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Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: A cohort study in China

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ABSTRACT

Objective: Pulmonary arterial hypertension (PAH) is a major cause of death in connective tissue disease patients. This study investigated the clinical characteristics and survival of CTD-PAH in Chinese patients.
Methods: This cohort study enrolled 190 consecutive PAH patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), or primary Sjögren's syndrome (pSS) who visited our referral center between May 2006 and December 2014. Baseline demographics, clinical features, laboratory results, and hemodynamic assessments were analyzed. Cox proportional hazards regression analysis was used to identify independent factors associated with increased risk of mortality.
Results: The PAH patients were more likely to have SLE (58.4%) as the underlying CTD than SSc (26.3%) or pSS (15.3%). Mean age was 37.8 ± 10.4 years, and patients with SLE were youngest at the time of PAH diagnosis. The most prevalent autoantibody was anti-U1RNP antibody (55.8%). The three groups did not differ significantly regarding World Health Organization functional class or hemodynamic results. The overall 1-, 3-, and 5-year survival rates were 87.1%, 79.1%, and 62.9%, respectively. The 3-year survival rate of 81.3% for those with SLE-PAH was significantly better than that for patients with SSc-PAH (63.6%, $P < 0.05$). Independent predictors of mortality were 6-minute walk distance (6MWD) ≤380 m (HR 3.222, 95% CI 1.485–6.987, $P = 0.003$) and underlying CTD (HR 1.684; 95CI% 1.082–2.622, $P = 0.021$).
Conclusion: Independent predictors of mortality for CTD-PAH were 6MWD <380 m and SSc as the underlying CTD. Increased awareness of pSS-PAH is needed because of its worse prognosis compared to SLE-PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a severe complication of connective tissue diseases (CTDs) and one of the leading causes of morbidity and mortality for patients with those diseases [1,2]. Among the CTDs, PAH is associated most often with systemic sclerosis (SSc), with a reported prevalence of 10%–12% based on right heart catheterization (RHC) in cohort studies conducted in the US [3] and Europe [4,5]. However, in cohort studies conducted in Japan [6], Korea [7], and China [8], PAH is most commonly associated with systemic lupus erythematosus (SLE), followed by primary Sjögren's syndrome (pSS) and mixed connective tissue disease (MCTD). These differences suggest that the characteristics and prognosis of Asian patients with CTD-PAH may differ from those of patients in Western countries.

Outcomes are generally poor for patients with CTD-PAH and are even worse than patients with idiopathic PAH [9–11]. Several prior cohort studies compared the clinical characteristics and prognosis of patients with PAH associated with various CTDs [3,12–14]. However, most of the data are from studies performed in Western countries, and studies that evaluated Asian patients [6,8] are limited by small sample sizes. For now, there is still no clear explanation for the difference in survival between SSc-, SLE- and pSS-associated PAH.

Our team at Peking Union Medical College Hospital (PUMCH) established the CTD-PAH cohort in2006. In previous studies, we estimated the prevalence of PAH in patients with SLE [15]; identified and confirmed several risk factors for CTD-PAH, such as pericardial effusion and antibodies against U1 small nuclear ribonucleoprotein (U1RNP) [16,17]; reviewed survival in patients with SLE-associated PAH [18]; identified a potential biomarker for PAH in SLE [19]; and provided evidence for the curability of early SLE-associated PAH [20]. The present

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study examined baseline clinical characteristics and hemodynamic findings in a well-characterized population of patients with PAH associated with one of three major CTDs and evaluated whether differences in these factors might affect survival.

2. Methods

2.1. Study population

Between May 2006 and December 2014, all patients with PAH associated with SLE, SSc, or pSS who were followed up at the Department of Rheumatology, PUMCH were enrolled in this study. This study was approved by Medical Ethics Committee of PUMCH and compliant with ethics committee requirements. All patients provided written informed consent before enrollment.

The type of CTD was defined at the time of enrollment as follows. SLE was diagnosed according to the American College of Rheumatology (ACR) criteria revised in 1997 [21]; limited or diffuse cutaneous SSc was diagnosed according to the American Rheumatism Association criteria established in1980 and confirmed by ACR/European League Against Rheumatism (EULAR) classification criteria developed in 2013 [22]; and pSS was diagnosed according to the revised criteria proposed by the American-European Consensus Group in 2002 [23]. Patients with overlap syndrome were excluded from the study.

