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Original Article

Characteristics of connective tissue disease-associated pulmonary arterial hypertension: a retrospective cohort study

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Abstract: *Background and aim:* Connective tissue diseases (CTD) often presents with pulmonary arterial hypertension (PAH). This study aimed to evaluate the clinical characteristics of patients with CTD-associated PAH (CTD-PAH). *Methods:* A retrospective cohort study was conducted at the PAH center in the Western China. Fifty-four consecutive adult patients with a diagnosis of CTD-PAH confirmed by right heart catheterization during the previous 3 years were enrolled. Patients' baseline characteristics were evaluated and log-rank test was applied to determine the predictors of all-cause mortality. *Results:* Fifty-four patients with CTD-PAH were included and followed for 46 months, of which 48.1% experienced pericardial effusion. Although univariate Cox regression analysis suggested that poor WHO-FCS (III and IV), lower cardiac index (<2.5 L/min/m^2) and the presence of pericardial effusion at baseline were significantly associated with all-cause death, pericardial effusion was the only independent predictor of mortality (HR=3.74, 95% CI=1.48-10.8, p=0.03). Moreover, the Log-rank tests indicated that patients with SLE-PAH had worse survival rates than those with PAH associated with other CTDs (p=0.001); while CTD patients with interstitial lung diseases (ILD) associated with PAH had worse survival than CTD-PAH patients without ILD. *Conclusions:* CTD-PAH is a severe clinical syndrome associated with high mortality. In these patients, pericardial effusion was an independent predictor of mortality. Patients with SLE-PAH or ILD also had poor clinical outcomes.

Keywords: Connective tissue diseases, pulmonary arterial hypertension

Introduction

Pulmonary arterial hypertension (PAH), often presenting with or secondary to connective tissue diseases (CTD), is severe clinical syndrome associated with increased morbidity and mortality [1]. Indeed, previous studies conducted in western countries have demonstrated that the mortality rate of patients with PAH-CTD is as high as 10% or 15% within the year following diagnosis [2]. Therefore, early identification of patients with CTDs for those who are vulnerable to PAH may aid the treatment and prevention of CTD-PAH. Strategies for the early detection of patients at an elevated risk of CTD-PAH have not been well developed, and the most commonly applied strategies for the identification of CTD patients with PAH are currently transthoracic echocardiography (TTE), pulmonary function tests, and measurement of N-terminal pro-B type natriuretic peptide (NT-ProBNP) [3]. However, few reports have evaluated the predictive efficacy of these parameters for CTD-PAH, and most of the previous studies primarily focus on patients from western countries [2]. Moreover, the mortality risk for patients with different CTDs complicated with PAH may differ. Indeed, accumulating evidence suggests that the mortality of patients with CTD-PAH remains high. For example, the prevalence of CTD in patients with SSc was reported to range from 4.9% to 38% (mean, 16%), varying with the characteristics of the cohort [2]. A previous study focusing on Chinese patients with CTD indicated that systemic lupus erythematosus (SLE) is the most common underlying disease contributing to CTD-PAH in China [2]. Further studies are required to characterize predictors of survivals for patients with CTDs complicated with PAH, particularly in Asian patients. There-

fore, this retrospective cohort study of patients with CTD-PAH at the PAH center in the Western of China was designed. In this study, we aimed to analyze the baseline characteristics of these patients with different CTD and to identify predictors of their morality. Our study may provide strategies for the early identification of patients with CTD-PAH at high risk of mortality.

