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# Clinical profile of idiopathic pulmonary fibrosis patients treated with nintedanib in routine clinical practice in Spain: the BROAD Study

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**Abstract**

*Background*. Few data are available on the clinical profile of patients diagnosed with idiopathic pulmonary fibrosis (IPF) treated with nintedanib. The primary objective of the study was to describe, based on pulmonary function variables, disease severity in IPF patients who initiated treatment with nintedanib in routine clinical practice. The secondary objectives were to analyze their clinical characteristics and comorbidities.

*Methods*. A multicenter, retrospective study including 173 patients from 32 Spanish hospitals. Patients were stratified by their forced vital capacity (FVC) % predicted and diffusing capacity for carbon monoxide ($DL_{CO}$) % predicted. These measures were taken as a marker of IPF severity.

*Results.* Mean age ± SD at treatment initiation was 70.1 ± 8.1, and 76.6% of patients were male. Based on FVC, 57% of patients had mild IPF (FVC ≥ 70%), 38.4% moderate IPF (FVC 50%-69%), and 4.7% severe IPF (FVC < 50%). Based on $DL_{CO}$, 42.5% of patients had mild IPF ($DL_{CO}$ ≥ 50%), 35.5% moderate IPF ($DL_{CO}$ 35%-49%), and 22.2% severe IPF ($DL_{CO}$ < 35%). Eighty-nine percent of patients had at least one comorbid condition. The most prevalent comorbidities were high blood pressure (45.9%), dyslipidemia (42.4%), gastroesophageal reflux (25.6%), diabetes (19.8%), emphysema (15.7%), and cardiovascular diseases (15.7%). Most patients received concomitant treatment (79.7%).

*Conclusions.* The study provides relevant information on the clinical characteristics of IPF patients who initiate nintedanib treatment. Classification of severity depends on the lung function parameter used. The proportion of patients classified as having severe IPF was up to 4 times greater when $DL_{CO}$, instead of FVC, was used.

**Key words:** Idiopathic pulmonary fibrosis; Pulmonary function; Forced vital capacity; Diffusing capacity for carbon monoxide; Nintedanib; Clinical practice.

**PERFIL CLÍNICO DE PACIENTES CON FIBROSIS PULMONAR IDIOPÁTICA TRATADOS CON NINTEDANIB EN LA PRÁCTICA CLÍNICA HABITUAL EN ESPAÑA: ESTUDIO BROAD**

**Resumen**

*Introducción*. Se dispone de pocos datos sobre el perfil clínico de los pacientes diagnosticados de fibrosis pulmonar idiopática (FPI) tratados con nintedanib. El objetivo principal del estudio fue describir, basándose en variables de función pulmonar, la gravedad de la enfermedad en pacientes con FPI que iniciaron tratamiento con nintedanib en la práctica clínica habitual. Los objetivos secundarios fueron analizar sus características clínicas y comorbilidades.

*Métodos*. Estudio retrospectivo y multicéntrico que incluyeron a 173 pacientes de 32 hospitales españoles. Los pacientes fueron estratificados por su capacidad vital forzada (CVF) % predicho y por la capacidad de difusión de monóxido de carbono ($DL_{CO}$) % predicho. Estas variables se consideraron como marcadores de la gravedad de la FPI.

*Resultados*. La edad media ± DE al inicio del tratamiento fue de 70,1 ± 8,1 y el 76,6% de los pacientes eran varones. Según la CVF, el 57% de los pacientes tenían FPI leve (CVF ≥ 70%), el 38,4% FPI moderada (CVF 50%-69%) y el 4,7% FPI grave (CVF < 50%). Según la $DL_{CO}$, el 42,5% de los pacientes tenían FPI leve ($DL_{CO}$ ≥ 50%), el 35,5% FPI moderada ($DL_{CO}$ 35%-49%) y el 22,2% FPI grave ($DL_{CO}$ < 35%). El 89% de los pacientes tenían al menos una comorbilidad, siendo las más prevalentes la hipertensión arterial (45,9%), dislipidemia (42,4%), reflujo gastroesofágico (25,6%), diabetes (19,8%), enfisema (15,7%) y enfermedades cardiovasculares (15,7%). La mayoría de los pacientes recibieron tratamientos concomitantes (79,7%).

