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1 **Research article**

2 **Impact of gender on the characteristics of patients with idiopathic pulmonary fibrosis**
3 **included in the RaDiCo-ILD cohort**

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39

40 **Running head:** Idiopathic pulmonary fibrosis and gender in the RaDiCo-ILD cohort

41

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45

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49 **Keywords:** idiopathic pulmonary fibrosis; idiopathic interstitial pneumonia; registry; gender;
50 patient characteristics; France [3–6 keywords]

51 **Abstract**

52 **Background:** There is growing evidence of gender-specific phenotypic differences amongst
53 patients with idiopathic pulmonary fibrosis (IPF), which may affect patient outcomes.

54 **Objectives:** We present the characteristics of patients with IPF at inclusion in the French
55 Rare Disease Cohort – Interstitial Lung Disease (RaDiCo-ILD) with the aim of characterising
56 gender-specific phenotypic differences.

57 **Methods:** Patients with IPF who were enrolled in the national, multicentre RaDiCo-ILD
58 cohort were included. Demographic characteristics, comorbidities, health-related quality of
59 life (HRQoL) scores, pulmonary function, chest imaging and IPF treatment were collected at
60 inclusion and described by gender.

61 **Results:** The cohort included 724 patients with IPF (54% of RaDiCo-ILD cohort), of whom
62 82.9% were male. The proportion of male and female patients with a prior history of smoking
63 was 75.0% and 26.8%, respectively. Emphysema was present in 17.0% (95% confidence
64 interval [CI]: 10.0, 24.0) of men and 5.4% (95% CI: 1.2, 9.6) of women. At inclusion, females
65 had poorer HRQoL than males based on St. George's Respiratory Questionnaire scores
66 (48.5 [95% CI: 43.9, 53.0] and 41.5 [39.4, 43.6], respectively). The mean forced vital
67 capacity percent predicted was 77.7% (95% CI: 76.2, 79.3) and 87.4% (83.4, 91.4) for males
68 and females, respectively. Honeycombing on high-resolution computed tomography (HRCT)
69 was present in 70.8% (95% CI: 61.0, 80.6) of males and 45.8% (95% CI: 35.1, 56.5) of
70 females.

71 **Conclusions:** This analysis of patients with IPF at inclusion in the RaDiCo-ILD cohort
72 provides evidence that comorbid emphysema, lung volume reduction and honeycombing on
73 HRCT are more common characteristics of males than females.

74 **Trial registration:** ClinicalTrials.gov (NCT04238871).

75

76 **Introduction**

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

85 IPF occurs predominantly in men, who account for approximately 70% of all cases [1, 3, 5].
86 The reason for this gender disparity is still largely unknown, but it has been hypothesised
87 that greater male exposure to cigarette smoke and environmental and occupational risk
88 factors may play a role [6]. The Gender, Age, Physiology (GAP) index and scoring system
89 has acknowledged gender as an important determinant of outcome in IPF, with male sex,
90 older age (>65 years) and poor pulmonary function associated with a higher risk of mortality
91 [7]. Recent studies have further demonstrated that patient sex can have clinical and
92 prognostic implications in IPF, with significantly poorer lung function observed in males
93 compared with females at registry inclusion [8] and 40% higher risk of death or lung
94 transplantation [5].

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

102 providing novel insights into the natural course of the disease and clinical management of
103 IPF [9].

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

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

121

122 **Materials and methods**

123 **The RaDiCo-ILD cohort**

124 RaDiCo-ILD is a national, multicentre, non-interventional cohort study in France. The
125 majority of participating centres are part of the French national networks of reference and
126 competence centres for rare respiratory diseases (OrphaLung and Rare Respiratory

127 Diseases Healthcare Faculty [RespiFIL] networks). The full list of participating centres and
128 investigators is included in [Supplementary Table S1](#).

