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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

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Title of study:	*Investigating idiopathic pulmonary fibrosis in Greece (INDULGE IPF)*		
Keywords:	Idiopathic pulmonary fibrosis, registry, Greece, INDULGE IPF, disease characteristics, clinical course, diagnosis, management		
Rationale and background:	Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, limited to the lungs. IPF predominantly presents in older individuals (cases in persons aged less than 50 years are rare), with a preponderance in men and previous or current smokers. Patients present with unexplained chronic exertional dyspnea, and commonly with cough, bibasilar inspiratory crackles, and finger clubbing. IPF is associated with a poor prognosis. At the time of the design of this registry, disease diagnosis was based on the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guidelines, requiring exclusion of identifiable causes of interstitial lung disease as well as identification of a pattern of usual interstitial pneumonia either on high-resolution computed tomography (HRCT) or on surgical lung biopsy. However, the clinical course of IPF is unpredictable for a given patient at the time of diagnosis, with some patients progressing slowly, others rapidly, and some patients experiencing acute exacerbations that are associated with increased morbidity and mortality. Since 2011, two agents, pirfenidone and nintedanib, have been introduced as therapeutic options for IPF following the results from phase III randomized clinical trials (RCTs). While substantial efforts have been made to investigate the efficacy and safety of new drugs in controlled clinical trials,		

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there are still many questions regarding the medical management of IPF patients that remain unanswered, and there is a paucity of data on the implementation of clinical practice guidelines in everyday clinical practice.

This is attributed to three main limitations: (1) the lack of epidemiological data for a disease with a relative low incidence, (2) the heterogeneity of the disease as reflected in the diagnostic criteria, the differences in the clinical course of patients, and the lack of approved predictive or prognostic biomarkers, and (3) the cost of novel agents that may affect their clinical use.

Regarding the first limitation, a national multicenter survey conducted in Greece in 2004 estimated an annual incidence of 0.93 cases per 100,000 and a prevalence of 3.38 cases per 100,000. However, since then, the international guidelines and the relevant diagnostic criteria, the standard medical care and the composition of the population have changed, and thus these data may not reflect the current IPF population. With regards to the second limitation, long-term data on the natural course of IPF are missing. Furthermore, there is a lack of information on detailed patient characteristics. The final limitation for further use of the available medicinal treatments in IPF is the cost. Since cost has been recognized as a major issue in the application of public health policies, more data are needed regarding the clinical use of these agents.

All of the above converge to the unmet medical need to collect data on the population of patients diagnosed with IPF, the natural course of the disease, and the medical treatment. In a call for action on an IPF registry by Wilson in 2008, it was noted that improved survival from this disease is dependent on better understanding of the epidemiology of the disease, its diagnostic spectrum and an analysis of outcomes from emerging therapies at a

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	significant level. Indeed, a significant achievement towards the above goal is the establishment of patient registries, with numerous national IPF registries already established in countries around the world. The ongoing experience with these registries has indeed provided valuable insights to guide clinical management of IPF in the "real-world" adjusted to local needs, as well as important information towards the development of a global registry. Data collected in these registries are expected to be complementary to those collected during clinical trials while avoiding potential selection bias, as patient populations included in registries have a broader spectrum of disease severity and comorbidities and can be followed for a longer period of time.		
Research question and objectives:	The main objective of this IPF registry was to gain further knowledge on the characteristics, management, disease progression and outcomes of patients with IPF as diagnosed and treated under real-world, clinical practice conditions in Greece. More specifically, this registry aimed to: • Provide a comprehensive clinical picture of IPF • Track access to health care and cost of caring for IPF patients over time • Examine the implementation of treatment guidelines used on patients diagnosed with IPF, according to the existing diagnosis guidelines • Characterize patients on different treatments Furthermore, this registry aimed to provide information regarding survival and mortality causes, IPF exacerbations as well as IPF patient co-morbidities including myocardial infarction, CNS infarction, other arterial thromboembolic events, deep vein thrombosis, hemorrhage, gastrointestinal perforation and pulmonary hypertension. In addition, data regarding IPF patient hospitalization would be collected and evaluated with regards to		

