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ORIGINAL ARTICLE

Survival and prognostic factors in patients with connective tissue disease-associated pulmonary hypertension diagnosed by echocardiography: results from a Korean nationwide registry

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Abstract

Objectives: Pulmonary arterial hypertension (PAH) is a major cause of mortality in connective tissue disease (CTD). The survival rates and mortality-predictive factors of a nationwide registry of Korean patients with CTD-PH measured by echocardiography were determined.

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Methods: Patients with CTD-PH were enrolled between April 2008 and December 2012. Hemodynamic parameters and clinical data (WHO-functional class [FC], organ involvement, laboratory tests and treatment agents) were recorded. Survival rates were calculated by using the Kaplan–Meier method. Mortality-associated factors were examined by Cox proportional hazards regression analysis.

Results: In total, 174 incident PH cases (61 with systemic lupus erythematosus, 50 with systemic sclerosis, 10 with mixed CTD, 22 with rheumatoid arthritis (RA) and 31 with other CTDs) were diagnosed by Doppler echocardiography. Of these, 25 (14%) died during the 3.8 ± 2.7 year follow-up period after PH diagnosis. The 1- and 3-year survival rates were 90.7% and 87.3%, respectively. Compared to the other CTD-PHs, RA-PH had the lowest survival rates (56% 3 year survival; $P = 0.022$). Multiple regression analysis revealed that low diffusion capacity of carbon monoxide (DLCO), pleural effusion and diabetes mellitus were poor prognostic factors ($P = 0.008$, 0.04 and 0.009, respectively). Anti-UI-RNP (ribonucleoprotein) antibody positivity was protective ($P = 0.022$). In patients with WHO-FC III/IV, patients who received vasodilators had lower mortality than those who did not ($P = 0.038$).

Conclusions: In Korean patients with CTD-PH, the 3-year survival rate was 87%. Low diffusion capacity of carbon monoxide (DLCO), pleural effusion and diabetes mellitus were independent poor prognostic factors. Anti-UI-RNP antibody was protective. Prompt PAH-specific vasodilator therapy may improve the survival of patients with severe CTD-PH.

Key words: connective tissue disease, pulmonary hypertension, survival, systemic lupus erythematosus, systemic sclerosis.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rapidly progressive disorder and is associated with a high mortality rate despite medical intervention.[1] It is a common complication in patients with connective tissue disease (CTD), including systemic lupus erythematosus (SLE) and mixed CTD (MCTD).[2,3] When combined with CTD, PAH significantly worsens the prognosis and is a major cause of mortality, especially in patients with systemic sclerosis (SSc).[4,5] While the outcome of patients with CTD-associated PAH (CTD-PAH) was very poor before 2000, since then PAH-specific vasodilative agents (e.g., endothelin receptor antagonists, phosphodiesterase five inhibitors and prostacyclins) have been used in both CTD-PAH and idiopathic PAH; these agents have been shown to markedly improve the prognosis of CTD-PAH.[2,6,7]

Despite PAH being a major cause of death in CTD, only a few nationwide studies have evaluated the survival and characteristics of patients with CTD-PAH.[6–8] Moreover, the patients in these studies were mostly White: few Asian patients were evaluated. A nationwide registry of CTD-PAH composed of Asians only was also lacking. In addition, the most common disease in the nationwide studies mentioned above was SSc (62–95% had SSc), which means that the results essentially reflected the outcomes of SSc. Thus, the characteristics of patients with non-SSc CTD remain poorly understood. Interestingly, a single-center study of Japanese patients with CTD-PAH revealed that the major underlying CTDs in this population were MCTD and SLE.[2] This suggests that the characteristics and survival rates of Asian patients with CTD-PAH may differ from those of White patients. However, the existing studies on the characteristics of this disease in Asian patients are only based on small patient registries or single-center data;[2,9] given that the incidence of CTD-PAH is low, an Asian nationwide CTD-PAH registry is needed to properly understand the features of this disease in Asians.

The REgistry Of Pulmonary Hypertension Associated with Rheumatic Disease (REOPARD) is a Korean nationwide, multicenter, observational registry established in 2008. Its baseline characteristics have been reported by Jeon *et al.*[10] The REOPARD patients are all Asian, and the most common CTD was SLE. This national registry was used in the present study to investigate the characteristics, survival and mortality-prognostic factors of a cohort of Korean patients with incident CTD-PH by echocardiography.

