac index, PVR=Pulmonary vascular resistance

regression analysis and showed that patients with RP had 48.5 times higher risk to develop PAH than patients who do not have RP (odds ratio [OR]: 48.58; confidence interval [CI]: 95% [3.727, 633.104]). Similarly, a shorter 6-min walk distance (6MWD) was associated with the development of PAH (OR: 1.017; CI: 95% [1.005, 1.03]) [Table 5].

Table 4: Serology in patients with systemic sclerosis

	Without PAH (*n*=17), *n* (%)	PAH (*n*=40), *n* (%)	*P*
ANA	17 (100)	37 (92.5)	0.34
ATA	9 (52.9)	20 (50)	0.84
Anti-RNP	0	10 (25)	0.02
Anti-Jo1	0	9 (22.5)	0.03
Anti-DsDNA	1 (5.9)	18 (45.5)	0.004
SSA	3 (17.6)	18 (45.5)	0.05
SSB	0	14 (35)	0.003

PAH=Pulmonary arterial hypertension, ANA=Antinuclear antibody, ATA=Anti-topoisomerase antibodies, Anti-RNP=Anti-ribonucleoprotein, Anti-DsDNA=Anti-double-stranded DNA, Anti-Jo1=Anti-histidyl-tRNA synthetase, SSA=Sjögren's-syndrome-related antigen A, SSB=Sjögren's syndrome type B

Table 5: Logistic regression analysis of variables associated with pulmonary arterial hypertension in patients with systemic sclerosis

Variable	*P*	OR	95% CI for OR	
			Lower	Upper
6MWT	0.007	1.02	1.005	1.03
Raynaud	0.003	48.58	3.73	633.10
Pro BNP	0.197	1.01	0.99	1.03
DLCO	0.69	0.99	0.98	1.01

6MWT=6-min walk test, Pro BNP=Brain natriuretic peptide, DLCO=Diffusing capacity of the lungs for carbon monoxide, OR=Odds ratio, CI=Confidence interval

Discussion

This is the first study reporting the clinical and hemodynamic characteristics and mortality of Saudi SSc-PAH patients. There was female predominance as reported in other populations.[7,13] However, we have found a younger mean age than SSc-PAH Caucasian patients (60.9 years) and patients with idiopathic PAH (IPAH).[9,12,13]

Most of the patients presented late with WHO Functional Class III and IV. This delay in presentation could be related in part to a selection bias, as patients were selected from tertiary care centers that accept referrals from all over the Kingdom of Saudi Arabia possibly resulting in diagnosis delay. This is addition to the vague nature of symptoms related to PH and the absence of systematic screening of PAH in SSc patients despite the presence of validated screening tools for PAH in SSc patients.[6,14] For example, the detect instrument, which incorporates 6MWD and BNP level, has been shown to increase the identification of PAH patients compared to clinical assessment alone.[14-17]

Similar to previous reports, the PAH in our study cohort of SSc-PAH patients were less severe than IPAH with similar functional class.[13] The mPAP pressure was 42.9 ± 12.7 mmHg, and the PVRI was 19.4 ± 7.7 woods unit [Figure 1]. On the other hand, the CI was low (2.4305 ± 0.68 min/m^2). This is consistent with the

findings of Hassoun PM, who reported the hemodynamics of 50 SSc-related PAH of SSc patients and compared them to IPAH.[7] This could be related to myocardial involvement by SSc as detected by echocardiography and magnetic resonance imaging.[17] This may compromise the ability of the right ventricle to adapt to the pressure overload in PAH, possibly due to vascular lesions, fibrosis, myocardial inflammation, and scarring.[18,19]

In our cohort, patients with PAH had more prevalent RP and a higher level of N-T pro-BNP in serum. This is consistent with other reports that identified additional risk factors for the development of SSc-PAH including limited subtype, late age of onset, long-standing disease, reduction in diffusing capacity of carbon monoxide DLCO, and antibodies (e.g., anti-U3 RNP). It also appears that patients who develop SSc later in life are at higher risk of developing PAH.[20,21] The PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in SSc) registry in the US revealed that the 131 SSc patients who developed PAH were older (age >60 years old), predominantly females with limited cutaneous SSc, and a predicted <50% DLCO.[3] We have not detected these differences due to the small sample evaluated.

