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Long-Term Prognosis of Connective Tissue Disease Associated Pulmonary Arterial Hypertension

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Abstract

Objective: Pulmonary Arterial Hypertension (PAH) is a progressive disease characterized by increased pulmonary arterial pressure and pulmonary vascular resistance that can lead to right heart failure. Connective Tissue Disease-Associated PAH (CTD-PAH) often has a worse outcome than idiopathic or Hereditary PAH (I/HPAH), suggesting the presence of non-PAH factors that may affect the prognosis of CTD-PAH patients. This study aimed to identify prognostic factors for CTD-PAH.

Methods: Medical records from the April 1999 through November 2014 period were reviewed to determine the time from treatment initiation to occurrence of a clinically worsening event (hospitalization for PAH exacerbation, progression to WHO Functional Class III or worse, decrease in 6-min walking distance by ≥ 15% from baseline, initiation of parenteral prostanoid therapy, or death), and the time elapsed until death. Data at baseline and final assessment were used to identify prognostic factors associated with these events.

Results: In 36 CTD-PAH patients analyzed, the proportions with no clinically worsening events at 1, 2 and 3 years after treatment initiation were 62, 52 and 45%, with survival rates of 88, 77 and 77%, respectively. In multivariate analysis for survival rate, no variable was identifiable as a prognostic factor. However, baseline hemoglobin, QR pattern in electrocardiogram lead V1, 60-min erythrocyte sedimentation rate and mean pulmonary artery pressure at the final assessment were identified as factors significantly associated with clinical worsening.

Conclusion: Not only hemodynamic status, but also non-PAH factors such as anemia, nutritional status and inflammatory activity of the underlying CTD were suggested to influence the prognosis of CTD-PAH patients. Development of a more multifactorial treatment strategy is necessary.

Keywords: CTD-PAH • Prognostic factors • Right hear catheter • Inflammatory markers • MPAP

Introduction

Pulmonary Arterial Hypertension (PAH) is a progressive disease characterized by increased pulmonary arterial pressure and pulmonary vascular resistance that can lead to death due to right heart failure. PAH 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 been better in more recent cohorts, benefitting from the advent of PAH specific treatments, than in historic cohorts [2,3], the different etiologies of PAH, including idiopathic, hereditary, and those induced by other diseases or drugs, have different 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 in Japanese patients with IPAH indicates the importance of hemodynamic management [6]. However, this cannot be simply applied to CTD-PAH because of differences in the underlying pathophysiological mechanisms between these two conditions, necessitating an investigation of prognostic factors for CTD-PAH alone.

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

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Methodology

Patients

We collected data from the medical records of patients who presented to Kobe University Hospital with Pulmonary Hypertension (PH) between April 1999 and November 2014. PH patients were classified according to the Nice classification system (JACC, 2013). PAH was classified into the following types: I/HPAH, CTD-PAH, Congenital Heart Disease-Associated PAH (CHD-PAH), Porto Pulmonary Hypertension (POPH), and other types. CTD-PAH was further classified into SSc-PAH and non-SSc-PAH.

Evaluation of outcomes

The time from 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 Functional Class III or worse, iii) decrease in 6-min walking distance by ≥ 15% from baseline, iv) initiation of parenteral prostanoid therapy, and v) death. The 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 also determined in the same manner.

Determination of prognostic factors

We then sought to identify prognostic factors based on the time to clinical worsening of CTD-PAH, survival rate and medical record data. The following variables were analyzed as possible prognostic factors: sex, age at diagnosis of PAH, time from first recognition of symptoms to treatment initiation, Electrocardiogram (ECG), cardiopulmonary hemodynamics, echocardiogram, clinical laboratory test values, CTD-related antibody titers, respiratory function tests, exercise tolerance, and items pertaining to WHO Functional Class. The medical record data obtained before treatment initiation (baseline) and those obtained on the day of the final post-treatment assessment were used for analysis.