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	potential respiratory causes, and there would be documentation of treatment patterns and economic aspects.		
Study design:	This was a national, multi-center, observational disease registry based on new data from a significant sample size of IPF patients in Greece. Participating physicians (experts in IPF) were not subjected to any instructions with regard to the diagnosis and therapy of their patients. All examinations were performed according to the discretion and routine clinical practice of the participating physicians. During the follow-up period, data were collected on standard clinical visits which usually were scheduled around: 3-months (+/- 1 month), 6-months (+/- 1 month), 12-months (+/- 2 month), 18-months (+/- 2 month) and 24 months (+/- 2 months), until the end of participation in the study. In case of events, unscheduled visits may have been required.		
Setting:	In order to ensure adequate patient numbers per center and high quality of data, seven (7) University Pulmonology Clinics and Reference Centers of Public Hospital Setting that follow up around 70%-80% of IPF patients within the Greek territory were involved. The registry was scheduled to run for 4 years in total (2 years recruitment + 2 years follow up) (April 2017 to Mar 2021).		
Subjects and study size, including dropouts:	Patients were considered eligible to participate in the registry, if they were fulfilling **ALL** the inclusion criteria and **NONE** of the exclusion criteria: ***Inclusion criteria*** • Newly diagnosed (less than 6 months) or previously diagnosed (more than 6 months from baseline visit) with IPF, based upon the consensus statement jointly issued by ATS/ERS/JRS/ALAT in 2011		

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	• Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) • Evaluation of IPF with HRCT or combination of HRCT and surgical lung biopsy, if available • Age ≥40 years old at the time of inclusion • Written informed consent for participation in the registry • Patients that could be followed up further, during the scheduled study period ***Exclusion criteria*** • Expected lung transplantation within the following 6 months • Participation in clinical trials Patients were included in a consecutive manner at each site in order to avoid selection bias. Approximately 300 patients were planned to be included in the study from the participating sites. The number of included patients was not defined by a formal sample size and power calculation but was mainly based on the availability of eligible IPF patients as well as the patient population in the selected sites.		
Variables and data sources:	At baseline, a relevant patient history was recorded including IPF-related events up to 12 months prior to this visit. Moreover, the current status of IPF patients were recorded in terms of • Basic (socio-)demographic data • Vital signs and physical examination • (Possible) IPF risk factors		

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- Co-morbidities
- Risk of bleeding and thrombosis
- Methods used in IPF diagnosis [including High-Resolution Computed Tomography (HRCT), surgical lung biopsy (SLB) and bronchoalveolar lavage (BAL), if available]
- IPF symptoms: dyspnea, cough, weight loss, fatigue, dizziness, chest pain, anxiety, clubbing, bibasilar crackles
- Functional assessment [including lung function test, cardiopulmonary exercise testing (CPET) and/or exercise capacity (6-minute walk test; 6MWT) if available]
- Serological evaluation – autoimmune biomarker results
- IPF treatment modalities
- Recording of therapeutic regimens. Assessment of the intensity of treatment, frequencies and resource utilization for pharmaco-economic analyses.
- Outcomes of interest (such as acute respiratory worsening, exacerbations, hospitalization due to any cause and due to IPF).
- Clinical events and hospitalizations
- Physician's clinical rating of the probable course of IPF
- Management of IPF and physician contacts

During follow up visits (prospectively until up to 2 years at least from the inclusion) at 3 months (+/- 1 month), 6-months (+/- 1 month), 12-months (+/- 2 month), 18-months (+/- 2 month) and 24 months (+/- 2 months), the following data were documented:

- Clinical course of IPF [e.g., regarding symptoms, lung functionality (lung function test), exercise capacity (6MWT and/or CPET), if performed]
- Vital status

