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

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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<sup>®</sup> 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/m<sup>2</sup> (26.8 kg/m<sup>2</sup> [95% CI: 26.4, 27.1] for male patients and 27.6 kg/m<sup>2</sup> [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<sub>CO</sub>) 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<sub>CO</sub>. 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  
416 2016 (approval no. IRB00003888) and the Commission Nationale de l'Informatique et des  
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#### 418 **Conflict of interest statement**

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  
467 Committee of Medical Journal Editors (ICMJE). All authors were involved in data collection,  
468 in writing the manuscript, and read and approved the manuscript before submission.

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)
<b>Mean age, years <math>\pm</math>SD</b>	<b>72.1<math>\pm</math>8.5</b>	<b>73.3<math>\pm</math>8.7</b>	<b>72.3<math>\pm</math>8.5</b>
95% CI	71.6, 72.8	72.9, 75.6	72.0, 73.1
<b>Mean age at diagnosis, years <math>\pm</math>SD</b>	<b>70.7<math>\pm</math>8.6</b>	<b>72.1<math>\pm</math>9.1</b>	<b>70.9<math>\pm</math>8.7</b>
95% CI	70.0, 71.3	70.5, 73.7	70.3, 71.5
<b>Median time between diagnosis and inclusion, months (IQR)</b>	<b>8.5 (0.7–25.8)</b>	<b>5.0 (0.0–22.1)</b>	<b>7.8 (0.5–25.4)</b>
<b>Median time between first symptoms and diagnosis, years (IQR)</b>	<b>2.0 (1.0–4.0)</b>	<b>2.0 (1.0–4.0)</b>	<b>2.0 (1.0–4.0)</b>
Missing, n	53	12	65
<b>Mean BMI, kg/m<sup>2</sup> <math>\pm</math>SD</b>	<b>26.8<math>\pm</math>4.0</b>	<b>27.6<math>\pm</math>5.2</b>	<b>26.9<math>\pm</math>4.2</b>
95% CI	26.4, 27.1	26.7, 28.6	26.6, 27.2
<b>Arterial hypertension</b>	<b>255 (42.9)</b>	<b>60 (48.8)</b>	<b>315 (43.9)</b>
95% CI	34.2, 51.7	40.0, 57.6	35.2, 52.7
Missing, n	6	1	7
<b>Gastroesophageal reflux disease</b>	<b>150 (25.0)</b>	<b>41 (33.1)</b>	<b>191 (26.4)</b>
95% CI	17.4, 32.6	24.8, 41.3	18.6, 34.1
Missing, n	11	2	13
<b>Diabetes</b>	<b>147 (24.5)</b>	<b>22 (17.7)</b>	<b>169 (23.3)</b>
95% CI	16.9, 32.1	11.0, 24.5	15.9, 30.8
Missing, n	11	3	14
<b>Coronary disease</b>	<b>146 (24.6)</b>	<b>12 (9.8)</b>	<b>158 (22.0)</b>
95% CI	17.0, 32.2	4.5, 15.0	14.7, 29.4
Missing, n	6	1	7
<b>Emphysema<sup>a</sup></b>	<b>93 (17.0)</b>	<b>6 (5.4)</b>	<b>99 (15.0)</b>



95% CI	10.0, 24.0	1.2, 9.6	8.4, 21.7
Missing, n	52	13	65
<b>Thyroid dysfunction</b>	<b>35 (5.8)</b>	<b>28 (22.6)</b>	<b>63 (8.7)</b>
95% CI	1.7, 10.0	15.2, 29.9	3.7, 13.7
<b>Tobacco status</b>			
<b>Active</b>	<b>32 (5.3)</b>	<b>10 (8.1)</b>	<b>42 (5.8)</b>
95% CI	1.4, 9.3	3.3, 13.0	1.7, 9.9
<b>Passive</b>	<b>4 (0.7)</b>	<b>15 (12.2)</b>	<b>19 (2.6)</b>
95% CI	0.0, 2.1	6.4, 18.0	0.0, 5.5
<b>Prior smoker (at least 6 months)</b>	<b>450 (75.0)</b>	<b>33 (26.8)</b>	<b>483 (66.8)</b>
95% CI	67.4, 82.7	19.0, 34.7	58.5, 75.1
<b>Never<sup>b</sup></b>	<b>114 (19.0)</b>	<b>65 (52.9)</b>	<b>179 (24.8)</b>
95% CI	12.1, 25.9	44.0, 61.7	17.1, 32.4
<b>Lung biopsy</b>	<b>135 (22.9)</b>	<b>36 (29.5)</b>	<b>171 (24.1)</b>
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 <sup>a</sup>Reported as a comorbidity at registry inclusion.