The 2015 European Society of Cardiology/European Respiratory Society guidelines define PAH as mean pulmonary artery pressure ≥25 mm Hg at rest, pulmonary artery wedge pressure ≤15 mm Hg, and pulmonary vascular resistance (PVR) >3 Wood units, as assessed by RHC [24]. Exclusion criteria were evidence of pulmonary venous hypertension (pulmonary capillary wedge pressure >15 mm Hg), chronic thromboembolic disease, or significant interstitial lung disease (ILD) based on the results of pulmonary function tests and chest high-resolution computed tomography (HRCT). Patients were excluded if total lung capacity (TLC) was <60% of predicted and were included if TLC was >70% of predicted. Patients with TLC between 60% and 70% of predicted were included if the HRCT scan showed only minimal interstitial fibrosis. Chronic thromboembolic disease was excluded based on the results of ventilation and perfusion scanning, contrast-enhanced CT, and if necessary, pulmonary angiography.

2.2. Data collection

A standard evaluation chart was developed to collect demographic data, CTD classification criteria, clinical characteristics, treatments, and results of laboratory tests, which included complete blood counts and levels of hepatic function enzymes, creatinine, complements, and N-terminal pro-brain natriuretic peptide (NT-proBNP). On the same day blood was collected, patients underwent the baseline 6-minute walk distance (6MWD) test, and the World Health Organization (WHO) functional class was determined.

HRCT scans and pulmonary functional tests were regularly performed as part of routine screening to evaluate ILD. Pulmonary function tests including forced vital capacity (FVC), TLC, and diffusing capacity for carbon monoxide (DLCO) were performed using standard methods.

At the time of enrollment, transthoracic echocardiography was performed according to the recommendations of the American Society of Echocardiography by experienced cardiologists who were blinded to the study protocol. For all patients, RHC was performed at baseline using standard methods.

Glucocorticoids and immunosuppressants were administered based on the underlying CTD. If necessary, basic treatments for PAH (e.g., diuretics, digoxin, oxygen, and anticoagulant therapy) were given. PAH-specific therapies included endothelial receptor antagonists (ERAs), phosphodiesterase type5 inhibitors, and prostacyclin derivatives. These treatments were given at the clinician's discretion according to current guidelines and based on their availability in China and the patient's ability to pay.

2.3. Follow-up

All patients were followed up in our rheumatology clinic every 3 to 6 months, and RHC was repeated if necessary. Cause of death was determined by direct contact with the attending clinician or a witness account from a family member. Survival was determined as the interval between the first cardiac catheterization and the recorded date of death or May 15, 2015 (censoring date). No patient was lost to follow-up.

2.4. Statistical analyses

Continuous variables were reported as mean and standard deviation (SD) and compared using Student's *t*-test. Categorical variables were reported as number and percentage (%) and compared using the chi-square test. Survival was estimated using Kaplan–Meier analysis and compared between groups using the log-rank test. Because cause of death could not always be confidently ascribed, all-cause mortality was analyzed. The primary end-point was all-cause death;1-, 3-, and 5-year survival rates were also assessed.

Univariate and forward stepwise multivariate Cox proportional regression analyses were performed to identify independent predictors of mortality. The potential predictive factors investigated were age, gender, underlying CTD type, disease duration, NT-proBNP, WHO functional class, 6MWD, mean PAP (mPAP), PVR, cardiac index, pericardial effusion, FVC % predicted, DLCO % predicted, autoantibodies, and treatment (PAH-specific therapies, glucocorticoids, and immunosuppressants).

Data were analyzed using IBM SPSS Statistics Version 22.0 (Chicago, IL, USA). A two-tailed *P*-value less than 0.05 was considered significant.

3. Results

3.1. Study population

A total of 190 consecutive PAH patients who met all inclusion criteria were enrolled in the study. Baseline demographics, clinical characteristics, and treatment regimens of all patients are shown in Table 1. Mean age was 37.8 ± 10.4 years, and 95.8% of the patients were female. The mean duration of CTD was 84.4 ± 79.3 months. SLE was the most common underlying CTD (58.4%), followed by SSc (26.3%), and pSS (15.3%). Raynaud phenomenon was diagnosed in 133 (70.0%) patients, and anti-U1RNP antibodies were detected in 106 (55.8%) patients. Based on HRCT findings, 37.4% of patients had evidence of ILD, but for all of these patients, disease extent was minimal on imaging, and ventilatory function was normal or only slightly impaired (FVC ≥ 70%).

