PharmacoEconomics
https://doi.org/10.1007/s40273-023-01278-3

ORIGINAL RESEARCH ARTICLE

Economic Burden of Idiopathic Pulmonary Fibrosis in Spain: A Prospective Real-World Data Study (OASIS Study)

Maria Jesus Rodríguez-Nieto[1] · Esteban Cano-Jiménez[2] · Ana D. Romero Ortiz[3] · Ana Villar[4] · Marta Morros[5] · Alba Ramon[6] · Silvia Armengol[6]

Accepted: 26 April 2023

Abstract

Background Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease associated with dyspnoea, cough and impaired quality of life affecting around 7500 patients in Spain.

Objective Our aim was to estimate the economic impact of IPF according to forced vital capacity (FVC) % predicted level in adult patients.

Methods We conducted a prospective, observational, multicentric study of patients with confirmed IPF in Spain. Total annual IPF-related costs were estimated per patient, and categorised according to the FVC% predicted value (FVC < 50%, FVC 50–80%, FVC > 80%) and total sample. Incurred direct health- and non-health-related costs and indirect costs were calculated considering the IPF-related healthcare resource use and the corresponding unitarian costs. Results were updated to 2023 euros.

Results Two hundred and four consecutive patients with IPF were included: 77% male, average age (standard deviation) 70.8 (7.6) years. At baseline, FVC% was < 50%, 50–80% and > 80% of predicted value in 10.8%, 74.5% and 14.7% of patients, respectively. The final cost-evaluable population included 180 subjects. The mean (standard deviation) total annual IPF-related cost was €26,997 (17,555), with statistically significant differences ($p = 0.0002$) between groups: €44,412 (33,389) for the FVC < 50%, €25,803 (14,688) for the FVC 50–80% and €23,242 (13,642) for the FVC > 80%. Annual direct health costs had the greatest weight and included pharmacological treatments [€22,324 (13,773)] and hospitalisation days [€1659 (7362)]. 14 patients had ≥ 1 acute exacerbation of IPF during the study; mean total cost of an acute exacerbation of IPF was €10,372. According to the multivariate analysis, an impaired lung function (FVC < 50%) and use of antifibrotic treatment were determinants of cost ($p < 0.0001$ both).

Conclusions We observed a significantly higher annual IPF-related cost at a lower level of predicted FVC%, the direct cost having the greatest weight to the total costs. Maintaining patients at early disease stages by slowing IPF progression is relevant to reduce the economic impact of IPF.

Clinical Trial Registration EU PAS register number EUPAS19387 (1 June, 2017).

✉ Maria Jesus Rodríguez-Nieto
mjrodriguezn@fjd.es

1 Servicio de Neumología, IIS-Hospital Universitario Fundación Jiménez Díaz, CIBERES, Av. Reyes Católicos, 2, 28040 Madrid, Spain

2 Servicio de Neumología, Hospital Universitario Lucus Augusti, Lugo, Spain

3 Servicio de Neumología, Hospital Universitario Virgen de las Nieves, Granada, Spain

4 Servei de Pneumologia, Hospital Universitari Vall d'Hebron, Barcelona, Spain

5 Adelphi Targis SL, Barcelona, Spain

6 Boehringer Ingelheim España, Sant Cugat del Vallès, Spain

1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a fatal, progressive fibrosing interstitial pneumonia of unknown aetiology typically occurring in adults aged > 50 years [1]. Idiopathic pulmonary fibrosis is characterised by progressive fibrosis, irreversible decline in lung function and early mortality [1]. Apart from progression, 5–10% of patients with IPF may experience acute respiratory exacerbations annually jeopardising patients' survival and quality of life [1].

Idiopathic pulmonary fibrosis prevalence ranges between 2 and 29 cases per 100,000 persons worldwide [1], and in Spain it is estimated to be around 13 cases per 100,000

Published online: 30 May 2023

Key Points

Previous studies of the cost of idiopathic pulmonary fibrosis are scarce and out of date.

Patients in whom idiopathic pulmonary fibrosis has progressed (forced vital capacity < 50%) require more healthcare resources and are more costly for the health system.

Maintaining patients at early disease stages by slowing idiopathic pulmonary fibrosis progression is relevant to reduce the economic impact of idiopathic pulmonary fibrosis.

inhabitants in women and 20 per 100,000 inhabitants in men, affecting about 7500 patients [2]. The disease has poor prognosis, with a 2- to 3-year survival time from diagnosis [1]. Higher mortality risk is associated with a decline in forced vital capacity (FVC) ≥ 10% [3] and with the occurrence of acute exacerbations among other factors: patients who experience at least one exacerbation have a ten-fold higher mortality risk than patients without exacerbations [3, 4]. Given that no cure exists, current therapies are aimed to slow the FVC decline, reduce acute exacerbations of IPF and to delay disease progression. As fibrosis was considered to be the main event in IPF course according to King et al. [5], the therapeutic approach changed, promoting the development of new antifibrotic agents (nintedanib and pirfenidone). Antifibrotic treatments significantly reduce the decline in lung function (disease progression) [6, 7] and nintedanib clinical trials also demonstrated a reduction in the risk of experiencing acute exacerbations of IPF in all FVC severity stages [7, 8].

Idiopathic pulmonary fibrosis substantially impairs patients' quality of life [9, 10] and represents a significant burden on healthcare resource use and costs [11]. Nevertheless, data on IPF costs are outdated and scarce [11–14]. The only study carried out in Spain was based on a Delphi panel [15]. This study showed that management of patients with IPF has a high economic impact on the Spanish National Health System, especially for patients with rapid disease progression [15]. Morell et al. showed that the main cost driver of managing patients with IPF was the healthcare resource use associated with hospitalisation because of acute exacerbations [15]; nevertheless, they did not provide any information on the burden of disease by the level of severity or from the societal perspective, and did not include antifibrotic treatment costs. Therefore, the real economic burden associated with IPF based on actual clinical practice in Spain is still unknown. The aim of the present study was to estimate the cost of IPF in Spain based on prospective real-world data considering direct and indirect costs, and to identify the main determinants of cost of disease.

2 Methods

2.1 Study Design

The OASIS study used a prospective non-interventional multicentre design to evaluate the cost of the disease in patients with confirmed IPF in Spain. The study was performed in the interstitial lung disease units of pulmonology services in 28 sites, where IPF is diagnosed and managed according to the healthcare system in Spain. Site selection was performed in order to ensure representativeness of the IPF patient population.

2.2 Patients

Patients were enrolled in a consecutive manner from December 2017 to July 2018. Inclusion criteria were: IPF diagnosis according to 2011 ATS/ERS/JRS/ALAT IPF guidelines [1], ≥ 40 years of age and signing a written informed consent prior to participation. Patients were excluded if they were unable to understand Spanish or complete the written informed consent and/or patients' questionnaires; if they were participating in any other clinical trial or if the further follow-up was not possible at the enrolling site. Included patients were divided in three groups according to their FVC% predicted value at baseline: FVC < 50%, FVC 50–80% and FVC > 80%. The follow-up of included patients was performed during 1 year.

