Impact of Gender on the Characteristics of Patients with Idiopathic Pulmonary Fibrosis Included in the RaDiCo-ILD Cohort

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\textbf{Keywords}

Idiopathic pulmonary fibrosis · Idiopathic interstitial pneumonia · Registry · Gender · Patient characteristics · France

Trial registration: ClinicalTrials.gov (NCT04238871).

\textbf{Abstract}

\textbf{Background:} There is growing evidence of gender-specific phenotypic differences among patients with idiopathic pulmonary fibrosis (IPF), which may affect patient outcomes.  

\textbf{Objectives:} We present the characteristics of patients with IPF at inclusion in the French Rare Disease Cohort – Interst-
tial Lung Disease (RaDiCo-ILD) with the aim of characterizing gender-specific phenotypic differences. **Methods:** Patients with IPF who were enrolled in the national, multicentre RaDiCo-ILD cohort were included. Demographic characteristics, comorbidities, health-related quality of life (HRQoL) scores, pulmonary function, chest imaging, and IPF treatment were collected at inclusion and described by gender. **Results:** The cohort included 724 patients with IPF (54% of RaDiCo-ILD cohort), of whom 82.9% were male. The proportion of male and female patients with a prior history of smoking was 75.0% and 26.8%, respectively. Emphysema was present in 17.0% (95% confidence interval [CI]: 10.0, 24.0) of men and 5.4% (95% CI: 1.2, 9.6) of women. At inclusion, females had poorer HRQoL than males based on St. George’s Respiratory Questionnaire scores (48.5 [95% CI: 43.9, 53.0] and 41.5 [39.4, 43.6], respectively). The mean forced vital capacity per cent predicted was 77.7% (95% CI: 76.2, 79.3) and 87.4% (83.4, 91.4) for males and females, respectively. Honeycombing on high-resolution computed tomography (HRCT) was present in 70.8% (95% CI: 61.0, 80.6) of males and 45.8% (95% CI: 35.1, 56.5) of females. **Conclusions:** This analysis of patients with IPF at inclusion in the RaDiCo-ILD cohort provides evidence that comorbid emphysema, lung volume reduction, and honeycombing on HRCT are more common characteristics of males than females.

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**Introduction**

Idiopathic pulmonary fibrosis (IPF), the most common and aggressive type of idiopathic interstitial pneumonia (IIP), is a chronic and progressive interstitial lung disease (ILD) of unknown aetiology [1]. It is characterized by progressive fibrosis on high-resolution computed tomography (HRCT), irreversible decline in lung function and worsening respiratory symptoms, and a high rate of mortality [1, 2]. Historically, patients with IPF survived for a median of 2–3 years following diagnosis of IPF [1]; however, increased recognition, earlier diagnosis, and the availability of antifibrotic therapy have improved survival over the last 5 years [2–4].

IPF occurs predominantly in men, who account for approximately 70% of all cases [1, 3, 5]. The reason for this gender disparity is still largely unknown, but it has been hypothesized that greater male exposure to cigarette smoke and environmental and occupational risk factors may play a role [6]. The Gender, Age, Physiology (GAP) index and scoring system has acknowledged gender as an important determinant of outcome in IPF, with male sex, older age (>65 years), and poor pulmonary function associated with a higher risk of mortality [7]. Recent studies have further demonstrated that patient sex can have clinical and prognostic implications in IPF, with significantly poorer lung function observed in males compared with females at registry inclusion [8] and 40% higher risk of death or lung transplantation [5].

Patient registries enable the systematic collection of real-world data, which can provide valuable insights into the clinical course of diseases and the health status of a defined population of patients. They also serve as tools to retrospectively evaluate the clinical effectiveness and safety of medical interventions [9, 10]. For rare diseases such as IPF, in which the estimated global prevalence is just 3–9 cases per 100,000 people per year, registries are particularly useful [11, 12]. In recent years, a number of IPF registries have been initiated across the world, collecting cumulative data on thousands of patients, thereby providing novel insights into the natural course of the disease and clinical management of IPF [9].

To date, there have been a small number of epidemiological studies in France. An observational study of patients with ILD in a French, urban, multi-ethnic county in the Paris area demonstrated a relatively low overall IPF prevalence (2.8 per 100,000 people per year), with a predominance in older males [12]. Gender was found to have a significant effect on baseline disease presentation and outcomes in a French, prospective IPF cohort (COhorte Fibrose [COFI]), which included 236 patients with incident IPF who did not receive antifibrotic therapy. Male patients had poorer lung function at IPF diagnosis and greater exposure to tobacco and occupational aero-contaminants compared with females, although female exposure to aero-contaminants may not have been fully captured (unpublished).

The Rare Disease Cohort – Interstitial Lung Disease (RaDiCo-ILD) was launched in 2017 as part of the RaDiCo research programme, co-ordinated by the Institut National de la Santé et de la Recherche Médicale in France (https://radico.fr/fr/). The overarching objectives of this national cohort study are to characterize and monitor the phenotypic features associated with IIP in France and to describe the natural history of the various forms of these diseases. More specifically in this study, we present the characteristics of patients at inclusion in this cohort who have a clinical diagnosis of IPF, with the aim of characterizing gender differences.
### Materials and Methods

**The RaDiCo-ILD Cohort**

RaDiCo-ILD is a national, multicentre, non-interventional cohort study in France. The majority of participating centres are part of the French national networks of reference and competence centres for rare respiratory diseases (OrphaLung and Rare Respiratory Diseases Healthcare Faculty [RespiFIL] networks). The full list of participating centres and investigators is included in online suppl. Table 1 (see www.karger.com/doi/10.1159/000518008 for all online suppl. material).

