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Pulmonary Hypertension

Long-Term Survival of Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension: A Single-Center Cohort

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Pulmonary arterial hypertension (PAH) is a rare but severe complication of connective tissue disease (CTD). CTD-associated PAH (CTD-PAH) is the most common subgroup of PAH in East Asia. We prospectively collected 41 patients with CTD-PAH and followed them for a mean period of 43 ± 36 months. The long-term survival rates of the CTD-PAH patients at 1, 2, 3 and 5 years were 90%, 80%, 77%, and 60%, respectively. The non-survivors had more dilated main pulmonary arteries, higher pulmonary artery pressure and pulmonary vascular resistance (PVR). PAH-specific therapy resulted in improvements in functional class, 6-minute walk distance, serum uric acid, right ventricular function and PVR. Increased C-reactive protein during follow-up, indicating inflammatory processes, was also crucial for the management of CTD-PAH. Therefore targeting both PAH and inflammation is important in this specific subgroup of PAH. The results of this study may help develop treatment strategies for CTD-PAH patients.

Key Words: Inflammation • Pulmonary arterial hypertension • Uric acid

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a subgroup of pulmonary hypertension (PH) that affects the small pulmonary arterioles and may be idiopathic, heritable, drug- or toxin-induced, or secondary to other diseases including connective tissue disease (CTD), congenital heart disease, portal hypertension, human immunodeficiency virus infection, and schistosomiasis.[1,2] CTD-related PAH (CTD-PAH) is the most common cause of PAH in Chinese and Korean populations.[3,4] The progression of PAH may lead to right heart failure (RHF) and may be fatal due to increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). The diagnosis of PAH requires right heart catheterization (RHC) with a mean pulmonary artery pressure (MPAP) > 20 mmHg at rest, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and PVR ≥ 3 Woods units (WU).[5,6] A recent national cohort study in Taiwan reported a low incidence of CTD-PAH, and systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) were the two major subtypes related to PAH.[7] This study aimed to investigate the outcomes of CTD-PAH patients at a single medical center in Taiwan.

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MATERIALS AND METHODS

Study population

Patients with PAH with underlying CTD diagnosed at Chang Gung Memorial Hospital (CGMH) were prospectively enrolled from March 1, 2005 to August 31, 2020.

Abbreviations

ALT	Alanine aminotransferase
BMI	Body mass index
BNP	B-type natriuretic peptide
CBC	Complete blood count
CGMH	Chang Gung Memorial Hospital
CI	Cardiac index
CO	Cardiac output
COMPERA	The Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CRP	C-reactive protein
CTD	Connective tissue disease
DBP	Diastolic blood pressure
DPAP	Diastolic pulmonary artery pressure
ECG	Electrocardiography
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FC	Functional class
FEV	Forced expiratory volume
FVC	Forced vital capacity
Hb	Hemoglobin
HR	Heart rate
LVeI	Eccentricity index of the left ventricle
MCTD	Mixed connective tissue disease
MPA	Main pulmonary artery
MPAP	Mean pulmonary artery pressure
MvO_2	Mixed venous oxygen saturation
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure
PDE5i	Phosphodiesterase type 5 inhibitor
PE	Pericardial effusion
PVR	Pulmonary vascular resistance
RA	Right atrium
RAP	Right atrial pressure
REVEAL	The Registry to Evaluate Early and Long-Term PAH Disease management
RHC	Right heart catheterization
RHF	Right heart failure
RV	Right ventricle
RVFAC	Right ventricular fraction area change
RVOT	Right ventricular outflow tract
SaO_2	Arterial oxygen saturation
SBP	Systolic blood pressure
SD	Standard deviation
SLE	Systemic lupus erythematosus
Sm	Maximal systolic velocity at the lateral aspect of the tricuspid annulus by tissue Doppler imaging
SPAP	Systolic pulmonary artery pressure
SpO_2	Oxygen saturation by pulse oximetry
SSc	Systemic sclerosis
TAPSE	Tricuspid annular plane systolic excursion
TRV	Peak tricuspid regurgitation velocity
VTI	Velocity time integral
WBC	White blood count
WHO	World Health Organization
WU	Woods units
6MWD	6-minute walk distance

Patients were included if they met the following criteria: age > 20 years, and newly diagnosed with PAH. All patients underwent RHC to confirm the diagnosis of PAH. Patients were excluded if they had left heart disease with significant valvular lesions or left ventricular diastolic/systolic dysfunction. Patients were also excluded if they had severe chronic lung disease [obstructive lung disease with forced expiratory volume in 1 s (FEV_1) < 60% or restrictive lung disease with forced vital capacity (FVC) < 70%] or PH related to thromboembolism or other systemic diseases including hemolytic anemia, thyroid disease, and end-stage renal disease. Patients were treated with PAH-specific medications, such as phosphodiesterase type 5 inhibitors (PDE5is), endothelin receptor antagonists (ERAs), and prostanoids after confirmation of the diagnosis of CTD-PAH.