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	• Vital signs and physical examination • Serological evaluation – autoimmune biomarker results • Risk of bleeding and thrombosis • Recording of therapeutic algorithms (change/complement/interrupt treatment) and non-pharmacological treatment (e.g., start of LTOT, new listing for lung transplantation) • Assessment of treatment intensity, frequencies and resource use for pharmacoeconomic analyses. • Outcomes of interest (such as acute respiratory worsening, exacerbations, hospitalization due to any cause and due to IPF). • Clinical events and hospitalizations • Physician's clinical rating of the probable course of IPF • Management of IPF and physician contacts The study mainly included the collection of new data recorded in a consecutive manner through an existing web-based database (electronic case report form, eCRF). Patients' source (primary) data related to their medical and IPF history were derived by the investigators from their medical records and were documented in the relevant eCRF section. Data were collected by the study doctors as they occurred according to standard clinical practice in the approximate visiting schedule indicated above. No tests or laboratory procedures that diverge from standard clinical practice were requested.		
Results:	A total of 301 patients were enrolled in the INDULGE-IPF registry from 5 Apr 2017 to 2 Apr 2019, 25 (8.3%) patients deriving from a general practice/primary care, 58 (19.3%) from a community hospital, and 218 (72.4%) patients from a university hospital. One-hundred twelve (37.21%) patients discontinued from the study; death was the discontinuation reason in 55 (18.27%).		

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Among patients in the total cohort, the majority were males (81.7%) and all patients were White/Caucasians. The mean age ± SD of patients at baseline was 71.6 ± 7.75 years, with 87.7% of them being retired and 97% covered by statutory health insurance. A smoking history was reported by 71.1% of patients (63.8% being former smokers and 7.3% being current smokers) accounting for a mean ± SD of 46.26 ± 30.018 pack-years. Environmental or occupational exposure was reported by 123 patients (40.9%). Among those, 43 patients had been exposed to metal dust, 30 in solvents, and 40 had been involved in farming. Exposure to drugs, alcohol and drug abuse and viral infections was reported by very few patients (<2%). Finally, 27 patients reported a family history of IPF.

The majority of patients (86.7%) had at least one comorbidity, with arterial hypertension being the most frequently reported (169 patients; 56.2%), followed by hyperlipidaemia (129 patients; 42.9%) and gastrointestinal reflux disease (GERD; 104 patients; 34.6%).

The first symptoms had occurred 26.75 (range 0-238.2) months prior to enrollment in the registry. A total of 31.9% of our patients were newly diagnosed at baseline with a diagnosis made within 6 months ("incident IPF") and in 68.1% disease duration was ⩾6 months ("prevalent IPF") with an overall median time since initial diagnosis of 10.40 (range 0-233.3) months. Diagnosis for all patients was based on HRCT. HRCT findings in 298 out of 301 patients (3 patients without available data) showed the following patterns, according to the ATS/ERS 2011 criteria: Usual Interstitial Pneumonia (UIP) pattern in 237 (79.5%) patients, possible UIP in 53 (17.8%) and inconsistent UIP pattern in 8 (2.7%). Lung biopsy was only performed in 24 (7.97%) patients. According to the ATS/ERS 2011 criteria, in 26 out of 27 patients (one patient without available data), UIP pattern was encountered in 19 (79.17%) patients, probable UIP pattern in 1 (4.17%) patient, possible UIP pattern in 2 (8.33%) patients and inconsistent

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UIP pattern in 2 (8.33%) patients. Bronchoalveolar lavage (BAL) was also performed in 149 (49.5%) patients; median time since the most recent BAL was 12.40 (range 0-154.9) months. The BAL differential count revealed elevated neutrophil (13.19 ± 10.764%) and eosinophil (4.44 ± 4.923%) counts, normal lymphocyte (13.19 ± 10.764%) counts and reduced macrophage counts (68.77 ± 20.959%).

During the diagnostic procedure, serological autoantibody testing had been performed in the majority of patients to exclude connective tissue disease (CTD). Among those screened for anti-nuclear antibodies (ANAs), only 27.42% (68/248) of patients tested positive, while negative results had been obtained for the majority of patients among those screened for other autoantibodies: the anti-cyclic citrullinated peptide (194/200; 97.00%), the rheumatoid factor (213/239; 89.12%), as well as the Scl70 (1/147; 97.28%), the SS-A (123/128; 96.09%) and SS-B (127/130; 97.69%) antibodies. Laboratory assessments of plasma levels of cardiovascular markers, namely natriuretic peptides, such as brain natriuretic peptide (BNP) or N-terminal prohormone BNP (NT-proBNP) was reported in 4 patients only (mean (SD) NT-proBNP 147.1 (79.20) ng/L).

