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Predictors of Long-term Outcomes in Patients With Connective Tissue Disease Associated With Pulmonary Arterial Hypertension

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Background/Objective: Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary arterial pressure and pulmonary vascular resistance that can lead to right-sided heart failure. Connective tissue disease–associated PAH (CTD-PAH) often has poorer outcomes than idiopathic or hereditary PAH, suggesting the presence of non-PAH factors that could affect the prognoses. This cohort study aimed to identify prognostic factors for CTD-PAH management.

Methods: Medical records from April 1999 to November 2014 were reviewed to determine the time from treatment initiation to the occurrence of a clinically worsening event and the time elapsed until death. Data at baseline and the final assessment were used to identify prognostic factors associated with events using univariate and multivariate analyses by the stepwise Cox regression method.

Results: In 36 patients with CTD-PAH analyzed, the proportions with no clinically worsening events at 1, 2, and 3 years after treatment initiation were 62%, 52%, and 45%, respectively, with survival rates of 88%, 77%, and 77%, respectively. The regression model showed that reduced hemoglobin at baseline, reduced qR pattern in electrocardiogram lead V_1, increased 60-minute erythrocyte sedimentation rate, and increased mean pulmonary arterial pressure at the final assessment were risk factors that were significantly associated with clinical worsening. For survival, no prognostic factor was identifiable.

Conclusions: Hemodynamic and non-PAH factors, such as anemia, nutritional status, and inflammatory activity of the underlying CTD, which are not listed in the risk assessment table of PAH guidelines, should be strictly controlled to improve the prognosis of patients with CTD-PAH. A more multifactorial treatment strategy should be developed.

Key Words: clinical worsening, CTD-PAH, predictor, prognosis, pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary arterial pressure and pulmonary vascular resistance (PVR) that can lead to death due to right-sided heart failure. Pulmonary arterial hypertension was previously associated with a median life expectancy of 2.8 years, with a 5-year survival rate of 34% after diagnosis.[1] Although the prognosis has improved in more recent cohorts due to the advent of PAH-specific treatments,[2,3] the various etiologies of PAH, including idiopathic, hereditary, and those induced by other diseases or drugs, have varying prognostic profiles.[4] Connective tissue disease–associated PAH (CTD-PAH) is the second most common type of PAH after idiopathic/hereditary PAH (I/HPAH). The prevalence of coexisting PAH and the prognosis differ substantially among underlying CTDs, with systemic sclerosis-associated PAH (SSc-PAH) reported to be associated with a particularly poor prognosis.[5]

A recent report on the long-term outcome of treatment for Japanese patients with IPAH indicates the importance of hemodynamic management.[6] However, this approach cannot simply be applied to CTD-PAH given the differences in the underlying pathophysiological mechanisms between these 2 conditions. An investigation of prognostic factors for CTD-PAH alone is needed.

Regarding the prognostic factors in CTD-PAH, Li et al.[7] evaluated the usefulness of the risk assessment table of the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines for Chinese patients with CTD-PAH. The ESC/ERS risk assessment was based on clinical signs of right-sided heart failure, progression of symptoms, syncope, World Health Organization (WHO) functional class (WHO-FC), 6-minute walk distance (6MWD), cardiopulmonary exercise testing (peak V_{O_2}), N-terminal pro–B-type natriuretic peptide level, imaging (presence of pericardial effusion, right atrium area by echocardiography or cardiac/vascular magnetic resonance imaging), and hemodynamics (right atrial pressure [RAP], cardiac index, and mixed venous oxygen saturation) as comprehensive factors for prognosis.[8] Meanwhile, Miyanaga et al.[9] had reported 6MWD and peak V_{O_2}/kg in exercise, mean pulmonary arterial pressure (mPAP), RAP, vascular resistance in hemodynamics, and right ventricle (RV) Tei index on echocardiography in exercise-induced patients with CTD-PH as independent prognostic factors. The RV Tei index might be a feasible predictor from receiver operating characteristic (ROC) curve analysis.[9] Ciancio et al.[10] had suggested that pulmonary function tests such as forced vital capacity and diffusing capacity for carbon monoxide were reliable markers in the diagnosis and follow-up of patients with CTD-PAH for improving both patient survival and quality of life. Condliffe and Howard[11] had suggested that prognostic factors

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identified by multivariate analysis have also differed between studies, but have included age, sex, diffusing capacity for carbon monoxide, functional class, PVR, pulmonary capacitance, stroke volume index, and estimated glomerular filtration rate. However, consensus on the best prognostic factor for CTD-PAH management in the everyday clinical setting has not yet been identified.