Clinical information, World Health Organization functional class (FC), complete blood count (CBC), biochemical data, 6-minute walk distance (6MWD), echocardiographic parameters, and hemodynamics by cardiac catheterization were obtained at the time of enrollment. The follow-up period for the analysis of the survivors ended on December 31, 2020. Electrocardiography (ECG), chest radiography, and echocardiography were performed at baseline and at the first follow-up between 3 and 6 months, 12 months, and every 6 months thereafter. Additionally, clinical symptoms, 6MWD, serum B-type natriuretic peptide (BNP), CBC, and biochemical studies were performed simultaneously. This study was reviewed and approved by the Institutional Review Board of CGMH.

Statistical analysis

Data are expressed as number and percentage for categorical variables and as mean ± standard deviation (SD) for continuous variables. Categorical variables were compared using the chi-square test, while continuous variables were compared using the Mann-Whitney U test. Follow-up data were analyzed using the binomial McNemar's and Wilcoxon signed-rank tests. Survival analysis was performed using the Kaplan-Meier method, and the survival rates of the different CTD subtypes were compared using the log-rank test. All analyses were performed using SPSS version 21.2 (IBM, Armonk, NY). Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics

A total of 41 patients were enrolled in this observational study. The mean follow-up period was 43 ± 36 months (range, 4-161 months). All study subjects were women. Table 1 shows the patients' demographic characteristics. The mean age at the time of the diagnosis of CTD-PAH was 46 ± 15 years (range, 25-78 years). Nineteen (46%) patients were diagnosed with SLE, 10 (25%) with SSc, and six (15%) with mixed CTD (MCTD). Six (15%) patients were diagnosed with other diseases, including two with rheumatoid arthritis, one with Sjögren's syndrome, one with dermatomyositis, one with polymyositis, and one with an unclassified autoimmune disease. Among them, six (15%) patients had FC IV, 30 (73%) had FC III, and five (12%) had FC II. The hemodynamic parameters by RHC were as follows: MPAP, 51 ± 12 mmHg; PAWP, 11 ± 3 mmHg; and PVR, 12.0 ± 7.3 WU. The BNP level at the time of enrollment was 491 ± 692 pg/mL. Other laboratory examination data are presented in Table 2.

The 6MWD at the time of enrollment was 328 ± 133 m. The echocardiographic findings at baseline were as follows: estimated systolic pulmonary artery pressure (SPAP), 78 ± 17 mmHg; tricuspid annular plane systolic excursion (TAPSE), 1.66 ± 0.46 cm; maximal systolic velocity at the lateral aspect of the tricuspid annulus by

Table 1. Demographic characteristics, hemodynamics, and clinical risk stratification of patients with connective tissue disease-associated pulmonary arterial hypertension

Variables	Mean ± SD or number (%)	Range
Demographics		
Female sex, n (%)	41 (100)	
Age, years	46 ± 15	25-78
Body height, cm	155.4 ± 7.5	144-173
Body weight, kg	52.6 ± 8.1	36-67
BMI, kg/m^2	21.8 ± 3.1	17.0-28.2
SBP, mmHg	121 ± 23	80-186
DBP, mmHg	75 ± 14	44-106
HR, bpm	85 ± 14	58-115
SpO_2, %	94 ± 4	80-100
FC II/III/IV, n (%)	5 (12)/30 (73)/ 6 (15)	
Etiology of CTD		
SLE, n (%)	19 (46)	
Scleroderma, n (%)	10 (24)	
Mixed, n (%)	6 (15)	
Others*, n (%)	6 (15)	
Hemodynamics by RHC		
RAP, mmHg	12 ± 5	2-26
SPAP, mmHg	76 ± 19	37-115
DPAP, mmHg	35 ± 9	17-55
MPAP, mmHg	51 ± 12	25-75
PAWP, mmHg	11 ± 3	3-15
PVR, Woods units	12.0 ± 7.3	3.0-46.0
CO, mL/min	3.7 ± 1.5	1.5-7.5
CI, mL/min/m^2	2.4 ± 0.9	1.0-4.7
MvO_2, %	61 ± 9	37-78
SaO_2, %	93 ± 4	85-99
PAH-specific medications		
Monotherapy, n (%)	24 (59)	
Sildenafil, n (%)	20 (49)	
Bosentan, n (%)	3 (7)	
Riociguat, n (%)	1 (2)	
Combination therapy, n (%)	15 (37)	
Sildenafil plus macitentan, n (%)	14 (34)	
Sildenafil plus treprostinil, n (%)	1 (2)	
Risk stratification		
REVEAL 2.0		
Low, n (%)	5 (12)	
Intermediate, n (%)	6 (15)	
High, n (%)	30 (73)	
COMPERA		
Low, n (%)	1 (2)	
Intermediate, n (%)	28 (68)	
High, n (%)	12 (29)	

