Characteristics of Japanese elderly patients with pulmonary arterial hypertension

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Abstract

Previous nationwide Japanese data suggested that pulmonary arterial hypertension (PAH) predominantly affects young women. However, the number of elderly patients diagnosed with PAH has been increasing in western countries. There have been no reports on elderly PAH patients in Asian countries. This study aimed to investigate the clinical characteristics of elderly PAH patients in a Japanese cohort. Idiopathic/heritable PAH (I/H-PAH) was included in the national research project on intractable diseases. The patients were required to submit a clinical research form completed by their attending physicians. We analyzed the characteristics of Japanese I/H-PAH using the newly registered forms in 2013 (Study 1, n = 148). Also, we did a retrospective, observational cohort study at Chiba University Hospital (Study 2, n = 42). We compared the characteristics of elderly PAH patients (≥65 years old) with younger patients (<65) in both studies. Study 1 revealed a predominance of males (51% male), better hemodynamics and poorer exercise capacity in the elderly group (n = 72), compared with the younger group (n = 76) in study 1. In Study 2, elderly patients showed a male predominance (63% male), a higher ratio of smokers, a lower % carbon monoxide diffusing capacity, and poorer exercise tolerance. Elderly patients in Study 2 showed less improvement in hemodynamics with therapy. There was no significant difference in disease-specific survival between elderly and younger patients. Japanese elderly patients with I/H-PAH showed poorer exercise capacity and impaired gas exchange, but better pulmonary hemodynamics than younger patients.

Keywords

pulmonary arterial hypertension, elderly PAH, IPAH

Introduction

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg as well as pulmonary vascular resistance (PVR) > 3 Wood units with normal pulmonary arterial wedge pressure (PAWP). PAH is a progressive disease leading to right heart failure and death without effective treatment. PAH includes idiopathic/heritable PAH (I/H-PAH), PAH associated with connective tissue disease (CTD-PAH), portal hypertension, congenital heart disease, HIV and drug use, pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH), and clinically diagnosed pulmonary tumor thrombotic microangiopathy.

Previously nationwide Japanese data suggested that PAH predominantly affected young women of childbearing age, similar to reports from western countries. However, some
reports from western countries have shown that the age at the time of diagnosis is higher in patients with IPAH. They suggested some differences in baseline characteristics, hemodynamics, therapeutic response, and survival rate between elderly and younger patients.  

Hoepfer et al. reported that elderly patients had a lower female to male ratio, lower baseline mPAP and PVR, worse exercise tolerance, lower survival rate, and poorer response to treatment than younger patients, according to a registry study (The European PH registry: Comparative, Prospective Registry of Newly Initiated Therapies of Pulmonary Hypertension (COMPERA)).  

However, there have been no reports on the characteristics of elderly patients with PAH from Asian countries. Therefore, the aim of the present study was to investigate the clinical characteristics, treatment, and survival of elderly PAH patients in a Japanese cohort.

**Methods**

**Ethics**

Patient identity was concealed, and data were compiled according to the requirements of the Japanese Ministry of Health, Labor and Welfare, which is dedicated to privacy, information technology, and civil rights. Based on Japanese legislation, the need for informed consent was waived. The protocol was approved by the Research Ethics Committee of Chiba University School of Medicine (approval number 2584). Since 2009, all survivors gave written informed consent for a prospective cohort study (approval number 826).

**Patients**

The first study (Study 1) used a nationwide registration system of patients with PAH. In Japan, PAH was included in the national research project of intractable diseases in 2009. The patients were required to submit an updated clinical research form filled out by their attending physicians every year to receive medical subsidies. The Respiratory Failure Research Group at the Ministry of Health and Welfare of Japan conducts an epidemiological survey using the clinical research forms. We analyzed the characteristics of Japanese PAH using the clinical research forms that were newly registered in 2013 as well as those that were updated in 2013. We excluded patients with no data on age or pulmonary hemodynamics, or mPAP <25 mmHg or PAWP >15 mmHg. The number of patients newly diagnosed with PAH and registered in 2013 (using the “registration form”) was 234 (148 with I/H-PAH, 36 with CTD-PAH, 31 with congenital heart disease, 14 with portopulmonary hypertension, and 5 with PVOD/PCH). The number of previously registered patients who updated the form in 2013 (using the “updated form”) was 1070 (730 with I/H-PAH, 107 with CTD-PAH, 176 with congenital heart disease, 46 with portopulmonary hypertension, 9 with PVOD/PCH, 1 with drug-induced PAH, and 1 with HIV-associated PAH).

We divided these patients into two groups: elderly patients (age at diagnosis ≥65 years) and younger patients (<65 years).

The documentation using the registration forms included demographics (sex, age at diagnosis, age of onset), hemodynamics (mPAP, PVR, PAWP, cardiac index (CI), mixed venous oxygen pressure), 6-min walk distance (6MWD), blood exam (brain natriuretic peptide (BNP), uric acid), transthoracic pressure gradient (TRPG), history of right heart failure, New York Heart Association Functional (NYHA) classification and treatment based on the PAH classification.

The documentation using the updated forms included demographics (sex, current age, age of onset), 6MWD, blood exam (BNP, uric acid), history of right heart failure, NYHA classification, and treatment based on the PAH classification.

The second study (Study 2) was a retrospective, observational cohort study at a single center, Chiba University Hospital. Inclusion criteria were as follows.

A total of 102 patients with suspected pulmonary hypertension (PH) and precapillary PH confirmed by right heart catheterization (RHC) were enrolled between January 1999 and December 2017.

Precapillary PH was based on the European Society of Cardiology/European Respiratory Society guideline.  

It was defined by mPAP ≥25 mmHg, PVR ≥240 dynes/s/cm⁻⁵, and PAWP ≤15 mmHg at rest, measured by RHC at the time of diagnosis.

The number of PAH patients without I/H-PAH and CTD-PAH in our center was too small to analyze prognosis; therefore, we decided to include only I/H-PAH and CTD-PAH patients. We excluded 29 patients with the following associated conditions: portopulmonary hypertension (n=12), congenital heart disease (n=4), drug-induced PH (n=1), PVOD/PCH (n=4). PH due to unclear multifactorial mechanisms (n=7), and pulmonary tumor thrombotic microangiopathy (n=1). Two of the remaining patients were excluded because of concomitant severe obstructive pulmonary impairment (forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <70% and FEV1 <50% of predicted), or severe restrictive pulmonary impairment (vital capacity <50% of predicted). The remaining 71 patients consisted of 41 with I/H-PAH, 1 with HIV-associated PH and 29 with CTD-PAH. The patient with HIV-associated PH was included in the I/H-PAH group (Fig. 1). I/H-PAH patients consisted of 8 patients with HPAH, 7 with mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene, and 1 with mutations in activin A receptor-like type 1 (ACVRL1). All patients with HPAH were ≤65 years old at the time of diagnosis. CTD-PAH patients consisted of 11 with systemic sclerosis (SSc), 8 with mixed connective tissue disease (MCTD), 9 with systemic lupus erythematosus, 3 with
rheumatoid arthritis and 12 with Sjogren’s syndrome. There was some overlap among these conditions.