The objective of this cohort study was to investigate prognostic factors for CTD-PAH by reviewing the medical records of patients with CTD-PAH, focusing particularly on their outcomes.

METHODS

Patients

We collected data from the medical records of patients who presented to Kobe University Hospital with PH between April 1999 and November 2014. Patients with PH were classified according to the Japanese PH guidelines[12] and the Nice classification system.[8] Pulmonary arterial hypertension was classified into the following types: I/HPAH, CTD-PAH, congenital heart disease–associated PAH (CHD-PAH), portopulmonary hypertension (POPH), and other types. CTD-PAH was further classified into SSc-PAH and non–SSc-PAH. In this cohort analysis, no specific inclusion/exclusion criteria were prespecified for enrolment except the hemodynamic definition of PAH (i.e., mPAP ≥25 mm Hg and pulmonary arterial wedge pressure ≤15 mm Hg) to conduct analysis in a real-world setting. No arbitrary case selection was anticipated. Hemodynamics by right-sided heart catheter were determined in patients with a clinical suspicion by right ventricular volume overload and electrocardiogram (ECG), or transtricuspid pressure gradient (TRPG) greater than 45 mm Hg by echocardiography. In addition, the patients who were referred to Kobe University Hospital because of symptoms of dyspnea were initially treated for their original disease at the clinic or hospital by a primary care doctor based on each screening program or were managed for their original disease at the Department of Rheumatology of Kobe University Hospital. All patients were followed up periodically every 1 to 3 months and were treated with an endothelin receptor antagonist, oral prostanoids, and phosphodiesterase 5 inhibitor, based on PH treatment guidelines in Japan.[12] However, we did not investigate the impact of PH treatment because the data interpretation would be complex because of the variety of treatments added or changed.

Evaluation of Outcomes

The time from the initiation of PAH-specific treatment to clinical worsening was determined for CTD-PAH and non–CTD-PAH (I/HPAH, CHD-PAH, and POPH) and each subtype of CTD-PAH (SSc-PAH and non–SSc-PAH). Clinical worsening was a composite endpoint defined as any of the following events: (i) hospitalization due to acute exacerbation of PAH; (ii) progression to WHO-FC III or worse; (iii) decrease in 6MWD ≥15% from baseline; (iv) initiation of parenteral prostanoid therapy; and (v) death. The first time at which any of the above events occurred was defined as the time of clinical worsening. The time to death (i.e., survival curve) was determined in the same manner.

Determination of Prognostic Factors

In the present study, we reviewed the medical records kept over a 15-year period at Kobe University Hospital. Numerous variables, including antibody and blood test results, in addition to hemodynamic, ECG, echocardiography information, and respiratory function variables regarded as prognostic factors and those that are commonly measured for diagnosis and monitoring for CTD-PAH, were examined to identify factors that might be relevant to improving the prognosis. We then sought to identify prognostic factors based on the time to clinical worsening of CTD-PAH, survival rate, and medical record data. The medical record data obtained before treatment initiation (baseline) and the data obtained on the day of the final posttreatment assessment were used for the analysis. These baseline prognostic factors can be affected by therapeutic interventions, and the analysis was not adjusted for therapeutic factors. Thus, the values of the clinical parameters at the final posttreatment assessment were used to clarify the association between the impact of PAH treatment and patient outcomes.

Statistical Analysis

For the analysis, the patients with PAH were divided into CTD-PAH and non–CTD-PAH groups. For the analysis of pretreatment (baseline) patient characteristics, the χ^2 test was used for analysis of the sex ratio, whereas the mean difference and its 95% confidence interval (CI) were calculated for the other variables. Survival and clinical worsening rates over time were analyzed using Kaplan-Meier curves, with the proportion of patients with no event defined as 100%, from which the proportions of patients were calculated who had not experienced any event at 1 to 5 years after treatment initiation. The log-rank test was used for comparisons among the groups. Potential prognostic variables were subjected to univariate analysis, and those with $p < 0.05$ underwent a stepwise Cox regression multivariate analysis as well, in which variables with $p < 0.10$ were identified as significant factors. Hazard ratios (HRs), 95% CIs, and p values are presented. For each significant factor identified by multivariate analysis, an ROC curve was constructed to determine the cutoff values using the Youden index. Kaplan-Meier curves were then generated based on the cutoff values.