For the RaDiCo-ILD cohort, all incident and prevalent patients who met the following criteria could be included: (1) a diagnosis of IIP established on presenting history, clinical, radiological, functional, and, if available, pathological findings (for full criteria, see online suppl. Methods) and (2) patients affiliated to a public health insurance provider. The RaDiCo-ILD study was registered with ClinicalTrials.gov (NCT04238871).

**IPF Cohort**

The IPF cohort was a subgroup of patients included in the RaDiCo-Co-ILD study. All patients in the IPF cohort who met the following criteria were included in the present study: (1) aged >18 years; (2) IPF diagnosed using the American Thoracic Society/European Respiratory Society (ATS/ERS) 2011 criteria [1] (until the revision of criteria in September 2018, which was subsequently used, allowing for the inclusion of patients with a diagnosis of probable IPF [13]); and (3) completion of a pulmonary function test at inclusion visit. A multidisciplinary discussion was recommended to obtain a diagnosis, based on clinical signs, radiological investigation, and surgical biopsy.

The study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Inserm UMR S 933 RaDiCo. REDCap is a secure, web-based application designed to support data capture for research studies. Data management was compliant with General Data Protection Regulation.

**Statistical Analyses**

The analyses in this study were mainly descriptive and were performed with SAS® 9.4 software. The characteristics of patients with IPF were described. For continuous variables, the number, number of missing values, median (range) or mean (standard deviation) according to the normality of the distribution, and 95% confidence interval (CI) of the means were included. For categorical variables, the number, percentage, and 95% CI of the proportion were included. Data including demographic characteristics, significant comorbidities, pulmonary function testing, chest imaging, health-related quality of life (HRQoL), and IPF treatment were collected at inclusion visit and described by gender. Comorbidities at inclusion were recorded by investigators as present or absent. HRCT scans were obtained and analysed in each reference centre by each investigator independently, according to the ATS/ERS recommendations. Although the study was not powered to assess the significance of gender comparisons, the population was described according to gender and the 95% CIs were calculated. An absence of CI overlap between gender subgroups was considered a statistically significant difference.

Results of predictive prognostic measures were collected, including normalized 6-min walk test (6 MWT) values and GAP index scores and stages. To normalize the score with age and stature, the 6 MWT is expressed as a percentage of the predicted value of a corresponding healthy subject [14]. The GAP index stratifies patients into 3 stages of increasing risk: Stage I with 0–3 points, Stage

| Gender | Male | Female |
|--------|------|--------|
| IPF    | 600  | 239    |
| Yes    | 124  |        |
| No     | 600  | 239    |
| Yes    | 124  |        |

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**Fig. 1.** Patient flowchart. IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; PFT, pulmonary function test; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease. *PFT at inclusion visit completed for patients included up to May 13, 2020.
II with 4–5 points, and Stage III with 6–8 points [7]. Measures of HRQoL included the 36-Item Short Form survey (SF-36) and St. George’s Respiratory Questionnaire (SGRQ) [15], with higher SF-36 scores and lower SGRQ scores indicating better health status.

### Results

Of 1,345 patients with ILD enrolled in the RaDiCo-ILD registry between July 3, 2017, and September 28, 2020, 963 were adult patients with IPF (83% male, 17% female). Of these, 724 patients had completed pulmonary function tests and were therefore included in this analysis. The gender distribution was 600 males (83%) and 124 females (17%) (Fig. 1).

### Demographic and Diagnostic Characteristics at Inclusion

Patient demographics for all patients with IPF are presented in Table 1. In the whole cohort, the mean age at diagnosis was 70.9 years and was similar for males and females (70.7 [95% CI: 70.0, 71.3] and 72.1 [95% CI: 70.5, 71.7]).