Data are expressed as mean ± SD for continuous variables and as number and percentage for categorical variables.
* Others includes two patients with rheumatoid arthritis, one with Sjögren's syndrome, one with dermatomyositis, one with polymyositis, and one with unclassified autoimmune disease.
BMI, body mass index; CI, cardiac index; CO, cardiac output; COMPERA, Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD, connective tissue disease; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; FC, WHO functional class; HR, heart rate; MPAP, mean pulmonary artery pressure; MvO_2, mixed venous oxygen saturation; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; RHC, right heart catheterization; SaO_2, arterial oxygen saturation; SBP, systolic blood pressure; SD, standard deviation; SLE, systemic lupus erythematosus; SpO_2, oxygen saturation by pulse oximetry; SPAP, systolic pulmonary artery pressure.

tissue Doppler imaging (Sm), 11.3 ± 3.3 cm/s; myocardial performance index of the right ventricle (Tei index), 0.60 ± 0.29; right ventricular fraction area change (RVFAC), 22 ± 9%; systolic and diastolic eccentricity index of the left ventricle (LVeI), 1.53 ± 0.45 and 1.40 ± 0.36; right atrium (RA) area, 22.2 ± 6.5 cm^2; main pulmonary artery (MPA) diameter, 3.53 ± 0.92 cm; and ratio of tricuspid regurgitation velocity and velocity time integral at right ventricular outflow tract (TRV/VTI_{RVOT}), 0.46 ± 0.19. Nineteen (46%) patients had pericardial effusion (Table 2).

Among the 39 (95%) patients who received PAH-specific therapy after being diagnosed with CTD-PAH, 24 (59%) received monotherapy and 15 (37%) received combination therapy. Among the patients treated with monotherapy, 20 (49%) received sildenafil (PDE5i) therapy, three (7%) received bosentan (ERA) therapy, and one (2%) received riociguat (soluble guanylate cyclase stimulator) therapy. All patients treated with combination therapy received sildenafil and macitentan (ERA) therapy, except for one who received sildenafil and subcutaneous treprostinil (prostanoid) combination therapy. Two patients (5%) did not receive PAH-specific therapy: one patient due to severe headache and gastrointestinal side effects after taking sildenafil, and the other who

Table 2. Laboratory and echocardiographic data at baseline, 3-6 months, 12 months, and last evaluation of patients with connective tissue disease-associated pulmonary arterial hypertension

Variables	Baseline	3-6 months	12 months	Last evaluation
Patients, n	41	38	34	32
FC I/II/III/IV, n	0/5/30/6	4/15/15/4*	4/18/9/3#	4/14/13/1†
6MWD, m	328 ± 133	366 ± 136*	391 ± 139*	411 ± 143*
Laboratory data				
WBC, 1000/μL	7.5 ± 3.4	7.6 ± 2.8	6.9 ± 2.8	7.2 ± 4.1
Hb, g/dL	12.8 ± 2.5	13.0 ± 1.9	12.1 ± 1.9#	12.0 ± 1.9#
Platelet, 1000/μL	212 ± 101	199 ± 104	201 ± 95	189 ± 80
ALT, U/L	28 ± 23	30 ± 36	23 ± 20	25 ± 20
Creatinine, mg/dL	0.64 ± 0.22	0.69 ± 0.21	0.72 ± 0.26	0.71 ± 0.22
Uric acid, mg/dL	7.0 ± 1.8	6.8 ± 2.0	5.9 ± 2.2*#	5.7 ± 1.8*†
CRP, mg/L	8.8 ± 13.4	8.1 ± 13.4	12.4 ± 22.6#	15.0 ± 22.5#
BNP, pg/mL	491 ± 692	383 ± 622	300 ± 552	445 ± 624
Echocardiographic data				
SPAP, mmHg	78 ± 17	69 ± 18*	64 ± 17*	65 ± 17*
TAPSE, cm	1.66 ± 0.46	1.79 ± 0.50*	1.83 ± 0.42*	1.80 ± 0.41*
Sm, cm/s	11.3 ± 3.3	11.7 ± 3.1	12.0 ± 2.6	11.0 ± 2.6†
Tei index	0.60 ± 0.29	0.47 ± 0.19	0.46 ± 0.21*	0.51 ± 0.23
RVFAC, %	22 ± 9	27 ± 11*	27 ± 9*	29 ± 12*
Systolic LVeI	1.53 ± 0.45	1.53 ± 0.74	1.40 ± 0.37	1.65 ± 0.74
Diastolic LVeI	1.40 ± 0.36	1.32 ± 0.31	1.26 ± 0.27*	1.35 ± 0.31
RA area, cm^2	22.2 ± 6.5	21.0 ± 6.9	20.0 ± 6.7	22.4 ± 11.0†
MPA, cm	3.53 ± 0.92	3.64 ± 1.07	3.24 ± 0.58	3.47 ± 0.54
TRV/VTI_{RVOT} ratio	0.46 ± 0.19	0.35 ± 0.13*	0.35 ± 0.14*	0.35 ± 0.14*
PE, n (%)	19 (46)	18 (47)	12 (35)#	17 (53)

Data are expressed as mean ± SD for continuous variables and as numbers and percentages for categorical variables. The last evaluation was performed at 43 ± 36 months (range, 4-161 months).