Genetic predisposition to bleeding was negative in 74.75% of patients, and unknown in the remaining 25.25% of patients. Accordingly, genetic predisposition to thrombosis was negative in 76.74% of patients with the remaining 23.26% being unknown). Other risk factors for bleeding included the presence of gastrointestinal (GI) ulcers in 9 (~3.0%) patients, major injury or surgery in 6 (~2.0%) patients and ongoing treatment with anticoagulants in 36 (~12.0%) patients.

Among symptoms indicative of IPF present at baseline, bibasilar crackles (84.39%), dyspnea (76.64%) and cough (70.43%) were the most frequently reported.

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The mean Forced Expiratory Volume (FVC) ± SD % at the time of enrolment in the INDULGE IPF was 78.22 ± 20.680% predicted and the mean Diffusing capacity of the lung for carbon monoxide (D_{LCO}) ± SD was 48.16 ± 17.771% predicted. A 6-min walking test was performed at baseline by 139 patients, with a median walking distance of 417 metres. Cardiopulmonary exercise testing was undertaken only by 12 patients and a mean maximal oxygen uptake of 24.75 ± 19.539 $mL \cdot min^{-1} \cdot kg^{-1}$ was measured.

Clinical course of IPF over the 12 months prior to enrolment

Within the last 12 months prior to enrolment to the registry, only 6 (2.0%) patients had experienced an acute exacerbation of IPF. During the abovementioned period, a total of 35 (11.63%) patients were hospitalized, 27 (77.14%) of which due to a respiratory cause. In particular, 5 (18.52%) patients were hospitalized due to an acute IPF exacerbation, 3 (11.11%) due to IPF worsening other than acute exacerbation and 19 (70.37%) due to other respiratory causes. Only 5 (14.29%) patients were hospitalized due to cardiovascular events (including cardiac failure).

According to physicians' overall clinical judgment with regards to the probable course of IPF based upon laboratory tests, physical examination, hospitalizations and/or clinical events in the past 12 months prior to entry to the registry, 78.7% of patients had a stable disease, 17.9% demonstrated slow progression, 1.7% demonstrated rapid progression and in 1.7% of cases, no judgment was considered possible.

As concerns the management of IPF and physician contacts, over the 12 months prior to enrolment physicians had a mean (± SD) of 3.651 ± 2.506 contacts with the subjects, subjects had a mean (± SD) of 2.844 ± 3.042 visits to outpatient departments, 3.027 ± 2.209 visits to pulmonologists, 1.056 ±

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2.012 visits to other physicians and a mean (± SD) of 2.638 ± 1.067 IPF related procedures were performed.

Clinical course of IPF over the 24 months of follow-up

Among IPF symptoms, dyspnea was present in 53.26% (139/261), 58.23% (145/249), 56.96% (135/237), 54.98% (116/211) and 63.49% (120/189) of patients at 3-, 6-, 12-, 18- and 24-month follow-up, respectively, cough was reported in 57.09% (149/261), 49.00% (122/249), 47.68% (113/237), 52.13% (110/211) and 50.79% (96/189) patients, while fatigue was reported in 17.31% (45/260), 19.28% (48/249), 18.99% (45/237), 19.91% (42/211) and 15.96% (30/188) patients at the five respective visits. Anxiety was reported only in 7.66% (20/261), 6.83% (17/249), 6.75% (16/237), 9.48% (20/211) and 9.57% (18/188) and weight loss was reported only in 6.56% (17/259), 6.43% (16/249), 9.70% (23/237), 8.53% (18/211) and 9.57% (18/188) patients at 3-, 6-, 12-, 18- and 24-month follow-up, respectively. Dizziness and chest pain were present in a minority of patients (<5%) at all study visits. In terms of IPF signs, at 3-, 6-, 12-, 18- and 24-month follow up, 94.64% (247/261), 95.18% (237/249), 94.51% (224/237), 93.40% (198/212) and 89.42% (169/189) patients had bibasilar crackles, respectively, and clubbing was present in 29.89% (78/261), 34.54% (86/249), 34.60% (82/237), 31.60% (67/212) and 26.46% (50/189 patients) patients, respectively.

