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A cohort study in HigAshi-nippon of Pulmonary hyPertensIoN in systEmic SclerosiS (HAPPINESS study): protocol and baseline data for an observational study

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Abstract

Background Pulmonary hypertension (PH) is the leading cause of death among patients with systemic sclerosis (SSc). Recently, early therapeutic intervention to improve the prognosis was suggested, and the definition of PH was recently revised by lowering the cut-off value of mean pulmonary arterial pressure (mPAP) from ≥ 25 to > 20 mmHg. However, the optimal threshold for therapeutic intervention remains unclear. We aim to evaluate the prognosis of patients with SSc and its relationship with mPAP.

Methods For this non-interventional retrospective and prospective cohort study, we enrolled patients with SSc or scleroderma spectrum disorders accompanied by other connective tissue diseases who underwent right heart catheterization (RHC) for suspected PH from 2010 to 2023. The date of the first RHC was defined as the baseline. Enrolled patients were classified into three groups based on their mPAP at the first RHC (≤ 20, 21-24, and ≥ 25 mmHg) and are being observed from baseline up to three years. The primary endpoint is the time between the first RHC and the first hospitalisation or death due to worsening PH.

Results This study was approved by the Ethics Committee of Hokkaido University Hospital. A total of 229 patients were enrolled from 12 participating centres, with 41 prospectively followed up and 188 retrospectively followed up. The number of patients in each group (an mPAP of ≤ 20, 21–24, and ≥ 25 mmHg) is 79, 26, and 124, respectively. The observation is expected to be completed by December 2026. Findings will be disseminated at scientific conferences, peer-reviewed journals.

Conclusions The findings of this study that we will obtain are expected to provide important information that will lead to improvements in the diagnosis of PH and the prognosis of patients.

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Trial registration This study was approved by the Ethics Committee of Hokkaido University Hospital (approval number 022-0109). It has been registered in the Japan Registry of Clinical Trials as jRCT1010220025 since November 7, 2022.

Keywords Pulmonary hypertension, Systemic sclerosis, Right heart catheterization, Mean pulmonary arterial pressure

Background

Pulmonary hypertension (PH) often aggravates connective tissue diseases (CTDs) and negatively affects exercise capacity, quality of life, and survival. It is the leading cause of death in systemic sclerosis (SSc) and develops owing to pulmonary vascular disease (group 1 PH, pulmonary arterial hypertension [PAH]), left heart disease (group 2 PH), and/or interstitial lung disease (group 3 PH), complicating clarification of the underlying pathological condition and decision-making regarding therapeutic interventions [1–5]. Compared with PAH associated with other CTDs, such as systemic lupus erythematosus (SLE), SSc-PAH reportedly has a poorer response to immunosuppressive drugs and a worse prognosis [6, 7].

Although right heart catheterization (RHC) is a requisite for the diagnosis of PH, owing to its invasiveness it is exclusively performed in cases with a strong suspicion of PH based on other clinical examinations, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, pulmonary function tests (such as the diffusing capacity of the lungs for carbon monoxide [DLCO]), ratio of forced vital capacity (FVC) to the DLCO, and tricuspid regurgitation velocity assessed via echocardiography [1, 8–10].

Recently, the definition of PH has been revised by lowering the cut-off value of mean pulmonary arterial pressure (mPAP) from ≥ 25 to > 20 mmHg [11]. Among patients with SSc, the mPAP = 21-24-mmHg group, traditionally referred to as those with borderline PH (or borderline PAP), is considered at risk of PAH, and cohort studies in different countries have revealed that 42-55% of these patients are classified as having overt PAH over time upon follow-up RHC [12, 13]. Furthermore, the mPAP = 21-24-mmHg group reportedly has similarly poor overall survival to the mPAP ≥ 25-mmHg group [14]. Therefore, early therapeutic interventions to improve prognosis have been suggested, particularly for patients with SSc-PAH [8, 15, 16], although the optimal threshold for therapeutic intervention remains unclear.

In this cohort study, we are aiming to evaluate the prognosis of patients with SSc and its relationship with the mPAP. We collected clinical data from patients with SSc who underwent RHC, dividing them into three groups based on their mPAP.

Methods

Study design

This is a non-interventional retrospective and prospective cohort study. We have enrolled patients with SSc or scleroderma spectrum disorders accompanying other CTDs who underwent RHC after 2010 for suspected PH. Patients were recruited from 12 specialized centers across eastern Japan (Table 1).

The date of the first RHC was defined as the baseline. Enrolled patients were classified into three groups based on their mPAP at the first RHC (≤ 20, 21-24, and ≥ 25 mmHg) and were observed from baseline for three years. Patients who had undergone their first RHC more than three years before enrolment were followed up retrospectively (Fig. 1A). For patients who underwent the first RHC within three years of enrolment, prospective follow-up was initiated after they provided informed consent (Fig. 1B). For these patients, the prospective observation period is three years minus the retrospective period. Patients newly undergoing RHC after the start of this study are being followed up in a fully prospective manner for three years from baseline after they provided informed consent (Fig. 1C).

This study was approved by the Ethics Committee of Hokkaido University Hospital (approval number: 022–0109). It has been registered in the Japan Registry of Clinical Trials as jRCT1010220025 since November 7, 2022. All researchers involved in this study will comply with the Declaration of Helsinki and the Ethical Guidelines for Medical Research Involving Human Subjects.