Patients and methods

Patient enrollment

The study was conducted at a PAH Center in the Northwestern China, and patients treated between August 2009 and March 2016 were retrospectively enrolled. All participants provided written informed consent and the study was approved by the local ethics committee. Adult patients with CTD who visited our centers with an established diagnosis of PAH confirmed by right heart catheterization (RHC) for the first time were enrolled into our database. The inclusion hemodynamic criteria for PAH by RHC were mean pulmonary artery pressure (mPAP) >25 mmHg at rest, pulmonary capillary wedge pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) ≥3 Wood units [3]. CTDs were classified according to the 1997 American Rheumatism Association (ACR) criteria for SLE [4], 2002 international classification criteria for primary Sjogren's syndrome (pSS) [5], 1990 ACR classification criteria for Takayasu arteritis (TA) [6], 1987 Sharp criteria for mixed connective tissue disease (MCTD) [7] and 1980 ACR classification criteria for SSc [9, 10]. CTD diagnoses were verified by two experienced rheumatologists at the PAH center. Patients with a history of idiopathic PAH, chronic obstructive pulmonary disease, obstructive sleep apnea, other pulmonary diseases with mixed restrictive or obstructive patterns, chronic thromboembolism, left heart disease, portal hypertension, HIV infection, drug and toxin exposure, or any other diseases known to be associated with pulmonary hypertension (PH) were excluded. Moreover, CTD patients who fulfilled the hemodynamic inclusion criteria but in whom high-resolution computed tomography (HRCT) revealed moderate interstitial lung disease (ILD, one- to two-thirds of the lung field involved) combined with a total lung capacity, 60% predicted by pulmonary function testing, or severe ILD (more than two-thirds of the lung field involved) were defined as having ILD-associated PH (ILD-PH) [11]. ILD-PH patients were excluded from our CTD-APAH cohort.

Baseline clinical assessment

The clinical characteristics of included patients were obtained before administration of any targeted therapies for PAH. The baseline assessment included medical and medication history, time of symptom onset and diagnosis, WHO functional class (WHO-FC) at diagnosis, tests used to diagnose PAH, including pulmonary function test (PFT) including diffusion capacity, high-resolution chest computerized tomography scan (HRCT), CT pulmonary angiography, V/Q scan, abdominal ultrasound, hepatic virology screen and liver function tests, immune screening, and HIV serology. Physiological functional assessment at diagnosis included a six-minute walk test (6MWT) [8], measurement of NT-proBNP levels, and echocardiographic evaluation for pericardial effusion and right ventricular function (TAPSE score). The hemodynamic parameters of the included patients were obtained via RHC, and parameters such as mPAP, right atrial pressure (RAP), cardiac index (CI), PAWP or LVEDP, and PVR were measured in each patient. Only idiopathic and congenital heart disease patients underwent vasoreactivity testing using inhaled iloprost as per the protocol. A positive vasoreactive response was defined as a drop in mPAP by more than 10 mmHg to reach an absolute value of less than 40 mmHg in response to administration of acute vasodilator agent [13].

Treatments and follow-up

After initial assessment, treatments targeting CTD-PAH were administered, and patients were followed-up regularly every 3-6 months. In cases of positive acute vasodilator testing [14, 15] a calcium channel blocker (CCB), most commonly diltiazem, was initiated. If no improvement was observed after 3-6 months of CCB (defined as O_2% fall in 6-min walk distance (6MWD), an increase in World Health Organization functional class (WHO FC), or increase in mPAP and PVR), PAH-targeted monotherapy was administered, including endothelin

Table 1. Baseline characteristics of CTD-PAH patients according to the original CTDs

Patients	All patients	SLE-PAH	SSc-PAH	TA-PAH	RA-PAH	pSS-PAH	MCTD	PM/DM
Number	54	32	8	3	2	2	3	2
Age (years) mean (median)	39.04 (37)	34.31 (32.5)	49.34 (52)	32.25 (27)	52.26 (56)	47.50 (46.5)	27 (27)	38 (38)
Females (N)	54	32	8	3	2	2	2	2
Duration from symptoms to diagnosis months mean (Median)	46.16 (24)	39.96 (36)	53.53 (60)	36.90 (24)	65.23 (54)	54.57 (52)	52.86 (41)	43.20 (24)
WHO FC III/IV (N)	26	15	4	1	1	2	1	1
6MWD mean (meters)	357.1	371.3	329.6	389.5	373	381.5	326	372.4
BNP (pg/ml) mean	3080	2293	4344	15410	1198	2049	2332	420
Medications (N)								
PAH-targeted therapy	9	4	2	1	1	1	0	0
Glucocorticoid	50	35	5	2	2	2	2	2
Immunosuppressant	18	9	4	1	1	1	1	1

SLE: systemic lupus erythematosus; APAH: associated pulmonary arterial hypertension; TA: Takayasu arteritis; SSc: systemic sclerosis; TTE: transthoracic echocardiography; sPAP: systolic pulmonary artery pressure; RVDD: right ventricular diastolic diameter; PCE: pericardial effusion; PFT: pulmonary function test; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; RHC: right heart catheterisation; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular disease; SvO_2: mixed venous oxygen saturation.