The mean change from baseline in Forced Vital Capacity (FVC) ± SD% at 3, 6, 12, 18 and 24 months was -0.30 ± 10.623%, -0.41 ± 8.986%, -2.35 ± 11.213%, -2.32 ± 11.536% and -5.18 ± 13.004% predicted and the mean change from baseline in Diffusing capacity of the lung for carbon monoxide (D_{LCO}) ± SD was -0.71 ± 10.407%, -1.96 ± 12.740%, -5.55 ± 13.340%, -7.21 ± 12.846% and -11.69 ± 15.923% predicted, Hb corrected.

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Overall, cardiopulmonary exercise testing (CPET) was not performed during the 3-, 6-, 12- and 18-month follow-up (reported only in 1 patient at the 24-month follow-up visit) and thus no data are presented.
Only 3 patients reported an acute exacerbation of their disease during the 24-month follow-up (each at the 6-, 18- and 24-month visit, respectively).

A limited number of patients were reported to be hospitalized, i.e., 2.30% (6/261), 2.81% (7/249), 5.06% (12/237), 4.23% (9/213), 3.70% (7/189) at the 3-, 6-, 12-, 18-, and 24-month follow-up from baseline; 2 (33.33%), 5 (71.43%), 6 (50%), 4 (44.44%), 3 (42.86%) due to respiratory cause, respectively. Only 4 patients were hospitalized due to cardiovascular events (including cardiac failure), 3 reported at the 12- and 1 at the 18-month follow-up visit, respectively. Finally, only 2 patients used the emergency room (ER) and 1 patient was in an intensive care unit (ICU) and on mechanical ventilation.

As per the physicians' overall clinical judgment, during the 24-month follow-up, the majority of patients had a stable disease, i.e., 88.51% (231/261), 84.74% (211/249), 83.54% (198/237), 83.02% (176/212) and 79.37% (150/189) followed by those demonstrating slow progression, i.e., 8.81 (23/261), 10.84% (27/249), 13.50% (32/237), 12.74% (27/212) and 16.40% (31/189), and with the minority demonstrating rapid progression i.e., 2.30% (6/261), 4.42% (11/249), 2.11% (5/237), 4.25% (9/212) and 4.23% (8/189) at 3-, 6-, 12-, 18- and 24-month follow-up, respectively.

As concerns the management of IPF and physician contacts, physicians had a mean (± SD) of 0.801 ± 1.033, 0.676 ± 0.832, 1.105 ± 1.406, 0.778 ± 0.985, 0.553 ± 0.842 contacts with the subjects, subjects had a mean (± SD) of 0.545 ± 0.899, 0.502 ± 0.852, 0.856 ± 1.358, 0.664 ± 1.217, 0.489 ± 0.939 visits to outpatient departments, a mean (± SD) of 0.654 ± 0.839, 0.624 ± 0.777, 0.928 ± 1.171, 0.698 ± 1.05, 0.479 ± 0.749 visits to pulmonologists, a mean (± SD) of 0.34 ± 0.626, 0.358 ± 0.749, 0.561 ± 0.979, 0.588 ± 1.098, 0.505 ± 0.831 visits to other physicians and a mean (± SD) of 1.216 ± 1.015,

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	1.271 ± 1.026, 1.722 ± 1.241, 1.613 ± 1.27 and a mean (± SD) of 1.569 ± 1.345 IPF related procedures during the 3-, 6-, 12-, 18- and 24-month follow-up. In total, 189 (62.79%) patients were known to be still alive at the end of follow-up; 57 (18.9%) discontinued for unknown reasons and 55 (18.27%) had died. The most common reasons for death were unknown (28 patients; 9.30%) and IPF (24 patients; 7.97%). Upon assessment of survival via Kaplan-Meier analysis in correlation to study enrollment (date of ICF signature), it is indicated that the 75% survival was approximately 24 months. When assessing survival via Kaplan-Meier analysis in correlation to the date of IPF diagnosis, our results indicate that the median survival was 12 years. One hundred twenty-six (126; 41.86%) patients were recorded to be taking nintedanib and 120 (39.87%) patients to be taking pirfenidone, whereas the most commonly recorded concomitant medications were GERD medications (112 patients; 37.21%) and anticoagulants (101 patients; 33.55%). With regards, to non-pharmacological treatment, no patient was reported as listed for lung transplantation or participating in a pulmonary rehabilitation program at baseline with the frequency up to the 24-month follow-up being <3%. Fifty-six (56; 18.60%) of the entire IPF cohort were receiving long-term oxygen supplementation at baseline; the frequency at 3-, 6-, 9-, 12-, 18- and 24-month follow-up remained the same, namely 19.16% (50/261), 18.47% (46/249), 20.25% (48/237), 18.31% (39/213) and 19.05% (36/189), respectively.		
Discussion:	The INDULGE IPF, is the first observational registry designed to assess the characteristics, management, progression and outcomes of patients with IPF as treated under “real-world”, clinical practice conditions in Greece [1].		