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*Conclusiones*. El estudio proporciona información relevante sobre las características clínicas de los pacientes con FPI que inician el tratamiento con nintedanib. La clasificación de la gravedad depende del parámetro de función pulmonar utilizado. La proporción de pacientes clasificados de FPI grave fue hasta 4 veces mayor cuando se utilizó la $DL_{CO}$ en lugar de la CVF.

**Palabras clave:** Fibrosis pulmonar idiopática; Función pulmonar; Capacidad vital forzada; Capacidad de difusión de monóxido de carbono; Nintedanib; Práctica clínica.

## 1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a type of chronic fibrosing interstitial pneumonia limited to the lung[1] and associated with a radiological and/or histological pattern of usual interstitial pneumonia (UIP)[1-3], mainly affecting people over 50 years of age[4]. In Spain, IPF is estimated to affect approximately 8,000-12,000 people[4,5].

Although the natural history of IPF varies greatly, it is associated with a poor prognosis[6], having a median survival of 3 to 5 years[7]. Consensus and international guidelines for IPF diagnosis and treatment have evolved since 2000[1,2]. The introduction of criteria based on high resolution computed tomography (HRCT) and the conditional recommendations for use of nintedanib and pirfenidone represented significant milestones[3].

Nintedanib is an inhibitor of tyrosine kinase (TK) activity initially developed to treat several types of cancer. In IPF, its action is due to inhibition of growth factor receptor TKs involved in the development of pulmonary fibrosis[8,9]. The efficacy of nintedanib for this disease has been tested in several clinical trials[9-14], with dosage defined in Phase II[10] as 150 mg twice daily. In Phase III INPULSIS studies[11], patients with forced vital capacity (FVC) ≥ 50% and diffusing capacity for carbon monoxide ($DL_{CO}$) ranging from 30%-79% were recruited. In both studies, significant differences were found between the nintedanib and the placebo groups, with a greater mean annual decrease in FVC in the placebo group[8,11]. In the extension study INPULSIS-ON[12], efficacy was confirmed by a reduction in FVC decline over the long term.

The results of these pivotal trials led to the approval of nintedanib for the treatment of IPF in the US, Japan, and the EU. In June 2014, a drug access program in special situations offering treatment with nintedanib to patients with FVC ≥ 50% was started in Spain. In January 2015, nintedanib was approved for all patients with IPF, regardless of their FVC. Nintedanib became available with reimbursement in Spain, especially in some autonomous communities for patients with FVC ranging from 50% to 80% in December of that same year. It is recommended to prioritize use of nintedanib in patients with mild-to-moderate IPF scheduled for lung transplant or ineligible for it, non-obstructive pattern (FEV1/FVC > 0.7), and predicted $DL_{CO}$ ranging from 35% to 90%[15].

Despite these recommendations[15] highlighting the importance of assessment of IPF severity as a key factor for initiating treatment[16], no data are available on the severity of IPF patients treated with nintedanib in a real post-authorization setting. In addition, data on the clinical characteristics of these patients in Spain, including the most common comorbidities, are very limited[12]. Because of this paucity of data, this study was designed to characterize the severity of disease and the clinical characteristics of IPF patients who initiated nintedanib in routine clinical practice in Spain.

## Materials and methods

The BROAD study was conducted in accordance with the protocol, the principles set forth in the Declaration of Helsinki, and the applicable Spanish regulations regarding the conduct of observational studies and was approved by the Ethics Committees of Virgen de la Macarena and Virgen del Rocío Hospitals. The study was performed at the Pneumology Departments of 32 Spanish hospitals, selected based on their previous experience in clinical research and in compassionate use programs, and on their access to nintedanib. The participating investigators reviewed the medical records since 1 January 2016.

