The Burden of Illness of Idiopathic Pulmonary Fibrosis: A Comprehensive Evidence Review

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Abstract

Background Idiopathic pulmonary fibrosis (IPF) is a debilitating condition with significant morbidity and poor survival. Since 2010, there has been increased activity in the development of treatments that aim to delay progression of the disease.

Objective Our study involves a comprehensive review of the literature for evidence on health-related quality of life (HRQoL), healthcare resource use (HCRU) and costs, and an assessment of the burden of illness of the condition.

Methods We carried out a systematic literature review (SLR) to identify economic evaluations and HRQoL studies. We searched EMBASE, MEDLINE and MEDLINE In Process for relevant studies from database origins to April 2017. Alongside the presentation of the study characteristics and the available evidence, we carried out a qualitative comparison using reference population estimates for HRQoL and national health expenditure for costs.

Results Our search identified a total of 3241 records. After removing duplicates and not relevant articles, we analysed 124 publications referring to 88 studies published between 2000 and 2017. Sixty studies were HRQoL and 28 were studies on costs or HCRU. We observed an exponential growth of publications in the last 3–5 years, with the majority of the studies conducted in Europe and North America. Among the HRQoL studies, and despite regional differences, there was some agreement between estimates on the absolute and relative level of HRQoL for patients with IPF compared with the general population. Regarding costs, after adjustments for the cost years and currency, the suggested annual per capita cost of patients with IPF in North America was estimated around US$20,000, 2.5–3.5 times higher than the national healthcare expenditure. Additionally, studies that analysed patients with IPF alongside a matched control cohort suggested a significant increase in resource use and cost.

Conclusion The reviewed evidence indicates that IPF has considerable impact on HRQoL, relative to the general population levels. Furthermore, in studies of cost and resource use, most estimates of the burden were consistent in suggesting an excess cost for patients with IPF compared with a control cohort or the national health expenditure. This confirms IPF as a growing threat for public health worldwide, with considerable impact to the patients and healthcare providers.

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1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown aetiology associated with significant morbidity and poor survival [1]. The symptoms include dyspnoea, dry cough, tiredness, aching of muscles and joints, unintended weight loss and finger clubbing [1]. The progression of the disease varies significantly between patients and depends on many clinical and external factors [2]. Overall, individuals with IPF have similar life expectancy to those with non-small cell lung cancer, with reported estimates of median survival being 50% at 3 years and 20% at 5 years post-diagnosis [1, 3–5]. The estimates of incidence and prevalence of IPF vary depending on the definition used, the study design, and the underlying population characteristics (such as age, gender, geographic location, etc.) [3, 6]. In general, studies agree that the condition is more common in men and in older people. In Europe, the British Thoracic Society estimates that the prevalence is around 50 per 100,000 population, with the highest rates in Northern Ireland, North West England, Scotland and Wales [7]. This is considerably higher than older estimates from other parts of Europe such as Norway (19.7–23.9/100,000) [8] and Belgium (1.25/100,000) [9]. In North America, two US studies placed the prevalence estimates between 42.7 [10] and 63 [11] patients per 100,000 population (using the broad definition); while a more recent Canadian study reported the prevalence to be as high as 115/100,000 (broad definition) [12]. Similarly, in Japan studies suggested prevalence estimates from 2.9/100,000 in 2005 [13] to 10/100,000 population in 2007 [4]. It follows that, although IPF is still treated as a rare condition in many countries, the evolution of diagnostic methods and greater physician awareness around the disease and an aging population may be leading to an increase in the prevalence and incidence rates over time [6, 14, 15].

There is also considerable activity in the development of treatments for the condition. Before 2010 there was no licensed pharmacological treatment for this devastating disease [1]. In 2008, pirfenidone was approved in Japan and in 2011 by the European Medicines Agency (EMA). In 2014 the US Food and Drug Administration (FDA) approved both pirfenidone and nintedanib, with EMA also confirming approval for nintedanib soon after [16–18].

Despite the recent termination of the clinical trial programmes for tralokinumab [19] and simtuzumab [20], a number of new agents are being tested in experimental trials for the treatment of IPF (SAR156597 [21], lebrikizumab [22], FG-3019 [23], PRM-151 [24] and others).

For healthcare providers, who often have to make difficult decisions about resource allocation across many conditions, in-depth knowledge of the overall burden of the disease is essential. Our study involves a comprehensive review of the literature for evidence on health-related quality of life (HRQoL) and costs. It also attempts a qualitative comparison with estimates of HRQoL for the general population and national healthcare expenditure to illustrate the burden of illness of IPF.

2 Methods

The study followed the PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) guidelines.

2.1 Search Strategy

Two separate systematic reviews were conducted for economic evaluations and HRQoL evidence. Using the Ovid interface, the databases EMBASE, MEDLINE and MEDLINE In Process were searched for relevant studies. Search terms included disease-specific, economic or cost, and HRQoL keywords such as ‘idiopathic AND pulmonary AND fibrosis’, ‘fibrosing alveolitis’, ‘interstitial pneumonia’, ‘costs and cost analysis’ and ‘health care costs’, ‘HRQoL’, ‘EQ-5D’.1

1 Nintedanib was also approved in Japan, Canada, Switzerland and many other countries.

2 For details on the search strings see the electronic supplementary material.
A review of HRQoL was conducted in August 2014 for the development of an economic analysis [25]. All the relevant records from the 2014 review were retrieved and the searches were updated from January 2014 to April 2017.

The economic data search was conducted from database origins to April 2017.

All references were imported into Endnote and duplicate citations were removed.

2.2 Study Selection

A review protocol with inclusion and exclusion criteria was developed at the outset of the study. The inclusion criteria were for adult patients with IPF without any restrictions on the therapy received. Other criteria included the reporting of unit costs, resource use, and HRQoL measures. To increase homogeneity in the study population characteristics, we excluded records that reported costs of diagnosis of interstitial lung disease (ILD).

The protocol was modified during the study to exclude abstract-only records published before 2015 (most often conference proceedings). Those records rarely provided sufficient information on methods and results that could be useful in our study and in general lack the scrutiny of full journal articles. Nevertheless, more recent records (post-2014) were included in our study, as we assumed that at the time of our search they were in development to a manuscript.

Screening of records was conducted in two phases (title/abstract and full-text). One experienced reviewer covered each dataset of records for economic evaluations and HRQoL evidence (EW and KV, respectively). A quarter of the records were screened independently by a second reviewer (AD, LC). If the decision for inclusion or exclusion was different in more than 10%, the full set of records were reviewed again. Because of a >10% disagreement in the HRQoL dataset, all records were screened in a double-blind manner. The bibliography of another literature review study [26] was used to validate our findings.

2.3 Data Extraction and Analysis

Key pieces of information from the selected studies were extracted in piloted tables by three experienced researchers (EW, KV, LC). A quality check of the data extraction was done by AD. The tables were different for HRQoL and economic evidence. Given the heterogeneity of the economic evidence, we later separated studies that reported healthcare resource use or costs from economic evaluations (cost-effectiveness or budget impact analyses).

3 Results

The database searches identified a total of 3241 records. After removing duplicate records, 2496 abstracts were screened against the eligibility criteria. Twelve additional records were identified via bibliography searches.

A total of 127 publications were included in the qualitative analysis, referring to 66 HRQoL and 28 economic studies. The economic studies were further categorised, with 18 reporting resource use or costs and 10 reporting on cost-effectiveness or budget impact analyses. The overall breakdown of the screening process in the reviews is presented in a PRISMA flow diagram (Fig. 1).