We divided these patients into two groups: elderly patients (age at diagnosis ≥ 65 years) and younger patients (<65 years). Documentation included demographics (sex, age, body mass index BMI, comorbidities, which were risk factors for left heart disease, especially for HFpEF as defined in the AMBITION trial\(^7,8\), date of diagnosis, hemodynamics (mPAP, PVR, PAWP, CI), blood gas analysis (PaO\(_2\), PaCO\(_2\)), 6MWD, pulmonary function, World Health Organization functional class (WHO-FC), and smoking habit.

We also divided the patients in Study 2 into two periods based on the time of diagnosis: a period from 1999 to 2010 (early period), and a period from 2011 to 2017 (late period). This was done to distinguish the era in which patients had more treatment choices (epoprostenol, bosentan, sildenafil, tadalafil, and ambrisentan were approved for use in Japan in 1999, 2005, 2008, 2009, and 2010, respectively).

We evaluated the changes in variables (mPAP, PVR, PaO\(_2\), CI, 6MWD, BNP levels and WHO-FC) from baseline to the first follow-up RHC. If any patient did not undergo follow-up RHC, we evaluated BNP levels, 6MWD, and WHO-FC at three months after the diagnosis. By the end of December 2017, follow-up data were obtained from 67 patients by either contacting them or their primary physicians. The remaining four patients were censored at the final visit date by their primary physician. Sixty patients had follow-up visits for laboratory data. Of those, 48 patients had follow-up RHC. The mean follow-up period was 5.9 ± 5.5 years.

In this study, two pulmonologists evaluated the lungs of patients using computed tomographic scans to exclude PAH due to lung disease. After selecting five slices from each lobe, we measured the abnormal area of the lung on these slices. Then we excluded patients with 25% or more parenchymal changes or emphysema of the total area of the lung. We included two elderly I/H-PAH patients and two younger I/H-PAH patients with mild lung disease who did not meet these exclusion criteria. Nine CTD-PAH patients with lung diseases, consisting of four elderly patients and five younger patients, were also included.

**Statistical analysis**

To evaluate baseline differences between the elderly and younger groups, we used Student’s t-tests to compare continuous variables and chi-square tests to compare categorical variables. The results are displayed as the mean ± SD or median (interquartile range) for continuous variables and the number (%) for categorical variables. Survival curves were determined using the Kaplan–Meier method, and compared with the log-rank test. Univariate and multivariate Cox proportional hazards analyses were used to determine prognostic factors. A p-value < 0.05 was considered significant.

All analyses were performed using JMP Pro 13.2.0, Japanese version, SAS Institute Inc.

**Results**

**Baseline characteristics of Japanese patients with PAH in Study 1**

**Baseline characteristics of newly diagnosed PAH patients using the registration forms in 2013.** The mean age of patients at the
The mean age of diagnosis was 56.0 ± 12.7 years. The mean age of onset was 52.0 ± 14.6 years (Table 1). In the I/H-PAH group, the mean age of patients at the time of diagnosis was 56.3 ± 13.2 years. The mean age of onset was 53.4 ± 13.6 years (Table 2). In the CTD-PAH group, the mean age of patients at the time of diagnosis was 61.0 ± 9.7 years. The mean age of onset was 59.0 ± 11.3 years (Table 3).

Compared with younger patients (age at diagnosis < 65 years), elderly patients (≥65 years) had a shorter 6MWD and higher BNP, in spite of a better PVR and mPAP in total (Table 1).

Compared with younger patients, elderly patients in the I/H-PAH group had a lower female to male ratio, a higher BNP and PAWP, and shorter 6MWD, in spite of a better PVR and mPAP (Table 2). When patients were divided into three groups according to the age of diagnosis, (≥75 years, 65–74 years, and <65 years), the number of patients with combination therapy was 4 of 29 (13.8%) in the ≥75 group, 8 of 43 (18.6%) in the 65–74 group, and 21 of 76 (22.3%) in the <65 group.

In the CTD-PAH group, elderly patients had a better mPAP, PVR and mixed venous oxygen pressure (%), compared with younger patients (Table 3).

Characteristics of Japanese PAH using the updated form. Compared with younger patients (n = 715), elderly patients with PAH

| Table 1. Baseline characteristics of newly diagnosed PAH patients using registration forms in 2013 (total, n = 234). |
|---------------------------------------------------------------|
| **Total**          | ≥65 yo | <65 yo | p-value |
|--------------------|--------|--------|---------|
| Number             | 234    | 109    | 125     | 0.0537 |
| Sex (F/M)          | 140/94 | 58/51  | 82/43   |         |
| Age at diagnosis (years) | 56.0 ± 12.7 | 72.9 ± 6.2 | 41.1 ± 16.3 | <0.0001 |
| Age of onset (years) | 52.0 ± 14.6 | 71.0 ± 7.3 | 36.3 ± 18.6 | <0.0001 |
| Diagnosis          |        |        |         |         |
| Idiopathic/heritable PAH | 148    | 72     | 76      |         |
| Associated PAH: connective-tissue disease | 36    | 20     | 16      |         |
| Congenital heart disease | 31    | 12     | 19      |         |
| Portal hypertension | 14     | 3      | 11      |         |
| PVOD/PCH           | 5      | 2      | 3       |         |
| Hemodynamics       |        |        |         |         |
| mPAP (mmHg)        | 45.3 ± 15.1 | 39.2 ± 11.4 | 50.7 ± 17.7 | <0.0001 |
| PAWP (mmHg)        | 9.2 ± 3.4   | 9.8 ± 3.5   | 8.7 ± 3.3   | 0.0094  |
| PVR (dyne/s/cm²)   | 835.1 ± 511.7 | 675.7 ± 362.4 | 980.7 ± 617.3 | <0.0001 |
| CI (L/min/m²)      | 2.5 ± 0.8   | 2.5 ± 0.7   | 2.6 ± 0.9   | 0.6365  |
| PaO₂ (mmHg)        | 42.3 ± 12.4  | 40.9 ± 10.8  | 43.9 ± 13.9  | 0.3425  |
| 6MWD               | 281.6 ± 133.3 | 224.5 ± 117.3 | 325.0 ± 144.3 | <0.0001 |
| Distance (m)       | 86.7 ± 7.9   | 86.4 ± 7.6   | 87.0 ± 8.2   | 0.6563  |
| Blood exam         |        |        |         |         |
| BNP (pg/ml)        | 437.6 ± 568.3 | 544.3 ± 601.9 | 344.5 ± 537.4 | 0.0098  |
| UA (mg/dl)         | 6.6 ± 2.1  | 6.5 ± 1.9   | 6.7 ± 2.3   | 0.5959  |
| TRPG (mmHg)        | 67.4 ± 24.2  | 65.2 ± 20.3  | 69.2 ± 27.1  | 0.2409  |
| History of right heart failure (⁺/⁻) | 98/134 | 45/64 | 53/70 | 0.7811 |
| NYHA (1/2/3/4)     | 6/71/119/33 | 2/33/55/17  | 4/38/64/16  |         |
| Modern PH therapy  |        |        |         |         |
| IV PGI₂ (⁺/⁻)      | 12/222 | 1/108  | 11/114  | 0.0030  |
| PO PGI₂ (⁺/⁻)      | 56/178 | 22/87  | 34/91   | 0.2078  |
| ERA (⁺/⁻)          | 72/162 | 32/77  | 40/85   | 0.6620  |
| PDE5i (⁺/⁻)        | 95/139 | 44/65  | 51/74   | 0.9464  |
| Combination therapy (⁺/⁻) | 45/189 | 17/92  | 28/97   | 0.1854  |

