**ORIGINAL RESEARCH**

# Pulmonary Hypertension With Interstitial Pneumonia

## Initial Treatment Effectiveness and Severity in a Japan Registry

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**ABSTRACT**

**BACKGROUND** Recent guidelines discourage the use of pulmonary arterial hypertension (PAH)-targeted therapies in patients with pulmonary hypertension (PH) associated with respiratory diseases. Therefore, stratifications of the effectiveness of PAH-targeted therapies are important for this group.

**OBJECTIVES** The authors aimed to identify phenotypes that might benefit from initial PAH-targeted therapies in patients with PH associated with interstitial pneumonia and combined pulmonary fibrosis and emphysema.

**METHODS** We categorized 270 patients with precapillary PH (192 interstitial pneumonia, 78 combined pulmonary fibrosis and emphysema) into severe and mild PH using a pulmonary vascular resistance of 5 WU. We investigated the prognostic factors and compared the prognoses of initial (within 2 months after diagnosis) and noninitial treatment groups, as well as responders (improvements in World Health Organization functional class, pulmonary vascular resistance, and 6-minute walk distance) and nonresponders.

**RESULTS** Among 239 treatment-naive patients, 46.0% had severe PH, 51.8% had mild ventilatory impairment (VI), and 40.6% received initial treatment. In the severe PH with mild VI subgroup, the initial treatment group had a favorable prognosis compared with the noninitial treatment group. The response rate in this group was significantly higher than the others (48.2% vs 21.8%, ratio 2.21 [95% CI: 1.17-4.16]). In multivariate analysis, initial treatment was a better prognostic factor for severe PH but not for mild PH. Within the severe PH subgroup, responders had a favorable prognosis.

**CONCLUSIONS** This study demonstrated an increased number of responders to initial PAH-targeted therapy, with a favorable prognosis in severe PH cases with mild VI. A survival benefit was not observed in mild PH cases. (Multi-institutional Prospective Registry in Pulmonary Hypertension associated with Respiratory Disease; UMIN000011541) (JACC: Asia 2024;4:403–417) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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## ABBREVIATIONS AND ACRONYMS

**6MWD** = 6-minute walk distance

**COPD** = chronic obstructive pulmonary disease

**CPFE** = combined pulmonary fibrosis and emphysema

**CTD-IP** = interstitial pneumonia with connective tissue disease

**DLCO** = low diffusing capacity of the lung for carbon monoxide

**ILD** = interstitial lung disease

**IP** = interstitial pneumonia

**mPAP** = mean pulmonary arterial pressure

**PAH** = pulmonary arterial hypertension

**PH** = pulmonary hypertension

**PVR** = pulmonary vascular resistance

**RHC** = right heart catheterization

**R-PH** = pulmonary hypertension associated with respiratory diseases

**VI** = ventilatory impairment

**WHO-FC** = World Health Organization functional class

A subset of patients with interstitial lung diseases (ILD) exhibit disproportionately severe pulmonary hypertension (PH) compared with the extent of lung disease and ventilatory impairment (VI), whereas in general, PH comorbidity rates increase in parallel with the degree of hypoxemia, VI, and parenchymal lung involvement.[1] Pulmonary arterial hypertension (PAH)-targeted therapy has not been approved for PH associated with ILD, other than inhaled treprostinil in Western countries.[2] However, in real-world practice, other PAH-targeted therapies may be considered for patients with Group 3 PH who exhibit a PAH phenotype.[3] COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) showed that the prognosis of responders, in which 6-minute walk distance (6MWD) or NYHA functional classification was improved by PAH-targeted therapy, was significantly better than that of nonresponders in patients with PH associated with ILD.[4] In addition, COMPERA exhibited that higher pulmonary vascular resistance (PVR) was a prognostic factor in ILD, and the presence or absence of severe PH was not related to prognosis.[5] The importance of PVR compared with PH was also reported in chronic obstructive pulmonary disease (COPD).[6]

In the JRPHS (Japan Respiratory PH Study), intended for patients with PH associated with respiratory diseases (R-PH), the prognosis in the group that received initial PAH-targeted therapies was favorable in the mild VI group (PAH phenotype), and the responders to those therapies appeared to be firmly related to the mild VI group.[7] However, the efficacy of initial treatment and prognostic factors for ILD cases was not clarified.

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) PH guideline recommends an individualized approach to treatment of cases with PVR >5 WU and does not recommend the use of pulmonary vasodilators for cases with PVR ≤5 WU.[8] Because the use of PAH-targeted therapies has been limited according to the PH guideline, the patient population that might benefit from their use is undefined. To identify the phenotypes that might benefit from those treatments, we searched for the prognostic factors for the use of PAH-targeted therapies and examined the effects of initial PAH-targeted therapies on prognosis when patients were stratified by PVR of 5 WU into 2 groups: PVR >5 WU and ≤5 WU, in cases of interstitial pneumonia (IP) and combined pulmonary fibrosis and emphysema (CPFE) based on the JRPHS.

## METHODS

**STUDY DESIGN.** The JRPHS is a prospective observational registry study that was conducted at 30 specialized respiratory and PH centers between September 2013 and December 2016 (JRPHS1) and between January 2017 and December 2021 (JRPHS2). The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000011541).

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**PARTICIPANTS.** We enrolled treatment-naive and pretreated patients older than 18 years with R-PH who had mean pulmonary arterial pressure (mPAP) ≥25 mm Hg in JRPHS1 and mPAP ≥20 mm Hg in JRPHS2, confirmed by right heart catheterization (RHC). The underlying diseases of R-PH were subdivided into COPD, IP, IP with connective tissue disease (CTD-IP), CPFE, and all other respiratory diseases. The diagnosis of Group 3 PH was made by specialists in respiratory disease and PH. Cases with low diffusing capacity of the lung for carbon monoxide (DLCO) and a history of smoking, but no or minimal pulmonary parenchymal disease, were excluded. In contrast, cases with mild parenchymal lung disease were included.

This study focused on IP and CPFE, and CTD-IP was excluded. Target cases of inhaled treprostinil in recent randomized controlled trials (RCTs) have included CPFE and CTD-IP.[2] However, our previous report demonstrated that CTD-IP has a better prognosis than IP or CPFE and more participants responded to PAH-targeted therapy.[7] Therefore, IP and CPFE were targeted for analysis in this study. IP and CPFE were diagnosed by individual respiratory specialists, and IP was classified as either idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, or idiopathic unclassifiable interstitial pneumonia, according to the guidelines of the American Thoracic Society at the time of diagnosis.[9] In CPFE cases, the degree of emphysema in the upper lung field was visually evaluated at each facility (on a scale of 0%-100%, with increments of 5%).

A total of 638 patients were enrolled in the JRPHS, with the main underlying diseases being IP (216 cases), COPD (155 cases), CTD-IP (83 cases), CPFE (91 cases), and others (93 cases). Among the 307 cases of IP and CPFE, 270 patients who underwent RHC and met the criteria of mPAP ≥20 mm Hg and pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg were investigated in this study.

**MEASUREMENTS.** The measured parameters included the World Health Organization functional class (WHO-FC), pulmonary hemodynamics, and laboratory data recorded using an electrical data capture system (Supplemental Material). Follow-up examinations were generally performed every 3 to 6 months and included adverse events and newly performed examinations.
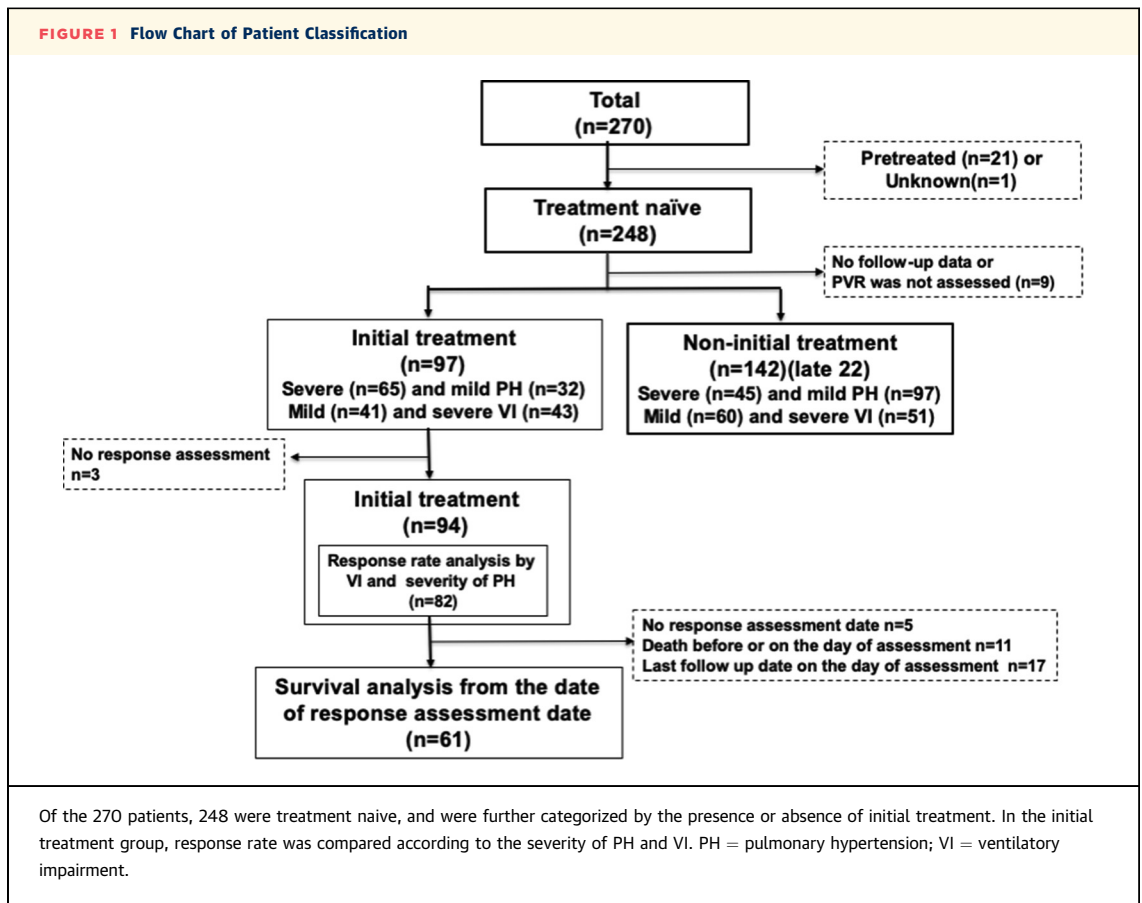
**ETHICS.** The registry study was initially approved by the Ethics Committee at Chiba University School of Medicine (Approved number 1569) and the ethics committees of Kyoto University Graduate School and Faculty of Medicine (Approved number R1919-13). The institutional review boards of all participating centers approved the study design. All participants provided written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki.