RESULTS

Patients' Baseline Characteristics

A medical record review revealed a total of 198 patients diagnosed with PH, including 90 patients with chronic thromboembolic PH, which accounted for the largest proportion, followed by 68 patients with PAH (Fig. 1). Among the patients with PAH, CTD-PAH was the most common (36 patients), followed in order by CHD-PAH (16 patients), I/HPAH (11 patients), and POPH (5 patients), with no patients having other PAH subtypes. Patients with CTD-PAH consisted of SSc-PAH (20 patients) and non–SSc-PAH (16 patients). Systemic sclerosis comprised 56% (20/36) of the CTD-PAH population; the other etiologies were 4 with systemic lupus erythematosus, 1 with mixed CTD; 5 with malignant rheumatoid arthritis; 3 with Sjögren syndrome; 2 with polymyositis/dermatomyositis; and 1 with antineutrophil cytoplasmic antibody–associated vasculitis. Baseline test variables for these patients divided into CTD-PAH and non–CTD-PAH groups are summarized in Table 1. The relevant data on those for whom antibody test results were available from prior records are summarized in Supplementary Table 1, http://links.lww.com/RHU/A190. Regarding the mode of presentation to our department in the 36 patients with CTD-PAH, 27 referrals via outpatient clinic and 9 referrals via hospital admission were recorded, and 22 patients were referred by rheumatologists. The follow-up period was 3.2 ± 2.6 years.

Evaluation of Outcomes

Kaplan-Meier curves were generated for analysis of the time to clinical worsening or death for the CTD-PAH and non–CTD-PAH groups. In terms of the time to clinical worsening (Fig. 2A),

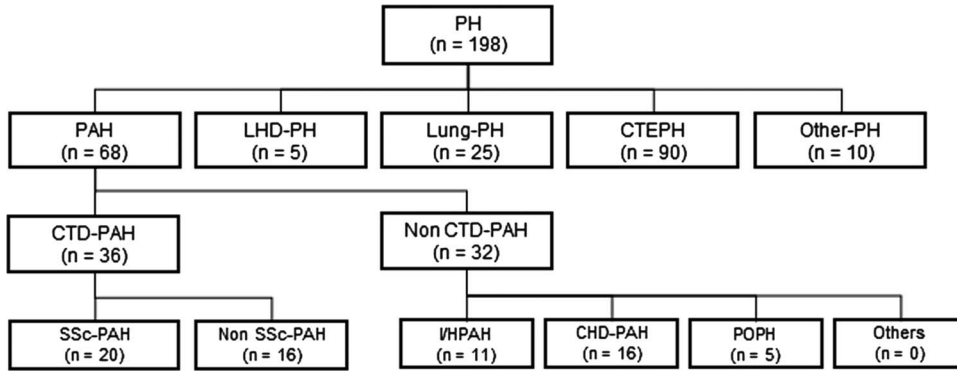

FIGURE 1. Patient composition. LHD-PH, left heart disease-associated PH; CTEPH, chronic thromboembolic PH.

no significant difference was found between the 2 groups, with proportions of patients with no events at 1, 2, and 3 years after treatment initiation of 62%, 52%, and 45%, respectively, in the CTD-PAH group, and 68%, 54%, and 37%, respectively, in the non–CTD-PAH group. The survival rates at 1, 2, and 3 years after treatment initiation were 88%, 77%, and 77%, respectively, in the CTD-PAH group, and 90%, 90%, and 86%, respectively, in the non–CTD-PAH group, being higher in the non–CTD-PAH group but without statistical significance ($p = 0.29$) (Fig. 2B). In a comparison between patients with and without SSc-PAH, survival rates tended to be higher in the non–SSc-PAH group, but the differences did not reach statistical significance (Fig. S1 http://links.lww.com/RHU/A189).