| Table 1. Patient characteristics at inclusion in the RaDiCo-ILD cohort |
|---------------------------------------------------------------|
| Male (n = 600) | Female (n = 124) | Total (N = 724) |
|----------------|-----------------|----------------|
| **Mean age ±SD, years** | 72.1 ± 8.5 | 73.3 ± 8.7 | 72.3 ± 8.5 |
| 95% CI | 71.6, 72.8 | 72.9, 75.6 | 72.0, 73.1 |
| **Mean age at diagnosis ±SD, years** | 70.7 ± 8.6 | 72.1 ± 9.1 | 70.9 ± 8.7 |
| 95% CI | 70.0, 71.3 | 70.5, 73.7 | 70.3, 71.5 |
| **Median time between diagnosis and inclusion (IQR), months** | 8.5 (0.7–25.8) | 5.0 (0.0–22.1) | 7.8 (0.5–25.4) |
| **Median time between first symptoms and diagnosis (IQR), years** | 2.0 (1.0–4.0) | 2.0 (1.0–4.0) | 2.0 (1.0–4.0) |
| Missing, n | 53 | 12 | 65 |
| **Mean BMI ±SD, kg/m²** | 26.8 ± 4.0 | 27.6 ± 5.2 | 26.9 ± 4.2 |
| 95% CI | 26.4, 27.1 | 26.7, 28.6 | 26.6, 27.2 |
| **Arterial hypertension** | 255 (42.9) | 60 (48.8) | 315 (43.9) |
| 95% CI | 34.2, 51.7 | 40.0, 57.6 | 35.2, 52.7 |
| Missing, n | 6 | 1 | 7 |
| **Gastro-oesophageal reflux disease** | 150 (25.0) | 41 (33.1) | 191 (26.4) |
| 95% CI | 17.4, 32.6 | 24.8, 41.3 | 18.6, 34.1 |
| Missing, n | 11 | 2 | 13 |
| **Diabetes** | 147 (24.5) | 22 (17.7) | 169 (23.3) |
| 95% CI | 16.9, 32.1 | 11.0, 24.5 | 15.9, 30.8 |
| Missing, n | 11 | 3 | 14 |
| **Coronary disease** | 146 (24.6) | 12 (9.8) | 158 (22.0) |
| 95% CI | 17.0, 32.2 | 4.5, 15.0 | 14.7, 29.4 |
| Missing, n | 6 | 1 | 7 |
| **Emphysema** | 93 (17.0) | 6 (5.4) | 99 (15.0) |
| 95% CI | 10.0, 24.0 | 1.2, 9.6 | 8.4, 21.7 |
| Missing, n | 52 | 13 | 65 |
| **Thyroid dysfunction** | 35 (5.8) | 28 (22.6) | 63 (8.7) |
| 95% CI | 1.7, 10.0 | 15.2, 29.9 | 3.7, 13.7 |
| **Tobacco status** | | | |
| Active | 32 (5.3) | 10 (8.1) | 42 (5.8) |
| 95% CI | 1.4, 9.3 | 3.3, 13.0 | 1.7, 9.9 |
| Passive | 4 (0.7) | 15 (12.2) | 19 (2.6) |
| 95% CI | 0.0, 2.1 | 6.4, 18.0 | 0.0, 5.5 |
| **Prior smoker (at least 6 months)** | 450 (75.0) | 33 (26.8) | 483 (66.8) |
| 95% CI | 67.4, 82.7 | 19.0, 34.7 | 58.5, 75.1 |
| Never | 114 (19.0) | 65 (52.9) | 179 (24.8) |
| 95% CI | 12.1, 25.9 | 44.0, 61.7 | 17.1, 32.4 |
| Lung biopsy | 135 (22.9) | 36 (29.5) | 171 (24.1) |
| 95% CI | 15.5, 30.4 | 21.4, 37.6 | 16.5, 31.6 |
| Missing, n | 11 | 2 | 13 |

Data are n (%) unless otherwise stated. BMI, body mass index; CI, confidence interval; IQR, interquartile range; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease; SD, standard deviation. a Reported as a comorbidity at registry inclusion. b Defined as having <100 cigarettes during lifetime.
The median time period between diagnosis and cohort inclusion was 7.8 months (interquartile range [IQR]: 0.5–25.4). The median time between first symptom and a diagnosis of IPF was 2.0 years (IQR: 1.0–4.0) for both male and female patients. The overall mean body mass index was 26.9 kg/m² (26.8 kg/m² [95% CI: 26.4, 27.1] for male patients and 27.6 kg/m² [95% CI: 26.7, 28.6] for female patients), indicating that most were in the overweight range. Consistent with current practice, lung biopsies were performed in 24.1% of all patients, and no significant differences were observed between male and female patients (22.9% [95% CI: 15.5, 30.4] and 29.5% [95% CI: 21.4, 37.6], respectively).

**Patient Comorbidities at Inclusion**

Comorbidities at inclusion are presented in Table 1. The most common conditions recorded were arterial hypertension (43.9%), gastro-oesophageal reflux disease (26.4%), and diabetes (23.3%). Of the total cohort, 22.0% had existing coronary heart disease recorded in a significantly higher proportion of male patients (24.6% [95% CI: 17.0, 32.2]) than female patients (9.8% [95% CI: 4.5, 15.0]). At inclusion, 15.0% of patients had emphysema (unadjusted for tobacco use), and it was also significantly more common in male patients than female patients (17.0% [95% CI: 10.0, 24.0] and 5.4% [95% CI: 1.2, 9.6], respectively). Thyroid dysfunction, which was hypothyroidism in most cases, was recorded in 8.7% of the total