**SUBCATEGORIES.** We first categorized the patients into 2 groups: pretreated patients who had received PAH-targeted therapies before undergoing catheterization at the time of enrollment, and treatment-naive patients. We further divided the treatment-naive patients into an initial treatment group (defined as those who initiated PAH-targeted therapies within 2 months after baseline RHC) and a noninitial treatment group (comprising patients who received treatment later or not at all). In addition, to identify the phenotype that would benefit from initial treatment, we subdivided patients into subgroups according to the PVR and degree of VI: 1) patients with severe PH (PVR >5 WU) or mild PH (PVR ≤5 WU); and 2) patients with mild VI (percent predicted forced vital capacity [FVC, %pred.] ≥70% and percent predicted forced expiratory volume in 1 second [FEV1, %pred.] ≥60%) or severe VI (%FVC <70% or %FEV1 <60%) (Figure 1). The classifications of "ex-severe PH" (mPAP ≥35 mm Hg or cardiac index <2.5 L/min/m$^2$) and "ex-mild PH" (mPAP <35 mm Hg and cardiac index ≥2.5 L/min/m$^2$) were also used according to the previous report.[7]

**SURVIVAL ANALYSIS.** The survival rate was calculated using the Kaplan-Meier method. The patients were followed from the date of the baseline RHC until death (from all causes) or lung transplantation, or the administrative censor date of December 31, 2021. We compared the survival rate between subgroups using previously reported prognostic factors[7] and between the initial and the noninitial treatment groups.

**DEFINITION OF RESPONDERS.** The patient's response to PAH-targeted therapies was evaluated in the initial treatment group. Responders were defined as those with improved WHO-FC, a PVR decrease >15%, or a 6MWD increase >15% at the first follow-up (median: 174 days; n = 159).[7] The survival from the date of response assessment, and clinical characteristics, were compared between responders and nonresponders. This comparison required exclusion of patients who died before or on the assessment date, patients who did not have follow-up information beyond the first follow-up, and patients whose exact assessment date was unknown.

**FIGURE 1  Flow Chart of Patient Classification**



Of the 270 patients, 248 were treatment naive, and were further categorized by the presence or absence of initial treatment. In the initial treatment group, response rate was compared according to the severity of PH and VI. PH = pulmonary hypertension; VI = ventilatory impairment.

**STATISTICAL ANALYSIS.** Data are represented as mean ± SD or median (IQR) for continuous variables, when appropriate, and number and percentage for categorical variables. The background characteristics of patients were assessed in the whole cohort as well as in subgroups using Pearson's chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Kaplan-Meier curves were created, and the log-rank test was used to compare survival rates between subgroups. Univariate and multivariate Cox proportional hazard models were constructed to identify prognostic factors for survival (Supplemental Methods).

All tests were 2-sided, and a $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute).

## RESULTS

**BASELINE CHARACTERISTICS.** Among the 270 patients, the mPAP was 31.5 ± 8.6 mm Hg, with 17.0% <25 mm Hg. The PVR was 5.8 ± 3.7 WU, with 47.8% classified as severe PH with PVR >5 WU. In addition, 52.3% of patients were classified as having mild VI. A detailed IP and CPFE classification is shown in Supplemental Table 1. Twenty-one patients received PAH treatment before baseline RHC, 248 were treatment naive, and 1 was unknown. Compared with IP, CPFE was more common in men than in women, and was associated with worse hemodynamics, lower DLCO, and lower 6MWD. However, CPFE was also associated with better ventilatory function (Table 1). The median extent of emphysema in the upper lung field was 50%, ranging from 10% to 80%.

**OVERALL SURVIVAL.** A total of 140 deaths, and 1 patient who received a lung transplant, were observed during follow-up. The 1-, 2-, 3-, and 5-year survival rates from the date of baseline RHC for all cases were 70.9% (95% CI: 64.4%-76.4%), 48.3% (95% CI: 40.8%-55.5%), 29.2% (95% CI: 22.0%-36.8%),

and 12.6% (95% CI: 6.3%-21.1%), respectively, with IP being 72.1% (95% CI: 64.3%-78.4%), 46.0% (95% CI: 37.1%-54.4%), 24.2% (95% CI: 16.2%-33.1%), and 13.6% (95% CI: 6.7%-22.9%) and CPFE being 68.2% (95% CI: 55.0%-78.2%), 54.0% (95% CI: 40.0%-66.1%), 40.7% (95% CI: 26.6%-54.3%), and 12.0% (95% CI: 2.7%-28.6%), respectively. No differences were seen between the survival curves of the 2 diseases (Figure 2). The median (IQR: 25%-75%) follow-up period was 390 (IQR: 191-750) days. The causes of death were aggravation of PH or right heart failure (n = 42), respiratory failure or progression of underlying disease or acute exacerbation (n = 57), pneumonia or infectious disease (n = 13), lung cancer or malignancy (n = 3), other causes (n = 11), and unknown causes (n = 14).

**BASELINE CHARACTERISTICS OF TREATMENT-NAIVE PATIENTS WITH OR WITHOUT INITIAL TREATMENT.** Of 248 treatment-naive patients, 239 with recorded PVRs and outcome were reviewed. Ninety-seven (40.6%) received initial treatment (ie, treatment within 2 months after baseline RHC) and 142 did not (22 and 120 were late and no treatment cases, respectively). Of the 239 patients, 46.0% had a severe PH with a PVR >5 WU, and 51.8% had mild VI. The initial treatment group had a higher proportion of CPFE cases compared with the noninitial treatment group. In addition, those patients were further classified into WHO-FC III or IV with impaired hemodynamics, PaO2, DLCO, and 6MWD (Table 2). Phosphodiesterase-5 inhibitors (PDE-5Is) were used in 86.6% of the initial treatment group, endothelin receptor antagonists (ERAs) in 38.1%, and prostanoid or selexipag in 14.4%. Monotherapy was used in 67.0%, dual therapy in 26.8%, and triple therapy in 6.2%. The same trend for choosing drugs was seen in the noninitial treatment group, although no patients received triple therapies.