Participants

Inclusion criteria

Patients who met the following criteria were included:

1. Aged 18 years or older at the time of inclusion.
2. Fulfilling the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc [17] or having scleroderma spectrum disorders (sclerodactyly or SSc-specific autoantibodies, including anti-Scl-70, anti-centromere, or anti-RNA polymerase III antibodies) and meeting one of the following criteria: the 2019 Japanese Ministry of Health, Labour, and Welfare diagnostic criteria for mixed connective tissue disease [18], the 1997 ACR classification criteria for SLE [19], the 2012 Systematic Lupus International Collaborating Clinics

Table 1 Number of enrolled patients

	n (%)
All patients (*n* = 229)	
- Hokkaido University Hospital	91 (39.7)
- Keio University Hospital	31 (13.5)
- Sapporo Medical University Hospital	26 (11.4)
- Tohoku University Hospital	26 (11.4)
- Obihiro-Kosei Hospital	17 (7.4)
- Asahikawa Medical University Hospital	11 (4.8)
- Tomakomai City Hospital	9 (3.9)
- Nippon Medical School Hospital	5 (2.2)
- Tokyo Women's Medical University Hospital	5 (2.2)
- Japanese Red Cross Kitami Hospital	4 (1.7)
- Sapporo City General Hospital	2 (0.9)
- Tohoku Medical and Pharmaceutical University Hospital	2 (0.9)
All patients (*n* = 229)	
- Prospective	7 (31.0)
- Prospective + retrospective	34 (14.8)
- Retrospective	188 (82.1)

n: number

classification criteria for SLE [20], the Bohan and Peter criteria for the diagnosis of polymyositis and dermatomyositis [21], or the 2016 ACR/EULAR classification criteria for primary Sjögren's syndrome [22].

3. Having had their first RHC later than 2010 for suspicion of PH owing to unexplained dyspnoea, increased NT-proBNP levels (more than twice the upper limit of the normal range), reduced pulmonary diffusing capacity (DLCO < 60% or FVC/DLCO > 1.6), or elevated tricuspid regurgitation velocity (> 2.8 m/s).
4. Voluntarily agreeing to participate in the study or not refusing to participate in the study.

Data collection

Schedules for data collection

Evaluation endpoints, treatment details, and outcomes will be collected regularly and registered in an anonymized database. Medical information, such as results of blood tests, skin evaluations, six-minute walk tests, pulmonary function tests, and transthoracic echocardiography, as well as RHC data, will be collected (Table 2). During the prospective observation period, participants will be followed up for up to three years. The clinical examinations and tests described below will be performed according to the schedule presented in Table 2. For the retrospective follow-up period, data will be extracted for each time point within the predefined time window, as described in Table 2.

Clinical information

Clinical information, including age, sex, date of first visit, the time from onset, diagnosis, social history, medical history, life history (such as smoking history), comorbidities, treatment up to the baseline, and classification of PH (groups 1, 2, 3, 4, and/or 5) will be collected at baseline. In addition, we will collected information on all immunosuppressive therapies, including mycophenolate mofetil (MMF), both at baseline and throughout follow-up. Details of concomitant medications will be regularly collected throughout the study. Information from physical examinations, such as the skin thickness, presence of skin ulcers, and vital signs, will also be collected regularly. When PH develops during the follow-up, each physician will determine the classification of PH based on the RHC results and other medical information.

In addition, patients' subjective measures of breathlessness and quality of life will be assessed using the World Health Organization (WHO) functional classification and emPHasis-10 questionnaire, a useful, disease-specific, patient-reported assessment of the decline in quality of life due to PH [23, 24]. The 10-item questionnaire for the assessment of health-related quality of life in PH (emPHasis-10 questionnaire) will be administered during the prospective observational period.

Tests, imaging, and procedures

Blood immunological tests (Table 2), including those for autoantibodies, will be performed during the screening period. We will conduct blood tests every three months, and skin evaluation, six-minute walk tests, pulmonary function tests, and transthoracic echocardiography annually from the date of inclusion. The frequency and interval of RHC will be coordinated by the physician, considering the patient's medical condition. During RHC, the mPAP, cardiac output, and pulmonary arterial wedge pressure will be measured, enabling us to calculate the pulmonary vascular resistance (PVR). For chest computed tomographic examinations, records of imaging conditions and equipment names will be preserved to enable future subgrouping.

Study endpoints

Primary endpoint

The primary endpoint is the time between the first RHC and first hospitalization or death due to worsening PH. The relationship between hospitalisation or death and PH will be determined by each physician, considering symptoms (e.g. WHO functional class) and the need for additional treatment for PH [25].