| Table 2. Lung function in patients with IPF at inclusion in the RaDiCo-ILD cohort |
|----------------------------------|------------------|------------------|------------------|
|                                 | Male ($n = 600$) | Female ($n = 124$) | Total ($N = 724$) |
| **FVC % predicted**             | 77.7±19.3        | 87.4±22.5        | 79.4±20.2        |
| 95% CI                           | 76.2, 79.3       | 83.4, 91.4       | 77.9, 80.9       |
| **DLCO % predicted**            | 46.1±16.8        | 46.9±13.9        | 46.2±16.4        |
| 95% CI                           | 44.6, 47.6       | 44.2, 49.7       | 44.9, 47.5       |
| Missing, $n$                     | 86               | 23               | 109              |
| **FEV1 % predicted**            | 83.0±19.5        | 90.2±23.5        | 84.3±20.4        |
| 95% CI                           | 81.5, 84.6       | 86.0, 94.4       | 82.8, 85.8       |
| Missing, $n$                     | 6                | 1                | 7                |
| **GAP index score**              | 4.2±1.3          | 3.0±1.2          | 4.0±1.4          |
| 95% CI                           | 4.1, 4.4         | 2.8, 3.2         | 3.9, 4.2         |
| Missing, $n$                     | 86               | 23               | 109              |
| **GAP stage, $n$ (%)**           |                  |                  |                  |
| I                                | 155 (30.2)       | 68 (67.3)        | 223 (36.3)       |
| 95% CI                           | 21.2, 59.1       | 58.2, 76.5       | 62.9, 45.6       |
| II                               | 270 (52.5)       | 32 (31.7)        | 302 (49.1)       |
| 95% CI                           | 42.8, 62.3       | 22.6, 40.8       | 39.4, 58.9       |
| III                              | 89 (17.3)        | 1 (1.0)          | 90 (16.4)        |
| 95% CI                           | 9.9, 24.7        | 0.0, 2.9         | 7.7, 21.5        |
| Missing, $n$                     | 86               | 23               | 109              |
| **CPI**                          | 47.6±13.4        | 43.8±11.8        | 47.0±13.2        |
| 95% CI                           | 46.4, 48.8       | 41.4, 46.1       | 45.9, 48.0       |
| Missing, $n$                     | 89               | 24               | 113              |
| **CPFE**                         | 4.5±7.1          | 7.1±8.0          | 5.0±7.3          |
| 95% CI                           | 4.0, 5.1         | 5.6, 8.5         | 4.4, 5.5         |
| **6 MWT, m**                     | 414.0±130.3      | 346.5±117.5      | 402.9±130.6      |
| 95% CI                           | 402.1, 425.9     | 322.2, 370.8     | 392.0, 413.7     |
| Missing, $n$                     | 134              | 32               | 166              |
| **Normalized 6 MWT, % predicted**| 65.4±19.8        | 67.7±19.8        | 65.8±19.8        |
| 95% CI                           | 63.5, 67.3       | 63.5, 71.9       | 64.1, 67.5       |
| Missing, $n$                     | 173              | 35               | 208              |

Data are mean ± SD unless otherwise stated. 6 MWT, 6-min walk test; CI, confidence interval; CPFE, combined pulmonary fibrosis and emphysema; CPI, composite physiologic index; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, Gender, Age, Physiology; IPF, idiopathic pulmonary fibrosis; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease; SD, standard deviation.
cohort, affecting 5.8% (95% CI: 1.7, 10.0) and 22.6% (95% CI: 15.2, 29.9) of male and female patients, respectively.

The proportion of active tobacco smokers was 5.3% (95% CI: 1.4, 9.3) and 8.1% (95% CI: 3.3, 13.0) in the male and female populations, respectively. More than half of female patients (52.9% [95% CI: 44.0, 61.7]) had never smoked (defined as having <100 cigarettes during their lifetime) compared with 19.0% (95% CI: 12.1, 25.9) of male patients. The majority of male patients used to smoke and had been cigarette-free for at least 6 months prior to inclusion (75.0% [95% CI: 67.4, 82.7]), compared with over a quarter of female patients (26.8% [95% CI: 19.0, 34.7]). A higher proportion of female patients had exposure to passive smoking compared with male patients (12.2% [95% CI: 6.4, 18.0] and 0.7% [95% CI: 0.0, 2.1], respectively).

Clinical Characteristics at Inclusion

A summary of the lung function of patients with IPF reported at inclusion in the cohort is presented in Table 2. The mean forced vital capacity (FVC) per cent predicted was statistically lower for male patients compared with female patients (77.7% [95% CI: 76.2, 79.3] and 87.4% [95% CI: 83.4, 91.4], respectively). The mean diffusing capacity for carbon monoxide (DLCO) percentage was 46.1% (95% CI: 44.6, 47.6) in males and 46.9% (95% CI: 44.2, 49.7) in females.

The mean GAP index score for the whole cohort at inclusion was 4.0. The proportion of male and female patients who were GAP Stage I was 30.2% (95% CI: 21.2, 39.1) and 67.3% (95% CI: 58.2, 76.5), respectively, whereas the proportion who were GAP Stage III was 17.3% (95% CI: 9.9, 24.7) and 1.0% (95% CI: 0.0, 2.9), respectively. The mean composite physiologic index at inclusion for all patients was 47.0, and this was higher for male patients than female patients (47.6 [95% CI: 46.4, 48.8] and 43.8 [95% CI: 41.4, 46.1], respectively). The estimated extent of emphysema predicted using the combined pulmonary fibrosis and emphysema (CPFE) index [16] was 5.0%, and was higher in female patients than male patients (7.1% [95% CI: 5.6, 8.5] and 4.5% [95% CI: 4.0, 5.1], respectively). Further lung function data recorded at inclusion in RaDiCo-ILD are presented in online suppl. Results. The prominent markers of pulmonary functional impairment at inclusion in the cohort were significantly less severe for women than for men.