The studies on HRQoL increased over time with almost half conducted and published in the 3.5 years between 2014 and 2017 (see Fig. 2). We did not identify any cost or economic evaluation studies conducted before 2010, while more than half of the cost studies were published in the last 3 years.

In terms of geographic regions, the majority of the studies were conducted in Europe and North America (USA and Canada) (Fig. 3). The most studied country was the USA with 13 HRQoL [27–40] and eight economic evidence publications [41–48]. From low income and lower middle income countries (using the World Bank definition [49]) we identified two studies on HRQoL from Egypt [50, 51] and one from India [52]. From east Asia the predominant country was Japan with nine HRQoL studies [53–61]; one study was identified from China (HRQoL) [62] and one from Korea (costs) [63]. In the HRQoL dataset, for a number of studies we did not identify a clear country of origin [64-67].

3.1 Health-Related Quality of Life Evidence

A total of 66 studies were identified (33 in the pre-2014 analysis and 33 post-2014) with HRQoL data in IPF populations. Details of the study location, the population, the HRQoL assessment tools used, and the time points, as well as the sources of funding, are presented in Table 1.

In all studies, apart from Jastrzebski et al. [69], the population mean age was over 50 years old, with the average age around 65–70 years old. The study populations were predominantly male with the exception of three studies reporting a higher proportion of female [32, 51] or an equal male/female ratio [30].

The majority of the studies used the disease-specific HRQoL instrument, St. George’s Respiratory Questionnaire (SGRQ), reported in 41 studies. Most of the studies measuring HRQoL with the SGRQ reported results for the

3 Note that searches were conducted in April of 2017; hence, only one quarter of the last year contributed to our results.
three categories: symptoms, impact and activity; in addition to the total score. Despite the development and validation of an IPF-specific version of the SGRQ, the SGRQ-I [70], most investigators, apart from Gaunaúrd et al. [28, 71, 72], continue to use the original version.

In addition, six studies reported other disease-specific HRQoL scores such as A Tool to Assess Quality of life in IPF (ATAQ-IPF) [37] or the King’s Brief Interstitial Lung Disease (K-BILD) [73]. The 36-Item Short Form Survey (SF-36) was reported in 26 studies, the EuroQol 5-level questionnaire (EQ-5D) in four studies [39, 40, 67, 74, 75], the SF-12 in two studies and one Canadian study reported Health Utilities Index Mark 2 (HUI2) scores. One study was assessing the mapping of SGRQ data to EQ-5D [76] and another study provided a mapping algorithm from SGRQ data to SF-36 [77]. Further, EQ-5D estimates from phase III trials with nintedanib in IPF (INPULSIS® I and II) were available from an economic evaluation identified during the economic data search [25].
Table 2 reports on a subsection of the studies we found that included HRQoL values based on multi-attribute preference-based measures (EQ-5D and HUI2). We obtained population reference scores for EQ VAS and EQ-5D from a survey conducted across 24 countries [78]. The survey presented scores by age and we selected the 65–74-year age category as the most representative of the IPF studies that we are using in our comparison. To obtain a reference for HUI2 scores, we looked at the US National Health Measurement Study (NHMS) using the scores for ages 65–74 years [79].

Overall, the HRQoL was found to be lower for patients with IPF compared with the general population (Fig. 4). In the German registry, INSIGHTS-IPF, the EQ VAS of the patients with IPF, was about 9 points lower on the scale compared with the population reference data [80–84]. The difference in the EQ-5D index score was 0.223 lower than the reference. The incremental difference between patients with IPF and the population reference is smaller in the US study STEP-IPF: around 7.5 points on EQ VAS and around 0.1 on EQ-5D index scores [67]. Furthermore, in the study by Rinciog et al. [25], the reported difference in EQ-5D index score ranges from a category with relatively good lung function (forced vital capacity [FVC] > 90% predicted: 0.84) to very poor (FVC < 50% predicted: 0.67).

On the HUI2 instrument, the IPF population utility estimates were substantially lower than those measured on the EQ-5D scale, both for the first year with IPF (0.585) and the fourth year (0.432) [12]. However, some of the difference with the reference scores may be attributed to country variations (US data were used for HUI2 reference).

Regarding other multi-attribute instruments, eight studies reported the average score or the mental and physical component scores (MCS and PCS) of SF-36 [27, 29, 34, 35, 39, 40, 67, 69, 85, 86]. One study reported an SF-36 score of 32 ± 11.4 for severe IPF (defined as diffusing capacity of the lungs for carbon monoxide [DLCO] < 30%) and 59.1 ± 17.8 for patients with mild-to-moderate IPF (DLCO > 30%) [27]. King et al. reported the SF-36 score of 45.7 for placebo and 45.2 for people treated with bosentan [86]. At baseline, SF-36 PCS scores varied between 26.0 ± 8.0 [85] to 40.6 ± 9.3 [40], with an average value of 35 and SF-36 MCS ranging from 42 [69] to 55.7 ± 7.4 [40] with an average value of 48. The 17 remaining studies detailed the SF-36 results by questionnaire items (physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality, bodily pain, and general health perceptions).

3.2 Cost and Healthcare Resource Use Evidence

A total of 18 studies were identified with HCRU and cost evidence (Table 3). The majority were retrospective cohort analyses of claims data. Three studies were based on a synthesis of HCRU and national costs or tariffs [87–89]. One study was based on randomised clinical trial evidence [90] and one study was based on clinical expert opinion [91].