### *Study design*

A national, multicenter, observational, cross-sectional study in which patients were characterized at the initiation of treatment with nintedanib. This was a non-interventional study, as the decision to start treatment had already been made independently from and prior to patient recruitment, thus reflecting real clinical practice.

### *Patients*

Patients were over 18 years-old and had been diagnosed with IPF according to the 2011 ATS/ERS/JRS/ALAT guidelines[2]. In addition, patients had initiated nintedanib *de novo* since January 2016 in accordance with the conditions stated in the prescribing information and had signed an informed consent before entering the study. The first patient was enrolled on 21 October 2016, and the last patient on 31 January 2018.

### *Data collection and statistical analysis*

All information was collected from the medical records of the patients. Baseline sociodemographic, anthropometric and clinical characteristics were extracted from medical records, including data from pulmonary function testing (FVC % predicted and $DL_{CO}$ % predicted). Based on these pulmonary function parameters, patient distribution was analysed according to different functional impairment levels (as surrogate variable of severity) of IPF, according to the stratification used by Nathan *et al*.[17] (FVC < 55%, 55%-69%, or ≥ 70%, and $DL_{CO}$ < 35%, 35%-49%, or ≥ 50%),

which takes into account the results of pulmonary function testing and differences in survival rates. In our study, stratification by the FVC was adapted to align with the INPULSIS study[11], with a FVC level < 50%, instead of < 55% (Table 1). IPF severity was also analysed, following the stratification based on the reimbursement threshold of nintedanib in Spain (FVC ranging from 50%-80%), so that patient stratification by FVC % predicted was FVC > 80%, 50%-80%, and < 50%.

Measures of central tendency and dispersion, including mean and standard deviation (SD), were used to report quantitative variables. Absolute (N) and relative (percentages) frequencies were used to report qualitative variables. All statistical analyses were performed using SPSS v22.0 software.

**Table 1.** Stratification of IPF severity based on the pulmonary function testing used for the BROAD study

| IPF severity | Stratification by FVC % predicted | Stratification by $DL_{CO}$ % predicted |
|---|---|---|
| Mild | ≥ 70% | ≥ 50% |
| Moderate | 50% - 69% | 35% - 49% |
| Severe | < 50% | < 35% |

## Results

### *Baseline patient characteristics*

A total of 173 patients were enrolled in the study. One patient was excluded for not meeting the inclusion criteria. Table 2 summarizes the characteristics of the patients in the BROAD study. Sociodemographic data show that a majority of patients were male, approximately 70 years old, and Caucasian. Anthropometric measurements indicated they were slightly overweight, as shown by body mass index (BMI) values of approximately 28 kg/m$^2$.Most patients had dyspnea, predominantly grade 1 and 2 (~40% each) according to the mMRC scale. Mean ± SD FVC % predicted was 74.3 ± 17.9% and mean ± SD $DL_{CO}$ % predicted was 48.2 ± 18.0%. As regards IPF diagnosis, surgical lung biopsy was performed in 25% of patients. Mean ± SD time from diagnosis to nintedanib treatment was 1.5 ± 3.8 years.

Twenty-eight (16.6%) of all patients had been previously treated with pirfenidone at a mean dose ± SD of 702.1 ± 198.0 mg/8 h. The main reasons for switching were adverse events in 53.6% of patients, and lack of efficacy in 28.6%.

