



Current status of pulmonary rehabilitation and impact on prognosis of patients with idiopathic pulmonary fibrosis in South Korea

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Background: The benefits of pulmonary rehabilitation (PR) for patients with idiopathic pulmonary fibrosis (IPF) have been limited to improving dyspnea, exercise capacity, and quality of life (QoL). This study aimed to assess the current status of PR and its effect on prognosis.

Methods: The Nationwide Korean Health Insurance Review and Assessment Service (HIRA) database was used in this study. Annual PR implementation rate since 2016 following its coverage in the health insurance was analyzed. IPF cases were defined using the International Classification of Diseases 10th Revision (ICD-10) codes and rare intractable diseases (RID) codes. Risk of acute exacerbation (AE) and mortality of IPF patients with or without PR were analyzed.

Results: Of the 4,228 patients with IPF, only 205 (4.85%) received PR. Patients in the PR group were more frequently treated with pirfenidone and systemic steroids than non-PR group. In patients treated with steroids, mortality risk increased regardless of PR application, with hazard ratio (HR) of 1.63 [95% confidence interval (CI): 1.26–2.10, P<0.001] in the PR group and 1.38 (95% CI: 1.21–1.57, P<0.001) in the non-PR group, compared to those not treated with steroids. Additionally, PR did not significantly affect mortality risk in patients not receiving steroids (HR, 1.49, 95% CI: 0.87–2.54, P=0.15). Similar patterns were seen for the risk of AE.

Conclusions: PR was applied in only a minority of patients with IPF. It did not succeed in reducing the risk of AE or mortality. A prospective study targeting early-stage patients is needed to evaluate the impact of PR considering the progressive nature of IPF disease itself.

Keywords: Idiopathic pulmonary fibrosis (IPF); pulmonary rehabilitation (PR); exacerbation; mortality; nationwide cohort study

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common type of progressive fibrosing interstitial lung disease (ILD). It is characterized by restrictive lung physiology, which is predominantly observed in older adults usually in the sixth to eighth decades of life (1). The natural course of IPF is highly variable among individuals. The prognosis of IPF is very poor generally, with approximately 50% of patients dying within 2–3 years after diagnosis (2), which is worse than that of many malignancies (3). IPF is a disease with a chronic, progressive course. As the disease progresses, worsening of pulmonary function and dyspnea on exertion can result in hypoxia and reduce exercise tolerance, which are associated with limitations in daily activities, poor self-perceived quality of life (QoL), and increased morbidity and mortality (4–8).

Pulmonary rehabilitation (PR) has shown benefits in chronic lung diseases including ILD (9,10). Several studies have reported short-term benefits of PR in ILDs in terms of dyspnea, exercise capacity, and improvements in QoL (11–15). However, studies regarding long-term benefits of PR in ILDs on dyspnea, exercise capacity, and QoL status are limited (13,16). Beyond improvements in self-perceived health status, there has been a lack of studies and clear evidence about the effect of PR on objective outcomes such

as exacerbation risk and mortality in ILDs.

While some clinical trials have reported that the use of antifibrotics can slow down lung function decline and improve exacerbation and mortality in patients with IPF (17–19), there are unmet needs between incurable and poor prognosis of IPF and limited treatment strategies to improve outcomes. Consequently, both pharmacological and non-pharmacological treatment options are essential for improving the prognosis. As part of a non-pharmacological treatment, PR has gained interest. In South Korea, PR has been covered by health insurance since 2016. Subsequently, total claims for PR increased more than two-fold over the next 2 years (20). This enabled us to examine the relationship between PR and long-term clinical outcomes in patients with IPF through a nationwide database. In this study, we aimed to investigate current status of PR application in patients with IPF and analyze the impact of PR on prognosis, focusing on acute exacerbation (AE) and mortality. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-24-1165/rc>).