At the time of PAH diagnosis, 100 (52.6%) patients were classified as WHO functional class III or IV, and mean 6MWD was 412 ± 92 m. Hemodynamic assessments showed an mPAP of 46.2 ± 10.4 mm Hg and cardiac index of 2.64 ± 0.78 L/min/m^2.

Table 1
Baseline demographic and clinical characteristics of survivors and non-survivors with pulmonary arterial hypertension associated with connective tissue disease (CTD).

	Total	Survivors	Non-survivors	*P*-value
Patients, n	190	149	41	
Female, n (%)	182(95.8)	143(96.0)	39(95.1)	0.683
Age, year, mean ± SD	37.8 ± 10.4	36.9 ± 10.3	41.3 ± 9.8	**0.016**
BMI, kg/m^2, mean ± SD	21.6 ± 3.7	21.6 ± 3.5	21.8 ± 4.1	0.751
Times since onset of CTD, months	84.4 ± 79.3	78.0 ± 72.8	107.7 ± 96.8	**0.034**
Time since onset of PAH, months	22.5 ± 27.9	23.0 ± 29.3	21.0 ± 22.3	0.685
Underlying CTD				
SLE, n (%)	111(58.4)	97(87.4)	14(12.6)	<**0.001**
SSc, n (%)	50(26.3)	30(60.0)	20(40.0)	
pSS, n (%)	29(15.3)	22(75.9)	7(24.1)	
Time since onset of PAH, months	22.5 ± 27.9	23.0 ± 29.3	21.0 ± 22.3	0.685
Mild interstitial lung disease, n (%)[a]	71(37.4)	48(32.2)	23(56.1)	**0.005**
Raynaud phenomenon, n (%)	133(70.0)	101(67.8)	32(78.0)	0.204
Anti-U1RNP, n (%)	106(55.8)	87(58.4)	19(46.3)	0.169
WHO functional class, n (%)				
I–II, n (%)	90(47.4)	76(51.0)	14(34.1)	0.056
III–IV, n (%)	100(52.6)	73(49.0)	27(65.9)	
6MWD, m, mean ± SD	412 ± 92	427 ± 86	354 ± 93	<**0.001**
mPAP, mm Hg	46.2 ± 10.4	45.6 ± 11.3	48.5 ± 11.3	0.156
Cardiac index, L/min/m^2	2.64 ± 0.78	2.71 ± 0.74	2.40 ± 0.88	**0.045**
PVR, Wood units	10.42 ± 9.40	9.93 ± 4.59	12.26 ± 6.50	**0.043**
Glucocorticoids, n (%)	185(97.4)	145(97.3)	40(97.6)	0.931
Immunosuppressants, n (%)	175(92.1)	143(96.0)	32(78.0)	<**0.001**
Use of medications for PAH, n (%)				
None, n(%)	63(33.2)	51(34.2)	12(29.3)	0.859
ERAs, n(%)	47(24.7)	35(23.5)	12(29.3)	
PDE5 inhibitors, n (%)	53(27.9)	43(28.9)	10(24.4)	
ERAs + PDE5 inhibitors, n (%)	18(9.5)	13(8.7)	5(12.2)	
Other, n (%)[b]	9(4.7)	7(4.7)	2(4.9)	

Bold value indicate significance at $p < 0.05$.
Abbreviations: 6MWD = 6-minute walk distance, BMI = body mass index, ERAs = endothelin receptor antagonists, PDE5 = phosphodiesterase type 5, pSS = primary Sjögren's syndrome, PVR = pulmonary vascular resistance, SLE = systemic lupus erythematosus, SSc = systemic sclerosis, WHO = World Health Organization.
[a] Mild interstitial lung disease indicates patients with TLC between 60% and 70% of predicted were included and the HRCT scan showed only minimal interstitial fibrosis.
[b] Other medications included inhaled iloprost, subcutaneous treprostinil, and selexipag.

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