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ORIGINAL ARTICLE

Outcomes and Risk Factors of Systolic Pulmonary Artery Pressure Progression in Patients With Systemic Rheumatic Diseases: Follow-up Results from a Korean Registry

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ABSTRACT

Objectives: This study aims to investigate the outcomes and risk factors associated with the progression of systolic pulmonary artery pressure (sPAP) in patients with systemic rheumatic diseases.

Patients and methods: A total of 532 patients (73 males, 459 females; median age 49 years; interquartile range (IQR), 36 to 62 years) registered with the Registry of Pulmonary Hypertension Associated with Rheumatic Diseases were included. Mortality curves were constructed using the Kaplan-Meier method and comparisons were performed using the log-rank test. A paired t-test was performed to evaluate the patients with markedly elevated sPAP between baseline and follow-up.

Results: The average follow-up duration was 31 months (IQR, 9 to 60 months). Of the patients, 196 had follow-up echocardiographs at least one year later. We defined the sPAP over 60 mmHg as markedly elevated. Patients in the increased sPAP above 60 mmHg at follow-up and persistently markedly elevated sPAP were associated with worse outcomes in all-cause mortality and pulmonary arterial hypertension-related mortality ($p<0.001$). In patients with systemic sclerosis, the majority of patients remained static within their pressure group or rose progressively: the patients with markedly elevated sPAP at follow-up were higher than those at baseline (32% versus 15%, $p<0.01$). In patients with mixed connective tissue disease (MCTD) or rheumatoid arthritis (RA), the majority of patients remained static within their pressure group or gradually improved: the patients with markedly elevated sPAP at follow-up were lower than those at baseline (RA=14% versus 29%, MCTD=5% versus 16%, $p<0.05$).

Conclusion: Persistently high sPAP or increase of sPAP over 60 mmHg at follow-up was associated with increased mortality. There were some differences in the progression of sPAP according to the underlying rheumatic diseases.

Keywords: Connective tissue diseases, hypertension, prognosis, pulmonary, rheumatic diseases, systolic pulmonary artery pressure.

Pulmonary arterial hypertension (PAH) is a rare disease that can lead to death if untreated.[1] Several systemic rheumatic diseases such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD) can cause PAH. PAH is an important complication associated with morbidity and mortality of systemic rheumatic diseases.[2] In addition, there may be some differences in the pathogenesis of PAH depending on the underlying rheumatic disease, which may lead to various outcome or treatment responses.[3]

An evaluation of the severity and progression of PAH is essential to evaluate the patient's response to treatment and to determine the therapy. Right heart catheterization (RHC) is an invasive procedure such that it cannot be used easily, and there is no evidence that regular RHC is associated with better outcome compared to a non-invasive follow-up.[1] Echocardiography is

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a useful tool for assessing PAH because it is a non-invasive, less expensive, and more easily available procedure at medical centers. The most common non-invasive test used for the screening and diagnosis of PAH is echocardiography. Furthermore, because the right ventricle function is a key determinant of prognosis in patients with PAH, echocardiography is an important follow-up tool.[1] The systolic pulmonary artery pressure (sPAP) by echocardiography can be estimated from the peak tricuspid regurgitation velocity and estimated right atrial pressure, assuming there is no pulmonary flow obstruction.[4] The sPAP is expected to reflect the mean PAP by RHC, which can be used for the prognosis of PAH. Although it is still questionable whether sPAP estimated by echocardiography reflects actual sPAP, a recent meta-analysis study has shown that although the sPAP estimated by echocardiography is less reliable in borderline cases, it can be used to reliably determine whether sPAP is normal, mildly elevated, or markedly elevated.[4]

The Registry of Pulmonary Hypertension Associated with Rheumatic Diseases (REOPARD) was established in 2008 as a Korean nationwide, multi-center, and observational registry.[5] Baseline characteristics, survival rates, and mortality predictive factors have been reported using data collected from April 2008 to December 2012.[5,6] Ethnicity may also be a factor affecting the prevalence and prognosis of rheumatic diseases. SSc-PAH accounts for most cases of PAH associated with rheumatic diseases in many previous studies, while SLE-PAH accounts for a similar number or more cases when compared to SSc-PAH in this registry-based study, and the prognosis was relatively good compared to other studies; the three-year survival rate was 87%. Since then, additional data have been collected. In this article, we used this resource to investigate the progression and effects of sPAP estimated by echocardiography, as well as to investigate the factors that contribute to the deterioration or improvement of sPAP. In addition, we investigated whether there were any differences in the progression of sPAP according to the underlying rheumatic disease. Thus, in this study, we aimed to investigate the outcomes and risk factors associated with the progression of sPAP in patients with systemic rheumatic diseases.