Data given as mean ± SD or n.
PVOD/PCH: pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; CI: cardiac index; PaO₂: mixed venous oxygen pressure; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; UA: uric acid; TRPG: transtricuspid pressure gradient; NYHA: New York Heart Association Functional; PGI₂: prostaglandin I₂; IV: intravenous; PO: per oral; ERA: endothelin-receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor.
patients (n = 355, current age ≥ 65 years) had a shorter 6MWD, higher BNP and less treatment with combination therapy (Supplemental file: Table 1). Even in the I/H-PAH group, similar results were observed (Supplemental file: Table 2). The number of patients with combination therapy was 27 of 108 (25%) in patients < 75, 66 of 141 (46.8%) in patients 65–74, and 300 of 481 (62.4%) in patients < 65.

There was no significant difference in treatment with combination therapy between younger and elderly patients in the groups that had CTD-PAH, congenital heart disease and portopulmonary hypertension (Supplemental file: Tables 3 to 5).

### Study at Chiba University Hospital (Study 2)

#### Baseline characteristics at the time of diagnosis stratified by an age of 65 years

When all patients were divided based on the time of diagnosis (1999–2010: early period; 2011–2017: late period), there was no significant difference between the age of patients who were diagnosed in the early and the late periods (47.7 ± 16.0 vs. 51.5 ± 20.8 years, p = 0.3837). Also, in the I/H-PAH group, there was no significant difference between the age of patients who were diagnosed in the early and the late periods (48.2 ± 16.1 vs. 48.5 ± 20.7 years, p = 0.9564).

We divided these patients into two groups: elderly patients (age at diagnosis ≥ 65 years) and younger patients (< 65 years). Compared with younger patients, elderly patients had a lower female to male ratio, lower PaO2 and %DLco, and shorter 6MWD in spite of better mPAP. Elderly patients had more comorbidities that were risk factors for left heart disease (Table 4).

In the I/H-PAH group, there was a predominance of males in the elderly group, whereas there was a predominance of females in the younger group. PaO2 and %DLco were lower (59.9 ± 13.7 vs. 73.9 ± 13.3 mmHg, p = 0.0118; 44.5 ± 7.3 vs. 66.6 ± 19.8%, p = 0.0116) and 6MWD was shorter (324.6 ± 80.7 vs. 427.8 ± 104.4 m; p = 0.0442) in the elderly than younger group. However, mPAP and PVR

### Table 2. Baseline characteristics using registration forms in 2013 (I/H-PAH, n = 148).

|                          | Total | ≥65 yo | <65 yo | p-value |
|--------------------------|-------|--------|--------|---------|
| Number                   | 148   | 72     | 76     |         |
| Sex (F/M)                | 88/60 | 35/37  | 53/23  | 0.0086  |
| Age at diagnosis (years) | 56.3 ± 13.2 | 73.5 ± 6.6 | 40.0 ± 17.3 | <0.0001 |
| Age of onset (years)     | 53.4 ± 13.6 | 71.7 ± 6.6 | 36.0 ± 17.9 | <0.0001 |
| Hemodynamics             |       |        |        |         |
| mPAP (mmHg)              | 46.1 ± 14.6 | 40.5 ± 11.2 | 51.3 ± 17.1 | <0.0001 |
| PAWP (mmHg)              | 9.1 ± 3.4  | 9.9 ± 3.6 | 8.5 ± 3.3 | 0.0152  |
| PVR (dyne/cm²)           | 895.4 ± 528.7 | 766.9 ± 389.1 | 1017.7 ± 612.1 | 0.0085  |
| CI (L/min/m²)            | 2.5 ± 0.8  | 2.5 ± 0.8 | 2.5 ± 0.8 | 0.9311  |
| PaO2 (mmHg)              | 42.7 ± 12.7 | 40.3 ± 9.1 | 45.5 ± 15.8 | 0.1874  |
| 6MWD                     |       |        |        |         |
| Distance (m)             | 282.1 ± 132.1 | 209.0 ± 118.4 | 335.2 ± 141.1 | <0.0001 |
| Lowest SpO2 (%)          | 87.4 ± 7.9  | 85.6 ± 8.2 | 89 ± 7.7 | 0.0398  |
| Blood exam               |       |        |        |         |
| BNP (pg/m)               | 464.9 ± 529.4 | 620.6 ± 603.5 | 317.0 ± 399.6 | 0.0017  |
| UA (mg/dl)               | 6.7 ± 2.1  | 6.6 ± 1.9 | 6.8 ± 2.3 | 0.5288  |
| TRPG (mmHg)              | 66.8 ± 22.1 | 66.7 ± 19.5 | 66.8 ± 24.5 | 0.9847  |
| History of right heart failure (+/-) | 57/91 | 29/43 | 28/48 | 0.6677 |
| NYHA (1/2/3/4)           | 5/40/75/24 | 1/18/37/14 | 4/22/38/10 |         |
| Modern PH therapy        |       |        |        |         |
| IV PGI2 (+/-)            | 9/139  | 1/71   | 8/68   | 0.0131  |
| PO PGI2 (+/-)            | 37/111 | 12/60  | 25/51  | 0.0215  |
| ERA (+/-)                | 50/98  | 23/49  | 27/49  | 0.6450  |
| PDE5i (+/-)              | 66/82  | 32/40  | 34/42  | 0.9715  |
| Combination therapy (+/-) | 33/115 | 12/60  | 21/55  | 0.1072  |

Data given as mean ± SD or n.