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

134

135 **IPF cohort**

136 The IPF cohort was a subgroup of patients included in the RaDiCo-ILD study. All patients in
137 the IPF cohort who met the following criteria were included in the present study: (1) aged
138 >18 years; (2) IPF diagnosed using the American Thoracic Society/European Respiratory
139 Society (ATS/ERS) 2011 criteria [1] (until the revision of criteria in September 2018, which
140 was subsequently used, allowing for the inclusion of patients with a diagnosis of probable
141 IPF [13]); and (3) completion of a pulmonary function test (PFT) at inclusion visit. A
142 multidisciplinary discussion was recommended to obtain a diagnosis, based on clinical signs,
143 radiological investigation and surgical biopsy.

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

148

149 **Statistical analyses**

150 The analyses in this study were mainly descriptive and were performed with SAS[®] 9.4
151 software. The characteristics of patients with IPF were described. For continuous variables,

152 the number, number of missing values, median (range) or mean (standard deviation)
153 according to the normality of the distribution, and 95% confidence interval (CI) of the means
154 were included. For categorical variables, the number, percentage and 95% CI of the
155 proportion were included. Data including demographic characteristics, significant
156 comorbidities, pulmonary function testing, chest imaging, health-related quality of life
157 (HRQoL) and IPF treatment were collected at inclusion visit and described by gender.
158 Comorbidities at inclusion were recorded by investigators as present or absent. HRCT scans
159 were obtained and analysed in each reference centre by each investigator independently,
160 according to ATS/ERS recommendations. Although the study was not powered to assess
161 the significance of gender comparisons, the population was described according to gender
162 and the 95% CIs were calculated. An absence of confidence interval overlap between
163 gender subgroups was considered a statistically significant difference.

164 Results of predictive prognostic measures were collected, including normalised 6-minute
165 walk test (6MWT) values and GAP index scores and stages. To normalise the score with
166 age and stature, the 6MWT is expressed as a percentage of the predicted value of a
167 corresponding healthy subject [14]. The GAP index stratifies patients into three stages of
168 increasing risk: Stage I with 0–3 points, Stage II with 4–5 points, and Stage III with 6–8
169 points [7].

170 Measures of HRQoL included the 36-Item Short Form survey (SF-36) and St. George's
171 Respiratory Questionnaire (SGRQ) [15], with higher SF-36 scores and lower SGRQ scores
172 indicating better health status.

173

174 **Results**

175 Of 1,345 patients with ILD enrolled in the RaDiCo-ILD registry between 3 July 2017 and 28
176 September 2020, 963 were adult patients with IPF (83% male, 17% female). Of these, 724

177 patients had completed PFTs and were therefore included in this analysis. The gender
178 distribution was 600 males (83%) and 124 females (17%) (Figure 1).

179

180 **Demographic and diagnostic characteristics at inclusion**

181 Patient demographics for all patients with IPF are presented in Table 1. In the whole cohort,
182 the mean age at diagnosis was 70.9 years and was similar for males and females (70.7
183 [95% CI: 70.0, 71.3] and 72.1 [95% CI: 70.5, 73.7] years, respectively). The median time
184 period between diagnosis and cohort inclusion was 7.8 months (interquartile range [IQR]:
185 0.5–25.4). The median time between first symptom and a diagnosis of IPF was 2.0 years
186 (IQR: 1.0–4.0) for both male and female patients. The overall mean body mass index was
187 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,
188 28.6] for female patients) indicating that most were in the overweight range. **Consistent with
189 current practice, lung biopsies were performed in 24.1% of patients, and no significant
190 differences were observed between male and female patients (22.9% [95% CI: 15.5, 30.4]
191 and 29.5 [95% CI: 21.4, 37.6], respectively).**

192

193 **Patient comorbidities at inclusion**

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

202 total cohort, affecting 5.8% (95% CI: 1.7, 10.0) and 22.6% (95% CI: 15.2, 29.9) of male and
203 female patients, respectively.

204 The proportion of active tobacco smokers was 5.3% (95% CI: 1.4, 9.3) and 8.1% (95% CI:
205 3.3, 13.0) in the male and female populations, respectively. More than half of female patients
206 (52.9% [95% CI: 44.0, 61.7]) had never smoked (defined as having less than 100 cigarettes
207 during their lifetime) compared with 19.0% (95% CI: 12.1, 25.9) of male patients. The
208 majority of male patients used to smoke and had been cigarette-free for at least 6 months
209 prior to inclusion (75.0% [95% CI: 67.4, 82.7]), compared with over a quarter of female
210 patients (26.8% [95% CI: 19.0, 34.7]). A higher proportion of female patients had exposure
211 to passive smoking compared with male patients (12.2% [95% CI: 6.4, 18.0] and 0.7% [95%
212 CI: 0.0, 2.1], respectively).