Determination of Prognostic Factors

The results of the univariate and multivariate analyses of the data for the CTD-PAH group, based on the baseline and final post-treatment assessment values (Supplementary Table 2, http://links.lww.com/RHU/A190), are summarized with significant variables in Table 2. Hemoglobin (Hb) level at baseline, qR pattern in lead V_1 of the ECG, erythrocyte sedimentation rate in 60 minutes (ESR 60 min), and mPAP at the final assessment were identified as factors significantly associated with clinical worsening, whereas no factor was identified as significantly associated with the survival rate (Supplementary Table 3, http://links.lww.com/RHU/A190). For the 3 prognostic factors identified as impacting clinical worsening by multivariate analysis (i.e., Hb, ESR 60 min, and mPAP), the areas under the ROC curves (AUCs) were calculated to be 0.70, 0.75, and 0.63, respectively (Fig. S2 http://links.lww.com/RHU/A189). Based on the ROC curves, the cutoff values were determined to be 12.7 g/dL, 38 mm, and 25 mm Hg, respectively. Kaplan-Meier curves according to these cutoff values are shown in Figure 3.

DISCUSSION

Prognosis and Characteristics of CTD-PAH

The evidence suggests that the progression of CTD-PAH is associated not only with the severity of PH but also with the severity of respiratory disease and inflammatory activity.[13,14] The distribution of PAH types at our institute was characterized by a substantially larger proportion of CTD-PAH (52.9%; Fig. 1) compared with that in previously reported large-scale registries (15.3% in the French Registry,[2] 25.3% in the REVEAL Registry,[3] and 25.4% in the Japan PH Registry[15]) and by a smaller proportion of I/HPAH (16.2%, compared with 52.5% in the French Registry,[2] 46.2% in the REVEAL Registry,[3] and 56% in the Japan PH Registry[15]) of all patients with PAH. This discrepancy could be due in part to the established CTD-PAH screening system at our institute via the collaboration between cardiologists and rheumatologists. The proportion of SSc-PAH among all patients with CTD-PAH (55.5%) was comparable to that in the REVEAL Registry (62.2%).[3]

Although the poorer prognosis of CTD-PAH compared IPAH has already been reported,[2,16] the survival rate of CTD-PAH in the present study (76.93%) was better than those reported previously (3-year survival rate: 60% in the French Registry[2] and 57.1% in the REVEAL Registry[3]). One of the major differences between the present and previous registry studies is a substantially different proportion of patients receiving PAH treatment with pulmonary vasodilators. In comparison to the REVEAL Registry, the ratio of WHO-FC III/IV patients was lower in the present study (64.3% in this study vs. 73.5% in the REVEAL Registry). Similarly, baseline mPAP (34.5 vs. 45.0 mm Hg) and PVR (7.7 Wood units [WU] vs. 9.8 WU) values were also lower in the present study. In the French Registry, the interval between the onset of symptoms and diagnosis was 27 months, whereas the mean disease duration from the first presentation of CTD-PAH in patients in this survey was shorter at 1.2 years, and all patients in this survey received PAH-specific treatment as soon as PAH was diagnosed. These data showed that diagnosis and treatment initiation as early as possible are important in the management of CTD-PAH. A comparison of survival rates between the CTD-PAH and non–CTD-PAH groups showed a slightly higher rate in the non–CTD-PAH group (3-year survival rate: 76.9% vs. 86.5%). Given the non–CTD-PAH group in this study included both IPAH (having a good prognosis) and POPH (having a poor prognosis), this might have resulted in the absence of a significant difference between the 2 groups. The lower survival rate of patients with CTD-PAH, despite a better hemodynamic status (mPAP: 34.5 ± 8.1 mm Hg in CTD-PAH vs. 44.9 ± 14.7 mm Hg in non–CTD-PAH), could be explained by factors unrelated to PAH, such as impaired renal function, higher inflammatory markers (ESR 60 min), and higher interstitial pneumonia markers (KL-6). Among patients with PAH, an older subgroup of patients with cardiovascular comorbidities (i.e., atypical PAH) has been recently highlighted because they demonstrate representative clinical features of heart failure with preserved ejection fraction, which is a notable prognostic factor for PH.[17] In this cohort, the involvement of heart failure with preserved ejection fraction can be considered, because the average age is slightly higher in CTD-PAH (57.3 ± 14.7, 51.6 ± 22.4 in CTD-PAH, and non–CTD-PAH, respectively), although it was not significantly different, and the details of comorbidities were unknown. When patients with CTD-PAH were divided into SSc-PAH and non–SSc-PAH subgroups (Fig. S1 http://links.lww.com/RHU/