The most common reported resource or cost was hospitalisation (all-cause and/or respiratory-related), emergency room visits, and acute IPF exacerbation events. The majority of the studies [14] reported costs alongside
| Study         | Country       | Population | Mean age of cohort (control) | Male gender (control) | Assessment tools                           | Time point                          | Sources of funding                                                                 |
|--------------|---------------|------------|------------------------------|----------------------|------------------------------------------|-------------------------------------|-----------------------------------------------------------------------------------|
| Alhamad [122]| Saudi Arabia  | PFN: 33 (25)| PFN: 63.3 ± 13.3 (62.4 ± 15.1) | PFN: 67% (44%)       | Arabic version of SF-36                   | Baseline and change during follow up | Actelion Pharmaceuticals Ltd.                                                      |
| Antoniou et al. [68] | Greece | IFNγ 1b: 32 Colchicine: 18 | IFNγ 1b: 66 (range 54–85) Colchicine: 69 (range 42–82) | IFNγ 1b 91% Colchicine 72% | SGRQ                                     | Change before and after 12 months of treatment | Boehringer Ingelheim Hellas and Society for Pulmonary and Intensive Care Research in the district of East Macedonia and Thrace |
| Baddini et al. [123] | Brazil | 30* Grade 3: 17 Grade 4: 17 Grade 5: 15 | 58.6 ± 2.0 60% | SF-36 | Cross-sectional study | NR |                                                                            |
| Bahmer et al. [124] | Germany | 48 | 67.1 ± 7.5 75% | SF-12 SGRQ | Baseline | Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen |
| Bors et al. [27] | USA | 46 | Severe IPF: 69 (52–79) Mild-moderate IPF: 63 (43–83) | Severe IPF: 58.3% Mild-moderate IPF: 64.7% | SGRQ | Baseline | University of Minnesota |
| Crooks et al. [125] | UK | 27* | NR | NR | SGRQ | Baseline (assumed)* | Hull York Medical School and Hull and East Yorkshire Hospitals NHS Trust |
| De Vries et al. [126] | The Netherlands | 10 | 61.1 ± 11.6 40% | SGRQ WHOQOL-100 | Baseline | NR |                                                                            |
| Downman et al. [127, 128] | Australia | Exercise: 32 (29) Exercise: 70 (73) | Exercise: 66% (69%) | SGRQ-1 | Baseline values and change from baseline at 9 weeks and 6 months | ATS Foundation/Pulmonary, Fibrosis Foundation, National Health and Medical Research Council, Eirene Lucas Foundation and Institute of Breathing and Sleep |
| Elfferich et al. [129] | The Netherlands | IPF: 49 (3678) | IPF: 63.1 ± 11.8 Control: NR | IPF: 62.5% Control: NR | WHOQOL-BREF | Baseline | NR |
| Fell et al. [12] | Canada | NR | NR | NR | HUI2 | 1st year 4th year | InterMune Canada Inc. |
| Ferrara et al. [73] | Sweden | 71 | 70 (range 47–86) 70.40% | K-BILD | Baseline | Swedish Heart and Lung Foundation, Karolinska University Hospital, Karolinska Institutet, Quality-Registry-Centre Stockholm, Boehringer Ingelheim, InterMune/Roche |
| Study                      | Country          | Population | Assessment tools | Time point | Sources of funding                        |
|----------------------------|------------------|------------|------------------|------------|------------------------------------------|
| Freemantle et al. [76]     | England and Wales | 181        | No. of participants (control) | Mean age of cohort (control) | Male gender (control) | SGRQ mapped to EQ-5D-3L | Baseline | No funding |
| Furukawa et al. [53]       | Japan            | 182        | 65.6 ± 8.0       | 85.20%     | SGRQ                                    | Baseline | No funding |
| Gaunaud et al. [28, 71, 72]| USA              | 11 (10)    | 71 ± 6 (66 ± 7)  | NR         | SGRQ-1                                  | Baseline | Change at 3 months | NR |
| Glaspole et al. [28, 71, 72]| Australia       | 516        | 71.3 ± 8.6       | 67.30%     | SGRQ                                    | Baseline | Australian IPF Registry |
| Richeldi et al. [25, 110–121] | International | NDB: 723 (508) | No. of participants (control) | Mean age of cohort (control) | Male gender (control) | SGRQ                                    | Baseline | TOMORROW and INPULSIS trials funded by Boehringer Ingelheim |
| Han et al. [33]            | USA              | 221        | Average male age 63.3 ± 8.2 | 66.50%     | SF-12, SGRQ                              | Cross-sectional study | Lung Tissue Research Consortium |
| Horton et al. [38]         | USA              | 23         | 67.6             | 78.3%      | SGRQ                                    | Baseline | Celgene Corporation |
| Jarosch et al. [64]        | Unclear          | 33         | 68 ± 9 (65 ± 10) | NR         | SF-36 mental score                      | Baseline | Change at 6 weeks | NR |
| Jastrzebski et al. [69]    | Poland           | 16         | 48.3             | 69%        | SF-36                                   | Cross-sectional study | NR |
| Jo et al. [131]            | Australia        | 647        | 70.9 ± 8.5       | 67.7%      | SGRQ                                    | Baseline | No funding |
| Jones et al. [132]         | UK               | 27 (30)    | 71.7 ± 7 (65.6 ± 5.3) | 63%        | VAS, LCQ                                | Unclear | No funding |
| Key et al. [133]           | UK               | 19         | 70.8 ± 8.6       | 73.70%     | VAS, LCQ                                | Two assessments in 24 hours | No funding |
| King et al. [77, 86, 134]  | International    | Bosentan: 71 (83) | No. of participants (control) | Mean age of cohort (control) | Male gender (control) | SF-36, SGRQ                                | Baseline | Actelion Pharmaceuticals Ltd |
| King et al. [75]           | International    | Bosentan: 407 (209) | No. of participants (control) | Mean age of cohort (control) | Male gender (control) | SF-36, EQ-SD, EQ-VAS                            | Baseline | Actelion Pharmaceuticals Ltd |
| Kotecha et al. [135]       | UK               | 75         | 76.4 ± 7.5       | 77%        | SGRQ                                    | Baseline | No funding |
| Study                  | Country    | Population | Assessment tools | Time point | Sources of funding                                      |
|-----------------------|------------|------------|------------------|------------|---------------------------------------------------------|
| Kozu et al. [58]      | Japan      | 45         | Mean age of cohort | SF-36      | Baseline Week 8 Month 6                                 |
|                       |            |            | Male gender       |            |                                                        |
|                       |            |            |                  |            |                                                        |
| Kozu et al. [59, 136] | Japan      | Grade 2: 16 | SGRQ, SF-36       | Baseline   | No commercial funding                                   |
|                       |            | Grade 3: 17 |                  |            |                                                        |
|                       |            | Grade 4: 17 |                  |            |                                                        |
|                       |            | Grade 5: 15 |                  |            |                                                        |
|                       |            |            |                  |            |                                                        |
| Kramer et al. [65]    | Unclear    | PRG:15 (13)| PRGQ: 68.8 ± 6    | Baseline   | No funding                                             |
|                       |            |            | (65.7 ± 8)        | 12 weeks   |                                                        |
| Kreuter et al. [80–84]| Germany    | 572        | PRGQ              | Baseline   | NR                                                     |
|                       |            |            |                  |            |                                                        |
| Lubin et al. [34]     | USA        | 102        | SF-36 (PCS and    | Baseline   | Genentech                                              |
|                       |            |            | MCS)              |            |                                                        |
| Lutogniewska et al. [137]| Poland | IPF: 30    | SF-36             | Baseline   | NR                                                     |
|                       |            |            | SGRQ              |            |                                                        |
| Martinez et al. [138] | Brazil     | IPF: 34 (34)| SF-36             | Cross-sectional study | NR                                                     |
|                       |            |            | (58 ± 1.89)       |            |                                                        |
| Matsuda et al. [54]   | Japan      | 106        | SGRQ              | Baseline   | Diffuse Lung Disease Research Group from the Ministry   |
|                       |            |            |                  |            | of Health, Labor and Welfare, NPO Respiratory Disease   |
|                       |            |            |                  |            | Conference                                             |
| Mermigkis et al. [139]| Greece     | 12         | SF-36             | Baseline   | NR                                                     |
|                       |            |            |                  |            |                                                        |
| Mermigkis et al. [140]| Greece     | 92         | SF-36             | Baseline   | No funding                                             |
|                       |            |            |                  |            |                                                        |
| Mishra et al. [52]    | India      | IPF: 6 (6)  | SGRQ              | Baseline   | Grants NBA2007 of DBT, IAP001 and CLP 261 of NTRF,     |
|                       |            |            |                  |            | India                                                  |
| Morsi et al. [50]     | Egypt      | 36         | SGRQ              | Baseline   | No funding                                             |
|                       |            |            |                  |            |                                                        |
| Study                  | Country         | Population | Assessment tools | Time point | Sources of funding                        |
|-----------------------|-----------------|------------|------------------|------------|------------------------------------------|
| Natalini et al. [29]  | USA             | 50         | 70.8 ± 8.3       | SF-36      | Baseline                                 |
| CAPACITY [141]        | International   | 338        | 66.5 ± 7.6       | SGRQ       | Baseline                                 |
| Nishiyama et al. [61] | Japan           | 41         | 64 ± 9           | SGRQ       | Baseline                                 |
| Nishiyama et al. [56] | Japan           | Rehabilitation group: 13 Control: 15 | 68.1 ± 8.9 (64.5 ± 8) | SGRQ | Baseline                                 |
|                       |                 |            |                  |            | Japanese Ministry of Health and Welfare |
| Nishiyama et al. [57] | Japan           | 87         | 66.3 ± 8.2       | SGRQ       | Baseline                                 |
| Nolan et al. [66]     | Unclear         | 61         | 70 ± 11          | SGRQ       | Baseline                                 |
| Ntolios et al. [142]  | Greece          | 36         | 69.6 ± 6.2       | SGRQ       | Baseline                                 |
| Ozalevli et al. [143] | Turkey          | 17         | 62.8 ± 8.5       | SF-36      | Baseline                                 |
| Peng et al. [62]      | China           | 68         | 64 ± 8           | Chinese version of SGRQ | Baseline |
| Raghu et al. [35]     | USA             | ETN: 46 (41) | ETN: 65.2 ± 7.7 (65.1 ± 7.1) | SF-36 | Baseline                                 |
| Raghu et al. [39, 40] | USA             | Combination therapy: 77 (78) | Combination therapy: 68.8 ± 7.3 (67.9 ± 8.1) | SGRQ EQ-5D | Baseline |
|                       |                 |            |                  |            | National Heart, Lung, and Blood Institute (NHLBI) |