* $p < 0.05$ data vs. baseline, # $p < 0.05$ data vs. 3-6 months, † $p < 0.05$ data vs. 12 months.

ALT, alanine aminotransferase; BNP, B-type natriuretic peptide; CRP, C-reactive protein; FC, functional class; Hb, hemoglobin; LVeI, left ventricular eccentricity index; MPA, diameter of the main pulmonary artery; PE, pericardial effusion; RA, right atrial; RVFAC, right ventricular fractional area change; Sm, maximal systolic velocity at the lateral aspect of the tricuspid annulus by tissue Doppler imaging; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, peak tricuspid regurgitation velocity; VTI_{RVOT}, velocity time integral at the right ventricular outflow tract; WBC, white blood count; 6MWD, 6-minute walk distance.

had associated coronary artery disease and was treated with isosorbide-5-mononitrate, which is contraindicated in combination with a PDE5i. None of the patients received triple combination therapy. Risk stratification was done using the Registry to Evaluate Early and Long-Term PAH Disease management (REVEAL) 2.0 risk score and the European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) study.[8,9] The following 13 variables were used to calculate the risk of 1-year mortality in the REVEAL 2.0 risk score: etiology, demographics, renal insufficiency, FC, all-cause hospitalization within the previous 6 months, blood pressure, heart rate, 6MWD, BNP, pericardial effusion, diffusion capacity of the lung, RA pressure, and PVR.[8] Thirty (73%) patients were at high risk based on the REVEAL 2.0 risk stratification. Meanwhile, the following six variables were used to calculate the COMPERA risk score: FC, 6MWD, BNP, RA pressure, cardiac index, and mixed venous oxygenation.[9] Overall, 28 (68%) patients were at intermediate risk according to COMPERA risk score.

Long-term follow-up

Functional capacity

Details of the follow-up data are presented in Table 2. The FC significantly improved during follow-up; 36 (88%) patients had FC III/IV at baseline, compared to 19 (50%) patients after treatment for 3-6 months. Most patients improved to FC I/II during the follow-up period. Overall, 18 (56%) patients were maintained at FC I/II, even at the last evaluation.

The 6MWD was significantly higher at 3-6 months, 12 months, and the last evaluation compared to baseline; the mean distances at baseline, 3-6 months, 12 months, and at the last evaluation were 328 ± 133 m, 366 ± 136 m (p = 0.040), 391 ± 139 m (p = 0.008), and 411 ± 143 m (p = 0.003), respectively.

Hematological and biochemical profiles

There were no significant changes in white blood and platelet counts; however, a slight decrease in hemoglobin was observed during follow-up from 13.0 ± 1.9 g/dL to 12.0 ± 1.9 g/dL. No significant changes in serum alanine transaminase or creatinine levels were observed. However, the mean serum uric acid level decreased significantly from 7.0 ± 1.8 mg/dL to 5.7 ± 1.8 mg/dL (p = 0.006) during the follow-up period. The mean C-reactive protein (CRP) level increased significantly from 8.1 ± 13.4 mg/dL to 15.0 ± 22.5 mg/L (p = 0.034) during follow-up. Nevertheless, no significant change in BNP level was noted during treatment.

Echocardiographic findings

The estimated SPAP decreased significantly after therapy. The SPAP at the time of enrollment was 78 ± 17 mmHg, which then decreased to 69 ± 18 mmHg (p = 0.004), 64 ± 17 mmHg (p = 0.001), and 65 ± 17 mmHg (p = 0.033) at 3-6 months, 12 months, and at the last evaluation, respectively. In addition, right ventricular (RV) function, including TAPSE and RVFCA, improved significantly during follow-up. There was no significant reduction in the size of the RA; however, an increase in RA area was noted at the last evaluation compared to 12 months of follow-up (22.4 ± 11.0 vs. 20.0 ± 6.7 cm^2, p = 0.040). The ratio of TRV/VTI_{RVOT} is proportional to the PVR.[10] A significant decrease in the ratio was seen during follow-up. The presence of pericardial effusion was less frequent at 12 months than at 3-6 months of follow-up (35% vs. 47%, p = 0.001); however, it was frequently observed again at the last evaluation (53%).

Overall survival

Table 3 shows the demographic characteristics and baseline laboratory data of the survivors and non-survivors. Thirteen (32%) patients died during the study period, including 11 with RHF, one with sepsis, and one with pneumonia. No significant intergroup differences were noted in age, FC, etiology, 6MWD, or hematological data. CRP level was the only biochemical parameter that increased significantly in the non-survivors versus the survivors (16.7 ± 19.4 vs. 5.6 ± 8.6 mg/L, p = 0.027).