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; CI: cardiac index; PaO2: mixed venous oxygen pressure; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; UA: uric acid; TRPG: transtricuspid pressure gradient; NYHA: New York Heart Association Functional; PGI2: prostaglandin I2; IV: intravenous; PO: oral; ERA: endothelin-receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor.
were better in the elderly I/H-PAH group. Furthermore, the number of current or former smokers was significantly higher in the elderly group. In addition, the serum creatinine level was significantly higher, but it was mostly within the normal range in the elderly group (Table 5).

In contrast to the I/H-PAH group, there was a predominance of females in the CTD-PAH group. There were no significant differences in PaO2, %D L CO, 6 MWD, mPAP, and PVR between the elderly and younger groups (Table 6). The number of current or former smokers was higher in the younger CTD-PAH group, and this was opposite to what was observed in the I/H-PAH patients.

Treatment for PAH. Our study showed that elderly patients were less often treated with combination PAH-targeted therapy (Table 4). Elderly I/H-PAH patients showed the same tendency for less treatment with combination therapy (Table 5). There were no differences in treatment between elderly and younger patients in the CTD-PAH group (Table 6).

Follow-up data. Regarding the follow-up data between baseline and the first follow-up, the elderly patients with PAH did not show significant positive changes in pulmonary hemodynamics or 6MWD in either the I/H-PAH or CTD-PAH group. Only 1 of 10 patients showed a decrease in mPAP/C21 by 20% in the elderly group compared with 9 of 38 in the younger group (p = 0.312). Likewise, 3 of 10 patients showed a decrease in PVR/C21 by 20% in the elderly group compared with 17 of 38 in the younger group (p = 0.3936).

However, there was a significant improvement in WHO-FC in elderly patients in the CTD-PAH group (Supplemental file: Table 6).

Moreover, when we evaluated all patients based on the four risk criteria proposed in the French study9 (low-risk criteria: WHO-FC I or II, 6MWD ≥ 440 m, right atrial pressure < 8 mmHg, and CI ≥ 2.5 L/min/m2), only 1 of 17 elderly patients were classified as low risk, whereas 11 of 53 younger patients were classified as low risk (p = 0.1213) at baseline. At the first follow-up, 1 of 10 elderly and 8 of 38 younger patients were classified as low risk (p = 0.2886). In the I/H-PAH group, the number of elderly patients who were...
Table 4. Baseline characteristics in the study at Chiba university hospital (total, n = 71).

|                          | Total  | ≥65 yo | <65 yo | p-value |
|--------------------------|--------|--------|--------|---------|
| **Number**               | 71     | 17     | 54     |         |
| **Sex (F/M)**            | 56/15  | 10/7   | 46/8   | 0.0272  |
| **Diagnosis (1999–2010)/2011–2017** | 36/35  | 7/10   | 29/25  | 0.3667  |
| **Age (years)**          | 49.6 ± 14.3 | 70.4 ± 9.6 | 43.0 ± 15.5 | <0.0001 |
| **Classification (IPAH/HPAH-HIV/CTD)** | 42/29  | 8/9    | 34/20  | 0.2476  |
| **Interval from initial presentation to diagnosis (month)** | 13 (4–54) | 7 (3–54.3) | 15 (4–54) | 0.4625 |

**Hemodynamics**

- **mPAP (mmHg)**
  - Total: 44.8 ± 13.0
  - ≥65 yo: 38.5 ± 11.8
  - <65 yo: 46.8 ± 13.3
  - p-value: 0.0245

- **PVR (dyne/s/cm²)**
  - Total: 760.8 ± 408.4
  - ≥65 yo: 627.6 ± 306.9
  - <65 yo: 802.8 ± 434.4
  - p-value: 0.1277

- **PAWP (mmHg)**
  - Total: 8.1 ± 2.9
  - ≥65 yo: 8.1 ± 2.9
  - <65 yo: 8.1 ± 2.9
  - p-value: 0.9309

- **CI (L/min/m²)**
  - Total: 2.7 ± 0.7
  - ≥65 yo: 2.6 ± 0.3
  - <65 yo: 2.8 ± 0.7
  - p-value: 0.2043

**Blood gas analysis (room air)**

- **PaO₂ (mmHg)**
  - Total: 71.5 ± 14.1
  - ≥65 yo: 63.2 ± 13.9
  - <65 yo: 74.3 ± 14.1
  - p-value: 0.0064

- **PaCO₂ (mmHg)**
  - Total: 35.9 ± 4.8
  - ≥65 yo: 36.8 ± 4.5
  - <65 yo: 35.7 ± 4.9
  - p-value: 0.4039

**6MWD**

- **Distance (m)**
  - Total: 397.0 ± 110.5
  - ≥65 yo: 329.5 ± 80.1
  - <65 yo: 413.0 ± 116.1
  - p-value: 0.0365

- **Lowest SpO₂ (%)**
  - Total: 83.7 ± 11.0
  - ≥65 yo: 77.4 ± 14.5
  - <65 yo: 85.6 ± 10.0
  - p-value: 0.0180

**Pulmonary function**

- **VC% predicted**
  - Total: 89.6 ± 16.7
  - ≥65 yo: 88.5 ± 17.1
  - <65 yo: 89.9 ± 16.6
  - p-value: 0.7704

- **FEV1% predicted**
  - Total: 83.2 ± 15.9
  - ≥65 yo: 83.7 ± 20.0
  - <65 yo: 83.0 ± 14.6
  - p-value: 0.9079

- **FEV1/FVC%**
  - Total: 79.3 ± 9.8
  - ≥65 yo: 76.0 ± 9.6
  - <65 yo: 80.3 ± 9.8
  - p-value: 0.1323

- **RV/TLC%**
  - Total: 38.3 ± 12.8
  - ≥65 yo: 37.4 ± 7.4
  - <65 yo: 38.6 ± 14.0
  - p-value: 0.7664

- **DLCO% predicted**
  - Total: 61.3 ± 17.3
  - ≥65 yo: 48.1 ± 15.1
  - <65 yo: 65.2 ± 18.0
  - p-value: 0.0019

- **DLCO/VA% predicted**
  - Total: 69.8 ± 16.6
  - ≥65 yo: 49.0 ± 19.2
  - <65 yo: 76.3 ± 15.8
  - p-value: <0.0001