PATIENTS AND METHODS

This study was conducted at Gil Medical Center, Gachon University College of Medicine using data from the REOPARD. The design and objectives of REOPARD are described elsewhere.[5] The registration process began in April 2008, and a total of 41 centers in Korea participated in the study until January 2016. The data gathered until January 31, 2016 were included in this analysis. A total of 581 patients were registered in REOPARD. There were 49 patients who did not meet the enrollment criteria of this registry and were excluded: 11 patients did not have an accompanying systemic rheumatic disease, and 38 patients did not meet the PAH criteria defined as sPAP >40 mmHg estimated by echocardiography or a mean PAP >25 mmHg at rest, and pulmonary capillary wedge pressure ≤15 mmHg measured by RHC.[5] Therefore, a total of 532 patients (73 males, 459 females; median age 49 years; interquartile range (IQR), 36 to 62 years) were included. The study protocol was approved by the Gil Medical Center, Gachon University College of Medicine Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data such as dyspnea on exertion (DOE), World Health Organization Functional Class (WHO-FC), pulmonary function testing, N-terminal-pro-B-type natriuretic peptide (NT-proBNP), and six-minute walk test (6MWT) were recorded at the initial visit and at follow-up. We used the results that were closest to the date of echocardiography and within one year. Clinical manifestations of organ involvement, serological profiles such as autoantibodies, and PAH specific treatments at initial visit and during the entire follow-up period were also recorded. The date of PAH diagnosis was defined as the date of the first echocardiography. The follow-up duration was defined from the date of PAH diagnosis to the date of the last follow-up. There is no definite definition for the classification of sPAP, but it is usually classified as a high rise when sPAP >60 mmHg.[7,8] The criterion for markedly and mildly elevated sPAP was defined as greater than or below 60 mmHg, respectively. Patients were divided into four groups according

to sPAP levels at the initial visit and follow-up: LL (persistently mildly elevated), LH (below 60 mmHg at baseline and above 60 mmHg at follow-up), HH (persistently markedly elevated), and HL (above 60 mmHg at baseline and below 60 mmHg at follow-up). We analyzed the clinical features and outcomes by sPAP at baseline and follow-up. The mortality rate according to the change of sPAP was analyzed. Finally, we compared the demographics, clinical features, and sPAP progression according to the underlying rheumatic disease.

Statistical analysis

Demographic and clinical characteristics were analyzed using descriptive statistics. Continuous variables were reported as median and interquartile range, and categorical variables as number and percentage. Comparisons were performed with the Chi-square (χ^2) test or Fisher's exact test for categorical variables and independent t-test, or one-way analysis of variance for continuous variables. A multiple comparison procedure was performed using the Duncan multiple comparison test. Variables with $p<0.1$ significance in the univariate analyses were used in a multivariate analysis with a logistic regression (backward stepwise method). A paired t-test was performed to evaluate the ratio of patients with markedly elevated sPAP between the time of the initial visit and follow-up according to underlying rheumatic diseases. Mortality curves were constructed using the Kaplan-Meier method, and comparisons were performed using the log-rank test. All statistical analyses were performed using the PASW for Windows version 18.0 software (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p<0.05$.