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| Study          | Country                      | Population                                                                 | Assessment tools | Time point                  | Sources of funding                                                                 |
|---------------|------------------------------|-----------------------------------------------------------------------------|------------------|----------------------------|------------------------------------------------------------------------------------|
| Raghu et al.  | Belgium, Canada, Germany, the| Carlsonab 1 mg/kg: 33, Carlsonab 5 mg/kg: 32, Carlsonab 15 mg/kg: 32        | SGRQ             | Baseline                   | NR                                                                                 |
|               | Netherlands and USA          | (29)                                                                        |                  |                            |                                                                                    |
|               |                              | Carlsonab 1 mg/kg: 63.2 ± 9.29, Carlsonab 5 mg/kg: 66.3 ± 7.89,              |                  |                            |                                                                                    |
|               |                              | Carlsonab 15 mg/kg: 65.9 ± 7.38 (64.5 ± 7.26, 79.3%)                        |                  |                            |                                                                                    |
|               |                              | SGRQ                                                                        |                  |                            |                                                                                    |
| Rifaat et al. | Egypt                        | 30                                                                          | SGRQ             | Baseline                   | No conflict of interest                                                            |
|               |                              | 54.4 ± 6.1                                                                  |                  |                            |                                                                                    |
|               |                              | 26.7%                                                                       |                  |                            |                                                                                    |
| Ryerson et al.| USA                          | 54                                                                          | SGRQ             | Baseline (before PR)       | No funding                                                                         |
|               |                              | 69.4 ± 10.8                                                                 |                  |                            |                                                                                    |
|               |                              | 48.00%                                                                      |                  |                            |                                                                                    |
| Shamma et al. | USA                          | IPF: 54 COPD: 456                                                          | SF-36            | Single assessment          | NR                                                                                 |
|               |                              | IPF: 66.3 ± 10.7 (COPD: 66.0 ± 9.1)                                         |                  |                            |                                                                                    |
|               |                              | No differences in gender                                                    |                  |                            |                                                                                    |
| Swigris et al.| USA                          | 95                                                                          | ATAQ-IPF         | Single assessment          | National Institutes of Health Career Development Award K23 HL092227, Mordecai Palliative Care Research Fund and Colorado Clinical and Translational Science Award 1U11 RR05780 |
|               |                              | 69.3 ± 7.6                                                                 |                  |                            |                                                                                    |
|               |                              | 82%                                                                         |                  |                            |                                                                                    |
| Swigris et al.| USA                          | 21                                                                          | SF-36            | Single assessment          | National Institutes of Health Career Development Award K23 HL092227, Mordecai Palliative Care Research Fund and Colorado Clinical and Translational Science Award 1U11 RR05780 |
|               |                              | 71.5 ± 7.4                                                                 |                  |                            |                                                                                    |
|               |                              | 85.70%                                                                      |                  |                            |                                                                                    |
| Tomioka et al.| Japan                        | 46                                                                          | SF-36            | Baseline (median 14 months)| NR                                                                                 |
|               |                              | 69.9 ± 5.8                                                                 |                  |                            |                                                                                    |
|               |                              | 70%                                                                         |                  |                            |                                                                                    |
| Tomioka et al.| Japan                        | 17                                                                          | SF-36            | Baseline                   | No funding                                                                         |
|               |                              | 76.5 ± 7.1                                                                 |                  |                            |                                                                                    |
|               |                              | 88.20%                                                                      |                  |                            |                                                                                    |
| Tzanakis et al.| Greece                       | IPF patients: 25 (30)                                                       | SGRQ, QWB, HAD   | Cross-sectional study      | NR                                                                                 |
|               |                              | 66 ± 11 (63.5 ± 10)                                                        |                  |                            |                                                                                    |
|               |                              | 84% (80%)                                                                   |                  |                            |                                                                                    |
| Study             | Country                  | Population | Assessment tools | Time point                                      | Sources of funding                                                                 |
|-------------------|--------------------------|------------|------------------|------------------------------------------------|-------------------------------------------------------------------------------------|
| Tzouvelekis et al. [146] | Greece                  | 14         | SGRQ             | Baseline 6 months post-infusion 12 months post-infusion | Godrej Group Adistem Ltd and the Hellenic National Research Foundation Stem Cell Bank Athens, Greece, Biohellenika SA Thessaloniki Greece |
| Vainshelboim et al. [147, 148] | Israel                  | ET: 15 (17) | SGRQ             | Baseline Week 12                                 | No funding                                                                          |
| Verma et al. [149] | Canada                   | 137        | SF-36            | Cross-sectional study NR                         | Dolly Roth Memorial Rheumatoid Arthritis Research Fund                                 |
| Wuyts et al. [150, 151] | Belgium and Luxemburg    | 147        | SGRQ             | Baseline                                        | InterMune, Inc.                                                                     |
| Yazdani et al. [85] | Canada                   | 53         | SF-36, SGRQ      | Baseline 1st post-treatment visit 2nd post-treatment visit | Biogen                                                                              |
| Yount et al. [32]  | USA                      | 220        | PROMISdyspnea PROMIS-29 ATAQ-IPF (6–30) FACTIT cough (0–4) | Baseline                                        | Biogen                                                                              |
| Zimmermann et al. [152] | Brazil                  | 20         | SF-36, SGRQ      | Baseline                                        | FAPESP and LIM HC-FMUSP                                                              |
### Table 1 continued

| Study            | Country | Population | Assessment tools | Time point | Sources of funding |
|------------------|---------|------------|------------------|------------|-------------------|
| Zisman et al.    | NR      | Sildenafil: 89 (91) | SF-36, SGRQ, EQ-5D, EQ-5DVAS | Baseline | NHLBI; the Cowlin Fund at the Chicago Community Trust; Pfizer donated sildenafil and matching placebo and Masimo donated pulse oximeters |

**ATAQ-IPF** A Tool to Assess Quality of life in IPF, **BIBF** Bahrain Institute of Banking and Finance, **COPD** chronic obstructive pulmonary disease, **DBT** Department of biotechnology, **EQ-5D** EuroQol 5-level, **ET** exercise and training, **ETN** etanercept, **FACIT** Functional Assessment of Chronic Illness Therapy, **FAPESP** Fundação de Amparo à Pesquisa do Estado de São Paulo, **HAD** Hospital anxiety and depression scale, **HRQoL** health-related quality of life, **HUI2** Health Utilities Index Mark 2, **IFN** infliximab, **IPF** idiopathic pulmonary fibrosis, **K-BILD** King’s Brief Intersitial Lung Disease, **LIM HC FMUSP** Laboratórios de Investigação Médica do Hospital das Clínicas, **LCQ** Licence Controller Qualification, **MCS** Mental Component Score, **NA** Not applicable, **NDB** nintedanib, **NR** not reported, **NTRF** National Tea Research Foundation, **PBO** placebo, **PCS** Physical Component Score, **PFN** pirfenidone, **PR** pulmonary rehabilitation, **PRG** Pulmonary Rehabilitation Group, **PROMIS** Patient Reported Outcomes Measurement Information System, **QWB** Quality of well-being scale, **SF-12** Short Form-12, **SF-36** Short Form-36, **SGRQ** St George’s Questionnaire, **SGRQ-I** IPF-specific version of the SGRQ, **UK** United Kingdom, **USA** United States of America, **VAS** Visual Analogue Scale, **WHQOL-BREF** WHO Quality of Life-BREF