- **DLCO% predicted (adjustment for Hb)**
  - Total: 71.2 ± 15.6
  - ≥65 yo: 49.2 ± 20.0
  - <65 yo: 78.0 ± 14.1
  - p-value: <0.0001

**Blood exam**

- **Creatinine (mg/dl)**
  - Total: 0.8 ± 0.4
  - ≥65 yo: 1.0 ± 0.6
  - <65 yo: 0.7 ± 0.3
  - p-value: 0.0434

- **Total bilirubin (mg/dl)**
  - Total: 0.9 ± 0.5
  - ≥65 yo: 0.9 ± 0.5
  - <65 yo: 0.9 ± 0.5
  - p-value: 0.9245

**Smoking habits**

- Never/former or current
  - Total: 43/28
  - ≥65 yo: 10/7
  - <65 yo: 33/21
  - p-value: 0.8003

- WHO FC (I/II/III/IV)
  - Total: (7/37/19/3)
  - ≥65 yo: (1/7/6/1)
  - <65 yo: (6/30/13/2)
  - p-value: 0.6608

**Comorbidity**

- **BMI ≥ 25 kg/m² (+/−)**
  - Total: 14/57
  - ≥65 yo: 4/13
  - <65 yo: 10/44
  - p-value: 0.6555

- **Systemic hypertension (+/−)**
  - Total: 7/64
  - ≥65 yo: 3/14
  - <65 yo: 4/50
  - p-value: 0.2437

- **Coronary artery disease (+/−)**
  - Total: 5/66
  - ≥65 yo: 3/14
  - <65 yo: 2/52
  - p-value: 0.0728

- **Atrial fibrillation (+/−)**
  - Total: 6/65
  - ≥65 yo: 2/15
  - <65 yo: 4/50
  - p-value: 0.5862

- **Diabetes mellitus (+/−)**
  - Total: 6/65
  - ≥65 yo: 3/14
  - <65 yo: 3/51
  - p-value: 0.1461

**Number of comorbidities**

- Two (+/−)
  - Total: 9/62
  - ≥65 yo: 5/12
  - <65 yo: 4/50
  - p-value: 0.0273

- Three (+/−)
  - Total: 2/69
  - ≥65 yo: 2/15
  - <65 yo: 0/54
  - p-value: 0.0151

- Modern PH therapy (any time) (+/−)
  - Total: 57/14
  - ≥65 yo: 13/4
  - <65 yo: 44/10
  - p-value: 0.6555

- **IV PGI2 (+/−)**
  - Total: 11/60
  - ≥65 yo: 0/17
  - <65 yo: 11/43
  - p-value: 0.0100

- **ERA (+/−)**
  - Total: 42/29
  - ≥65 yo: 10/7
  - <65 yo: 32/22
  - p-value: 0.9746

- **PDE5i (+/−)**
  - Total: 44/27
  - ≥65 yo: 8/9
  - <65 yo: 36/18
  - p-value: 0.1507

- **Combination therapy (+/−)**
  - Total: 39/32
  - ≥65 yo: 5/12
  - <65 yo: 34/20
  - p-value: 0.0147

Data given as mean ± SD, median (interquartile range) or n.

mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; CI: cardiac index; 6MWD: 6-min walk distance; VC: vital capacity; FEV1: forced expiratory volume in 1s; RV: residual volume; TLC: total lung capacity; DLco: diffusing capacity of the lung for carbon monoxide; WHO FC: World Health Organization functional class; PGI2: prostaglandin I2; ERA: endothelin-receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor.
Table 5. Baseline characteristics in the study at Chiba university hospital (IPAH/HPAH/HIV-associated PAH, n = 42).

|                                | Total | ≥65 yo | <65 yo | p-value |
|--------------------------------|-------|--------|--------|---------|
| Number                         | 42    | 8      | 34     |         |
| Sex (F/M)                      | 29/13 | 3/5    | 26/8   | 0.0384  |
| Diagnosis (1999–2010/2011–2017)| 19/23 | 3/5    | 16/18  | 0.6231  |
| Age (years)                    | 48.3 ± 14.4 | 72.5 ± 4.3 | 42.6 ± 15.8 | <0.0001 |
| Interval from initial presentation to diagnosis (month) | 18.5 (5–53.8) | 15 (3.3–68.8) | 18.5 (6.5–50) | 0.8874 |
| Hemodynamics                   |       |        |        |         |
| mPAP (mmHg)                    | 47.9 ± 14.0 | 39.8 ± 12.6 | 49.8 ± 13.5 | 0.0638  |
| PVR (dyne/s/cm⁻⁵)              | 832.7 ± 433.0 | 702.8 ± 386.0 | 863.2 ± 442.3 | 0.3514  |
| PAWP (mmHg)                    | 8.0 ± 3.2 | 7.6 ± 3.2 | 8.0 ± 3.2 | 0.7498  |
| CI (L/min/m²)                  | 2.6 ± 0.6 | 2.4 ± 0.3 | 2.7 ± 0.1 | 0.2350  |
| Blood gas analysis (RA)        |       |        |        |         |
| PaO₂ (mmHg)                    | 71.1 ± 13.4 | 59.9 ± 13.7 | 73.9 ± 13.3 | 0.0118  |
| PaCO₂ (mmHg)                   | 35.9 ± 4.3 | 35.9 ± 3.2 | 35.9 ± 3.2 | 0.9786  |
| 6MWD                           |       |        |        |         |
| Distance (m)                   | 412.6 ± 101.7 | 324.6 ± 80.7 | 427.8 ± 104.4 | 0.0442  |
| Lowest SpO₂ (%)                | 85.3 ± 8.2 | 80.3 ± 9.5 | 86.0 ± 8.1 | 0.2747  |
| Pulmonary function             |       |        |        |         |
| VC% predicted                  | 94.2 ± 16.2 | 93.0 ± 14.1 | 94.4 ± 16.6 | 0.8323  |
| FEV₁/FVC% predicted            | 83.9 ± 15.5 | 77.9 ± 17.3 | 85.8 ± 15.1 | 0.3963  |
| RV/TLC% predicted              | 77.8 ± 9.6 | 73.2 ± 8.6 | 78.8 ± 9.8 | 0.1746  |
| DLCO% predicted                | 36.0 ± 6.6 | 37.2 ± 8.5 | 35.8 ± 6.2 | 0.6365  |
| DLCO/VA% predicted             | 63.0 ± 18.6 | 44.5 ± 7.3 | 66.6 ± 19.8 | 0.0116  |
| DLCO/VA% predicted (adjustment for Hb) | 70.3 ± 15.2 | 33.5 ± 17.8 | 77.7 ± 14.7 | <0.0001 |
| DLCO/VA% predicted (adjustment for Hb) | 63.0 ± 18.9 | 45.0 ± 9.5 | 66.5 ± 20.0 | 0.0151  |
| Blood exam                     |       |        |        |         |
| Creatinine (mg/dl)             | 0.7 ± 0.3 | 0.9 ± 0.4 | 0.7 ± 0.2 | 0.0081  |
| Total bilirubin (mg/dl)        | 1.0 ± 0.5 | 0.9 ± 0.7 | 1.0 ± 0.5 | 0.5542  |
| Smoking habits                 |       |        |        |         |
| Never/former or current        | 27/15 | 2/6    | 25/9   | 0.0111  |
| WHO FC (I/II/III/IV)           | 4/23/11/1 | 0/4/2/1 | 4/19/9/0 | 0.1701  |
| Comorbidity                    |       |        |        |         |
| BMI≥25 kg/m² (+/-)             | 10/32 | 2/6    | 8/26   | 0.9303  |
| Systemic hypertension (+/-)    | 4/38  | 2/6    | 2/32   | 0.1374  |
| Coronary artery disease (+/-)  | 2/40  | 1/7    | 1/33   | 0.3102  |
| Atrial fibrillation (+/-)      | 4/38  | 1/7    | 3/31   | 0.7574  |
| Diabetes mellitus (+/-)        | 3/39  | 2/6    | 1/33   | 0.0580  |
| Number of comorbidities        |       |        |        |         |
| Two                            | 5/37  | 3/5    | 2/32   | 0.0274  |
| Three                          | 1/41  | 1/7    | 0/34   | 0.0643  |
| Modern PH therapy (any time) (+/-) | 37/5  | 6/2    | 31/3   | 0.2416  |
| IV PGI₂ (+/-)                  | 10/32 | 0/8    | 10/24  | 0.0267  |
| ERA (+/-)                      | 25/17 | 3/5    | 22/12  | 0.1618  |
| PDE5i (+/-)                    | 34/8  | 5/3    | 29/5   | 0.1658  |
| Combination therapy (+/-)      | 30/12 | 2/6    | 28/6   | 0.0020  |