TABLE 1. Baseline Characteristics of Patients

	n	CTD-PAH (n = 36)	n	Non–CTD-PAH (n = 32)	Mean Difference	95% CI
Age, y	36	57.3 ± 14.7	32	51.6 ± 22.4	−5.68	(−15.02, 3.6)
Disease duration from symptom presentation, y	30	1.2 ± 3.7	30	5.8 ± 10.7	4.66	(0.46, 8.87)
Female, n (%)	36	30 (83.3)	32	26 (81.3)		—
CTD subtype	36	36		0		—
SSc		20	—	—		
Mixed CTD		1	—	—		
Systemic lupus erythematosus		4	—	—		
Sjögren syndrome		3	—	—		
Malignant rheumatoid arthritis		5	—	—		
polymyositis or dermatomyositis		2	—	—		
ANCA-associated vasculitis		1	—	—		
WHO-FC I/II/III/IV, n	28	1/9/15/3	29	2/6/14/7		0.47*
RHC						
RAP, mm Hg	26	4.5 ± 3.7	29	4.8 ± 3.6	0.24	(−1.74, 2.22)
mPAP, mm Hg	28	34.5 ± 8.1	29	44.9 ± 14.7	10.43	(4.11, 16.75)
PAWP, mm Hg	28	7.3 ± 4.2	29	8.1 ± 3.9	0.76	(−1.38, 2.91)
Cardiac index, L/min per m^2	28	2.7 ± 0.7	29	3.1 ± 1.8	0.41	(−0.32, 1.13)
PVR, WU	28	7.7 ± 3.7	29	11.4 ± 9.2	3.71	(−0.04, 7.47)
Sa_{O_2}, %	27	93.7 ± 3.7	28	89.6 ± 8.7	−4.15	(−7.78, −0.53)
Sv_{O_2}, %	24	68.1 ± 6.2	27	65.9 ± 8.3	−2.20	(−6.28, 1.88)
O_2 condition, L/min	27	0.0 ± 0.0	28	0.0 ± 0.0	0.00	(0.00, 0.00)
Echo						
TRPG, mm Hg	22	62.0 ± 19.6	25	71.4 ± 26.0	9.39	(−4.07, 22.85)
ECG						
IIp, mm	26	1.6 ± 0.7	24	1.4 ± 1.1	−0.12	(−0.63, 0.40)
Axis, degrees	25	58.6 ± 43.6	27	105.0 ± 67.0	46.36	(14.99, 77.73)
6MWT						
6MWD, m	19	340 ± 174	22	305 ± 115	−35.0	(−130.6, 60.6)
Baseline Spo_2, %	16	93.9 ± 3.3	19	91.6 ± 5.9	−2.31	(−5.55, 0.94)
Minimum Spo_2, %	16	85.7 ± 9.5	18	81.1 ± 10.7	−4.58	(−11.66, 2.51)
O_2 condition, L/min	10	0.0 ± 0.0	10	1.2 ± 2.0	1.20	(−0.22, 2.62)
Blood tests						
BNP, pg/mL	27	273 ± 463	25	320 ± 486	47.1	(−217.9, 311.9)
Hb, g/dL	27	12.0 ± 1.8	29	14.7 ± 2.7	2.61	(1.39, 3.83)
KL-6, U/mL	19	847 ± 1061	6	264 ± 108	−582.8	(−1100.3, −65.4)
Creatinine, mg/dL	28	1.0 ± 1.4	25	0.7 ± 0.1	−0.32	(−0.86, 0.22)
eGFR, mL/min per 1.73 m^2	18	68.2 ± 34.0	21	79.5 ± 20.7	11.26	(−7.61, 30.14)
Uric acid, mg/dL	26	5.9 ± 2.0	22	5.9 ± 1.8	−0.04	(−1.15, 1.07)
Albumin, g/dL	27	3.6 ± 0.6	25	3.5 ± 0.6	−0.13	(−0.47, 0.20)
CRP, mg/dL	28	0.5 ± 0.7	25	0.7 ± 1.3	0.16	(−0.42, 0.74)
WBC, /μL	28	7346 ± 3024	25	6888 ± 4423	−458	(−25,844, 1667)
ESR 30 min, mm	21	14.7 ± 16.6	19	5.6 ± 8.3	−9.04	(−17.38, −0.69)
ESR 60 min, mm	23	41.5 ± 34.8	19	15.9 ± 21.4	−25.57	(−43.33, −7.82)
IgG, mg/dL	23	1705 ± 771	6	1234 ± 604	−471.1	(−1129.1, 187.0)
IgM, mg/dL	22	130.8 ± 109.5	6	82.7 ± 19.2	−48.11	(−98.85, 2.64)
IgA, mg/dL	22	327 ± 207	6	271 ± 133	−56.4	(−208.5, 95.6)
CH_{50}, U/mL	24	44.7 ± 9.4	8	45.6 ± 14.3	0.95	(−11.30, 13.19)
C3, mg/dL	24	94.8 ± 17.0	8	102.4 ± 22.7	7.63	(−11.92, 27.17)
C4, mg/dL	24	20.7 ± 6.2	8	23.1 ± 7.8	2.38	(−4.40, 9.16)