METHODS

The design and objectives of REOPARD are described elsewhere.[10] The registration process began in April 2008, and 20 centers in Korea participated in the study. In total, 513 consecutive patients presenting at the 20

centers were enrolled between April 2008 and December 2012. The database was locked on December 31, 2012 for the present analyses. Of the 513 patients enrolled in REOPARD, 342 were followed up. Among 342 patients, four patients with only follow-up data and 33 patients who registered in two or more hospitals were excluded. Eleven patients were excluded because their underlying diseases were not CTDs. Additionally, five patients who died before April 2008 and 16 patients without the record of the diagnosis by echocardiography or right heart catheterization (RHC) were excluded. A total of 273 patients among 342 follow-up patients were identified as CTD-PH by echocardiography follow-up data. While patients with either incident or previously diagnosed PH could be enrolled in the study, only the 174 registered patients with incident PH were analyzed in this study. Institutional Review Board approval was obtained at each study site.

All patients were cared for by rheumatologists. All patients had an underlying CTD, such as rheumatoid arthritis (RA), SLE, MCTD, overlap syndrome, Sjögren's syndrome (SS), or inflammatory myositis. These diseases were diagnosed on the basis of the following criteria: American College of Rheumatology diagnostic criteria for SSc,[11] RA[12] and SLE,[13] and the Alarcon-Segovia diagnostic criteria for MCTD.[14] Overlap syndrome is defined as an entity that satisfies the diagnostic criteria of at least two CTDs.[15] SS was diagnosed on the basis of the revised criteria proposed by the American-European Consensus Group.[16] Dermatomyositis (DM) and polymyositis (PM) were diagnosed by the Bohan and Peter diagnosis and classification criteria.[17] Undifferentiated CTD (UCTD) was defined by classification critiera.[18] Adult-onset Still disease (AOSD) was diagnosed by Yamaguchi's criteria for classification.[19] In the analysis, SS, DM, PM, UCTD and AOSD were categorized as 'other'.

The date of PH diagnosis was defined as the date of Doppler echocardiography. PH was diagnosed on the basis of the following criteria: a systolic pulmonary arterial pressure (sPAP) > 40 mmHg, as measured by Doppler echocardiography. Patients were excluded if they had severe interstitial lung disease (ILD) or other lung disease or other conditions associated with pulmonary hypertension.

Demographic data were collected when the patient registered in REOPARD. The data collected at the time of PH diagnosis included age, sex, time of CTD diagnosis, underlying CTD type, tests used to diagnose PH, date of PH diagnosis, hemodynamic parameters, World Health Organisation (WHO)-functional class (FC), pulmonary functional test (PFT), N-termainal pro-brain natriuretic peptide (NT-pro-BNP) levels, and comorbidities. Clinical manifestations, such as Raynaud's phenomenon, ischemic ulcer, pleural effusion, pericardial effusion proteinuria and ILD, and serological autoantibody profiles were collected. PAH treatment data were also collected. The presence of pericardial effusion on echocardiography was documented. Pleural effusion was defined on the basis of X-ray and/or chest computed tomography (CT) scan. Clinical and hemodynamic variables were recorded during follow-up. The status (alive or dead) of the patients at the time of censoring was ascertained from the REOPARD website. To calculate survival, an end point of either date of death or last follow-up date in the outpatient clinic was used.

Statistical analysis was performed by using SPSS version 18 (SPSS Inc., Chicago, IL, USA). Mean and standard deviation (SD) were used to describe continuous data. Survivors and non-survivors were compared in terms of continuous and categorical variables by using an independent *t*-test and the χ^2 test, respectively. Survival estimates were calculated by using the Kaplan–Meier method, and groups were compared in terms of survival by using the log-rank test. Mortality-associated factors were examined by using Cox proportional hazards regression analysis. Variables selected by univariate analysis were further subjected to multivariate analysis. The results were presented as hazard ratios (HRs) with 95% confidential intervals (CIs). A P-value < 0.05 was considered to indicate statistical significance. No imputation was performed for missing data.