Methods

Data source and study population

The present study is a nationwide population-based retrospective cohort study using the Health Insurance Review and Assessment Service (HIRA) database. The HIRA database collects all claims from hospitals in Korea and evaluates their adequacy. Consequently, this database provides comprehensive information on all subscribers, including general demographics, type of medical center, diagnoses of inpatients and outpatients through the International Classification of Diseases 10th Revision (ICD-10), prescribed medications, and medical costs.

IPF was defined based on both ICD-10 codes for IPF (J84.1 or J84.18) and the rare intractable diseases (RID) code V236. The diagnosis and management of IPF necessitates a multidisciplinary approach. As a result, we only included data from referral hospitals. For the diagnosis of IPF, chest computed tomography (CT) is a fundamental requirement for identifying usual interstitial pneumonia (UIP) pattern suggestive of IPF and evaluating the extent of lung parenchymal involvement. Moreover, pulmonary function tests are essential for evaluating functional impairment due to IPF and need for insurance coverage for the use of antifibrotic agents in Korea. Therefore, only patients who underwent

Highlight box

Key findings

- Pulmonary rehabilitation (PR) did not significantly affect both mortality and acute exacerbation (AE) risk in patients with idiopathic pulmonary fibrosis (IPF).

What is known, and what is new?

- Current guidelines for IPF endorse PR as an effective and safe non-pharmacological intervention, though its long-term benefits lack despite clear short-term benefits.
- In this nationwide cohort study, only 4.85% IPF patients received PR, likely indicating more severe disease treated with more antifibrotic agent and systemic steroids. The risk of AE and mortality was higher in patients receiving steroids, while PR itself had no significant effect on outcomes in either group, regardless of steroid use.

What is the implication, and what should change now?

- The PR implementation rate was low and primarily applied to patients with more severe cases of IPF.
- Timely identification and intervention to explore the efficacy of PR in individuals with less severe and at earlier-stages patients can lead to improve outcome.

both chest CT and pulmonary function test within a year prior to their diagnosis were included (Figure S1). Furthermore, to clarify the definition of IPF, other forms of ILD were excluded (Table S1). The Institutional Review Board (IRB) of Seoul St. Mary's Hospital approved the study protocol (No. KC22ZASE0545) and waived the need for informed consent due to the retrospective nature of this study. The study was performed in accordance with the principles of the Declaration of Helsinki (as revised in 2013) concerning the ethical principles for medical research.

Implementation rate of PR

Patients who received PR were tracked using prescription code MM440 (rehabilitation exercise for pulmonary disease). Information regarding PR was collected from 2016 to 2020, as PR has been covered by national insurance since 2016. Under insurance policies of South Korea described in Table S2, PR is intended for patients with chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, lung cancer, and ILD who experience shortness of breath or difficulties in daily activities due to respiratory symptoms. Doctors prescribe a PR program for these patients, considering each patient's exercise capacity, degree of breathlessness, and comorbidities. The PR program consisted of approximately 60 minutes of aerobic and muscle strength training. The cost per PR prescription during the study period was \$46.45 USD based on the exchange rate in October 2023 (1,358 won per US \$).

Definition of AE of IPF

The definition of AE of IPF encompasses cases in which the diagnostic code for IPF is either a primary or secondary diagnosis at the time of admission. To ascertain the occurrence of an acute event, a chest CT performed within one month of admission was mandatory. Initiation of systemic steroid treatment was required within three days of admission. To refine the accuracy of this definition, we applied exclusion criteria to cases in which heart failure or fluid overload was diagnosed. Diagnostic criteria for AE of IPF were aligned with those proposed by the International Working Group in 2016 (21).

Study outcomes

The primary object of this study was to assess the current

status of PR implementation in patients with IPF in Korea. Additionally, the study aimed to analyze the effect of PR on mortality and AE risk as secondary outcomes. Mortality cases were identified based on the absence of claim data from healthcare facilities for more than 1 year.