213

214 **Clinical characteristics at inclusion**

215 A summary of the lung function of patients with IPF reported at inclusion to the cohort is
216 presented in [Table 2](#). The mean forced vital capacity (FVC) percent predicted was
217 **statistically lower for male patients compared with female patients** (77.7% [95% CI: 76.2,
218 79.3] and 87.4% [95% CI: 83.4, 91.4], respectively). The mean diffusing capacity of the lungs
219 for carbon monoxide (DL_{CO}) percentage was 46.1% (95% CI: 44.6, 47.6) in males and
220 46.9% (95% CI: 44.2, 49.7) in females.

221 The mean GAP index score for the whole cohort at inclusion was 4.0. The proportion of male
222 and female patients who were GAP Stage I was 30.2% (95% CI: 21.2, 39.1) and 67.3%
223 (95% CI: 58.2, 76.5), respectively, whereas the proportion who were GAP Stage III was
224 17.3% (95% CI: 9.9, 24.7) and 1.0% (95% CI: 0.0, 2.9), respectively. The mean composite
225 physiologic index (CPI) at inclusion for all patients was 47.0, and this was higher for male
226 patients than female patients (47.6 [95% CI: 46.4, 48.8] and 43.8 [95% CI: 41.4, 46.1],
227 respectively). The estimated extent of emphysema predicted using the combined pulmonary

228 fibrosis and emphysema (CPFE) index [16] was 5.0%, and was higher in female patients
229 than male patients (7.1% [95% CI: 5.6, 8.5] and 4.5% [95% CI: 4.0, 5.1], respectively).

230 Further lung function data recorded at inclusion in RaDiCo-ILD are presented in
231 **Supplementary Results**. The prominent markers of pulmonary functional impairment at
232 inclusion to the cohort were significantly less severe for women than for men.

233 At cohort inclusion, the mean SF-36 physical and mental scores for the whole population
234 were 52.4 (95% CI: 50.4, 54.3) and 56.8 (95% CI: 54.9, 58.7), respectively (**Table 3**). For
235 male patients, the mean SF-36 physical and mental scores were 53.7 (95% CI: 51.6, 55.8)
236 and 58.0 (95% CI: 56.0, 60.1), respectively. Both scores were numerically lower in female
237 patients (45.7 [95% CI: 40.9, 50.6] and 50.6 [95% CI: 45.8, 55.4], respectively), indicating
238 worse HRQoL.

239 The mean SGRQ total score was 42.6, with the greatest HRQoL impairment recorded in the
240 activity score (56.4), followed by the symptom (49.3) and impact scores (34.9). The mean
241 SGRQ total score was 41.5 (95% CI: 39.4, 43.6) for male patients and 48.5 (95% CI: 43.9,
242 53.0) for female patients, suggesting worse overall HRQoL for female patients. Male patients
243 had SGRQ activity and impact scores of 54.8 (95% CI: 52.4, 57.2) and 34.0 (95% CI: 31.8,
244 36.2), respectively, which were also lower than the respective scores for female patients
245 (64.6 [95% CI: 59.5, 69.7] and 39.1 [95% CI: 33.9, 44.3], respectively). However, SGRQ
246 symptom scores were similar for both male and female patients (49.0 [95% CI: 47.1, 50.9]
247 and 50.8 [95% CI: 46.8, 54.9], respectively).

248

249 **Chest HRCT scans at inclusion**

250 HRCT scans at inclusion revealed reticular abnormalities as the most common feature
251 across the whole cohort, present in 97.6% of patients and prominent in 56.5% of patients
252 (**Table 4**). Traction bronchiectasis was also present in almost all HRCT scans (95.2%), which
253 may reflect diagnosis of probable IPF in line with the 2018 IPF classification [13].