RESULTS

Clinical characteristics

The registry contained 174 incident cases of PH by echocardiography in total. All patients were Asian. Table 1 shows the clinical data of the patients at the time PH was diagnosed. Most of the patients were female ($n = 149$, 85.6%), and the mean age when PH was diagnosed was 51 ± 17 years. SLE was the most common underlying CTD (35%), followed by SSc (29%), RA (13%), and MCTD (6%). There were 25 deaths (14%) during the 3.8 ± 2.7 year follow-up period after PH diagnosis. Comparison of the survivors and non-survivors revealed that they did not differ in age at PH diagnosis (50 ± 17 *vs.* 60 ± 14 years old, $P = 0.172$), sex ($P = 0.212$), or underlying CTD type ($P = 0.11$). In total, 140 patients (80%) were positive

Table 1 Demographic and clinical characteristics at the time of pulmonary arterial hypertension diagnosis of all patients and patients stratified according to survival

	Total	Survivors	Non-survivors	*P*-value†
Number	174	149	25	
Female	149	130	19	0.212
Age	50.9 ± 16.9	50.1 ± 17.2	60.0 ± 14.2	0.172
Underlying CTD				
SSc	50	44	6	0.11
SLE	61	54	7	
MCTD	10	10	0	
RA	22	15	7	
Overlap syndrome	7	5	2	
Others‡	24	21	3	
Auto-antibodies§				
ANA	140	123	17	0.25
Anti-centromere Ab	16	14	2	0.57
Anti-Scl 70 Ab	25	21	4	0.489
Anti-phospholipid Ab	35	29	6	0.57
Anti-RNP Ab	47	45	2	0.083
WHO functional class¶				
Class I	53	50	3	< 0.001
Class II	50	45	5	
Class III	46	38	8	
Class IV	15	6	9	
Baseline RHC mPAP (mmHg)††	39.4 ± 21.2			
Baseline echo sPAP (mmHg)	55.1 ± 17	55.5 ± 17.8	51.9 ± 11.4	0.106
Baseline PFT				
DLCO	55.6 ± 26.9	58.7 ± 26.2	39.6 ± 25.5	0.025
DLCO/VA	77.1 ± 31.5	80.4 ± 31.6	58.8 ± 25.1	0.028
FVC	66.6 ± 21.5	68.7 ± 20.5	55.4 ± 24.1	0.027
FEV_1	69.6 ± 22.1	71 ± 21.3	62.6 ± 25.2	0.18
Baseline NT-proBNP (pg/mL)‡‡	4308 ± 8476	4101 ± 8597	5238 ± 8145	0.839
Smoking	6	4	2	0.261
Hypertension	50	42	8	0.815
Hepatitis	25	23	2	0.219
Diabetes mellitus	24	17	7	0.057
Pericardial effusion	51	44	7	0.574
Pleural effusion	46	34	12	0.012
Proteinuria	52	43	9	0.33
Vasodilator therapy	53	46	7	0.771
Monotherapy	46	41	5	0.442
Combination therapy	7	5	2	

Values are presented as mean ± SD, unless otherwise indicated. CTD, connective tissue disease; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; MTCD, mixed connective tissue disease; RA, rheumatoid arthritis; RNP, ribonucleoprotein; RHC, right heart catheterisation; NT-pro BNP, N-terminal pro-brain natriuretic peptide.
†Comparison between survivors and non-survivors.
‡Other CTDs include Sjogren's syndrome, dermatomyositis, polymyositis, undifferentiated connective tissue disease and adult-onset Still disease.
§Available data in 170 patients.
¶Available data in 164 patients.
††These data are available for only 17 patients.
‡‡Available data in 101 patients.

for anti-nuclear antibody (ANA), with the most prevalent ANA being anti-U1-ribonucleoprotein (RNP) antibody (27% of the cohort had this antibody). The survivors were more likely than the non-survivors to be positive for anti-U1-RNP (ribonucleoprotien) antibodies ($P = 0.083$).

