Health and Quality of Life Outcomes

REVIEW

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Health-related quality of life and health state utility value in idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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Abstract

Background Idiopathic pulmonary fibrosis (IPF) is associated with high mortality, heavy economic burden, limited treatment options and poor prognosis, and seriously affects the health-related quality of life (HRQoL) and life expectancy of patients. This systematic review and meta-analysis of HRQoL and health state utility value (HSUV) in IPF patients and the instruments used in this assessment aimed to provide information sources and data support for the future research on IPF HRQoL and HSUV.

Methods We searched the PubMed, EMBASE, Web of Science and Cochrane Library databases for studies reporting the HRQoL or HSUV of IPF patients, with the retrieval time from the establishment of each database to April 2024. After two researchers independently screened the literature, extracted the data, and evaluated the risk of bias in the included studies, pooled analysis was performed on the measurement tools adopted in more than two studies. Subgroup analysis was employed to explore the source of heterogeneity, and sensitivity analysis was used to assess the robustness of the results. Funnel-plot directed evaluation combined with Egger's test quantitative evaluation was conducted to detect publication bias.

Results Sixty-nine studies were ultimately included, covering eighteen measurement tools. The literature quality was generally excellent. The St. George's Respiratory Questionnaire (SGRQ), EuroQoL Five Dimensions Questionnaire (EQ-5D), Short Form-36 (SF-36) and the King's Brief Interstitial Lung Disease (KBILD) were the most common instruments, among which the EQ-5D included the HSUV and the visual analog scale (VAS). The results of the meta-analysis revealed that the pooled SGRQ total score was 45.28 (95% confidence interval [CI] 41.10-49.47), the mean EQ-5D utility score was 0.75 (95% CI: 0.72–0.79), the total EQ-5D VAS score was 66.88 (95% CI: 63.75–70.01), and the pooled SF-36 physical component summary (PCS) and mental component summary (MCS) score were 36.70 (95% CI: 32.98–40.41) and 48.99 (95% CI: 47.44–50.55), respectively. The total KBILD score was 58.31 (95% CI: 55.43–61.19), the IPF specific version of the SGRQ (SGRQ-I) was 40.38 (95% CI: 28.81–51.96) and the Leicester Cough Questionnaire (LCQ) score was 16.09 (95% CI: 15.45–16.74). The pooled result of the University of California San Diego Shortness of Breath Questionnaire (USCD-SOBQ) was 45.05 (95% CI: 41.56–48.55). The results of other instruments, such as the tool to assess quality of life in IPF (ATAQ-IPF), the World Health Organization Quality of Life assessment 100 (WHOQoL-100) and the 12-item short-form health survey (SF-12) were similar to those of the above measurement tools. Regretfully,

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subgroup analyses did not identify the source of heterogeneity, but sensitivity analyses demonstrated robustness of our results. Except for the SGRQ total, our results showed little possibility of publication bias.

Conclusions HRQoL in IPF patients is generally poor, and all domains are severely affected. With the aggravation of disease, HRQoL and HSUV shows a relatively downward trend, and income level is also an important factor affecting HRQoL and HSUV. At present, the published studies on IPF HRQoL and HSUV have applied many measurement tools with high interstudy heterogeneity, and future research on the optimal disease measurement tools should be strengthened. Our study provides high-quality comprehensive evidence for IPF HRQoL and HSUV, which can be used to guide clinical and economic evaluation in the future.

Keywords Idiopathic pulmonary fibrosis, Health-related quality of life, Health state utility value, Systematic review, Meta-analysis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic interstitial lung disease with high disability and mortality rates [1–3], and mostly occurs in elderly individuals [4]. Although the course of the disease may differ, the progression of patients from diagnosis to end-stage respiratory failure and even death is usually only 2 to 4 years [5–7]. Current treatment methods, such as nintedanib and pirfenidone, are insufficient and only slow the deterioration of the disease without providing a cure [8]. The progressive aggravation of dyspnea, dry cough, and fatigue in IPF patients seriously affects their quality of life (QoL) and life expectancy [9, 10]. Given the symptomatic burden [11], limited treatment schemes [12], poor prognosis [13], and uncertainty of the disease course in patients [14], the comprehensive management of patients should consider improving clinical outcomes, as well as pay more attention to health-related QoL (HRQoL).