**Table 2.** Baseline patient characteristics.

| Variable | Value |
|---|---|
| Age at study start [(years), ($N_{TOTAL}$ = 172), mean ± SD] | 71.0 ± 8.1 |
| Sex [N, (%)] | |
| Male | 131 (76.6) |
| Female | 40 (23.4) |
| Race/ethnicity [N, (%)]: | |
| Caucasian | 170 (98.8) |
| Other | 2 (1.2) |
| BMI [(kg/m$^2$), ($N_{TOTAL}$ = 159), mean ± SD] | 28.4 ± 3.8 |
| Dyspnea ($N_{TOTAL}$ = 172) [N, (%)]: | 160 (94.7) |
| 6-min walk test [(m), ($N_{TOTAL}$ = 136), mean ± SD] | 421.7 ± 118.6 |
| Pulmonary function: | |
| FVC % predicted [($N_{TOTAL}$ = 172), mean ± SD] | 74.3 ± 17.9 |
| $DL_{CO}$ % predicted [($N_{TOTAL}$ = 153), mean ± SD] | 48.2 ± 18.0 |
| Frequency of patients by smoking habit ($N_{TOTAL}$ = 172) [N, (%)]: | |
| Non-smokers | 57 (33.1) |
| Ex-smokers | 110 (64.0) |
| Active smokers | 5 (2.9) |
| Number of pack-years [($N_{TOTAL}$ = 96), mean ± SD] | 38 ± 24.9 |
| Disease duration from diagnosis to study start [(years), ($N_{TOTAL}$ = 172), mean ± SD] | 2.4 ± 3.9 |
| Disease duration from diagnosis to initiation of treatment with nintedanib [(years), ($N_{TOTAL}$ = 172), mean ± SD] | 1.5 ± 3.8 |
| Patients with emphysema ($N_{TOTAL}$ = 172) [N, (%)] | 27 (15.7) |
| Frequency of patients by diagnostic method ($N_{TOTAL}$ = 172) [N, (%)][1]: | |
| Interdisciplinary team discussion | 92 (53.5) |
| Lung biopsy | 43 (25.0) |
| Other | 26 (15.1) |
| Frequency of patients with UIP histological pattern ($N_{TOTAL}$ = 172) [N, (%)] | 53 (69.7) |
| Frequency of patients with UIP radiological pattern ($N_{TOTAL}$ = 172) [N, (%)] | 153 (90.0) |

[1]*Other diagnostic methods apart from HRCT. Patients may have been diagnosed using more than one procedure*