**COMPARISON OF SURVIVAL CURVES FOR TREATMENT-NAIVE PATIENTS.** Men had a worse prognosis than women (2-year survival rate: 43.7% [95% CI: 34.8%-52.8%] vs 61.2% [95% CI: 44.6%-74.2%]) (Figure 3A), and the prognosis differed according to the severity of WHO-FC (Figure 3B). Patients with mild VI had a significantly better prognosis than those with severe VI (61.4% [95% CI: 49.7%-71.1%] vs 34.2% [95% CI: 22.7%-46.1%]) (Figure 3C). Patients with PVR >5 WU had a worse prognosis than those with PVR ≤5 WU (42.2% [95% CI: 31.1%-52.8%] vs 53.9% [95% CI: 42.8%-63.8%]) (Figure 3D), although no difference in prognosis was observed when limited to the initial treatment group
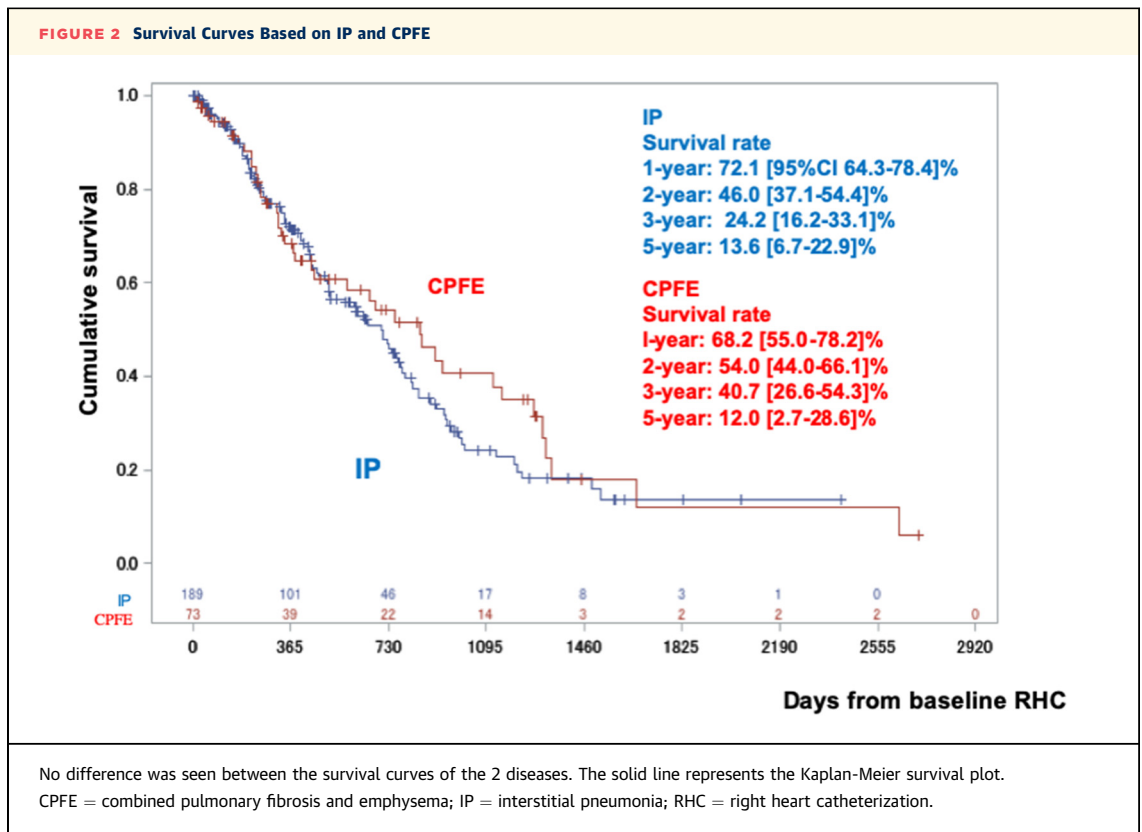
| TABLE 1 Baseline Characteristics of Patients With PH Associated With IP and CPFE | | | |
|---|---|---|---|
| | Total (N = 270) | IP (n = 192) | CPFE (n = 78) |
| Age (y) | 70.7 ± 9.5 | 70.0 ± 10.1 | 72.3 ± 7.8 |
| Female | 66 (24.4) | 63 (32.8)[a] | 3 (3.8)[a] |
| WHO-FC I/II/III/IV | 11/74/150/35 | 10/58/98/26 | 1/16/52/9 |
| Right atrial pressure (mm Hg) | 4.9 ± 4.0 | 5.0 ± 3.9 | 4.7 ± 4.1 |
| mPAP (mm Hg) | 31.5 ± 8.6 | 30.8 ± 8.9[a] | 33.3 ± 7.5[a] |
| PAWP (mm Hg) | 8.9 ± 3.5 | 9.0 ± 3.4 | 8.6 ± 3.8 |
| Cardiac index (L/min/m²) | 2.7 ± 0.8 | 2.8 ± 0.8[a] | 2.5 ± 0.8[a] |
| PVR (WU) | 5.8 ± 3.7 | 5.5 ± 3.9[a] | 6.5 ± 2.9[a] |
| Severe PH (PVR >5 WU) | 128 (47.8) | 65 (34.2)[a] | 47 (60.3)[a] |
| mPAP <25 mm Hg | 46 (17.0) | 40 (20.8)[b] | 6 (7.7)[b] |
| mPAP ≥35 mm Hg | 71 (26.3) | 45 (23.4) | 26 (33.3) |
| Ex-severe PH | 146 (54.3) | 91 (47.6)[a] | 55 (70.5)[a] |
| PaO₂ (Torr) room air | 62.7 ± 13.5 | 64.6 ± 13.9[a] | 57.1 ± 10.4[a] |
| PaCO₂ (Torr) room air | 40.6 ± 7.3 | 41.5 ± 7.6[b] | 37.8 ± 5.6[b] |
| FVC, %pred. | 71.5 ± 22.0 | 65.8 ± 19.9[a] | 84.2 ± 21.4[a] |
| FEV1, %pred. | 76.3 ± 22.2 | 72.5 ± 21.7[a] | 85.0 ± 21.1[a] |
| Mild VI | 116 (52.3) | 61 (39.6)[a] | 55 (80.9)[a] |
| DLCO, %pred | 35.8 ± 14.6 | 39.1 ± 15.1[a] | 29.0 ± 10.6[a] |
| DLCO, %pred <35% | 90 (51.7) | 48 (41.0)[a] | 42 (73.7)[a] |
| BNP (pg/mL) | 63 (22-218) | 59 (23-175) | 71 (20-391) |
| 6MWD (m) | 297 (162-399) | 315 (170- 429)[a] | 203 (146-307)[a] |
| Emphysema >50% | 23 (51.1) | NA | 23 (51.1) |
| KL-6 | 1,307 ± 1,104 | 1,450 ± 1,184[a] | 1,003 ± 842[a] |
| Pretreated/treatment naive | 21/248 | 17/175 | 4/73 |
| Nintedanib, % | 33 (12.2) | 23 (12.0) | 10 (12.8) |
| Pirfenidone, % | 15 (5.6) | 9 (4.7) | 6 (7.7) |

Values are mean ± SD, n (%), or median (IQR). [a]P < 0.01. [b]P < 0.05.

% pred = % predicted; 6MWD = 6-minute walk distance; BNP = brain natriuretic peptide; CPFE = combined pulmonary fibrosis and emphysema; DLCO = diffusing capacity of the lung for carbon monoxide; Ex-severe PH = mPAP ≥25 or cardiac index <2.5 L/min/m²; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IP = interstitial pneumonia; KL-6 = Krebs von den Lungen-6; mPAP = mean pulmonary arterial pressure; NA = not assessed; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; VI = ventilatory impairment; WHO-FC = World Health Organization functional class.

(50.7% [95% CI: 35.8%-63.9%] vs 51.9% [95% CI: 31.5%-69.0%]) (Figure 4A). In contrast, in the noninitial treatment group, a significant difference in prognosis was observed (30.9% [95% CI: 16.1%-47.0%] vs 54.5% [95% CI: 41.1%-66.1%]) (Figure 4B). Survival between the ex-severe and mild PH groups was similar (49.4% [95% CI: 38.8%-59.2%] vs 46.6% [95% CI: 34.9%-57.6%]) The comparison of survival curves, based on the prognostic factors when the patients were divided into CPFE and IP groups, is shown in Supplemental Figure 1.

**COMPARISON OF SURVIVAL AND BASELINE CHARACTERISTICS BASED ON INITIAL TREATMENT, STRATIFIED WITH A PVR OF 5 WU.** The prognosis of the initial and noninitial treatment groups in cases with PVR >5 WU and PVR ≤5 WU did not differ (Figures 5A and 5B). In cases of PVR >5 WU with mild

**FIGURE 2** Survival Curves Based on IP and CPFE

IP
Survival rate
1-year: 72.1 [95%CI 64.3-78.4]%
2-year: 46.0 [37.1-54.4]%
3-year: 24.2 [16.2-33.1]%
5-year: 13.6 [6.7-22.9]%

CPFE
Survival rate
1-year: 68.2 [55.0-78.2]%
2-year: 54.0 [44.0-66.1]%
3-year: 40.7 [26.6-54.3]%
5-year: 12.0 [2.7-28.6]%

No difference was seen between the survival curves of the 2 diseases. The solid line represents the Kaplan-Meier survival plot.
CPFE = combined pulmonary fibrosis and emphysema; IP = interstitial pneumonia; RHC = right heart catheterization.

VI, the initial treatment group showed significantly better survival than the noninitial treatment group (2-year survival rate: 76.4% [95% CI: 54.7%-88.6%] vs 32.3% [95% CI: 12.1%-54.6%]) (**Figure 6A**). In contrast, no difference in prognosis was observed between the initial and noninitial treatment groups in cases of PVR ≤5 WU with mild VI (72.9% [95% CI: 36.8%-90.5%] vs 66.1% [95% CI: 45.8%-80.3%]) (**Figure 6B**). The comparison of survival curves between the initial and noninitial treatment groups, when the patients were divided into CPFE and IP groups, are shown in Supplemental Figure 2. In patients with PVR >5 WU, the initial treatment group was younger, had more CPFE cases, and had more impaired WHO-FC, pulmonary hemodynamics, DLCO, and 6MWD, but lower Krebs von den Lungen-6 (KL-6) values than the noninitial treatment group. In contrast, in patients with PVR ≤5 WU, the initial treatment group had more CPFE cases and more impaired pulmonary hemodynamics, lower PaO2, and lower 6MWD than the noninitial treatment group (**Table 3**).

**MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS FOR TREATMENT-NAIVE PATIENTS STRATIFIED WITH A PVR OF 5 WU.** The log-log survival functions for the

predictor variables in the Cox models did not suggest violations of the assumptions of proportional hazards. In cases with PVR >5 WU, a multivariate analysis corrected for age, gender, WHO-FC, and disease (IP vs CPFE) showed that female sex and initial treatment were favorable prognostic factors (**Table 4**). In contrast, in cases with PVR ≤5 WU, WHO-FC I-II and mild VI were favorable prognostic factors, but initial treatment was not a prognostic factor (**Table 5**). The results of the multiple imputation analyses remained mostly unchanged from the complete case analyses (Supplemental Tables 2 and 3).