Table 2. Baseline echocardiographic and RHC parameters in patients with CTD-PAH

Patients	All patients	SLE-APAH	SSc-APAH
n	54	32	8
TTE results			
sPAP (mmHg)	78.06±22.08	69.7±23.87	89.59±17.4
PFT results			
FVC (% pred)	83.9±12.5	85.4±12.1	82.4±13.0
DLCO (% pred)	68.2±22.3	70.1±15.3	66.8±30.1
FVC/DLCO	1.42±0.37	1.61±0.50	1.59±1.32
RHC results			
MAP (mmHg)	52.20±26.1	55.16±29.63	57.88±23.5
mRAP (mmHg)	12.0±1.21	11.5±1.2	12.7±1.65
mPAP (mmHg)	45.8±16.2	42.1±21.6	43.6±16.9
Cardiac index ($L/min^{-1}/m^{-2}$)	1.78±0.01	1.9±0.13	1.6±0.11

Data were presented as mean ± SD unless otherwise stated. SLE: systemic lupus erythematosus; APAH: associated pulmonary arterial hypertension; TA: takayasu arteritis; SSc: systemic sclerosis; TTE: transthoracic echocardiography; sPAP: systolic pulmonary artery pressure; RVDD: right ventricular diastolic diameter; PCE: pericardial effusion; PFT: pulmonary function test; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; RHC: right heart catheterisation; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure.

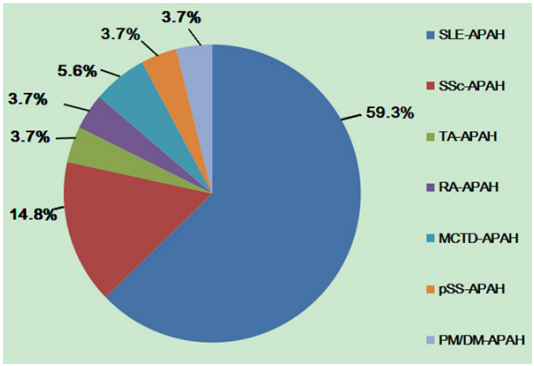

Figure 1. Distributions of various underlying connective tissue diseases (CTDs) in 54 included patients with CTD-PAH. SLE-PAH was the most common underlying type of CTD (n=32, 59.3%), while only 40.7% of patients had SSC-PAH (n=8, 14.8%); pSS-PAH (n=2, 3.7%); TA-PAH (n=3, 5.6%); MCTD-PAH (n=3, 5.6%); RA-PAH (n=2, 3.7%); PM/DM-PAH (n=2, 3.7%); and CTD-PAH (n=2, 3.7%). SLE: systemic lupus erythematosus; APAH: associated pulmonary arterial hypertension; TA: Takayasu arteritis; SSc: systemic sclerosis; TTE: transthoracic echocardiography; sPAP: systolic pulmonary artery pressure; RVDD: right ventricular diastolic diameter; PCE: pericardial effusion; PFT: pulmonary function test; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; RHC: right heart catheterization; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular disease; SvO_2: mixed venous oxygen saturation.

receptor antagonists, prostanoids or phosphodiesterase inhibitors. In cases of negative results were obtained from acute vasodilator testing, PAH-targeted immunotherapies were selected by physicians, and combined PAH-targeted therapies were initiated if the symptoms were not relieved after 3-6 months of monotherapy. If necessary, essential medical treatments for PAH including diuretics, digoxin, oxygen or warfarin were given. Glucocorticoids and immunosuppressants were administered when required for the underlying CTD rather than PAH itself.

The primary outcome was all-cause mortality, confirmed by hospital medical records, or by the date of death provided by relatives of the patients via telephone if the patients died outside the hospital. The duration of follow-up was defined as the time from the first diagnosis of CTD-PAH by RHC until death or known status at the last follow-up.