At cohort inclusion, the mean SF-36 physical and mental scores for the whole population were 52.4 ± 23.1 (95% CI: 50.4, 54.3). The mean GAP index score for the whole cohort at inclusion was 4.0. The proportion of male and female patients who were GAP Stage I was 30.2% (95% CI: 21.2, 39.1) and 67.3% (95% CI: 58.2, 76.5), respectively, whereas the proportion who were GAP Stage III was 17.3% (95% CI: 9.9, 24.7) and 1.0% (95% CI: 0.0, 2.9), respectively. The mean composite physiologic index at inclusion for all patients was 47.0, and this was higher for male patients than female patients (47.6 [95% CI: 46.4, 48.8] and 43.8 [95% CI: 41.4, 46.1], respectively). The estimated extent of emphysema predicted using the combined pulmonary fibrosis and emphysema (CPFE) index [16] was 5.0%, and was higher in female patients than male patients (7.1% [95% CI: 5.6, 8.5] and 4.5% [95% CI: 4.0, 5.1], respectively). Further lung function data recorded at inclusion in RaDiCo-ILD are presented in online suppl. Results. The prominent markers of pulmonary functional impairment at inclusion in the cohort were significantly less severe for women than for men.

Table 3. HRQoL in patients with IPF at inclusion in the RaDiCo-ILD cohort

|                    | Male (n = 600) | Female (n = 124) | Total (N = 724) |
|--------------------|---------------|-----------------|----------------|
| SF-36 physical score | 53.7 ± 22.9   | 45.7 ± 23.0     | 52.4 ± 23.1    |
| 95% CI             | 51.6, 55.8    | 40.9, 50.6      | 50.4, 54.3     |
| Missing, n         | 152           | 34              | 186            |
| SF-36 mental score  | 58.0 ± 22.4   | 50.6 ± 23.3     | 56.8 ± 22.7    |
| 95% CI             | 56.0, 60.1    | 45.8, 55.4      | 54.9, 58.7     |
| Missing, n         | 142           | 31              | 173            |
| SGRQ total score   | 41.5 ± 21.5   | 48.5 ± 20.1     | 42.6 ± 21.4    |
| 95% CI             | 39.4, 43.6    | 43.9, 53.0      | 40.7, 44.5     |
| Missing, n         | 194           | 48              | 242            |
| SGRQ activity score| 54.8 ± 26.1   | 64.6 ± 24.4     | 56.4 ± 26.1    |
| 95% CI             | 52.4, 57.2    | 59.5, 69.7      | 54.2, 58.6     |
| Missing, n         | 139           | 33              | 172            |
| SGRQ symptom score | 49.0 ± 21.0   | 50.8 ± 19.2     | 49.3 ± 20.7    |
| 95% CI             | 47.1, 50.9    | 46.8, 54.9      | 47.5, 51.0     |
| Missing, n         | 146           | 36              | 182            |
| SGRQ impact score  | 34.0 ± 24.2   | 39.1 ± 25.2     | 34.9 ± 24.4    |
| 95% CI             | 31.8, 36.2    | 33.9, 44.3      | 32.8, 36.9     |
| Missing, n         | 139           | 30              | 169            |

Data are mean ± SD unless otherwise stated. CI, confidence interval; HRQoL, health-related quality of life; IPF, idiopathic pulmonary fibrosis; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease; SD, standard deviation; SF-36, 36-Item Short Form survey; SGRQ, St. George’s Respiratory Questionnaire.
and 50.6 [95% CI: 45.8, 55.4]), indicating worse HRQoL.

The mean SGRQ total score was 42.6, with the greatest HRQoL impairment recorded in the activity score (56.4), followed by the symptom (49.3) and impact scores (34.9). The mean SGRQ total score was 41.5 (95% CI: 39.4, 43.6) for male patients and 48.5 (95% CI: 43.9, 53.0) for female patients, suggesting worse overall HRQoL for female patients. Male patients had SGRQ activity and impact scores of 54.8 (95% CI: 52.4, 57.2) and 34.0 (95% CI: 31.8, 36.2), respectively, which were also lower than the respective scores for female patients (64.6 [95% CI: 59.5, 69.7] and 39.1 [95% CI: 33.9, 44.3]). However, SGRQ symptom scores were similar for both male and female patients (49.0 [95% CI: 47.1, 50.9] and 50.8 [95% CI: 46.8, 54.9], respectively).