**PREVALENCE BASED ON THE SEVERITY OF PH AND VI AND DIFFERENCES IN RESPONSE RATES.** The prevalence of severe PH with severe VI, mild PH with severe VI, severe PH with mild VI, and mild PH with mild VI was 20.0%, 28.2%, 26.7%, and 25.1%, respectively. In the initial treatment group of 94 cases (excluding 3 cases with unknown outcomes), response rates were evaluated based on the severity of PH and VI (n = 82). The response rate in the severe PH with mild VI group was 48.1% (13 of 27), whereas it was only 16.7% (4 of 24) in the severe PH with severe VI group. In the mild PH with mild VI group, the

response rate was 23.1% (3 of 13), whereas it was 27.8% (5 of 18) in the mild PH with severe VI group. The response rate in the severe PH with mild VI group was significantly higher than that in the other groups (48.1% vs 21.8%, ratio 2.21 [95% CI: 1.17-4.16]) (Central Illustration). The response rate was consistently high in the group with severe PH and mild VI, regardless of the disease (IP: 55.6% vs 22.2%, ratio 2.50 [95% CI: 1.07-5.82]; CPFE: 44.4% vs 21.1%, ratio 2.11 [95% CI: 0.77-5.81]).

## COMPARISON OF BACKGROUND FACTORS AND PROGNOSIS FROM THE DATE OF ASSESSMENT FOR RESPONSE BETWEEN RESPONDERS AND NONRESPONDERS IN THE INITIAL TREATMENT GROUP STRATIFIED BY A PVR OF 5WU.

Of the 94 cases, 11 patients who died before or on the day of assessment, 17 patients whose assessment date coincided with the last follow-up date, and 5 patients with unknown assessment dates were excluded. In the remaining 61 cases, when comparing the background factors between responders and nonresponders, in cases with PVR >5 WU, responders were 18 of 43 (41.9%) and had a higher proportion of mild VI cases than nonresponders. In contrast, in cases with PVR ≤5 WU, responders were 6 of 18 (33.3%) and nonresponders had a higher proportion of men (Table 6). Regarding prognosis, in cases with PVR >5 WU, responders had a better prognosis from the response assessment date than did nonresponders (1-year survival rate: 81.5% [95% CI: 52.2%-93.7%] vs 11.3% [95% CI: 2.1%-29.5%]) (Figure 7A). The prognosis after the response assessment was better for responders, even when divided into IP and CPFE (Supplemental Figure 3); however, in cases with PVR ≤5 WU, the number of cases was too small to be evaluated (Figure 7B).

## MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS IN THE INITIAL TREATMENT GROUP STRATIFIED WITH A PVR OF 5 WU.

In the initial treatment group, a multivariate analysis was conducted with age, sex, WHO-FC, and disease (IP vs CPFE) as covariates. In cases with PVR >5 WU, only mild VI was a favorable prognostic factor. In contrast, in cases with PVR ≤5 WU, IP and mild VI were favorable prognostic factors, whereas WHO-FC III-IV was an unfavorable prognostic factor (Supplemental Table 4).
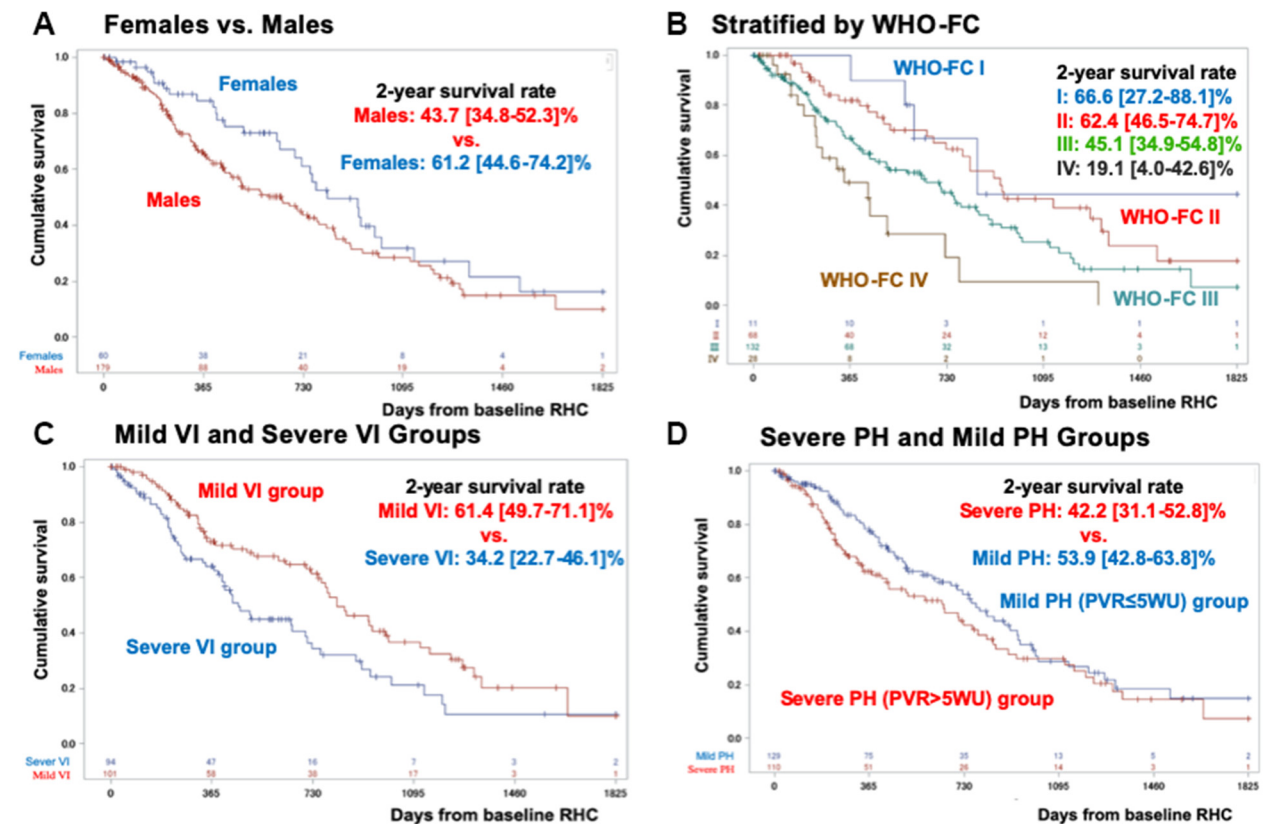
## DISCUSSION

This is the first multi-institutional registry study to analyze the background factors, prognostic factors, and the effects of initial PAH-targeted therapies on prognosis when patients were stratified by PVR of 5 WU into severe PH (PVR >5 WU) and mild PH (PVR ≤5 WU) associated with IP and CPFE. Female sex, better WHO-FC, PVR ≤5 WU, and mild VI were associated with a favorable prognosis in treatment-naive patients, whereas initial treatment did not show the same favorable effect. However initial treatment showed a favorable prognosis in severe PH with mild VI compared with noninitial treatment. The multivariate analysis revealed that for severe PH, initial treatment showed a favorable prognosis, whereas for mild PH, WHO-FC I-II and mild VI were good prognostic factors, and initial treatment was not a prognostic factor. The response rate to initial PAH-targeted therapy in the severe PH with mild VI group was significantly higher than that in the other groups (48.1% vs 21.8%, $P = 0.0149$). Among cases with PVR >5 WU, responders had a better prognosis from the response assessment date than did nonresponders.

| TABLE 2 | Comparison of Baseline Characteristics of Treatment-Naive Patients Between Initial and Noninitial Treatment Groups | |
|---|---|---|
| | Initial Treatment (n = 97) | Noninitial Treatment (n = 142) (Late 22) |
| Age (y) | 69.8 ± 9.7 | 71.3 ± 9.7 |
| Female | 26 (26.8) | 34 (23.9) |
| IP/CPFE | 53(54.6)/44(45.4)[a] | 118 (83.1)/24(16.9)[a] |
| WHO-FC III/IV | 78(80.4)[a] | 82(57.7)[a] |
| mPAP (mm Hg) | 36.3 ± 9.9[a] | 27.9 ± 5.8[a] |
| PAWP (mm Hg) | 8.8 ± 3.7 | 9.0 ± 3.5 |
| Cardiac index (L/min/m$^2$) | 2.6 ± 0.8[a] | 2.8 ± 0.7[a] |
| PVR (WU) | 7.8 ± 4.8[a] | 4.4 ± 2.0[a] |
| Severe PH (PVR >5 WU) | 65(67.0)[a] | 45(31.7)[a] |
| mPAP <25 mm Hg | 1(1.0)[a] | 41(28.9)[a] |
| mPAP ≥35 mm Hg | 43(44.3)[a] | 15(10.6)[a] |
| Ex-severe PH | 70(72.2)[a] | 58(40.8)[a] |
| PaO$_2$ (Torr) room air | 56.9 ± 11.0[a] | 66.5 ± 13.6[a] |
| PaCO$_2$ (Torr) room air | 42.7 ± 8.7[b] | 40.1 ± 7.2[b] |
| FVC, %pred. | 69.6 ± 21.4 | 72.4 ± 22.0 |
| FEV1, %pred. | 71.9 ± 20.1[b] | 78.9 ± 23.4[b] |
| Mild VI | 41(48.8) | 60(54.1) |
| DLCO, %pred. | 31.9 ± 13.0[a] | 39.7 ± 15.0[a] |
| DLCO, %pred. <35% | 39(65.0)[a] | 38(40.4)[a] |
| BNP (pg/mL) | 97 (23-457)[a] | 44 (21-107)[a] |
| 6MWD (m) | 188 (122-305)[a] | 380 (236-450)[a] |
| Oxygen therapy at baseline | 85(87.6)[a] | 75(52.8)[a] |
| PDE-5I | 84 (86.6) | 16(72.7) |
| ERA | 37 (38.1) | 6(27.3) |
| Prostanoid or selexipag | 14 (14.4) | 3(13.6) |
| Mono/dual/triple therapy | (67.0)/(26.8)/(6.2) | (86.3)/(13.7)/(0) |

Values are mean ± SD, n (%), or median (IQR). [a]$P < 0.01$. [b]$P < 0.05$.