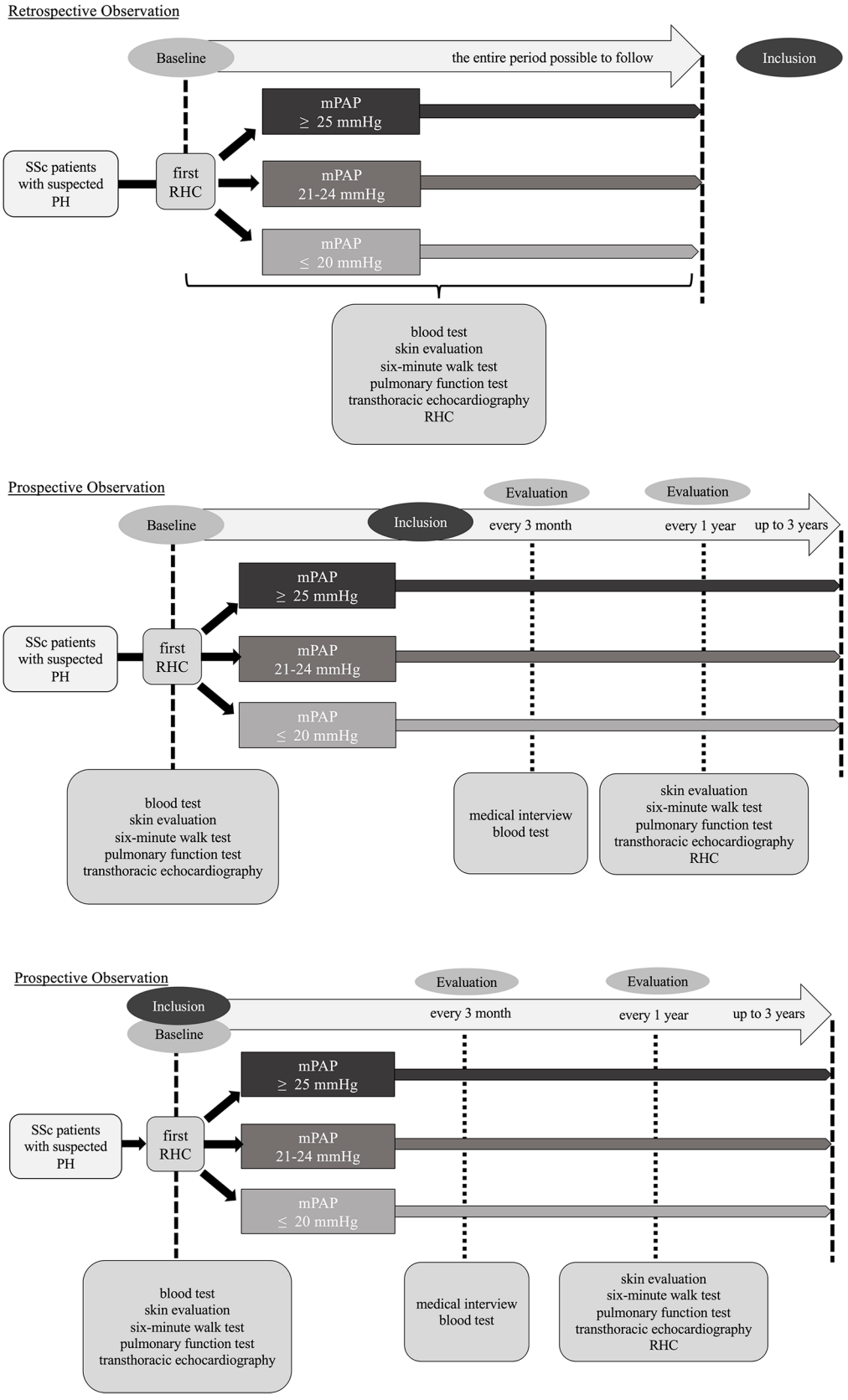

Fig. 1 Study design. (**A**) Retrospective observation. (**B**) Prospective observation of patients who underwent RHC before inclusion. (**C**) Prospective observation of patients who underwent RHC at the same time as inclusion. SSc: systemic sclerosis; PH: pulmonary hypertension; RHC: right heart catheterisation; mPAP: mean pulmonary arterial pressure

Table 2 Study schedules

Study phase	Screening period	Study period		
Day	**Days -30 to 0**	**Baseline**	**Every 3 month**	**Every 12 month**
Allowance		± 30 days	± 30 days	± 180 days
Consent	•			
Medical information*1	•			
Details of treatment*2	•	•	•	
Physical examination*3		•	•	
WHO functional class		•	•	
emPHasis-10		•		•
6-minute-walk test		•		•
Blood test				
- Immunological test*4	•			
- CBC, biochemistry, immunological test*5		•	•	
Transthoracic echocardiography		•		•
Pulmonary function tests		•		•
RHC		•		
Events*6		←	—	→

*1: Age, sex, date of first visit, diagnosis, medical history, life history (such as smoking history), comorbidities, treatment up to baseline, classification of PH

*2: Concomitant medications, such as pulmonary vasodilators, immunosuppressive agents, diuretics, and antihypertensives

*3: Vital signs (blood pressure, pulse rate), height (only at baseline), body weight, skin thickness (modified Rodnan total skin thickness score), and presence of skin ulcers

*4:SP-A and SP-D for all patients; ANAs, anti-Scl-70 antibodies, anti-centromere antibodies, and anti-RNA polymerase III antibodies for patients with SSc; ANAs, anti-dsDNA antibodies, anti-RNP antibodies, anti-Sm antibodies, C3, C4, and CH50 in patients with SLE; anti-SS-A and anti-SS-B antibodies in patients with pSS; anti-RNP antibodies in patients with MCTD; anti-ARS, anti-Jo-1, anti-MDA5, anti-Mi-2, and anti-TIF1-g antibodies in patients with PM/DM

*5: Haemoglobin, haematocrit, red blood cell count, white blood cell count, platelet count, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, gamma-glutamyl transferase, creatine phosphokinase, creatinine, blood urea nitrogen, estimated glomerular filtration rate, BNP, N-terminal proBNP, uric acid, haptoglobin, KL-6, and C-reactive protein

*6: First hospitalization for worsening PH or death due to worsening PH. The relationship between hospitalization and PH was determined by each physician

WHO: World Health Organization; emPHasis-10: 10-item questionnaire for assessing health-related quality of life in pulmonary hypertension; CBC: complete blood cell count; RHC: right heart catheterization; PH: pulmonary hypertension; ANA: anti-nuclear antibodies; SP: surfactant protein; RNP: ribonucleoprotein; Sm: Smith; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; SS-A: Sjögren's-syndrome-related antigen; pSS: primary Sjögren's syndrome; MCTD: mixed connective tissue disease; ARS: aminoacyl tRNA synthetase; MDA5: melanoma differentiation-associated protein 5; TIF1-g: transcriptional intermediary factor 1-γ; PM/DM: polymyositis and dermatomyositis; BNP, brain natriuretic peptide