Table 2 Causes of death according to underlying connective tissue disease

Underlying disease (no. of deaths)	SSc (6)	SLE (7)	RA (7)	Overlap syndrome (2)	Other diseases (3)
PAH-related death	2	0	0	0	0
PAH non-related death	4	7	7	2	3
Infection	4	3	5	1	
Disease activity		3		1	2
Cardiovascular disease			1		
Malignancy		1			
Other causes			1†		1‡

SSc, systemic sclerosis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; PAH, pulmonary arterial hypertension.
†Pulmonary embolism.
‡Thrombotic thrombocytopenic purpura.

Most patients had mild symptoms at diagnosis: 59.2% had WHO-FC I/II disease. However, the non-survivors were significantly more likely to have severe symptoms (class III/IV; 68%) than the survivors (29.3%; $P < 0.001$). At diagnosis, the mean pulmonary artery pressure (mPAP) of the cohort (as measured by RHC) was 39 ± 21 mmHg. All patients underwent echocardiography at diagnosis and the mean systolic PAP (sPAP) was 55 ± 17 mmHg. The survivors and non-survivors did not differ significantly in terms of baseline sPAP or NT-pro-BNP levels.

Of the PFT parameters, the non-survivors had lower DLCO, DLCO/VA (alveolar volume) and forced vital capacity values than the survivors ($P = 0.025$, 0.028 and 0.027, respectively). In total, 75 patients (43%) had radiological evidence of ILD. In terms of co-morbid disease, the non-survivors were more likely to have diabetes mellitus than the survivors ($P = 0.057$), but the two groups did not differ in terms of smoking history, hypertension or hepatitis. The non-survivors were significantly more likely to have pleural effusion than the survivors ($P = 0.012$), but the two groups did not differ in terms of pericardial effusion or proteinuria.

Table 2 showed the cause of death according to underlying CTD. The most common cause of death was infection (52%) and disease activity (24%). PAH-related death was two among 25 deaths (8%) and the two patients' underlying disease was SSc.

Survival rates

The 1-, 3- and 5-year survival rates were 90.7%, 87.3%, and 73%, respectively (Fig. 1). When the patients were divided according to the underlying CTD, the survival rates differed markedly ($P = 0.022$): the 1- and 3-year survival rates of SLE-PH (91.7% and 91.7%, respectively), SSc-PH (91.8% and 89.2%, respectively), and MCTD-PH (100% and 100%, respectively) were quite high, whereas the 1- and 3-year survival rates for RA-PH were poor (76.5% and 56.1%, respectively). Thus, SLE-PH, SSc-PH and MCTD-PH were associated with significantly better survival compared to RA-PH ($P = 0.006$, 0.017 and 0.044, respectively). SLE-PH and SSc-PH did not differ significantly in survival rates.

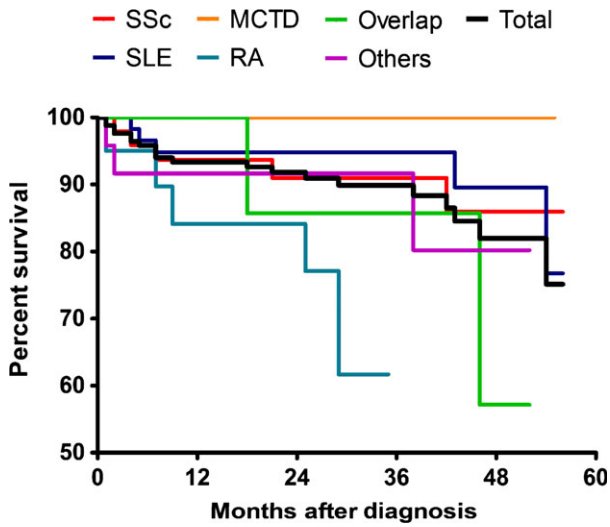

Figure 1 Cumulative survival rates in 174 patients with connective tissue disease-associated pulmonary hypertension and comparison of survival rates according to the underlying connective tissue disease. SLE, systemic lupus erythematosus; SSc, systemic sclerosis; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; overlap, overlap syndrome; others, other CTDs. The groups were compared using the log-rank test.