The estimated SPAP was higher in the non-survivors than in the survivors (87 ± 14 vs. 73 ± 17 mmHg, p < 0.001). An increased MPA diameter was observed in the non-survivors versus the survivors (4.43 ± 1.35 vs. 3.20 ± 0.47 cm, p = 0.036). There was no significant intergroup difference in the presence of pericardial effusion. The PVR by RHC was higher in the non-survivors than in the survivors (15.4 ± 9.5 vs. 10.3 ± 5.2 WU, p = 0.038), which was due to a higher PAP and lower cardiac output

Table 3. Demographic characteristics, laboratory data, echocardiographic parameters, hemodynamics, and clinical risk stratification between survivors and non-survivors among patients with connective tissue disease-associated pulmonary arterial hypertension

Variables	Survivors (n = 28)	Non-survivors (n = 13)	p value
Demographics			
Age, years	45 ± 14	49 ± 15	0.357
Body height, cm	156.6 ± 7.1	152.9 ± 7.8	0.121
Body weight, kg	53.6 ± 7.6	50.7 ± 9.1	0.205
BMI, kg/m^2	21.9 ± 2.9	21.7 ± 3.6	0.497
SBP, mmHg	120 ± 20	121 ± 29	0.609
DBP, mmHg	76 ± 14	73 ± 14	0.923
HR, bpm	84 ± 14	88 ± 16	0.589
SpO_2, %	94 ± 4	93 ± 5	0.382
6MWD, m	352 ± 140	279 ± 106	0.105
WHO functional class, n (%)			0.526
II	4 (14)	1 (8)	
III	21 (75)	9 (69)	
IV	3 (11)	3 (23)	
Etiologies of CTD, n (%)			0.813
Systemic lupus erythematosus	13 (46)	6 (46)	
Scleroderma	6 (21)	4 (31)	
Mixed CTD	4 (14)	2 (15)	
Others	5 (18)	1 (8)	
Laboratory data			
WBC, 1000/μL	7.7 ± 3.7	7.1 ± 2.9	0.570
Hb, g/dL	12.5 ± 2.6	13.2 ± 2.1	0.446
Platelet, 1000/μL	224 ± 109	189 ± 81	0.311
ALT, U/L	30 ± 26	24 ± 16	0.430
Creatinine, mg/dL	0.63 ± 0.16	0.67 ± 0.32	0.552
Uric acid, mg/dL	6.8 ± 2.0	7.2 ± 1.5	0.393
CRP, mg/L	5.6 ± 8.6	16.7 ± 19.4	0.027
BNP, pg/mL	506 ± 779	462 ± 521	0.475
Echocardiographic data			
SPAP, mmHg	73 ± 17	87 ± 14	< 0.001
TAPSE, cm	1.60 ± 0.41	1.79 ± 0.55	0.197
Sm, cm/s	10.9 ± 2.8	12.2 ± 4.0	0.382
Tei index	0.63 ± 0.30	0.55 ± 0.28	0.329
RVFAC, %	22 ± 8	23 ± 9	0.501
Systolic LVeI	1.46 ± 0.35	1.66 ± 0.58	0.441
Diastolic LVeI	1.35 ± 0.28	1.49 ± 0.47	0.588
RA area, cm^2	21.3 ± 6.1	23.7 ± 7.1	0.407
MPA, cm	3.20 ± 0.47	4.43 ± 1.35	0.036
TRV/VTI_{RVOT} ratio	0.32 ± 0.19	0.31 ± 0.20	0.738
Pericardial effusion, n (%)	12 (43)	7 (54)	0.511
Hemodynamics by RHC			
RAP, mmHg	12 ± 6	11 ± 5	0.186
SPAP, mmHg	72 ± 19	82 ± 18	0.066
DPAP, mmHg	35 ± 9	37 ± 9	0.497
MPAP, mmHg	49 ± 12	54 ± 12	0.367
PAWP, mmHg	12 ± 3	11 ± 4	0.367
PVR, Woods units	10.3 ± 5.2	15.4 ± 9.5	0.038
CO, mL/min	4.1 ± 1.6	3.1 ± 1.0	0.090
CI, mL/min·m^2	2.6 ± 1.0	2.1 ± 0.6	0.177
MvO_2, %	62 ± 9	59 ± 10	0.570
SaO_2, %	93 ± 4	92 ± 4	0.609

Table 3. Continued

Variables	Survivors (n = 28)	Non-survivors (n = 13)	p value
PAH-specific therapy, n (%)			0.103
Monotherapy	14 (50)	11 (85)	
Two combines	13 (46)	2 (15)	
Risk stratification			
REVEAL 2.0			0.142
Low, n (%)	5 (18)	0 (0)	
Intermediate, n (%)	5 (18)	1 (8)	
High, n (%)	18 (64)	12 (92)	
COMPERA			0.631
Low, n (%)	1 (4)	0 (0)	
Intermediate, n (%)	18 (64)	10 (77)	
High, n (%)	9 (32)	3 (23)	