2.3 Data Collection

Sociodemographic and clinical data were collected from medical records and study questionnaires completed by patients. Idiopathic pulmonary fibrosis-related data, according to the investigator's criteria, were collected at three visits as per clinical practice: baseline visit and the closest visits to month 6 and month 12 from baseline. In order to reduce recall bias, patients were asked to complete a patient diary during the study, which included recording the use of IPF-related resources (health and non-health) and missed days of work.

The study protocol (BOE-MAC-2017-01) was approved by the ethical boards of all participant hospitals. The Ethical Board of H. Fundación Jiménez Díaz in Madrid, Spain acted as the reference ethics committee.

2.4 Cost Description and Analysis

The total costs were obtained as the sum of the direct health costs, direct non-health costs and indirect costs from the societal perspective. All costs were estimated per patient per year, and categorised according to the FVC% predicted value (FVC < 50%, FVC 50–80%, FVC > 80%) and total sample.

Average annual IPF-related healthcare resource use per patient was collected at T6 and/or T12, in addition to those resources related to acute exacerbations of IPF. The annual direct health resources included medical visits, emergency room visits, hospital admissions, outpatient tests, non-pharmacological treatments and pharmacological treatments registered at 6 months, at 12 months and because of acute exacerbations, all of them only related to IPF. Direct non-health resources included: transport (taxi or ambulance), paid caregivers, orthopaedic material, financial aid, and structural changes at 12 months and because of acute exacerbations. Indirect costs, defined as the costs associated with the impact of the disease borne by the patient, included patients' missed days of work in 12 months and an informal caregiver, at 12 months and because of acute exacerbations. Additionally, a final living cost [16] was defined as the estimated cost of the patient in palliative care until his/her death and attributed to patients who died after a 6-month follow-up.

Total annual IPF costs were obtained at the patient level as the sum of direct health costs, direct non-health costs and indirect costs. Costs were calculated by multiplying the number of resources used (i.e. medical visits, emergency room visits, tests, treatments—including mean doses and duration of treatment—and hospitalisations) by their corresponding unit costs. Unit costs were obtained from Spanish databases (Electronic Supplementary Material [ESM]) [17–21]. The costs were consulted at the time of the analysis, and all costs were expressed in 2019 euros and updated accordingly. At the time of publication, results were updated to 2023 euros using the published cumulative consumer price index [22]. Official notified prices for pharmacological treatments were used [18].

For indirect costs, the calculation was based on the human capital method, assuming the salary reflects the productivity of the worker and that a period of absence because of illness can be valued based on gross income. The opportunity cost method was used to calculate informal care costs. The indirect costs were estimated by applying salary costs based on the latest data published by the Spanish *Instituto Nacional de Estadística* (INE) from the salary structure survey [23], adjusted to age. With this method, the indirect cost of patients or caregivers not actively employed during the study period (e.g. unemployed and retired workers) was 0.

As pre-specified in the protocol, to explore the determinants of costs in patients with IPF, the following variables, relevant in clinical practice according to scientific advisors, were considered: sociodemographic variables, anthropometric variables, characteristics of IPF—time of IPF diagnosis FVC (L), FVC% predicted, FVC annual rate of decline, DL_{CO}, the Barthel Index, 6MWT distance, concomitant diseases related to IPF, pharmacological (antifibrotic or non-antifibrotic treatment) and non-pharmacological treatments related to IPF, smoking status, work with animals (current or prior), use of formal and/or informal caregiver, patients with acute exacerbations (≥ 1 vs 0) and predefined groups according to FVC% predicted at baseline. To estimate the cost variation associated with a FVC decline, a FVC decline was estimated as relative change as follows: [(final FVC% predicted–initial FVC% predicted)/initial FVC% predicted] × 100.

2.5 Statistical Analysis

A descriptive analysis was performed of all the variables recorded for the study population. For continuous variables, the mean, standard deviation and valid samples (*n*) are presented. Categorical variables were presented as absolute and relative frequencies (percentages).

For the bivariate analysis, continuous variables were compared across subgroups of the population using two-sample t-tests or an analysis of variance or the Mann–Whitney *U* test or Kruskal–Wallis test, as appropriate. The categorical variables were analysed using the Chi-square or Fisher test, as appropriate. Spearman correlations were used to estimate linear correlations between continuous variables.

Bivariate exploratory methods, analysis of variance, Mann–Whitney *U* test or Kruskal–Wallis test, and Spearman correlation were used to explore the predictors of costs. Multivariate linear regression analyses were applied to all samples, including costs as a dependent variable. The explanatory variables were included based on previous bivariate analyses and clinical relevance (with a $p < 0.1$). Given that the final number of patients in the FVC < 50% and FVC > 80% groups were small, only an exploratory bivariate analysis was performed in those groups.

Descriptive analyses were carried out of direct and indirect costs according to the absolute and relative change in FVC (FVC decline > 10 %, FVC decline 5–10%, FVC decline < 5 %) between baseline and the 12-month visit.

A statistical significance level of 0.05 was applied in all the statistical tests. The evaluation was carried out using SAS® software, version 9.4.

3 Results

A total of 204 patients with IPF were enrolled in this study. Twenty-four patients were lost during the follow-up and the final evaluable population for the cost analysis included 180 subjects, with a mean follow-up of 12.40 (1.07) months (ESM). The cost-evaluable population included those patients with at least 6 months of follow-up (with data at the T6 visit).

3.1 Baseline Sociodemographic and Clinical Characteristics of the Study Population

Table 1 shows sociodemographic and clinical characteristics of patients at baseline. Patients were mostly male (77%) with a mean age of 70.8 years. The time since IPF diagnosis at the baseline visit was 1.92 (1.85) years and 72.1% of the patients showed comorbidities associated with IPF. At baseline, 10.8% of patients had a FVC% predicted < 50%, 74.5% a FVC 50–80% and 14.7% a FVC > 80%. No significant sociodemographic differences were observed between groups.

Regarding clinical characteristics, and as expected, lung function parameters ($p < 0.0001$) and distance and final oxygen saturation in the 6-minute walk test differed between FVC% predicted groups ($p < 0.05$, both variables) (Table 1). Overall, 22 (10.8%) patients had one or more acute exacerbations during the study, with a higher percentage of patients having at least one acute exacerbation in the FVC < 50% group (27.3%) than in the FVC 50–80% and FVC > 80% groups (8.6% and 10%, respectively).