Statistical analysis

For analysis, PAH patients were divided into CTD-PAH and non-CTD-PAH groups. For analysis of pre-treatment (baseline) patient characteristics, the chi-squared test was used for analysis of the sex ratio, while the mean difference and its 95% confidence interval (CI) were calculated for 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 who had not experienced any event at 1-5 years after treatment initiation were calculated, and log-rank test was conducted for comparisons among the groups. Potential prognostic variables were subjected to univariate analysis, and those with $p<0.05$ were subjected to stepwise multivariate analysis, where variables with $p<0.10$ were identified as significant factors. For each significant factor identified by multivariate analysis, a Receiver Operating Characteristic (ROC) curve was drawn to determine the cut-off values using the Youden Index. Kaplan-Meier curves were then drawn based on the cut-off values.

Results

Baseline characteristics of patients

Medical record review revealed a total of 198 patients diagnosed with PH, including 90 patients with chronic thromboembolic PH (CTEPH), which accounted for the largest proportion, followed by 68 patients with PAH (Figure 1). Among PAH patients, CTD-PAH was the most common (36 patients), followed in order by CHD-PAH (16), I/HPAH (11) and POPH (5), with no patients having other PAH subtypes. CTD-PAH patients consisted of SSc-PAH (20) and non-SSc-PAH (16). Baseline test variables for these patients divided into CTD-PAH and non-CTD-PAH groups are summarized in Table 1. For those in whom antibody test results were available from prior records, the relevant data are summarized in Table 2.

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

Determination of prognostic factors

The results of univariate and multivariate analyses of the data for the CTD-PAH group, based on the baseline and final post-treatment assessment values (Table 3), are summarized in Table 3. Hemoglobin (Hb) level at baseline, qR pattern in lead V1 of ECG, erythrocyte sedimentation rate in 60 minutes (ESR 60 min) and Mean Pulmonary Arterial Pressure (mPAP) at the final assessment were identified as factors significantly associated with clinical worsening, whereas no factor was identified as being significantly associated with the survival rate. For the three prognostic factors identified as impacting clinical worsening by multivariate analysis (i.e. Hb, ESR 60 min and mPAP), the areas under the ROC curves were calculated to be 0.70, 0.75 and 0.63, respectively (Figure 3). Based on the ROC curves, the cut-off values were determined to be 12.7 g/dL, 38 mm and 25 mmHg, respectively. Kaplan-Meier curves according to these cut-off values are shown in Figure 4.

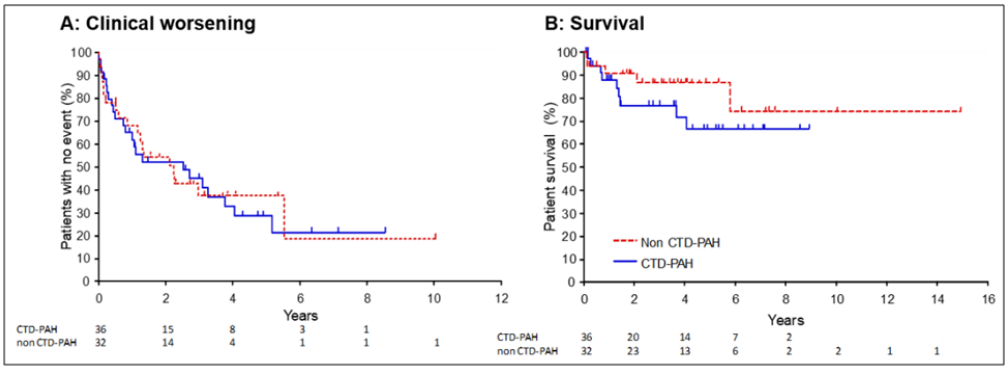

Figure 1. Kaplan-Meier curves in PAH subgroups.
Note: Kaplan-Meier curves of CTD-PAH and non-CTD-PAH groups. (A) Clinical worsening; (B) Survival. Log-rank test was conducted for comparison between the two groups. (---) Non CTD-PAH; (—) CTD-PAH.