Prognostic factors

Univariate analysis to identify mortality-predictive variables recorded at PH diagnosis revealed that an age

> 60 years, WHO-FC III/IV disease, low DLCO (< 60%), presence of pleural effusion, diabetes mellitus and anti-RNP antibody positivity were associated significantly with higher mortality (Table 3). When these variables were subjected to multivariate analysis, low DLCO (< 60%), presence of pleural effusion and diabetes mellitus were prognostic factors of mortality (P = 0.008, 0.04 and 0.009, respectively). Anti-RNP antibody positivity signaled a favorable outcome (P = 0.022; Table 3).

Effect of vasodilator therapy on survival

Table 3 indicates the agents used to treat the patients. Of the 174 patients, 121 (69.5%) were treated with a calcium channel blockers, 16 (9.2%) received anticoagulant agents and 53 (30.5%) received PH-specific therapy. Of the latter treatments, an endothelin receptor antagonist was the most commonly prescribed PAH-specific medication; it was used by 37 patients (21.3%). Prostacyclin was the next most common PAH-specific medication (19 patients, 10.9%), followed by phosphodiesterase type V inhibitor (four patients, 2.3%). Seven patients (4%) received combination vasodilator therapy (Table 4). The different treatment agents did not associate with significantly different survival rates in univariate analysis (data not shown). However, to confirm that vasodilator therapy improves survival in CTD-PAH, the patients with WHO-FC I/II disease were separated from the patients with III/IV disease; within these subgroups, the survival of the patients who did or did not receive vasodilator therapy were assessed (Fig. 2). In the patients with WHO-FC I/II disease, vasodilator therapy did not affect survival. By contrast, in the patients with WHO-FC III/IV disease, the patients who received vasodilators survived significantly longer than the patients who did not (P = 0.038).

DISCUSSION

This present study is the first nationwide study of CTD-PH detected by echocardiography in Asians. Its cohort included the majority of patients with CTD-PH within Korea during the study period. The survival outcomes of only the incident CTD-PH cases were assessed. The association between survival and comorbidities was also evaluated.

This study is the first national registry to include Asian patients only. Although studies performed in other East Asian countries have been reported,[2,9,20] they may be prone to selection bias because of the small

Table 3 Predictors of mortality in patients with connective tissue disease-associated pulmonary arterial hypertension, as determined by univariate and multivariate analyses

Variable	*n*/25	Univariate analysis†	Multivariate analysis‡	
		P-value	Hazard ratio	*P*-value
Age		0.048		
< 60 years	12			
≥ 60 years	13			
Echo sPAP (mmHg)		0.21		
< 60	19			
60–79	6			
≥ 80	0			
WHO functional class		0.001		
Class I/II	8			
Class III/IV	17			
PFT DLCO (%)		<0.001		0.008
≥ 80	3		Reference	
60–79	5		11.3 (0.5–239.5)	0.119
40–59	8		172.9 (6.3–4712.1)	0.002
<40	9		62.3 (2.7–1447.1)	0.01
Pleural effusion	12	0.006	5.9 (1.1–32.7)	0.04
Anti-RNP Ab	2	0.033	0.001 (0.0–0.35)	0.022
Diabetes mellitus	7	0.014	11.5 (2.0–16.1)	0.009

Echo sPAP, echocardiography systolic pulmonary arterial pressure; PFT DLCO, pulmonary functional test diffusion capacity of carbon monoxide; RNP, ribonucleoprotein.
†Log-rank test.
‡Multivariate proportional hazard regression analysis.

Table 4 Pulmonary arterial hypertension-specific therapies for patients with connective tissue disease- associated pulmonary arterial hypertension

Drug	*n* (%)	Survivors	Non-survivors	*P*-value†
CCB	121 (69.5)	104	14	0.819
Diuretics	30 (17.2)	21	9	0.018
Anti-coagulation	16 (9.2)	14	2	0.823
Vasodilators	53 (30.5)	46	7	0.773
ERA	37 (21.3)	33	4	0.604
PDE5i	4 (2.3)	2	2	0.099
PC	19 (10.9)	16	3	0.074
Combination	7 (4)	2	5	

CCB, calcium channer blocker; ERA, endothelin receptor antagonists; PDE5i, phosphodiesterase 5 inhibitors; PC, prostacyclins.
†Comparison between survivors and non-survivors.