Regarding pharmacological treatment associated with IPF, 166 (81.4%) patients were receiving antifibrotics: 74 (44.6%) nintedanib and 92 (55.4%) pirfenidone. Forty-one (20.1%) patients were receiving non-pharmacological treatments (mainly oxygen therapies). Patients with lower FVC% predicted at baseline received significantly more non-pharmacological treatment, more systemic corticosteroids and more help from a caregiver (Table 1). Of note, 9 out of 30 (30%) patients with IPF with a preserved lung function (FVC% predicted > 80%) remained untreated despite the availability of antifibrotic therapies.

3.2 Annual Direct and Indirect IPF-Related Costs Per Patient

Table 2 shows the total annual costs of IPF per patient categorised by direct health-related, direct non-health-related and indirect costs. The mean total annual IPF-related cost per patient was €26,997, and differed between FVC% predicted groups ($p = 0.0002$), which ranged from €23,242 in the FVC > 80% group to €44,412 in the FVC < 50% group (Table 2 and Fig. 1).

Direct health IPF-related costs accounted for 98.7% of total annual costs. The cost with the greatest weight was pharmacological treatment, with a mean of €22,324 per patient per year, followed by the cost of hospitalisations (Table 2). Direct health IPF-related costs differed between groups ($p = 0.0007$), being higher in patients who had FVC < 50% predicted at baseline (mean cost per patient per year €42,426) than in patients who had FVC 50–80% or FVC > 80% at baseline (€25,588 and €23,042, respectively) [Table 2]. Patients with worse lung function at baseline had significantly higher costs in days of hospitalisation ($p = 0.0001$), hospitalisations in the ICU ($p = 0.0006$), non-pharmacological treatment use ($p < 0.0001$), primary care visits ($p = 0.0244$) and secondary care visits ($p = 0.0485$) [Table 2].

Direct non-health IPF-related costs also differed significantly between FVC% predicted groups ($p < 0.0001$), which ranged from €1892 per patient per year in the FVC < 50% group to €170 and €200 in the FVC 50–80% and the FVC > 80% groups, respectively (Table 2). Transport in ambulance ($p = 0.0065$), transport in taxi ($p = 0.0002$), formal caregiver ($p = 0.0017$) and orthopaedic material costs ($p = 0.0218$) were higher in patients with lower FVC% predicted at baseline (Table 2). Last, no significant differences between FVC% predicted groups were observed regarding indirect costs (Table 2).

3.3 Cost Associated with Acute Exacerbations

Among the cost-evaluable study population ($n = 180$), 14 patients had at least one acute exacerbation during the follow-up. Estimated mean total cost of an acute exacerbation was €10,371.64 and did not differ among patients with different FVC% predicted at baseline (data not shown).

3.4 Cost Variation Associated with FVC Decline

Cost associated with a FVC decline, considered as the relative change of FVC% at 12 months versus baseline, was also estimated. FVC% decreased on average by 2.50% (95% confidence interval − 5.98 to 0.98). Relative change of FVC% did not differ among patients with different FVC% predicted at baseline ($p = 0.1131$).

In order to analyse cost variation associated with a FVC decline, patients were categorised into three subgroups: patients with a FVC decline > 10%, patients with a FVC decline 5–10% and patients with a FVC decline < 5%. No significant differences in total annual IPF-related costs were observed among patients with different FVC declines (Fig. 2). Seven out of nine (77.8%) of patients in the FVC%

Table 1 Baseline characteristics of the study population by FVC% predicted at baseline

Characteristic	Total sample $N = 204$	FVC% predicted[f] at baseline			
		FVC < 50% $N = 22$	FVC 50–80% $N = 152$	FVC > 80% $N = 30$	*P*-value
Sex, male, *n* (%)	157 (77.0%)	18 (81.8%)	120 (78.9%)	19 (63.3%)	0.1516
Age (years), mean (SD)	70.80 (7.60)	70.32 (8.52)	71.36 (7.21)	68.33 (8.54)	0.1992
Employment status, active worker, *n* (%)	24 (11.8%)	2 (9.1%)	14 (9.2%)	8 (26.7%)	0.0232
BMI (kg/m^2), mean (SD)[g]	28.13 (3.97)	27.15 (3.73)	28.29 (3.88)	28.06 (4.62)	0.5682
Occupational and/or environmental exposure factors, *n* (%)					0.7718 (3)
Yes	97 (47.5%)	10 (45.5%)	75 (49.4%)	12 (40.0%)	
No	103 (50.5%)	12 (54.5%)	73 (48.0%)	18 (60.0%)	
Unknown	4 (2.0%)	0 (0.0%)	4 (2.6%)	0 (0.0%)	
Smoking habit, *n* (%)					0.5300 (3)
Non smokers	64 (31.4%)	8 (36.4%)	48 (31.6%)	8 (26.7%)	
Former smokers[a]	135 (66.2%)	14 (63.6%)	101 (66.4%)	20 (66.7%)	
Smokers	5 (2.4%)	0 (0.0%)	3 (2.0%)	2 (6.6%)	
Time since IPF diagnosis (years), mean (SD)	1.92 (1.85)	2.00 (1.69)	1.95 (1.91)	1.73 (1.67)	0.6416
Lung function, mean (SD)					
Predicted FVC%	65.78 (14.42)	41.96 (5.83)	64.66 (8.42)	88.94 (8.35)	< 0.0001(1)
DL_{CO}-c predicted (%)[g]	49.99 (17.39)	36.17 (12.27)	50.29 (17.36)	57.83 (15.29)	< 0.0001(2)
Six-minute walk test, mean (SD)[g]					
Distance (metres), mean (SD)	443.70 (101.32)	376.45 (122.65)	449.78 (92.71)	472.55 (103.70)	0.0036 (1)
Need for oxygen (yes), *n* (%)	17 (10.7%)	5 (25.0%)	12 (10.3%)	0 (0.0%)	0.0307 (3)
Initial oxygen saturation (%), mean (SD)	94.87 (2.54)	94.10 (2.43)	94.84 (2.59)	95.73 (2.19)	0.0533 (2)
Final oxygen saturation (%), mean (SD)	86.71 (6.97)	85.50 (6.20)	86.66 (6.69)	90.15 (7.95)	0.0009 (2)
Pharmacological treatment associated with IPF, *n* (%)					
Antifibrotic[b]	166 (81.4%)	16 (72.7%)	129 (84.9%)	21 (70.0%)	0.0876
Systemic corticosteroids[c]	10 (4.9%)	4 (18.2%)	5 (3.3%)	1 (3.3%)	0.0320 (3)
Antacids[d]	72 (35.3%)	7 (31.8%)	57 (37.5%)	8 (26.7%)	0.4921
Antibiotics for systemic use[e]	6 (2.9%)	1 (4.5%)	4 (2.6%)	1 (3.3%)	0.6290 (3)
Other	11 (5.4%)	2 (9.1%)	7 (4.6%)	2 (6.7%)	n.a.
Non-pharmacological treatment associated with IPF, *n* (%)	41 (20.1%)	14 (63.6%)	26 (17.1%)	1 (3.3%)	< 0.0001
Liquid oxygen therapy, *n* (%)	13 (6.4%)	5 (22.7%)	7 (4.6%)	1 (3.3%)	0.0142(3)
Electric portable oxygen therapy, *n* (%)	9 (4.4%)	2 (9.1%)	7 (4.6%)	0 (0.0%)	0.2849(3)
Oxygen therapy with oxygen concentrator, *n* (%)	12 (5.9%)	6 (27.3%)	6 (3.9%)	0 (0.0%)	0.0007(3)
Oxygen therapy portable device, *n* (%)	6 (2.9%)	2 (9.1%)	3 (2.0%)	1 (3.3%)	0.1153(3)
High-flow nasal cannulas, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Non-invasive mechanical ventilation, *n* (%)	3 (1.5%)	2 (9.1%)	1 (0.7%)	0 (0.0%)	0.0410(3)
Flu and pneumococcal vaccination, *n* (%)	9 (4.4%)	4 (18.2%)	5 (3.3%)	0 (0.0%)	0.0153(3)
Nutritional supplements, *n* (%)	2 (1.0%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	0.0112(3)
Other, *n* (%)	1 (0.5%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0.1078(3)
Acute IPF exacerbations, *n* (%)	22 (10.8%)	6 (27.3%)	13 (8.6%)	3 (10.0%)	0.0333 (3)

