CLINICAL AND PARACLINICAL CHARACTERISTICS OF PULMONARY ARTERIAL HYPERTENSION IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Systemic sclerosis - related pulmonary arterial hypertension (SSc - PAH) is the leading cause of death in scleroderma patients. This study aimed to describe the clinical and paraclinical characteristics of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) and to evaluate the correlation between cardiac biomarkers and pulmonary hypertension. A cross - sectional study was conducted on 19 in - patients with SSc - PAH at the Allergy and Clinical Immunology Centre, Bach Mai Hospital between February 2018 and December 2018. PAH was diagnosed based on transthoracic echocardiography (TTE). The average age at PAH diagnosis was 47.4 ± 14 years. The median duration of SSc at PAH confirmation was 1.25 years. 68.4% of patients were in World Health Organisation Functional Classification for Pulmonary Hypertension Class I and II. The average estimated systolic pulmonary arterial pressure (sPAP) on TTE was 50.8 ± 14.3 mmHg (median 45, range 37 - 85). There was a strong positive correlation between serum NT - proBNP levels and sPAP, with correlation coefficient r = 0.689 (p = 0.002). Cardiac troponin T (cTnT) levels correlated positively with sPAP, with r = 0.522; however, the correlation was not statistically significant (p = 0.288). Scleroderma patients should be undergone TTE early to detect PAH. NT - proBNP should be combined with echocardiography to screen PAH, whereas further studies on cTnT are needed.

Keywords: pulmonary hypertension, pulmonary arterial hypertension, systemic sclerosis

I. INTRODUCTION

Systemic sclerosis (SSc) is a disease characterised by the progressive fibrosis of the skin and the internal organs, hence the risk of premature organ failure and death.[1] Among all of the organ involvement in the context of scleroderma, the prevalence of systemic sclerosis - associated pulmonary arterial hypertension (SSc - PAH) is estimated to be around 12%.[2] More importantly, systemic sclerosis - associated pulmonary arterial hypertension is the leading cause of mortality, with close to 30% of scleroderma - related deaths being due to pulmonary arterial hypertension (PAH).[3] Establishing the presence of SSc - PAH at an early stage is a priority in order to improve outcomes. Besides, emerging evidence suggests that cardiac biomarkers help screen pulmonary arterial hypertension in patients with systemic sclerosis.[4,5]

In Vietnam, however, there are relatively few evidence - based descriptive studies on pulmonary arterial hypertension in patients with systemic sclerosis and on biomarkers for screening pulmonary hypertension. Therefore, we have conducted this study with the following aims:

To describe the clinical and paraclinical characteristics of pulmonary arterial hypertension in patients with systemic sclerosis.

To evaluate the correlation between cardiac biomarkers and pulmonary hypertension.

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Received: 25/12/2019
Accepted: 14/02/2020

II. METHODS

1. Subject

The study was designed as a cross - sectional investigation, in which patients were sampled by a convenience sampling scheme. The study setting was the Allergy and Clinical Immunology Centre in Bach Mai Hospital, Vietnam. Participants were recruited between February 2018 and December 2018.

Patients aged over 18 years old with a diagnosis of SSc - PAH were eligible for inclusion. The definitive diagnosis of SSc was based on the 2013 American College of Rheumatism/ European League Against Rheumatism classification criteria for systemic sclerosis, while the 2009 European Society of Cardiology/ European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension were applied to confirming pulmonary arterial hypertension. Patients were excluded from the study if they had had pulmonary arterial hypertension confirmed by right heart catheterisation (RHC) or transthoracic echocardiography (TTE) before the diagnosis of SSc, or had previous evidence of clinically relevant left heart disease, or had overlap syndromes or mixed connective tissue disease with SSc features. The specific procedure is summarised in figure 1.