**Table 4. Chest imaging results for patients at inclusion in the RaDiCo-ILD cohort**

|                          | Male      | Female    | Total     |
|--------------------------|-----------|-----------|-----------|
| Chest scans recorded     | 580       | 123       | 703       |
| Reticular abnormalities  |           |           |           |
| Present                  | 364 (98.1)| 78 (95.1) | 442 (97.6)|
| 95% CI                   | 95.2, 101.1| 90.5, 99.8| 94.2, 100.9|
| Present prominent        | 210 (56.6)| 46 (56.1) | 256 (56.5)|
| 95% CI                   | 45.9, 67.3| 45.4, 66.8| 45.8, 67.2|
| Missing, n               | 209       | 41        | 250       |
| Bronchiectasis           |           |           |           |
| Present                  | 356 (96.0)| 76 (91.6) | 432 (95.2)|
| 95% CI                   | 91.7, 100.2| 85.6, 97.5| 90.5, 99.8|
| Present prominent        | 43 (11.6) | 10 (12.1) | 53 (11.7) |
| 95% CI                   | 4.7, 18.5 | 5.0, 19.1 | 4.8, 18.6 |
| Missing, n               | 209       | 40        | 249       |
| Honeycombing             |           |           |           |
| Present                  | 264 (70.8)| 38 (45.8) | 302 (66.2)|
| 95% CI                   | 61.0, 80.6| 35.1, 56.5| 56.1, 76.4|
| Present prominent        | 43 (11.6) | 10 (12.1) | 53 (11.7) |
| 95% CI                   | 22.4, 42.5| 10.8, 27.8| 20.2, 39.9|
| Missing, n               | 207       | 40        | 247       |
| Emphysema                |           |           |           |
| Present                  | 86 (23.5) | 6 (7.2)   | 92 (20.5) |
| 95% CI                   | 14.4, 32.6| 1.7, 12.8 | 11.8, 29.2|
| Present prominent        | 8 (2.2)   | 1 (1.2)   | 9 (2.0)   |
| 95% CI                   | 0.0, 5.3  | 0.0, 3.6  | 0.0, 5.0  |
| Missing, n               | 214       | 40        | 254       |
| Ground-glass opacity     |           |           |           |
| Present                  | 233 (62.1)| 63 (76.8) | 296 (64.8)|
| 95% CI                   | 51.6, 72.6| 67.7, 86.0| 54.4, 75.1|
| Present prominent        | 13 (3.5)  | 9 (11.0)  | 22 (4.8)  |
| 95% CI                   | 0.0, 7.4  | 4.2, 17.7 | 0.2, 9.5  |
| Missing, n               | 205       | 41        | 246       |

Data are n (%) unless otherwise stated. CI, confidence interval; HRCT, high-resolution computed tomography; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease.

The chest scans of 4 patients were missing. HRCT scans were available for all patients but were not always recorded due to no physician interpretation.

**Chest HRCT Scans at Inclusion**

HRCT scans at inclusion revealed reticular abnormalities as the most common feature across the whole cohort, present in 97.6% of patients and prominent in 56.5% of patients (Table 4). Traction bronchiectasis was also present in almost all HRCT scans (95.2%), which may reflect diagnosis of probable IPF in line with the 2018 IPF classification [13]. Honeycombing was present in the HRCT scans of 66.2% of the total cohort and was present in a higher proportion of male patients (70.8% [95% CI: 61.0, 80.6]) than female patients (45.8% [95% CI: 35.1, 56.5]). There was a numerically higher proportion of male patients with prominent honeycombing compared with female patients (32.4% [95% CI: 22.4, 42.5] and 19.3% [95% CI: 10.8, 27.8], respectively). Emphysema was present in
IPF and Gender in the RaDiCo-ILD Cohort

Prescribed Medication at Inclusion

A summary of the treatments for IPF reported at inclusion is presented in Table 5. The median time between diagnosis and first treatment was 1.1 (IQR: 0.0–3.7) months. The most prescribed first treatment during the time between diagnosis and cohort inclusion for the whole cohort was pirfenidone (36.1%), followed by nintedanib (29.2%). At diagnosis, 21.6% of patients received no treatment (20.6% and 26.5% for male and female patients, respectively). For 13.1% of patients with IPF, glucocorticoids were the first initiated treatment.

Discussion

We conducted an analysis of patients with IPF included in the multicentre RaDiCo-ILD registry in France over a 3-year period. In the present study, we report a comprehensive summary of data recorded at inclusion from patients with IPF according to gender, in terms of demographics, clinical and radiological characteristics, HRQoL, and treatment initiation at the time of study inclusion.

The present study enrolled 724 patients with IPF, of whom 83% were male, representing a higher proportion than those seen across other IPF registries [3, 8, 10, 17]. Patient gender bias at the time of IPF diagnosis is a topic of increasing interest, with a recent study by Assayag et al. [18] demonstrating that male patients are more likely to receive a diagnosis of IPF compared with females, after adjusting for age, smoking history, environmental exposures, and autoantibodies. This suggests that females may be under-diagnosed and males may be over-diagnosed with IPF [18]. An indirect, observational study that used data from the French hospital discharge database presented a very different picture of the IPF diagnosis disparity between genders in France, with a male population of 56.4% (n = 3,650/6,467) [19]. Other large, national, epidemiological studies based on hospital databases in countries such as Finland, Italy, and Denmark also demonstrated lower percentages of male patients than the RaDiCo-ILD cohort [20–23]. Despite study limitations with regard to the use of International Classification of Diseases codes to identify populations with IPF [19], which may present a risk of disease misclassification, the differences in gender distribution suggest that female patients may be under-diagnosed in the RaDiCo-ILD cohort. We speculate that this finding may be related to the low frequency of honeycombing as a prominent HRCT feature, as it is a key component of the usual interstitial pneumonia pattern on HRCT [13].