Data given as mean ± SD or n.

mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; CI: cardiac index; 6MWD: 6-min walk distance; VC: vital capacity; FEV₁: forced expiratory volume in 1s; RV: residual volume; TLC: total lung capacity; DLco: diffusing capacity of the lung for carbon monoxide; WHO FC: World Health Organization functional class; PGI₂: prostaglandin I₂; ERA: endothelin-receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor.
Table 6. Baseline characteristics in the study at Chiba university hospital (CTD, n = 29).

|                          | Total | ≥65 yo | <65 yo | p-value |
|--------------------------|-------|--------|--------|---------|
| Number                   | 29    | 9      | 20     |         |
| Sex (F/M)                | 27/2  | 7/2    | 20/0   | 0.0250  |
| Diagnosis (1999–2010/2011–2017) | 17/12 | 4/5    | 13/7   | 0.3003  |
| Age (years)              | 51.3 ± 18.5 | 68.6 ± 12.6 | 43.6 ± 15.3 | 0.0002  |
| Interval from initial presentation to diagnosis (month) | 7 (2–55) | 5.5 (3–31) | 8 (1–70) | 0.2870  |
| Hemodynamics             |       |        |        |         |
| mPAP (mmHg)              | 40.3 ± 11.6 | 37.3 ± 11.6 | 41.7 ± 11.6 | 0.3576  |
| PVR (dyne/s/cm⁻⁵)        | 656.9 ± 364.0 | 560.8 ± 217.7 | 700.1 ± 411.1 | 0.3499  |
| PAWP (mmHg)              | 8.3 ± 2.5      | 8.4 ± 2.7      | 8.3 ± 2.5      | 0.8891  |
| CI (L/min/m²)            | 2.9 ± 0.7      | 2.9 ± 0.3      | 3.0 ± 0.8      | 0.3172  |
| Blood gas analysis (RA)  |       |        |        |         |
| PaO₂ (mmHg)              | 72.2 ± 15.5 | 66.2 ± 14.1 | 74.9 ± 15.6 | 0.1667  |
| PaCO₂ (mmHg)             | 36.0 ± 5.8 | 37.6 ± 5.5 | 35.3 ± 5.9 | 0.3199  |
| 6MWD                     | 367.5 ± 125.2 | 334.4 ± 88.7 | 380.2 ± 137.7 | 0.5033  |
| Lowest SpO₂ (%)          | 79.8 ± 15.5 | 75.3 ± 20.4 | 81.5 ± 14.2 | 0.5131  |
| Pulmonary function        |       |        |        |         |
| VC% predicted            | 83.3 ± 15.6 | 85.0 ± 19.1 | 82.5 ± 14.1 | 0.7004  |
| FEV1% predicted          | 82.3 ± 16.4 | 89.6 ± 23.0 | 79.8 ± 14.0 | 0.3192  |
| FEV1/FVC%                | 81.3 ± 9.9 | 78.2 ± 10.3 | 82.7 ± 9.6 | 0.2637  |
| RV/TLC%                  | 41.7 ± 18.1 | 37.6 ± 7.1 | 43.7 ± 21.4 | 0.4455  |
| DLCO% predicted          | 58.7 ± 16.3 | 50.8 ± 19.2 | 62.6 ± 13.6 | 0.0922  |
| DLCO/VA% predicted       | 69.4 ± 16.8 | 60.5 ± 9.9 | 73.8 ± 18.0 | 0.0663  |
| DLCO% predicted (adjustment for Hb) | 61.3 ± 17.4 | 51.6 ± 21.3 | 66.4 ± 12.9 | 0.5793  |
| DLCO/VA% predicted (adjustment for Hb) | 72.8 ± 17.3 | 61.0 ± 12.2 | 79.1 ± 16.6 | 0.5404  |
| Blood exam               |       |        |        |         |
| Creatinine (mg/dl)       | 0.8 ± 0.6 | 1.0 ± 0.8 | 0.7 ± 0.5 | 0.3698  |
| Total bilirubin (mg/dl)  | 0.7 ± 0.3 | 0.8 ± 0.4 | 0.6 ± 0.3 | 0.1146  |
| Smoking habits           |       |        |        |         |
| Never/former or current  | 16/13 | 8/1    | 8/12   | 0.0097  |
| WHO FC (III/III/IV)      | 3/14/8/2 | 1/3/4/0 | 2/11/4/2 | 0.3397  |
| Comorbidity              |       |        |        |         |
| BMI ≥25 kg/m² (+/-)      | 4/25 | 2/7    | 2/18   | 0.3926  |
| Systemic hypertension (+/-) | 3/26 | 1/8    | 12/18  | 0.9280  |
| Coronary artery disease (+/-) | 3/26 | 2/7    | 1/19   | 0.1779  |
| Atrial fibrillation (+/-) | 2/27 | 1/8    | 1/19   | 0.5623  |
| Diabetes mellitus (+/-)  | 3/26 | 1/8    | 2/18   | 0.9280  |
| Number of comorbidities  |       |        |        |         |
| Two                      | 4/25 | 2/7    | 2/18   | 0.3926  |
| Three                    | 1/28 | 1/8    | 0/20   | 0.1190  |
| Modern PH therapy (any time) (+/-) | 20/9 | 7/2    | 13/7   | 0.4839  |
| IV PGI₂ (+/-)            | 1/28 | 0/9    | 1/19   | 0.3836  |
| ERA (+/-)                | 17/12 | 7/2     | 10/10  | 0.1497  |
| PDE5i (+/-)              | 10/19 | 3/6     | 7/13   | 0.9303  |
| Combination therapy (+/-) | 9/20 | 3/6     | 6/14   | 0.8580  |