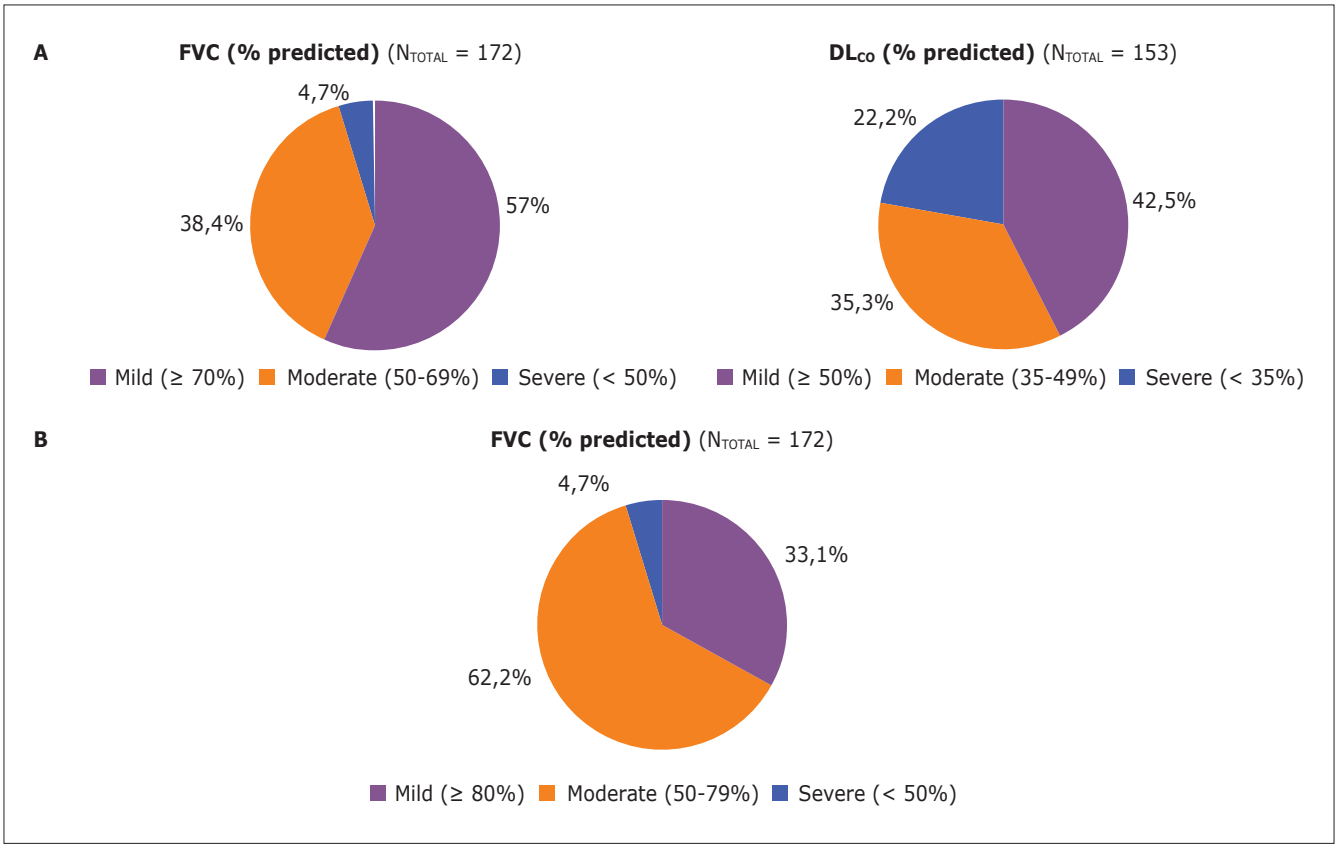


**Figure 1.** Patient distribution by IPF severity, stratified based on pulmonary function testing. A) Percentages of patients are depicted according to the severity of their disease. On the left, frequencies based on stratification by percent predicted forced vital capacity (FVC) are depicted, while frequencies on the right correspond to the stratification by percent predicted diffusing capacity for carbon monoxide ($DL_{CO}$). B) Percentages of patients are depicted according to severity of their disease, stratified by pulmonary function test using FVC and according to the reimbursement threshold of nintedanib in Spain (FVC > 80%, 50%-80%, and < 50%).

On the other hand, 88.9% of all patients given nintedanib, regardless of their previous treatment, initiated treatment at a dose of 150 mg/12 h, and the remaining 11.1% at a dose of 100 mg/12 h.

***Patient distribution by functional impairment of IPF***

Figure 1A shows the distribution of patients with IPF according to FVC % predicted and $DL_{CO}$ % predicted. Figure 1B represents the patient distribution by FVC % predicted, this time taking into account the reimbursement thresholds for nintedanib. Patient distribution by level of severity varies depending on the parameter used. Thus, while 4.7% of patients are classified as having severe IPF based on FVC, the proportion of patients with severe IPF increases to 22.2% when $DL_{CO}$ is used. The proportion of patients classified as having moderate IPF is 38.4% based on FVC and 35.3% based on $DL_{CO}$. Finally, 57% and 42.5% of patients are classified as having mild IPF based on FVC and $DL_{CO}$, respectively.

***Concomitant diseases of patients***

Eighty-nine percent of patients had at least one comorbid condition. A total of 26.2%, 20.3%, 15.1% and 27.4% of patients had one, two, three, or four or more comorbidities, respectively. Of note are the high frequency of cardiovascular conditions and/or risk factors (high blood pressure [45.9%], dyslipidaemia [42.4%], diabetes mellitus [19.8%], and cardiovascular disease [15.7%]), as well as the presence of gastroesophageal reflux (25.6%) and emphysema (15.7%), among others (Figure 2).

The presence of these comorbidities is consistent with the data recorded on concomitant medications (classified by ATC codes, Table 3).