All patients meeting with inclusion criteria were invited to participate in the study. Upon giving the informed consent, data collection was conducted by using a structured questionnaire. The four groups of variables were (A) demographic data (i.e., age, sex), date of initial physician diagnosis of scleroderma and date of first echocardiogram with evidence of PAH, (B) clinical examination results (e.g. exertional dyspnoea, classification of dyspnoea in patients with pulmonary hypertension, Raynaud's phenomenon, telangiectasia), (C) investigations: transthoracic echocardiography (e.g. systolic pulmonary arterial pressure, pericardial effusion), electrocardiogram (e.g. right axis deviation, right ventricular hypertrophy), chest radiograph and thoracic computed tomography/ high resolution computed tomography, and (D) serum tests (e.g. cardiac troponin T levels and plasma N - terminal pro - brain natriuretic peptide (NT - proBNP) levels). The clinical assessment of stages of pulmonary hypertension (PH) was based on the World Health Organisation (WHO) Classification of Functional Status of Patients with PH. In the present study, we defined the age of SSc diagnosis by using the date of initial physician diagnosis of scleroderma, and the duration of disease at PAH confirmation using the period from the date of SSc diagnosis to the date of the first echocardiogram with evidence of PAH.

2. Transthoracic Echocardiography (TTE) protocol

Transthoracic echocardiographic studies were performed using a Vivid 7 machine (3.5 MHz), GE Vingmed Ultrasound at Vietnam National Heart Institute (Bach Mai Hospital), Hanoi, Vietnam. Recorded variables were estimated systolic pulmonary arterial pressure, left ventricular ejection fraction (LVEF) and pericardial effusion. The estimation of systolic pulmonary arterial pressure (sPAP) on echocardiography is as follows:

- Simplified Bernoulli Equation:

$\Delta P = 4 \times V^2$

ΔP: peak pressure gradient of tricuspid regurgitation (mmHg)

V: tricuspid regurgitation velocity (m/s)

- Estimation of the pulmonary arterial systolic pressure (sPAP):

sPAP (mmHg) = ΔP+estimated right atrial pressure (mmHg)

Right atrial pressure can be estimated based on the diameter and respiratory variation of the inferior vena cava although often a fixed value of 5 or 10 mmHg is assumed.[6]

3. Cardiac Biomarkers

Blood samples were used for analysing cardiac biomarkers at the Biochemistry Department of Bach Mai Hospital. The results were compared with the reference range provided by the Bach Mai Hospital.

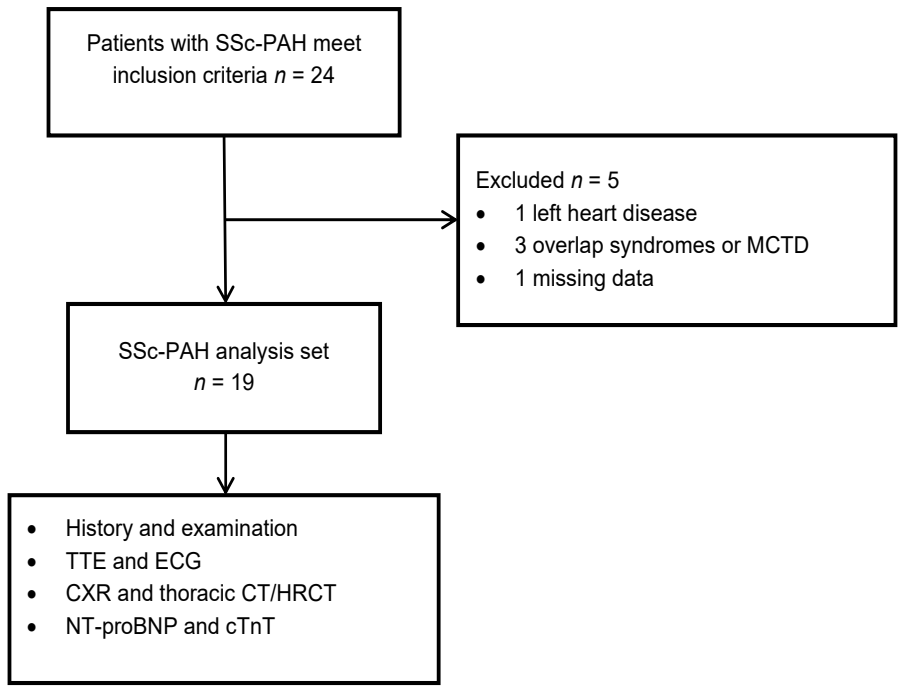

Figure 1. Patient selection and data collection. SSc - PAH, systemic sclerosis - related pulmonary arterial hypertension; MCTD, mixed connective tissue disease; TTE, transthoracic echocardiography; ECG, electrocardiogram; CXR, chest radiograph; CT/HRCT, computed tomography/high resolution computed tomography; NT - proBNP, N - terminal pro - brain natriuretic peptide; cTnT, cardiac troponin T.