Data given as mean ± SD or n.

mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; CI: cardiac index; 6MWD: 6-min walk distance; VC: vital capacity; FEV1: forced expiratory volume in 1s; RV: residual volume; TLC: total lung capacity; DLco: diffusing capacity of the lung for carbon monoxide; WHO FC: World Health Organization functional class; PGI₂: prostaglandin I₂; ERA: endothelin-receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor.
classified as low risk was 0 of 8, whereas 7 of 33 younger patients were classified as low risk ($p = 0.0663$). At the first follow-up, 1 of 4 elderly and 8 of 28 younger patients were classified as low risk ($p = 0.4491$). Regarding 6MWD in all patients, the proportion of patients with $\text{6MWD} > 440 \text{ m}$ increased from 10% to 14% in the elderly group and from 50% to 74% in the younger group from baseline to follow-up. The ratios of elderly patients with $\text{6MWD} > 440 \text{ m}$ were significantly less at both baseline and follow-up.

**Survival.** Seventeen patients died during follow-up. Fifteen patients died from a PAH-related cause, and two died of other causes (acute myocardial infarction ($n = 1$), or gastric cancer ($n = 1$)). There was no significant difference in overall survival between elderly and younger patients with PAH (five-year survival: 80.2% vs. 83.8%, $p = 0.13$) (Fig. 2A). There was no significant difference in disease-specific survival between elderly and younger patients with PAH, although more elderly patients died after five years (five-year survival: 88.2% vs. 85.7%, $p = 0.20$) (Fig. 2B). There was no significant difference in disease-specific survival between elderly and younger I/H-PAH patients, although more elderly patients died after five years (five-year survival: 87.5% vs. 87.7%, $p = 0.13$) (Fig. S1). In the CTD-PAH group, there was also no significant difference in disease-specific survival between the two groups (five-year survival: 88.9% vs. 82.5%, $p = 0.62$) (Fig. S2).

**Fig. 2.** (a) Overall survival in PAH (total, $n = 71$), (b) Disease-specific survival in PAH (total, $n = 71$).
When the time of diagnosis was divided into two periods (1999–2010: early period; and 2011–2017: late period), there was a significant difference in disease-specific survival between elderly and younger I/H-PAH patients who were diagnosed in the early period (five-year survival: 66.7% vs. 81.3%, p = 0.05) (Fig. S3), but there was no significant difference between elderly and younger I/H-PAH patients who were diagnosed in the late period (five-year survival: 100% vs. 94.4%, p = 0.60) (Fig. S4). Regarding prognostic factors for PAH-specific death in all patients, univariate analysis indicated that combination therapy and late diagnosis were prognostic factors. Multivariate analysis revealed that combination therapy was an independent prognostic factor (Supplemental file: Table 7).

Discussion

This is the first and largest study that investigated the characteristics of elderly Japanese patients with PAH. In Study 1, the analyses of PAH patients who were newly registered in 2013 showed that elderly I/H-PAH patients (age at diagnosis ≥ 65 years) had a lower female to male ratio, higher BNP, and lower exercise capacity than younger patients, in spite of better pulmonary hemodynamics in the elderly group.

The analyses of the updated form in 2013 showed that elderly I/H PAH patients (current age ≥ 65 years, n = 249) had less treatment with combination therapy compared with younger patients (n = 481) at follow-up.

Because of the inability to perform a longitudinal study using registration data, we also examined the data at Chiba University Hospital. In Study 2, elderly patients (age at diagnosis ≥ 65 years) showed poorer exercise capacity but better pulmonary hemodynamics, and this was similar to the registration data in Study 1. Additionally, elderly patients in Study 2 showed lower %DLco, lower PaO₂, and a poorer response to PAH therapy.

The prevalence of PAH in elderly patients has been increasing in western countries. In the first IPAH registry (the US-NIH registry) created in 1981, the mean age of patients with IPAH at diagnosis was 36 ± 15 years. However, in the French registry created in 2002, the US-REVEAL registry in 2006, and the COMPERA study in 2007, the mean age of patients with IPAH at diagnosis was 52 ± 15 years, 50 ± 15 years, and 65 ± 15 years, respectively.

Similar to analyses in western countries, the registration forms for PAH in 2013 showed that the mean age of PAH patients at diagnosis increased over time (48.4 years old in 2005 vs. 56.0 years in 2013) in Japan. Both Study 1 and 2 revealed that elderly patients with I/H-PAH had male predominance, shorter 6MWD, but better pulmonary hemodynamics at baseline. These results were consistent with previous registry data from western countries. The COMPERA and Swedish studies showed that elderly patients were characterized by a lower female to male ratio and worse exercise tolerance, regardless of lower baseline mPAP and PVR.

Regarding the poorer exercise tolerance in elderly patients, multiple other factors such as comorbidities might have affected the results of our study. However, not only 6MWD but also %DLco showed significant differences between elderly and younger patients in Study 2. Thus, we speculate that impaired gas exchange may have considerably influenced the poorer exercise capacity.

Study 2 also showed that there was a higher frequency of current or former smokers and lower %DLco in elderly patients in the I/H-PAH group, even though we excluded patients with severe emphysema and interstitial lung disease. We believe that the severe reduction in %DLco might be related to smoking. Some previous studies suggested that smoking might cause vascular damage and pulmonary vascular remodeling leading to PH. Similarly, Olsson’s study suggested that elderly I/H-PAH patients, who had a greater smoking history and more parenchymal lung disease, had a lower %DLco and more hypoxemia. They suggested that smoking damaged the capillaries of the lung, causing lower %DLco and poor oxygenation.