RESULTS

Demographics and disease characteristics of the patients were presented in Table 1. The sPAP at baseline was 50 mmHg (IQR, 43 to 67). The underlying rheumatic diseases included SLE (35.5%), SSc (30.3%), rheumatoid arthritis (RA) (10.5%), MCTD (6.0%), overlap syndrome (6.0%), and other diseases (11.7%). Of the 532 patients, 196 patients had follow-up echocardiographs at least one year later. There was no statistically significant difference in baseline characteristics between the total patients and patients with follow-up echocardiography. The time interval between the initial and last echocardiographs was 45 months (IQR, 30 to 68 months). There was a mildly elevated sPAP at baseline in 67.5% of patients, whereas 32.5% of patients had markedly elevated sPAP at baseline (Figure 1). There were 104 (53.1%), 30 (15.3%), 38 (19.4%), and 24 (12.2%) patients in the LL, LH,

Table 1. Demographics and disease characteristics

	Total (n=532)				Follow-up echocardiographs* (n=196)			
	n	%	Median	IQR	n	%	Median	IQR
Females	459	86.3			174	88.8		
Age at diagnosis of RD (years)			42	30-56			41	31-54
Age at diagnosis of PAH (years)			49	36-62			47	36-59
sPAP at baseline (mmHg)			50	43-67			50	43-67
Underlying rheumatic diseases								
Systemic lupus erythematosus	189	35.5			62	31.6		
Systemic sclerosis	161	30.3			65	33.2		
Mixed connective tissue disease	32	6.0			19	9.7		
Rheumatoid arthritis	56	10.5			14	7.1		
Overlap syndrome	32	6.0			16	8.2		
Others	62	11.7			20	10.2		
Follow-up period (months)	31	9-60					59	41-85

* Patients with systolic pulmonary artery pressure estimated by echocardiography at least one year after pulmonary artery hypertension diagnosis; IQR: Interquartile range; RD: Rheumatic disease; PAH: Pulmonary artery hypertension; sPAP: Systolic pulmonary artery pressure.

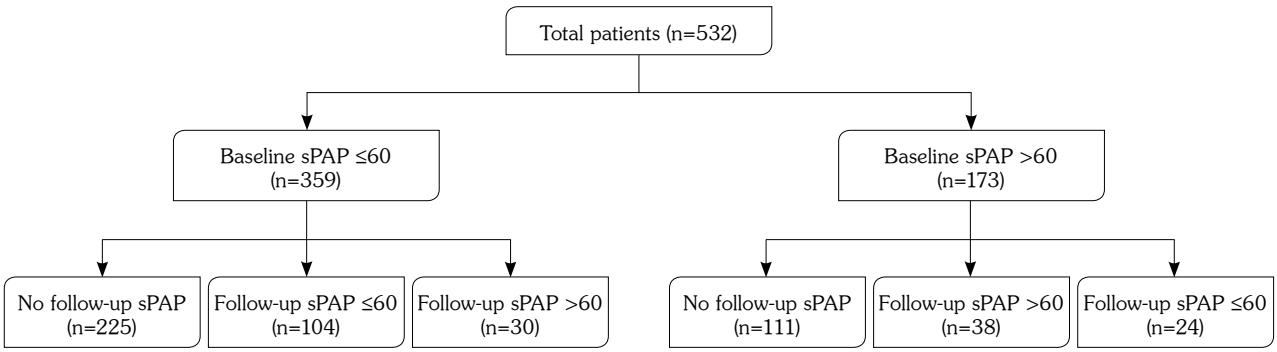
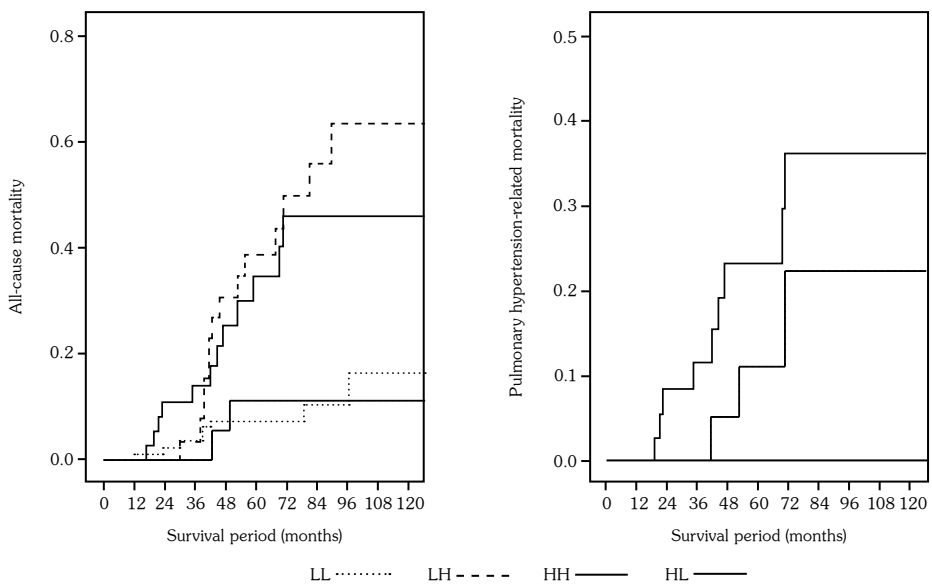