BD bronchodilator, *BMI* body mass index, DL_{CO}-*c* carbon monoxide lung diffusion capacity (corrected for hemoglobin), *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *n.a.* not available, *SD* standard deviation

[a]Former smoker: person who, having smoked, has maintained abstinence for at least the last 6 months

[b]Includes nintedanib 74 (26.9%) and pirfenidone 92 (33.5%)

[c]Includes methylprednisolone 1 (0.4%) and prednisone 9 (3.3%)

[d]Includes esomeprazole 12 (4.4%), lansoprazole 5 (1.8%), omeprazole 18 (6.5%), pantoprazole 33 (12.0%), rabeprazole 2 (0.7%) and ranitidine 2 (0.7%)

[e]Includes azithromycin 5 (1.8%) and sulfametoxazol plus trimetoprime 1 (0.4%)

(1) Analysis of variance

(2) Kruskal–Wallis test

(3) Exact Fisher test

[f]FVC% predicted value was automatically calculated within the eCRF based on available patient data [43]: men: FVC% predicted (%) = 100 FVC/(0.0678 T – 0.0147 E – 6.0548) and women: FVC% predicted (%) = 100 FVC /(0.0454 T – 0.0211 E – 2.8253) [FVC is FVC in liters, T is

Table 1 (continued)

height in cm and *E* is age in years]

[g]There were missing values

Table 2 Total direct health-related, direct non-health-related and indirect annual IPF-related costs by FVC% predicted at baseline

Annual costs per patient (euros)	Total $N = 180$	FVC% predicted at baseline			
		FVC < 50% $N = 15$	FVC 50–80% $N = 140$	FVC > 80% $N = 25$	*P*-value
Total IPF-related costs, mean (SD)	26,997 (17,555)	44,412 (33,389)	25,803 (14,688)	23,242 (13,642)	0.0002
Direct health IPF-related costs, mean (SD)	26,638 (17,239)	42,426 (32,480)	25,588 (14,591)	23,042 (13,875)	0.0007
Primary care visits	34 (75)	82 (104)	33 (76)	16 (34)	0.0244
Secondary care visits (specialised care visits)	461 (387)	694 (610)	436 (357)	462 (345)	0.0485
Emergency visits (primary care visits)	10 (48)	29 (89)	10 (47)	0 (0)	0.1971
Emergency visits (hospital)	71 (207)	131 (218)	73 (220)	24 (87)	0.2776
Hospitalisations, admission in emergency room	147 (895)	154 (377)	147 (968)	145 (685)	0.9995
Hospitalisations, days of hospitalisation	1659 (7362)	9293 (21,870)	992 (3656)	814 (2841)	0.0001
Hospitalisations, in ICU	448 (3122)	3363 (8872)	216 (1901)	0 (0)	0.0006
Outpatients tests (laboratory test, pulmonary function test, other examinations)	844 (737)	1154 (1206)	841 (713)	677 (414)	0.1408
Pharmacological treatment (except treatments administered in hospital)	22,324 (13,773)	24,688 (14,613)	22,384 (13,573)	20,569 (1471)	0.6560
Non-pharmacological treatment (except treatments administered in hospital)	436 (1487)	2668 (4187)	270 (697)	26 (89)	< 0.0001
End of life (palliative care)	202 (697)	173 (670)	186 (671)	311 (861)	0.6994
Direct non-health IPF-related costs, mean (SD)	317 (1340)	1892 (3593)	170 (801)	200 (672)	< 0.0001
Transport in taxi	6 (65)	72 (222)	0 (1)	0 (0)	0.0002
Transport in ambulance (€/service)	126 (589)	577 (1167)	94 (529)	30 (148)	0.0065
Formal caregiver	90 (1046)	1002 (3596)	8 (100)	0 (0)	0.0017
Orthopaedic material	30 (175)	144 (380)	15 (124)	42 (209)	0.0218
Economic aid	24 (240)	96 (371)	21 (243)	0 (0)	0.4437
Structural adaptations	43 (414)	0 (0)	33 (386)	128 (639)	0.5252
Indirect costs, mean (SD)	42 (335)	95 (366)	44 (362)	0 (0)	0.6839
Missed days of work in 12 months	0 (0)	0 (0)	0 (0)	0 (0)	-
Informal caregiver	42 (335)	95 (366)	44 (362)	0 (0)	0.6839

All values are expressed as mean (SD)

FVC forced vital capacity, *ICU* intensive care unit, *IPF* idiopathic pulmonary fibrosis, *n* number of patients, *SD* standard deviation

predicted < 50% group at baseline reported a relative FVC decline of < 5%, probably because their FVC was already severely deteriorated at baseline, compromising a further decrease. In this regard, five patients in FVC% predicted < 50% died before reaching T6, not allowing their inclusion in this analysis. Of note, patients who experienced at least one acute exacerbation during the study showed a substantial mean FVC decline (10.14% compared with 2.21% in patients without exacerbations), although this difference was not statistically significant probably owing to the small sample size ($p = 0.4385$).