Statistical analysis

Study participants were divided into PR and non-PR groups for comparison using Student's *t*-test for continuous variables and χ^2 test for categorical variables. Results are presented as mean \pm standard deviation for continuous variables and as proportions for categorical variables. Cox proportional hazard analysis was used to analyze the risk of AE and mortality according to PR implementation (non-PR *vs.* PR). Hazard ratios (HRs) and 95% confidence intervals (CIs) were also estimated. Covariates including age, sex, insurance type, modified Charlson comorbidity index (mCCI), history of AE within a previous year, use of systemic steroid and antifibrotic agent were adjusted. Survival analysis was performed using Kaplan-Meier survival curves. All analyses were performed using the SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of study participants

Among a total of 4,228 patients with IPF enrolled in this study, 205 (4.85%) received PR while 4,023 (95.15%) did not receive PR during the study period (Figure S1). The mean time interval between the index date of IPF diagnosis and the implementation of PR was 191.94 \pm 225.54 days. Characteristics of patients with IPF who received or did not receive PR are presented in Table 1. The mean age of the PR group was younger than that of the non-PR group (68.33 \pm 8.68 *vs.* 71.76 \pm 9.04 years, $P < 0.001$). The PR group also had a higher proportion of males than the non-PR group (83.9% *vs.* 73.7%, $P = 0.001$). The PR group had more patients prescribed pirfenidone (61.0% *vs.* 38.3%, $P < 0.001$) and systemic steroids (74.6% *vs.* 50.3%, $P < 0.001$) than the non-PR group. There was no significant difference in previous AE events within a year of IPF diagnosis between PR and non-PR groups.

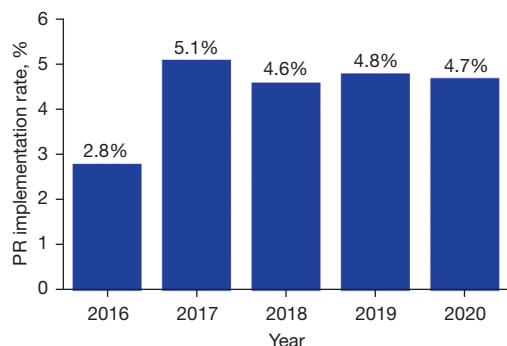
PR implementation rate

The annual trend of PR implementation rate during the study period is shown in Figure 1. Following the

Table 1 General characteristics of study subjects

| Clinical variables | PR (n=205) | Non-PR (n=4,023) | P value |
|--------------------------|------------|------------------|---------|
| Age, years | 68.33±8.68 | 71.76±9.04 | <0.001 |
| Sex (male) | 172 (83.9) | 2,966 (73.7) | 0.001 |
| Insurance type | | | |
| NHI | 181 (88.3) | 3,475 (86.4) | 0.43 |
| Medical aid | 24 (11.7) | 548 (13.6) | |
| mCCI | 3.35±1.99 | 3.31±2.21 | 0.83 |
| Medication | | | |
| Pirfenidone | 125 (61.0) | 1,539 (38.3) | <0.001 |
| Systemic steroid use | 153 (74.6) | 2,024 (50.3) | <0.001 |
| Steroid daily dose (mg)* | 7.02±5.50 | 7.69±6.27 | 0.16 |
| AE in previous year | 4 (2.0) | 47 (1.2) | 0.32 |

Data are presented as n (%) or mean ± standard deviation. *, daily steroid dose was calculated and presented as an approximate equivalent dose to prednisolone. PR, pulmonary rehabilitation; NHI, National Health Insurance; mCCI, modified Charlson comorbidity index; AE, acute exacerbation.

**Figure 1** Annual trend of PR implementation rate from 2016 to 2020. PR, pulmonary rehabilitation.

initiation of national insurance coverage in 2016, the implementation rate of PR increased from 2.8% in 2016 to 5.1% in 2017. However, there were no further increase in the implementation rate from 2017 to 2020. When analyzing PR implementation rates by age and sex, it was obvious that males of all age groups received more PR than females (Table 2).