Registries have provided a wealth of information about the characteristics of patients with IPF. The RaDiCo-ILD registry included patients with IPF who had been treated in participating reference centres, representing the most severe and atypical cases; as such, it is difficult to compare our registry findings with those from other registries, especially given that each have their own population particularities. The Australian IPF Registry included all patients with a diagnosis of IPF referred from their treating pulmonologist. Patients from the Australian IPF Registry

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Table 5. IPF treatment reported at inclusion in the RaDiCo-ILD cohort

| Treatment initiated at diagnosis | Male (n = 600) | Female (n = 124) | Total (N = 724) |
|---------------------------------|---------------|-----------------|---------------|
| Pirfenidone                     | 213 (37.5)    | 36 (29.8)       | 249 (36.1)    |
| Nintedanib                      | 167 (29.4)    | 34 (28.1)       | 201 (29.2)    |
| No drug                         | 117 (20.6)    | 32 (26.5)       | 149 (21.6)    |
| Glucocorticoids                 | 71 (12.5)     | 19 (15.7)       | 90 (13.1)     |
| Median oxygen delay (IQR), months | 2.4 (−1.1 to 21.8) | −0.5 (−9.4 to 10.8) | 1.9 (−1.4 to 20.3) |

Note: Data are n (%) unless otherwise stated. IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease.
had greater baseline lung function, with higher FVC %, DL_{CO} %, and longer 6 MWT distance compared with patients with IPF in the RaDiCo-ILD cohort [3]. However, compared with the Pulmonary Fibrosis Foundation Patient Registry and a smaller Swiss registry, which were also reference centre registries, RaDiCo-ILD patients had less impaired lung function at inclusion [10, 24].

Within the RaDiCo-ILD cohort of patients with IPF, there were no remarkable gender differences in age or time intervals between onset of symptoms and diagnosis, or between diagnosis and cohort inclusion. When compared with participants in EMPIRE, RaDiCo-ILD participants experienced a longer delay between the onset of symptoms and diagnosis [25]. They were also older at inclusion compared with other published IPF cohorts [3, 25–29], but younger compared with studies based on claims data [19, 30]. Hence, the RaDiCo-ILD cohort may better reflect the age of patients with IPF in the population, with less referral bias compared with other IPF registries.

The World Health Organization reports that the prevalence rate of current smokers in France is 31.9% according to the most recent nationally representative survey in 2017, with prevalence in men and women of 35.2% and 28.7%, respectively [31], but no data are available regarding ex-smokers. In our study, we found that 75% of male patients had a history of smoking, compared with 27% of female patients, representing a far greater gender disparity than in the general population today. However, our study represents an ageing population who are likely to have started smoking in the 1970s and 1980s when there were greater differences in the proportions of male and female smokers in France [32]. This high proportion of male smokers is in accordance with previous reports [5, 18, 24], including COFI, a national, multicentre, prospective IPF cohort with a study enrolment period of 2007–2010 (unpublished). Of note, more than half of female patients with IPF had never smoked. Since smoking is known to be one of the main triggers in IPF pathophysiology, this could indicate different mechanisms of IPF occurrence in males and females.

Comorbidity prevalence was similar to previously reported registries, with gastro-oesophageal reflux disease and arterial hypertension the most common comorbidities reported across both genders [10, 24, 29]. Coronary heart disease, diabetes, and emphysema were more prevalent among males at study inclusion compared with females, whereas thyroid dysfunction, which was mostly hypothyroidism, was more common among female patients. Given that female gender is a confounding factor for thyroid dysfunction, this finding was expected. The Swedish IPF registry demonstrated similar findings and showed that coronary heart disease was more prevalent in males regardless of smoking history, whereas thyroid diseases were more prevalent in ex-smoking females [8]. These differences likely reflect the imbalance of these conditions in the general population.

In the current study, males had lower FVC and forced expiratory volume in 1 s per cent predicted at inclusion compared with females, suggesting a lung volume disadvantage that is consistent with previous reports [8, 33]. Interestingly, the difference is observed despite similar mean duration of symptoms before diagnosis between male and female patients. Although it is possible that female patients have an earlier perception of their symptoms, this could be associated with more extensive fibrosis at diagnosis in male patients compared with females, especially since male patients had higher composite physiologic index scores (which reflect the extent of fibrosis on HRCT regardless of the emphysema extent). Despite the high prevalence of smoking history, a relatively low proportion of patients had emphysema on HRCT, as reflected by low values of CPFE index (which reflect the extent of emphysema on HRCT regardless of the extent of fibrosis). Female patients had significantly higher CPFE index scores compared with males, which suggests that the observation of greater lung volume in females compared with males in our cohort may be associated with more extensive emphysema. Overall, GAP index scores were higher for male patients than female patients, and more males were in GAP Stage III. The inclusion of male gender in the GAP index calculation may account for this gender imbalance, since male gender contributes 1 point to the index out of a maximum of 8 [7].

Female patients had poorer HRQoL based on SF-36 and total SGRQ scores, despite having higher FVC at inclusion than male patients and similar DL_{CO}. Interestingly, our data suggest that men and women were similarly affected by IPF symptoms, although women were more acutely affected by psychosocial dysfunction (SGRQ impact score) and disruption of daily physical activity (SGRQ activity score) than men. This discrepancy illustrates the multidimensional aspect of HRQoL in IPF. For instance, lung function decline, cough frequency, dyspnoea intensity, anxiety, and depression all influence HRQoL in patients with IPF [17, 34]. This difference in HRQoL between genders has also been described for other chronic respiratory diseases such as chronic obstructive pulmonary disease [35].
Although reticulations were the most common imaging characteristics at cohort inclusion, there were some key gender discrepancies. Honeycombing was present in the chest scans of a greater proportion of male patients than females, while ground-glass opacities were present in a greater proportion of female scans. This study is one of few to have access to HRCT scans at inclusion, according to gender. In accordance with our data, the COFI cohort demonstrated a significant predominance of honeycombing and emphysema within the male population, although it was more prevalent overall (unpublished). This may have contributed to gender imbalance in the RaDiCo-ILD cohort of patients with IPF, with honeycombing facilitating the non-invasive diagnosis of IPF in males.