3. Statistics

Statistical analyses were performed by SPSS version 20.0. Data were presented as either mean ± SD or median (range) for continuous variables and the number (%) for categorical variables. For correlations between numeric variables, the Spearman correlation analysis method was applied. The two - tailed t - test for the Spearman method was used to determine the significance level. P values less than 0.05 were considered statistically significant. Linear regression analysis was then used to determine the correlation between plasma BNP levels, cardiac troponin T levels and systolic PAP.

4. Ethical issues

We protected the confidential information of participants. The study did not harm patients. We fully informed patients about all aspects of the study and participants had the right to refuse to participate in the study at any time. All patients gave informed consent and they could withdraw from the study at any time without giving reasons.

III. RESULTS

1. Demographics

Our study recruited 19 patients with SSc - PAH; among them, 73.7% was female (female to male ratio of 2.8:1). The average age (SD) at diagnosis of SSc was 44.7 (13.1), while the mean age (SD) at confirmation of PAH was 47.4 (14). The median value of SSc duration at PAH diagnosis was 1.25 years (range 0 - 11).

2. Clinical and paraclinical characteristics

Clinical manifestations

Table 1. Cardiopulmonary and microvascular features

Variables		n (observed)	N (total)	%
Exertional dyspnoea		15	19	78.9
Chest pain		10	19	52.6
Dry cough		5	19	26.3
Raynaud's phenomenon		15	19	78.9
Telangiectasia		5	19	26.3
Fingertip lesions	Digital ulcer	8	19	42.1
	Pitting scar	14	19	73.7
Digital necrosis		5	19	26.3
Digital amputation		1	19	5.3
WHO Functional Classification for PH			19	
Class I		5		26.3
Class II		8		42.1
Class III		6		31.6
Class IV		0		0

Paraclinical characteristics

The most frequent feature of the cardiopulmonary system was exertional dyspnoea (78.9%). Raynaud's phenomenon (RP) was the most common microvascular feature, at 78.9%.

Table 2. Paraclinical characteristics

Variables		n (observed)	N (total)	%
Electrocardiography				
Right axis deviation present		3	18	16.7
Right ventricular hypertrophy present		2	18	11.1
Diagnostic imaging techniques				
X - ray	Enlarged central pulmonary artery	3	17	17.6
	Cardiothoracic ratio > 0.5	8	17	47.1

Variables		n (observed)	N (total)	%
CT or HRCT	Honeycombing	2	7	28.6
	Ground glass opacity	3	7	42.9
Echocardiography (N=19)				
Pericardial effusion present		7	19	36.8
		Median (range)	Mean (SD)	
sPAP (mmHg)		45 (37 - 85)	50.8 (14.3)	
LVEF (%)		67 (57 - 80)	67 (7)	
Cardiac Biomarkers		NT - proBNP(pmol/L)	cTroponin T(ng/L)	
Median (range)		45.9 (3.59 - 3795)	27.5 (20 - 147.9)	
Mean (SD)		322.2 (907.7)	51.9 (50.1)	
The proportion of patients having biomarker higher than normal		11/17	6/6	

The largest proportion of lung abnormalities went on ground glass opacity (42.9%), which was 14.3% more than the figure for honeycombing. All participants had left ventricular ejection fraction within the normal range. Out of 19 patients, 7 patients had mild pericardial effusion on echocardiography. Whereas 11/17 (64.7%) of patients had serum NT - proBNP level higher than the reference range, 6/6 (100%) of patients had elevated troponin T levels.

Correlation between cardiac biomarkers and estimated sPAP on TTE

Correlation of serum NT - proBNP levels with sPAP (N = 17)