Values are mean ± SD or number (percent).

*p value by χ^2 test.

6MWT, 6-minute walk test; ANCA, antineutrophil cytoplasmic antibody; BNP, brain natriuretic peptide; CH50, total hemolytic complement; CRP, C-reactive protein; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; PAWP, pulmonary arterial wedge pressure; Sa_{O_2}, arterial oxygen saturation; Sv_{O_2}, mixed venous oxygen saturation; WBC, white blood cell count.

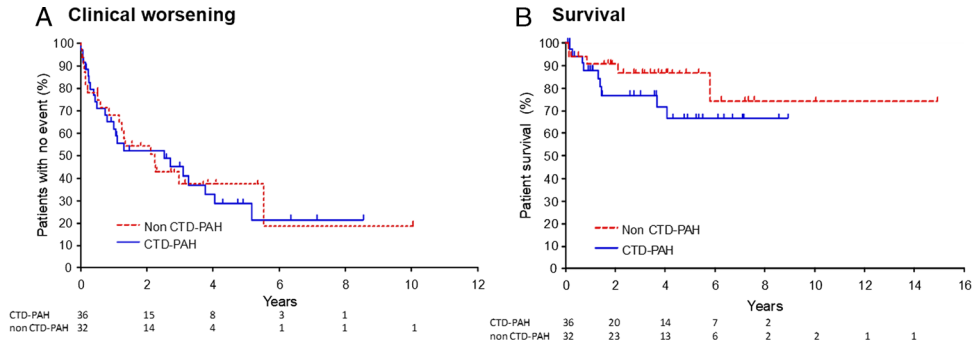

FIGURE 2. Kaplan-Meier curves in PAH subgroups Kaplan-Meier curves of CTD-PAH and non–CTD-PAH groups. Clinical worsening (A), (B) survival (B). Log-rank test was conducted for comparison between the 2 groups.

A189), the patients in the SSc-PAH subgroup had poorer outcomes in terms of survival rates, as reported previously.[18,19]

Predictors for Long-term Outcome in Patients With CTD-PAH

In the present data, a multivariate analysis of the baseline variables identified no significant independent prognostic factors for death, but Hb was identified as a significant factor for clinical worsening. Similarly, no independent prognostic factors were identified for death, whereas the qR pattern, ESR 60 min, and mPAP were identified as significant factors for clinical worsening at the final assessment. Recently, Waligóra et al.[20] had reported that the qR pattern in the ECG, which is a sign of right ventricular hypertrophy, was an independent prognostic factor for survival in patients with PAH, although most of the participants in their study had IPAH (78.8%). Our results also indicated the qR pattern to be a prognostic factor for clinical worsening of patients with CTD-PAH, indicating that preventive care to prevent right ventricular hypertrophy development is important for improving the long-term prognosis of patients with CTD-PAH.