HRQoL is a comprehensive index used to evaluate the overall QoL of individuals from psychological, physiological and social dimensions. It has been widely used in many fields, such as health care evaluation and health service effect evaluation. Among them, the health state utility value (HSUV) is a quantitative index used to measure the impact of health status on the QoL of individuals. It reflects people's preference for a certain health status, which could make comparisons between different health states of patients more objective and standardized [15]. The HSUV is also a key parameter in health economics evaluation and could help strategy formulators to make more scientific and effective decisions in various of medical and public health settings [16].

To clarify the HRQoL of IPF patients, we should first determine the optimal measurement tool. To our knowledge, the HRQoL instruments currently used to measure IPF include St. George's Respiratory Questionnaire (SGRQ), the Short Form-36 (SF-36) and the EuroQol Five Dimensions Questionnaire (EQ-5D) [17, 18]. These generic instruments can quantify and compare QoL between diseases, but multifarious measurement tools affect the accurate assessment of IPF HRQoL. Therefore, it is urgent to standardize HRQoL assessment in IPF patients to understand and improve patients' QoL. As a major instrument for HSUV in IPF patients, the EQ-5D could help identify the most effective medical interventions by calculating quality-adjusted life years and performing cost-utility analysis, resource allocation, and policy formulation [19]. The accuracy of HSUV measurements directly affects the evaluation results of pharmacoeconomics. Consequently, the evaluation of the HSUV in IPF is highly important for health decision-making.

Although studies have attempted to review HRQoL for IPF [18, 20], some interstitial lung diseases with different etiologies (such as connective tissue disease-related interstitial lung disease and chronic hypereosinophilic pneumonia) have been identified. The heterogeneity between diseases has led to its failure to truly reflect the HRQoL of IPF [21], and studies of HSUV are limited [18]. Another study [20] published in 2005, included only seven studies with 512 patients, covering three measurement tools, which were insufficient, with incomplete information and limited results. Our study greatly expanded the sample size, summarized and updated more high-quality studies, strictly limited the population to IPF patients, and provided accurate and updated evidence-based evidence of HRQoL for IPF patients through comprehensive analysis to further promote the optimal allocation of health resources.

Methods

The protocol of this systematic review has been prospectively registered in the Prospective Register of Systematic Reviews (CRD42024540743), and our study was performed strictly in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [22].

Search strategy

The original studies on the HRQoL of patients with IPF were searched through the PubMed, EMBASE, Web of Science and Cochran Library databases with the retrieval

time from the establishment of each database to April 26, 2024. The search strategy was carried out by combining medical subject heading terms and key words, and adjusting the results according to the characteristics of each database, without language restrictions. References of relevant literature were traced to supplement possible studies. The detailed retrieval strategies are presented in Supplement Table 1.

Eligibility criteria

The participants were patients with a clear diagnosis of IPF, without restriction of the study type involving HSUV. For the QoL assessment, we included only observational studies. When multiple articles reported the same result from the same population source, we analyzed only the latest study with the most complete data. None of the included studies were restricted by language.

Exclusion criteria

Nonoriginal studies such as conference abstracts, editorials, and systematic reviews, and duplicated published studies were included. For QoL assessment, we did not include controlled trials to avoid strict participant limitations affecting overall estimates of HRQoL in IPF patients. Furthermore, many trials may not be identifiable by title or abstract because the HRQoL is a secondary indicator. Studies with incorrect data and studies without reported specific HRQoL-related data for IPF were excluded.

Study selection and data extraction

Two reviewers (GX Z and SY L) independently screened and cross-checked the literature using Endnote X9 software. Disagreements were resolved via group discussion. Rounds of screening were conducted according to the inclusion and exclusion criteria. First, the retrieved literature was uniformly imported into EndNote X9 to eliminate duplicate literature. Second, the literature that was inconsistent with the research topic was removed by reading the title and abstract. Finally, the full text was read and screened to determine the number of original studies that ultimately met the inclusion criterion.

The predesigned data extraction form was used to extract relevant information from the included studies in Microsoft Excel 2016, including the first author, publication data, country, study type, population source, disease diagnosis criteria, total IPF population, number of males and females, age, smoking information, force vital capacity percent predicted (FVC% pred), transfer factor for carbon monoxide as a Percentage of predicted value (TLCO% pred), measurement tools and scores of HRQoL, and ethics. For intervention studies involving the HSUV, only baseline information was included.