In this study, patients with SSc-PAH had a higher level of N-T pro-BNP. This is in agreement with the findings of Williams *et al*., who reported a significantly higher N-T pro-BNP level in SSc-PAH compared to SSc patients without PAH. This high level reflects the severity of PAH. Moreover, for every order of magnitude increase, there was a 4-fold increase in the risk of death. This indicates the importance of baseline and serial N-T pro-BNP in the detection and prognosis of SSc-PAH, respectively.[22]

In our cohort, the 6MWT was significantly lower in PAH patients than patients without PAH. Despite the limitation of the 6MWT in SSc patients, such as the lack of data on content validity and inadequate data on reproducibility and sensitivity to change over time, it is still a valuable tool in assessing disease severity and drug response.[23] In addition, exercise-induced hypoxia and lower 6MWT were found to be associated with increased risk for PH in SSc patients.[14,20]

The most common PAH-specific therapy used in SSc-PAH patients was sildenafil followed by bosentan. The use of sildenafil in SSc-PAH was evaluated in *post hoc* subgroup analysis from the sildenafil use in PH super study. The 6MWT, hemodynamics, and functional class improved after 12 weeks of sildenafil, 20 mg, three times per day. All our patients who were on sildenafil were tolerant to a similar dose, as there is no convincing evidence that higher doses significantly improve hemodynamics, rather it may increase side effects.[24]

Bosentan was the most commonly prescribed era in our patients. It is the first drug of it class approved by the Saudi Food and Drug Administration and is available in all PAH centers in Saudi Arabia. Compared to sildenafil, its clinical effect was inconspicuous when used as monotherapy.[25]

Most of our patients were receiving combination therapy, which was mostly sildenafil and bosentan. This probably reflects the severity of the disease, late presentation, suboptimal response to monotherapy, and is in accordance to the European Respiratory Society guidelines.[4] Recent reports suggest that adding sildenafil to patients with SSc-PAH who failed bosentan monotherapy resulted in preventing the clinical deterioration of these patients.[26]

The combination of inhaled prostacyclin (iloprost) and sildenafil was rarely used in our cohort of SSc-PAH patients. This could be due to the clinicians' choice or the unavailability of the inhaled prostacyclin. This combination was studied in various groups of PAH patients and has shown a favorable response.[27,28]

Another challenge for using inhaled iloprost is the need for repeated doses of (up to 9 times) which may have affected drug adherence.

There was no significant difference between the groups in regard of the use of calcium channel blockers. This is due to its prevalent use in RP. Studies have shown that most of SSc-PAH fail to show a vasodilator response to acute testing and current guidelines do not advocate vasodilator challenge during RHC.[29] Therefore, it is not routinely performed in when assessing SSc-PAH patients.

Patients without PAH received more immunosuppressive therapy than those with PAH. This might be due to the fact that significant ILD was more observed in the non-PAH group due to our inclusion criteria.

The short-term mortality in this study was 25%. It is well known that PAH in SSc patients significantly worsens their survival, and after ILD, is the leading cause of death in these patients.

The mortality rate in our study is lower than that reported in the literature (56%–75%).[1,2,7]

We think that this could be related to the younger age of our study patients that allows better right ventricle and pulmonary vascular adaptation to high pulmonary artery pressure.[3,7]

Limitations of our study include the retrospective design, small sample size, and selection bias. One

important variable that was not available for patients was the anticentromere antibody testing (ELISA) which is an important component in the detect tool. We also found that rheumatologists do not routinely perform outcome measures such as the modified Rodnan skin score or scleroderma health assessment questionnaire. Finally, we could not calculate the incidence of PAH overtime as many of the SSc were referred to the three centers included at the time, PAH was suspected.

Conclusion

This is the first study reporting the clinical and hemodynamic characteristics of Saudi patients with RHC-proven SSc-PAH. There is a clear delay in the diagnosis of PAH and late presentation with low functional class, thus requiring combination therapy. There is an urgent need to implement validated screening programs for the early detection of SSc-PH. The mortality rate in our cohort is lower than reported elsewhere which could partially be explained by the younger age. Larger prospective studies are needed to confirm these findings.

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Conflicts of interest

There are no conflicts of interest.

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