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ORIGINAL RESEARCH

Patient and Therapeutic Profiles of Pulmonary Hypertension in Chronic Lung Diseases in Japan: A Cohort Study Using a Claims Database

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ABSTRACT

Introduction: Pulmonary hypertension (PH) is often complicated by chronic lung diseases (CLDs) such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Differentiating between PH associated with CLD (group 3 PH) and pulmonary arterial hypertension (PAH) in CLD is often difficult and reporting on the efficacy of PAH-specific therapies is inconsistent as a result of the lack of understanding of the heterogeneity of patients with PH.

Methods: A retrospective observational cohort study was conducted to understand the baseline characteristics, comorbidities, and treatment profiles of patients with PH in CLD in a real-world setting using a large-scale claims database (Medical Data Vision). Administrative and clinical data for patients admitted to acute-care hospitals in Japan between April 2008 and January 2021 were analyzed.

Results: A total of 115,921 patients with CLD (109,578 with COPD and 6343 with ILD, of whom 569 and 176 had PH, respectively) were analyzed. This study found lower PH diagnosis rates among patients with COPD and patients with ILD than in previous studies. The majority of PH with CLD patients were elderly (mean age 75.7 years) and male (80.81%). Among patients with CLD prescribed PAH-specific therapies (105 patients with COPD; 64 patients with ILD), most received these as monotherapy (COPD, 84.76%; ILD, 75.56%); the most common were phosphodiesterase 5 inhibitors (COPD, 42.70%; ILD, 18.37%), prostacyclins (oral; COPD, 48.31%; ILD, 24.49%), and endothelin receptor antagonists (ERA) (COPD, 8.99%; ILD, 18.37%). Comorbidities (e.g., pulmonary, cardiac, kidney), home oxygen therapy (HOT), and echocardiography (ECHO) were factors associated with the diagnosis of PH.

Conclusion: This is the first study using an administrative database that provides real-world data on patients with PH in CLD in Japan. Our results indicate that PH may be misdiagnosed or underdiagnosed in Japan which may lead to suboptimal treatment for patients, and supports the need for further evidence to guide appropriate treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41030-023-00243-x.

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PLAIN LANGUAGE SUMMARY

Pulmonary hypertension is a disorder affecting the arteries in the lungs and the right heart. It can be associated with a variety of heart and lung conditions, including many chronic lung diseases such as chronic obstructive pulmonary disease and interstitial lung disease. Patients with pulmonary hypertension with chronic lung disease and/or hypoxia can be hard to tell apart from patients with pulmonary arterial hypertension coinciding with chronic lung disease. In Japan, there is not enough data on patient demographics and their disease characteristics for patients with pulmonary hypertension and chronic lung disease, including treatment profiles, and disease management. We identified these patients from a large medical claims database in Japan and analyzed their data. Our study focused on the use of therapies for pulmonary arterial hypertension on patients with pulmonary hypertension and chronic lung disease. The diagnosis rates of pulmonary hypertension for patients with chronic obstructive pulmonary disease and interstitial lung disease were low compared to previous reports, meaning patients with pulmonary hypertension may be misdiagnosed or underdiagnosed which may be resulting in suboptimal treatments. Furthermore, the majority of patients with pulmonary hypertension treated with pulmonary arterial hypertension medication received a single drug as treatment, even though the guidelines recommend the use of combination therapies in certain situations. This study emphasizes the need for further evidence generation for improvements in diagnoses and treatment of patients with pulmonary hypertension in Japan.

Keywords: Claims database; Chronic obstructive pulmonary disease; Interstitial lung disease; Pulmonary hypertension; Real-world evidence

Key Summary Points

Why carry out this study?

There is lack of real-world evidence on the characteristics, factors associated with pulmonary hypertension (PH) diagnosis, and treatment patterns for patients with PH in chronic lung diseases (CLDs) in Japan.

This study utilizes a large Japanese claims database to understand the characteristics of patients with PH in CLD and their treatment profiles with a focus on pulmonary arterial hypertension (PAH)-specific therapies.

What was learned from the study?

PH diagnosis rates among patients with chronic obstructive pulmonary disease (COPD) and patients with interstitial lung disease (ILD) were found to be lower than in previous studies, monotherapy was the most prescribed PAH-specific therapy, and the characteristics of patients receiving continuous PAH-specific therapy were shown to differ between COPD and ILD.

The results from this study indicate that patients with PH in CLD may be misdiagnosed or underdiagnosed which may be resulting in suboptimal treatments for patients.

Further evidence on the real-world clinical state of patients with PH in Japan is necessary for the appropriate treatment of patients.

INTRODUCTION

Pulmonary hypertension (PH) is a pathophysiologic disorder with a poor prognosis which is associated with various circulatory and respiratory diseases. The global prevalence of PH is approximately 1%, with a higher prevalence in

individuals over 65 years old [1]. PH is clinically classified into five groups, of which group 1 PH in particular now has more treatment options in Japan owing to the launch of pulmonary vasodilators [2]. Furthermore, PAH-specific therapies are now subsidized by the designated intractable disease medical expenses subsidy when patients are diagnosed with a group 1 PH complicated by respiratory disease [3].

Patients with group 3 PH are classified as either non-severe (pulmonary vascular resistance; PVR≤5 Wood units [WU]) or severe PH (PVR>5 WU), both of which have poor prognoses [2]. With the exception of inhaled treprostinil, there have been no convincing studies demonstrating improved outcomes with PAH-specific therapies such as pulmonary vasodilators (PVs) in patients with group 3 PH [4, 5]. Despite the lack of evidence, extensive use of PAH-specific therapies for patients with group 3 PH has been reported in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry study [6]. However, the European Society of Cardiology and the European Respiratory Society (ESC/ERS) guidelines [2] do not recommend the use of PAH-specific therapies as a result of the limited evidence and potential negative impact of these drugs on gas exchange, hemodynamics, and outcomes. Patients with severe PH are recommended for referral to PH centers for personalized treatments [2]. The variability in treatment recommendations from these guidelines and studies reflects the clinical difficulties of selecting appropriate treatments for patients with PH.

The gold standard diagnostic approach for PH is right heart catheterization (RHC); however, other approaches include electrocardiography (ECG), chest radiography, pulmonary function tests, lung scans, echocardiography (ECHO), and the evaluation of biomarkers B-type natriuretic peptides (BNP) and N-terminal-pro hormone BNP (NT-proBNP) [2, 7, 8]. Despite the availability of multiple assessment techniques, it remains difficult to differentiate between patients with group 3 PH and those with group 1 PH with coincident chronic lung disease (CLD) as the severity of pulmonary vascular disease and parenchymal CLD likely overlap with each other [7]. Chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) are among the CLDs that can cause complications in PH and patients demonstrate reduced functional ability and worse outcomes, with COPD being the most prevalent [7, 9, 10].

Although there are previous reports on the diagnosis and treatment of group 3 PH and group 1 PH in Japan, these are mainly limited to specialized centers [11–13] and there is no comprehensive analysis of patients with group 3 and group 1 PH including non-specialists to date. There is thus a lack of real-world data on PH particularly from non-specialized centers in Japan. This study aimed to understand the demographics, clinical characteristics, and actual clinical practices used for the treatment of patients with CLDs (COPD and ILD) with PH, including group 1 PH, using electronic health records from Medical Data Vision (MDV)—a large, anonymized administrative claims database of Diagnosis Procedure Combination (DPC) hospitals in Japan. The overall objective of this study was divided into four sub-objectives and included the analysis of (1) demographics and clinical characteristics of patients with PH in CLDs; (2) treatment patterns of PAH-specific therapies; (3) factors associated with diagnosis of PH with CLDs by comparing patients with and without PH; and (4) comparison of patient characteristics of three groups of patients with PH categorized by the length of their respective PAH drug treatments.

METHODS

Study Design and Data Sources

This retrospective observational cohort study of Japanese patients with PH in CLD using the MDV database, a hospital-based administrative claims database in Japan, was conducted between April 2008 and January 2021. The database comprised anonymized administrative and laboratory data from approximately 460 acute care hospitals and covers over 40 million patients, including 39% of elderly patients [14]. The MDV dataset includes patient IDs, month and year of birth, diagnoses coded according to

the International Classification of Diseases, Tenth Revision (ICD-10) codes, Japanese standard disease codes, medications, laboratory tests, months of diagnoses, dates of procedures, prescriptions, and dates of admission and discharge. The anonymized MDV data are used for epidemiological, and health economics and outcomes research. Informed consent for the analyses in this study was waived because of the anonymous nature of the database.

Study Population

The study population was identified from the database between April 2008 to January 2021 (Fig. 1). All potential incident cases were identified using a systematic algorithm developed by a clinical expert by referring to previous studies [15–18]. In accordance with previous studies, a multidirectional approach was applied to identify patients with PH in CLD to ensure the accuracy of the diagnosis. Patients with PH were identified as patients who had a confirmed diagnosis of PH based on ICD-10 code I27.0 and had received ECHO and/or RHC within 1 month before/after the first recorded ICD-10 code for PH. Patients meeting the selection criteria were followed up from their initial definitive identification of PH (index date) until the earliest of the end of the observational period, death, or known exit from the data source (follow-up period). Further, a minimum look-back period of 6 months from the first claims record to the index month was included. Patient data were examined for PAH-associated comorbidities and factors associated with diagnosis during the baseline period (6 months prior to the month of first diagnosis of PH, i.e., index month). The study population was identified from the database as per the eligibility criteria (patient selection and attrition can be found in Fig. 2).