Quality assessment

At present, there is no unified consensus on the tools for quality assessment in the practice guide for systematic review of HSUV [23]. To our knowledge, the standard framework set described by Papaionanou et al. [24] considered varied key factors in assessing the quality of included studies, such as sample size, inclusion/exclusion criteria, response rate, reporting missing data, which is also the reason why our study chose it as a tool for HSUV quality evaluation. In addition, it has been widely used in numerous related studies [25–28]. Regarding the quality of observational studies, cohort studies and case-control studies were assessed according to the Newcastle-Ottawa scale (NOS) [29], which mainly evaluated 8 items in 3 dimensions, including the selection of research subjects, comparability between groups and outcome measurement. The total score is 9, with higher the score, the higher the literature quality, among which 1–3, 4–6, and 7–9 score is represented as low-quality, medium quality and high quality, respectively. The cross-sectional studies were scored using the quality evaluation checklist recommended by the American Agency for Healthcare Research and Quality (AHRQ) [30], with 0–3 score classified as low-quality, 4–7 score as medium-quality, and 8–11 score as high-quality.

Statistical analysis

Charts were used to illustrate the basic characteristic of the included studies by descriptive statistics, such as publication time trend, country, diagnostic criteria, and HRQoL assessment tools. Stata (version 15.1) software was used for the statistical analysis, and the effect size (ES) and its 95% confidence interval (CI) were used as the effect statistics. The statistical analysis was performed via the "metan" command on the basis of the mean and standard deviation (SD). If related information was not reported in the included studies, we calculated the mean and sd by sample size, quartile values, maximum, minimum, and 95% CI. The chi-square test and I^2 value were used to assess heterogeneity. If $P<0.1$ or $I^2>50\%$, the included studies had high heterogeneity, and the random effect model was used for data integration; otherwise, the fixed effect model was employed. To further explore the source of heterogeneity between studies, subgroup analysis was conducted on the basis of disease severity, country, World Health Organization (WHO) regional classification and income level. A sensitivity analysis was conducted to evaluate the stability of the study results via the one-by-one elimination method. For outcome indicators with more than 10 included studies, funnel plots and Egger's test were used to analyze the possible publication bias. For the results with publication bias, correction were made via the trim-and-fill method.

Table 1 Basic characteristics of the included studies

Author, Year	Country	Study design	Diagnose standard	DS year	Study period	sample size	Male/ Female	Ages	FVC% predit	Measurement instrument	Ethic
Duke et al. 2024 [31]	USA	prospective cohort	chest computed tomography	NA	2018.9-2021.8	65	51/14	72.0	73.9	CRQ	YES
Sridhar et al. 2024 [32]	USA	prospective cohort	ATS/ERS/JRS	NR	2016–2018	70	47/23	70.4	66.5	SGRQ	YES
Cox et al. 2023 [33]	Australia	prospective cohort	ATS/ERS/JRS/ALAT	2018	2018.8-2019.10	162	99/63	73.8	87.6	EQ-5D AQoL-8D SGRQ	YES
Rautajoki et al. 2023 [34]	Finland	prospective cohort	ATS/ERS/JRS/ALAT	2018	2015.4-2017.10	247	263/84	74.3	82.9	15D	YES
Saari et al. 2023 [35]	Finland	case control	HRCT and transbronchial lung biopsy	NA	2015.1-2021.12	68	39/29	67.4	79.95	LCQ	YES
Veit et al. 2023 [36]	Germany	prospective cohort	ATS/ERS	2013	2017.7-2018.8	13	10/3	65.3	68.5	SGRQ KBILD	YES
Zheng et al. 2023 [37]	Australia	prospective cohort	ATS/ERS/JRS/ALAT	2018	2018.8-2019.12	157	95/62	74.0	79.9	HSUs	YES
Park et al. 2022 [38]	South Korea	prospective cohort	ATS/ERS/JRS/ALAT	2015	2017.6-2018.9	70	52/18	67.9	77.25	EQ-5D SGRQ CQLQ	YES
Phua et al. 2022 [39]	Singapore	cross-sectional	ATS/ERS	2013	2019.12-2022.1	27	NR	NR	78.1	EQ-5D KBILD	YES
Reinaldo et al. 2022 [40]	Brazil	cross-sectional	pulmonary function with lung biopsy or HRCT	NA	NR	27	19/8	60.7	51.10	SGRQ	YES
Scallan et al. 2022 [41]	USA	cross-sectional	ATS/ERS/JRS/ALAT	2018	2019.9.-2019.10	100	67/33	71.2	70.5	EQ-5D KBILD	YES
Wuyts et al. 2022 [42]	multi-country	prospective cohort	ATS/ERS/JRS/ALAT	2011	2013.10-2016.1	277	213/64	69.6	80.6	EQ-5D SGRQ	YES
Bloem et al. 2021 [43]	Netherlands	cross-sectional	ATS/ERS/JRS/ALAT	2011	2018.5-2019.3	61	47/14	73.7	82.8	EQ-5D	YES
Chen et al. 2021 [44]	Canada	prospective cohort	ATS/ERS/JRS/ALAT	2018	2015.1-2020.3	539	413/126	69.0	76	EQ-5D SGRQ	YES
Cox et al. 2021 [45]	Australia	prospective cohort	ATS/ERS/JRS/ALAT	2018	2018.8-2019.10	155	99/56	74.0	87.5	EQ-5D	YES
Ebihara et al. 2021 [46]	Japan	cross-sectional	ATS/ERS/JRS/ALAT	2011	2014.7-2017.7	27	21/6	76.1	72.0	SGRQ	YES
Gao et al. 2021 [47]	Sweden	prospective cohort	ATS/ERS/JRS/ALAT	2011	2014.9-2020.4	662	490/172	72.8	72.4	KBILD	YES