Our study revealed that 22% of patients did not receive treatment at diagnosis; however, it is likely that some patients with good lung function and few symptoms may have only initiated treatment once disease progression was confirmed. More than half of patients (65%) received antifibrotic treatment at diagnosis, which reflected the availability of nintedanib and pirfenidone at the time of study enrolment. Glucocorticoids were prescribed to 13% of patients at diagnosis, which may represent the population with the most advanced disease, requiring palliation of symptoms.

As with any observational study, several potential biases are possible. Data bias was limited by the French organization of reference and competence centres, which agreed to diagnose IPF in accordance with international and national guidelines defining a common diagnosis algorithm. Our study does not include data on the proportion of patients who had lung biopsies at diagnosis or were diagnosed with definite or probable IPF due to challenges in collecting such data in a real-life cohort and the change in ATS/ERS IPF diagnosis criteria during the course of patient inclusion. HRCT scans were obtained and analysed in each reference centre and were not systematically reviewed by a panel of radiologists; hence, it is possible that there are inconsistencies across centres. In addition, although HRCT scans were available for all patients at inclusion, there were missing data. Physician-associated selection bias is also possible, as patients included from the southern part of France are under-represented, with these centres being inactive due to administrative authorization concerns. However, the most active French OrphaLung or RespiFIL centres participated and enrolled most of their patients with IPF, which should ensure the representativeness of selected centres and minimize bias.

Conclusions

In conclusion, our multicentre registry study conducted at reference centres throughout France provides further evidence of gender imbalance in lung volume and chest HRCT features at diagnosis of IPF, with male patients more likely to have emphysema, a greater lung volume reduction, and more honeycombing on HRCT than female patients. Interestingly, our study suggests that female patients have a poorer HRQoL despite better lung volume, highlighting the multidimensional aspect of HRQoL in IPF.

Acknowledgements

Medical writing assistance was supported financially by RaDiCo and Boehringer Ingelheim and provided by Hannah Cook, PhD, of MediTech Media, under the authors’ conceptual direction and based on feedback from the authors. Boehringer Ingelheim is an industrial supporter of the RaDiCo-ILD cohort. A full list of investigators is included in the online suppl. material. REDCap is a secure, web-based application from the Vanderbilt University, USA, designed to support data capture for research studies.

Statement of Ethics

The registry was conducted in accordance with the ethical principles detailed in the Declaration of Helsinki, and written informed consent was obtained from all patients. The registry was approved by the ethical committee of the Inserm Institute, France on October 6, 2016 (approval no. IRB00003888), and the Commission Nationale de l’Informatique et des Libertés on November 3, 2016.

Conflict of Interest Statement

V.C. reports grants from Boehringer Ingelheim (BI); personal fees from Actelion, BI, Bayer/Merck, Sharp & Dohme (MSD), Novartis, Roche/Promedior, Sanofi, Celgene, Galapagos, Galecto, Shionogi, and AstraZeneca; and non-financial support from Roche/Promedior, Actelion, and BI, outside the submitted work. S.G. is an employee of RaDiCo and reports financial support of the RaDiCo-ILD cohort from BI, during the conduct of the study. S.J. reports personal fees from Actelion, AIRB, AstraZeneca, Bristol Myers Squibb (BMS), BI, Chiesi, Galecto Biotech, Gilead, GlaxoSmithKline (GSK), Lieven Van Landuyt Medipharm, Mundipharma, Novartis, Pfizer, Roche, Savara Pharmaceuticals, and Genzyme. He is a clinical trial investigator for Bellerophon Therapeutics, Biogen, Plant Therapeutics, and Pharm-Olam, outside the submitted work. H.N. reports grants from Roche/Genentech and BI; and personal fees from Roche/Genentech, BI, and Galapagos. He is also a clinical trial investigator for Sanofi, Gilead, Novartis, and Galecto Biotech, outside the submitted work. B.C. reports grants from AstraZeneca and BI; personal fees from AstraZeneca, BI, Roche, Sanofi, Gen-
zyme, and BMS; and non-financial support from AstraZeneca, BI, Roche, Sanofi, Genzyme, and BMS, outside the submitted work. P.B. reports personal fees from Roche, BI, Novartis, Teva, and AstraZeneca. He has also received congress travel fees and/or speaker honoraria from Roche, BI, Novartis, Chiesi, Stallerenge, and Sanofi, outside the submitted work. L.W.-S. reports personal fees from BI, Roche, BMS, and Sanofi; and non-financial support from BI and Roche, outside the submitted work. M.R.-G. has nothing to disclose. D.L.-B. has nothing to disclose. J.C. has nothing to disclose. S.M.-A. received congress travel fees and/or speaker honoraria from BI, Roche, and Novartis, outside the submitted work. S.H. has nothing to disclose. S.H. has nothing to disclose. D.I.-B. has nothing to disclose. J.C. has nothing to disclose.

**Funding Sources**

The RaDiCo-ILD cohort was implemented as part of the RaDiCo research programme, funded by the French National Research Agency under the “cohorts” programme of the Investissements d’Avenir (Investments for the Future) (ANR-10-COHO-0003) and coordinated by the French National Institute for Health and Medical Research (Inserm Unité UMR S933, Hôpital Trousseau).

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