Figure 1. Change of systolic pulmonary artery pressure during follow-up period.
sPAP: Systolic pulmonary artery pressure.

HH, and HL groups, respectively. The changes in the levels of sPAP were as follows: 10 mmHg (IQR, 5 to 16) in the LL group, 30 mmHg (IQR, 28 to 50) in the LH group, 16 mmHg (IQR, 4 to 30) in the HH group, and 31 mmHg (IQR, 24 to 44) in the HL group ($p<0.01$). The time intervals of the initial and last echocardiography were as follows: 44 months (IQR, 30 to 64 months) in the LL group, 52 months (IQR, 38 to 80 months) in the LH group, 39 months (IQR, 24 to 68 months) in the HH group, and 52 months (IQR, 37 to 66 months) in the HL group.

Patients with markedly elevated sPAP at baseline were associated with PAH-related death



Figur 2. All-cause mortality and pulmonary hypertension-related mortality of patients according to change of systolic pulmonary artery pressure (sPAP). Kaplan-Meier curves showing effect of change of sPAP on all-cause mortality (left) and pulmonary hypertension-related mortality (right). Patients in LH or HH group were associated with worse outcomes for all-cause mortality and pulmonary hypertension-related mortality. Groups were compared using log-rank test.

Patients were divided into four groups according to sPAP levels at baseline and at follow-up as LL: Persistently mildly elevated; LH: Below 60 mmHg at baseline and above 60 mmHg at follow-up; HH: Persistently markedly elevated; HL: Above 60 mmHg at baseline and below 60 mmHg at follow-up. Markedly elevated sPAP was defined as sPAP greater than 60 mmHg, and mildly elevated sPAP was defined as sPAP below 60 mmHg.

(p=0.002). There were significantly more deaths (p<0.001), PAH-related deaths (p<0.001), patients with WHO-FC III or IV (p<0.001), and frequent home oxygen therapies (p≤0.001) in patients with markedly elevated sPAP at the time of follow-up. Furthermore, the diffusing capacity of the lungs for carbon monoxide (DLCO) (p<0.05) and 6MWT (p<0.001) were significantly lower in patients with markedly elevated sPAP at the time of follow-up. NT-proBNP was significantly higher in patients with markedly elevated sPAP at the time of follow-up (p<0.01). Patients in the LH and HH groups were associated with worse outcomes in all-cause mortality and PAH-related mortality (p<0.001) (Figure 2). The five-year mortality rates were 11.3%, 15.4%, 41.7%, and 43.5% in the LL, HL, LH, and HH groups, respectively. The five-year PAH-related mortality rates were 0%, 0%, 13.3%, and 35.0% in LL, HL, LH, and HH groups, respectively.

The factors associated with markedly elevated sPAP at follow-up in the univariate analysis included a younger age of PAH diagnosis, SLE, non-MCTD, markedly elevated sPAP at baseline, DOE at baseline, WHO-FC III or IV at baseline, no previous history of synovitis or pleural effusion, and no presence of anti-cardiolipin antibodies (Table 2). In the multivariate analysis, independent factors associated with markedly elevated sPAP at the time of follow-up included WHO-FC III or IV at baseline, and no previous history of synovitis at baseline (data not shown).