3.5 Determinants of Costs

The bivariate analysis identified the clinically relevant, significant explanatory variables ($p < 0.1$) [ESM], which were: patients' age, time from diagnosis, FVC% predicted at baseline and at 6 months, DL_{CO} predicted at baseline, FVC rate change by year, having pulmonary emphysema, receiving antifibrotic treatment, experiencing at least one acute IPF exacerbation and having a FVC% predicted value below 50% at baseline. Results of the multivariate linear regression analysis revealed that, among these, impaired lung function and antifibrotic treatment ($p < 0.0001$) are

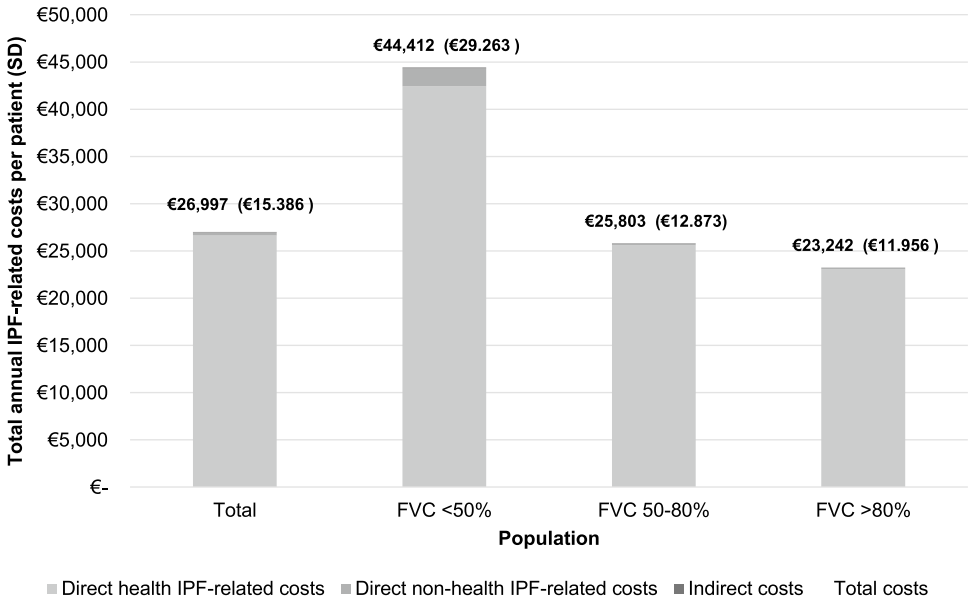

Fig. 1 Total annual idiopathic pulmonary fibrosis (IPF)-related costs per patient by predicted forced vital capacity (FVC%) at baseline. All values are expressed as mean [standard deviation (SD)]. *n* number of patients

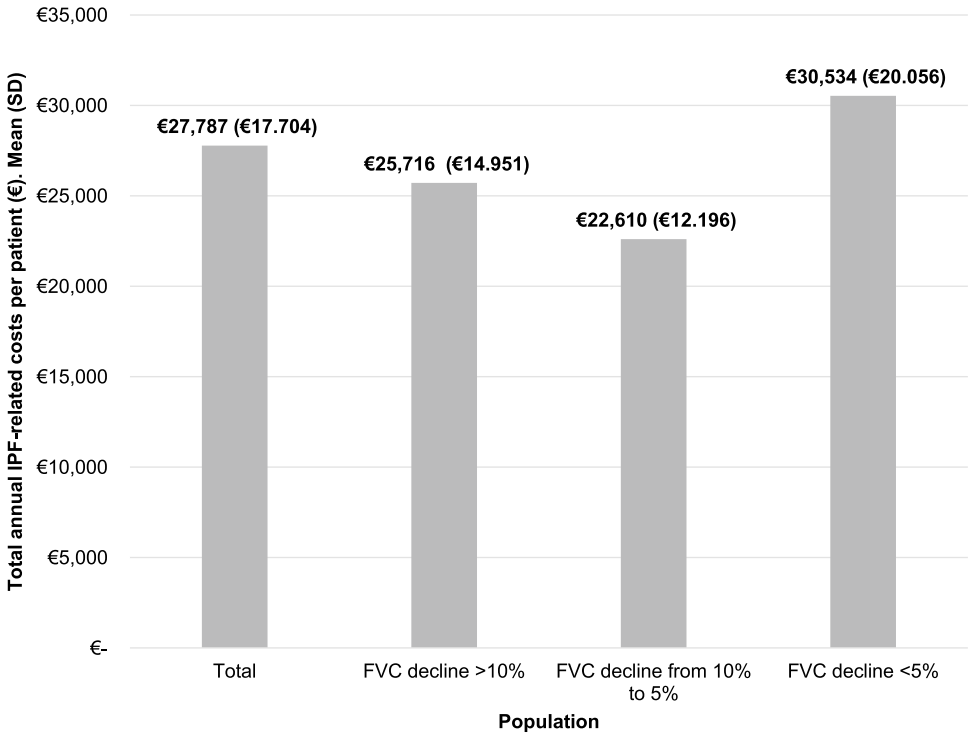

Fig. 2 Cost variation associated with forced vital capacity (FVC) decline. *P*-value for FVC decline (relative change) group comparison = 0.2682. FVC decline (relative change) was calculated as: [(final FVC% predicted − initial FVC% predicted)/initial FVC% predicted] ×100. *IPF* idiopathic pulmonary fibrosis, *n* number of patients, *SD* standard deviation

the main determinants of cost in IPF patients (Table 3). Total annual IPF-related costs from patients with FVC% predicted < 50% were €13,580 and €14,224 higher compared with those of patients with a more preserved lung function (vs FVC > 80% and vs FVC 50–80% groups, $p = 0.0070$ and $p = 0.0006$, respectively) [Table 3]. The total annual IPF-related costs were also significantly higher in patients who received antifibrotic treatment during the study compared with patients not treated with antifibrotics ($p < 0.0001$) [Table 3].

4 Discussion

Idiopathic pulmonary fibrosis affects a significant number of patients in Spain [2], but there is no information about healthcare resource use and its economic burden in

Table 3 Multivariate linear regression analysis for total annual IPF-related costs (total sample)

Parameter	*df*	Estimate (95% CI)	SE	*P*-value
Constant	1	17,863.5 (− 7588.06; 43,314.63)	12,887.60	0.1676
Age	1	− 14.55 (− 308.3; 279.2)	148.74	0.9222
Time since IPF diagnosis	1	− 261.49 (− 1431.82; 908.83)	592.60	0.6596
DL_{CO}, predicted at baseline	1	− 11.87 (− 143.64; 119.92)	66.73	0.8591
Pulmonary emphysema associated with IPF (yes vs no)	1	6833.72 (− 1544.02; 15,211.47)	4242.11	0.1092
Antifibrotic treatment related to IPF along the study (yes vs no)	1	25,483.09 (17,824.17; 33,142.51)	3878.26	< 0.0001
Patients with acute exacerbations [≥ 1 acute exacerbation] (yes vs no)	1	6718.28 (− 1300.88; 14,737.44)	4060.53	0.1000
Patients according predicted FVC% at baseline (FVC 50–80% vs FVC < 50%)	1	− 14,224.85 (− 22,235.47; − 6213.97)	4056.28	0.0006
Patients according predicted FVC% at baseline (FVC > 80% vs FVC < 50%)	1	− 13,580.18 (− 23,403.98; − 3755.36)	4974.58	0.0070

$N = 169$

Goodness of fit: R-squared 0.313455

CI confidence interval, *df* degrees of freedom, DL_{CO} carbon monoxide lung diffusion capacity, *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *SE* standard error

a real-world setting in Spain coming from observational studies. However, in other countries, there are some retrospective real-world studies showing that IPF is associated with a high economic burden [24, 25]. The present study assessed direct healthcare, direct non-healthcare and indirect costs incurred by patients with IPF in Spain. The results of this prospective study show a significant effect of FVC% predicted on the economic burden of the disease, being higher in patients with more impaired FVC. Patients with lower FVC% predicted incurred significantly higher total direct health-related and non-health related costs than patients with higher FVC% predicted. In addition, experiencing at least one exacerbation throughout the study period also entailed a significant effect on the annual direct IPF-related costs.