Statistical analysis

Continuous variables were presented as mean ± SD for parametric data or median (interquartile range) for nonparametric data, whereas categorical variables were presented as number (percentile, %). Continuous variables were compared using t-tests for parametric data or Mann-Whitney U-tests for nonparametric data. Categorical variables were compared using Chi-squared tests. Survival analysis was performed using the Kaplan-Meier method and compared by log-rank test. The primary endpoint was all-cause mortality. Univariate and multivariate Cox proportional hazards models were performed to determine the variables associated with risk of death. The potential predictive factors evaluated in the Cox Model were age, sex, CTD type, WHO FC, 6MWD, right ventricular diastolic diameter, pericardial effusion, mean right atrial pressure, mPAP, cardiac index, PVR, mixed venous oxygen saturation (SvO_2), regular biochemical parameters, autoantibody, and application of PAH-targeted therapies, as well as use of glucocorticoids and immunosuppressant. A two-tailed p-value <0.05 was considered to indicate statistical significance. All sta-

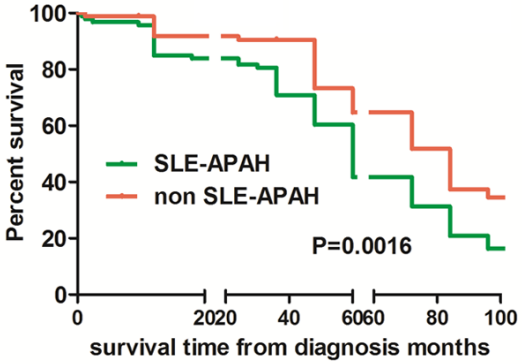

Figure 2. Log-rank (Mantel-Cox) Test for comparing the survival of patients with systemic lupus erythematosus (SLE)-associated pulmonary arterial hypertension (PAH) (n=32) and other connective tissue disease-PAH (non-SLE-PAH) patients (n=54). Patients with SLE-PAH had worse survival data as compared those without SLE. Log-rank (Mantel-Cox) Test showed that the survival of patients with SLE-APAH was significantly worse than that of isolated non-SLE-APAH patients ($p<0.05$).

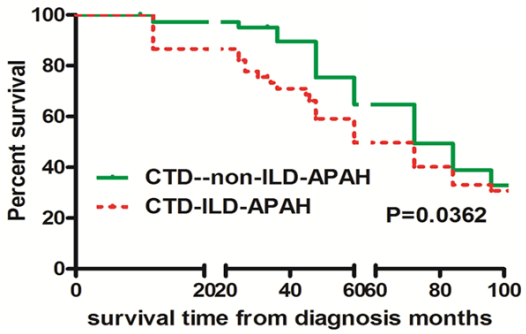

Figure 3. Log-rank (Mantel-Cox) Test of for comparing the survival of CHD-PAH patients with and without ILD. The 1- and 3-year survival rates for the ILD group were 90.6% and 79.2%, and for the isolated CTD-APAH-NON-ILD group they were 97.5% and 87.4%, respectively. Log-rank (Mantel-Cox) Test showed that the survival of patients with ILD-PAH was significantly worse than those CTD-PAH patients without ILD ($p<0.05$).

tistical analyses were performed using SPSS 17.0 statistical software (IBM, Armonk, NY, USA).

Results

Patient characteristics at baseline

Overall, 54 patients (mean age 32.1±11.0 years, female 81.5%) with CTD-PAH confirmed via RHC were included in this study (including

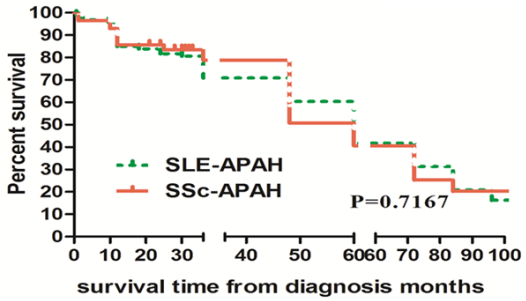

Figure 4. Log-rank (Mantel-Cox) Test for comparing the survival of patients with Systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) (n=8) and systemic lupus erythematosus (SLE)-associated pulmonary arterial hypertension (PAH) (n=32) patients. No significant difference in survival was detected for patients between the two groups. The 1-and 3-year survival rates for the SSc-APAH group were 87.5% and 75.0%, and for SLE-APAH group they were 96.8% and 93.8%, respectively.