When comparing patients with SLE-PAH to other patients, the age of PAH diagnosis was lower, the number of patients with markedly elevated sPAP at baseline was higher, and the number of patients belonging to the LH or HL group was higher (Table 3). The number of patients who were older than 60 years when diagnosed with PAH was highest for patients with RA-PAH. The interval between diagnosis of underlying rheumatic disease and PAH was longest for patients with RA-PAH. In patients with SSc-PAH, the number of patients in the

Table 2. Baseline characteristics associated with markedly elevated systolic pulmonary artery pressure at time of follow-up

	sPAP ≤60 mmHg (n=128)		sPAP >60 mmHg (n=68)			
	n	%	n	%	OR (95% CI)	*p**
Female	113	88.3	61	89.7	1.16 (0.45-2.99)	0.76
Age at diagnosis of PAH (≥50 years)	65	50.8	23	33.8	0.50 (0.27-0.91)	0.02
Hypertension	31	24.8	18	27.7	1.16 (0.59-2.23)	0.67
Diabetes mellitus	14	11.2	5	7.7	0.66 (0.23-1.92)	0.45
Current or ex-smoker	2	5.6	1	5.0	0.90 (0.08-10.53)	1.00
Underlying rheumatic diseases						
Systemic lupus erythematosus	31	24.2	31	45.6	2.62 (1.40-4.90)	<0.01
Systemic sclerosis	44	34.4	21	30.9	0.85 (0.45-1.60)	0.62
Rheumatoid arthritis	12	9.4	2	2.9	0.29 (0.06-1.35)	0.14
Mixed connective tissue disease	18	14.1	1	1.5	0.09 (0.01-0.70)	<0.01
sPAP (>60 mmHg)	24	18.8	38	55.9	5.49 (2.86-10.54)	<0.01
Dyspnea on exertion	67	67.7	53	91.4	5.06 (1.85-13.89)	<0.01
WHO-FC III/IV	19	26.8	18	51.4	2.90 (1.24-6.75)	0.01
DLCO (<50% of predicted)	25	43.9	11	45.8	1.08 (0.42-2.82)	0.87
Six-minute walk test (<428 m)	2	66.7	0	0	0.33 (0.07-1.65)	0.40
proBNP (>457 pg/mL)	22	47.8	7	53.8	1.27 (0.37-4.37)	0.70
Synovitis	23	35.4	1	3.1	0.06 (0.01-0.46)	<0.01
Pleural effusion	19	27.5	3	9.1	0.26 (0.07-0.97)	0.04
Anti-cardiolipin Ab (+)	21	28.4	6	13.0	0.38 (0.14-1.03)	0.05

* Comparisons performed with Chi-square test or Fisher's exact test, and statistical significance was defined as p<0.05; sPAP: Systolic pulmonary artery pressure; CI: Confidence interval; OR: Odds ratio; PAH: Pulmonary artery hypertension; WHO-FC: World Health Organization Functional Class; DLCO: Diffusing capacity of lungs for carbon monoxide; Pro-BNP: N-terminal-pro-B-type natriuretic peptide; Ab: Antibodies.

Table 3. Clinical features and change of systolic pulmonary artery pressure levels depending on underlying rheumatic disease

	SLE-PAH (n=189)				SSc-PAH (n=161)				MCTD-PAH (n=32)				RA-PAH (n=56)				Overlap-PAH (n=32)				
	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	n	%	Median	IQR	p*
Female	173	91.5			136	84.5			27	84.4			45	80.4			28	87.5			0.15
Age at diagnosis of RD (years)			29	23-38[a]			51	41-62[c]			43	36-53[b]			56	48-64[c]			43	34-53[b]	<0.01
Age at diagnosis of PAH (years)			35	28-41[a]			56	47-65[c]			46	39-55[b]			68	57-75[d]			51	39-59[b]	<0.01
Late onset of PAH (age ≥60 years)	14	7.4[a]			67	41.6[c]			4	12.5[a,b]			39	69.6[d]			8	25.0[b]			<0.01
Interval between RD and PAH (months)			29	0-76[a]			30	0-79[a]			2	0-69[a]			100	51-145[b]			47	0-96[a]	<0.01
sPAP at baseline (mmHg)			62	46-77[b]			46	42-55[a]			48	42-57[a]			48	43-58[a]			52	44-63[a]	<0.01
sPAP at follow-up (mmHg) (n=174)			61	38-89[b]			47	36-64[a,b]			38	32-46[a]			45	33-53[a,b]			61	40-76[b]	<0.01
All-cause mortality	29	15.3			21	13.0			1	3.1			13	23.2			4	12.5			0.12
PAH-related mortality	10	5.4			4	2.5			0	0			0	0			2	6.5			0.17

IQR: Interquartile range; * Comparisons were performed with Chi-square test or Fisher's exact test for categorical variables, and one-way analysis of variances for continuous variables. Statistical significance was defined as p<0.05. Post hoc multiple comparisons were performed using Duncan's test. Different letters (a,b,c, or d) indicate significant differences between groups in the row, while the same ones do no differences; SLE: Systemic lupus erythematosus; PAH: Pulmonary artery hypertension; SSc: Systemic sclerosis; MCTD: Mixed connective tissue disease; RA: Rheumatoid arthritis; RD: Rheumatic diseases; sPAP: Systolic pulmonary artery pressure.