In this study, two populations were included on the basis of the study objectives (Fig. S1). Population 1 included patients who met either the COPD or ILD algorithms (Figs. S2 and S3) and those who met the PH algorithms (Fig. S4) during the data period. Patients who did not have any claims records during or prior to the 6 months before the index month were excluded. This population was analyzed for objectives 1, 2, and 4. The study population was divided into two cohorts. Patients in cohort A were defined as patients with PH who also received a PAH-specific treatment on or after the index month. These patients are represented in this study as the "PAH therapy group." Cohort B comprised patients who were not prescribed PAH-specific therapies on or after the index month in the population, and are referred to as the "no treatment group" in this study. Cohort A was further divided into two subcohorts: cohort A-1, which included patients in cohort A who were prescribed PAH-specific therapies continuously (90% proportion of days covered) for at least 6 months; and cohort A-2, consisting of patients in cohort A who were not included in cohort A-1. Population 2 was analyzed for objective 3 and included patients who met either the COPD or ILD algorithms during the data period. Patients who did not have any claims records for more than 6 months before the CLD month (first definitive diagnosis month of CLD) and within 6 months before the CLD month were excluded.

Variables and Outcomes

In this study, the outcomes—including treatment patterns and factors associated with diagnosis—were measured for three patient groups: patients with CLDs (COPD or ILD, i.e., the entire study population), patients with COPD, and patients with ILD. Patients with CLDs who met both the COPD and ILD algorithms were assigned to "patients with ILD" and not "patients with COPD." These assignments were made when both ILD and COPD are present (ILD generally being the more severe disease), which is referred to as combined pulmonary fibrosis and emphysema (CPFE) and is generally classified as a type of pulmonary fibrosis. With this background in mind, Japanese clinical experts have expressed the opinion that the inclusion of patients with both ILD and COPD into the ILD group is appropriate. Furthermore, a feasibility study prior to this investigation found that there were very few

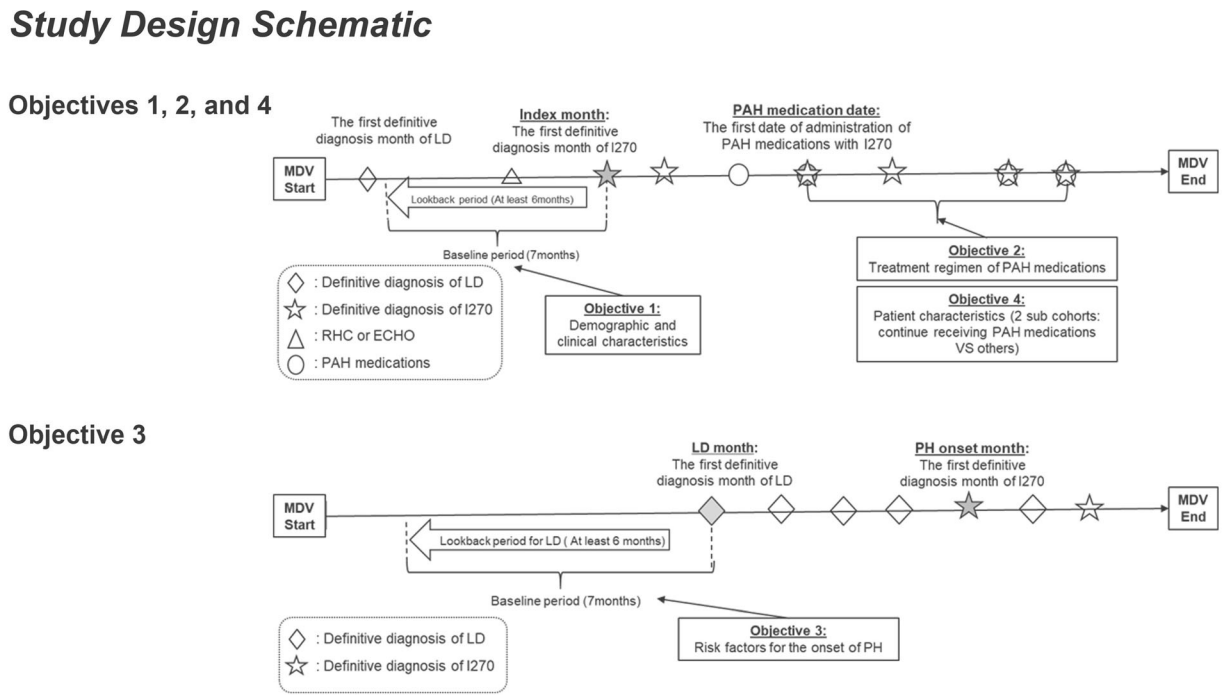

Fig. 1 Study overview. Study design with patient definitions for objectives 1, 2, 3, and 4 and the definitions of index date, index month, PAH medication date, baseline period, CLD month, and PH onset month. *ECHO* echocardiography, *I270* ICD-10 code for primary pulmonary hypertension, *LD* lung disease, *MDV* Medical Data Vision, *PAH* pulmonary arterial hypertension, *PH* pulmonary hypertension, *PV* pulmonary vasodilator, *RHC* right heart catheterization

patients with both ILD and COPD in the target population.

The variables and outcomes are described in Table S1 of the electronic supplementary material. In this study, the ECHO for determining PH was performed between the month before and the month after the index month as described above. In the outcomes, however, ECHO was performed from between 12 to 2 months before the index date. Therefore, the timelines do not overlap between the ECHO used for diagnosis and those used for the outcomes. The ECHO variable simply indicates that the tests were performed and are not indicative of abnormalities.

The variables and outcomes (demographic and clinical characteristics) measured in this study were gender, age group, body mass index (BMI), smoking status, New York Heart Association (NYHA) Functional Class (FC), Charlson Comorbidity Index, and the corresponding 1-year mortality risk [19, 20]. These variables were assessed for all patients with CLDs (Tables S2, S3) and compared between patients with COPD and patients with ILD (Table S4). Baseline comorbidities, which are typically concurrent with CLDs, were also reported and considered covariates in the multivariate analysis. Baseline laboratory data, such as BNP and NT-proBNP levels, were also considered as they were generally measured in patients with CLDs and PH.

Treatment patterns of PAH-specific therapy were described in terms of monotherapy (one drug class), double therapy (two different drug classes), and triple therapy (three different drug classes) of PAH-specific drugs. The drug classes of PAH-specific therapy used were also described from baseline (first PAH medication) to 5 years (from the index date) for the overall population with CLDs, patients with COPD, and patients with ILD.

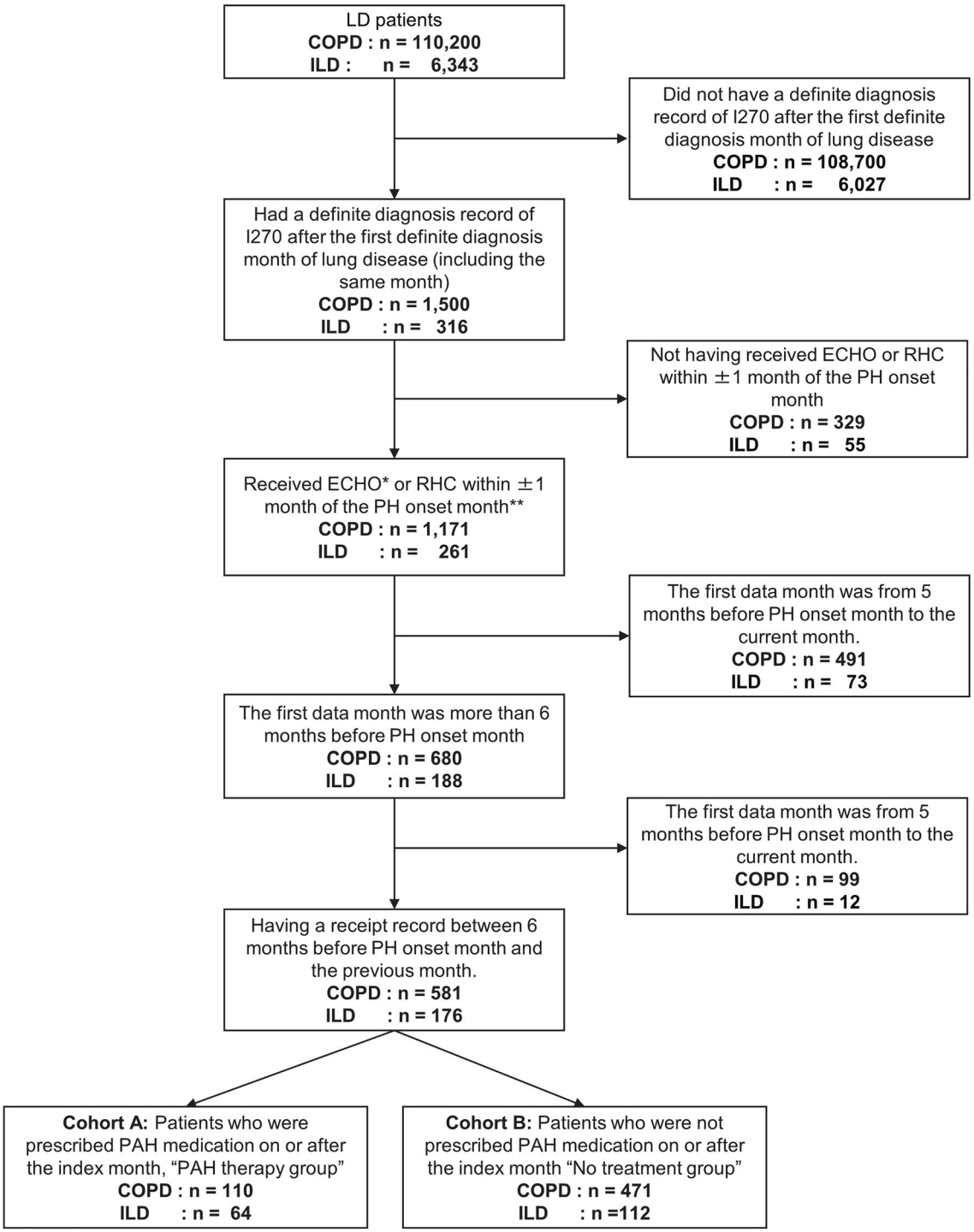

Fig. 2 Attrition diagram. Flow of patient selection and patient attrition over the observational period. *COPD* chronic obstructive pulmonary disease, *ECHO* echocardiography, *IPF* idiopathic pulmonary fibrosis, *I270* ICD-10 code for primary pulmonary hypertension, *LD* lung disease, *PAH* pulmonary arterial hypertension, *PH* pulmonary hypertension, *RHC* right heart catheterization