**a**No. of patients assessed

**b**INPULSIS I and II studies also collected EQ-5D available from Rinciog et al. [25] (identified in the economic evaluations)
| Study                      | Patient characteristics                                                                 | HRQoL multi-attribute measurement tool | IPF utility score     | Population reference dataa |
|---------------------------|-----------------------------------------------------------------------------------------|----------------------------------------|-----------------------|---------------------------|
| INSIGHTS-IPF [80–84]      | \( N = 572 \) patients; 77.1% males; mean age 69.4 ± 8.8 years; disease 2.1 ± 3.3 years; FVC % predicted 72.6 ± 19.2; DLCO % predicted 36.1 ± 17.1 | EQ VAS                                 | 59.8 ± 19.8          | Germany, age 65–74 years: 68.6 |
|                           |                                                                                         | EQ-5D-5L                               | 0.668 ± 0.214         | Germany, age 65–74 years: 0.891 |
| BUILD-1 [77, 86, 134]     | \( N = 407 \) patients; 73% males; mean age 65.12 ± 8.93; disease < 3 years; FVC % predicted 66.97 ± 12.17; DLCO % predicted 40.98 ± 10.08 | EQ VAS                                 | Placebo: 69.5 ± 19.4 | N/A (international study)   |
|                           |                                                                                         | EQ-5D                                 | Placebo: 70.4 ± 18.7  |              |
|                           |                                                                                         |                                      | Bosentan: 0.718 ± 0.242 |              |
|                           |                                                                                         |                                      | Bosentan: 0.758 ± 0.185 |              |
| STEP-IPF [67]             | Placebo \( N = 91 \) patients; 84% males; mean age 68.20 ± 9.25; disease 1.87 ± 1.93 years; FVC % predicted 58.73 ± 14.12; DLCO % predicted 26.73 ± 6.16 | EQ VAS                                 | Baseline: 67.66 ± 16.98 | USA, age 65–74 years: 75.1 |
|                           |                                                                                         | EQ-5D-5L                               | Change at 12 weeks: −1.81 (−5.34 to 1.73) |              |
|                           | Sildenafil \( N = 89 \) patients; 86% males; mean age 69.76 ± 8.71; disease 2.03 ± 1.94 years; FVC % predicted 54.89 ± 14.00; DLCO % predicted 25.81 ± 6.03 | EQ VAS                                 | Baseline: 66.49 ± 17.45 | USA, age 65–74 years: 75.1 |
|                           |                                                                                         | EQ-5D-5L                               | Change at 12 weeks: 0.48 (−3.10 to 4.06) |              |
|                           |                                                                                         |                                      | Change at 12 weeks: 0.71 ± 0.24 (−0.06 to 0.01) |              |
| INPULSIS I and II [25]    | Placebo \( N = 423 \) patients; 79% males; mean age 67 ± 7.9 years; disease 1.57 ± 1.31 years; FVC % predicted 79.27 ± 18.22 | EQ-5D-3L                               | FVC ≥ 90% 0.84 ± 0.18 | N/A (international study)   |
|                           | Nintedanib \( N = 638 \) patients; 79.5% males; mean age 66.6 ± 8.1 years; disease 1.65 ± 1.36 years; FVC % predicted 79.74 ± 17.57 |                                      | FVC 80–89% 0.81 ± 0.21 |              |
|                           | Both arms were pooled for this analysis                                                  |                                      | FVC 70–79% 0.78 ± 0.22 |              |
|                           |                                                                                         |                                      | FVC 60–69% 0.77 ± 0.24 |              |
|                           |                                                                                         |                                      | FVC 50–59% 0.74 ± 0.23 |              |
|                           |                                                                                         |                                      | FVC 40–49% 0.66 ± 0.26 |              |
pirfenidone contributed to the treatment costs in that study [91].

3.3 Economic Evaluations

Ten studies were identified assessing the cost effectiveness, or budget impact, of specific treatment interventions. Details of the methods and results of the studies are presented in Table 5. Three studies were from the UK [25, 26, 98], while the remaining were from France [99], Greece [100], Italy [101, 102], Spain [103], Mexico [104] and USA [105]. The comparators included triple therapy (azathioprine, NAC and steroids), a combination of triple therapy and a genotypic assay thiopurine S-methyltransferase (TPMT), co-trimoxazole, sildenafil, pirfenidone, nintedanib and best supportive care. Only one economic evaluation included lung transplantation as an option for patients [26].

Most studies used a model to synthesise clinical, HRQoL and cost evidence. Moreover, the majority of the analyses used the direct healthcare perspective. Wilson et al. [98] conducted an economic evaluation alongside a multi-centre, randomised, placebo-controlled, double-blind trial of 12 months duration, and reported cost-effectiveness results on both the healthcare direct medical and societal perspectives.