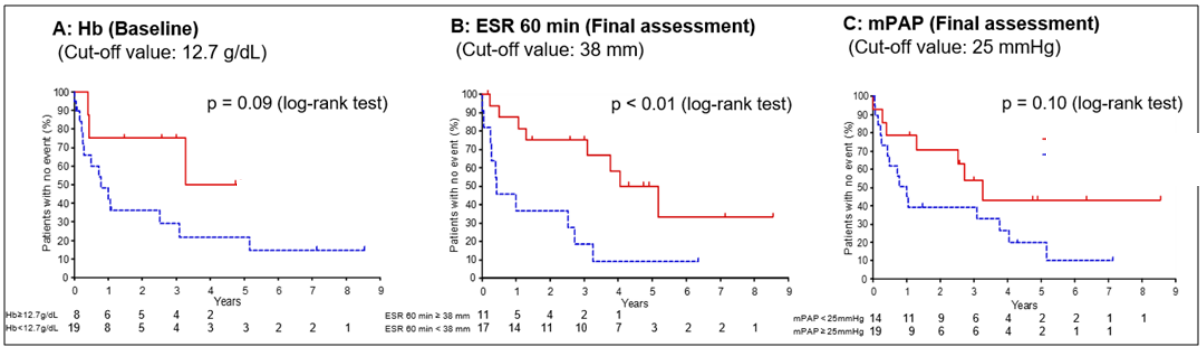

Figure 2. Kaplan-Meier curves divided by cut-off values in CTD-PAH.
Note: Log-rank test was conducted in CTD-PAH for comparisons among the groups divided by each cut-off value. (A)Hb: Haemoglobin; (B)ESR: Erythrocyte Sedimentation Rate; (C)mPAP: Mean Pulmonary Arterial Pressure. CTD-PAH: Connective Tissue Disease-Associated Pulmonary Arterial Hypertension.

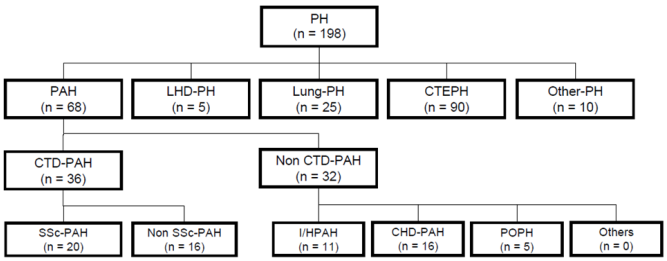

Figure 3. Patient composition.

Note: PH: Pulmonary Hypertension; PAH: Pulmonary Arterial Hypertension; LHD-PH: Left Heart Disease-Associated PH; CTEPH: Chronic Thromboembolic PH; CTD-PAH: Connective Tissue Disease-Associated PAH; SSc-PAH: Systemic Sclerosis-Associated PAH; I/HPAH: Idiopathic Or Hereditary Types of PAH; CHD-PAH: Congenital Heart Disease-Associated PAH; POPH: Portopulmonary Hypertension.

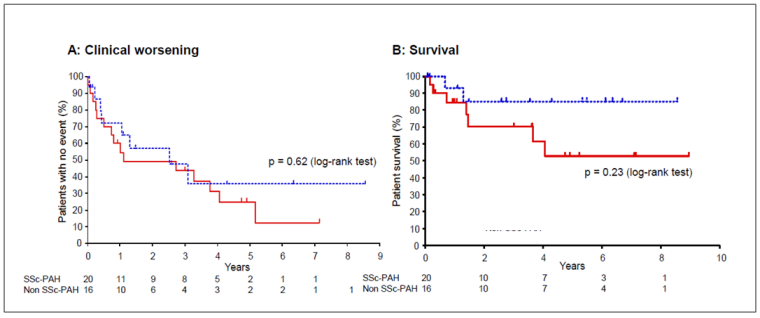

Figure 4. Kaplan-Meier curves of SSc-PAH and non-SSc-PAH.

Note: Kaplan-Meier curves of SSc-PAH and non-SSc-PAH groups. (A)Clinical worsening, (B)Survival. (---) Non CTD-PAH; (—) CTD-PAH.