The observation that mPAP was identified as a prognostic factor at the final assessment only and not at baseline suggests that PAH-specific treatment influenced the prognosis. In addition to mPAP, reduced respiratory function has been shown to affect the prognosis of patients with CTD-PAH.[5] In the present study, however, percent vital capacity and percent 1-second forced expiratory volume were identified as significant factors in the univariate analysis, but not as independent prognostic factors in the multivariate analysis (Supplementary Table 3, http://links.lww.com/RHU/A190). This result could be attributable to the small sample size for conducting a multivariate analysis, because 33% (12/36) of patients lacked respiratory function testing data. To address this issue, a further analysis with a larger sample size will be needed. Moreover, among the baseline variables, factors related to oxygen supply (such as Hb) were identified as independently associated with clinical worsening. Among the test variables at the final assessment, albumin was identified as a prognostic factor by univariate analysis. In addition, renal function (creatinine, uric acid) and an inflammatory marker (C-reactive protein) were identified as prognostic factors for CTD-PAH death, although they were identified by univariate analysis. These results suggest that the prognosis of CTD-PAH is affected not only by hemodynamic status, but also markedly by the systemic condition. Therefore, comprehensive management, including control of renal function and inflammation, is needed.

In the ROC analysis, AUCs of baseline mPAP for death and clinical worsening were 0.53 and 0.60, respectively (data not shown), indicating that this variable was not prognostic. In contrast, for mPAP at the final assessment, the AUC of ROC was 0.63 for clinical worsening prediction, indicating it to be prognostic (Fig. S2 http://links.lww.com/RHU/A189, C), and it was also relatively high (0.73) for death prediction, whereas it was not shown to be prognostic (data not shown). The cutoff value of mPAP for clinical worsening at the final assessment was determined to be 25 mm Hg (Youden index). This cutoff value was much lower than the target mPAP value (42.5 mm Hg[6]) previously reported for prognostic improvement in patients with IPAH. Considering the definition of PAH based on mPAP of 25 mm Hg or greater in the Japanese PH guidelines[12] and the recent proposal by the World Symposium on Pulmonary Hypertension (Nice) of a resting mPAP of greater than 20 mm Hg,[21] more strict control (i.e., normalization of hemodynamics) of PH is needed in CTD-PAH. Our estimated cutoff value supports this idea.

For the test variables identified by multivariate analysis as independent prognostic factors (Hb at baseline, ESR 60 min at final

TABLE 2. Prognostic Factors for Clinical Worsening in CTD-PAH

	Baseline Assessment				Final Assessment			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Clinical worsening								
mPAP					1.07 (1.01–1.14)	0.022	1.15 (1.01–1.31)	0.027
Hb	0.53 (0.36–0.79)	0.002	0.54 (0.36–0.80)	0.002				
ESR 60 min					1.03 (1.01–1.05)	0.011	1.05 (1.01–1.09)	0.007
qR					4.24 (1.17–15.45)	0.028	0.03 (0.00–0.33)	0.004

qR patterns in ECG. See Supplementary Table 3 for all statistic results.

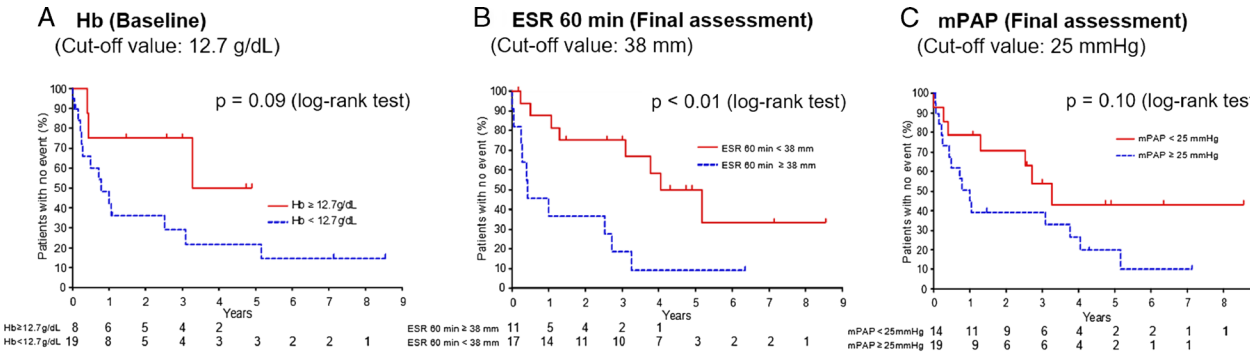

FIGURE 3. Kaplan-Meier curves divided by cutoff values in CTD-PAH. A log-rank test was conducted in CTD-PAH for comparisons among the groups divided by each cutoff value. Hemoglobin (A), ESR (B), mPAP (C).