Secondary endpoints

1. Change in the parameters of RHC, including the mPAP and PVR (measured one or more times during follow-up).
2. WHO functional class.
3. emPHasis-10 score.
4. Six-minute walk distance.
5. Plasma and serum biochemical markers, including BNP, NT-proBNP, haemoglobin, uric acid, haptoglobin, and KL-6.
6. Pulmonary function tests, including DLCO and FVC/DLCO ratio.
7. Transthoracic echocardiography parameters, including the tricuspid regurgitation velocity, left ventricular ejection fraction, ratio of the transmitral early peak velocity to the early diastolic mitral annulus velocity, septal early diastolic mitral annulus velocity, lateral early diastolic mitral annulus velocity, and left atrial volume index.
8. Modified Rodnan total skin thickness score.

The above evaluations will be performed within the predefined time window described in Table 2.

In addition, to explore indicators to discriminate the spectrum/phenotype of PH between groups 1, 2, and 3 from an early stage, factors affecting secondary endpoints, such as the time from onset and detail of therapies, will be examined in the baseline data.

Data management

Information related to the study will be managed by replacing personal information, such as names and addresses, with control numbers (research IDs) to prevent participant identification. The principal investigator will supervise the strict storage of the corresponding chart. No identifying information will be included in the publication of the information obtained in this study. This study is being monitored by the Clinical Research and Medical Innovation Center of Hokkaido University Hospital.

Statistical analysis

Statistical analyses are conducted by a statistician using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous data are presented as means with standard deviations or medians with interquartile ranges, and categorical data are presented as frequencies and percentages. Survival analysis with comparison of different subgroups according to the mPAP at the first RHC (≤ 20, 21-24, and ≥ 25 mmHg) as the primary endpoint will be performed using Kaplan–Meier analysis, log-rank tests, and covariate-adjusted Cox regression analysis. The primary analysis will be the comparison between the group with an mPAP of ≤ 20 mmHg and that with an mPAP of 21-24 mmHg. Other comparisons will be performed as secondary endpoints. Cox regression analysis will be performed for baseline parameters, including age, sex, the time from onset, social history, medical history, comorbidities, mPAP, PVR, WHO functional class,

the emPHasis-10 score, the six-minute walk distance, DLCO, FCV/DLCO ratio, and immunosuppressive therapies, including MMF. We will analyze whether patients receiving long-term MMF differ in terms of mPAP, progression to PH, or survival compared to those who never received it or received it only for a short period. Survival may also be analyzed by dividing the participants into two groups, that with an mPAP of ≤ 20 mmHg and that with an mPAP of ≥ 21 mmHg. In addition, we will also perform the analysis comparing between the group with an mPAP of < 25 mmHg and that with ≥ 25 mmHg.

Statistical power calculations

Based on other literature [14, 26] and our previous study [27], the enrolled patients are expected to be classified into three groups in a 2:1:2 ratio based on the mPAP (≤ 20, 21–24, and ≥ 25 mmHg). The primary comparison groups will be the mPAP ≤ 20-mmHg group and the mPAP = 21-24-mmHg group. In a previous multicentre study involving patients with SSc, the three-year incidence rates of PH were 4.2% in the group with normal haemodynamics (mPAP ≤ 20 mmHg) and 18.5% in the mPAP = 21-24-mmHg group [12]. Assuming that 10% of participants who underwent RHC owing to suspected PH were not diagnosed with the condition, the estimated three-year incidence rates of hospitalization owing to suspected PH are 4.7% and 20.6% for these groups, respectively. Based on these figures, the sample size required to achieve 80% power with a log-rank test at a 5% significance level, considering a 12-month enrolment period and a 36-month follow-up period, was calculated as 85 patients for the mPAP ≤ 20-mmHg group and 43 patients for the mPAP = 21-24-mmHg group. Including the mPAP ≥ 25-mmHg group, the total required sample size is 213 (85 + 43 + 85) patients. Considering an anticipated dropout rate of approximately 10%, the target sample size was set at 230 patients.

Results

Baseline characteristics

A total of 229 patients were enrolled from 12 participating centres, with 41 patients prospectively followed up and 188 retrospectively followed up. Seven of 41 patients are observed prospectively for a full 3 years (Table 1). The clinical characteristics of the patients in each group are summarised in Table 3. The number of patients in each group (an mPAP of ≤ 20, 21–24, and ≥ 25 mmHg) was 79, 26 and 124, respectively (Table 4).

Discussion

In this non-interventional retrospective and prospective cohort study, we are collecting clinical data of patients with SSc who underwent RHC for suspected PH to evaluate the life prognosis and its relationship with mPAP. We achieved registration of more patients than the required number, which has been calculated in advance. Patients were recruited from 12 hospitals associated with connective tissue diseases across eastern Japan. By enrolling patients from different regions, environments and backgrounds, we increase the diversity of the geographical and demographic statistics. This would increase the potential for generalizing the results of the analysis. In addition, this study can reduce the influence and bias of the practices of individual physicians and centers.

In contrast to PAH associated with CTDs other than SSc, SSc-PAH often develops chronically, and has been reported to have a poorer response to immunosuppressive drugs and a worse prognosis [6, 7]. In non-SSc CTD-related PAH, vasculitis with thickening of the tunica media, plexiform lesions, and fibrinoid necrosis with proliferation of vascular smooth muscle cells is seen in the pulmonary arteries, whereas in SSc-PAH, inflammatory cell infiltration has been reported to be scarce, but fibrous intimal thickening and luminal narrowing have been observed in a wide range of pulmonary vessels, including pulmonary arteries, pulmonary capillaries, and pulmonary veins [28]. These histological features may explain differences in clinical presentation and response to immunosuppressive drugs, and may be associated with poorer life expectancy. We cannot evaluate histologically in each patients, but we can estimate the pathological condition by regularly assessing the clinical data such as echocardiography and pulmonary function tests.