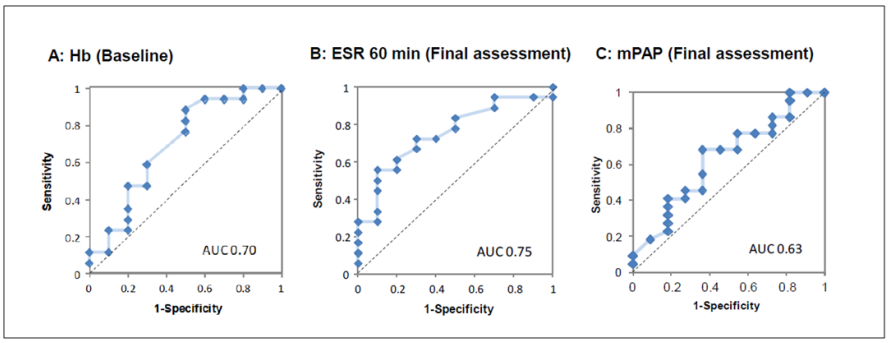

Figure 5. ROC curves based on time to clinical worsening.

Note: (A)Hb: Haemoglobin; (B)ESR: Erythrocyte Sedimentation Rate; (C)mPAP: Mean Pulmonary Arterial Pressure.

Table 1. Data at baseline and final post-treatment assessment in CTD-PAH.

Characteristics		n	Baseline (n=36)	n	Final assessment (n=36)	p value (Wilcoxon)
Age (years)		36	57.3 ± 14.7	-	-	-
Disease duration from presentation, years		30	1.2 ± 3.7	-	-	-
Female (no. [%])		36	30 (83.3)	-	-	-
WHO-FC I/II/III/IV		28	1/9/15/3	33	1/11/16/5	0.96*
RHC	RAP (mmHg)	26	4.5 ± 3.7	29	2.8 ± 3.3	0.03
	mPAP (mmHg)	28	34.5 ± 8.1	33	26.9 ± 8.7	<0.01
	PAWP (mmHg)	28	7.3 ± 4.2	31	7.8 ± 4.3	0.97
	Cardiac index (L/min/m2)	28	2.7 ± 0.7	30	2.9 ± 0.8	0.14
	PVR (WU)	28	7.7 ± 3.7	30	5.5 ± 5.5	<0.01
	SaO_2 (%)	27	93.7 ± 3.7	30	92.8 ± 9.6	0.22
	SvO_2 (%)	24	68.1 ± 6.2	26	69.7 ± 8.5	0.08
	O2 condition (L/min)	27	0.0 ± 0.0	30	0.1 ± 0.5	-
Echo	TRPG (mmHg)	22	62.0 ± 19.6	31	51.4 ± 20.1	0.05

ECG	IIp (mm)	26	1.6 ± 0.7	29	1.5 ± 0.6	0.41
	Axis (°)	25	58.6 ± 43.6	31	55.6 ± 48.0	0.99
6MWT	6MWD (m)	19	339.9 ± 174.1	19	294.8 ± 128.1	0.24
	Baseline SpO_2(%)	16	93.9 ± 3.3	18	94.2 ± 4.1	0.13
	Minimum SpO_2(%)	16	85.7 ± 9.5	18	82.2 ± 10.1	0.7
	O_2 condition (L/min)	10	0.0 ± 0.0	11	1.0 ± 1.5	-
Blood test	BNP (pg/mL)	27	273 ± 463	34	334 ± 1098	0.78
	Hemoglobin (g/dL)	27	12.0 ± 1.8	32	11.6 ± 2.0	0.11
	KL-6 (U/mL)	19	847 ± 1061	20	778 ± 1090	0.5
	Creatinine (mg/dL)	28	1.0 ± 1.4	33	0.9 ± 1.0	0.98
	eGFR (mL/min/1.73m^2)	18	68.2 ± 34.0	29	73.5 ± 33.0	0.83
	Uric acid (mg/dL)	26	5.9 ± 2.0	32	6.3 ± 2.2	0.92
	Albumin (g/dL)	27	3.6 ± 0.6	31	3.7 ± 0.6	0.82
	CRP (mg/dL)	28	0.5 ± 0.7	33	0.6 ± 1.0	0.63
	WBC (/μL)	28	7346 ± 3024	33	6118 ± 2418	0.03
	ESR 30 min (mm)	21	14.7 ± 16.6	25	10.3 ± 9.5	0.53
	ESR 60 min (mm)	23	41.5 ± 34.8	28	34.2 ± 25.7	0.42
	IgG (mg/dL)	23	1705 ± 771	24	1740 ± 869	0.38
	IgM (mg/dL)	22	130.8 ± 109.5	18	89.9 ± 49.2	0.53
	IgA (mg/dL)	22	327.1 ± 207.4	18	303.6 ± 156.6	0.54
	CH50 (U/mL)	24	44.7 ± 9.4	19	37.8 ± 10.9	0.02
	C3 (mg/dL)	24	94.8 ± 17.0	20	79.5 ± 21.5	0.12
	C4 (mg/dL)	24	20.7 ± 6.2	20	23.2 ± 27.0	0.6