LL group was highest, but the number of patients with markedly elevated sPAP was statistically significantly higher at the time of follow-up than that at baseline (p<0.01) (Figure 3). These results were similar for patients with overlap-PAH (p=0.02). On the other hand, in patients with MCTD-PAH (p=0.02) or RA-PAH (p=0.01), the number of patients with markedly elevated sPAP was lower at the time of follow-up than that at baseline. In patients with SLE-PAH, the proportion of patients with markedly elevated sPAP was similar at baseline and at the follow-up, while 40% of patients had improved or worse sPAP levels.

DISCUSSION

Our current study showed that sPAP was variable during the disease course, with 15% of patients in the LH group and 12% of patients in the HL group. In addition, there may be some differences in the change of sPAP according to the underlying rheumatic disease. In patients with SSc-PAH, the majority of patients had similar or worse sPAP at the follow-up compared to baseline. Of patients with SLE-PAH, 40% had either improved or worse sPAP at the follow-up compared to baseline. In patients with RA-PAH or MCTD-PAH, the majority patients had the same or better sPAP at the follow-up compared to baseline.

There have been other studies that tracked changes in sPAP with echocardiography in patients with PAH-associated rheumatic disease. In one study, in patients with SSc, PAH occurred in 39% (141/361) of patients without PAH at the initial diagnosis; among them 65% had mild to moderate PAH (defined by 36-55 mmHg of sPAP) and 35% had severe PAH (defined by ≥56 mmHg of sPAP) over a mean follow-up period of 3.2 years.[7] The probability of severe PAH was higher in patients with limited SSc, mild-moderate PAH, and DLCO <50%. In another study of patients with SSc, the majority of the patients with PAH remained static within their pressure group or their sPAP increased progressively, and a smaller number of patients had decreasing sPAP during the follow-up.[8] Furthermore, that study also reported an increased mortality risk associated with high initial pressures (defined by

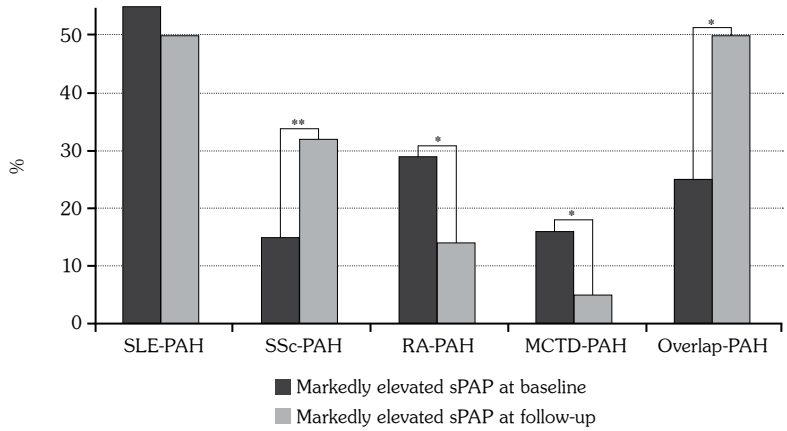


Figure 3. Change of sPAP according to underlying rheumatic disease. Number of patients with markedly elevated sPAP at follow-up was higher than that at baseline in patients with systemic sclerosis-PAH or overlap-PAH. A paired t-test was performed. Markedly elevated sPAP was defined as sPAP >60 mmHg.

SLE: Systemic lupus erythematosus; PAH: Pulmonary artery hypertension; SSc: Systemic sclerosis; RA: Rheumatoid arthritis; MCTD: Mixed connective tissue disease; sPAP: Systolic pulmonary artery pressure; * $p<0.05$; ** $p<0.01$.