Table 1 Demographics of PAH therapy group and no treatment group

Demographic characteristics	PAH therapy group		No treatment group	
	COPD ($n=105$)	ILD ($n=64$)	COPD ($n=464$)	ILD ($n=112$)
Age at index date				
n	105	64	464	112
Mean (SD)	75.19 (8.80)	69.13 (13.01)	77.25 (8.55)	73.63 (8.27)
Median	76	72	78	74.5
Min–max	47–90	21–89	49–96	38–91
IQR (25%–75%)	11.00 (70.00–81.00)	11.00 (66.00–77.00)	12.00 (72.00–84.00)	7.25 (70.75–78.0)
Missing	0	0	0	0
Age group at index date (*n*, %)				
n	105	64	464	112
15–39 years	0 (0.00%)	2 (3.13%)	0 (0.00%)	1 (0.89%)
40–64 years	12 (11.43%)	11 (17.19%)	35 (7.54%)	12 (10.71%)
65–74 years	28 (26.67%)	28 (43.75%)	132 (28.45%)	43 (38.39%)
≥75 years	65 (61.90%)	23 (35.94%)	297 (64.01%)	56 (50.00%)
Missing	0	0	0	0
Sex (*n*, %)				
n	105	64	464	112
Male	88 (83.81%)	43 (67.19%)	383 (82.54%)	88 (78.57%)
Female	17 (16.19%)	21 (32.81%)	81 (17.46%)	24 (21.43%)
Missing	0	0	0	0
Smoking status (*n*, %)				
n	65	35	285	67
No	16 (24.62%)	11 (31.43%)	72 (25.26%)	26 (38.81%)
Yes	37 (56.92%)	21 (60.00%)	184 (64.56%)	34 (50.75%)
Unknown	12 (18.46%)	3 (8.57%)	29 (10.18%)	7 (10.45%)
Missing	40	29	179	45
BMI				
n	63	35	274	67
Mean (SD)	20.79 (4.93)	22.36 (4.04)	21.1 (4.24)	22.11 (4.38)
Median	20.76	21.84	20.71	22.85
Min–max	0.0–32.23	15.47–31.24	12.23–47.34	0.0–32.01
IQR (25%–75%)	5.25 (18.61–23.85)	6.09 (18.96–25.04)	4.95 (18.62–23.57)	4.38 (20.39–24.77)

Table 1 continued

Demographic characteristics	PAH therapy group		No treatment group	
	COPD (*n* = 105)	ILD (*n* = 64)	COPD (*n* = 464)	ILD (*n* = 112)
Missing	42	29	190	45
HOT				
n	65 (61.90%)	51 (79.69%)	213 (45.91%)	86 (76.79%)
ECHO				
n	53 (50.48%)	37 (57.81%)	214 (46.12%)	43 (38.39%)
ECG				
n	103 (98.10%)	62 (96.88%)	442 (95.26%)	103 (91.96%)
RHC				
n	39 (37.14%)	24 (37.50%)	89 (19.18%)	18 (16.07%)

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *ECG* echocardiogram, *ECHO* echocardiography, *HOT* home oxygen therapy, *ILD* interstitial lung disease, *IQR* interquartile range, *n* number of patients, *PAH* pulmonary arterial hypertension, *PH* pulmonary hypertension, *RHC* right heart catheterization, *SD* standard deviation

Table 2 Comorbidities of PAH therapy group and no treatment group

Comorbidity (*n*, %)	PAH therapy group		No treatment group	
	COPD (*n* = 105)	ILD (*n* = 64)	COPD (*n* = 464)	ILD (*n* = 112)
Systemic arterial hypertension	56 (53.33%)	27 (42.19%)	276 (59.48%)	57 (50.89%)
Dyslipidemia	41 (39.05%)	18 (28.13%)	134 (28.88%)	34 (30.36%)
Diabetes mellitus	34 (32.38%)	24 (37.50%)	161 (34.70%)	45 (40.18%)
Chronic kidney disease	15 (14.29%)	3 (4.69%)	67 (14.44%)	10 (8.93%)
Coronary artery disease	42 (40.00%)	15 (23.44%)	147 (31.68%)	31 (27.68%)
Left heart failure	3 (2.86%)	2 (3.13%)	11 (2.37%)	3 (2.68%)
Valvular disease	6 (5.71%)	3 (4.69%)	81 (17.46%)	7 (6.25%)
Arrhythmia	31 (29.52%)	3 (4.69%)	150 (32.33%)	23 (20.54%)
Sleep apnea	3 (2.86%)	0 (0.00%)	13 (2.80%)	3 (2.68%)
Malignancy	35 (33.33%)	13 (20.31%)	156 (33.62%)	33 (29.46%)
Thyroid disease	12 (11.43%)	4 (6.25%)	34 (7.33%)	5 (4.46%)
Obesity	0 (0.00%)	0 (0.00%)	4 (0.86%)	1 (0.89%)
CTD	9 (8.91%)	21 (32.81%)	18 (3.88%)	13 (11.61%)
Lung cancer	15 (14.29%)	1 (1.56%)	46 (9.91%)	11 (9.82%)

COPD chronic obstructive pulmonary disease, *CTD* connective tissue disease, *ILD* interstitial lung disease, *n* number of patients, *PAH* pulmonary arterial hypertension

Table 3 CCI and NHYA classes of PAH therapy group and no treatment group

	PAH therapy group		No treatment group	
	COPD (*n*=105)	**ILD (*n*=64)**	**COPD (*n*=464)**	**ILD (*n*=112)**
CCI score				
n	105	64	464	112
Mean (SD)	3.94 (2.23)	2.84 (1.52)	4.03 (2.69)	3.21 (2.19)
Median	4	2	3	3
Min–max	1.0–13.0	1.0–9.0	0.0–15.0	0.0–12.0
IQR (25%–75%)	3.0 (2.0–5.0)	2.0 (2.0–4.0)	3.0 (2.0–5.0)	2.0 (2.0–4.0)
Missing	0	0	0	0
CCI score category (*n*, %)				
n	105	64	464	112
0	0 (0.00%)	0 (0.00%)	2 (0.43%)	5 (4.46%)
1	10 (9.52%)	10 (15.63%)	58 (12.50%)	22 (19.64%)
≥2	95 (90.48%)	54 (84.38%)	404 (87.07%)	85 (75.89%)
Missing	0	0	0	0
NYHA class (*n*, %)				
n	20	10	71	9
FC I	1 (5.00%)	0 (0.00%)	10 (14.08%)	0 (0.00%)
FC II	4 (20.00%)	1 (10.00%)	14 (19.72%)	3 (33.33%)
FC III	7 (35.00%)	6 (60.00%)	22 (30.99%)	2 (22.22%)
FC IV	5 (25.00%)	0 (0.00%)	21 (29.58%)	1 (11.11%)
Uncategorized	3 (15.00%)	3 (30.00%)	4 (5.63%)	3 (33.33%)
Missing	85	54	393	103

CCI Charlson Comorbidity Index, *COPD* chronic obstructive pulmonary disease, *FC* functional class, *ILD* interstitial lung disease, *IQR* interquartile range, *n* number of patients, *NYHA* New York Heart Association, *PAH* pulmonary arterial hypertension, *SD* standard deviation

Data Analysis

Patient data were analyzed for baseline characteristics, treatment profiles, and clinical outcomes. The analyses conducted throughout the study were primarily descriptive in nature and were performed using R version 4.1.0 or higher. The only missing data was from the laboratory values which are labeled in the tables and were excluded. No attempts at imputation were made.

Descriptive statistics were summarized for demographics, baseline clinical characteristics, and the outcomes of interest. Frequencies and percentages were reported as categorical variables, while means, standard deviations (SDs), medians, minimum and maximum values, 25th and 75th percentile values, and interquartile

Table 4 Treatment patterns of PAH-specific therapies for all patients with CLD

Treatment patterns	COPD (*n* = 105)	ILD (*n* = 64)
Index treatment (first 90 days)		
n	105	64
n of patients who ceased PAH-specific treatments or were censored according to the 90 days observation period	0	0
Mono	89 (84.76%)	49 (76.56%)
Double	10 (9.52%)	11 (17.19%)
Triple or more	6 (5.71%)	4 (6.25%)
No treatment	0 (0.00%)	0 (0.00%)
Bosentan hydrate (oral)	11 (10.48%)	6 (9.38%)
Ambrisentan (oral)	2 (1.90%)	2 (3.12%)
Macitentan (oral)	9 (8.57%)	13 (20.31%)
Sildenafil citrate (oral)	25 (23.81%)	20 (31.25%)
Tadalafil (oral)	25 (23.81%)	20 (31.25%)
Beraprost sodium (oral)	46 (43.81%)	21 (32.81%)
Epoprostenol sodium (injection)	0 (0.00%)	0 (0.00%)
Treprostinil (injection)	0 (0.00%)	0 (0.00%)
Iloprost (inhalation)	0 (0.00%)	0 (0.00%)
Selexipag (oral)	6 (5.71%)	2 (3.12%)
Riociguat (oral)	4 (3.81%)	2 (3.12%)
1 year from the index date (the last 90 days)		
n	44	33
n of patients who ceased PAH-specific treatments or were censored according to the 90 days observation period	61	31
Mono	26 (59.09%)	18 (54.55%)
Double	3 (6.82%)	4 (12.12%)
Triple or more	5 (11.36%)	5 (15.15%)
No treatment	10 (22.73%)	6 (18.18%)
Bosentan hydrate (oral)	3 (6.82%)	3 (9.09%)
Ambrisentan (oral)	1 (2.27%)	1 (3.03%)
Macitentan (oral)	6 (13.64%)	8 (24.24%)
Sildenafil citrate (oral)	10 (22.73%)	4 (12.12%)
Tadalafil (oral)	10 (22.73%)	13 (39.39%)