Note: *p value by chi-squared test.

Abbreviations: Values are mean ± standard deviation or number (percent). 6MWD: Six-Minute Walk Distance; 6MWT: Six-Minute Walk Test; BNP: Brain Natriuretic Peptide; CH50: Total Hemolytic Complement; CTD-PAH: Connective Tissue Disease-Associated PAH; CRP: C-Reactive Protein; ECG: Electrocardiography; eGFR: Estimated Glomerular Filtration Rate; ESR: Erythrocyte Sedimentation Rate; mPAP: Mean Pulmonary Arterial Pressure; PAWP: Pulmonary Arterial Wedge Pressure; PVR: Pulmonary Vascular Resistance; RAP: Right Atrial Pressure; SaO_2: Arterial Oxygen Saturation; SvO2: Mixed Venous Oxygen Saturation; TRPG: Tricuspid Regurgitation Pressure Gradient; WBC: White Blood Cell Count; WHO-FC: World Health Organization-Functional Class.

Table 2. Prognostic factors for CTD-PAH.

Characteristic		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
Survival									
-	mPAP	-	-	-	-	1.15 (1.04-1.26)	0.004	-	-
-	PVR	-	-	-	-	1.19 (1.04-1.36)	0.01	-	-
-	TRPG	-	-	-	-	1.03 (1.01-1.06)	0.003	-	-
-	SaO_2	0.73 (0.55-0.95)	0.02	-	-	0.92 (0.87-0.98)	0.007	-	-
-	SvO_2	-	-	-	-	0.90 (0.82-1.00)	0.041	-	-
-	%VC	0.92 (0.86-1.00)	0.046	-	-	-	-	-	-
-	%FEV1	0.94 (0.88-1.00)	0.036	-	-	-	-	-	-
-	BNP(Log)	6.47 (1.13-36.86)	0.036	-	-	4.51 (1.78-11.41)	0.002	-	-
-	Hemoglobin	0.13 (0.02-0.73)	0.021	-	-	-	-	-	-
-	Albumin	-	-	-	-	0.22 (0.09-0.58)	0.002	-	-
-	Creatinine	1.45 (1.01-2.08)	0.046	-	-	1.54 (1.05-2.27)	0.026	-	-
-	eGFR	-	-	-	-	0.95 (0.91-0.99)	0.013	-	-
-	Uric acid	-	-	-	-	1.39 (1.01-1.89)	0.04	-	-
-	CRP	4.36 (1.36-14.00)	0.013	-	-	1.68 (1.17-2.42)	0.005	-	-
-	IIp	-	-	-	-	7.19 (1.29-40.17)	0.025	-	-
-	qR	-	-	-	-	21.67 (3.48-134.91)	0.001	-	-