In recent years, there have been reports on the prognosis of mPAP = 21-24-mmHg patients [14]. In this study, we will further analyze the changes in subjective symptoms, each parameter including follow-up RHC after enrolment, and treatment information. The findings of this study that we will obtain are expected to provide important information that will lead to improvements in the diagnosis of PH and the prognosis of patients.

Trial status

The HAPPINESS study received ethical approval on September 27, 2022. Recruitment started on October 19, 2022 and finished on November 8, 2023. Observation is expected to be completed by December 2026.

Table 3 Clinical characteristics at the baseline

	All patients (*n* = 229)	**mPAP (mmHg) at the baseline**		
		≤ 20 (*n* = 79)	**21–24 (*n* = 26)**	**≥ 25 (*n* = 124)**
Sex (male), n (%)	30 (13.1)	12 (15.2)	4 (15.4)	14 (11.3)
Age (year), median (IQR)	62.0 (51.0–70.0)	64.0 (51.0–70.0)	61.5 (54.0–72.0)	62.0 (49.0–69.5)
Height (cm), median (IQR)	154.6 (149.2–160.0)	155.2 (149.1–161.5)	154.4 (151.0–162.8)	153.0 (149.0–158.1)
- N missing	20 (8.7)	3 (3.8)	1 (3.8)	16 (12.9)
Body weight (kg), median (IQR)	50.0 (44.0–58.9)	50.2 (44.5–56.0)	51.0 (47.9–57.0)	49.0 (41.7–59.9)
- N missing	20 (8.7)	3 (3.8)	1 (3.8)	16 (12.9)
Diagnosis, n (%)				
- Systemic sclerosis	186 (81.2)	70 (88.6)	19 (73.1)	97 (78.2)
- Mixed connective tissue disease	22 (9.6)	6 (7.6)	5 (19.2)	11 (8.9)
- Systemic lupus erythematosus	17 (7.4)	1 (1.3)	1 (3.8)	15 (12.1)
- Polymyositis/Dermatomyositis	8 (3.5)	2 (2.5)	2 (7.7)	4 (3.2)
- Primary Sjögren's syndrome	7 (3.1)	0 (0.0)	0 (0.0)	7 (5.6)
Classification of PH, n (%)				
- Group 1, PAH	143 (62.4)	-	22 (84.6)	121 (97.6)
- Group 2, PH associated with left heart disease	15 (6.6)	-	4 (15.4)	11 (8.9)
- Group 3, PH associated with lung diseases and/or hypoxia	50 (21.8)	-	11 (42.3)	39 (31.5)
- Group 4, PH associated with chronic pulmonary artery obstruction	5 (2.2)	-	1 (3.8)	4 (3.2)
- Group 5, PH with unclear and/or multifactorial mechanisms	0 (0)	-	0 (0)	0 (0)
History of smoke, n (%)	83 (36.2)	37 (46.8)	11 (42.3)	35 (28.2)
Comorbidities, n (%)				
- Interstitial lung disease	104 (45.4)	40 (50.6)	19 (73.1)	45 (36.3)
- Chronic obstructive pulmonary disease	3 (1.3)	2 (2.5)	0 (0)	1 (0.8)
- Bronchial asthma	4 (1.7)	1 (1.3)	0 (0)	3 (2.4)
- Cardiac diseases	19 (8.3)	5 (6.3)	3 (11.5)	11 (8.9)
- Hypertension	48 (21.0)	17 (21.5)	6 (23.1)	25 (20.2)
- Chronic kidney disease	4 (1.7)	0 (0)	0 (0)	4 (3.2)
- Hepatic diseases	12 (5.2)	5 (6.3)	3 (11.5)	4 (3.2)
- Rheumatoid arthritis	18 (7.9)	7 (8.9)	2 (7.7)	9 (7.3)
- Secondary Sjögren's syndrome	45 (19.7)	20 (25.3)	3 (11.5)	22 (17.7)
- Malignancy	3 (1.3)	2 (2.5)	0 (0)	1 (0.8)
mRSS, median (IQR)	6.0 (2.0–12.0)	10.0 (2.0–21.0)	7.0 (0.0–10.0)	4.0 (2.0–8.0)
- N missing	104 (45.4)	35 (44.3)	8 (30.8)	61 (49.2)
Skin ulcer (presence), n (%)	50 (25.4)	22 (29.3)	5 (20.8)	23 (23.5)
- N missing	32 (14.0)	4 (5.1)	2 (7.7)	26 (21.0)
WHO functional class, n (%)	26 (11.4)	18 (22.8)	3 (11.5)	5 (4.0)
- I	61 (26.6)	17 (21.5)	8 (30.8)	36 (29.0)
- II	46 (20.1)	8 (10.1)	5 (19.2)	33 (26.6)
- III	14 (6.1)	1 (1.3)	0 (0)	13 (10.5)
- IV	82 (35.8)	35 (44.3)	10 (38.5)	37 (29.8)
- N missing				
emPHasis-10, median (IQR)	10.5 (2.5–27.5)	10.0 (2.0–18.0)	-	20.0 (3.0–37.0)
- N missing	225 (98.2)	77 (97.5)	26 (100)	122 (98.4)
6-minute walk test	353.5 (251.3–430.0)	380.0 (270.0–470.0)	395.0 (240.0–430.0)	334.5 (245.0–395.0)
- Distance (m), median (IQR)	137 (59.8)	46 (58.2)	13 (50.0)	78 (62.9)
- N missing	90.0 (85.0–95.0)	95.0 (90.0–97.0)	90.0 (87.0–95.0)	86.0 (82.0–93.0)
- SpO_2 (%), median (IQR)	139 (60.7)	46 (58.2)	13 (50.0)	80 (64.5)
- N missing				
Blood test				
- Hemoglobin (g/dL)	12.3 (11.1–13.5)	12.3 (11.0–13.2)	12.2 (11.5–13.2)	12.4 (11.1–13.9)
- N missing	13 (5.7)	3 (3.8)	0 (0)	10 (8.1)