Medical costs

Trends in annual medical costs for both PR and non-PR

Table 2 Number of PR implementations by age group and sex

| Year | Age groups, years | | | |
|--------|-------------------|-----------|-----------|-----------|
| | 40–49 | 50–59 | 60–69 | ≥70 |
| 2016 | | | | |
| Total | 0 | 1 | 8 | 14 |
| Male | 0 | 1 | 6 (75.0) | 12 (85.7) |
| Female | 0 | 0 | 2 (25.0) | 2 (14.3) |
| 2017 | | | | |
| Total | 1 | 10 | 32 | 38 |
| Male | 1 | 9 (90.0) | 25 (78.1) | 34 (89.5) |
| Female | 0 | 1 (10.0) | 7 (21.9) | 4 (10.5) |
| 2018 | | | | |
| Total | 2 | 13 | 59 | 51 |
| Male | 2 | 10 (76.9) | 52 (88.1) | 44 (86.3) |
| Female | 0 | 3 (23.1) | 7 (11.9) | 7 (13.7) |
| 2019 | | | | |
| Total | 2 | 29 | 69 | 63 |
| Male | 2 | 27 (93.1) | 56 (81.2) | 49 (77.8) |
| Female | 0 | 2 (6.9) | 13 (18.8) | 14 (22.2) |
| 2020 | | | | |
| Total | 4 | 21 | 76 | 86 |
| Male | 3 (75.0) | 17 (81.0) | 63 (82.9) | 69 (80.2) |
| Female | 1 (25.0) | 4 (19.0) | 13 (17.1) | 17 (19.8) |

Data are presented as number or n (%). PR, pulmonary rehabilitation.

groups are illustrated in Figure S2. Medical costs in the PR group were approximately 3–6 times higher than those in the non-PR group. Furthermore, after implementation of PR, there was an increasing trend in direct medical costs for the PR group from 2016 to 2018, although there was no further increase after 2018. By contrast, for those who did not receive PR, no significant changes in medical expenses were observed throughout the study period.

Mortality

During the follow-up period, the mortality rate was higher in the PR group than that in the non-PR group (43.4% vs. 33.9%, $P=0.005$). Factors influencing mortality in the overall cohort of IPF patients are shown in Table 3. In multivariate

Table 3 Factors related to the risk of mortality in patients with IPF

| Clinical variables | HR (95% CI) | P value | Adjusted HR (95% CI)* | P value* |
|--------------------|------------------|---------------|-----------------------|----------|
| Age categories | | | | |
| 40–49 | | 1 (Reference) | | |
| 50–59 | 1.41 (0.74–2.67) | 0.30 | 1.42 (0.75–2.69) | 0.28 |
| 60–69 | 1.80 (0.98–3.29) | 0.06 | 1.84 (1.00–3.36) | 0.05 |
| ≥70 | 2.97 (1.64–5.40) | <0.001 | 3.04 (1.67–5.51) | <0.001 |
| Sex (male) | 1.37 (1.19–1.56) | <0.001 | 1.39 (1.22–1.59) | <0.001 |
| Type of insurance | | | | |
| NHI | | 1 (Reference) | | |
| Medical aid | 0.99 (0.86–1.16) | 0.98 | | |
| mCCI | 1.08 (1.05–1.10) | <0.001 | 1.07 (1.04–1.09) | <0.001 |
| Previous AE | 3.66 (2.74–4.89) | <0.001 | 3.38 (2.53–4.51) | <0.001 |
| Pirfenidone use | 0.82 (0.73–0.92) | <0.001 | 0.82 (0.73–0.92) | <0.001 |
| Steroid use | 1.38 (1.21–1.56) | <0.001 | 1.40 (1.23–1.61) | <0.001 |
| PR (vs. non-PR) | 1.54 (1.15–2.07) | 0.004 | 1.37 (1.10–1.70) | 0.005 |

*, adjusted for age, sex, mCCI, previous exacerbation, pirfenidone treatment and systemic steroid use. IPF, idiopathic pulmonary fibrosis; HR, hazard ratio; CI, confidence interval; NHI, National Health Insurance; mCCI, modified Charlson comorbidity index; AE, acute exacerbation; PR, pulmonary rehabilitation.