>60 mmHg of sPAP) and rising pressures. A rapid increase in sPAP was observed more frequently in males, older patients, and patients with limited SSc. In a study of patients with SLE, 266 patients were followed-up for mean period of 3.8 years and 43% of patients showed improvements in their sPAP, whereas 26% of patients showed aggravation of PAH.[9]

Our findings and these previous studies suggest that sPAP, estimated by echocardiography, is variable during the course of the disease and may also vary according to the underlying rheumatic disease.

The differences in the change of sPAP may be due to some differences in the pathogenesis of PAH depending on the underlying rheumatic disease. SSc-PAH is primarily an obliterative vasculopathy characterized by progressive remodeling of the small vessels with intimal proliferation, medial hyperplasia, and adventitial fibrosis leading to vessel obliteration.[2] Endothelial injury and activation with the expression of cell adhesion molecules, inflammatory cell recruitment, and a procoagulant state are early vascular changes of SSc-PAH, though the initial trigger is unknown.[10] Disequilibrium between vasoactive proliferative mediators (e.g., endothelin-1 and thromboxane A2) and anti-proliferative vasodilators (e.g., nitric oxide and prostacyclin) results in vasoconstriction in the small- to medium-sized pulmonary vessels. Several antibodies are frequently found in patients with SSc-PAH such as angiotensin II type 1 receptor antibodies, endothelin-1 receptor type A antibodies, anti-endothelial cell antibodies, and anti-fibroblast antibodies.[11] The pathogenesis of SLE-PAH is unclear, and is generally thought to be a heterogeneous condition.[12] One subset is pulmonary vasculopathy, which is similar to SSc-PAH, and another subset is immune-mediated vasculopathy leading to pulmonary vasculitis. The role of anti-phospholipid antibodies in pathogenesis has been suggested, and possible mechanisms include abnormal coagulation and the effect on the endothelium.[13] Histopathological features of PAH in each rheumatic disease are varied.[14] Fibrosis is relatively dominant in SSc-PAH, but rare in SLE-PAH. MCTD-PAH had both characteristics of SLE and SSc. The SLE-PAH findings include plexogenic arteriopathy or fibrinoid vasculitis. In SSc-PAH, characteristic findings include fibrous intimal thickening of medium-sized arteries and branching small vessels, while plexiform lesions are considered rare. Differences are also seen in the treatment response for immunosuppressive therapy. There

was no distinct response to immunosuppressive therapy in patients with SSc-PAH, whereas it may result in clinical improvement in a subset of patients with SLE-PAH and MCTD-PAH.[3,15]

Our study results showed that the independent factors associated with markedly elevated sPAP at the time of follow-up were WHO-FC III or IV at baseline, and no previous history of synovitis at baseline. When analyzed separately for each disease, the independent factor associated with markedly elevated sPAP at the time of follow-up was WHO-FC III or IV at baseline in patients with SLE-PAH, and markedly elevated sPAP at baseline in patients with SSc-PAH. In this study, patients with SLE-PAH accounted for 46% of patients with markedly elevated sPAP at the time of follow-up, and 50% of patients with SLE-PAH had markedly elevated sPAP at the time of follow-up. However, patients with SSc-PAH accounted for 31% of patients with markedly elevated sPAP at the time of follow-up, and 68% of patients with SSc-PAH had mildly elevated sPAP at the time of follow-up. Therefore, factors associated with markedly elevated sPAP at the time of follow-up may include clinical characteristics of patients with SLE such as young age. The clinical manifestations are very different depending on the underlying rheumatic disease; thus, common factors associated with the progression of sPAP when there is a difference in sPAP change depending on underlying rheumatic disease may reflect the characteristics of a certain disease. WHO-FC is known to be one of the most powerful indicators of PAH progression.[16] To our knowledge, there have been no other previous studies that showed the relationship between synovitis and PAH. One SLE-PAH study reported opposite results.[17] In our study, the ratio of patients with synovitis was higher in patients with RA or MCTD, and these diseases were found in many patients with mildly elevated sPAP at the time of follow-up and the HL group. Although synovitis is not a statistically significant factor associated with markedly elevated sPAP at the time of follow-up when analyzed separately for each disease, there were no patients with previous histories of synovitis among the patients with SLE or SSc with markedly elevated sPAP at the time of follow-up. We believe it is necessary to perform additional research on PAH progression factors including broader factors for each disease.