Table 3 (continued)

	All patients (*n* = 229)	mPAP (mmHg) at the baseline		
		≤ 20 (*n* = 79)	21–24 (*n* = 26)	≥ 25 (*n* = 124)
- Uric acid (mg/dL)	5.1 (4.1–6.4)	4.9 (3.9–5.6)	4.5 (4.1–6.6)	5.3 (4.3–7.0)
- N missing	22 (9.6)	4 (5.1)	1 (3.8)	17 (13.7)
- Haptoglobin (mg/dL)	101.0 (67.0–155.0)	108.0 (81.0–155.0)	107.0 (67.0–147.0)	52.0 (34.0–163.0)
- N missing	199 (86.9)	58 (73.4)	24 (92.3)	117 (94.4)
- BNP (pg/mL)	58.2 (25.1–220.3)	43.8 (15.2–80.8)	36.8 (16.5–49.5)	135.4 (39.5–427.2)
- N missing	87 (38.0)	32 (40.5)	9 (34.6)	46 (37.1)
- NT-proBNP (pg/mL)	200.0 (101.0–893.0)	121.0 (67.1–190.0)	198.0 (65.0–780.2)	810.0 (298.0–4385.0)
- N missing	134 (58.5)	38 (48.1)	13 (50.0)	83 (66.9)
- KL-6 (U/mL)	524.0 (326.0–985.0)	440.0 (256.0–1338.0)	669.0 (453.0–1576.0)	518.0 (340.0–910.0)
- N missing	96 (41.9)	26 (32.9)	9 (34.6)	61 (49.2)
Transthoracic echocardiography				
- LVDd (mm)	42.0 (38.0–45.3)	42.5 (40.0–47.0)	43.5 (41.0–48.6)	40.0 (34.9–44.0)
- N missing	66 (28.8)	15 (19.0)	10 (38.5)	41 (33.1)
- LVDs (mm)	25.0 (23.0–28.0)	25.0 (23.0–30.0)	27.0 (25.0–28.0)	24.0 (22.0–28.0)
- N missing	66 (28.8)	15 (19.0)	10 (38.5)	41 (33.1)
- LAD (mm)	34.0 (30.0–40.0)	33.5 (28.0–38.0)	36.0 (33.5–40.4)	34.0 (30.0–40.3)
- N missing	69 (30.1)	15 (19.0)	10 (38.5)	44 (35.5)
- LVEF (%)	66.0 (61.0–70.6)	66.5 (61.5–70.0)	65.0 (61.0–70.1)	66.0 (60.0–72.9)
- N missing	81.0 (35.4)	19 (24.1)	11 (42.3)	51 (41.1)
- RVDd (mm)	35.0 (29.0–39.0)	33.0 (25.0–37.0)	33.5 (29.0–36.0)	37.0 (31.0–41.2)
- N missing	140 (61.1)	49 (62.0)	16 (61.5)	75 (60.5)
- RAD (mm)	40.0 (34.5–45.0)	37.0 (34.0–41.0)	37.0 (33.0–46.5)	44.0 (39.0–46.0)
- N missing	153 (66.8)	48 (60.8)	16 (61.5)	89 (71.8)
- IVCd (mm)	13.0 (11.0–17.0)	12.0 (10.0–14.0)	14.0 (11.0–14.6)	15.0 (12.0–19.0)
- N missing	73 (31.9)	18 (22.8)	9 (34.6)	46 (37.1)
- TAPSE (mm)	18.0 (15.0–22.0)	22.0 (19.0–25.2)	21.0 (17.8–23.5)	15.3 (13.0–19.8)
- N missing	128 (55.9)	51 (64.6)	16 (61.5)	61 (49.2)
- TRV (m/sec)	3.4 (3.0–3.8)	2.5 (2.4–3.0)	3.3 (3.3–3.3)	3.7 (3.4–4.0)
- N missing	196 (85.6)	70 (88.6)	25 (96.2)	101 (81.5)
- TRPG (mmHg)	43.2 (32.0–61.3)	27.7 (22.0–36.0)	38.0 (37.5–41.8)	57.0 (46.0–77.0)
- N missing	99 (43.2)	37 (46.8)	17 (65.4)	45 (36.3)
Pulmonary function tests				
- VC (L)	2.2 (1.6–2.6)	2.2 (1.9–2.8)	1.9 (1.6–2.3)	2.1 (1.4–2.5)
- N missing	91 (39.7)	26 (32.9)	9 (34.6)	56 (45.2)
- VC (% predicted)	82.1 (59.9–97.7)	89.6 (73.0–100.7)	77.0 (60.7–84.5)	76.6 (55.8–97.1)
- N missing	91 (39.7)	26 (32.9)	9 (34.6)	56 (45.2)
- FVC (L)	2.1 (1.6–2.6)	2.2 (1.8–2.8)	1.8 (1.6–2.2)	2.1 (1.4–2.5)
- N missing	89 (38.9)	24 (30.4)	9 (34.6)	56 (45.2)
- FVC (% predicted)	79.6 (71.8–85.5)	80.2 (74.4–86.4)	77.4 (68.9–83.2)	78.6 (69.0–85.6)
- N missing	90 (39.3)	24 (30.4)	10 (38.5)	56 (45.2)
- FEV1/FVC (%)	82.1 (59.9–97.7)	89.6 (73.0–100.7)	77.0 (60.7–84.5)	76.6 (55.8–97.1)
- N missing	91 (39.7)	26 (32.9)	9 (34.6)	56 (45.2)
- DLCO (% predicted)	49.9 (36.2–65.4)	58.5 (47.6–80.3)	49.8 (41.9–58.7)	37.6 (26.8–52.5)
- N missing	116 (50.7)	27 (34.2)	11 (42.3)	78 (62.9)
- DLCO/VA (% predicted)	64.0 (50.1–77.2)	68.2 (56.6–83.1)	69.5 (62.6–82.2)	51.5 (40.7–70.2)
- N missing	118 (51.5)	29 (36.7)	11 (42.3)	78 (62.9)
Treatment before the baseline				
- None	189 (82.5)	60 (75.9)	21 (80.8)	108 (87.1)
- Glucocorticoid	12 (5.2)	4 (5.1)	0 (0)	8 (6.5)
- IVCY	18 (7.9)	8 (10.1)	2 (7.7)	8 (6.5)
- Tacrolimus	9 (3.9)	3 (3.8)	4 (15.4)	2 (1.6)
- Methotrexate	7 (3.1)	6 (7.6)	0 (0)	1 (0.8)
- Azathioprine	3 (1.3)	1 (1.3)	1 (3.8)	1 (0.8)
- Cyclosporine A	3 (1.3)	1 (1.3)	0 (0)	2 (1.6)