254 Honeycombing was present in the HRCT scans of 66.2% of the total cohort and was present
255 in a higher proportion of male patients (70.8% [95% CI: 61.0, 80.6]) than female patients
256 (45.8% [95% CI: 35.1, 56.5]). There was a numerically higher proportion of male patients
257 with prominent honeycombing compared with female patients (32.4% [95% CI: 22.4, 42.5]
258 and 19.3% [95% CI: 10.8, 27.8], respectively). Emphysema was present in 20.5% of the total
259 cohort and was more common in male patients than female patients (23.5% [95% CI: 14.4,
260 32.6] and 7.2% [95% CI: 1.7, 12.8], respectively). In the total cohort at cohort inclusion,
261 64.8% had ground-glass opacities on HRCT, present in 62.1% (95% CI: 51.6, 72.6) of male
262 patients and 76.8% (95% CI: 67.7, 86.0) of female patients.

263

264 **Prescribed medication at inclusion**

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

272

273 **Discussion**

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

279 The present study enrolled 724 patients with IPF, of whom 83% were male, representing a
280 higher proportion than those seen across other IPF registries [3, 8, 17, 10]. Patient gender
281 bias at the time of IPF diagnosis is a topic of increasing interest, with a recent study by
282 Assayag et al. demonstrating that male patients are more likely to receive a diagnosis of IPF
283 compared with females, after adjusting for age, smoking history, environmental exposures
284 and autoantibodies. This suggests that females may be under-diagnosed and males may be
285 over-diagnosed with IPF [18]. An indirect, observational study that used data from the
286 French hospital discharge database presented a very different picture of the IPF diagnosis
287 disparity between genders in France, with a male population of 56.4% (n=3,650/6,467) [19].
288 Other large, national, epidemiological studies based on hospital databases in countries such
289 as Finland, Italy and Denmark also demonstrated lower percentages of male patients than
290 the RaDiCo-ILD cohort [20-23]. Despite study limitations with regards to the use of
291 International Classification of Diseases codes to identify populations with IPF [19], which
292 may present a risk of disease misclassification, the differences in gender distribution suggest
293 that female patients may be under-diagnosed in the RaDiCo-ILD cohort. We speculate that
294 this finding may be related to the low frequency of honeycombing as a prominent HRCT
295 feature, as it is a key component of the usual interstitial pneumonia pattern on HRCT [13].
296 Registries have provided a wealth of information about the characteristics of patients with
297 IPF. The RaDiCo-ILD registry included patients with IPF who had been treated in
298 participating reference centres, representing the most severe and atypical cases; as such, it
299 is difficult to compare our registry findings with those from other registries, especially given
300 that each have their own population particularities. The Australian IPF Registry (AIPFR)
301 included all patients with a diagnosis of IPF referred from their treating pulmonologist.
302 Patients from the AIPFR had greater baseline lung function, with higher FVC%, DLCO% and
303 longer 6MWT distance compared with patients with IPF in the RaDiCo-ILD cohort [3].
304 However, compared with the Pulmonary Fibrosis Foundation Patient Registry and a smaller

305 Swiss registry, which were also reference centre registries, RaDiCo-ILD patients had less
306 impaired lung function at inclusion [24, 10].

307 Within the RaDiCo-ILD cohort of patients with IPF, there were no remarkable gender
308 differences in age or time intervals between onset of symptoms and diagnosis, or between
309 diagnosis and cohort inclusion. When compared with participants in EMPIRE, RaDiCo-ILD
310 participants experienced a longer delay between the onset of symptoms and diagnosis [25].
311 They were also older at inclusion compared with other published IPF cohorts [26, 27, 3, 28,
312 29, 25], but younger compared with studies based on claims data [19, 30]. Hence, the
313 RaDiCo-ILD cohort may better reflect the age of patients with IPF in the population, with less
314 referral bias compared to other IPF registries.