22 patients with ILD). Participants' baseline characteristics and comorbidities of CTDs are listed in **Tables 1** and **2**, respectively. SLE was the leading underlying CTD (32/54, 59.3%), followed by SSc (8/54, 14.8%), MCTD (3/54, 5.6%), TA (3/54, 5.6%), RA (2/54, 3.7%), pSS (2/54, 3.7%), PM/DM (2/54, 3.7%), and CTD-PAH (2/54, 3.7%; **Figure 1**). At the time of PAH diagnosis, the mean 6MWD was 357.5±121.9 m (n=54), and 48.1% (n=26) of the patients were in WHO FC III/IV. Pericardial effusion was detected in 13.0% (n=7) of the patients in WHO FC III/IV. The mPAP was 52.20±26.1 mmHg. No patients exhibited a positive acute vasodilator response, and PAH-targeted medications were administered to 38.9% (21/54) patients, including sildenafil 14.8% (n=8), beraprost in 13.0% (n=7), bosentan in 11.1% (n=6). According to the predefined treatment protocols, 92.6% (n=50) of patients received glucocorticoids, and 33.3% (n=18) received immunosuppressants, including cyclophosphamide, cyclosporine, azathioprine, mycophenolate mofetil or methotrexate. Cyclophosphamide was the most frequently used immunosuppressant, administered to 24.1% (n=13) of these patients.

Survival of patients with CTD-PAH

During the follow-up, 4 patients were lost. The remaining 50 patients were followed for a median of 6 months (range 3-96 months), during which time 9.3% patients died, mostly of chronic right heart failure. The overall survival rates

Table 3. Survival rates for patients with CHD-PAH according to the literatures and current study

	Overall	SLE-APAH		SSc-APAH	
Follow-up duration (years)	1 year	1 year	3 years	1 year	3 years
REVEAL [16]	86	94	NA	82	NA
CONDLIFFE et al. [19]	NA	78	74	78	47
LAUNAY et al. [27]	NA	NA	NA	90	56
Zhicheng Jing et al. [3]	92	91	88	100	60
Present study	96.2	96.8	94	87.5	75

Data were presented as percentages. SLE: systemic lupus erythematosus; APAH: associated pulmonary arterial hypertension; SSc: systemic sclerosis; REVEAL: Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; NA: not available.

at 1 and 3 years were 96.3% (n=52) and 92.6% (n=50), respectively. The 1- and 3-year survival rates for patients with SLE-PAH were 96.9% and 87.5%, for patients with pSS, TA, MCTD and RA were 100% and 100%, and for patients with SSc were 87.5% and 75%, respectively. Log-rank (Mantel-Cox) test revealed no significant difference in survival among PAH patients secondary to the different CTDs (data not shown). Log-rank (Mantel-Cox) Test showed that survival of patients with SLE-PAH was significantly worse than that of isolated non-SLE-APAH patients ($p<0.05$, **Figure 2**), although survival did not differ significantly between SSc-APAH and non-SSc-APAH patients (**Figure 3**).

Characteristics and survival of patients with SLE- and non-SLE-PAH

In our cohort, 32 patients had SLE-APAH, and 22 had non-SLE-APAH. Compared with those with non-SLE-PAH, patients with SLE-APAH were younger and more often females. The percentage of anti-U1 ribonucleoprotein positive patients was higher in the SLE-PAH group than in non-SLE-APAH group (61.9% *vs.* 7.2%, $p<0.001$) and the percentage of patients receiving glucocorticoids was higher (SLE-APAH 81.25% [26/32] *vs.* non-SLE-APAH 68.1% [15/22]). However, functional status, echocardiography findings, or hemodynamic and biochemical parameters did not differ significantly between the two subgroups (**Figure 2**). In CTD-PAH patients with ILD, the 1- and 3-year survival rates were 90.7% and 73.2%, respectively. The Log-rank (Mantel-Cox) test showed that the survival of patients with ILD-PAH was worse than those without ILD ($p<0.05$; **Figure 3**), but did not differ significantly from patients with SLE-PAH and SSc-PAH. Of note, further analysis showed that survival of patients with SLE-PAH was significantly worse than that of those with the other CTD-PAHs (**Figure 4**, **Table 3**).