In Study 2 at Chiba University Hospital, elderly PAH patients had more risk factors for left heart disease. Opitz et al. showed that atypical PAH patients who had ≥3 risk factors for left heart disease (hypertension, diabetes mellitus, atrial fibrillation, obesity) were older and had a shorter 6MWD but similar mPAP and CI compared with typical PAH patients. These characteristics resembled heart failure with preserved ejection fraction (HFpEF-PH). Our study excluded patients with HFpEF but might have included some patients with a phenotype of atypical IPAH similar to their report.

Regarding the follow-up data (Supplemental file: Table 6), not only PAH treatment but various other factors such as comorbidities or disease progression might have affected the results. Further study is needed on this problem.

Although there were no long-term survivors in the elderly group, there was no significant difference in survival between the elderly and younger groups, in contrast to poorer survival in elderly patients from western countries.

The COMPERA and Swedish studies (they used WHO-FC, 6MWD, BNP, echocardiography, and hemodynamics as risk criteria) suggested that patients with high risk were older and had a lower survival rate. In the French study, they selected WHO-FC I or II, 6MWD > 440 m, right atrial pressure < 8 mmHg, and CI ≥ 2.5 L/min/m² as low-risk criteria. In their study, the low-risk group showed a better transplant-free survival rate.

In Study 2, fewer elderly patients with PAH were classified as low risk based on the four criteria used in the French study. In the I/H-PAH group, there were 0 of 8 elderly patients who met all four low-risk criteria, whereas 7 of 33 (21%) younger patients met these criteria at baseline. Furthermore, one of
four (25%) elderly patients, and 8 of 28 (29%) younger patients met these criteria at the first follow-up.

We were unable to confirm a significant difference in disease-specific survival between elderly and younger patients. The small number of subjects might have resulted in similar survival between the elderly and younger groups in addition to better pulmonary hemodynamics in the elderly group. Although the survival curves were similar between the elderly and younger patients for the initial five years, they separated after five-years of follow-up with reduced survival in elderly patients, especially in the I/H-PAH group. Our study showed that elderly patients were less often treated with combination PAH-targeted therapy, suggesting that combination therapy may result in longer survival. In univariate analysis, combination therapy and late diagnosis were associated with prognosis. In multivariate analysis, we included parameters that were significantly different in univariate analysis (combination therapy and late diagnosis), comorbidities, age and PVR. It is well known that PVR is associated with PAH prognosis, so we included PVR in multivariate analysis as one of the parameters. Multivariate analysis showed that combination therapy was an independent predictor of PAH-specific survival. The use of combination therapy was one of the main differences between the elderly and younger patients, and it might have affected survival (Supplemental file: Table 7).

In addition, there was no elderly I/H-PAH patient who survived for ≥8 years during follow-up. According to the Japanese abridged life table compiled by the Ministry of Health, Labour and Welfare, the Japanese life expectancy at 65 years old is 19 years in men and 24 years in women. This means that the prognosis of elderly I/H-PAH patients was much worse than that of the normal population. Accordingly, treatment of elderly patients with I/H-PAH still remains a problem that needs to be solved.

In the part of Study 1 that used the registration forms, the number of patients with combination therapy was 4 of 29 (13.8%) in those diagnosed at the age of ≥75, 8 of 43 (18.6%) in those diagnosed at the age of 65–74, and 21 of 76 (22.3%) in those diagnosed at the age of <65. In the part of Study 1 that used the updated forms, the number of patients with combination therapy was 27 of 108 (25%) in those aged ≥75, 66 of 141 (46.8%) in those aged 65–74, and 300 of 481 (62.4%) in those aged <65. This suggested that a large proportion of patients had monotherapy at the time of diagnosis, and then gradually changed to combination therapy, especially in younger patients.

Study 2 also showed that elderly patients were less often treated with combination PAH targetted therapy, which is similar to previous studies. These studies speculated that avoiding combination therapy might have resulted in poorer treatment response and worse survival. Problems with combination therapy in elderly patients, who have impaired gas exchange and risk factors for left heart disease, may have reduced the use of combination therapies in the present study. Thus, strict risk assessment and successful upfront combination therapy with caution for adverse effects might solve this problem. In Study 2, there was a significant difference in disease-specific survival between elderly and younger I/H-PAH patients who were diagnosed in the early period (1999–2010), but there was no significant difference between elderly and younger I/H-PAH patients who were diagnosed in the late period (2011–2017). The number of patients who had combination therapy and were diagnosed in the early period was 0 of 3 (0%) elderly patients and 11 of 16 (69%) younger patients. The number of patients who had combination therapy and were diagnosed in the late period was 2 of 5 elderly patients (40%) and 17 of 18 (94%) younger patients. Both elderly and younger groups diagnosed in the late period showed better five-year survival rates than those diagnosed in the early period. This result might suggest that combination therapy increased from year to year, and it might be able to improve survival rates, even among elderly patients. However, further studies are needed. Regardless of a small number of patients, we added Study 2 because the registry data did not include survival. Tamura et al. reported improved survival (three-year survival 90.4%) including elderly I/H-PAH and drug-induced patients in the recent era, and this was similar to the improved survival of patients with I/H-PAH after 2011 in our center (five-year survival 94.4%). Male predominance, lower 6MWD, more comorbidities, and less intravenous prostaglandin I2 in elderly PAH were similar between Study 2 and Study 1. The sample size of Study 2 was so small that it might have affected these results. In addition, our center was an expert center, and the survival data in our center might not represent Japanese survival data in the real world. However, this is the first study that investigated the characteristics of elderly Japanese patients with PAH, and the survival data may help to understand their course. This study should lead to larger, more detailed studies in the future, so we decided to present Study 2.

There are some limitations of both studies. In Study 1, not all patients were registered, and patients with CTD-PAH might have been registered as CTD instead of PAH, because the national research project on intractable diseases also includes collagen diseases. Our study only included one year of data on the clinical research forms that were registered in 2013. Study 2 was a retrospective, single-center study, with a small sample size. There were some data missing at follow-up, especially data for RHC.

The conclusion is that Japanese elderly patients with PAH showed poorer exercise capacity and impaired gas exchange, but better pulmonary hemodynamics than younger patients, especially in the I/H-PAH group.

Conflict of interest
The author(s) declare that there is no conflict of interest.

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Supplemental Material
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