315 The World Health Organization reports that the prevalence rate of current smokers in France
316 is 31.9% according to the most recent nationally representative survey in 2017, with
317 prevalence in men and women of 35.2% and 28.7%, respectively [31], but no data are
318 available regarding ex-smokers. In our study, we found that 75% of male patients had a
319 history of smoking, compared with 27% of female patients, representing a far greater gender
320 disparity than in the general population today. However, our study represents an ageing
321 population who are likely to have started smoking in the 1970's and 1980's when there were
322 greater differences in the proportions of male and female smokers in France [32]. This high
323 proportion of male smokers is in accordance with previous reports [24, 18, 5], including
324 COFI, a national, multicentre, prospective IPF cohort with a study enrolment period of 2007–
325 2010 [unpublished]. Of note, more than half of female patients with IPF had never smoked.
326 Since smoking is known to be one of the main triggers in IPF pathophysiology, this could
327 indicate different mechanisms of IPF occurrence in males and females.

328 Comorbidity prevalence was similar to previously reported registries, with GERD and arterial
329 hypertension the most common comorbidities reported across both genders [24, 29, 10].
330 Coronary heart disease, diabetes and emphysema were more prevalent among males at
331 study inclusion compared with women, whereas thyroid dysfunction, which was mostly

332 hypothyroidism, was more common among female patients. Given that female gender is a
333 confounding factor for thyroid dysfunction, this finding was expected. The Swedish IPF
334 registry demonstrated similar findings and showed that coronary heart disease was more
335 prevalent in males regardless of smoking history, whereas thyroid diseases were more
336 prevalent in ex-smoking females [8]. These differences likely reflect the imbalance of these
337 conditions in the general population.

338 In the current study, males had lower FVC and forced expiratory volume in 1 second percent
339 predicted at inclusion compared with females, suggesting a lung volume disadvantage that is
340 consistent with previous reports [33, 8]. Interestingly, the difference is observed despite
341 similar mean duration of symptoms before diagnosis between male and female patients.
342 Although it is possible that female patients have an earlier perception of their symptoms, this
343 could be associated with more extensive fibrosis in HRCT scans at diagnosis in male
344 patients compared with females, especially since male patients had higher CPI scores
345 (which reflect the extent of fibrosis on HRCT regardless of the emphysema extent). Despite
346 the high prevalence of smoking history, a relatively low proportion of patients had
347 emphysema on HRCT, as reflected by low values of CPFE index (which reflects the extent
348 of emphysema on HRCT regardless of the extent of fibrosis). Female patients had
349 significantly higher CPFE index scores compared with males, which suggests that the
350 observation of greater lung volume in women compared with males in our cohort may be
351 associated with more extensive emphysema. Overall, GAP index scores were higher for
352 male patients than female patients, and more males were in GAP Stage III. The inclusion of
353 male gender in the GAP index calculation may account for this gender imbalance, since
354 male gender contributes one point to the index out of a maximum of eight [7].

355 Female patients had poorer HRQoL based on SF-36 and total SGRQ scores, despite having
356 higher FVC at inclusion than male patients and similar DL_{CO}. Interestingly, our data suggest
357 that men and women were similarly affected by IPF symptoms, although women were more
358 acutely affected by psychosocial dysfunction (SGRQ impact score) and disruption of daily

359 physical activity (SGRQ activity score) than men. This discrepancy illustrates the
360 multidimensional aspect of HRQoL in IPF. For instance, lung function decline, cough
361 frequency, dyspnoea intensity, anxiety and depression all influence HRQoL in patients with
362 IPF [34, 17]. This difference in HRQoL between genders has also been described for other
363 chronic respiratory diseases such as chronic obstructive pulmonary disease [35].

364 Although reticulations were the most common imaging characteristics at cohort inclusion,
365 there were some key gender discrepancies. Honeycombing was present in the chest scans
366 of a greater proportion of male patients than females, while ground-glass opacities were
367 present in a greater proportion of female scans. This study is one of few to have access to
368 HRCT scans at inclusion, according to gender. In accordance with our data, the COFI cohort
369 demonstrated a significant predominance of honeycombing and emphysema within the male
370 population, although it was more prevalent overall [unpublished]. This may have contributed
371 to gender imbalance in the RaDiCo-ILD cohort of patients with IPF, with honeycombing
372 facilitating the non-invasive diagnosis of IPF in males.