Demographic and clinical characteristics of patients with IPF included in our study are in accordance with those reported by the IPF National Registry of the Spanish Respiratory Society (SEPAR) [26]. Most patients were male, had a history of smoking, an FVC% predicted between 50% and 80%, and a 5–10% annual exacerbation rate. As previously reported by other IPF national registers [27], our study population showed a progressive decline in lung function over 12 months, confirming the progressive nature of IPF [28]. Almost half of the patients (46.4%) in our study showed a relative lung capacity deterioration of FVC% > 5% and up to 30.0% of the evaluable population had a relative lung capacity deterioration > 10%. Similar data can be found in other IPF registries [27, 29, 30].

The results of our study provide information about the costs of IPF in Spain. We showed that the estimated annual cost per IPF patient was €26,997, with direct health expenses, in particular pharmacological treatment and hospitalisations, accounting for the majority of cost. Our real-world results were similar to those published in 2016 by Morell et al., a Delphi study, where the estimated cost for IPF patient per year was €26,435 [15]. Morell et al. did not include antifibrotics in their cost analysis because nintedanib was not available at that time and pirfenidone was only available through compassionate use, but they included the cost of lung transplantation, in contrast to our study. During the OASIS study, three lung transplantations were reported. According to 2020 Spanish regional health public prices [31], an estimated cost of €113,441 per grade 4 lung transplantation could be considered. Despite the methodological differences, a similar cost is obtained in our study, which includes new IPF-approved treatments. Although comparisons are difficult because of the differences in other healthcare systems, data published revealed average annual costs related to IPF for the 1-year post-diagnosis period of around $20,887 (US, 2012) [13], $17,398–$32,676 (Canada, 2018) [25]. As reported by Morell et al., according to our results, total annual costs are significantly higher for those patients with worse lung function at baseline, both direct health-related costs, in particular hospitalisations, and direct non-health IPF-related costs. When compared with the Spanish burden of other life-threatening diseases and despite clinical and methodological differences, the IPF-related costs per patient are higher than lung cancer (3-year follow-up costs for stage IV disease: €13,503, Spain, 2021) [32] but remain lower than the pancreatic cancer cost per patient (annual cost: €37,620, Spain, 2022) [33].

We observed that patients with well-preserved FVC at baseline were also at risk of experiencing acute exacerbations; in agreement with that, clinical trials have also showed that 2.8% of patients with FVC > 90% predicted at baseline experience an acute exacerbation within the following year

[34]. Experiencing at least one acute exacerbation yearly is associated with a higher risk of future mortality [3, 4]. The management of patients with IPF in Spain was previously reported to have a high economic impact especially for patients with rapid disease progression [15]. Hospitalisations because of acute exacerbations was the parameter that contributed the most to the annual cost of IPF, representing nearly half of the total cost [15]. In our study, patients who had at least one exacerbation during the study also incurred significantly higher costs. As the use of nintedanib has been shown to reduce acute exacerbations [7, 8] and patients with preserved lung function may also experience acute exacerbations according to our results, it can be hypothesised that starting early treatment could prevent the occurrence of such exacerbations and in turn reduce disease costs. However, this would require confirmatory studies.

In the present study, lower FVC% predicted at baseline is one of the main determinants of IPF-related costs, highlighting the importance of maintaining patients with IPF at early disease stages. Nevertheless, a similar relative FVC decline was observed in all patient groups, irrespective of lung function at baseline. Previous studies also showed that patients with IPF with FVC > 90% predicted had a similar FVC decline than patients with more impaired lung volume [34]. Antifibrotic treatment (nintedanib and pirfenidone) reduces the rate of decline in FVC [6, 7, 34–36]. Furthermore, treatment with nintedanib has demonstrated a benefit in patients irrespective of lung function at baseline [34]. Even in those with very well-preserved lung function, a reduced rate of decline in FVC was observed with nintedanib 12 weeks after treatment initiation [37]. Given that impaired lung function at baseline is a main determinant of cost and that nintedanib has been shown to reduce the exacerbation rate and slow disease progression in patients at an early stage of the disease [7, 34], our results suggest that early treatment of IPF with nintedanib could reduce the economic burden of IPF. Moreover, it should be noted that preserving lung function in less severe cases may also allow patients to keep their active employment status for longer, thus avoiding extra costs related to time off work and disability. On the other hand, treatment with antifibrotics was also identified as a determinant of IPF cost as it is found for treatments prescribed for other rare diseases [38]. Idiopathic pulmonary fibrosis is a life-threatening disease that needs to be treated with specific treatments with proven efficacy in terms of slowing disease progression and acute exacerbations, resulting in important changes in a patient's daily life. However, the actual cost of pharmacological treatments might be lower owing to the existence of more advantageous non-publicly available financing conditions, in addition to the official notified price used in our study.

In our study and despite the availability of IPF-approved treatments, 30% of patients with IPF with a preserved lung function (FVC% predicted > 80%) remained untreated. A European IPF survey showed that 54% of patients with IPF did not receive treatment with an approved antifibrotic, in particular patients who had FVC > 80% at diagnosis [39]. According to data from the IPF-PRO Registry, patients with more severe disease at baseline were more likely to be treated [40]. This reflects a reticence to treat patients with a more preserved lung function, despite these patients experiencing a similar FVC decline to patients with a more advanced disease [41]. In line with previous studies, we also observed a low use of pharmacological treatment in patients with less impaired lung function [39, 42]. It may be explained by the historical evolution of therapeutic alternatives of IPF. Before the widespread use of antifibrotics, pharmacologic treatment options for IPF were limited and associated with low efficacy. Moreover, until 2016, Spain had treatment access constraints for patients with a FVC% predicted > 80%. In fact, access restrictions were cited as a barrier to treatment in a 2018 survey of pulmonologists [42]. This is the first prospective real-world study to estimate the economic burden of IPF in Spain from the societal perspective in a real-world setting.