This study also demonstrated that the changes in sPAP were linked to the outcomes. In patients with markedly elevated sPAP at the time of follow-up, the poor prognosis was reflected by the following outcomes: survival, WHO-FC, DLCO, home oxygen therapy, 6MWT, and NT-proBNP.

It has been questioned whether sPAP can predict the outcomes; for example, is there an association between initial sPAP and prognosis of PAH? Are changes in sPAP linked to outcomes? A previous study using the REOPARD data showed that the initial sPAP was not a predictor of all-cause mortality.[6] However, there have been only two patients who died from PAH. We showed that PAH-related deaths were more likely in patients with markedly elevated sPAP at baseline, while all-cause mortality was not related with initial sPAP. Our study showed that increased sPAP or persistently markedly elevated sPAP was associated with worse outcomes, including mortality. In another registry study, when patients with PAH were divided into three groups (regression, stable, or progression group) depending on tricuspid regurgitation, the severity of tricuspid regurgitation at the first echocardiography did not imply poor outcome, while a progressive increase in tricuspid regurgitation severity was associated with a mortality risk, and increasing sPAP independently predicted mortality.[18] In another study in patients with SSc-PAH, an increasing mortality was observed in patients with increasing sPAP compared to those with static and decreasing sPAP, and an initial high sPAP was an independent related factor to mortality.[8] In our study, the only independent factor associated with markedly elevated sPAP at the time of follow-up was baseline sPAP in patients with SSc-PAH; therefore, baseline sPAP may be used to predict survival in patients with SSc-PAH, while baseline sPAP could not be used to predict markedly elevated sPAP at the time of follow-up in patients with other rheumatic diseases, including SLE.

The survival according to the changes of sPAP was analyzed separately for each underlying rheumatic disease. An increase in sPAP was associated with all-cause mortality in patients with SSc-PAH ($p<0.001$, data not shown). In patients with SLE-PAH, an increase in sPAP was associated with PAH-related mortality ($p=0.03$,

data not shown), but not with all-cause mortality. This may be explained by the fact that the main causes of death in SSc patients are lung fibrosis or PAH.[19] On the other hand, in SLE patients, there are many other causes of death besides PAH. In patients with RA-PAH, the changes of sPAP were not associated with all-cause mortality and there were no patients who died related with PAH.

Our study have some limitations, although we could collect a large amount of patient data of rare PAH associated with rheumatic disease and obtain relatively long-term follow-up data. The majority of the patients were diagnosed by echocardiography and this was not a prospective study; therefore, there were some missing data, and the values were measured through different instruments and investigators in each institution. In addition, the patients with follow-up echocardiographs constituted only 35% of the study population. Patients with very poor prognosis may have died without follow-up echocardiograph. Conversely, those with good prognosis may also have not undergone follow-up examination. Furthermore, data on disease activity and history of immunosuppressive therapy were not gathered. Although the patients with severe interstitial lung disease or other lung disease at the time of baseline were excluded, data on initial lung disease status and its progression were not collected. In addition, it is well known that pulmonary artery pressure is related with arterial oxygen saturation. Oxygen supplement therapy also showed the effect of mortality in PAH patients with severe DLCO reduction.[20] Our study did not collect artery oxygen saturation results and, due to the limitations of the study design, did not evaluate the effect of oxygen therapy on sPAP. Our study showed that the patients with severe disease received more home oxygen therapy and PAH specific treatments.

In conclusion, the sPAP was variable during the disease course and the change in sPAP was linked to the outcomes. Increasing sPAP and persistent markedly elevated sPAP appeared to predict all-cause mortality and PAH-related mortality. Moreover, there may be some differences in sPAP progression according to the underlying rheumatic disease. Furthermore, changes in sPAP were most frequently observed in patients with SLE-PAH. In patients with SSc-PAH, most patients maintained the same baseline sPAP or had worse sPAP, while there were a few patients whose sPAP decreased. Therefore, we suggest that it may be beneficial to track echocardiography in patients with elevated sPAP with systemic rheumatic diseases.

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