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

380 As with any observational study, several potential biases are possible. Data bias was limited
381 by the French organisation of reference and competence centres, which agreed to diagnose
382 IPF in accordance with international and national guidelines defining a common diagnosis
383 algorithm. Our study does not include data on the proportion of patients who had lung
384 biopsies at diagnosis or were diagnosed with definite or probable IPF due to challenges
385 collecting such data in a real-life cohort and the change in ATS/ERS IPF diagnosis criteria

386 during the course of patient inclusion. HRCT scans were obtained and analysed in each
387 reference centre and were not systematically reviewed by a panel of radiologists; hence, it is
388 possible that there are inconsistencies across centres. In addition, although HRCT scans
389 were available for all patients at inclusion, there were missing data. Physician-associated
390 selection bias is also possible, as patients included from the southern part of France are
391 under-represented, with these centres being inactive due to administrative authorisation
392 concerns. However, the most active French OrphaLung or RespiFIL centres participated and
393 enrolled most of their patients with IPF, which should ensure the representativeness of
394 selected centres and minimise bias.

395

396 **Conclusions**

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

403

404 **Statements**

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412 **Statement of ethics**

413 The registry was conducted in accordance with the ethical principles detailed in the
414 Declaration of Helsinki, and written informed consent was obtained from all patients. The
415 registry was approved by the ethical committee of the Inserm Institute, France on 6 October
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419 VC reports grants from Boehringer Ingelheim (BI); personal fees from Actelion, BI,
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465 **Authors' contributions**

466 The authors meet the criteria for authorship as recommended by the International
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469 Vincent Cottin and Isabelle Dufaure-Garé contributed to the data analysis and interpretation
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471

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- 575

Table 1. Patient characteristics at inclusion in the RaDiCo-ILD cohort

	Male (n=600)	Female (n=124)	Total (N=724)
Mean age, years \pmSD	72.1\pm8.5	73.3\pm8.7	72.3\pm8.5
95% CI	71.6, 72.8	72.9, 75.6	72.0, 73.1
Mean age at diagnosis, years \pmSD	70.7\pm8.6	72.1\pm9.1	70.9\pm8.7
95% CI	70.0, 71.3	70.5, 73.7	70.3, 71.5
Median time between diagnosis and inclusion, months (IQR)	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, years (IQR)	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, kg/m² \pmSD	26.8\pm4.0	27.6\pm5.2	26.9\pm4.2
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
Gastroesophageal 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^a	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^b	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

577 Data are n (%) unless otherwise stated.

578 ^aReported as a comorbidity at registry inclusion.

579 ^bDefined as having less than 100 cigarettes during lifetime.

580 BMI, body mass index; CI, confidence interval; IQR, interquartile range; RaDiCo-ILD, Rare

581 Disease Cohort – Interstitial Lung Disease; SD, standard deviation.

582

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
DL_{CO} % 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, 39.1	58.2, 76.5	26.9, 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 (14.6)
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

6MWT, metres	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
Normalised 6MWT, % 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

584 Data are mean±SD unless otherwise stated.

585 6MWT, 6-minute walk test; CI, confidence interval; CPFE, combined pulmonary fibrosis and
586 emphysema; CPI, composite physiologic index; DL_{CO}, diffusing capacity for carbon
587 monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GAP,
588 Gender, Age, Physiology; IPF, idiopathic pulmonary fibrosis; RaDiCo-ILD, Rare Disease
589 Cohort – Interstitial Lung Disease; SD, standard deviation.

590

591

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

	Male	Female	Total
	(n=600)	(n=124)	(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

593 Data are mean±SD unless otherwise stated.

594 CI, confidence interval; HRQoL, health-related quality of life; IPF, idiopathic pulmonary
 595 fibrosis; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease; SD, standard
 596 deviation; SF-36, 36-Item Short Form survey; SGRQ, St. George's Respiratory
 597 Questionnaire.

598

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

	Male	Female	Total
Chest scans recorded^a	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	121 (32.4)	16 (19.3)	137 (30.0)
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

600 Data are n (%) unless otherwise stated.

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

603 CI, confidence interval; HRCT, high-resolution computed tomography; IPF, idiopathic
604 pulmonary fibrosis; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease.