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Based on patient demographics, the INDULGE IPF registry participants were predominantly of an advanced age and males similar to other registry and clinical trial cohorts [2-15].

A high prevalence of ex-smokers among IPF patients was observed in our registry, which was also similar to the one reported in most other registries [4-15] and confirms the established role of cigarette smoking as a common risk factor in IPF [16]. Moreover, almost 1 out of 3 IPF patients reported exposure to environmental or occupational factors associated with IPF, a frequency higher to that reported in the Italian FIBRONET and the German INSIGHTS-IPF registries [4, 15]. We also identified a family history of IPF in <10% of patients, which is similar to that reported by the Finnish IPF [8], EMPIRE [9], BTS [12], PROOF [13] and SEPAR [14] registries. However, a higher percentage of an affected first-degree relative has been observed in other registries [7, 10, 15].

Comorbidities were unsurprisingly quite common in our registry, with the vast majority of patients (86.7%) reporting at least one. Among those, the leading comorbidity was arterial hypertension, followed by hyperlipidaemia, GERD, diabetes mellitus, CAD and COPD. This comorbidity profile appears to be characteristic of IPF [17] and consistent with that of other previously described registries [4, 7, 10-15, 18].

The present registry also allowed us to explore the potential diversity in clinical practice in Greece with regard to routinely adopted diagnostic approaches and adherence to relevant guidelines. Participating physicians seem to align with the ATS/ERS/JRS/ALAT guidelines being in force at the time of diagnosis [19], as all patients in our registry had an IPF diagnosis based on clinical-radiological assessments (HRCT), with the vast majority (79.5%) demonstrating a definite UIP pattern and only approximately 8%

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undergoing a lung biopsy. Interestingly, a decreased utilization of lung biopsies was noted in the clinical practice of Greek doctors as well as in that of the Italian doctors [15] when compared to the 20-35% rate of biopsies reported by the INSIGHTS, PROOF, SEPAR and eurIPFreg registries, even in those with a definitive UIP pattern on HRCT [4, 7, 13, 14]. Although information on the reasons why surgical lung biopsy was not performed was not documented, the decline in lung biopsies could reflect the growing awareness and recognition amongst specialists in IPF in Greece of the risk of acute exacerbation and progression of IPF associated with the procedure. Despite the fact that the 2011 guidelines were against BAL routine use in the diagnostic evaluation of IPF patients, half of our patients underwent BAL. This was even more pronounced in the German registry where the majority of patients had a BAL [4]. Although in the latter registry this was attributed to the national adaptation of guidelines, in our case this may just constitute a different local clinical practice. It should be noted though that initiation of INDULGE IPF registry also coincided with the most recent revision of the guidelines, that of 2018, which recommend BAL again in the diagnostic algorithm of IPF [20].

Cardiopulmonary exercise testing is not commonly employed in clinical practice in Greece according to our registry. This reflects the fact that, although available for decades, there is still insufficient evidence supporting its value in IPF prognosis and thus its utilization is currently limited [21, 22]. Nevertheless, almost half of the patients performed the 6MWT at the time of their enrolment in our registry in line with the increasing interest in the recent years in its utilization in IPF patients to test for their exercise capacity not only in routine clinical practice but also in controlled clinical trials [23, 24]. The mean distance was 401.7 ± 119.11 metres, which is similar to that from other registries [5, 10, 13, 14, 15] and greater than the ones reported in the INSIGHTS-IPF and eurIPFreg registries [4, 7].