ERA = endothelin receptor antagonists; PDE-5I = phosphodiesterase-5 inhibitor; other abbreviation as in Table 1.

**FIGURE 3**  Comparison of Survival Curves in Treatment-Naive Patients



(A) Women vs men: Men had a worse prognosis compared with women. (B) Stratified by WHO-FC: The prognosis differed according to the severity of WHO-FC. (C) Mild and severe VI groups: Patients with mild VI had a significantly better prognosis than those with severe VI. (D) Severe and mild PH groups: Patients with PVR >5 WU had a worse prognosis than those with PVR ≤5 WU. PVR = pulmonary vascular resistance; WHO-FC = World Health Organization Functional Class; other abbreviations as in **Figure 1**.

It is necessary to discuss several aspects of these results. First, according to the ESC/ERS guidelines, severe PH is defined as a PVR >5 WU, and individualized treatment with PAH medication is recommended for these cases but not for cases with PVR ≤5 WU.[8] However, there has been no evidence regarding the prognosis of initial and noninitial treatment groups stratified by a PVR of 5 WU. In the present study, no significant difference in survival was observed between the initial and noninitial treatment groups, regardless of the severity of the PH. Despite more impaired pulmonary hemodynamics in the initial treatment group, similar survival to the noninitial treatment group may suggest the effectiveness of initial treatment. In addition, multivariate analysis showed that for cases with PVR >5 WU, initial treatment showed a favorable prognosis, whereas for cases with PVR ≤5 WU, it did not.

Responders in the severe PH group might have an improved prognosis, but treatment for mild PH might not have the same result. These results support the statement that PAH therapies would not be effective in mild PH.[8]

Second, initial treatment showed a favorable prognosis only in severe PH with mild VI compared with the noninitial treatment group. The response rate in the severe PH with mild VI group was significantly higher than that in the other groups, contributing to favorable outcome in this specific group. Individualized treatment for severe PH should prioritize addressing ventilatory impairment.

Third, patients with PVR ≤5 WU had a better prognosis than those with PVR >5 WU in the overall and noninitial treatment groups, but no difference in prognosis was observed in the initial treatment group. This result differs from that of the study by

**FIGURE 4** Survival Comparisons Between the Severe and Mild PH Groups
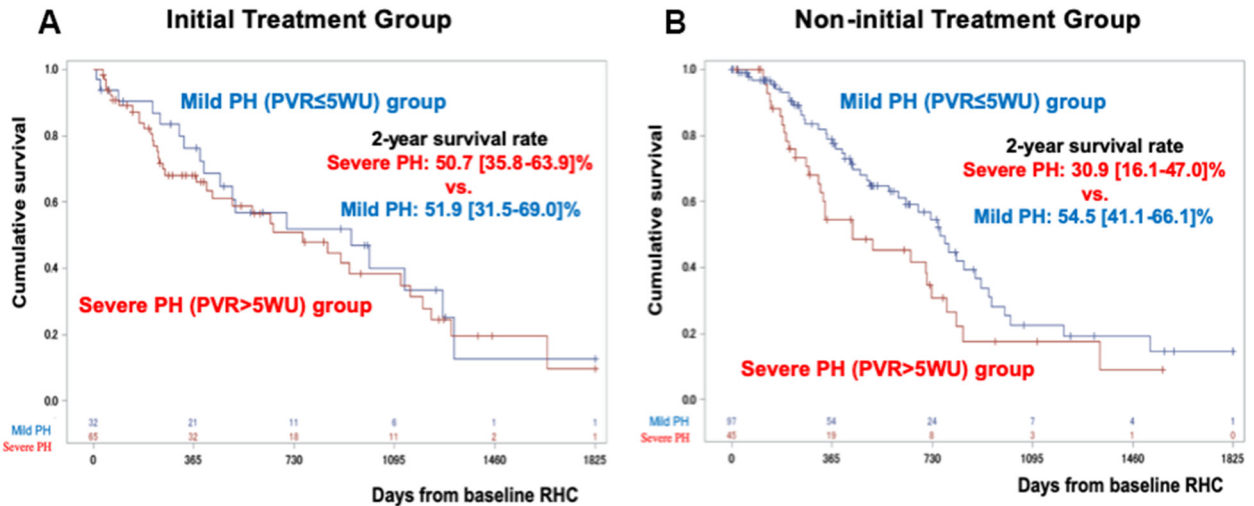


(A) Initial treatment group: There was no difference in prognosis between severe and mild PH when limited to the initial treatment group. (B) Noninitial treatment group: There was a significant difference in prognosis between severe and mild PH in the noninitial treatment group. Abbreviation as in **Figure 1**.
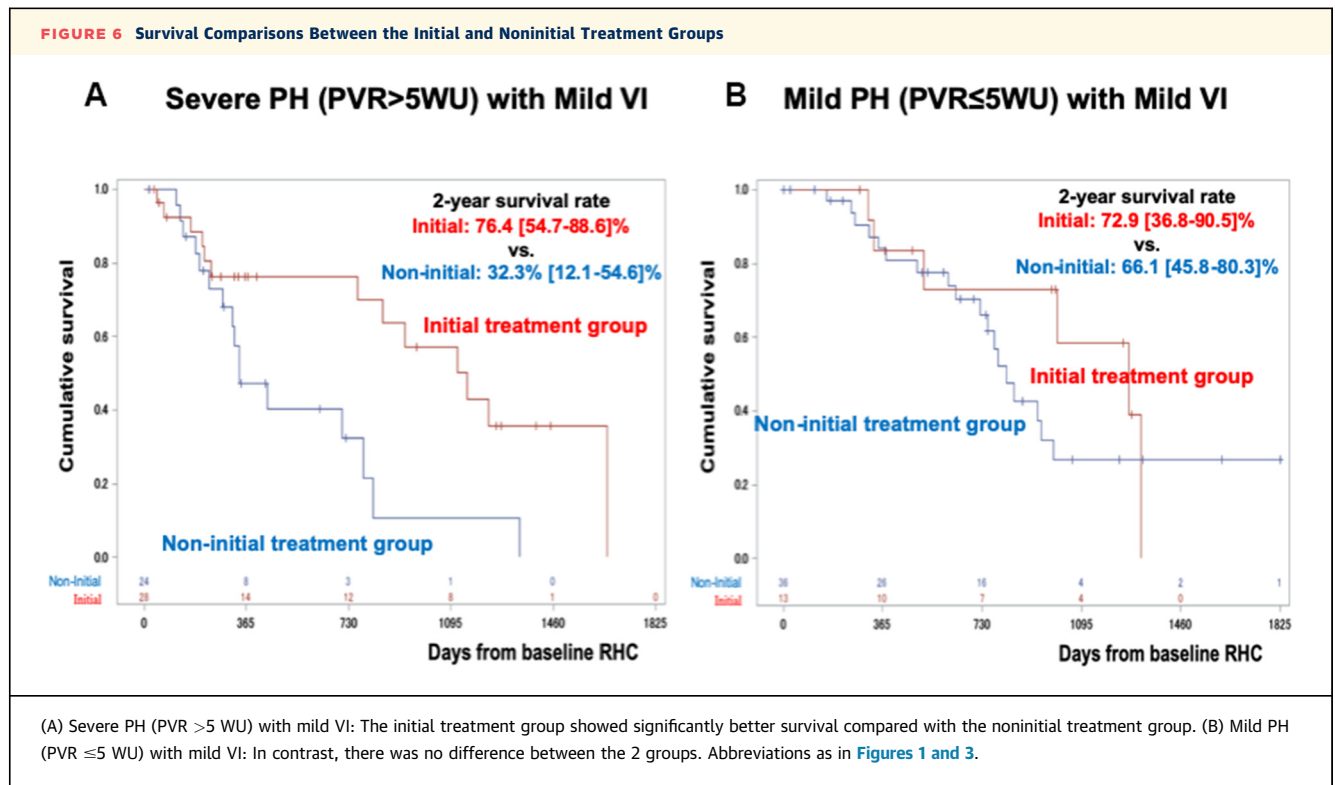
Olsson et al,[5] which identified a PVR >5 WU as a prognostic factor in the treatment group. In our study, the severe PH group showed a better prognosis than the severe PH group in their study, whereas the mild PH group demonstrated a similar or slightly worse prognosis compared with their study. There are several possible reasons for the differences between the 2 studies. In our study, we had a higher proportion of responders in patients with PVR >5 WU, indicating a higher prevalence of cases with mild VI