605

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

	Male (n=600)	Female (n=124)	Total (N=724)
Median time between diagnosis and first treatment, months (IQR)	1.1 (0.0–3.8)	1.0 (0.0–3.1)	1.1 (0.0–3.7)
Missing, n	89	24	113
Treatment initiated at diagnosis^a			
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, months (IQR)	2.4 (-1.1–21.8)	-0.5 (-9.4–10.8)	1.9 (-1.4–20.3)
Missing, n	10	1	11

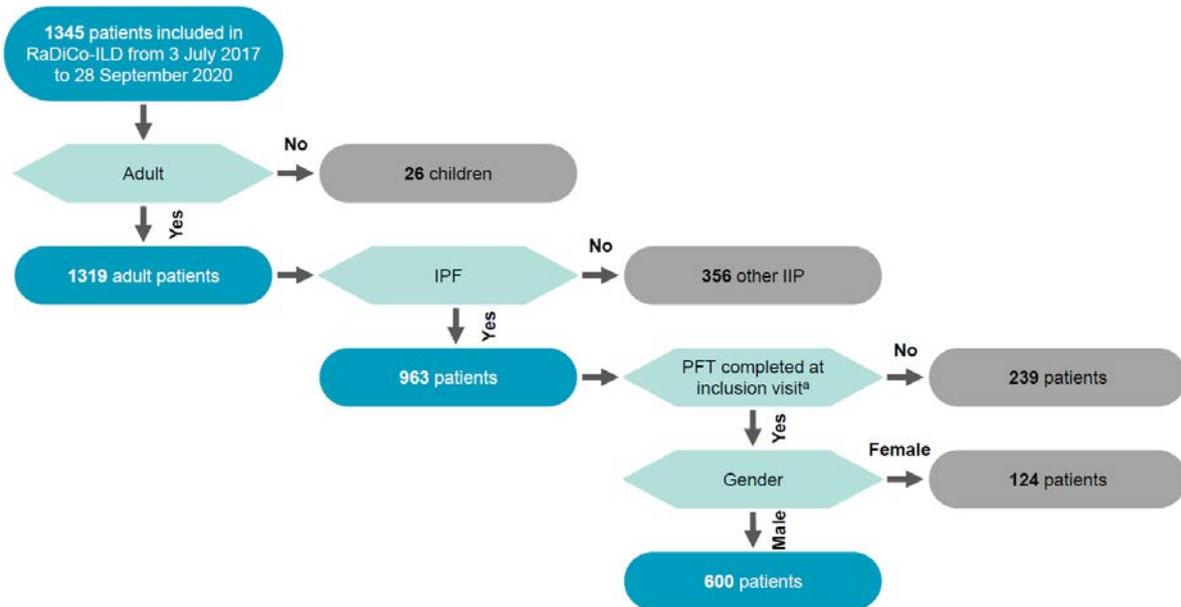
607 Data are n (%) unless otherwise stated.

608 ^aDefined as the first treatment during the time between diagnosis and inclusion in the cohort.

609 IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; RaDiCo-ILD, Rare Disease

610 Cohort – Interstitial Lung Disease.

611 **Figure 1. Patient flow chart**



612

613 ^aPFT at inclusion visit completed for patients included up to 13 May 2020.

614 IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; PFT, pulmonary
615 function test; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease.

616

617 **Supplementary Methods. Inclusion/exclusion criteria for the RaDiCo-ILD cohort**

- 618 • Inclusion criteria:
- 619 ○ Patient with a diagnosis of idiopathic interstitial pneumonia (IIP).
- 620 ○ Clinical criteria:
- 621 ▪ Chronic respiratory insufficiency manifestations, including
- 622 dyspnoea/tachypnoea, cough and cyanosis during exercise or at rest.
- 623 ○ Radiological criteria:
- 624 ▪ Characteristic chest high-resolution computed tomography abnormalities,
- 625 including widespread ground-glass opacity or alveolar attenuation,
- 626 reticulation often associated with traction bronchiectasis, and
- 627 honeycombing.
- 628 ○ Functional criteria:
- 629 ▪ Pulmonary function test abnormalities reflecting a restrictive pattern and
- 630 including loss of lung volume, vital capacity, total lung capacity; reduction
- 631 in diffusing capacity of the lungs for carbon monoxide, gas exchange
- 632 abnormalities, and altered ventilatory response to exercise.
- 633 ○ Patients affiliated to the “Régime National d’Assurance Maladie”.
- 634 • Exclusion criteria:
- 635 ○ Patients with diffuse parenchymal lung diseases caused by drug toxicity,
- 636 immunodeficiency, proliferative disorders including histiocytosis, and metabolic
- 637 disorders.
- 638 ○ Patients (parents/guardians for paediatric patients) not able to
- 639 approve/understand the protocol.
- 640 • Participation in another study (clinical trial/non-interventional studies) is not an exclusion
- 641 criterion of the RaDiCo-ILD cohort.