Data are expressed as mean ± SD for continuous variables and as number and percentage for categorical variables.
ALT, alanine aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; CRP, C-reactive protein; CI, cardiac index; CO, cardiac output; COMPERA, the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD, connective tissue disease; DBP, diastolic blood pressure; Hb, hemoglobin; HR, heart rate; LVeI, left ventricular eccentricity index; MPA, diameter of main pulmonary artery; MPAP, mean pulmonary artery pressure; MvO_2, mixed venous oxygen saturation; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PE, pericardial effusion; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; REVEAL, the Registry to Evaluate Early and Long-Term PAH Disease management; RHC, right heart catheterization; RVFAC, right ventricular fractional area change; SaO_2, arterial oxygen saturation; SBP, systolic blood pressure; SLE, systemic lupus erythematosus; Sm, maximal systolic velocity at the lateral aspect of the tricuspid annulus by tissue Doppler imaging; SpO_2, oxygen saturation by pulse oximetry; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, peak tricuspid regurgitation velocity; VTI_{RVOT}, velocity time integral at the right ventricular outflow tract; WBC, white blood count; WHO, World Health Organization; 6MWD, 6-minute walk distance.

in the non-survivors than in the survivors. However, no significant intergroup difference in PAH-specific therapy was found. Risk stratification by the REVEAL 2.0 and COMPERA risk scores was similar between the survivors and non-survivors.

The overall survival of patients with CTD-PAH is shown in Figure 1. The median survival was 7.9 years. The 1-, 2-, 3-, and 5-year survival rates were 90%, 80%, 77%, and 60%, respectively. With regards to the survival rates, the patients with SSc had the poorest survival, followed by those with SLE and MCTD; however, the intergroup differences were not significant (Figure 2). The low- and intermediate-risk patients had better survival than the high-risk patients as assessed by the COMPERA risk score. However, this difference between risk groups was not shown by the REVEAL 2.0 risk score (Figure 3).

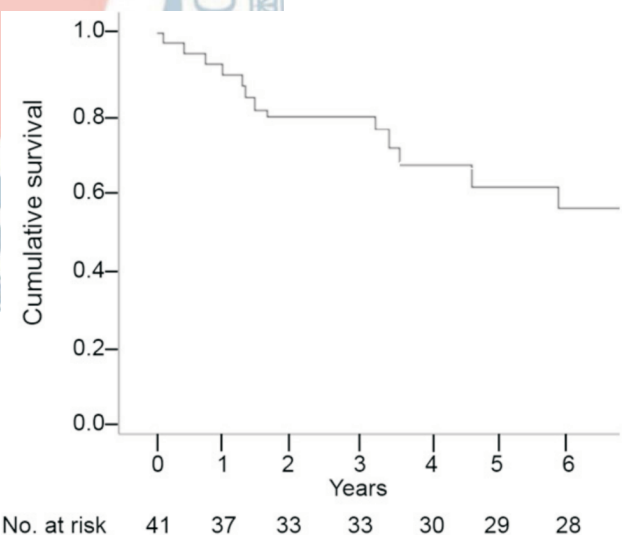

Figure 1. *Kaplan-Meier estimates of overall survival in 41 patients with connective tissue disease-associated pulmonary arterial hypertension. The 1-, 2-, 3-, and 5-year survival rates were 90%, 80%, 77%, and 60%, respectively.*

DISCUSSION

The long-term outcome of CTD-PAH is unsatisfactory.[11] Overall, 41 patients with CTD-PAH were included in this cohort study. Among them, SLE was the most common subtype, followed by SSc and MCTD. Overall, 95% of the patients received PAH-specific therapy, of

which monotherapy with PDE5is was the most common treatment. One-third of the patients received add-on macitentan therapy. Improvements in FC, 6MWD, serum uric acid, SPAP, TAPSE, and the ratio of TRV/VTI_{RVOT} were seen during follow-up. Notably, increased CRP levels were common during the study period. Baseline CRP level, SPAP, MPA diameter, and PVR were important factors related to mortality. The overall 1-, 2-, 3-, and 5-year survival rates were 90%, 80%, 77%, and 60%, respectively. Most patients died of RHF. Of note, the outcomes in this study are worse than those in our previous report on patients with PAH.[12]

The prevalence of PAH varied between the subtypes of CTD. A national cohort study reported that the highest prevalence of PAH was in patients with SSc (7.68%) and the lowest rate was in patients with rheumatoid arthritis (0.04%).[7] However, cases of CTD-PAH were more common in patients with SLE due to the higher prevalence of SLE than SSc.[7] In the present cohort study, the most common subtype of CTD-PAH was SLE, followed by SSc and MCTD, similar to reports from China and Korea.[3,4] In contrast, SSc is the most common CTD-PAH in Europe and the US.[13,14] The prognosis of patients with CTD-PAH has been reported to be worse than that of patients with idiopathic PAH.[15] The survival of CTD-PAH has been reported to differ between subtypes, with SSc-PAH having a worse prognosis than SLE-PAH and MCTD-PAH.[16] This is consistent with the results of this study; however, the difference between subtypes was insignificant (Figure 2). The survival between the risk groups was better discriminated by the COMPERA risk score than the REVEAL 2.0 risk score in this cohort (Figure 3). More patients were in the high risk group than the intermediate risk group according to the REVEAL 2.0 risk score, possibly due to vital signs (systolic blood pressure < 110 mmHg and heart rate > 96 bpm) and hospitalization within 6 months before enrollment in this study.