**FIGURE 5** Survival Comparisons Between the Initial and Noninitial Treatment Groups
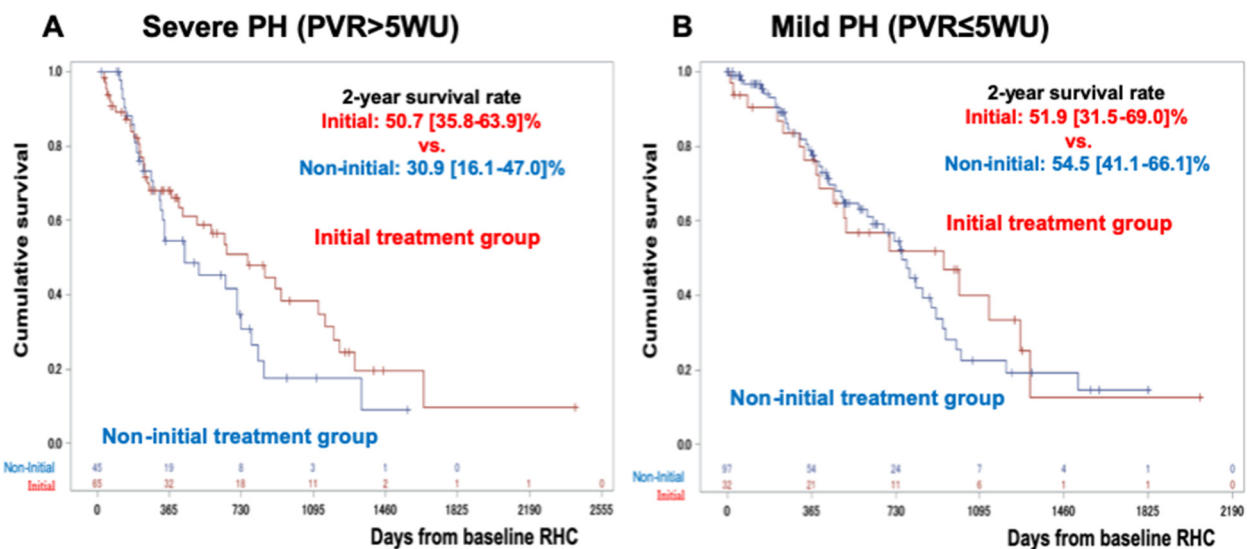


(A) Severe PH (PVR >5 WU): There was no difference in prognosis between the initial and noninitial treatment groups in cases with PVR >5 WU. (B) Mild PH (PVR ≤5 WU): Similarly, there was no difference in prognosis between the initial and noninitial treatment groups in cases with PVR ≤5 WU. Abbreviations as in **Figures 1 and 3**.

**FIGURE 6  Survival Comparisons Between the Initial and Noninitial Treatment Groups**

(A) Severe PH (PVR >5 WU) with mild VI: The initial treatment group showed significantly better survival compared with the noninitial treatment group. (B) Mild PH (PVR ≤5 WU) with mild VI: In contrast, there was no difference between the 2 groups. Abbreviations as in **Figures 1 and 3**.

and severe PH, resembling PAH. The underlying diseases of IP differed between the studies. In addition, in cases with PVR ≤5 WU, there was a higher prevalence of respiratory failure and acute exacerbation of IP, and even among the responders, the prognosis was poor. These factors contribute to the observed differences between the studies.

Fourth, the previous JRPHS, which used the same definition of "responders" as the current study, found that the prognosis from the date of diagnosis was more favorable for responders than for nonresponders.[7] Because the prognosis was studied from the date of diagnosis, cases of death before the response assessment date were included among the nonresponders in the previous study.[7] To rigorously evaluate the impact on the prognosis of the responders, the prognosis from the date of response assessment was compared between responders and nonresponders in this study. For cases with PVR >5 WU, the prognosis from the response was good, whereas for cases with PVR ≤5 WU, it was not clear. Vizza et al[10] reported a good prognosis for severe PH with COPD for responders defined by an improvement of 6MWD >30 m or improvement in NYHA functional class; however, this did not differ from that of nonresponders with mild PH from the date of assessment. The present study was similar to theirs, even though

the underlying diseases were different. There is a possibility that responders contribute to an improvement in prognosis in severe PH, whereas in mild PH, even responders may have a poor prognosis, which supports avoidance of excessive use of PAH-targeted therapies in mild PH.

Fifth, when considering prognostic factors limited to the initial treatment group, mild VI was a favorable prognostic factor in patients with PVR >5 WU and ≤5 WU. In cases with PVR ≤5 WU with mild VI, it can be difficult to differentiate between PAH coexisting with lung disease, in which PAH therapies are recommended, and R-PH, in which PAH therapies are not recommended. For patients with mild lung parenchymal disease, if physicians believe that mPAP is elevated proportional to the degree of lung disease, they should be included in Group 3 PH. However, there are no papers that provide a clear definition of minimal and mild parenchymal lung disease after considering PH severity. We are currently conducting a study in JRPHS to quantify normal lung volume to clarify the definition of Group 3 PH and PAH with lung disease (UMIN000052015).

Sixth, in the initial treatment group in our study, ERA use was 38.1% and dual/triple therapy use was 33.0%. However, in the initial treatment group with mild PH and severe VI, ERA use was only 11.1%, and

**TABLE 3** Characteristics of Treatment-Naive Patients Between Initial and Noninitial Treatment Groups Stratified by Severity of PH

| | PVR >5 WU | | PVR ≤5 WU | |
|---|---|---|---|---|
| | Initial Treatment (n = 65) | Noninitial Treatment (n = 45) (Late 7) | Initial Treatment (n = 32) | Noninitial Treatment (n = 97) (Late 15) |
| Age (y) | 70.1 ± 9.1[a] | 75.8 ± 6.3[a] | 69.1 ± 11.0 | 69.2 ± 10.2 |
| Female | 19(29.2) | 9 (20.0) | 7 (21.9) | 25 (25.8) |
| IP/CPFE | (53.8/41.2)[b] | (73.3/26.7)[b] | (56.3/43.7)[b] | (87.6/12.3)[b] |
| WHO-FC I/II/III/IV | 1/6/42/16[a] | 0/15/26/4[a] | 0/12/19/1 | 10/35/45/7 |
| mPAP (mm Hg) | 40.2 ± 9.8[a] | 31.4 ± 6.7[a] | 28.4 ± 3.2[b] | 26.3 ± 4.6[b] |
| PAWP (mm Hg) | 8.2 ± 3.6 | 7.0 ± 3.5 | 9.9 ± 3.6 | 9.9 ± 3.1 |
| Cardiac index (L/min/m$^2$) | 2.3 ± 0.6 | 2.4 ± 0.5 | 3.1 ± 0.8 | 3.0 ± 0.8 |
| PVR (WU) | 9.8 ± 4.7[a] | 6.7 ± 1.8[a] | 3.7 ± 0.9[b] | 3.3 ± 1.0[b] |
| mPAP <25 mm Hg | 0 (0.0)[a] | 6 (13.3)[a] | 1 (3.1)[a] | 35 (36.1)[a] |
| mPAP ≥35 mm Hg | 42 (64.6)[a] | 10 (22.2)[a] | 1 (3.1) | 5 (5.2) |
| Ex-severe PH | 61 (93.8)[a] | 34 (75.6)[a] | 9 (28.1) | 24 (24.7) |
| PaO$_2$ (Torr) room air | 54.4 ± 11.2[a] | 61.8 ± 11.7[a] | 59.7 ± 10.2[a] | 68.8 ± 13.9[a] |
| PaCO$_2$ (Torr) room air | 42.3 ± 10.8 | 37.5 ± 5.6 | 43.1 ± 5.6 | 40.9 ± 7.0 |
| FVC, %pred. | 72.4 ± 22.0[a] | 78.6 ± 20.6[a] | 64.8 ± 19.9 | 69.1 ± 22.1 |
| FEV1, %pred. | 75.0 ± 21.6[a] | 86.1 ± 17.4[a] | 66.7 ± 16.2 | 75.2 ± 25.2 |
| Mild VI | 28 (52.8) | 24 (63.2) | 13 (41.9) | 36 (49.3) |
| DLCO, %pred. | 28.7 ± 13.6[a] | 35.4 ± 10.2[a] | 36.1 ± 11.1 | 41.4 (16.3) |
| DLCO, %pred. <35% | 25 (73.5)[b] | 12 (44.4)[b] | 14 (53.8) | 26 (38.8) |
| BNP (pg/mL) | 208(61-616)[b] | 75(28-178)[b] | 28(11-103) | 33(15-66) |
| 6MWD (m) | 149(105-202)[a] | 298(165-392)[a] | 304(197-360)[a] | 395(280-490)[a] |
| KL-6(U/mL) | 968 ± 676[a] | 1,342 ± 732[a] | 1,436 ± 1,491 | 1,566 ± 1,325 |
| PDE-5I | 58 (89.2) | 6 (85.7) | 26 (81.3) | 10 (66.7) |
| ERA | 32 (49.2) | 2 (28.6) | 5 (15.6) | 4 (26.7) |
| Mono/Dual and triple therapy | (53.9)/(46.1) | (85.7)/(14.3) | (93.8)/(6.2) | (86.7)/(13.3) |

Values are mean ± SD, n (%), or median (IQR). [a]Initial vs noninitial treatment $P < 0.01$. [b]Initial vs noninitial treatment $P < 0.05$.

Abbreviations as in **Table 1**.