Table 4 continued

Treatment patterns	COPD ($n=105$)	ILD ($n=64$)
Beraprost sodium (oral)	11 (25.00%)	10 (30.30%)
Epoprostenol sodium (injection)	0 (0.00%)	0 (0.00%)
Treprostinil (injection)	0 (0.00%)	0 (0.00%)
Iloprost (inhalation)	0 (0.00%)	0 (0.00%)
Selexipag (oral)	4 (9.09%)	1 (3.03%)
Riociguat (oral)	2 (4.55%)	1 (3.03%)
2 years from the index date		
n	24	16
n of patients who ceased PAH-specific treatments or were censored according to the 90 days observation period	81	48
Mono	14 (58.33%)	7 (43.75%)
Double	1 (4.17%)	3 (18.75%)
Triple or more	3 (12.50%)	2 (12.50%)
No treatment	6 (25.00%)	4 (25.00%)
Bosentan hydrate (oral)	1 (4.17%)	3 (18.75%)
Ambrisentan (oral)	0 (0.00%)	1 (6.25%)
Macitentan (oral)	4 (16.67%)	3 (18.75%)
Sildenafil citrate (oral)	6 (25.00%)	0 (0.00%)
Tadalafil (oral)	4 (16.67%)	6 (37.50%)
Beraprost sodium (oral)	6 (25.00%)	6 (37.50%)
Epoprostenol sodium (injection)	0 (0.00%)	0 (0.00%)
Treprostinil (injection)	0 (0.00%)	0 (0.00%)
Iloprost (inhalation)	0 (0.00%)	0 (0.00%)
Selexipag (oral)	2 (8.33%)	1 (6.25%)
Riociguat (oral)	2 (8.33%)	0 (0.00%)
3 years from the index date		
n	10	9
n of patients who ceased PAH-specific treatments or were censored according to the 90 days observation period	95	55
Mono	6 (60.00%)	3 (33.33%)
Double	1 (10.00%)	3 (33.33%)
Triple or more	3 (30.00%)	1 (11.11%)

Table 4 continued

Treatment patterns	COPD ($n=105$)	ILD ($n=64$)
No treatment	3 (30.00%)	2 (22.22%)
Bosentan hydrate (oral)	0 (0.00%)	2 (22.22%)
Ambrisentan (oral)	0 (0.00%)	1 (11.11%)
Macitentan (oral)	1 (10.00%)	2 (22.22%)
Sildenafil citrate (oral)	1 (10.00%)	0 (0.00%)
Tadalafil (oral)	3 (30.00%)	3 (33.33%)
Beraprost sodium (oral)	3 (30.00%)	3 (33.33%)
Epoprostenol sodium (injection)	0 (0.00%)	0 (0.00%)
Treprostinil (injection)	0 (0.00%)	0 (0.00%)
Iloprost (inhalation)	0 (0.00%)	0 (0.00%)
Selexipag (oral)	0 (0.00%)	1 (11.11%)
Riociguat (oral)	1 (10.00%)	0 (0.00%)
4 years from the index date		
n	4	5
n of patients who ceased PAH-specific treatments or were censored according to the 90 days observation period	101	59
Mono	3 (75.00%)	2 (40.00%)
Double	1 (25.00%)	2 (40.00%)
Triple or more	0 (0.00%)	1 (20.00%)
No treatment	0 (0.00%)	1 (20.00%)
Bosentan hydrate (oral)	0 (0.00%)	2 (40.00%)
Ambrisentan (oral)	0 (0.00%)	1 (20.00%)
Macitentan (oral)	1 (25.00%)	0 (0.00%)
Sildenafil citrate (oral)	0 (0.00%)	0 (0.00%)
Tadalafil (oral)	2 (50.00%)	1 (20.00%)
Beraprost sodium (oral)	1 (25.00%)	2 (40.00%)
Epoprostenol sodium (injection)	0 (0.00%)	0 (0.00%)
Treprostinil (injection)	0 (0.00%)	0 (0.00%)
Iloprost (inhalation)	0 (0.00%)	0 (0.00%)
Selexipag (oral)	1 (25.00%)	0 (0.00%)
Riociguat (oral)	1 (25.00%)	0 (0.00%)
5 years from the index date		

Table 4 continued

Treatment patterns	COPD ($n=105$)	ILD ($n=64$)
n	3	2
n of patients who ceased PAH-specific treatments or were censored according to the 90 days observation period	102	62
Mono	2 (66.67%)	1 (50.00%)
Double	1 (33.33%)	1 (50.00%)
Triple or more	0 (0.00%)	0 (0.00%)
No treatment	0 (0.00%)	0 (0.00%)
Bosentan hydrate (oral)	0 (0.00%)	0 (0.00%)
Ambrisentan (oral)	0 (0.00%)	1 (50.00%)
Macitentan (oral)	1 (33.33%)	1 (50.00%)
Sildenafil citrate (oral)	0 (0.00%)	0 (0.00%)
Tadalafil (oral)	2 (66.67%)	0 (0.00%)
Beraprost sodium (oral)	1 (33.33%)	1 (50.00%)
Epoprostenol sodium (injection)	0 (0.00%)	0 (0.00%)
Treprostinil (injection)	0 (0.00%)	0 (0.00%)
Iloprost (inhalation)	0 (0.00%)	0 (0.00%)
Selexipag (oral)	1 (33.33%)	0 (0.00%)
Riociguat (oral)	0 (0.00%)	0 (0.00%)

CLD chronic lung disease, *COPD* chronic obstructive pulmonary disease, *ILD* interstitial lung disease, *n* number of patients, *PAH* pulmonary arterial hypertension

ranges (IQRs) were reported as continuous variables.

PAH-specific therapies were described as combination subgroups of PAH-specific therapies (mono/double/triple), their utilization, and concomitant diuretic use for the initial treatment (0–90 days from the index date) and at 1–5 years (the last 90 days for each timepoint). Sankey diagrams were used to visualize treatment patterns over 5 years for PAH-specific therapies. All PAH-specific therapies administered during the initial treatment (or the last 90 days for each timepoint, after the 90-day initial treatment period) were composed of one of the combination therapies. The number of patients who ceased PAH-specific treatment or dropped out from the cohort for each 90-day observation period was reported in the "*n* of patients ceased PAH-specific treatments or censored by the 90-day observation period" variable.

Inferential analysis was conducted to estimate the factors associated with PH diagnosis using a multivariate Cox proportional hazard model. The starting point for the analysis was identified by the index date (the time of diagnosis of COPD/ILD) and the end point was the diagnosis of PH. The onset of CLD was confirmed retroactively to estimate the factors associated with PH diagnosis. The potential

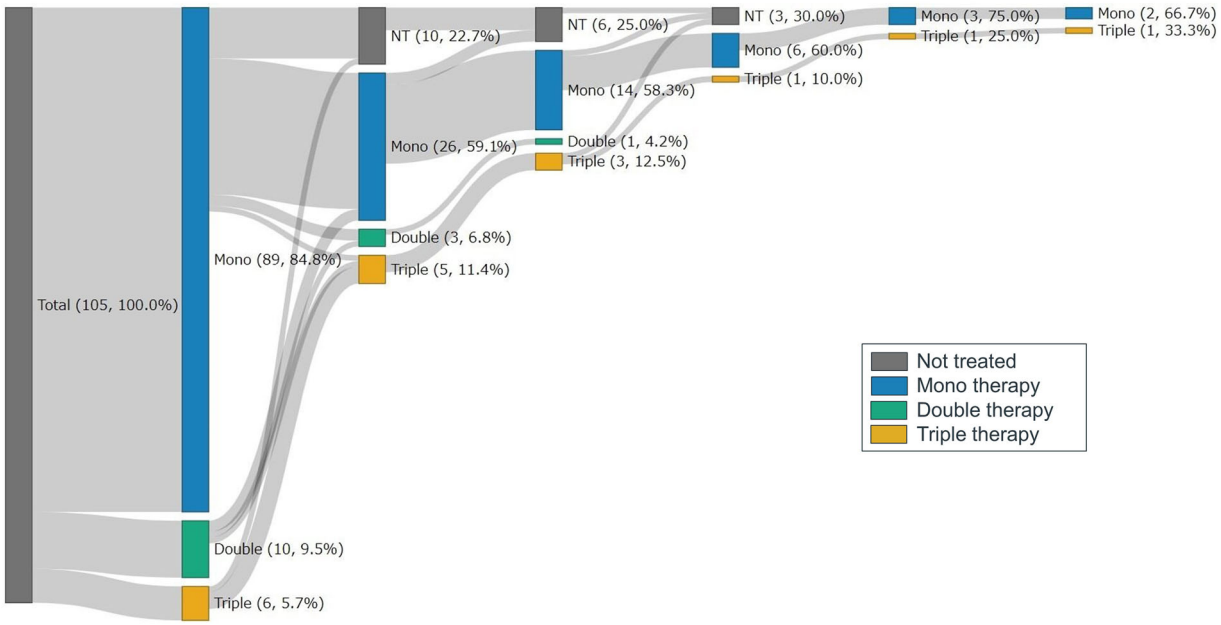

Fig. 3 Sankey diagram representing PAH-specific combination treatment pattern of population with COPD. This figure represents patient flows of PAH-specific combination patterns for the overall population with COPD from the baseline (first PAH medication) to the 90-day period after 5 years from the index date. Each node (Mono/Double/Triple/Not treated) represents the PAH-specific treatment combinations during baseline (90 days) and the last 90-day period after 1–5 years from the index date. The size of the nodes represents the proportion of patients in each 90-day period. In the parentheses, the first number is the number of patients and the second is the percentage of patients out of the total. *COPD* chronic obstructive pulmonary disease, *PAH* pulmonary arterial hypertension

factors (explanatory variables) for each model were determined with assistance from clinical experts in the field. Firth's penalized likelihood was applied in both analyses to mitigate the bias caused by rare events in the dataset if complete separation was detected [21].