assessment; Table 2), the cutoff values for clinical worsening were calculated to be Hb; 12.7 g/dL and ESR 60 min; 38 mm (Figs. 3A, B), suggesting the need to prevent anemia and control inflammation. However, the interpretation of Hb cutoff values should be carefully considered, given the normal value of Hb differs between men and women. Women accounted for 83.3% (30/36) of the patients in this CTD-PAH cohort.

Kaplan-Meier curves drawn according to these cutoff values indicated that even those patients with CTD-PAH who met each cutoff value might have a poor prognosis, that is, a high likelihood of clinical worsening (Fig. 3), suggesting the presence of other clinical variables requiring careful control, in addition to those identified in the present study. To address the sample size limitation of the present study, further efforts are needed to reveal as yet unidentified clinical variables by including more patients.

The major limitation of this study is that it was conducted at a single center with a retrospective design, using long-term follow-up patient data. Therefore, patient selection and lead-time bias were unavoidable. The prognosis and treatment response can vary among countries or regions. There might be concern about the generalizability of our data, due to variations in the distribution by etiology of CTD-PAH. Our treatment strategy is based on the Japanese PH guidelines,[12] which are based on the ESC/ERS guidelines.[8] Furthermore, no specific information about CTD itself (i.e., disease-related characteristics, organ involvement by CTD, or use of immunosuppressive agents) was obtained for this analysis, because the management of CTD as the original disease was by rheumatologists in another hospital or in a different department. We could not examine the associations with comorbidity. However, further analysis is needed regarding the association between CTD disease activity, comorbidity, and prognostic factors. Recently, it has been recognized that CTD-PAH involves PH attributable to pulmonary fibrosis, pulmonary thrombosis, or left ventricular diastolic dysfunction in addition to PAH.[12] Some patients with SSc-PAH are known to have the complication of pulmonary veno-occlusive disease, or diastolic dysfunction of the myocardium, and myocardial fibrosis.[12] In the present study, no specific investigation of the association of PAH drugs was conducted, because the treatment course in each patient varied. Endothelin receptor antagonists (bosentan, ambrisentan), phosphodiesterase 5 inhibitors (sildenafil, tadalafil), and oral/parenteral prostanoids were prescribed by a mainly sequential combination method based on the PH guidelines,[12,22] but the efficacy was unknown. The appropriateness of echocardiographic parameters is another limitation, because the importance of the evaluation of RV function has recently been emphasized, including tricuspid annular plane systolic excursion, right ventricular strain, and right ventricular fractional area change.[23] We examined only TRPG from echocardiography. Moreover, the small sample size, missing data, and long follow-up period (which exposes patients to more confounding factors) make interpretation of the data difficult. In addition, the sample size was too small to compare the Kaplan-Meier curves for each group or to conduct a multivariate analysis for prognostic factors, especially for comparison of survival. Multicenter studies with more patients or further analysis using PAH registry data could clarify the significance of these analyses.

CONCLUSIONS

We sought to identify prognostic factors for CTD-PAH by analyzing a wide range of variables, including systemic serum markers, hemodynamics, respiratory function, cardiac function, inflammation, and renal function. Notably, the target mPAP for CTD-PAH was calculated to be 25 mm Hg, which is much lower than that previously reported for IPAH. Our results suggest the need for stricter control of PH, that is, normalization of hemodynamics, as well as control of anemia and inflammatory activity of the underlying CTD, for successful management of CTD-PAH. Thus, the establishment of a more multifactorial treatment strategy, including collaboration between cardiologists and rheumatologists, is needed to improve the prognosis of patients with CTD-PAH.

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