**TABLE 4** Univariate and Multivariate Analyses of Prognostic Factors for Treatment-Naive Patients With Severe PH (n = 129)

| | Univariate HR (95% CI) | P Value | Multivariate HR (95% CI) | P Value |
|---|---|---|---|---|
| Age | 0.994 (0.966-1.024) | 0.708 | 0.998 (0.960-1.038) | 0.916 |
| Female vs male | 0.55 (0.29-1.03) | 0.060 | 0.42 (0.19-0.95) | 0.036 |
| IP vs CPFE | 1.13 (0.68-1.86) | 0.645 | 0.92 (0.48–1.77) | 0.802 |
| WHO-FC III-IV vs I-II | 1.69 (0.86-3.32) | 0.129 | 1.91 (0.88-4.12) | 0.100 |
| Right atrial pressure | 1.02 (0.96-1.09) | 0.512 | | |
| mPAP | 0.99 (0.96-1.02) | 0.375 | | |
| Cardiac index | 1.16 (0.78-1.70) | 0.465 | | |
| PVR | 1.000 (0.999-1.000) | 0.277 | | |
| Ex-severe PH | 0.61 (0.31-1.20) | 0.154 | | |
| BNP | 1.000 (0.999-1.000) | 0.322 | | |
| 6MWD | 1.000 (0.997-1.002) | 0.688 | | |
| PaO$_2$ (room air) | 0.89 (0.96-1.02) | 0.440 | | |
| DLCO, %pred. | 1.01 (0.98-1.03) | 0.543 | | |
| DLCO, %pred. <35% | 0.75 (0.36-1.53) | 0.423 | | |
| FVC, %pred. | 0.994 (0.981-1.007) | 0.340 | | |
| FEV1, %pred. | 1.009 (0.995-1.024) | 0.212 | | |
| Mild VI | 0.81 (0.47-1.41) | 0.466 | 0.58 (0.31-1.11) | 0.100 |
| Initial treatment | 0.71 (0.43-1.17) | 0.182 | 0.53 (0.28-0.99) | 0.047 |

Abbreviations as in **Table 1**.

**TABLE 5** Univariate and Multivariate Analyses of Prognostic Factors for Treatment-Naive Patients With Mild PH (n = 110)

| | Univariate HR (95% CI) | P Value | Multivariate HR (95% CI) | P Value |
|---|---|---|---|---|
| Age | 0.99 (0.97-1.01) | 0.272 | 1.01 (0.98-1.03) | 0.652 |
| Female vs male | 0.83 (0.48-1.46) | 0.522 | 0.74 (0.39-1.39) | 0.341 |
| IP vs CPFEf | 1.12 (0.60-2.07) | 0.723 | 0.62 (0.26-1.43) | 0.259 |
| WHO-FC III-IV vs I-II | 2.03 (1.20-3.43) | 0.009 | 2.22 (1.19-4.17) | 0.013 |
| Right atrial pressure | 0.94 (0.87-1.01) | 0.076 | | |
| mPAP | 0.99 (0.93-1.05) | 0.632 | | |
| Cardiac index | 1.07 (0.76-1.52) | 0.688 | | |
| PVR | 1.00 (1.00-1.00) | 0.961 | | |
| Ex-severe PH | 0.71 (0.40-1.27) | 0.249 | | |
| BNP | 1.001 (0.999-1.003) | 0.334 | | |
| 6MWD | 0.998 (0.996-1.000) | 0.075 | | |
| PaO$_2$ (room air) | 1.00 (0.98-1.03) | 0.923 | | |
| DLCO, %pred. | 0.98 (0.96-1.00) | 0.061 | | |
| DLCO, %pred. <35% | 1.39 (0.80-2.42) | 0.237 | | |
| FVC, %pred. | 0.983 (0.972-0.995) | 0.005 | | |
| FEV1, %pred. | 0.988 (0.978-0.999) | 0.025 | | |
| Mild VI | 0.42 (0.25-0.72) | 0.002 | 0.37 (0.19-0.74) | 0.005 |
| Initial treatment | 0.90 (0.51-1.56) | 0.696 | 0.75 (0.41-1.37) | 0.341 |

Abbreviations as in Table 1.

dual/triple therapy use was only 5.6%. PVR for patients using ERA was 9.9 ± 5.6 WU, higher than the 7.8 ± 4.8 WU for the entire group. Because of the unclear and continuous boundary between PAH with lung disease and the pulmonary vascular remodeling-dominant type of Group 3 PH, ERA may have been used in the pulmonary vascular remodeling-dominant type. There are no RCTs showing the effect of ERA or prostanoid/selexipag on PH associated with IP. They may also exacerbate gas exchange, especially ambrisentan, which is contraindicated for idiopathic pulmonary fibrosis.[11] In our study, ambrisentan was used in only 1 case.

Combination therapy is not recommended for Group 3 PH or PAH with comorbidities. In fact, in our study, combination therapy was sequential in inadequate response cases; it was not initial therapy. However, because there was no difference in prognosis between the initial and noninitial treatment groups in most cases other than in those with severe PH and mild VI, we should be cautious about off-label use of ERA, prostanoid/selexipag, and combination therapy.

Seventh, even in cases of mild VI, including initial and noninitial treatment groups, the 2-year survival rate was 61.4% (95% CI: 49.7%-71.1%), but the 3-year survival rate was only 36.8% (95% CI: 25.0%-48.5%), which is poor. Several studies suggested that the presence of lung disease in PAH was an unfavorable prognostic factor.[12,13] Moreover, a registry analysis reported similar survival rates between idiopathic
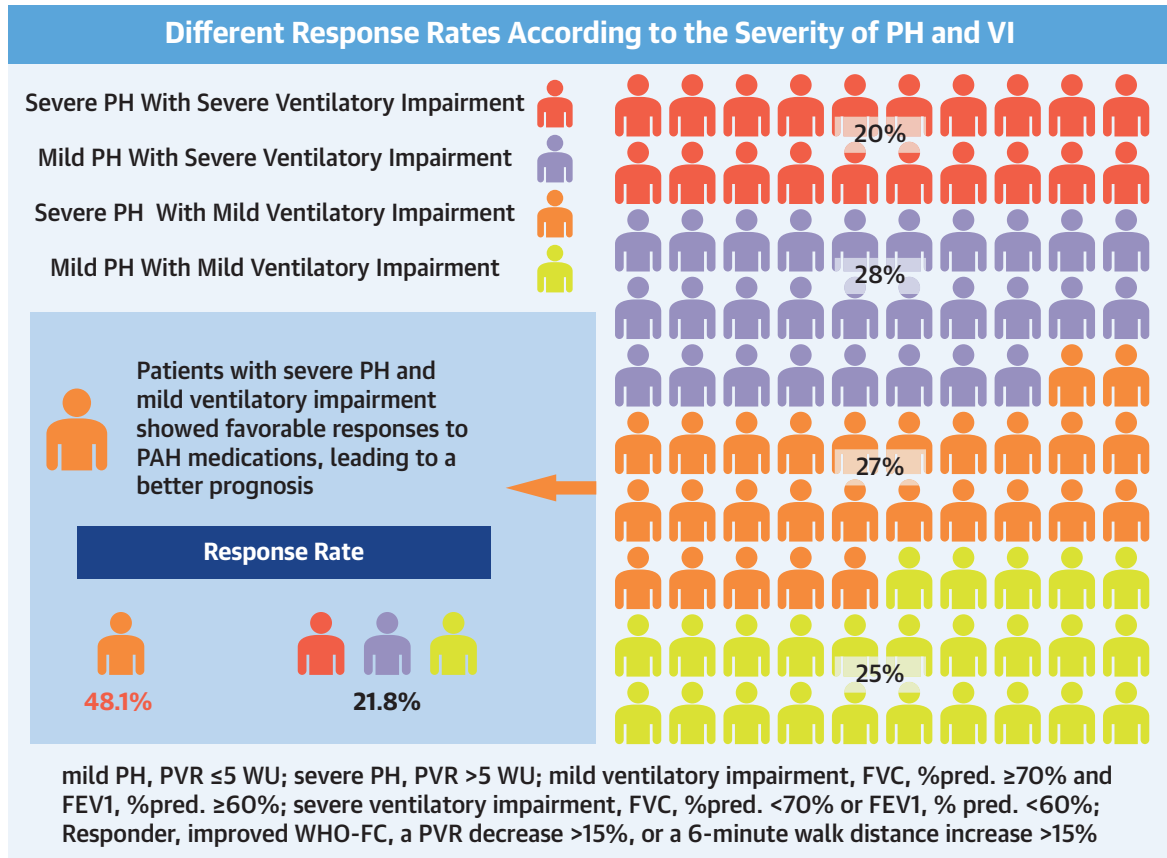
PAH with a pulmonary phenotype and Group 3 PH, which were much worse than that observed in classical idiopathic PAH.[14] For R-PH, worsening of blood gas levels and increased oxygen requirements may occur due to oral PAH-targeted therapies, despite a reduction in PVR,[15] sometimes resulting in respiratory failure and death. Recently, an RCT reported that inhaled treprostinil improved the 6MWD in IP.[2] Inhaled drugs have the advantage of not worsening ventilation/perfusion mismatches, although their effects on prognosis remain unknown and further study is necessary.

Eighth, the impact of drug discontinuation is discussed in the discussion section of the Supplemental Material.

Finally, CPFE has been reported to have milder VI and poorer prognosis than IP[16,17]; however, we found no differences in the prognoses between IP and CPFE in JRPHS.[7] Moreover, the distinction between CPFE and IP remains ambiguous, leaving us uncertain about the extent to which emphysema should be categorized as CPFE. Therefore, we analyzed them together.

When we analyzed them separately, within the severe PH and mild VI group, patients with IP had significantly better outcomes with initial treatment, whereas with CPFE, the difference in prognosis between the initial and noninitial treatment groups was smaller. Nonetheless, the 3-year survival rates showed a favorable trend, with 54.1% vs 38.2%, indicating better outcomes.