Table 3 (continued)

	All patients (*n* = 229)	mPAP (mmHg) at the baseline		
		≤ 20 (*n* = 79)	21–24 (*n* = 26)	≥ 25 (*n* = 124)
- Tocilizumab	2 (0.9)	0 (0)	0 (0)	2 (1.6)
- Mycophenolate mofetil	1 (0.4)	1 (1.3)	0 (0)	0 (0)
- Belimumab	1 (0.4)	1 (1.3)	0 (0)	0 (0)
- Infliximab	1 (0.4)	0 (0)	0 (0)	1 (0.8)
- Rituximab	1 (0.4)	0 (0)	1 (3.8)	0 (0)
- Nintedanib	2 (0.9)	1 (1.3)	0 (0)	1 (0.8)
- Alprostadil	8 (3.5)	2 (2.5)	2 (7.7)	4 (3.2)

mPAP: mean pulmonary arterial pressure; n: number; IQR: interquartile range; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; mRSS: modified Rodnan total skin thickness score; WHO: World Health Organization; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; LVDd: left ventricular end-diastolic dimension; LVDs: eft ventricular internal dimension in systole; LAD: left atrial dimension; LVEF: left ventricular ejection fraction; RVDd: right ventricular end-diastolic diameter; RAD: right atrial diameter; IVCd: inferior vena caval dimension; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitant velocity; TRPG: tricuspid regurgitant pressure gradient; VC: vital capacity; FVC: forced vital capacity; FEV1: forced vital capacity in one second; DLCO: diffusing capacity of the lung for carbon monoxide; VA: alveolar volume; IVCY: intravenous cyclophosphamide

Table 4 Result of baseline right heart catheterization

	All patients (*n* = 229)	mPAP (mmHg) at the baseline		
		≤ 20 (*n* = 79)	21–24 (*n* = 26)	≥ 25 (*n* = 124)
PAWP (mmHg), median (IQR)	8.0 (6.0–11.0)	7.0 (6.0–9.0)	7.5 (6.0–10.0)	9.0 (6.0–13.0)
- N missing	0 (0)	0 (0)	0 (0)	0 (0)
sPAP (mmHg), median (IQR)	38.0 (30.0–58.0)	28.0 (24.0–31.0)	35.5 (34.0–37.0)	56.0 (44.0–72.0)
- N missing	1 (0.4)	0 (0)	0 (0)	0 (0)
dPAP (mmHg), median (IQR)	15.0 (10.0–22.0)	10.0 (7.0–11.0)	13.0 (11.0–14.0)	21.0 (18.0–27.0)
- N missing	1 (0.4)	0 (0)	0 (0)	1 (0.8)
mPAP (mmHg), median (IQR)	25.0 (18.0–35.0)	17.0 (15.0–19.0)	22.0 (21.0–23.0)	35.0 (27.5–42.5)
- N missing	0 (0)	0 (0)	0 (0)	0 (0)
sRVP (mmHg), median (IQR)	39.0 (31.0–58.0)	29.0 (25.0–32.0)	35.0 (33.0–38.0)	57.5 (42.0–68.0)
- N missing	4 (20.5)	0 (0)	0 (0)	4 (3.2)
dRVP (mmHg), median (IQR)	1.0 (0.0–4.0)	1.0 (0.0–2.0)	0.0 (0.0–1.5)	3.0 (0.0–5.0)
- N missing	47 (20.5)	11 (13.9)	2 (7.7)	34 (27.4)
RVEDP (mmHg), median (IQR)	7.0 (5.0–10.0)	6.0 (4.0–8.0)	7.0 (5.0–8.0)	8.0 (6.0–12.0)
- N missing	6 (2.6)	0 (0)	0 (0)	6 (4.8)
RAP (mmHg), median (IQR)	4.0 (3.0–7.0)	3.1 (2.0–4.0)	4.0 (3.0–7.0)	6.0 (3.0–8.0)
- N missing	1 (0.4)	0 (0)	0 (0)	1 (0.8)
CO (L/min), median (IQR)	3.9 (3.3–4.8)	4.4 (3.5–5.1)	3.9 (3.4–5.3)	3.6 (3.0–4.5)
- N missing	1 (0.4)	1 (1.3)	0 (0)	0 (0)
CI (L/min/m^2), median (IQR)	2.7 (2.2–3.2)	3.0 (2.5–3.5)	2.8 (2.3–3.2)	2.5 (2.1–3.0)
- N missing	2 (0.9)	1 (1.3)	0 (0)	1 (0.8)
PVR (Wood units), median (IQR)	3.8 (2.3–7.3)	2.0 (1.6–2.6)	3.3 (2.7–4.1)	7.1 (4.7–10.4)
- N missing	1 (0.4)	1 (1.3)	0 (0)	0 (0)
SvO_2 (%), median (IQR)	70.4 (64.0–74.0)	73.7 (70.4–76.8)	71.6 (67.6–74.9)	66.0 (59.1–72.0)
- N missing	47 (20.5)	16 (20.2)	3 (11.5)	28 (22.6)