In the economic models, the time horizon ranged between 1, 5 and 30 years, and patient lifetime. A state transition model was used for all papers, and when reported, results were calculated by a cohort analysis. In the long time-horizon models, the cost results varied between US$4000 (£3000) for BSC, US$7000 for NAC and over US$90,000 for new treatments such as pirfenidone and nintedanib. HRQoL benefits ranged between 3 and 4 QALYs. There was a noticeable distinction in the cost effectiveness of old pharmacologic technologies such as triple therapy or NAC, with estimates between US$5000–US$70,000 per QALY, and that of new treatments that exceeded US$100,000 per QALY.
| Study                          | Country | Valuation method                        | Population                                                                 | Inclusion criteria                                                                                                                                                                                                 | Mean age of cohort (control) | Male gender (control) | Evidence reported                                                                 | Sources of funding |
|-------------------------------|---------|-----------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------|----------------------------------------------------------------------------------|-------------------|
| Collard et al. [42]           | USA     | Retrospective cohort analysis; claims data | Age ≥ 55 years; IPF patients with ≥ 2 claims with a code for idiopathic fibrosing alveolitis (ICD-9 516.3), or 1 claim with ICD-9 516.3 and a subsequent claim with a code for post-inflammatory pulmonary fibrosis (ICD-9 515). Matched control cohort also analysed | 74                                                                                                                      | 54.6 (54.6)                  | Total costs for IPF and control patients. Breakdown of healthcare resource use: hospital admissions, ER, OP, physician visits, oxygen, rehabilitation, monitoring | Actelion Pharmaceuticals Ltd |
| Collard et al. [41, 153]      | USA     | Retrospective database analysis; claims data | All patients received Medicare cover between Jan 2000 and Dec 2011. Age ≥ 65 years. At least one claim with ICD-9-CM diagnosis code 516.3 | 78.5 ± 6.9 (78.4 ± 6.9)                                                                                                                                  | 43.3 (43.1)                  | Total costs for IPF and control, including cost breakdown. HCRU breakdown: all-cause hospitalisation, all-cause ER visits, all-cause outpatient visits, physician office visits, respiratory related visits, oxygen therapy, pulmonary rehab, monitoring | Biogen             |
| Cottin et al. [154, 155]      | France  | Retrospective observational study        | Patients with a first hospitalization for IPF (ICD-10 code: J841) and aged ≥ 50 y | 75.4 ± 10.3                                                                                                                                            | 56%                         | Mean total cost of hospitalisations, specific cost drivers, acute exacerbations, cardiac events, acute respiratory infections, inhospital mortality rate, arterial thrombosis, palliative care and associated costs | NR                 |
| Diamantopoulos et al. [90]    | International | Post-hoc clinical trial data analysis | Patients from the INPULSIS trial | NR                                                                                                                                       | NR                         | The impact on a patient’s hospitalisation from changes in disease status (FVC% predicted) and exacerbations | Boehringer Ingelheim |
| Goode et al. [87]             | UK      | Cost analysis based on MRU              | Patients with IPF                                                          | NR                                                                                                                                       | NR                         | Cost associated with diagnosing IPF, including specific test costs and overall total cost | Boehringer Ingelheim |
| Hill et al. [88]              | UK      | Cost analysis based on MRU              | NR (abstract); evidence taken from IPF services                              | NR                                                                                                                                       | NR                         | Estimated mean cost per patient for first year of diagnosis, management and monitoring | NR                 |
| Study               | Country | Valuation method | Population | Inclusion criteria                                                                 | Mean age of cohort (control) | Male gender (control) | Evidence reported                                                                 | Sources of funding |
|---------------------|---------|------------------|------------|-------------------------------------------------------------------------------------|-----------------------------|-----------------------|----------------------------------------------------------------------------------|-------------------|
| Kim et al. [63, 156]| Korea   | Retrospective database analysis; claims data | Patients with IPF who had made ≥ 2 claims per year under the K-J84.18 code (IPF) of the medical care system, using the KCD-6 codes | Mean age for males: 2009: 66.0 ± 13.1 years 2010: 66.9 ± 12.5 years 2011: 67.0 ± 12.8 years 2012: 67.9 ± 12.1 years 2013: 68 ± 12.1 | 2009: 60.7 2010: 61.1 2011: 62.2 2012: 62.5 2013: 62.9 | Total costs for IPF patients per year, person per year, and per unit/item per year. HCRU breakdown: all-cause hospitalisation, LOS, all-cause ER visits, intensive care, monitoring | NR |
| Mittmann et al. [94]| Canada  | Retrospective, longitudinal cohort study; chart review analysis | Adults with a confirmed diagnosis of IPF and a minimum of one respirologist visit | 71.3 (range 39–89) 66.7% | Overall: 70 ±0.32 a Overall: 50.9% a | All-cause hospitalisation, total admission costs | Genentech and Boehringer Ingelheim Pharmaceuticals |
| Mooney et al. [43, 157]| USA     | Retrospective cross-sectional study; claims data | Patients with ≥ 1 IP claim of IPF (ICD-9-CM code 516.3) between 2009 and 2011. Principal diagnosis of respiratory disease (ICD-CM 460-519) | Overall: 70 ±0.32 a Overall: 50.9% a | All-cause hospitalisation, total admission costs | Genentech and Boehringer Ingelheim Pharmaceuticals |
| Morell et al. [91]| Spain   | Three-round Delphi consensus panel | Patients with IPF | NR | NR | Total costs, including specific unit costs. HCRU breakdown: Numbers of patients with IPF and their resource use, including specific drug, exacerbations, IPF-related hospitalisations, ICU, IPF-related outpatient visits, oxygen, pulmonary rehab, lung transplant, AEs, palliative care and monitoring | Boehringer Ingelheim |
| Nasr et al. [89]| UK      | Cost analysis based on 11 different sources | Adults with IPF | NR | NR | Average annual cost of NAC | NR |
| Study                  | Country | Valuation method                  | Population                                                                 | Inclusion criteria                                                                 | Mean age of cohort (control) | Male gender (control) | Evidence reported                                                                 | Sources of funding                                                                 |
|-----------------------|---------|----------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------|---------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Navaratnam et al. [158] | UK      | Retrospective database analysis | Patients with fibrotic lung disease of unknown origin with ICD codes J84.1 and J84.9; study looks at the burden of IPF | 49–71 b                                                                         | NR                          |                     | Cost of inpatient bed days, hospital admission rates, LOS, cost of hospital admission | Dr Navaratnam: research grant from the Medical Research Council. Dr Hubbard: the GlaxoSmithKline/British Lung Foundation chair of Epidemiological Respiratory Research |
| Pedraza-Serrano et al. [97] | Spain   | Retrospective descriptive epidemiological study; administrative data | All patients hospitalised for IPF (ICD-9-CM 561.3) | 73.11 ± 12.28 c                                                               | 57.35% c                    |                     | Total costs, all-cause hospitalisation, lung transplant and monitoring             | URJC–Banco Santander to the Grupo de Excelencia Investigadora ITPSE                |
| Raimundo et al. [44, 159] | USA     | Retrospective database analysis; claims data | Patients with ≥ 1 inpatient claim or 2 outpatient claims with IPF as one of the listed diagnosis codes (ICD-9-CM 516.3) in 1 year excluding other interstitial lung disease diagnosis | Ages reported for years 2009–2011 2009: 69.8 ± 11.1 2010: 70.0 ± 11.4 2011: 71.3 ± 10.6 | 48.10% |                     | Total costs, hospitalisation, ER and OP visits, (reported for all-cause and IPF related). As well, oxygen, pulmonary rehab, lung transplant and monitoring | Genentech Inc.                                                                   |
| Sharif et al. [45] | USA     | Retrospective database analysis | Patients categorized into IPF group from patients with acute exacerbation of COPD (ICD-9 491.21), rheumatoid lung disease, systemic sclerosis interstitial lung disease, other CTD-ILDs and IPF (ICD-9 of 516.31) | NR                                                                             | NR                          |                     | Total cost of hospitalisation, total costs per day, LOS, ICU days                 | No funding                                                                      |
| Yu et al. [46] | USA     | Retrospective database analysis; claims data | Adult patients with a new IPF diagnosis (≥ 2 claims of idiopathic interstitial pneumonia (ICD-9-CM 516.3) OR one claim of 516.3 and one claim of post-inflammatory pulmonary fibrosis (ICD-9-CM 515) | 66                                                              | 57% |                     | Comorbidities, mortality rates, hospital admissions, LOS, ER admissions, outpatient admissions, office visits, oxygen, pulmonary lung biopsy procedures, and monitoring | Boehringer Ingelheim Pharmaceuticals, Inc. |
Table 3 continued

| Study                        | Country | Valuation method                  | Population                                                                 | Inclusion criteria                                                                 | Mean age of cohort (control) | Male gender (control) | Evidence reported                                                                 | Sources of funding       |
|------------------------------|---------|-----------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------|----------------------|----------------------------------------------------------------------------------|--------------------------|
| Yu et al. [47]               | USA     | Retrospective chart review        | Patients aged ≥ 40 years, diagnosed with IPF (diagnosis between Jan 2011 and June 2013) | With early acute exacerbation: 59.0 ± 10.8 Without: 61.4 ± 10.7                    | With early acute exacerbation: 63.9% Without: 69.1% | Acute exacerbations, IPF-related hospitalisations, ER visits, OP visits, urgent care visits | Boehringer Ingelheim     |
| Yu et al. [48, 93]           | USA     | Retrospective database analysis; claims data | Adults newly diagnosed with IPF between Jan 2007 and Dec 2011              | 71.5 ± 12.7                                                                      | 54%                         | Total IPF-related hospitalisation costs, all-cause hospitalizations, IPF-related hospitalisations, possible acute exacerbations requiring hospitalization, and possible acute exacerbations not requiring hospitalization | Boehringer Ingelheim     |

AE adverse event, COPD chronic obstructive pulmonary disease, CTD-ILD connective tissue diseases–idiopathic lung disease, ER emergency room, FVC forced vital capacity, HCRU healthcare resource use, ICD-9-CM International Classification of Diseases, ninth revision, clinical modification, ICU intensive care unit, IP in-patient, IPF idiopathic pulmonary fibrosis, LOS length of stay, MRU medical resource use, NAC N-acetylcysteine, NR not reported, OP outpatient

*aMean age and gender given for years 2009–2011, results reported are mean over 3 years
*bNavaratnam [158] report mean age at admission for groups J84.1 and J84.9 for years 1998–2010
*cAges and genders for years 2004–13 reported
4 Discussion

This was a review of HRQoL, resource use, costs and treatment cost-effectiveness studies conducted over the last 20 years in many countries, and with a variety of objectives, sources of data, and methodologies. As such, it is difficult to express with one coherent estimate the burden of illness of IPF. Nevertheless, several trends appeared in both quality of life and costs.