**CENTRAL ILLUSTRATION** Different Response According to the Severity of Pulmonary Hypertension and Ventilatory Impairment



**Different Response Rates According to the Severity of PH and VI**

Severe PH With Severe Ventilatory Impairment

Mild PH With Severe Ventilatory Impairment

Severe PH With Mild Ventilatory Impairment

Mild PH With Mild Ventilatory Impairment

20%

28%

27%

25%

Patients with severe PH and mild ventilatory impairment showed favorable responses to PAH medications, leading to a better prognosis

**Response Rate**

48.1%

21.8%

mild PH, PVR ≤5 WU; severe PH, PVR >5 WU; mild ventilatory impairment, FVC, %pred. ≥70% and FEV1, %pred. ≥60%; severe ventilatory impairment, FVC, %pred. <70% or FEV1, % pred. <60%; Responder, improved WHO-FC, a PVR decrease >15%, or a 6-minute walk distance increase >15%

Tanabe N, et al. JACC: Asia. 2024;4(5):403–417.

The prevalence of severe PH with severe VI, mild PH with severe VI, severe PH with mild VI, and mild PH with mild VI was 20.0%, 28.2%, 26.7%, and 25.1%, respectively. The response rate in the severe PH with mild VI group was significantly higher than that in the other groups (48.1% vs 21.8%, ratio 2.21 [95% CI: 1.17-4.16]). Prevalence percentages were calculated by using the total number of treatment-naive patients as the denominator. The response rate was based on the number of patients who responded in each group. FEV1, %pred. = percent predicted forced expiratory volume in 1 second; FVC, %pred. = percent predicted forced vital capacity; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; VI = ventilatory impairment; WHO-FC = World Health Organization's functional class.

The response rate was consistently high in the group with severe PH and mild VI, regardless of the disease (IP: 55.6% vs 22.2%, ratio 2.50 [95% CI: 1.07-5.82]; CPFE: 44.4% vs 21.1%, ratio 2.11 [95% CI: 0.77-5.81]), and the prognosis after the response assessment was better for responders, even when divided into IP and CPFE groups.

**STUDY LIMITATIONS.** The most significant limitation of this study is that the decision to use PAH-targeted therapies was made by the physician at each facility, and the registry could not account for the selection bias. Although it is a nationwide registry, the number of cases stratified by PVR was small, and there were not enough cases to enable a response assessment for

PVR <5 WU. As previously mentioned, R-PH may include Group 1 (PAH) and pure Group 3 PH phenotypes. Therefore, it is possible that the mild VI group should have been classified as having PAH.

## CONCLUSIONS

This study demonstrated an increased number of responders of initial PAH-targeted therapy with a favorable prognosis in severe PH cases with mild VI and IP or CPFE. Conversely, for patients presenting with mild PH, the survival benefit of initial treatment was not observed. These findings support the recent ESC/ERS guideline recommendations for individualized treatment of patients with severe R-PH and non-

**TABLE 6  Comparison of Baseline Characteristics Between Responders and Nonresponders with PVR >5 or ≤5 WU**

| | PVR >5 WU | | PVR ≤5 WU | |
|---|---|---|---|---|
| | Responders[a] (n = 18) | Nonresponders (n = 25) | Responders[a] (n = 6) | Nonresponders (n = 12) |
| Age (y) | 69.1 ± 8.7 | 69.8 ± 11.2 | 72.7 ± 6.9 | 73.4 |
| Female | 4 (22.2) | 7 (28.0) | 3 (50)[b] | 1 (8.3)[b] |
| IP/CPFE | 11/7 | 13/12 | 3/3 | 6/6 |
| WHO-FC III/IV | 18 (100) | 21 (84) | 5 (83.3) | 5 (41.7) |
| mPAP (mm Hg) | 40.3 ± 10.5 | 40.3 ± 10.9 | 27.3 ± 2.9 | 28.2 ± 2.9 |
| PAWP (mm Hg) | 8.2 ± 3.6 | 8.2 ± 3.1 | 8.7 ± 5.3 | 10.8 ± 2.3 |
| Cardiac index (L/min/m²) | 2.3 ± 0.7 | 2.4 ± 0.7 | 3.0 ± 0.8 | 2.7 ± 0.4 |
| PVR (WU) | 10.1 ± 5.4 | 9.2 ± 3.5 | 3.8 ± 0.7 | 3.9 ± 0.6 |
| mPAP <25 mm Hg | 0 (0) | 0 (0) | 1 (16.7) | 0 (0) |
| mPAP ≥35 mm Hg | 10 (55.6) | 16 (64.0) | 0 (0) | 0 (0) |
| Ex-severe PH | 16 (88.9) | 25 (100) | 2 (33.3) | 3 (25.0) |
| PaO2 (Torr) room air | 59.8 ± 21.5 | 51.5 ± 5.8 | 68.0 ± 11.3 | 57.8 ± 10.2 |
| PaCO2 (Torr) room air | 45.7 ± 8.6 | 43.1 ± 17.3 | 44.0 ± 5.2 | 42.2 ± 4.5 |
| FVC , %pred. | 76.7 ± 16.4 | 72.2 ± 27.2 | 64.2 ± 26.6 | 72.6 ± 18.6 |
| FEV1, %pred. | 80.6 ± 16.4 | 73.3 ± 25.9 | 69.2 ± 17.2 | 74.2 ± 12.2 |
| Mild VI | 11 (78.6)[b] | 9 (42.9)[b] | 3 (50) | 7 (63.6) |
| DLCO, %pred. | 25.6 ± 11.1 | 29.2 ± 10.3 | 39.0 ± 7.0 | 35.5 ± 12.5 |
| DLCO,%pred. <35% | 10 (83.3) | 9 (75) | 2 (40) | 7 (63.6) |
| BNP (pg/mL) | 254 (70-527) | 137 (62-400) | 27 (10-171) | 24 (11-92) |
| 6MWD (m) | 130 (68-169) | 152 (110-210) | 256 (153-355) | 325 (210, 396) |

Values are mean ± SD, n (%), or median (IQR). [a]Responders were defined as those having a %decrease in PVR >15%, or %increase in 6MWD >15%, or improvement in WHO-FC. [b]$P < 0.05$.

Abbreviations as in Table 1.

**FIGURE 7  Survival Comparisons From the Assessment Date Between Responders and Nonresponders**
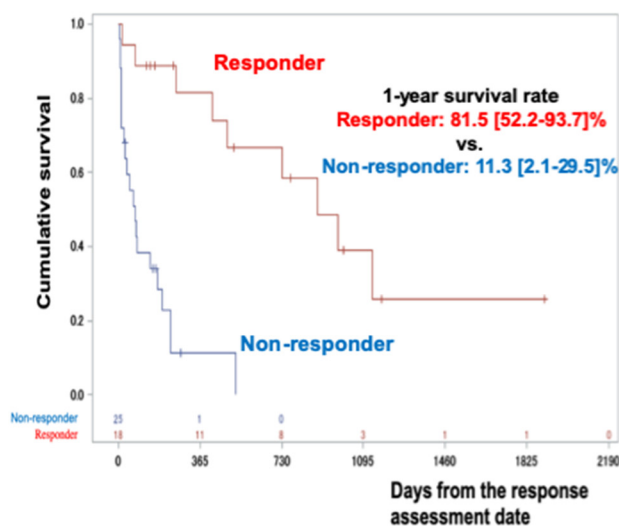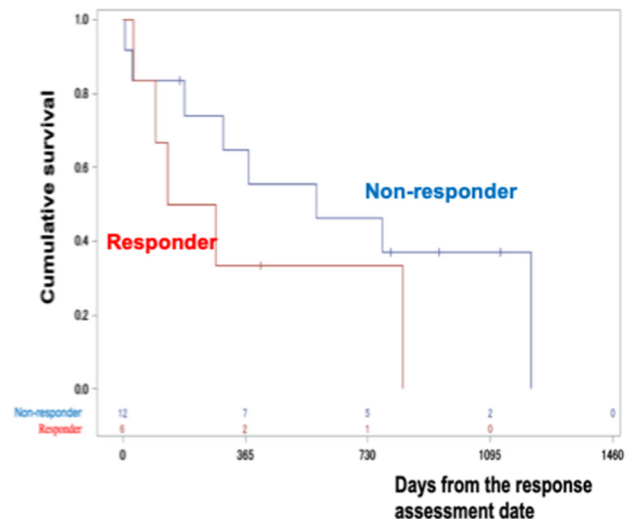


(A) Severe PH (PVR >5 WU): Responders had a better prognosis than nonresponders from the response assessment date. (B) Mild PH (PVR ≤5 WU): The number of cases was too small to be evaluated. No better trend for prognosis was observed in responders compared with nonresponders. Abbreviations as in Figures 1 and 3.

use of PAH-targeted therapies for patients with mild R-PH.

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PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** This study illustrates the characteristics of responders to PAH-targeted therapy for PH with respiratory diseases, highlighting a favorable prognosis with treatment in cases of severe PH with mild ventilatory impairment.

**TRANSLATIONAL OUTLOOK:** More research integrating respiratory function analysis and imaging data is essential for a comprehensive understanding of the effectiveness of PAH drugs in patients with PH associated with respiratory diseases.

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**KEY WORDS** interstitial pneumonia, multicenter registry, pulmonary hypertension, respiratory disease, ventilatory impairment

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**APPENDIX** For supplemental material, tables, figures, and list of members of the JRPHS group, please see the online version of this paper.