All patients in this study were referred from the Department of Rheumatology. Most had severe symptoms with FC III/IV and intermediate/high-risk status at the time of PAH diagnosis. This indicates that an early diagnosis of CTD-PAH is difficult to establish. One of the reasons for this may be due to the nonspecific presentation of the symptoms in PAH, such as dyspnea, chest tightness, palpitation, syncope, or leg edema, which are also commonly reported in patients without PAH. More importantly, patients with CTD typically have other associ-

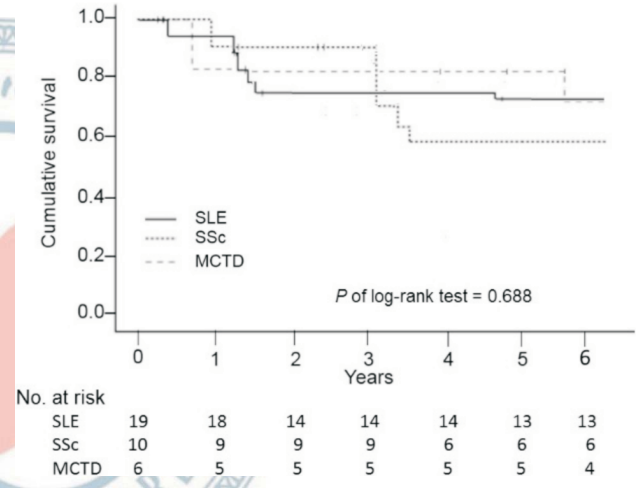

Figure 2. *Survival rate of different CTD-PAH subtypes, including SSc-PAH, SLE-PAH and MCTD-PAH. CTD, connective tissue disease; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.*

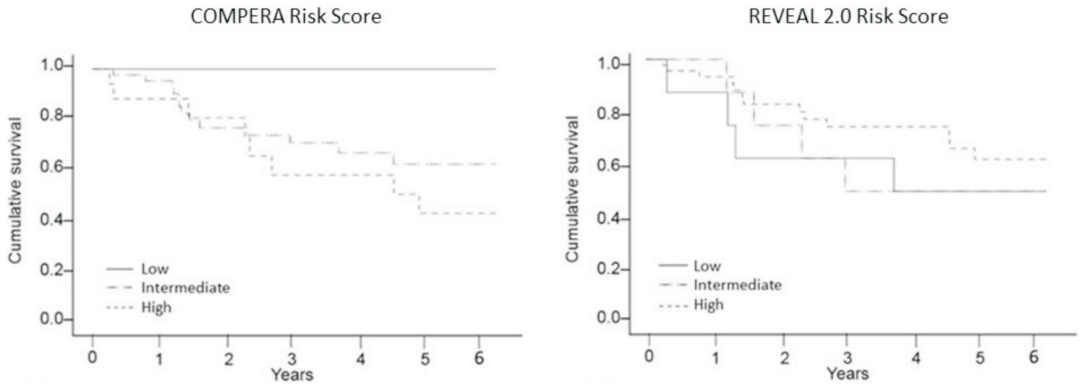

Figure 3. *Kaplan-Meier survival estimates in patients with connective tissue disease-associated pulmonary arterial hypertension by the COMPERA and REVEAL 2.0 risk stratification at baseline. COMPERA, the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; REVEAL, the Registry to Evaluate Early and Long-Term PAH Disease management.*

ated systemic diseases, including musculoskeletal disorders, interstitial lung disease, and diastolic dysfunction of the left ventricle. All of these systemic diseases limit the patient's functional capacity and performance, which makes the early diagnosis of CTD-PAH challenging.[17] Therefore, a screening program is recommended, especially for high-risk groups such as those with SSc.[2] Screening allows for the earlier detection of PAH in patients with SSc.[16] Patients identified by screening programs for SSc-PAH have been shown to have a better prognosis than those who only received routine care.[18]

Although limitations in functional performance are caused by other associated conditions in patients with CTD, 6MWD is still considered a good measure of functional capacity.[19,20] The baseline 6MWD was not different between the survivors and non-survivors in this study; however, an improvement in 6MWD was seen after PAH-specific therapy. This finding is in line with previous clinical trials of CTD-PAH.[21,22]

Elevated serum uric acid levels are associated with severity and mortality in patients with PAH.[23,24] The baseline uric acid level did not differ between the survivors and non-survivors in this study. However, a significant reduction was observed during the follow-up period, which is similar to our previous report on PAH.[12] Therefore, monitoring serum uric acid is important in the clinical follow-up of patients with CTD-PAH.