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In our registry, patients were highly symptomatic, and the symptom profile was characteristic of that of IPF, with bibasilar crackles being consistently the leading sign. Dyspnoea and cough were the cardinal symptoms, being present in the majority of patients.

A mild-to-moderate lung function impairment, as reflected in the observed FVC of 78.22% predicted and D_{LCO} of 48.16% predicted, was recorded at baseline. These values were somewhat analogous to those reported in most other registries [5, 8, 9, 10, 12-15] with the exception of the INSIGHTS-IPF registry [4]. The above values were also similar or higher compared to those of patients enrolled in randomized controlled clinical trials [2, 3, 18]. The INSIGHTS-IPF registry appears to be an exception since patients within this registry demonstrated a more severe gas exchange impairment at baseline (mean D_{LCO}, 35.5% predicted) [4, 18]. A closer look at our study, suggests a worse baseline function, characterized by lower FVC% predicted and D_{LCO}% predicted values, in patients with an older diagnosis (≥6 months) when compared with newly diagnosed patients (<6 months), highlighting the potential decline in lung function during the course of IPF. Moreover, during the 2 years of follow-up, the annual decline for the entire cohort was approximately 2.5 units of FVC% predicted/year and approximately 5.6 units of DLCO% predicted/year. Interestingly, in the INSIGHTS-IPF registry, physiological changes between baseline and 2-year follow-up were categorised as stable if FVC did not change or was improved by ≥5%; as a moderate decrease if decreased by >5–10%; or as a significant decrease if decreased by >10% [25]. In line with that, an absolute or relative decline in % predicted FVC ≥10 within 6 or 12 months has been associated with increased mortality [19]. However, despite consistent trends for FVC decline in the IPF population, the rate of disease progression on an individual patient basis is unpredictable and highly variable [26]. On the other hand, as per the physicians' overall clinical judgment, who took into account several other factors including physical examination, acute exacerbations and

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hospitalizations, during these 2 years, the majority of patients continued to demonstrate a stable disease. It should be however taken into consideration that patients who attended follow-up visits may have had more stable disease than those who were lost to follow-up.

In our registry, pirfenidone and nintedanib were reported to be administered to 39.87% and 41.86% of patients, respectively. Similarly, a large number of patients were on treatment with antifibrotics in the Italian and Swedish IPF registries (83.9% and 64.3%, respectively) [15, 27]. These percentages seem to be higher than the ones reported in similar registries established in other countries, with only 23% in the Australian registry [10], 44% in the German registry [4] and 26% in the Finnish registry [8]. These differences may arise from the fact that these drugs may not have been commercially available during the time of patient enrolment in the respective registries or due to their potential high cost or limited level of reimbursement by the relevant national health authorities [4, 8, 10, 27].

In terms of supportive therapies, approximately a quarter of patients (21%) were receiving supplemental oxygen therapy at baseline, which is similar to that reported in the INSIGHTS, the EMPIRE and the SEPAR registries [4, 9, 14]. This frequency has not significantly changed over the 2 years of follow-up possibly indicating the stability of the disease. Despite accumulating evidence indicating that rehabilitation improves quality of life and symptoms in patients with IPF, the absence of participation in pulmonary rehabilitation programs was evident in our registry. Moreover, as also reported by other registries, the proportion of patients assessed and listed for lung transplantation was quite small (<3%) [4, 7, 12, 15].

The published registries have confirmed the high mortality associated with IPF. Indicatively, a mortality rate of 38%, 26.7% and 15% was reported by the eurIPFreg, INSIGHTS-IPF and the IPF-PRO registries during the

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	respective follow-up periods [4, 7, 28]. The mortality rate reported in our registry was 18.3% but it is unlikely it represents real IPF mortality in Greece as survival data are incomplete. Overall, based upon analysis of baseline data of a cohort of 301 patients, the main clinical features of Greek IPF patients enrolled in the INDULGE IPF registry seem to resemble the clinical presentation of IPF as reported in large randomized clinical trials and patient registries from other countries.		
Marketing Authorisation Holder(s):	Not Applicable		
Names and affiliations of principal investigators:	The names and affiliations of the study principal investigators are kept in the trial master file and can be provided upon request.		