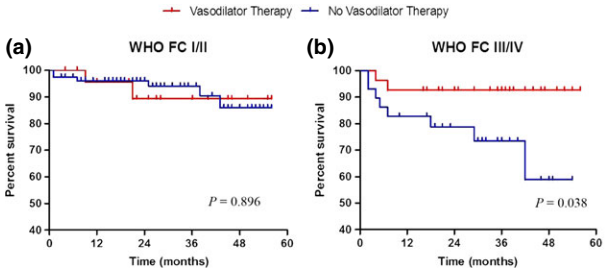

Figure 2 Comparison of the effect of vasodilator therapy on the survival of patients stratified according to disease severity. The patients with World Health Organization (WHO)-functional class (FC) I/II disease (a) were separated from the patients with WHO-FC III/IV disease (b), and the effect of pulmonary arterial hypertension-specific vasodilator therapy on the survival rates was assessed by using the Kaplan–Meier method.

sample number and the fact that the data were from a few centers only. Since the present study was based on an unselected national registry, it may be less affected by selection bias.

The present study showed that the 1- and 3-year survival rates in CTD-PH were 90.7% and 87.3%, respectively. This 91% 1-year survival rate is similar to the 94% 1-year survival rate of an Australian cohort[7] but is higher than the survival rates reported for cohorts in the United States and United Kingdom: in the US cohort (REVEAL), the 1-year survival rate was 86%,[8] while the incident cases in a United Kingdom registry had respective 1- and 3-year survival rates of 78% and 47% for SSc-PH, and 78% and 74% for SLE-PH.[6] The better outcomes of our patients may reflect the fact that their symptoms at the time of enrolment were milder than those of the patients in the other registries;[2,6,8] supporting this is that the present cohort had a high frequency of WHO-FC I/II disease. This may ultimately lead to a relatively good survival rate. Another possible explanation for the better survival of our study cohort is that our study focused on Asian patients, whereas the other studies largely evaluated Whites. This racial disparity was reflected by a different distribution of the underlying CTDs in our cohort compared to the distribution in other national registry cohorts: whereas SSc predominated in the Western cohorts, in our cohort, SLE was the most common underlying CTD and SSc was less frequent. This observation is consistent with a recent single-center study on Japanese patients with CTD-PAH.[2] Similarly, a report from China showed that Asians are more likely to have SLE as the underlying CTD than SSc.[9] The cause of this racial discrepancy is not yet clear, but it may reflect genetic and environmental factors.

The present study showed that independent mortality predictors in CTD-PH were low DLCO, pleural effusion and diabetes mellitus at PH diagnosis, while anti-RNP antibody positivity predicted a good outcome. The association of low DLCO with higher mortality reflects the presence of an ILD, a diminishing vascular area with reduced metabolic activity[21] and the underlying systemic vasculopathy in SSc.[8] While we included the CTD-PAH patients who had ILD in our survival analysis, Chang *et al.*[22] found that SSc patients with pulmonary hypertension alone did not differ in terms of survival from SSc patients with both pulmonary hypertension and restrictive lung disease.

That pleural effusion was also a predictor of mortality in CTD-PAH is consistent with a previous study that showed that patients with pleural effusion had a poorer survival than patients without pleural effusion.[23] Luo *et al.* reported that pleural effusion is common in both CTD-PAH and idiopathic PAH.[23,24] Although the physiology of pleural effusion accumulation is incompletely understood, pleural effusion may be related to right heart failure.[23] This may explain why our patients with pleural effusion had higher mortality than patients without pleural effusion. The other explanation is that the serositis caused by CTD itself causes pleural effusion. While one study found pleural effusion due to serositis is common in SLE, RA and MCTD, but is uncommon in SSc,[25] another study found about 50% of patients with SSc-PAH have pleural effusion.[23] This suggests that the higher mortality of our patients with pleural effusion is due to the concomitant right heart failure rather than the serositis in CTD.

The association between anti-UI-RNP antibodies and lower mortality in the present study is interesting. While these antibodies can be found in SLE and SSc, they mainly associate with MCTD. Although it is not clear whether this antibody has any pathological effects, it does associate with various clinical features. One study showed that in SSc, anti-U1-RNP antibodies are associated with PAH.[26] MCTD shares several clinical features with SLE and SSc, which makes it difficult to distinguish MTCD from SLE or SSc. MCTD responds well to steroid treatment and has a relatively good outcome. Thus, it is possible that some of the SLE or SSc patients with anti-U1-RNP antibody in our cohort actually had MTCD. This may explain why anti-U1-RNP antibody positivity was predictive of a better survival rate in the present study.