-		rsR	12.07 (1.64-88.82)	0.014	-	-	-	-	-	-
-		Scl-70	6.14 (1.35-27.93)	0.019	-	-	-	-	-	-
-		Centromere	23.98 (1.50-383.60)	0.025	-	-	-	-	-	-
Clinical worsening										
-	mPAP		-	-	-	-	1.07 (1.01-1.14)	0.022	1.15 (1.01-1.31)	0.027
-	SaO_2		-	-	-	-	0.91 (0.85-0.98)	0.008	-	-
-	Hemoglobin		0.53 (0.36-0.79)	0.002	0.54 (0.36-0.80)	0.002	-	-	-	-
-	Albumin		-	-	-	-	0.43 (0.24-0.80)	0.007	-	-
-	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
-	rS		0.28 (0.10-0.78)	0.015	-	-	-	-	-	-
-	rsR		4.45 (1.16-17.08)	0.03	-	-	-	-	-	-

Abbreviations: qR, rsR, and rS are QRS patterns in electrocardiogram. HR: Hazard Ratio; %VC: Vital Capacity as percent of predicted; %FEV1: percentage of Predicted Forced Expiratory Volume in one second.

Table 3. Baseline characteristics of patients.

Characteristics	n	CTD-PAH (n=36)	n	Non-CTD-PAH (n=32)	Mean difference	95% CI
Age (years)	36	57.3 ± 14.7	32	51.6 ± 22.4	−5.68	(−15.02, 3.6)
Disease duration from presentation (years)	30	1.2 ± 3.7	30	5.8 ± 10.7	4.66	(0.46, 8.87)
Female (no. [%])	36	30 (83.3)	32	26 (81.3)	-	-
WHO-FC I/II/III/IV (no.)	28	1/9/15/3	29	2/6/14/7	-	0.47
RHC						
RAP (mmHg)	26	4.5 ± 3.7	29	4.8 ± 3.6	0.24	(−1.74, 2.22)
mPAP (mmHg)	28	34.5 ± 8.1	29	44.9 ± 14.7	10.43	(4.11, 16.75)
PAWP (mmHg)	28	7.3 ± 4.2	29	8.1 ± 3.9	0.76	(−1.38, 2.91)
Cardiac index (L/min/m2)	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)
SaO_2 (%)	27	93.7 ± 3.7	28	89.6 ± 8.7	−4.15	(−7.78, 0.53)
SvO_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	(0.00, 0.00)
Echo						
TRPG (mmHg)	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 (°)	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 SpO2 (%)	16	93.9 ± 3.3	19	91.6 ± 5.9	−2.31	(−5.55, 0.94)
Minimum SpO2 (%)	16	85.7 ± 9.5	18	81.1 ± 10.7	−4.58	(−11.66, 2.51)
O2 condition (L/min)	10	0.0 ± 0.0	10	1.2 ± 2.0	1.2	(−0.22, 2.62)
Blood tests						
BNP (pg/mL)	27	273 ± 463	25	320 ± 486	47.1	(−217.9, 311.9)
Hemoglobin (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/1.73m^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	(−25844, 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)
CH50 (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)

Note: *p value by chi-squared test.

Abbreviations: Values are mean ± standard deviation or number (percent). 6MWD: Six-Minute Walk Distance; 6MWT: Six-Minute Walk Test; BNP: Brain Natriuretic Peptide; CH50: Total Haemolytic Complement; CTD-PAH: Connective Tissue Disease-Associated PAH; CRP: C-Reactive Protein; ECG: Electrocardiography; eGFR: Estimated Glomerular Filtration Rate; ESR: Erythrocyte Sedimentation Rate; mPAP: Mean Pulmonary Arterial Pressure; PAWP: Pulmonary Arterial Wedge Pressure; PVR: Pulmonary Vascular Resistance; RAP: Right Atrial Pressure; SaO_2: Arterial Oxygen Saturation ; SvO2: Mixed Venous Oxygen Saturation; TRPG: Tricuspid Regurgitation Pressure Gradient; WBC: White Blood Cell Count; WHO-FC: World Health Organization-Functional Class.

Table 4. Prevalence of various antibodies determined by antibody testing.