## Discussion

Our study shows that the demographic, functional, and clinical profile of patients with IPF treated with nintedanib in Spain is similar to that of other patients with IPF from national and international studies[18-25], although the degree of variability among studies is greater in functional and clinical characteristics than in demographic characteristics. It should be noted that the mean values in markers of IPF severity such as the 6-minute walk test (6MWT), FVC % predicted , and $DL_{CO}$ % predicted seen in our study were very similar to those found in a recently reported IPF Spanish multicenter registry that included patients treated with nintedanib and pirfenidone[26]. Interestingly, when our patients are compared to patients treated with nintedanib in the community of Madrid[18]], the latter showed slightly higher mean functional

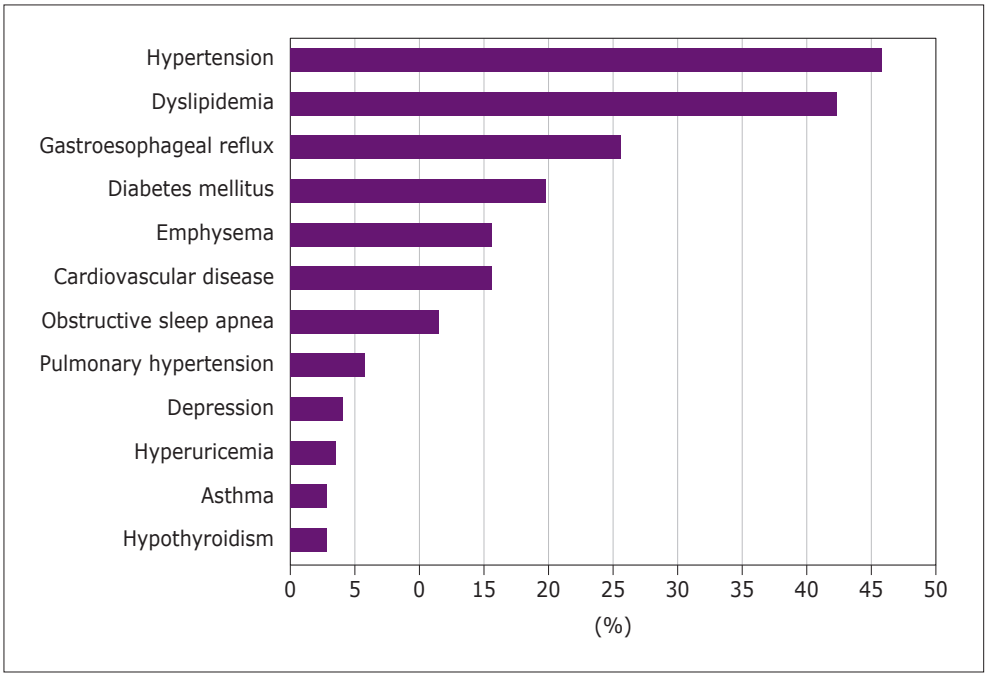


**Figure 2.** Percentage of patients with other comorbidities

**Table 3.** Concomitant treatments.

| **Therapeutic class** | **%** |
|---|---|
| Antihypertensives | 76.3 |
| Peptic ulcer and gastroesophageal reflux disease (GERD) | 54.3 |
| Lipid-modifying agents | 48.0 |
| Treatments for lung disease or symptoms associated to IPF | 30.5 |
| Treatments for diabetes | 26.3 |
| Antithrombotics /Antiplatelets | 21.9 |
| Antidepressants | 13.8 |
| Anxiolytics | 13.1 |
| **Most common drugs** | |
| Omeprazole | 29.2 |
| Simvastatin | 21.1 |
| Acetylsalicylic acid | 19.0 |
| Atorvastatin | 13.1 |
| Pantoprazole | 13.1 |
| Metformin | 12.4 |
| Allopurinol | 9.5 |
| Bisoprolol | 8.0 |
| Levothyroxine | 7.3 |

values in all three severity markers mentioned: mean ± SD FVC % predicted 83% ± 18%, $DL_{CO}$ % predicted 59% ± 17%, and 479 ± 98 meters in the 6MWT in their study, as compared to FVC % predicted 74.3% ± 17.9%, $DL_{CO}$ % predicted 48.2% ± 18% and 421.7 ± 118.6 meters in the 6MWT in our study. Such differences could be due to the fact that patients in our study pertained to hospitals widely distributed throughout Spain, while the Nieto-Barbero *et al* study[18] was limited to hospitals in the community of Madrid. They may also reflect differences in times from the onset of symptoms to diagnosis of the disease. In any case, these results reflect the need to provide new data that allow for a more homogeneous description of the clinical profile of patients with IPF who initiate antifibrotic treatment.