The present study showed that the presence of diabetes mellitus elevated the risk of mortality in CTD-PH. This is consistent with the REVEAL study, which found that several co-morbid diseases are associated with a higher risk of death in idiopathic PAH[27]. In addition, Belly *et al.*[28] reported that high HbA1c levels in patients with PAH but without diabetes mellitus independently predicted a poorer long-term prognosis. Impaired glucose metabolism has been noted in PAH, and one clinical study found that this disease associates with a higher insulin-resistance rate.[29] Similarly, we found that diabetes mellitus was predictive of higher mortality in CTD-PH. The high prevalence of diabetes mellitus in the PAH population emphasizes the need for well-designed studies that consider the impact of diabetes mellitus on CTD-PAH.

Our univariate analysis showed that higher baseline WHO-FC also predicted greater mortality. However, after adjusting for multivariate factors, it no longer associated significantly with mortality. This may reflect the fact that it is a subjective measure that does not always correlate with mPAP and 6-min walking distance.[30] In the present study, vasodilator use did not predict survival on multivariate analysis, but this may reflect the high frequency of patients with WHO-FC I/II disease. By contrast, studies on cohorts with a high proportion of patients with WHO-FC III/IV disease suggest that vasodilator therapy is an independent predictor of better survival.[2] Indeed, when we separated the patients with WHO-FC I/II and WHO-FC III/IV disease and assessed the effect of PAH-specific vasodilator use on survival, we found that PAH-specific vasodilator therapy was associated with significantly better survival in the patients with WHO-FC III/IV disease; this effect was not observed in the patients with WHO-FC I/II disease. Thus, prompt PAH-specific vasodilator therapy may improve the survival of patients with severe CTD-PAH.

This study had several advantages over other nationwide registry studies.[6,8] While the other studies were primarily designed by cardiologists, rheumatologists played a leading role in designing the REOPARD registry. This meant that we could investigate the association between auto-antibodies and survival. Furthermore, this nationwide registry was managed by the Korean College of Rheumatology, which is likely to have minimized selection bias.

Our study also had several limitations. First, since the RHC data were not always present, PH cases were defined on the basis of sPAP $>$ 40 mmHg, as measured by Doppler echocardiography. The prominent use of echocardiography for diagnosis may have increased the likelihood that patients with better WHO-FC disease were selected. It was reported previously that RHC-based diagnosis in Korea may be less frequent than in Western countries.[10] Korean national health insurance approved the result by echocardiography, without the RHC data, as evidence for the diagnosis and the PAH-specific therapy. As a result, Korean rheumatologists prefer to use less invasive diagnostic tools. The resting Doppler echocardiography provides a reasonably reliable and comprehensive assessment of the right heart and pulmonary circulation. A sPAP value $\geq$ 40 mmHg, as measured by echocardiography, is considered to be a cut-off value for PAH diagnosis.[31] Another limitation was that, although all echocardiography data were reported by the cardiology specialist, the central interpretation of these data was not. This raises the possibility of inter-observer variation in measurements. The other limitation of this study is its uncontrolled nature and the fact that many of the data were collected retrospectively, meaning that there were unavoidable gaps in the database. The analysis of the effect of PAH-specific therapy in this study was also based on uncontrolled data. This reflects the fact that there is no treatment guideline for CTD-PAH in Korea; thus, PAH-specific therapies are recommended at the discretion of individual physicians and centers. The usefulness of PAH-specific therapies should be evaluated by randomized controlled clinical trials.

In conclusion, the present study, which was based on a Korean nationwide registry that only included incident cases, is the first to report the clinical characteristics of CTD-PH by echocardiography in Asians and the mortality-prognostic factors. SLE was the most common underlying CTD, unlike in Western cohorts, where SSc predominates. Moreover, low DLCO, pleural effusion and diabetes melllitus were poor prognostic factors,

while anti-UI-RNP antibody positivity was associated with lower mortality.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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