Characteristics		**CTD-PAH**			**Non-CTD-PAH**
		(n=36)			**(n=32)**
	n		(+)	n	(+)
Rheumatoid factor	32	11	34.4	21	7 (33.3)
CCP	14	2 (14.3)		8	1 (12.5)
MMP3	14	8 (57.1)		4	2 (50.0)
Anti-nuclear antibody	34	30	88.2	24	6 (25.0)
dsDNA	25	4 (16.0)		10	0 (0.0)
ssDNA	21	11	52.4	9	1 (11.1)
U1-RNP	30	9 (30.0)		11	0 (0.0)
Sm	27	4 (14.8)		9	0 (0.0)
SS-A/Ro	24	6 (25.0)		7	0 (0.0)
SS-B/La	29	4 (13.8)		8	0 (0.0)
Scl-70	30	5 (16.7)		12	0 (0.0)
Centromere	31	10	32.3	10	0 (0.0)
RNA polymerase III*	17	0	0	2	0 (0.0)
Jo-1	26	0	0	9	0 (0.0)
CL	23	5 (21.7)		16	1 (6.3)
CLβ2GPI complex	28	2	7.1	20	0 (0.0)
Lupus anticoagulant	27	1	-3.7	20	0 (0.0)
c-ANCA	21	0	0	13	0 (0.0)
p-ANCA	20	1	5	12	1 (7.7)

Abbreviations: ANCA: Antineutrophil Cytoplasmic Antibodies; CCP: Cyclic Citrullinated Peptide; CL: Cardiolipin; CLβ2GPI: Cardiolipin B 2 -Glycoprotein I; dsDNA: Double-Strand DNA; MMP3: Matrix Metalloproteinase-3; Scl-70: Topoisomerase I; Sm, Smith; ssDNA: Single-Strand DNA; U1-RNP: U1-Ribonucleoprotein.

Discussion

Evidence suggests that the progression of CTD-PAH is associated with not only the severity of pulmonary hypertension, but also the severity of respiratory disease and inflammatory activity [7, 8]. In the present study, numerous variables, including antibody and blood test results, in addition to hemodynamic and respiratory function variables, were examined to identify factors that might be relevant to improving the prognosis of CTD-PAH patients, by reviewing the medical records kept over a 15-year period at Kobe University Hospital. The distribution of PAH types at our institute was characterized by a substantially larger proportion of CTD-PAH (52.9%; Figure 5) compared to that in previously reported large-scale registries (15.3% in the French Registry [2], 25.3% in the REVEAL Registry [3] and 24% in the Japan PH Registry [9]), and by a smaller proportion of I/HPAH (16.2%, compared to 52.5% in the French Registry [2], 46.2% in the REVEAL Registry [3] and 56% in the Japan PH Registry [9]) of all PAH patients. This discrepancy may be due, in part, to the established CTD-PAH screening system at our institute. The proportion of SSc-PAH among all CTD-PAH patients (55.5%) was comparable to that in the REVEAL Registry (62.2%) [3].

Although the poorer prognosis of CTD-PAH compared to IPAH has already been reported [2,10], 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 mmHg vs. 45.0 mmHg) and PVR (7.7 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, being 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%). Since the non-CTD-PAH group in this study included both IPAH (carrying a good prognosis) and POPH (carrying a poor prognosis), this might have

resulted in the absence of a significant difference between the two groups. The lower survival rate of CTD-PAH patients, despite better hemodynamic status (mPAP: 34.5 ± 8.1 mmHg in CTD-PAH vs. 44.9 ± 14.7 mmHg in non-CTD-PAH), may be explained by factors not related to PAH, such as impaired renal function (creatinine [Cr]: 1.0 ± 1.4 vs. 0.7 ± 0.1 mg/dL), higher inflammatory markers (ESR 60 min: 41.5 ± 34.8 vs. 15.9 ± 21.4 mm) and higher interstitial pneumonia markers (KL-6: 846.8 ± 1060.8 vs. 264.0 ± 107.7 U/ml). When CTD-PAH patients were divided into SSc-PAH and non-SSc-PAH subgroups Figure 4, patients in the SSc-PAH subgroup had poorer outcomes in terms of survival rates, as reported previously [11,12].