The novelty of this study lies in the description, based on real world data, of disease stratification by pulmonary function (FVC < 50%, 50%-69% or ≥ 70% and $DL_{CO}$ < 35%, 35%-49% or ≥ 50%) in patients who initiate treatment with nintedanib. Previously reported observational studies have detailed the mean functional parameters (FVC and $DL_{CO}$) at the initiation of antifibrotic treatment in clinical practice[18,21-23,25,27], but not patient distribution according to disease severity. We believe that this study provides, for the first time, information about the distribution of the severity of IPF in patients treated with nintedanib in Spain.

The results showed that most patients had mild IPF, followed by moderate IPF, and then severe IPF. However, assignment of patients to each of these categories of severity depended on the parameter used. Interestingly, the proportion of patients classified as having severe IPF was up to four times greater when the $DL_{CO}$ % predicted was considered than when FVC % predicted was used. On the other hand, more patients were classified as having mild IPF based on FVC than when $DL_{CO}$ was used.

The importance of stratifying IPF patients by severity is that the $DL_{CO}$ % predicted could improve the quality of information given to patients on their disease. It could also have an impact on healthcare systems in which treatment with nintedanib is reimbursed, as these severity thresholds could mark the most adequate time to initiate treatment. Traditionally, IPF severity has been described using heterogeneous terms. Different variables (clinical, physiological, functional, and imaging) have been proposed for stratification[16]. To date, there is no consensus on how IPF severity

should be assessed, and there is no specific stratification of severity in the latest clinical practice guidelines[2].

Because of the importance of patient stratification, it would be expected that a consensus is reached in the near future on the variables and the most useful ranges to describe severity. Among these variables, FVC and, to a lesser extent, $DL_{CO}$, have been the most widely used pulmonary function parameters[16]. The results achieved with an IPF classification model (GAP model) demonstrated the value of these parameters as markers of IPF severity. In this model, FVC and $DL_{CO}$, together with age and gender, were shown to be the best predictors of mortality in IPF [28]. Some studies have showed that $DL_{CO}$ % predicted, predicted patient survival slightly better than FVC % predicted[18,19], especially in patients with risk factors such as emphysema or pulmonary hypertension[29]. Another study has recently shown that preserved FVC would not be representative of early or mild IPF, in patients presenting UIP radiological pattern and moderate-severe $DL_{CO}$ decrease at diagnosis[30]. In addition, in a Spanish IPF registry, $DL_{CO}$ at diagnosis was the only factor significantly associated with mortality[26]. FVC remains the gold standard pulmonary function variable most commonly used as the primary endpoint in clinical trials[31,32]. This is due to limitations related to $DL_{CO}$, a measure more difficult to obtain in patients with severe disease, subject to greater within-subject variability and measurement heterogeneity, and more sensitive to comorbidities such as emphysema[16].

There is evidence that late diagnosis is associated to a worse course of disease and greater mortality because it delays use of both non-pharmacological measures (rehabilitation, oxygen therapy, smoking cessation or lung transplantation) and pharmacological measures (nintedanib or pirfenidone) that could have a significant impact on prognosis[33,34]. There is growing agreement that the *wait and see* strategy is not the best option for patients with IPF [35] and that treatment with antifibrotics should be started as soon as possible[36], as it increases survival regardless of disease stage[23]. Our study shows that, on average, patients initiate nintedanib a year and a half after diagnosis of IPF. This delay in starting nintedanib would not be explained by previous antifibrotic treatment with pirfenidone, since this had only been administered to 16% of patients. In line with this observation, the INSIGHT-IPF registry demonstrated that almost 18% of patients were not receiving drug therapy, despite having a mean FVC % predicted of 72% and a $DL_{CO}$ % predicted of 35%[19]. As these treatments slow the decline in FVC, it seems reasonable to initiate treatment when there is still little pulmonary function loss as measured by FVC. There is evidence to confirm that treatment could be more effective in the early stages of disease[37], or has at least the same effectiveness between patients with preserved lung volume (FVC > 90% predicted) compared to patients with more impaired lung volume[38]. The reason for the delay in the start of treatment seen in clinical practice may be to avoid potential adverse events. However, this should not influence the initiation of treatment, as studies in clinical practice settings have shown that nintedanib has a good safety profile consistent with the results of clinical trials[17,27,39].