4.1 Strengths and Limitations

Our study included more than 200 patients with IPF, which is an achievement in a rare disease context. Without antifibrotic treatment, the median time of survival of the IPF patients is 2–3 years, and the study design considered a 1-year follow-up; therefore, it provides an accurate overview of the mid-term burden of IPF. Patients were recruited from 28 sites all over Spain, thus providing a geographically balanced sample distribution. The study has some limitations that should be mentioned. Bias because of a loss to follow-up may have affected the cost analysis estimation. We observed higher end-of-life costs for patients with FVC > 80% than for those with FVC < 50%. This atypical finding may be explained as a *final living cost* was only assigned to those patients who were evaluable for a cost analysis, i.e. those who died 6 months or more after baseline. Patients who died before were not included in the analysis as no data in terms of resource use could be collected. In the same line, we found no significant differences in total annual IPF-related costs according to FVC decline groups. A possible explanation for these unexpected results could be that five patients with baseline FVC% predicted < 50% died before reaching the T6 visit, not allowing their inclusion in the FVC decline analysis or in the cost analysis.

The sample size in some subgroups also limited some testing and the statistical power to see differences in the subgroup analysis, although differences could be detected in some subgroups. Moreover, clinical impairment of patients with IPF during the follow-up may have impacted data

for specific variables (e.g. inability to perform respiratory function tests). Regarding the completeness of data, some variables had missing data, for which no imputations were made except for the number of visits to pneumologists and concomitant medications. No adjustment for multiple testing was performed. Finally, estimation of the use of some resources may have been affected by recall bias by patients.

4.2 Future Applications

At the present time, no other real-world cost studies of IPF have been conducted in Spain. Hence, these results may help health authorities to programme, plan and design public policies to deal with the IPF socioeconomic burden. It would be interesting to take advantage of data included in already available national registers for patients with IPF to facilitate real-world data research with the potential to improve patients' management and decision making.

5 Conclusions

To our knowledge, this is the first study to describe overall IPF-related costs and to shed light on the economic burden associated with the disease in Spain. Our results confirm that patients with lower FVC% predicted at baseline entail higher IPF-related costs; therefore, maintaining patients at early disease stages would reduce healthcare costs. Approved IPF treatments that prevent disease progression would reduce patient deterioration, improve patient outcomes and reduce the economic burden of illness.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-023-01278-3.

Acknowledgements Alba Gómez, PhD provided writing support and/or formatting assistance. Adelphi Targis, SL, which was contracted and funded by Boehringer Ingelheim España, provided editorial support.

Declarations

Funding The study was supported and funded by Boehringer Ingelheim.

Conflict of interest Maria Jesus Rodríguez Nieto has received funding for research (data monitoring boards), consulting fees and honoraria for presentations/lectures and for being an advisor from Boehringer Ingelheim and Roche. Esteban Cano Jiménez has received funding for research and consulting fees for presentations/lectures and for being an advisor from Boehringer Ingelheim, Galapagos and Roche. Ana Dolores Romero Ortiz has received funding for research and consulting fees for presentations/lectures and for being an advisor from Boehringer Ingelheim and Roche. Ana Villar has received consulting fees from Boehringer Ingelheim and Roche; fees for talks/lectures from Boehringer Ingelheim, GlaxoSmithKline and Roche; and funding for conferences attendances and courses from Boehringer Ingelheim, Chiesi, Novartis and Roche. Marta Morros is a full-time employee of Adelphi Targis. Alba Ramon and Silvia Armengol are full-time employees of Boehringer Ingelheim España.

Ethics approval The study was approved by the ethical board of all participant hospitals. The Ethical Board of H. Fundación Jiménez Díaz in Madrid, Spain acted as a reference ethical board. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Consent to participate All patients provided written informed consent prior to their participation.

Consent for Publication Not applicable (not idividual data reported).

Availability of data and material The datasets generated and/or analysed during the current study are not publicly available because of participants privacy protection but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions AR and SA were responsible for the original idea and study conceptualisation, methodology and supervision, as well as manuscript writing (review and editing). MM contributed in the formal analysis of results, data interpretation and data visualisation, and drafting the manuscript. EC, MJR, ADR and AV were involved in the study conceptualisation, methodology and investigation, as well as the review and writing of the results (review and editing). All authors read and approved the final manuscript.

References

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824. https://doi.org/10.1164/rccm.2009-040GL.
2. Xaubet A, Ancochea J, Bollo E, et al. Guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. Arch Bronconeumol. 2013;49(8):343–53. https://doi.org/10.1016/j.arbr.2013.06.003.
3. Paterniti MO, Bi Y, Rekić D, Wang Y, Karimi-Shah BA, Chowdhury BA. Acute exacerbation and decline in forced vital capacity are associated with increased mortality in idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2017;14(9):1395–402. https://doi.org/10.1513/AnnalsATS.201606-458OC.
4. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: Incidence, risk factors and