Compliance with Ethics Guidelines

This retrospective database analysis study did not collect, transmit, or use identifiable patient data. Based on the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects, this study did not require any approval from an institutional review board. Permission was obtained from the MDV database for the use of their data for this study.

RESULTS

Demographic and Clinical Characteristics

As the study focused on whether PAH-specific therapies were prescribed at least once (PAH therapy group) or not (no treatment group), the demographics (Table 1) and clinical characteristics (Tables 2 and 3) of these patients were studied and compared. Overall, 109,578 patients with COPD and 6343 patients with ILD were included in the analysis. Patients with COPD in the PAH therapy group had a mean (SD) age of 75.19 (8.80) years and 83.81% were male, while those in the no treatment group had a mean (SD) age of 77.25 (8.55) years and 82.54% were male. Patients with ILD who were in the PAH therapy group had a mean (SD) age of 69.13 (13.01) years and 67.19% were male, while those in the no treatment group had a

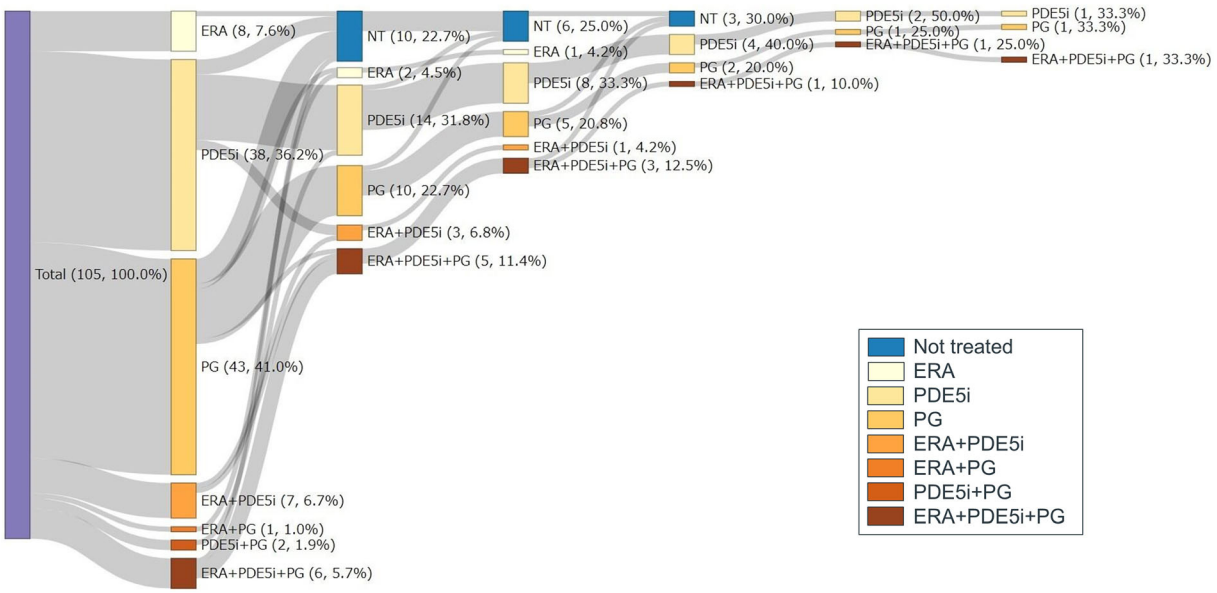

Fig. 4 Sankey diagram representing drug classes for treatment of population with COPD. This figure represents patient flows of PAH-specific therapeutic categories for the COPD population from the baseline (first PAH medication) to the 90-day period after 5 years from the index date. Each node represents the PAH-specific therapeutic categories during baseline (90 days) and the last 90-day period after 1–5 years from the index date. The size of the nodes represents the proportion of patients in each 90-day period. In the parentheses, the first number is the number of patients and the second is the percentage of patients out of the total. *ERA* endothelin receptor antagonist, *NT* not treated, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase 5 inhibitor, *PG* oral prostaglandin

mean (SD) age of 73.63 (8.27) years and 78.57% were male.

Patients with CLD also received different tests for the diagnosis of PH. Patients with COPD in the PAH therapy group had a higher rate of RHC when compared with the no treatment group (37.14% vs 19.18%, respectively). This trend remained true for the ILD group, where patients in the PAH therapy group also had a higher rate of RHC compared to the no treatment group (37.50% vs 16.07%, respectively). The usage rate of ECG was high across all groups (>90%). The results related to comorbidities can be found in Table 2.

The demographic and clinical characteristics of patients who underwent RHC were compared with patients who did not undergo RHC (PAH therapy group, Table S5; no treatment group, Table S6). Although there were some differences in specific categories, the overall characteristics were comparable between the two patient groups.

Treatment Patterns of PAH-Specific Therapies

Treatment patterns were analyzed both independently and together for patients with COPD and patients with ILD (Table 4 and Table S7, respectively), and for patients with CLD as a whole (Figs. S5 and S6). Monotherapy was the most used treatment among patients with COPD (58.33–84.76%, depending on data collection period), compared to those patients receiving double (4.17–33.33%) and triple therapies (0.00–30.00%), as shown in Fig. 3 and Table 4. During the follow-up period, most patients who were initially treated with PAH-specific monotherapy stayed on monotherapy, and a few patients were de-escalated (i.e., triple to double, double to mono, and triple to monotherapy). During the initial treatment, oral prostaglandin (PG, 40.96%) was the most common PAH-specific therapy, followed by phosphodiesterase 5 inhibitor (PDE5i)

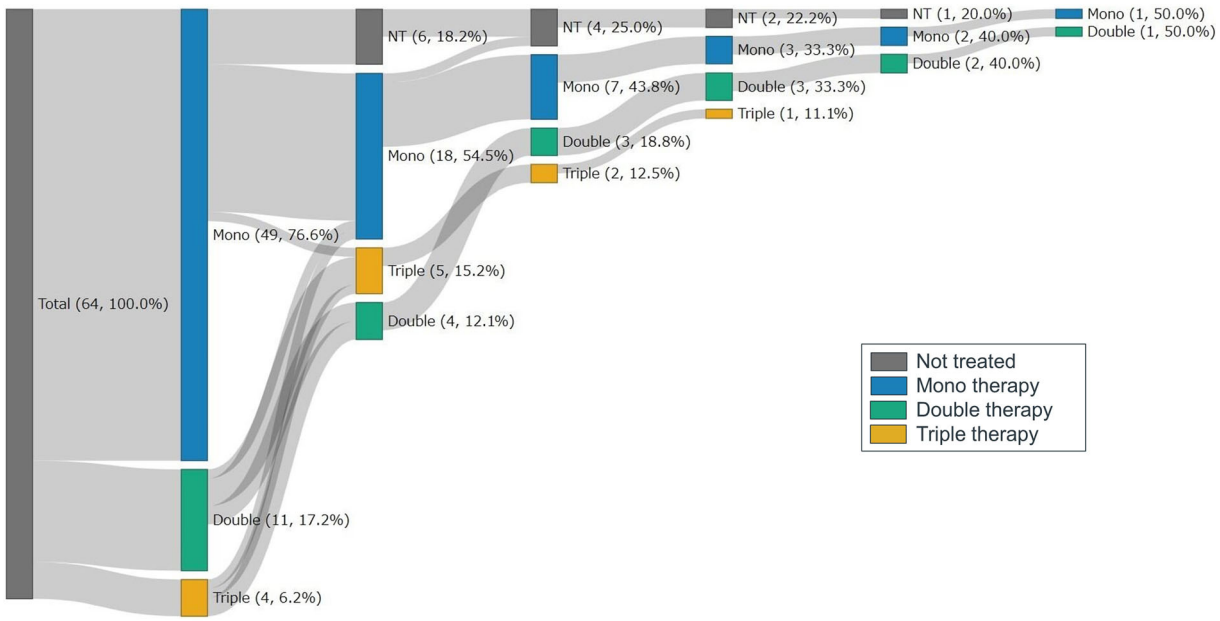

Fig. 5 Sankey diagram representing PAH-specific combination treatment pattern of population with ILD. This figure represents patient flows of PAH-specific combination patterns for the overall population with ILD from the baseline (first PAH medication) to the 90-day period after 5 years from the index date. Each node (Mono/Double/Triple/Not treated) represents the PAH-specific combinations during baseline (90 days) and the last 90-day period after 1–5 years from the index date, respectively. The size of the nodes represents the proportion of patients in each 90-day period. In the parentheses, the first number is the number of patients and the second is the percentage of patients out of the total. *ILD* interstitial lung disease, *NT* not treated, *PAH* pulmonary arterial hypertension

monotherapy (36.19%) (Fig. 4). Throughout the follow-up period, PDE5i was the most frequently used PAH-specific therapy (31.82–50.00%), followed by oral PG (20.00–40.96%). Most patients who stopped PAH-specific treatment did not restart it throughout the follow-up period.

Monotherapy was the most commonly used PAH-specific treatment (33.33–76.56%) among patients with ILD throughout the observational period (Table 4, Fig. 5). The most common PAH-specific therapy used during the initial treatment was PDE5i monotherapy (43.75% of the overall population), followed by oral PG (18.75%) and ERA monotherapy (14.06%) (Fig. 6). During the follow-up period, PDE5i monotherapy was the most common PAH-specific therapeutic category at 1 and 2 years after the initial treatment (33.33% and 18.75% of patients, respectively), while ERA+oral PG double combination therapy was more common after 3 years from initial treatment (22.22–50.00%).