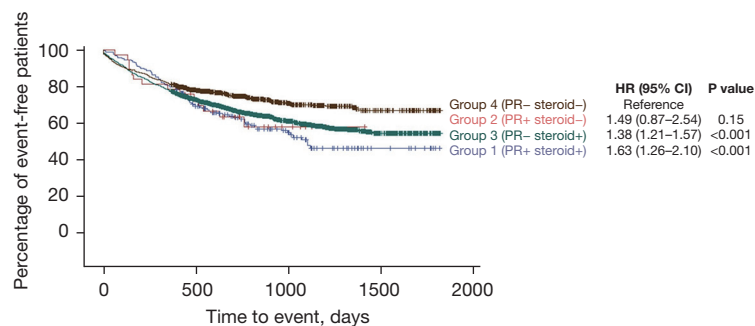


Figure 2 Time to all-cause mortality by PR implementation and steroid use. PR, pulmonary rehabilitation; HR, hazard ratio; CI, confidence interval.

analysis, older age, male sex, higher comorbidity index, history of previous AE, use of systemic steroid and PR were related to increased mortality risk. The use of pirfenidone was identified as a factor that reduced the mortality risk. *Figure 2* illustrated the all-cause mortality risks associated with PR status and steroid use, showing varying outcomes among different groups. Specifically, in patients who did not receive steroids, PR had no significant risk of mortality (HR, 1.49, 95% CI: 0.87–2.54, $P=0.15$). In contrast, steroid use significantly increased the mortality risk in both the PR

(PR+ steroid+) and non-PR (PR- steroid+) groups, with HRs of 1.63 (95% CI: 1.26–2.10, $P<0.001$) and 1.38 (95% CI: 1.21–1.57, $P<0.001$), respectively.

AEs

The incidence of AE was higher in the PR group compared to the non-PR group, with 56.6% (116 out of 205) in the PR group versus 30.0% (1,208 out of 4,023) in the non-PR group. Time-to-AE analysis revealed a significantly

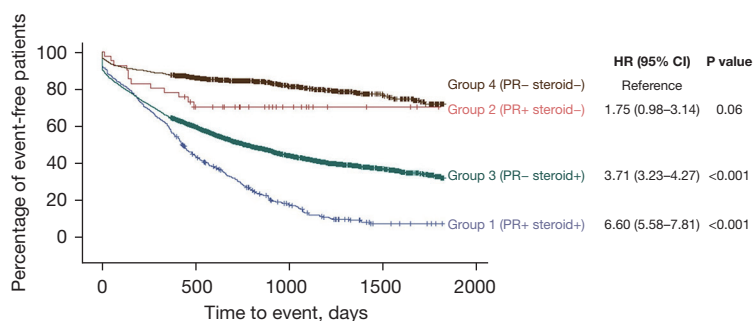


Figure 3 Time to first exacerbation by PR implementation and steroid use. PR, pulmonary rehabilitation; HR, hazard ratio; CI, confidence interval.

increased risk in the PR group relative to the non-PR group. Additional analyses were performed considering impact of systemic steroid use, as detailed in *Figure 3*. The data revealed distinct outcomes across different groups. Specifically, for patients not treated with steroids, PR did not significantly alter the risk of AE, with a HR of 1.75 (95% CI: 0.98–3.14, $P=0.06$). Conversely, the use of steroids consistently increased the risk of AE across both PR (PR+ steroid+) and non-PR (PR- steroid+) groups, as evidenced by HRs of 6.60 (95% CI: 5.58–7.81, $P<0.001$) and 3.71 (95% CI: 3.23–4.27, $P<0.001$), respectively.