Although IPF is a disease limited to the lung, patients usually have comorbid conditions[40] that modify the clinical course and prognosis of the disease. Early detection and treatment of comorbidities may have a positive clinical impact on the overall course of patients. Our study has shown that the most common comorbidities are similar to those reported in other studies. Consistent with our results, real-world data for patients treated with nintedanib in Germany[27] showed that the predominant comorbidity was high blood pressure, followed by coronary artery disease (CAD), diabetes, gastroesophageal reflux, and emphysema. The high prevalence of hypertension seen in our study (46%) is also consistent with that reported in registries of IPF[19,25] regardless of treatment. Continued collection of data on the prevalence of comorbidities in IPF is important because there is a great variability among studies. In fact, a systematic review analyzing 126 studies showed large ranges in the prevalence of the different comorbidities (pulmonary hypertension [3%-86%], gastroesophageal reflux [0%-94%], and coronary heart disease [3%-68%][40]. This may be attributed to the different diagnostic criteria used to classify comorbidities in the different studies or to the data collection methods.

Most of our patients with IPF had several comorbidities. Eighty-nine percent of them had at least one, and approximately 60% had 1 to 3 comorbidities. Our observations agree with a previous study where 88% of IPF patients had at least one comorbidity, 58% had between 1 and 3 comorbidities, and 30% had between 4 and 7 comorbidities[41]. This study also showed that the number of comorbidities had a negative impact on survival. Patients with more comorbidities had shorter survival[41].

Our study is not devoid of limitations. Firstly, although the proportion of patients with histological and radiological UIP pattern was collected, the UIP patterns (definite, possible, probable) were not collected in the study. Secondly, since patients were enrolled in the study before the publication of the new ATS/ERS/JRS/ALAT clinical practice guidelines[42], all patients recruited were diagnosed with IPF based on the previous guidelines[2]. Finally, the study was not designed to observe the impact of clinical characteristics, including disease severity, on the efficacy or safety of nintedanib, and no conclusions can therefore be drawn in this regard. These and other pending issues must be addressed in potential future studies. Although participation of more sites could have strengthened the study results, the number of patients enrolled is quite high and representative of the Spanish population treated with nintedanib.

## Conclusions

The study reflects the clinical characteristics of patients with IPF who start treatment with nintedanib in Spanish clinical practice. Our data show that classification of disease severity depends on the lung function parameter used, with the proportion of patients classified as having severe IPF being up to 4 times higher when $DL_{CO}$ was considered than when FVC was used. The prevalence of comorbidities in our study is high,

which supports the importance of identifying comorbidities in patients on antifibrotic treatment in clinical practice.

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***Author contribution***

AC and JARP contributed to the design of the study and the analysis of data. All authors have contributed to the acquisition of the data, drafted the manuscript, critically revised the manuscript for important intellectual content, and gave final approval of the version to be published.

***Conflict of interest***

**AC** received research support from Roche and GSK and served as a speaker for Boehringer Ingelheim, Roche and GSK. **JMC** received research support and served as a speaker for Boehringer Ingelheim, Roche and Actelion. **MBS** none. **RS** none. **JSA** served on an advisory committee and received research support from Boehringer Ingelheim and Roche. **JARP** served as a speaker and as consultant for Boehringer Ingelheim, Roche, Bristol-Myers Squibb and Novartis.

***Data sharing statement***

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can also be requested via the link https://trials.boehringer-ingelheim.com/

All requests will be governed by a Document Sharing Agreement. Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use the https://trials.boehringer-ingelheim.com/ link to request access to study data.

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