Predictors of mortality

In the univariate Cox regression analysis, WHO-FCS of III&IV, a cardiac index (CI) ≤2.5 L/min/m^2, and the presence of pericardial effusion at baseline were significantly associated with increased mortality, while the multivariate Cox proportional hazard analysis, which adjusted for presence of pericardial effusion as an independent variable, revealed that pericardial effusion (HR=0.71, 95% CI=-0.02-1.45, p=0.04) and mRAP >10 mmHg (HR=0.74, 95% CI=0.48-1.13, p=0.03) were independently associated with increased risk of all-cause death. When WHO-FC was included in multivariate Cox hazard analysis, instead of pericardial effusion, only CI <2.5 L/min/m^2 (HR=1.4, 95% CI=0.71-2.09, p=0.02) was associated with increased mortality (**Table 4**).

Discussion

In this retrospective pilot cohort study, we evaluated the clinical characteristics and determinants of mortality in patients with CTD-associated PAH at a national center in North-Western China. We found that the unique and prognosis of each subtype of CTD-PAH differed according to the original CTD. Specifically, by using RHC, the currently accepted gold standard for PAH diagnosis [16], our results suggest that SLE is the leading cause of CTD-PAH in our cohort, which is consistent with a previous study from China [3, 17]. Moreover, we found that pericardial effusion was an independent predictor of mortality in CTD-PAH patients. Regarding the association between the type of CTD and mortality risk, we found that mortality risk was higher for patients with SLE or ILD than patients without these clinical features. Our results provide further evidence that in Chinese patients with CTDs, those with SLE are at an elevated risk for development of PAH and subsequent mortality, particularly those with ILD.

Although previous studies have indicated that patients with SSc were at higher risk of developing PAH than patients with other CTDs, these

Table 4. Determinants of all-cause mortality for patients with CTD-PAH: univariate and multivariate regression analyses

Variables	Univariate analysis			Multivariable analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (10-year increases)	1.05	0.70-1.59	0.98			
Gender	1.15	0.73-1.81	0.55			
WHO-FC (III&IV)	2.66	0.43-1.02	0.02			
Uric acid (≥7 mg/dl)	1.21	0.05-2.96	0.67			
BNP (≥170 pg/ml)	1.26	0.49-3.28	0.63			
Resting BPs (10 mmHg increase)	1.21	0.76-1.92	0.21			
Resting HR (≥80/min)	0.94	0.80-1.09	0.4			
Combination therapy (mPAP)	0.83	0.16-1.50	0.42			
mPAP (≥50 mmHg)	1.38	0.60-3.19	0.45			
CI (≤2.5 L/min/m^2)	2.49	0.71-4.09	0.02			
mRAP (≥10 mmHg)	2.46	0.91-6.66	0.08	0.35	1.48-2.13	0.03
PVR (≥520 dyn s/cm^5)	1.10	0.70-1.59	0.98			
TRPG (≥50 mmHg)	1.00	0.31-1.69	0.81			
Presence of pericardial effusion	1.66	1.17-2.36	0.00	1.71	1.02-2.85	0.04

95% CI: 95% confidence intervals; HR: hazard ratios; BNP: brain natriuretic peptide; BPs: systolic blood pressure; HR: heart rate; mPAP: mean pulmonary arterial pressure; CI: cardiac index; mRAP: mean right atrial pressure; PVR: pulmonary vascular resistance; TRPG: tricuspid regurgitation pressure gradient.

results were generally retrieved from the Western populations [2, 3]. In this study, we found that SLE was the leading underlying CTD associated with PAH (48.5% of the patients), followed by SSc, RA, pSS, TA, MCTD, and PM/DM. These findings are consistent with other Chinese cohorts [2, 3, 18]. Taken together, these results reveal that the CTDs with highest rates of PAH differed between Chinese groups and western cohorts [19], indicating the potential influence of ethnic or genetic factors. Moreover, patients with ankylosing spondylitis were recently reported to also suffer with PAH [9], indicating that PAH comorbidities might be common in most CTDs.

Another important finding of our study was that pericardial effusion and higher mRAP seemed to be independent predictors of mortality in patients with CTD and PAH. In fact, these two factors may be related as the extent of pericardial effusion was previously reported to be associated with the level of mRAP [21]. Indeed, pericardial effusion has been associated with RV impairment [10], and higher mRAP has been associated with increased RV filling pressure [23]. Pathophysiologically, these two factors reflect impairment of right ventricular function, which may be caused by the increased pulmonary arterial pressure, and contribute to the clinical deterioration of the patients.