For the COPD and ILD populations, 22.22–66.67% of the patients with group 1 PH received concomitant diuretics, with loop diuretics being commonly administered throughout the follow-up period (Table S8).

Factors Associated with Diagnosis of PH

In this study, simple and multiple Cox regression analyses were performed to understand the factors associated with the diagnosis of PH (Tables 5 and 6). The simple Cox regression observed differences in hazard ratios based on differences in diagnostic methods and disease background. The multiple Cox regression model also showed factors associated with the diagnosis of COPD with higher hazard ratios (HRs) for HOT and ECHO (HR 3.501 [$p<0.001$] and 3.955 [$p<0.001$], respectively) compared with

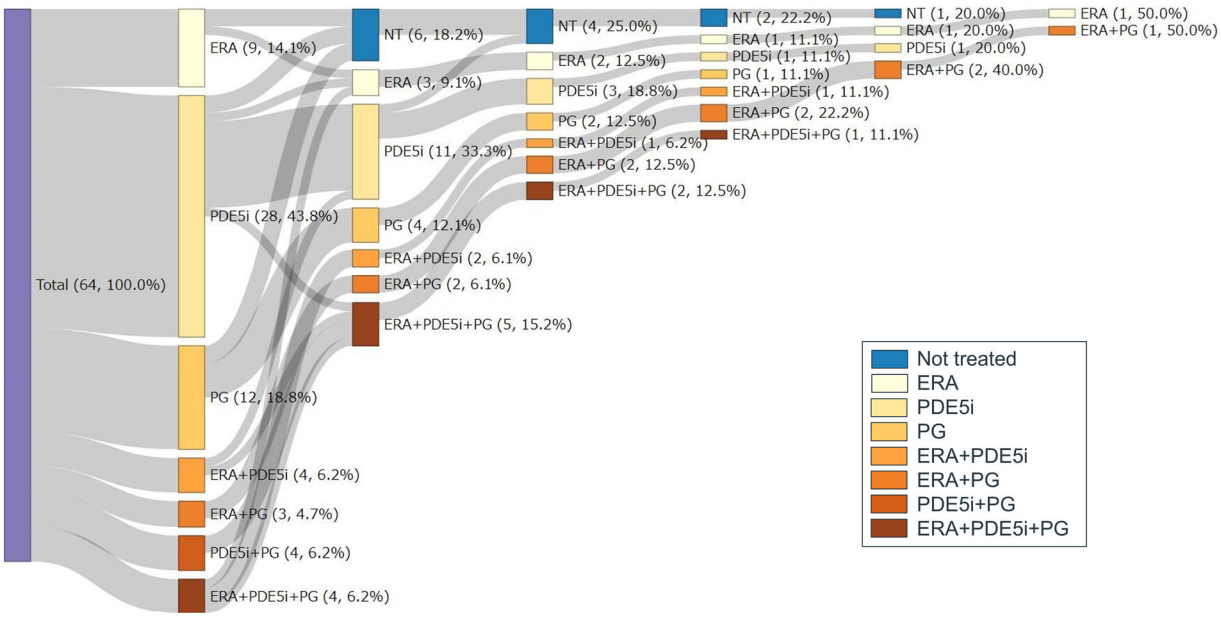

Fig. 6 Sankey diagram representing drug classes for treatment of population with ILD. This Sankey diagram represents patient flows of PAH-specific therapeutic categories for the ILD population from the baseline (first PAH medication) to the 90-day period after 5 years from the index date. Each node represents the PAH-specific therapeutic categories during baseline (90 days) and the last 90-day period after 1–5 years from the index date, respectively. The size of the nodes represents the proportion of patients in each 90-day period. In the parentheses, the first number is the number of patients and the second is the percentage of patients out of the total. *ERA* endothelin receptor antagonist, *NT* not treated, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase 5 inhibitor, *PG* oral prostaglandin

ILD (HR 2.898 [p=0.010] and 2.384 [p=0.002], respectively), indicating a statistical significance of these factors in the diagnosis of COPD ($p<$ 0.001). All values from the COPD simple Cox regression model shown in Table 5 were significant; however, only malignancy, HOT, pulmonary gas distribution test, and ECHO were significant for the multiple Cox model (Table 6).

Comparison of Demographic Characteristics of Cohort Subgroups

The patients in the study were categorized as patients receiving a PAH-specific therapy (cohort A) and the no treatment group (cohort B); their demographics were compared to analyze the characteristics of the patients receiving PAH-specific therapy (for at least 6 months) versus those who were not (Table 7). Among the patients with COPD, cohort B consisted of patients older than those in cohorts A-1 and A-2 (mean age of 77.25 [8.55], 73.76 [8.79], and 76.85 [8.01] years, respectively). Cohort B also had a higher percentage of patients with smoking history (64.56%) than cohorts A-1 (55.17%) and A-2 (36.36%). There was also a statistically significant difference found in HOT between the three cohorts.

Among the patients with ILD, those in cohort B were older than those in cohorts A-1 and A-2 (mean ages of 73.63 [8.27], 68.37 [14.49], and 70.00 [12.05] years, respectively). Patients in both cohorts A and B with COPD and ILD were predominantly male (57.14–100%). There were differences in the complication rates among cohorts A-1, A-2, and B for CTD (45.71%, 25.00%, and 11.61%, respectively), and arrhythmia (2.86%, 0.00%, and 20.54%, respectively). The laboratory data comparison of these cohorts is presented in Table S4.

Table 5 Factors associated with diagnosis of PH in patients with COPD and patients with ILD, simple Cox regression

CLD	All patients	Patients with disease	Patients with PH onset	Disease	HR	SE	*p* value
COPD	34,467	2699	39	CKD	1.899	0.172	<0.001***
		2701	43	Valvular diseases	1.908	0.165	<0.001***
		6644	90	Arrhythmia	1.811	0.126	<0.001***
		15,914	103	Malignancy	0.629	0.121	<0.001***
		2020	26	Thyroid disease	1.502	0.205	0.047*
		671	12	CTD	2.123	0.295	0.011*
		1675	44	HOT	4.116	0.164	<0.001***
		33,253	300	CT	6.299	0.710	0.009**
		610	18	Pulmonary gas distribution test	3.362	0.243	<0.001***
		3570	45	Alveolar function tests (dead space volume test, pulmonary diffusing capacity test, pulmonary shunt test)	1.464	0.162	0.018*
		14,169	224	ECHO	4.401	0.132	<0.001***
		23,715	245	ECG	1.899	0.172	<0.001***
ILD	1971	83	5	CKD	2.768	0.470	0.030*
		128	8	CTD	2.534	0.383	0.015*
		113	7	HOT	3.528	0.408	0.002**
		602	27	ECHO	2.734	0.273	<0.001***

CKD chronic kidney disease, *CLD* chronic lung disease, *CT* computed tomography, *CTD* connective tissue disease, *COPD* chronic obstructive pulmonary disease, *ECG* electrocardiography, *ECHO* echocardiography, *HOT* home oxygen therapy, *HR* hazard ratio, *ILD* interstitial lung disease, *PH* pulmonary hypertension, *SE* standard error
*$p<0.05$, **$p<0.01$, ***$p<0.001$

DISCUSSION

Demographic and Clinical Characteristics of Patients with PH in CLDs

As the first nationwide database study on patients with PH in CLD in Japan, our study allows for the comparison of clinical characteristics with studies from Western countries. The estimated nationwide prevalence of idiopathic pulmonary fibrosis, a common type of ILD, as per the MDV database (2008–2019) was 27 per 100,000 population of Japan, which was similar for men in the USA. On the other hand, the prevalence was lower in Japanese women aged< 79 years [22] compared with earlier studies (10 per 100,000 population) [23]. Japan had previously reported around 16–60% of patients with COPD-related PH [24]. However, this study reports much lower PH diagnosis rates among patients with COPD and ILD (0.87% and 1.79%, respectively) compared with previous reports [6, 14, 25], implying that patients may be underdiagnosed and/or misdiagnosed with other diseases. The difference in diagnosis rate may also stem from this being the first study to investigate the prevalence of PH based on COPD and ILD in Japan using a nationwide

Table 6 Factors associated with diagnosis of PH in patients with COPD and patients with ILD, multiple Cox regression

CLD	All patients	Patients with PH onset	Factor	HR	SE	*p* value
COPD	34,467	302	CKD	1.352	0.174	0.083
			Valvular diseases	1.133	0.171	0.465
			Arrhythmia	1.244	0.132	0.097
			Malignancy	0.588	0.123	<0.001***
			Thyroid disease	1.203	0.209	0.376
			CTD	1.760	0.298	0.058
			HOT	3.474	0.165	<0.001***
			CT	4.015	0.715	0.052
			Pulmonary gas distribution test	2.988	0.285	<0.001***
			Alveolar function tests (dead space volume test, pulmonary diffusing capacity test, pulmonary shunt test)	1.061	0.190	0.755
			ECHO	3.952	0.152	<0.001***
			ECG	0.915	0.169	0.599
ILD	1971	55	CKD	2.447	0.472	0.058
			CTD	2.394	0.385	0.023*
			HOT	2.898	0.412	0.010**
			ECHO	2.384	0.277	0.002**

CKD chronic kidney disease, *CLD* chronic lung disease, *CTD* connective tissue disease, *COPD* chronic obstructive pulmonary disease, *ECG* electrocardiography, *ECHO* echocardiography, *HOT* home oxygen therapy, *HR* hazard ratio, *ILD* interstitial lung disease, *PH* pulmonary hypertension, *SE* standard error
*$p<0.05$, **$p<0.01$, ***$p<0.001$

administrative database that reflects the clinical practices in both referral centers and non-referral hospitals, while previous reports mainly focused on referral centers. It is also suggested that proper diagnosis of PH including group 1 PH, a rare disease, requires expertise such as from referral centers.