As with other respiratory conditions, the impact of IPF is not only limited to a worsening of the patient’s breathing function. It has wider consequences for HRQoL including physical (body weight loss, fatigue, clubbing) and social ones (recreational activities, relationships etc.). When reviewing the HRQoL evidence, this review reported on most instruments used in the literature, but focused on generic preference-based measures (such as EQ-5D) to quantify the burden of the disease. By using EQ-5D it is possible to make a comparison between the HRQoL levels with the condition versus the general population, and a comparison across other non-respiratory diseases. Furthermore, EQ-5D is increasingly used in health economic evaluations to calculate quality-adjusted life-years (QALYs), and this work presents a comprehensive review of the available evidence.

Despite the regional differences, there was some agreement between study estimates on the absolute level of HRQoL for patients with IPF; in EQ-5D, scores varied between 0.67 (± 0.242) [67] and 0.8 (± 0.2) [106]. To put this in context, the EQ-5D of patients with arthritis/rheumatism/fibrositis was reported to be 0.597 (CI 0.584–0.609; N = 4145), with hypertension/high blood pressure 0.777 (CI 0.765–0.788; N = 3172) and with asthma 0.797 (CI 0.779–0.814; N = 2452) [107, 108]. In the studies analysed, the decrement in HRQoL for patients with IPF compared with the reference population statistics was between 0.1 and 0.2 points in the EQ-5D.

With regards to costs, three US studies produced comparable estimates of costs per patient around US$20,000 [41, 42, 44]. After adjustments for the study years and currency, the suggested annual per capita cost of IPF patients in North America was estimated between 2.5–3.5 times the national health care expenditure.

We observed discrepancy in the estimates coming from two Spanish studies. This is probably attributed to the methods used. Pedraza-Serrano et al. [97] used data from a Spanish National Hospital Database (CMBD, Conjunto Mínimo Básico de Datos) and conducted a retrospective, descriptive, epidemiological study. Morell et al. [91] took a different approach by synthesising expert opinion from 15 clinicians with unit costs from national formularies. Moreover, Morell et al. [91] included treatments costs, although treatment allocation was not reported. The two estimates are very different to values from the other countries (in absolute and relative terms), which makes it very challenging to select the most accurate. The study by Pedraza-Serrano et al. [97] follows the general trend of a higher per annum cost than the national health care expenditure.

Among the cost evidence identified in the literature, we emphasised the existence of matched control cohort studies [41, 42, 93]. These papers provided a direct comparison of the excess costs and resource use of IPF patients versus a
| Study | Country | Cost year | Currency | Type of economic evaluation | Population | Time horizon | Comparators | Effectiveness | Costs | Cost effectiveness | Sources of funding |
|-------|---------|-----------|----------|----------------------------|------------|--------------|-------------|---------------|--------|------------------|-------------------|
| Benard et al. [99] | France | NR | Euros | Cost utility analysis | Adults with IPF | Cohort lifetime | Pirfenidone | NR (Abstract) | €82,667 | €76,668 | Nintedanib 57.1% chance of being more effective and 76.2% chance of being cheaper than pirfenidone | Boehringer Ingelheim |
| Capano et al. [101] | Italy | NR | Euros | Cost-effectiveness analysis | Adults with IPF | 1 year | Pirfenidone | NR (Abstract) | Budget impact: €11,121,549 | €76,668 | 59,712 €/ΔFVC% | NR |
| Hagaman et al. [105] | USA | 2007 | USD | Model-based cost-utility analysis | IPF patients stratified by TPMT prevalence: normal (high) 87.6%, 85.6–90%, intermediate 11.9%, 7.8–13.5%, and low (absent) 0.5% 0–3% | 1 year | Conservative therapy | 2.50 QALYs | $9969 | TPMT + triple vs conservative $49,156 per QALY. TPMT vs triple $29,662 per QALY gained | NR |
| Loveman et al. [26, 160] | UK | NR | GBP | Model-based cost-effectiveness analysis | Patients with IPF | 30 years | BSC Azathioprine and prednisolone NAC triple therapy Inhaled NAC Sildenafil Pirfenidone Nintedanib | 2.98 2.66 3.03 3.37 3.11 | £3084 £4313 £5021 £5029 £12,008 £70,118 £139,613 | £41,811 per QALY gained £5037 per QALY gained £68,116 per QALY gained £190,146 per QALY gained £132,658 per QALY gained | Reference NIHR | Dominated by BSC |
| Study                          | Country         | Cost year | Currency | Type of economic evaluation | Population | Time horizon | Comparators       | Effectiveness | Costs         | Cost effectiveness | Sources of funding |
|-------------------------------|-----------------|-----------|----------|------------------------------|------------|--------------|------------------|---------------|---------------|------------------|-------------------|
| Pozo and Paladino-Hernandez   | Mexico          | NR        | Costs converted to USD from MXN | Model-based cost-effectiveness analysis | NR: study looks at treating IPF | 1 year | Triple therapy | Pirfenidone  | –             | $154,582        | $121,293          | NR                |
| Ravasio et al. [102]          | Italy           | NR        | Euros    | Model-based cost-utility analysis | Adult patients with mild/moderate IPF | Cohort lifetime | BSC Nintedanib | Pirfenidone | NR Incremental effectiveness to BSC: +2.42 LYs; +1.95 QALYs and to nintedanib: +1.30 LYs; +1.04 QALYs | €26,570 | €93,948 | €102,504 | €31,360/LY and €39,012/QALY versus BSC and €6460/LY and €8199/QALY vs nintedanib | NR                |
| Rinciog et al. [25]           | UK              | 2012/2013 | GBP      | Model-based cost-effectiveness analysis | Adults with IPF | Cohort lifetime | BSC NAC | Pirfenidone | 3.0999 QALYs | £20,029          | Reference dominated by BSC | £172,198/QALY vs BSC |
| Soulard and Crespo [103]      | Spain           | 2016      | Euros    | Model based cost-effectiveness analysis | Adult patients with IPF (hypothetical cohort) | Cohort lifetime | Pirfenidone | Nintedanib | 3.62 QALYs | £78,351          | Nintedanib dominated pirfenidone | NR                |
| Tritaki et al. [100]          | Greece          | 2016–2020 | Euros    | Budget impact model | Adults with IPF. Clinical data were obtained from clinical trials INPULSIS I and II for nintedanib, CAPACITY for pirfenidone | 5 years | Pirfenidone | Nintedanib | NR Reduction of acute exacerbations 2016: – 5 events 2010: – 18 events | NR | Net budget impact of nintedanib at 2016 = €2,088,281 | NR | NR |
| Study            | Country   | Cost year | Currency | Type of economic evaluation | Population                                                                 | Time horizon | Comparators | Effectiveness | Costs          | Cost effectiveness | Sources of funding                                                                 |
|------------------|-----------|-----------|----------|-----------------------------|-----------------------------------------------------------------------------|--------------|-------------|---------------|----------------|------------------|----------------------------------------------------------------------------------|
| Wilson et al. [98] | UK        | 2011/2012 | GBP      | Cost-utility analysis based on an RCT | Patients with a diagnosis of fibrotic IP including either IPF or fibrotic non-specific interstitial pneumonia, aged ≥ 40 y, MRC dyspnoea score of ≥ 2 whose treatment regimens had remained unchanged for ≥ 6 weeks | 1 year       | Placebo     | ITT NHS: 0.539 QALys | ITT NHS: £3136 ITT Societal: £17,210 PP NHS: £3161 PP Societal: £18,587 | Unadjusted ITT NHS: ICER £1567 ITT Societal: active dominant PP NHS: £993 PP Societal: active dominant Adjusted for baseline utility and costs ITT NHS: ICER £6818 ITT Societal: ICER £22,012 PP NHS: £4849 PP Societal: £11,400 | East Anglia Thoracic Society, NIHR for Patient Benefit (RIPB) Programme, Cambridge BRC, Boehringer Ingelheim non-commercial educational grant |