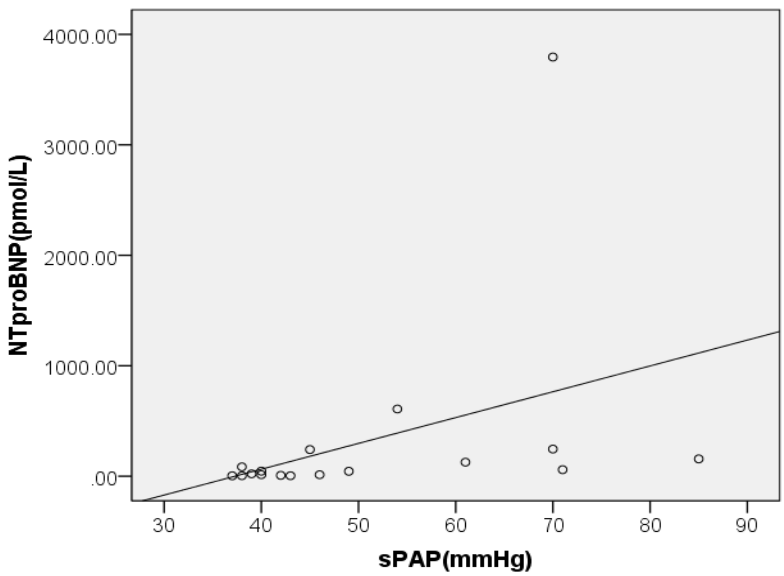

Figure 2. Correlation between serum NT - proBNP values and sPAP on TTE

Correlation of cardiac troponin T levels with sPAP estimated on TTE (N = 6)

There was a large positive correlation between cardiac troponin T levels and sPAP, with correlation coefficient r = 0.522. However, this correlation was not statistically significant (p = 0.288).

We found that there was a strong positive correlation between serum NT - proBNP levels and

sPAP (Figure 2), with correlation coefficient r = 0.689 (p = 0.002 < 0.01). Notably, one patient with significant PAH (severely elevated sPAP of 70 mmHg on TTE) had a plasma NT - proBNP value of 3795 pmol/L.

V. DISCUSSION

Establishing the presence of SSc - PAH at an early stage is essential to improving the outcomes. Our present study addressed this issue by an evidence - based description and possible biomarkers for predicting pulmonary hypertension.

Our study showed that the average age at PAH diagnosis was 47.4 ± 14 years, while the mean age at PAH confirmation in the study by Mathai et al. was 60 ± 12.[7] This difference may be partly because our study sample is smaller than that of Mathai et al. (n = 59). The median SSc duration at PAH diagnosis in our study was 1.25 years, which is lower than that in the study by Mathai and colleagues, at 4 years.[7] This is probably because we utilised transthoracic Doppler echocardiography (DE) as a diagnostic tool, while the cohort of Mathai and associates used right heart catheterisation. As the accuracy of DE was in part influenced by poor Doppler imaging of the tricuspid regurgitation jet or bias in the estimation of right atrial pressure, the use of DE could lead to diagnoses of PAH earlier than expected.

Our study is agreeable with the study by Rich et al.,[8] in which exertional dyspnoea was the most common cardiopulmonary feature. According to the WHO Functional Classification for PH, our study confirmed that the majority of patients were in Class I and II rather than in Class III, and no patients were in Class IV. This is agreeable with the DETECT study of Coghlan et al.[9] and the reason could be that most of the participants participating in our study might have had a short duration of PAH at recruitment. We found that Raynaud's phenomenon was the most frequent microvascular feature, comparable with prior studies.[10] Our study indicated that a minority of patients had right axis deviation, comparable with a previous study by Coghlan et al. (13.3%),[9] but lower than the findings of Rich and associates (79%).[8] The presence of right ventricular hypertrophy on ECG in our study was less common than in the study by Rich et al. (87%).[8] This is probably because most of our patients were in the early stages of PH (WHO Class I, II), whereas the majority of patients in the study by Rich et al. were more symptomatic (WHO Class III and IV). This suggests that abnormal ECG is more likely in advanced rather than early stages of PH. Our study showed that a minority of patients with SSc - PAH had enlarged central pulmonary artery on frontal chest radiograph, significantly lower than the reported result of Rich et al.[8] This is partly because, in the study by Rich et al., the majority of patients with primary PH had moderate or severe PH (WHO Class III or IV), whereas most of SSc - PAH patients in our study had no or mild symptoms of PH (WHO Class I or II). Ground glass opacity and honeycombing, which are suggestive findings of ILD, could be the underlying cause of pulmonary hypertension as well as dyspnoea in scleroderma patients in our study. This is confirmed by the study of Young et al.,[11] in which 31.2% of patients with systemic sclerosis - associated interstitial lung disease had co - existing PH. Our study indicated that the presence of pericardial effusion was relatively frequent among patients with SSc - PAH, which is consistent with the study by Zhao et al.[10]