Discussion

In this study, we analyzed the rate of PR implementation and impact on outcomes of patients with IPF using a nationwide database. The PR group had a significantly higher proportion of patients receiving antifibrotics and systemic steroids than the non-PR group, suggesting greater disease severity. In the non-steroid group, PR did not significantly affect the risk of AE. However, in the steroid group, regardless of PR application, consistently increased the risk of AE. Similar results were observed for all-cause mortality. Although we did not observe a beneficial impact of PR on the outcomes of IPF, factors such as the low implementation rate of PR in Korea and disease severity should be taken into consideration. Furthermore, given that IPF has an extremely poor prognosis with a median survival of only just a few years, our study highlights the need for early implementation of PR in patients with non-severe IPF and underscores the importance of confirming this through prospective studies.

Current guidelines for IPF and chronic respiratory disease consistently recommend PR as a non-pharmacological

intervention that is both effective and safe (22,23). PR has been shown to improve the health-related QoL (HRQoL), shortness of breath, and exercise capacity in patients with ILDs (13,14,16,24). Nevertheless, in research focused exclusively on IPF patients, although short-term benefits were evident, there was a lack of adequate evidence supporting the long-term sustainability of these improvements (25,26). There is a lack of clear evidence of long-term effects of PR on IPF patients. One randomized controlled trial (RCT) involving 61 IPF patients showed that although exercise training program improved QoL and 6-minute walk distance (6MWD) initially, these effects diminished after 6 months. However, in patients with mild disease who had better baseline lung function, clinical benefits were sustained (13). A recent RCT involving 88 patients with IPF taking nintedanib, a 12-week program of twice-weekly ET followed by a 40-week at-home rehabilitation, showed significant improvement in only endurance time in the PR group at week 52 (27). However, there were no differences in 6MWD, QoL, dyspnea, lung function, or saturation between the two groups. Although a high mortality rate in IPF is evident, the progression of IPF is highly variable among patients. The effectiveness of PR might be different depending on the rate of progression and sustainability to PR program. In comparison with other ILDs, IPF showed less improvement in dyspnea from PR, with benefits mainly for cases with a mild disease (26), thus it could be difficult to expect effectiveness from PR in advanced disease stages.

In a recent study showing beneficial effect of PR on AE and mortality of COPD patients in Korea, the rate of PR implementation was only 1.43%, but this accounted for 6,630 patients with a continuous upward trend each year (28). In contrast, rate of PR implementation in IPF patients

was 4–5%, but remained unchanged over several years and covered only 205 patients. Although we utilized nationwide database, relatively small sample size in IPF may have been insufficient to extract meaningful statistical analysis. This disparity may be attributed to the fact that IPF, as a rare intractable disease, is primarily treated at tertiary, referral hospitals, has a lower prevalence compared to COPD, and is associated with higher mortality (3- and 5-year cumulative survival rates of about 60% and 45%, respectively) (29). In an 8-week outpatient PR program in IPF patients, the PR completion rate was similar to that of propensity score matched COPD patients (30). However, even for those who completed the program, if they did not reach the minimal important difference in the incremental shuttle walk test distance (non-responders), the mortality risk was just as high as that of non-completers. This highlights the importance of the patient's condition and sustainability to benefit from PR, rather than simply undergoing the program itself.

South Korea has implemented a unique government-established healthcare insurance system since 1998. It covers almost all citizens (31), enabling us to analyze the long-term impact of PR on health status using a nationwide IPF cohort. Although we found that the PR significantly increased mortality risk, PR had no significant effect on both AE and mortality in the non-steroid group, but the risk elevated regardless of PR in the steroid group. The use of corticosteroids in stable IPF has been discouraged in recent guidelines due to the lack of evidence supporting their benefit and the potential for harm, including an increased incidence of infections (22,32). However, the PR group received steroid treatment more frequently in this study. Like other claim data-based studies, claim database does not have data on disease related severity indicators, such as Gender-Age-Physiology (GAP) index, which limits our ability to accurately assess the severity of IPF. Furthermore, in Korea, the reimbursement criteria for the prescription of pirfenidone in IPF patients are based on a lung function impairment. Pirfenidone was included in the health insurance coverage of South Korea in October 2015. However, until 2019, health insurance coverage for pirfenidone was restricted to patients who met specific criteria, including a predicted forced vital capacity (FVC) of 50–90%, a diffusion capacity for carbon monoxide (DLco) of at least 35%, and a 6MWD of more than 150 meters. Although from January 2019, the prescription of pirfenidone is covered by insurance for IPF patients whose FVC and DLco are less than 90% and 80% of the predicted value, respectively, it still does not cover all IPF patients,