642

643 **Supplementary Results. Additional lung function parameters in patients at inclusion**
 644 **in the RaDiCo-ILD cohort**

	Male (n=600)	Female (n=124)	Total (N=724)
RV % predicted	83.6±30.1	89.4±30.5	84.7±30.2
95% CI	80.9, 86.4	83.6, 95.3	82.2, 87.2
Missing, n	136	17	153
KCO %	76.9±21.2	73.4±17.1	76.3±20.6
95% CI	75.0, 78.7	70.0, 76.8	74.7, 78.0
Missing, n	97	26	123
TLC, predicted	71.7±15.4	73.5±20.1	72.1±16.4
95% CI	70.4, 73.1	69.7, 77.2	70.7, 73.4
Missing, n	106	14	120
RV/TLC	1.2±4.8	3.2±15.1	1.6±7.8
95% CI	0.8, 1.6	0.3, 6.1	0.9; 2.2
Missing, n	118	15	133

645 Data are mean±SD unless otherwise stated.

646 CI, confidence interval; IPF, idiopathic pulmonary fibrosis; KCO; carbon monoxide transfer
 647 coefficient; RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease; RV, residual
 648 volume; SD, standard deviation; TLC, total lung capacity.

649

650 **Supplementary Table S1. Participating centres in the RaDiCo-ILD registry**

Participating centres	Investigators
Hôpital Louis Pradel, Lyon	Kaïs Ahmad Vincent Cottin Mouhamad Nasser Yasmine Rebaïne Julie Traclet Sabrina Zeghmar (research coordinator)
CHU Dijon-Bourgogne, Dijon	Guillaume Beltramo Philippe Bonniaud Maximilien Spanjaard
CHU Rennes, Rennes	Mallorie Kerjouan Alexandre Salé Cécile Daoudal Anne Marie Pilet Stéphane Jouneau
CHU Strasbourg, Strasbourg	Tristan Degot Sandrine Hirschi
Hôpital Avicenne, Paris	Hilario Nunes Yurdagül Uzunhan Dominique Valeyre Diane Bouvry Olivia Freynet Morgane Didier Aurélie Hervé Cecile Rotemberg Warda Khamis

	Florence Jeny
	Lucile Sesé
Hôpital Bichat, Paris	Bruno Crestani
CHU de Lille, Lille	Lidwine Wémeau-Stervinou
	Cécile Chenivresse
	Victor Valentin
	Victor Margelidon-Cozzolino
CHRU de Tours, Tours	Sylvain Marchand-Adam
	Gaëlle Fajole
	Rabia Rouis-Bouabdallah
Hôpital Nord, Marseille	Martine Reynaud-Gaubert
	Ana Nieves
Hôpital Européen Georges Pompidou, Paris	Dominique Israël-Biet
	Jean Pastré
	Karine Juvin
Hôpital Tenon, Paris	Jacques Cadranel
	Jean-Marc Naccache
	Antoine Parrot
CHU Grenoble-Alpes, La Tronche	Sébastien Quétant
	Loïc Falque
	Bruno Degano
	Gilbert Ferretti
Hôpital de Bicêtre, Le Kremlin Bicêtre	David Montani
	Marc Humbert
	Xavier Jaïs
CHU Montpellier	Anne-Sophie Gamez
	Arnaud Bourdin

651 RaDiCo-ILD, Rare Disease Cohort – Interstitial Lung Disease.

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