NT - proBNP is a cardiac biomarker mainly secreted from the ventricular myocardium. We found that there was a significantly positive correlation between NT - proBNP level and estimated sPAP on TTE, which is consistent

with previous studies.[5] A prior study showed that serum NT - proBNP levels secreted concomitantly with BNP were elevated owing to the supportive role of BNP in modulating the pulmonary hypertensive response to chronic hypoxia.[12] Besides, Nagaya et al.,[13] in a longitudinal study, indicated that plasma BNP levels increase in proportion to the extent of RV dysfunction in patients with chronic PH. Taken together, these results suggest that serum NT - proBNP level is probably a helpful biomarker of systemic sclerosis - related pulmonary arterial hypertension. Cardiac Troponin T is the preferred biomarker of myocardial cell damage. Our study showed that cardiac troponin T levels correlated positively with sPAP; however, this correlation was not statistically significant, which was probably due to a small study sample (n = 6). This is differing from a previous study by Avouac et al.,[4] in which high - sensitivity cardiac Troponin T is a possible biomarker for the detection of pre - capillary PH in conjunction with serum NT - proBNP. Taken together, these results suggest that it would be premature to formally recommend cardiac troponin T as a biomarker for systemic sclerosis - related pulmonary arterial hypertension.

The limitation of our study was that echocardiography was not uniformly obtained in all scleroderma patients attending the Centre, meaning that we could have missed patients with no or mild symptoms of PAH.

VI. CONCLUSION

The median duration of systemic sclerosis at diagnosis of pulmonary arterial hypertension was 1.25 years (range 0 - 11). 68.4% of patients were in the early clinical stages of PH (WHO Class I and II). These results suggest that scleroderma patients should be undergone transthoracic echocardiography early to detect pulmonary arterial hypertension.

There was a strong positive correlation between NT - proBNP levels and estimated sPAP on TTE, which was statistically significant. NT - proBNP should be used to screen pulmonary arterial hypertension in combination with transthoracic echocardiography. Cardiac troponin T levels positively correlated with sPAP; however, this relationship was not statistically significant. Further studies are needed to determine whether cardiac Troponin T is of benefit.

REFERENCE

1.Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med.* 2004;140(1):37 - 50.

2.Morrisroe K, Stevens W, Sahhar J, Rabusa C, Nikpour M, Proudman S, et al. Epidemiology and disease characteristics of systemic sclerosis - related pulmonary arterial hypertension: results from a real - life screening programme. *Arthritis Res Ther.* 2017;19(1):42.

3.Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972 - 2002. *Ann Rheum Dis.* 2007;66(7):940 - 944.

4.Avouac J, Meune C, Chenevier - Gobeaux C, Borderie D, Lefevre G, Kahan A, et al. Cardiac Biomarkers in Systemic Sclerosis: Contribution of High - Sensitivity Cardiac Troponin in Addition to N - Terminal Pro - Brain Natriuretic Peptide. *Arthritis Care & Research*. 2015;67(7):1022 - 1030.

5.Thakkar V, Stevens WM, Prior D, Moore OA, Byron J, Liew D, et al. N - terminal pro - brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case - control study. *Arthritis Res Ther.* 2012;14(3):R143.

6.Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary

hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30(20):2493 - 2537.

7.Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: Impact of interstitial lung disease. *Arthritis & Rheumatism*. 2009;60(2):569 - 577.

8.Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med.* 1987;107(2):216 - 223.

9.Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, et al. Evidence - based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis.* 2014;73(7):1340 - 1349.

10.Zhao J, Wang Q, Liu Y, Tian Z, Guo X, Wang H, et al. Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: A cohort study in China. *Int J Cardiol.* 2017;236:432 - 437.

11.Young A, Vummidi D, Visovatti S, Homer K, Wilhalme H, White ES, et al. Prevalence, Treatment and Outcomes of Coexistent Pulmonary Hypertension and Interstitial Lung Disease in Systemic Sclerosis. *Arthritis Rheumatol.* 2019.

12.Hill NS, Klinger JR, Warburton RR, Pietras L, Wrenn DS. Brain natriuretic peptide: possible role in the modulation of hypoxic pulmonary hypertension. *The American journal of physiology*. 1994;266(3 Pt 1):L308 - 315.

13.Nagaya N, Nishikimi T, Okano Y, Uematsu M, Satoh T, Kyotani S, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. *J Am Coll Cardiol.* 1998;31(1):202 - 208.