In the CTD-PAH group, univariate analysis of baseline test variables identified blood oxygen saturation level (SaO_2), an inflammatory marker (C-reactive protein [CRP]), cardiac function (brain natriuretic peptide [BNP]), respiratory function (% vital capacity [VC], % forced expiratory volume 1 [FEV1]), antigen expression (anti-scleroderma antibody), renal function (Cr) and anemia (Hb) markers as significant factors for survival Table 4, suggesting the involvement of underlying diseases and associated systemic dysfunction. These baseline prognostic factors may be affected by therapeutic interventions, and the analysis was not adjusted for therapeutic factors. Therefore, further analysis would be required to confirm the prognostic value of these baseline variables identified as significant. We thus conducted another analysis using the test variables at the final assessment. Univariate analysis of test variables at the final assessment identified hemodynamic variables (mPAP, PVR), SaO2, BNP, Cr, uric acid (UA), albumin (Alb), CRP and ECG as being significantly associated with death, and mPAP, SaO_2, Alb, ESR 60 min and ECG as being significantly associated with clinical worsening.

Multivariate analysis of the baseline variables identified no significant independent prognostic factors for CTD-PAH death, and 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. reported that the qR pattern in the ECG, which is a sign of right ventricular hypertrophy (RVH), is an independent prognostic factor for survival in PAH patients [13], despite most of the participants in their study having had IPAH (78.8%). Our results also indicated the qR pattern to be a prognostic factor for clinical worsening of CTD-PAH patients, indicating that preventive care to avoid RVH development is important for improving the long-term prognosis of CTD-PAH patients.

The observation that mPAP was identified as a prognostic factor at the final assessment only and not at baseline suggested that PAH specific treatment influenced the prognosis. In addition to mPAP, decreased respiratory function has been shown to affect the prognosis of patients with CTD-PAH, especially those with SSc-PAH [12]. In the present study, however, %VC and %FEV1 were identified as significant factors in univariate analysis, but not as independent prognostic factors in multivariate analysis Table 4. This may be attributable to the sample size being too small for conducting 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 being independently associated with clinical worsening. Among the test variables at the final assessment, Alb was identified as a prognostic factor by multivariate analysis. In addition, renal function (Cr, UA) and an inflammatory marker (CRP) were identified as prognostic factors for CTD-PAH death, though 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 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, as for mPAP at the final assessment, the AUC of ROC was 0.63 for clinical worsening prediction, indicating it to be prognostic (Figure 4), and it was also relatively high (0.73) for death prediction, while it was not shown to be prognostic (data not shown). The cut-off value of mPAP for clinical worsening at the final assessment was determined to be 25 mmHg (You den index). This cut-off value is lower than the target mPAP value previously reported for IPAH (42.5 mmHg [6]), suggesting the need for more strict control of pulmonary hypertension in CTD-PAH. For the test variables identified by multivariate analysis as independent prognostic factors (Hb at baseline, ESR 60 min at final assessment; Table 4), the cut-off values for clinical worsening were calculated to be Hb; 12.7 g/dL and ESR 60 min; 38 mm (Figure 5), suggesting the need for preventing anemia and controlling inflammation. Kaplan-Meier curves drawn according to these cut-off values indicated that even those CTD-PAH patients who met each cut-off value might have a poor prognosis, i.e. a high likelihood of clinical worsening (Figure 5), suggesting the presence of other clinical variables requiring careful control, in addition to those identified in the present study. Further efforts are needed to reveal as yet unidentified clinical variables by including more patients, to address the sample-size limitation of the present study.

The major limitation of this study is that it was conducted at a single center with a retrospective design. Therefore, selection bias might have been unavoidable. In addition, the sample size was too small to compare the Kaplan-Meier curves for each group or to conduct multivariate analysis for prognostic factors. Multicenter studies with more patients are anticipated to clarify the significance of these analyses.

Conclusion

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 blood pressure level for CTD-PAH was calculated to be mPAP=25 mmHg, which is much lower than that previously reported for IPAH. Our results suggest the need for more strict control of pulmonary hypertension, as well as control of anemia and inflammatory activity of the underlying CTD, for successful management of CTD-PAH. Thus, a more multifactorial treatment strategy must be developed to improve the prognosis of CTD-PAH patients.

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