n: number; IQR: interquartile range; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; sPAP: systolic pulmonary arterial pressure; dPAP: diastolic pulmonary arterial pressure; sRVP: systolic right ventricular pressure; dRVP: diastolic right ventricular pressure; RVEDP: right ventricular end-diastolic pressure; RAP: right atrial pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SvO_2: mixed venous saturation

Abbreviations

ACR	American College of Rheumatology
CTD	Connective tissue disease
DLCO	Diffusing capacity of the lungs for carbon monoxide
EULAR	European League Against Rheumatism
FVC	Forced vital capacity
mPAP	Mean pulmonary arterial pressure
MMF	Mycophenolate mofetil
NT-proBNP	N-terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
USA	The United States of America
WHO	World Health Organization

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Author contributions
ST, HH, AH, YI, YS, TT, SS, MK, TH, MY, HK, YS, RH, KK, SI, TH, TA, MK contributed to data interpretation and manuscript development, critique and revision for important intellectual content by providing comment, reading, editing and approving the final version of the manuscript. KO and YMI were involved in the statistical planning of this study and carried out sample size calculations.

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Hokkaido University Hospital (approval number: 022–0109). It has been registered in the Japan Registry of Clinical Trials as jRCT1010220025 since November 7, 2022. All researchers involved in this study will comply with the Declaration of Helsinki and the Ethical Guidelines for Medical Research Involving Human Subjects. For retrospective observation (Fig. 1A), participants have the opportunity to opt out of the study. Information regarding the study is disclosed on the webpage of each participating facility. For the prospective observation (Fig. 1B C), written informed consent was obtained from all patients before prospective study procedures were performed.

Consent for publication
Study participants are informed that their anonymized data will be published in academic journals and provide the written consent form for publication.

Competing interests
This study will be conducted fairly by the principal researcher (and group) of this university and will be funded by Janssen Pharmaceutical K.K. Approval for conflicts of interest in this study has been obtained from the Conflict-of-Interest Committee of Hokkaido University Hospital, ensuring fairness. H Hanaoka has received speaking fees from Asahi-Kasei, Chugai, Astellas, and Eli Lilly. A Hashimoto has received speaking fees from Eisai, Janssen, Mochida Pharmaceutical, Nippon Shinyaku, Daiichi Sankyo Company. M Kuwana has received research grants from MBL, consultant/speaking fees from Asahi-Kasei, AstraZeneca, Boehringer-Ingelheim, Chugai, GSK, Janssen, Kissei, MBL, Mochida, and Ono Pharmaceuticals. T Higuchi has received speaking fees or consulting fees from Chugai, Pfizer, Boehringer, Asahi Kasei, Gilead, Eli Lilly, Janssen, and RIBOMIC, and belongs to an endowment department that is supported with an unrestricted grant from Ayumi, Asahi Kasei, Taisho, Mochida, Chugai, and AbbVie. YM Ito is a member of Independent Data Monitoring Committee of Janssen Pharmaceutical K.K. R. Hisada has received speaking fees from AbbVie Inc., Asahi-Kasei Co., Astellas Pharma Inc., Ayumi Pharmaceutical Co., Bristol-Myers Squibb Co., Chugai Pharmaceutical Co., Ltd.; Daiichi Sankyo Co., Ltd., Eisai Co. Ltd., Janssen Pharmaceutical K.K., Nippon Boehringer Ingelheim Co., Mitsubishi Tanabe Pharma Co., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc. T Atsumi has received research grants from Astellas, Takeda, Mitsubishi Tanabe, Chugai, Daiichi-Sankyo, Otsuka, Pfizer, Alexion, Bayer, Otsuka, Chugai, Takeda, Eisai, Bristol-Myers Squibb, Daiichi Sankyo, Mitsubishi Tanabe, and Asahi Kasei; consultant fees from Ono, Sanofi, Daiichi Sankyo, and Pfizer; and speaking fees from Mitsubishi Tanabe, Chugai, Astellas, Takeda, Pfizer, Daiichi Sankyo, Bristol-Myers Squibb, and Eli Lilly. M Kato has received research grants from AbbVie, Actelion, GlaxoSmithKline, Janssen, Nippon Shinyaku, and Novartis, and speaking fees from Astellas, Boehringer, Eisai, Eli Lilly, Janssen, Mitsubishi Tanabe, and Pfizer. The other authors have nothing to declare.

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