BSC best supportive care, FVC forced vital capacity, GBP Great British Pound, ICER incremental cost effectiveness ratio, IIP idiopathic interstitial pneumonia, IPF idiopathic pulmonary fibrosis, IIP idiopathic interstitial pneumonia, ITT intention to treat, LY life-year, MRC Medical Research Council, MXN Mexican Pesos, NAC N-acetylcysteine, NHS National Health Service England, NIHR National Institute for Health Research, NR not reported, PP prescription prepayment, QALY quality-adjusted life-years, RCT randomised controlled trial, TPMT thiopurine S-methyltransferase, UK United Kingdom, USA United States of America, USD United States Dollars
reference population. Given that these studies were large in sample size and from a contemporary (2012 and 2015) and generalisable database, they produced relevant estimates for the cost burden of illness of IPF. Therefore, we recommend the use of control or reference cohorts when conducting cost analyses as it provides the relevant benchmark for comparison with the general population.

Two studies also suggested a strong correlation between acute exacerbations of IPF and other external conditions such as seasonality. Collard et al. [41] reported that acute exacerbations of IPF become more frequent in spring and winter. Kim et al. [63] highlighted spring as the season with most events, and linked that to the yellow dust phenomena occurring during that period in Korea, where this study was conducted.

The reader should note the relevance of national guidelines and prescription rules when comparing costs from different countries. Countries with a single (public) payer system, like the UK, have different practices and prescription rules to multiple-payer systems such as Germany in Europe or the US. It is also relevant to consider that some countries may have delayed access to new treatments; for instance, Australia only gained access to new anti-fibrotic agents in 2017, while Europe and the US has had access since 2010-2015.

The evidence on treatment economic evaluations was sparser. The cross-comparison of cost-effectiveness analyses is often hindered by different methodologies, time horizons, approaches in the presentation of the results and many other factors. On this occasion, an additional challenge was that most studies were published only as conference abstracts and, as such, provided little information on their methods and results. This made any comparison or synthesis of cost-effectiveness estimates very difficult.

One omission of our cost estimates is related to the diagnosis of IPF. The diagnostic procedures are largely in common with other ILDs and in most diagnostic cost studies evidence was presented from a heterogenous cohort that included patients with IPF as a subgroup [87, 109]. To include only studies that had an IPF subgroup may have been a misrepresentation of the actual management costs. For internal consistency with our population criteria, we decided to keep the reference database specific to IPF and excluded diagnostic cost studies from our review.

Our qualitative comparison of HRQoL and cost estimates with population reference statistics has further limitations. The synthesis of evidence from various studies involved the comparison of different EQ-5D versions (3L vs 5L) and conversions of cost estimates to one currency. This required several assumptions about the comparability of the data.

This review excluded relevant conference proceedings (published only as abstracts) before 2015. Records published since 2015 were included. Although the information from an abstract is often limited and the research lacks the scrutiny of an academic journal, we considered it important to include more recent records that report relevant information and that could later be published as full manuscripts. This improves the comprehensiveness of the records presented in this review.

However, the inclusion of abstracts could bias the synthesised data used to estimate the burden of illness. For instance, in the HRQoL studies we included data from the INSIGHTS-IPF registry [80–84] and Fell et al. [12] that at the time were available only as abstracts. In the cost studies we included Hill et al. [88] and Mittmann et al. [94].

In our search for evidence on the burden of IPF, we identified other similar literature reviews. Loveman et al. [26] conducted a systematic review with the objective being the comparison of the clinical effectiveness and cost-effectiveness of IPF treatment interventions. Our study was not searching specifically for treatment effects, although there was a lot of overlap in our searches for HRQoL and economic evaluations; we identified the same papers in HRQoL and economic evaluations as Loveman et al. In addition, we have used Loveman et al. to validate our review findings [26] within the overlapping time periods. 4

Lee et al. [6] reported on the unmet public health need with IPF. Although they cover quality of life and resource utilisation, their analysis on the burden of the disease was focused more around the epidemiology, comorbidities and symptoms of IPF.

The treatment of IPF has changed substantially in recent years, and has evolved a lot since the first paper identified in our search was published (2000). We identified an exponential growth of publications in the last 3–5 years. This trend probably follows the development of new pharmacological interventions such as pirfenidone and nintedanib. For instance, we identified many publications referring to results from three nintedanib clinical trials—TOMORROW, INPULSIS® I and II [25, 110–121].

With the exception of the evidence reported in the cost-effectiveness studies, our review did not capture the full effect of new treatments in IPF. As the pipeline of available treatments expands, new research will be added to the existing data. We recommend a timely update of this review to capture the influx of new studies and any contemporary research. This will be crucial when informing policy decisions in diagnosis, treatment and palliation of patients with IPF.

4 Some studies included in Loveman et al., not available in the English language, were not selected in our review, given our protocol inclusion criteria.
5 Conclusion

IPF is a chronic, debilitating condition affecting a growing proportion of the population; predominantly male and the elderly. Our review found evidence of an important health burden of the disease in comparison with HRQoL levels of the general population. Furthermore, our review highlighted an excess cost and resource use for healthcare providers. This confirms IPF as a growing threat for public health worldwide with considerable impact on both patients and healthcare providers.

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Author Contributions AD designed and supervised the study and wrote the manuscript with editorial and content input from NS and TM. KV, EW and AD developed the search strategy for the HRQoL and the economic and resource use review. KV, EW, and LC had a substantial contribution to screening of titles, abstracts and full texts with any discrepancies discussed with AD. KV, EW and LC performed the analysis and interpretation of data. All authors approved the final version of the report.

Data availability The datasets generated and analysed during the current study are available from the corresponding author on request.

Compliance with Ethical Standards

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Conflict of interest KV, EW, LC and AD are employed by Symmetry Limited, which received funding from Boehringer Ingelheim for this project. AD has in the past received funding from Boehringer Ingelheim for the contribution to original research and similar articles. TM has received consulting fees from Symmetry Limited; industry-academic research funding from GlaxoSmithKline R&D and UCB; and consultancy or speakers fees from AstraZeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Cipla, Dosa, Galapagos, GlaxoSmithKline R&D, ProMetic, Roche (and previously InterMune), Sanofi-Aventis, Takeda and UCB. TM is supported by an NIHR Clinician Scientist Fellowship (NIHR Ref: CS-2013-13-017) and British Lung Foundation Chair in Respiratory Research (C17-3). NS is an employee of Boehringer Ingelheim.

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