CRP is a sensitive inflammatory marker that is frequently used to monitor disease activity in CTD.[25,26] We only initiate PAH-specific therapy after reducing disease activity. CRP is a risk predictor of cardiovascular and coronary artery diseases.[27] Increased CRP levels have been reported to be a predictor of poor outcomes in patients with PAH and chronic thromboembolic PH.[28] This observation is in line with the results of this study, in which we observed higher CRP levels in the non-survivors than in the survivors. Notably, increased CRP levels were observed during follow-up. This indicates that inflammation may lead to PAH progression.[29,30] Therefore, targeting both PAH and inflammation is crucial during the treatment of patients with CTD-PAH.

Serum BNP is an important prognostic parameter in patients with PAH.[2,8] However, BNP levels in this study did not differ between the survivors and non-survivors. This may be due to the fact that most patients were at intermediate/high risk with FC III/IV at the time of diagnosis, which resulted in relatively high BNP levels at baseline. In addition, although the reduction in BNP levels was insignificant during follow-up, FC improved. This indicates that BNP as a prognostic biomarker in CTD-PAH may not be as sensitive for idiopathic, heritable, and anorexigen-induced PAH.

Echocardiography is an important modality for diagnostic and follow-up studies in patients with PAH.[2] A higher estimated SPAP was found in the non-survivors than in the survivors in this study. Although estimated SPAP by echocardiography has good correlation with SPAP obtained by RHC, under- and over-estimations by echocardiography are common.[31,32] Therefore, echocardiography should be considered to evaluate the probability rather than the definite presence or absence of PH.[2] RHC is necessary for the confirmation of PAH. PAPs (including SPAP, DPAP and MPAP) were insignificantly different between the survivors and non-survivors in this study. However, there was a trend of lower cardiac output in the non-survivors than in the survivors. As a result a significantly higher PVR was found in the non-survivors than in the survivors. PVR is considered to be a predictor of outcomes rather than PAPs in PAH patients.[2] The presence of pericardial effusion is an indicator of RHF and poor prognosis.[33] Although the presence of pericardial effusion at baseline did not differ between the survivors and non-survivors in this study, pericardial effusion was less frequent at 12 months of follow-up compared to baseline. This finding is compatible with the improvement in RV function, such as a reduced Tei index and increased TAPSE and RVFAC values. However, the presence of pericardial effusion was common again in long-term follow-up, which may have been caused by the progression of CTD-PAH.

The SUPER study is the first clinical trial to show that sildenafil therapy can increase 6MWD in patients with CTD-PAH.[21,22] This is in line with our results. Most patients in this study received PAH-specific therapy with sildenafil monotherapy. One-third of the patients received add-on macitentan combination therapy due to an inadequate clinical response to monotherapy. In subgroup analysis of 33 cases with CTD-PAH in our previous report, 28 (85%) received monotherapy and 3 (9%) received combination therapy. The 1-, 2-, 3-, and 5-year survival rates were 88%, 82%, 82%, and 76%, respectively.[12] Although more patients (37%) received combination therapy in this study, the overall survival rate was

not significantly different between these two cohorts. This is likely due to the small number of cases in the studies. However, the SERAPHIN study showed that macitentan add-on therapy reduced morbidity and mortality by 42% versus monotherapy.[34] Additionally, selexipag combined with ERA and/or a PDE5i resulted in a 44% reduction in morbidity and mortality compared with ERA and/or a PDE5i in the GRIPHON study.[35] However, selexipag therapy was not used in this study.

This study has some limitations. First, this was a single center cohort study and the number of cases was relatively small; in addition, all cases were referred from the Department of Rheumatology. Therefore, our findings may not represent all patients with CTD-PAH. Additionally, 29 (41%) patients with CTD with a high probability of PH were excluded due to their refusal to undergo RHC. Three of these patients were men. Hence, selection bias may have occurred. Also, PAH-specific therapy was dependent on the National Health Insurance program in Taiwan, and sildenafil is the only PDE5i permitted as a first-line therapy in patients with CTD-PAH. Macitentan is the only ERA that can be used as a sequential add-on in the event of an inadequate clinical response to sildenafil therapy. These treatment limitations may have influenced our subjects' outcomes.

CONCLUSIONS

PAH is a serious complication of CTD in which RHF has become a major cause of mortality. The overall survival of patients with CTD-PAH is unsatisfactory. Non-survivors had more dilated MPA, a higher PAP, and PVR. Improvements in FC, 6MWD, serum uric acid, RV function, and PVR were seen during PAH-specific therapy. Increased CRP, indicating the presence of an inflammatory processes, was observed during follow-up, and it is also crucial for the management of CTD-PAH. Therefore, targeting both PAH and inflammation is important in patients with CTD-PAH. Further multicenter investigations are required to determine the optimal treatment strategy for CTD-PAH.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflicts of interest.

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