outcome. Eur Respir J. 2011;37(2):356–63. https://doi.org/10.1183/09031936.00159709.
5. King TEJ, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378(9807):1949–61. https://doi.org/10.1016/S0140-6736(11)60052-4.
6. King TEJ, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92. https://doi.org/10.1056/NEJMoa1402582.
7. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82. https://doi.org/10.1056/NEJMoa1402584.
8. Kreuter M, Koegler H, Trampisch M, Geier S, Richeldi L. Differing severities of acute exacerbations of idiopathic pulmonary fibrosis (IPF): insights from the INPULSIS® trials. Respir Res. 2019;20(1):71. https://doi.org/10.1186/s12931-019-1037-7.
9. Kreuter M, Swigris J, Pittrow D, et al. Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: insights-IPF registry. Respir Res. 2017;18(1):139. https://doi.org/10.1186/s12931-017-0621-y.
10. Swigris JJ, Brown KK, Abdulqawi R, et al. Patients' perceptions and patient-reported outcomes in progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018;27(150): 180075.
11. Diamantopoulos A, Wright E, Vlahopoulou K, Cornic L, Schoof N, Maher TM. The burden of illness of idiopathic pulmonary fibrosis: a comprehensive evidence review. Pharmacoeconomics. 2018;36(7):779–807.
12. Loveman E, Copley VR, Colquitt JL, et al. The effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: systematic review, network meta-analysis and health economic evaluation. BMC Pharmacol Toxicol. 2014;15:63. https://doi.org/10.1186/2050-6511-15-63.
13. Collard HR, Ward AJ, Lanes S, Cortney Hayflinger D, Rosenberg DM, Hunsche E. Burden of illness in idiopathic pulmonary fibrosis. J Med Econ. 2012;15(5):829–35. https://doi.org/10.3111/13696998.2012.680553.
14. Hilberg O, Bendstrup E, Ibsen R, Løkke A, Hyldgaard C. Economic consequences of idiopathic pulmonary fibrosis in Denmark. ERJ Open Res. 2018;4(2):00045–2017. https://doi.org/10.1183/23120541.00045-2017.
15. Morell F, Esser D, Lim J, et al. Treatment patterns, resource use and costs of idiopathic pulmonary fibrosis in Spain: results of a Delphi Panel. BMC Pulm Med. 2016;16(1):1–9.
16. Gómez-Batiste X, Caja C, Espinosa J, et al. The Catalonia World Health Organization demonstration project for palliative care implementation: quantitative and qualitative results at 20 years. J Pain Symptom Manag. 2012;43(4):783–94. https://doi.org/10.1016/j.jpainsymman.2011.05.006.
17. Gisbert R, Brosa M. Base de datos de costes sanitarios y ratios coste-efectividad españoles: eSalud. 2007. http://www.oblikue.com/bddcostes/. Accessed.
18. Consejo General de Colegios Oficiales de Farmacéuticos. Base de Datos de Medicamentos: Bot PLUS 2.0. 2017. https://botplusweb.portalfarma.com/. Accessed.
19. FACUA. Estudio comparativo de las tarifas de los taxis de 52 ciudades españolas. 2018. https://www.facua.org/es/documentos/estudio_tarifas_taxi_2018.pdf. Accessed.
20. Ministerio de Sanidad Consumo y Bienestar Social. Orden SCB/45/2019, de 22 de enero. Boletín Oficial del Estado núm. 22. 2019. https://www.boe.es/boe/dias/2019/01/25/pdfs/BOE-A-2019-856.pdf. Accessed 5 Mar 2019.
21. Ministerio de Sanidad Consumo y Bienestar Social. Instituto de Información Sanitaria. Registro de Altas 2017: CMBD. http://pestadistico.inteligenciadegestion.msssi.es/publicoSNS/comun/DefaultPublico.aspx. Accessed 10 April 2023.
22. Instituto Nacional de estadística. Cálculo de variaciones del Índice de Precios de Consumo (sistema IPC base 2021): enero 2019 a enero 2023. https://www.ine.es/varipc/verVariaciones.do;jsessionid=3D690670881EC9EE56C25F8CBD0A524A.varipc03?idmesini=1&anyoini=2019&idmesfin=1&anyofin=2023&ntipo=1&enviar=Calcular. Accessed 17 Mar 2019.
23. Instituto Nacional de Estadística. Encuesta anual de estructura salarial (2017). Notas de prensa. 21 June 2019.
24. Lassenius MI, Toppila I, Pöntynen N, et al. Forced vital capacity (FVC) decline, mortality and healthcare resource utilization in idiopathic pulmonary fibrosis. Eur Clin Respir J. 2019;7(1):1702618. https://doi.org/10.1080/20018525.2019.1702618.
25. Tarride J-E, Hopkins RB, Burke N, et al. Clinical and economic burden of idiopathic pulmonary fibrosis in Quebec, Canada. Clinicoecon Outcomes Res. 2018;10:127–37. https://doi.org/10.2147/CEOR.S154323.
26. Fernández-Fabrellas E, Molina-Molina M, Soriano JB, et al. Demographic and clinical profile of idiopathic pulmonary fibrosis patients in Spain: the SEPAR National Registry. Respir Res. 2019;20(1):127. https://doi.org/10.1186/s12931-019-1084-0.
27. Culver DA, Behr J, Belperio JA, et al. Patient registries in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2019;200(2):160–7. https://doi.org/10.1164/rccm.201902-0431CI.
28. Ley B, Collard HR, King TEJ. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183(4):431–40. https://doi.org/10.1164/rccm.201006-0894CI.
29. Doubková M, Švancara J, Svoboda M, et al. EMPIRE Registry, Czech Part: impact of demographics, pulmonary function and HRCT on survival and clinical course in idiopathic pulmonary fibrosis. Clin Respir J. 2018;12(4):1526–35. https://doi.org/10.1111/crj.12700.
30. Jo HE, Glaspole I, Moodley Y, et al. Disease progression in idiopathic pulmonary fibrosis with mild physiological impairment: analysis from the Australian IPF registry. BMC Pulm Med. 2018;18(1):19.
31. Osakidetza. Tarifas para facturación de servicios sanitarios y docentes de Osakidetza para el año 2020. Informe. 2019.
32. Ibarrondo O, Lizeaga G, Martínez-Llorente JM, Larrañaga I, Soto-Gordoa M, Álvarez-López I. Health care costs of breast, prostate, colorectal and lung cancer care by clinical stage and cost component. Gac Sanit. 2022;36(3):246–52. https://doi.org/10.1016/j.gaceta.2020.12.035.
33. Hernandez D, Wagner F, Hernandez-Villafuerte K, Schlander M. Economic burden of pancreatic cancer in Europe: a literature review. J Gastrointest Cancer. 2022;36(3):246–52. https://doi.org/10.1007/s12029-022-00821-3.
34. Kolb M, Richeldi L, Behr J, et al. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. Thorax. 2017;72(4):340–6. https://doi.org/10.1136/thoraxjnl-2016-208710.
35. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365(12):1079–87. https://doi.org/10.1056/NEJMoa1103690.
36. Richeldi L, Cottin V, du Bois RM, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS trials. Respir Med. 2017;113:74–9. https://doi.org/10.1016/j.rmed.2016.02.001.
37. Maher TM, Stowasser S, Nishioka Y, et al. Biomarkers of extracellular matrix turnover in patients with idiopathic pulmonary fibrosis given nintedanib (INMARK study): a randomised, placebo-controlled study. Lancet Respir Med. 2019;7(9):771–9. https://doi.org/10.1016/S2213-2600(19)30255-3.
38. Armeni P, Cavazza M, Xoxi E, Taruscio D, Kodra Y. Reflections on the importance of cost of illness analysis in rare diseases:

a proposal. Int J Environ Res Public Health. 2021;18(3):1101. https://doi.org/10.3390/ijerph18031101.
39. Maher TM, Molina-Molina M, Russell A-M, et al. Unmet needs in the treatment of idiopathic pulmonary fibrosis-insights from patient chart review in five European countries. BMC Pulm Med. 2017;17(1):124.
40. Salisbury ML, Conoscenti CS, Culver DA, et al. Antifibrotic drug use in patients with idiopathic pulmonary fibrosis: data from the IPF-PRO Registry. Ann Am Thorac Soc. 2020;17(11):1413–23. https://doi.org/10.1513/AnnalsATS.201912-880OC.
41. Maher TM, Strek ME. Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. Respir Res. 2019;20(1):205. https://doi.org/10.1186/s12931-019-1161-4.
42. Maher TM, Swigris JJ, Kreuter M, et al. Identifying barriers to idiopathic pulmonary fibrosis treatment: a survey of patient and physician views. Respiration. 2018;96(6):514–24.
43. Castellsagué J, Burgos F, Sunyer J, Barberà JA, Roca J. Prediction equations for forced spirometry from European origin populations. Respir Med. 1998;92(3):401–7. https://doi.org/10.1016/S0954-6111(98)90282-7.