Our results demonstrated that even in the PAH therapy group (patients receiving PAH-specific medication), RHC was only performed approximately 37% of the time at diagnosis. Proper training about rare diseases such as group 1 PH and the use of the appropriate diagnostic procedures are required among health professionals, especially general practitioners, so that patients can be appropriately referred to a specialist/cardiologist for RHC [26]. Poor general awareness regarding these rare diseases, delays in referrals, misdiagnoses, and poor compliance to the treatment guidelines may lead to worse prognoses [27]. Our analysis suggests that in the clinical practice of respiratory medicine, which mainly treats CLDs, there are still many barriers to the diagnosis and management of patients with PH in CLD, and there is a need to improve the time to referral, diagnosis, and initiation of treatment.

With regards to demographics of patients with PH, our study population was characterized by higher proportions of elderly patients

Table 7 Comparison of demographics and clinical characteristics of patients with COPD and ILD cohort subgroups

	COPD			ILD		
	Cohort A-1 (*n*=42)	**Cohort A-2 (*n*=20)**	**Cohort B (*n*=464)**	**Cohort A-1 (*n*=35)**	**Cohort A-2 (*n*=12)**	**Cohort B (*n*=112)**
Age at index date						
n	42	20	464	35	12	112
Mean (SD)	73.76 (8.79)	76.85 (8.01)	77.25 (8.55)	68.37 (14.49)	70.0 (12.05)	73.63 (8.27)
Median	75.50	77.50	78.00	72.00	72.50	74.50
Min–max	47–88	58–88	49–96	21–89	43–82	38–91
IQR (25%–75%)	9.0 (70.00–79.00)	8.5 (74.00–82.50)	12.0 (72.00–84.00)	9.00 (67.50–76.50)	14.5 (65.50–80.0)	7.25 (70.75–78.00)
Missing	0	0	0	0	0	0
Age group at index date (*n*, %)						
n	42	20	464	35	12	112
15–64 years	5 (11.90%)	2 (10.00%)	35 (7.54%)	7 (20.00%)	3 (25.00%)	13 (11.61%)
65–74 years	11 (26.19%)	3 (15.00%)	132 (28.45%)	15 (42.86%)	4 (33.33%)	43 (38.39%)
≥75 years	26 (61.90%)	15 (75.00%)	297 (64.01%)	13 (37.14%)	5 (41.67%)	56 (50.00%)
Missing	0	0	0	0	0	0
Gender (*n*, %)						
n	42	20	464	35	12	112
Male	35 (83.33%)	20 (100.00%)	383 (82.54%)	20 (57.14%)	9 (75.00%)	88 (78.57%)
Female	7 (16.67%)	0 (0.00%)	81 (17.46%)	15 (42.86%)	3 (25.00%)	24 (21.43%)
Missing	0	0	0	0	0	0

Table 7 continued

	COPD			ILD		
	Cohort A-1 (*n*=42)	**Cohort A-2 (*n*=20)**	**Cohort B (*n*=464)**	**Cohort A-1 (*n*=35)**	**Cohort A-2 (*n*=12)**	**Cohort B (*n*=112)**
Smoking status (*n*, %)						
n	29	11	285	17	8	67
No	5 (17.24%)	5 (45.45%)	72 (25.26%)	6 (35.29%)	1 (12.50%)	26 (38.81%)
Yes	16 (55.17%)	4 (36.36%)	184 (64.56%)	9 (52.94%)	7 (87.50%)	34 (50.75%)
Unknown	8 (27.59%)	2 (18.18%)	29 (10.18%)	2 (11.76%)	0 (0.00%)	7 (10.45%)
Missing	13	9	179	18	4	45
BMI						
n	28	11	274	17	8	67
Mean (SD)	21.66 (5.57)	21.21 (4.61)	21.1 (4.24)	22.41 (3.64)	24.33 (4.14)	22.11 (4.38)
Median	22.11126	20.48765	20.70626	22.09671	23.67908	22.85377
Min–max	0.0–32.23	14.56–30.42	12.23–47.34	17.10–29.35	18.83–31.24	0.0–32.01
IQR (25%–75%)	4.21 (20.19–24.40)	3.76 (18.91–22.67)	4.95 (18.62–23.57)	3.66 (20.28–23.94)	4.48 (21.67–26.15)	4.38 (20.39–24.77)
Missing	14	9	190	18	4	45
Comorbidity (*n*, %)						
Systemic arterial hypertension	21 (50.00%)	13 (65.00%)	276 (59.48%)	13 (37.14%)	5 (41.67%)	57 (50.89%)
Dyslipidemia	16 (38.10%)	9 (45.00%)	134 (28.88%)	10 (28.57%)	3 (25.00%)	34 (30.36%)
Diabetes mellitus	15 (35.71%)	9 (45.00%)	161 (34.70%)	12 (34.29%)	5 (41.67%)	45 (40.18%)
Chronic kidney disease	4 (9.52%)	5 (25.00%)	67 (14.44%)	2 (5.71%)	0 (0.00%)	10 (8.93%)

Table 7 continued

	COPD			ILD		
	Cohort A-1 (*n*=42)	**Cohort A-2 (*n*=20)**	**Cohort B (*n*=464)**	**Cohort A-1 (*n*=35)**	**Cohort A-2 (*n*=12)**	**Cohort B (*n*=112)**
Coronary artery disease	18 (42.86%)	9 (45.00%)	147 (31.68%)	7 (20.00%)	4 (33.33%)	31 (27.68%)
Left heart failure	1 (2.38%)	0 (0.00%)	11 (2.37%)	2 (5.71%)	0 (0.00%)	3 (2.68%)
Valvular disease	1 (2.38%)	2 (10.00%)	81 (17.46%)	2 (5.71%)	0 (0.00%)	7 (6.25%)
Arrhythmia	13 (30.95%)	5 (25.00%)	150 (32.33%)	1 (2.86%)	0 (0.00%)	23 (20.54%)
Sleep apnea	1 (2.38%)	0 (0.00%)	13 (2.80%)	0 (0.00%)	0 (0.00%)	3 (2.68%)
Malignancy	10 (23.81%)	7 (35.00%)	156 (33.62%)	7 (20.00%)	3 (25.00%)	33 (29.46%)
Thyroid disease	5 (11.90%)	2 (10.00%)	34 (7.33%)	2 (5.71%)	2 (16.67%)	5 (4.46%)
Obesity	0 (0.00%)	0 (0.00%)	4 (0.86%)	0 (0.00%)	0 (0.00%)	1 (0.89%)
CTD	4 (9.52%)	1 (5.00%)	18 (3.88%)	16 (45.71%)	3 (25.00%)	13 (11.61%)
Lung cancer	4 (9.52%)	1 (5.00%)	46 (9.91%)	1 (2.86%)	0 (0.00%)	11 (9.82%)
CCI score						
n	42	20	464	35	12	112
Mean (SD)	3.71 (2.23)	4.4 (2.21)	4.03 (2.69)	3.2 (1.69)	2.17 (0.83)	3.21 (2.19)
Median	3	4	3	3	2	3
Min–max	1.0–10.0	2.0–8.0	0.0–15.0	1.0–9.0	1.0–4.0	0.0–12.0
IQR (25%–75%)	3.0 (2.0–5.0)	4.0 (2.0–6.0)	3.0 (2.0–5.0)	2.0 (2.0–4.0)	0.25 (2.0–2.25)	2.0 (2.0–4.0)
Missing	0	0	0	0	0	0
CCI score category (*n*, %)						
n	42	20	464	35	12	112

Table 7 continued

	COPD			ILD		
	Cohort A-1 (*n*=42)	**Cohort A-2 (*n*=20)**	**Cohort B (*n*=464)**	**Cohort A-1 (*n*=35)**	**Cohort A-2 (*n*=12)**	**Cohort B (*n*=112)**
0	0 (0.00%)	0 (0.00%)	2 (0.43%)	0 (0.00%)	0 (0.00%)	5 (4.46%)
1	7 (16.67%)	0 (0.00%)	58 (12.50%)	4 (11.43%)	2 (16.67%)	22 (19.64%)
≥ 2	35 (83.33%)	20 (100.00%)	404 (87.07%)	31 (88.57%)	10 (83.33%)	85 (75.89%)
Missing	0	0	0	0	0	0
NYHA class (*n*, %)						
n	12	2	71	7	1	9
FC I	1 (8.33%)	0 (0.00%)	10 (14.08%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
FC II	1 (8.33%)	0 (0.00%)	14 (19.72%)	1 (14.29%)	0 (0.00%)	3 (33.33%)
FC III	4 (33.33%)	1 (50.00%)	22 (30.99%)	5 (71.43%)	0 (0.00%)	2 (22.22%)
FC IV	3 (25.00%)	1 (50.00%)	21 (29.58%)	0 (0.00%)	0 (0.00%)	1 (11.11%)
Uncategorized	3 (25.00%)	0 (0.00%)	4 (5.63%)	1 (14.29%)	1 (100.00%)	3 (33.33%)
Missing	30	18	393	28	11	103
HOT						
Yes	29 (69.05%)	14 (70.00%)	213 (45.91%)	27 (77.14%)	11 (91.67%)	86 (76.79%)
Tests to diagnose PH						
CT (*n*, %)						
Yes	42 (100.00%)	20 (100.00%)	464 (100.00%)	35 (100.00%)	12 (100.00%)	112 (100.00%)
Close respiratory function test (*n*, %)						
All	38 (90.48%)	17 (85.00%)	352 (75.86%)	30 (85.71%)	11 (91.67%)	106 (94.64%)