579 <sup>b</sup>Defined 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**

	<b>Male</b> <b>(n=600)</b>	<b>Female</b> <b>(n=124)</b>	<b>Total</b> <b>(N=724)</b>
<b>FVC % predicted</b>	<b>77.7±19.3</b>	<b>87.4±22.5</b>	<b>79.4±20.2</b>
95% CI	76.2, 79.3	83.4, 91.4	77.9, 80.9
<b>DL<sub>CO</sub> % predicted</b>	<b>46.1±16.8</b>	<b>46.9±13.9</b>	<b>46.2±16.4</b>
95% CI	44.6, 47.6	44.2, 49.7	44.9, 47.5
Missing, n	86	23	109
<b>FEV<sub>1</sub> % predicted</b>	<b>83.0±19.5</b>	<b>90.2±23.5</b>	<b>84.3±20.4</b>
95% CI	81.5, 84.6	86.0, 94.4	82.8, 85.8
Missing, n	6	1	7
<b>GAP index score</b>	<b>4.2±1.3</b>	<b>3.0±1.2</b>	<b>4.0±1.4</b>
95% CI	4.1, 4.4	2.8, 3.2	3.9, 4.2
Missing, n	86	23	109
<b>GAP stage, n (%)</b>			
<b>I</b>	<b>155 (30.2)</b>	<b>68 (67.3)</b>	<b>223 (36.3)</b>
95% CI	21.2, 39.1	58.2, 76.5	26.9, 45.6
<b>II</b>	<b>270 (52.5)</b>	<b>32 (31.7)</b>	<b>302 (49.1)</b>
95% CI	42.8, 62.3	22.6, 40.8	39.4, 58.9
<b>III</b>	<b>89 (17.3)</b>	<b>1 (1.0)</b>	<b>90 (14.6)</b>
95% CI	9.9, 24.7	0.0, 2.9	7.7, 21.5
Missing, n	86	23	109
<b>CPI</b>	<b>47.6±13.4</b>	<b>43.8±11.8</b>	<b>47.0±13.2</b>
95% CI	46.4, 48.8	41.4, 46.1	45.9, 48.0
Missing, n	89	24	113
<b>CPFE</b>	<b>4.5±7.1</b>	<b>7.1±8.0</b>	<b>5.0±7.3</b>
95% CI	4.0, 5.1	5.6, 8.5	4.4, 5.5

<b>6MWT, metres</b>	<b>414.0±130.3</b>	<b>346.5±117.5</b>	<b>402.9±130.6</b>
95% CI	402.1, 425.9	322.2, 370.8	392.0, 413.7
Missing, n	134	32	166
<b>Normalised 6MWT, % predicted</b>	<b>65.4±19.8</b>	<b>67.7±19.8</b>	<b>65.8±19.8</b>
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<sub>CO</sub>, diffusing capacity for carbon  
587 monoxide; FEV<sub>1</sub>, 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.

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

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

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

	<b>Male</b>	<b>Female</b>	<b>Total</b>
<b>Chest scans recorded<sup>a</sup></b>	580	123	703
<b>Reticular abnormalities</b>			
<b>Present</b>	<b>364 (98.1)</b>	<b>78 (95.1)</b>	<b>442 (97.6)</b>
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
<b>Bronchiectasis</b>			
<b>Present</b>	<b>356 (96.0)</b>	<b>76 (91.6)</b>	<b>432 (95.2)</b>
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
<b>Honeycombing</b>			
<b>Present</b>	<b>264 (70.8)</b>	<b>38 (45.8)</b>	<b>302 (66.2)</b>
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
<b>Emphysema</b>			
<b>Present</b>	<b>86 (23.5)</b>	<b>6 (7.2)</b>	<b>92 (20.5)</b>
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**

<b>Present</b>	<b>233 (62.1)</b>	<b>63 (76.8)</b>	<b>296 (64.8)</b>
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

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600 Data are n (%) unless otherwise stated.

601 <sup>a</sup>The 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**

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

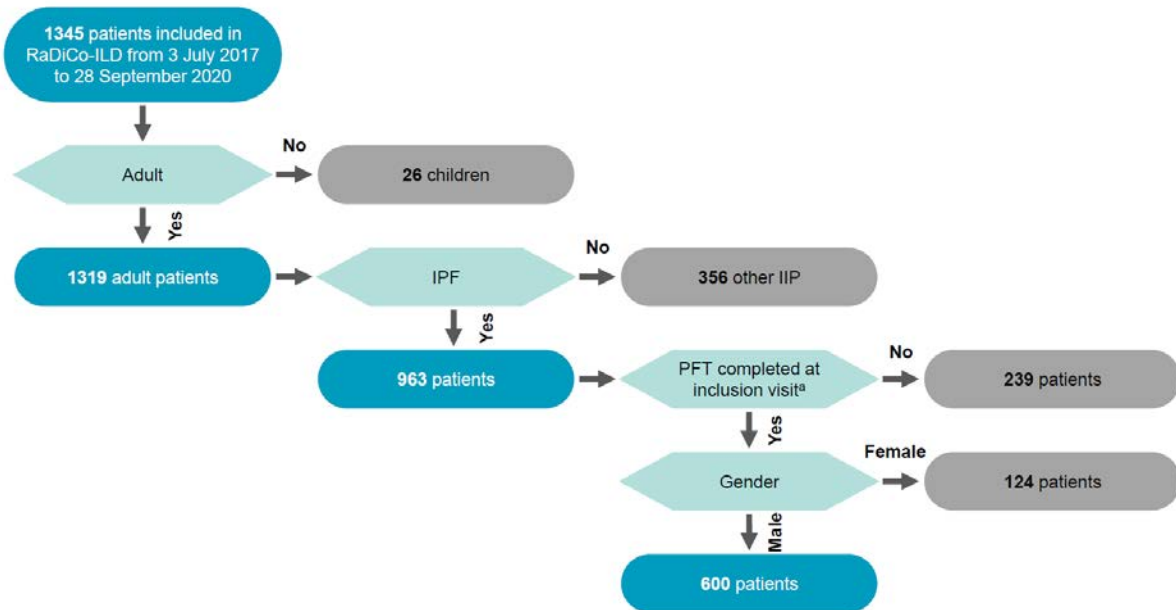
607 Data are n (%) unless otherwise stated.

608 <sup>a</sup>Defined 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 <sup>a</sup>PFT 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**

	<b>Male</b> <b>(n=600)</b>	<b>Female</b> <b>(n=124)</b>	<b>Total</b> <b>(N=724)</b>
<b>RV % predicted</b>	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
<b>KCO %</b>	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
<b>TLC, predicted</b>	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
<b>RV/TLC</b>	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**

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

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

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

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