Of note, we found that the prognosis for patients with SLE-PAH was worse than for non-SLE PAH patients, although previous studies indicated that the prognosis for SSc-PAH patients might be worse than for patients with the other CTD-related PAH [19]. However, by direct comparison of the prognosis in patients with SLE-PAH and SSc-PAH, our study revealed that mortality did not differ significantly between these two groups. These findings may be limited by the limited statistical power of this study which included only a small sample of patients. Otherwise, this finding may reflect epidemiological differences in status and clinical treatment between the Chinese and western cohorts. Interestingly, a recent study indicated that the prognosis of a particular subset of SLE-PAH patients was worse than that of SSc-PAH patients [10]. Obviously, further studies with adequate sample size and statistical power are needed.

We compared our results with previously published survival rates of CTD-PAH patients (**Table 5**) [24]. Survival rate was higher in our study, potentially indicating improvement of early identification and treatment of CTD-PAH (primarily via the application of immunosuppressive agents and steroids). Whether response to steroids and immunosuppressive medications differs between different CTD-PAHs according to the CTDs involved remains to be seen.

Table 5. Univariate and multivariate hazards ratios among PAH patients

Variable	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (10-year increase)	1.05	0.70-159	0.98			
Gender (female)	1.15	0.73-1.81	0.55			
WHO-FC (III&IV)	10.66	1.43-81.02	0.017			
Uric acid (≥360 umol/L)	1.22	1.51-2.97	0.46			
BNP (≥170 pg/ml)	1.26	0.49-3.28	0.63			
Resting BPs (10 mmHg increase)	1.21	0.76-1.92	0.21			
Resting HR (80/min)	0.94	0.80-1.09	0.4			
Combination therapy (mPAP)	0.83	0.16-1.5	0.42			
mPAP (≥50 mmHg)	1.38	0.6-3.19	0.45			
CI (<2.5 L/min/m^2)	2.49	0.91-7.09	0.05			
mRAP (≥10 mmHg)	2.46	0.91-6.76	0.08	3.74	1.48-10.8	0.03
PVR (≥520 dyn s/cm^5)	1.1	0.70-1.59	0.98			
TRPG (≥50 mmHg)	1.6	0.71-1.69	0.81			
Presence of pericardial effusion	3.66	1.17-7.36	0.01	3.71	1.02-10.4	0.04
EF≤55%	3.94	2.96-9.47	0.01			
TAPSE≤16 mm	4.69	2.03-18.36	0.00			

95% CI: 95% confidence intervals; HR: hazard ratios; BNP: brain natriuretic peptide; BPs: systolic blood pressure; HR: heart rate; mPAP: mean pulmonary arterial pressure; CI: cardiac index; mRAP: mean right atrial pressure; PVR: pulmonary vascular resistance; TRPG: tricuspid regurgitation pressure gradient; EF: ejection fraction; TAPSE: tricuspid annular plane systolic excursion.

For example, glucocorticoids and immunosuppressant without pulmonary vasodilators could effectively treat SLE- or MCTD-associated PAH, but not SSc-associated PAH [11]. In our study, the doses of steroids administered in SLE-PAH were much higher in the SLE group, consistent with reports from Western countries and recent data from China [3, 17], while in the other CTD-PAH, such as SSc, the doses were lower. Therefore, whether immunosuppressive therapy is useful for CTD-PAH may depend on the CTD subtype involved. In PAH, administration of steroids may also be harmful to the cardiovascular system as they induce sodium retention and cause irreversible pathological changes to the myocardium [26]. Further study will be required to clarify whether immunosuppressive therapy and target drugs are helpful to each subtype of CTD-PAH.

Our study has several limitations that should be noted when interpreting the results. First, participants were recruited at regional medical centers in China, and the results may not be generalizable into all Asian patients. Second, this retrospective cohort study has limited statistical power. Finally, the use of medication was not standardized between physicians, which may have influenced the survival analyses. Nonetheless, this pilot study of CTD-PAH patients is clinically important.

In summary, we found that CTD-PAH was a severe clinical syndrome, associated with high mortality, and SLE may be the CTD most often associated with PAH in Chinese patients. Moreover, we found that pericardial effusion was an independent predictor of mortality in patients with CTD-PAH. Patients with SLE-PAH or ILD also had worse clinical outcomes. Our results may inform early identification of patients with CTD-PAH who were at high risk of mortality, particularly in China.

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Disclosure of conflict of interest

None.

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