Table 7 continued

	COPD			ILD		
	Cohort A-1 (*n* = 42)	**Cohort A-2 (*n* = 20)**	**Cohort B (*n* = 464)**	**Cohort A-1 (*n* = 35)**	**Cohort A-2 (*n* = 12)**	**Cohort B (*n* = 112)**
Spirographic examination	38 (90.48%)	17 (85.00%)	351 (75.65%)	30 (85.71%)	11 (91.67%)	106 (94.64%)
Ventilatory mechanical test	5 (11.90%)	1 (5.00%)	17 (3.66%)	0 (0.00%)	0 (0.00%)	8 (7.14%)
Pulmonary gas distribution test	0 (0.00%)	0 (0.00%)	28 (6.03%)	7 (20.00%)	2 (16.67%)	17 (15.18%)
Alveolar function tests (dead space volume test, pulmonary diffusing capacity test, pulmonary shunt test)	12 (28.57%)	2 (10.00%)	111 (23.92%)	18 (51.43%)	7 (58.33%)	65 (58.04%)
ECHO (*n*, %)						
Yes	22 (52.38%)	9 (45.00%)	214 (46.12%)	21 (60.00%)	5 (41.67%)	43 (38.39%)
ECG (*n*, %)						
Yes	41 (97.62%)	20 (100.00%)	442 (95.26%)	34 (97.14%)	12 (100.00%)	103 (91.96%)

BMI body mass index, *CCI* Charlson Comorbidity Index, *CT* computed tomography, *CTD* connective tissue disease, *COPD* chronic obstructive pulmonary disease, *ECG* electrocardiography, *ECHO* echocardiography, *FC* functional class, *HOT* home oxygen therapy, *ILD* interstitial lung disease, *IQR* interquartile range, *ILD* interstitial lung disease, *IQR* interquartile range, *n* number of patients, *NYHA* New York Heart Association, *PH* pulmonary hypertension, *SD* standard deviation
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

and male patients. For example, a registry study by Tanabe et al. [11] on patients with PH associated with respiratory disease had a population with a mean age of 67±11 years and was 70% male. Other studies using data extracted from the MDV database in Japan on patients with idiopathic pulmonary fibrosis and COPD also estimated a high percentage of elderly patients and a predominantly male population which is in line with our study [22, 28]. Our findings are consistent with studies using the COMPERA registry which involved elderly patients [6, 29, 30] as well as another recently published study using data from both the COMPERA and ASPIRE registries [30] which partially observed patients (patients with idiopathic pulmonary artery hypertension (IPAH) with a lung phenotype and patients with group 3 PH) with similar backgrounds to our study. The trends in our study population are aligned with these previous reports, suggesting that our study has properly identified patients with COPD and patients with ILD in Japan and may describe the real-world clinical practices for PH in these populations.

Treatment Patterns of PAH-Specific Therapies

The proportion of patients on PAH monotherapy in this study (84.76% for COPD and 76.56% for ILD during the initial treatment period) was markedly higher than that in a recent Japanese registry study, where the proportion of patients on oral/inhaled monotherapy was 23.1% and 20.3% between 2008–2015 and 2016–2020, respectively [13]. In contrast, most patients with IPAH with CLD received monotherapy [31], thus showing a similar trend to our study. The higher proportion of the patients in this study receiving monotherapy may indicate a preference for conservative treatments to avoid side effects in high-risk patients. Moreover, this study demonstrated that few patients were de-escalated in their treatments, which was also reported in previous studies [32, 33]. This suggests the underutilization of combination therapies, which have shown better adherence and lower discontinuation rates compared with monotherapy treatments [32]. The latest guidelines recommend initial monotherapy for patients with group 1 PH with cardiopulmonary comorbidities, followed by regular follow-up assessments and individualized therapies. In group 3 PH, if the patient has severe PH, an individualized treatment approach is recommended, but there is no consensus treatment strategy. In order to facilitate the development of new treatment options such as inhaled treprostinil [4, 5], further research is required to understand the patient backgrounds and physician perspectives regarding treatment strategies for PH.

A retrospective study using data from Japanese Respiratory Society (JRS)-approved institutions reported that 80% of patients with severe PH associated with respiratory diseases were treated with a PAH-specific therapy, especially PDE5i [34]; however, beraprost sodium was the most commonly used medication in our study. Moreover, the percentage of ERA usage was higher than expected with the third highest usage rate following PDE5i. The guidelines for the diagnosis and treatment of PH in Japan are prepared by the Japanese Circulation Society (JCS) and are based on ESC/ERS guidelines [35]. The latest guidelines released in 2022 will impact the JCS guidelines, which describe recommendations for PDE5i or ERA as initial monotherapy of group 1 PH with cardiopulmonary comorbidities [2]. Our findings may highlight the need to generate more evidence for PDE5i and ERA in these patients.

It is often difficult to differentiate between patients with group 1 and group 3 PH because of their overlapping characteristics. As a chronic disease, patients with group 1 PH typically require continuous treatment with a PAH-specific therapy. Therefore, it is possible that patients who received PAH-specific therapy for more than 6 months in this present study (cohort A-1) were patients with group 1 PH. On the other hand, patients who discontinued PAH-specific therapy within 6 months (cohort A-2) may have been identified as patients with group 1 PH at the initiation of treatment, but may have in fact been patients with group 3 PH who discontinued treatments because of the

negative effects of PAH-specific therapies on patients with group 3 PH [36, 37].

Patients with COPD taking PAH-specific therapies were generally treated with HOT, suggesting that PAH-specific therapies were being used for severe patients with COPD.

A lower proportion of patients with ILD were treated with HOT compared to patients with COPD, suggesting that patients with ILD had mild-to-moderate lung disease compared to those with COPD. When patients with mild-to-moderate ILD were diagnosed with group 1 PH and administered PAH-specific therapies, they tended to receive continuous treatment for over 6 months. Our results imply that the stage of disease at which PAH-specific therapy is prescribed may differ between COPD and ILD. Further research is needed on PH in each type of CLD.

Factors Associated with PH Diagnosis

This study showed that a lung disease diagnosis followed by active ECHO results in higher rates of PH diagnosis in both patients with COPD and patients with ILD. ECHO is readily accessible in Japanese clinical practice, and our results offer real-world data with further confirmation of its importance for PH diagnosis in Japan. Our multivariate analysis also indicated that CTD, including systemic sclerosis, was associated with the diagnosis of PH in patients with ILD. This is in agreement with the JRS guidelines [38]. RHC is still considered the gold standard for the hemodynamic evaluation of pulmonary circulation and should be performed in most patients diagnosed with PH to understand the severity of PH and initiate the appropriate treatment [39]. Even with a mild concomitant lung disease, the prognostic impact on patients with IPAH is significant [40].

In another study conducted by JRS-approved institutions, Tanabe et al. evaluated the status of diagnostic and treatment modalities in patients with PH with respiratory diseases [25]. It is important to note that although there are studies challenging the usage of ECHO for the diagnosis of PH [41–43], ECHO is used for both the determination of group 1 and group 3 PH in real-world practices both in Japan [25] and in other countries such as the Netherlands [44]. ECHO was used for diagnosis in 99% of the institutions, while RHC was used in only 36% of institutions with more than half of the pulmonologists considering RHC as only necessary prior to the initiation of a PAH-specific therapy. Despite this, PAH-specific therapies were used in 45% of the institutions, even without confirmation from RHC [25]. This discrepancy, along with the low usage of RHC, indicates the potential for under/misdiagnoses and suboptimal treatments for many patients and emphasizes the need for further studies.

As expected, HOT was shown to be a factor associated with the diagnosis of PH in both patients with COPD and patients with ILD. Since a diagnosis of PH in Japan is medically indicated for the initiation of HOT, our results are consistent with clinical practice.

Study Limitations

There are limitations to be considered in this study. (1) The MDV database predominantly comprises administrative claims data. Therefore, several key variables associated with the diagnosis, severity, and prognosis of PH overall or specifically group 1 PH were not available meaning the clinical classification of PH groups could not be fully assessed. Furthermore, lab-value data were limited to what was available in the database, meaning that data such as lung function testing (e.g., forced expiratory volume in 1 s [FEV1]) was not available as a measure of disease severity. (2) MDV data are limited to a small number of medical institutions in Japan; these institutions are subject to DPC and may not fully reflect the general population, and extrapolation outside of Japan should be approached with caution. In addition, clinical and drug treatment information received at medical institutions other than the target DPC hospitals cannot be obtained or tracked. (3) The use of claims data has limitations in patient identification (e.g., patients with PH or COPD/ILD in the insurance-based name of the disease). (4) This study included a small minority of patients with left-sided heart failure who may

have been difficult to categorize between groups 1, 2, and 3. (5) There may have been unmeasured confounding factors that may have influenced the results. (6) This study analyzed patients with group 3 and group 1 PH with CLDs together although there is likely overlap between the two populations as it was not possible to distinguish them on the basis of the available data. Further studies are needed to confirm the robustness of the findings of this study.

CONCLUSION

To our knowledge, this is the first study to describe the patient and treatment profiles of patients with PH in CLD using a Japanese nationwide administrative database. Considering the low diagnosis rates and high use of monotherapy in our study, it is possible that PH is being under/misdiagnosed in the real-world Japanese clinical setting. Thus, more accurate diagnostic methods for identifying patients with PH can lead to earlier treatment and improved outcomes. We emphasize the need for further evidence for early diagnosis, appropriate evaluation, and treatment of patients with PH in CLD.

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Data Availability. The datasets generated and/or analyzed during the current study are not publicly available due to the commercial nature of the data.

Declarations

Conflict of Interest. Kazuki Kitahara and Junichi Omura are employees of Janssen Pharmaceutical K.K. Shingo Wada and Seok-Won Kim have nothing to disclose.

Ethical Approval. This retrospective database analysis study did not collect, transmit, or use identifiable patient data. Based on the Japanese Ethical Guidelines for Medical and Biological Research Involving Human Subjects, this study did not require any approval from an institutional review board. Permission was obtained from the MDV database for the use of their data for this study.

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