particularly those with mild IPF who have preserved lung function (33). Moreover, only approximately 2% of IPF patients were treated with nintedanib, a tyrosine kinase inhibitor used to treat fibrotic ILDs including IPF, because it is not yet covered by health insurance in South Korea. This economic barrier limited the use of medication for many IPF patients (34). Consequently, patients with IPF receiving pirfenidone are likely to have more advanced and severe disease, which could adversely affect patient outcomes, regardless of whether they received PR.

To the best of our knowledge, this is the first study that investigates the impact of PR on prognosis including exacerbation and mortality risk in patients with IPF through nationwide database. The importance of PR has been emphasized through previous studies and guidelines. Moreover, PR became covered by health insurance. However, the overall application rate of PR was low, only 4.85% in our cohort, reflects the limited availability of medical resources dedicated to PR in Korea. This low application rate further constrained our ability to evaluate PR's impact comprehensively. To overcome these issues, alternative strategies such as tele-rehabilitation and remote monitoring are emerging as viable options for future PR implementation (14,35,36). Another noteworthy aspect of this study was the inclusion of AE as an outcome measure. Defining AE in the context of IPF is challenging when using claim databases because there is no specific ICD-10 code for AE-IPF. Previous studies analyzing AE based on claim databases have mainly defined it as cases where IPF patients receiving high-dose or pulse-dose corticosteroid therapy during hospitalization (37,38). However, the evidence for the effectiveness of such treatment in AE-IPF is unclear. Therefore, we primarily adopted the definition of AE provided by the International Working Group and established a definition of AE-IPF that reflected the real clinical practice and current guidelines (21,22), considering that steroid treatment is predominantly carried out despite its low evidence level in AE-IPF management.

This study had several limitations. First, HIRA data did not provide information on subjective symptoms or exercise performance during PR in patients with IPF, hindering the confirmation of positive effects noted in other studies. Second, information regarding the severity of IPF based on pulmonary function tests and the extent of lung involvement on chest CT scans was unattainable. Third, mortality was defined as no medical reimbursement for a 1-year follow-up, which prevented the analysis of specific causes and restricted our study to assessing the risk of all-cause

mortality. Fourth, we were unable to utilize a frailty index that could predict the sustainability and effectiveness of PR. Fifth, the low application rate of PR in Korea may decrease the statistical reliability of its impact on outcomes. Lastly, the retrospective design and absence of randomization in this study might have introduced bias. Additionally, since the analysis was limited to a South Korean population, the generalizability of our findings to certain countries with easy access to PR related resources or to different racial and ethnic groups remains uncertain.

Conclusions

PR is administered to a minority of patients with IPF in South Korea. Those undergoing PR tended to have a higher prescription rate of pirfenidone and steroids, indicating a potentially greater disease severity than those who did not. PR did not have a significant effect on the risk of AEs or mortality in either group, when analyzed based on steroid use. Given the progressive and irreversible nature of IPF itself, prospective studies are necessary to expand the application of PR to less severe cases and to assess its clinical efficacy at an early stage.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-24-1165/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Institutional Review Board (IRB) of Seoul St. Mary's Hospital approved the study protocol (No. KC22ZASE0545) and waived the need for informed consent due to the retrospective nature of this study. The study was performed in accordance with the principles of the Declaration of Helsinki (as revised in 2013) concerning the ethical principles for medical research.

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