Table 1 (continued)

Author, Year	Country	Study design	Diagnose standard	DS year	Study period	sample size	Male/ Female	Ages	FVC% predit	Measurement instrument	Ethic
Kanjrawi et al. 2021 [48]	Australia	prospective cohort	Medical records	NA	2019.8-2019.10	27	19/8	71.0	77	EQ-5D KBILD	YES
Machado et al. 2021 [49]	Germany	prospective cohort	ATS/ERS/JRS/ALAT	2011	2012.3-2017.10	98	84/14	68.0	64	SF-36	YES
Prior et al. 2021 [50]	Denmark	prospective cohort	ATS/ERS/JRS/ALAT	2011	2016.8-2018.3	150	122/28	72.9	87.2	SGRQ-I	YES
Behr et al. 2020 [51]	Germany	prospective cohort	ATS/ERS/JRS/ALAT	2011	2012.12-2018.12	588	476/112	69.8	68.6	EQ-5D	YES
Bloem et al. 2020 [52]	Netherlands	cross-sectional	ATS/ERS/JRS/ALA	2011	2018.5-2019.3	59	45/14	73.7	83.2	EQ-5D QoL-RIQ	YES
Case et al. 2020 [53]	USA	retrospective cohort	ATS/ERS/JRS/ALAT	2011	2014.6-2017.10	662	496/166	70.0	69.8	EQ-5D SGRQ SF-12	YES
Durheim et al. 2020 [54]	Norway	cross-sectional	ATS/ERS/JRS/ALAT	2011	2017.9-2018.10	57	41/16	71.0	73	EQ-5D SGRQ KBILD LCQ	YES
Leuschner et al. 2020 [55]	Germany	prospective cohort	ATS/ERS/JRS/ALAT	2011	2012.11-2019.12	1009	814/195	75.3	67.89	EQ-5D SGRQ	YES
Moor et al. 2020 [56]	Netherlands	RCT	ATS/ERS/JRS/ALAT	2018	2018.1-2019.1	46	39/7	68.6	82.6	EQ-5D KBILD PESaM	YES
O'Brien et al. 2020 [57]	USA	Cross-Sectional	ATS/ERS/JRS/ALAT	2011	2014.6-2018.7	859	639/220	70.0	69.7	EQ-5D SGRQ SF-12	YES
Prior et al. 2020 [58]	Denmark	prospective cohort	ATS/ERS/JRS/ALAT	2011	2016.8-2019.3	150	122/28	72.9	87.2	SGRQ KBILD SGRQ-I	YES
Tzouvelekis et al. 2020 [59]	Greece	prospective cohort	ATS/ERS/JRS/ALAT	2011	2016–2017	98	80/18	70.8	77.0	SGRQ KBILD	YES
Eken et al. 2019 [60]	Turkey	cross-sectional	ATS/ERS/JRS/ALAT	2011	2016.10-2016.10	40	31/9	65.1	86.60	SGRQ	YES
Kalafatis et al. 2019 [61]	Sweden	cross-sectional	ATS/ERS/JRS/ALAT	2011	2014.9-2017.12	384	250/98	71.8	70.2	KBILD	YES
Pan et al. 2019 [62]	China	cross-sectional	ATS/ERS/JRS/ALAT	2011	2014.1-2015.8	20	14/6	58.3	NR	SGRQ ATAQ-IPF	YES
Prior et al. 2019 [63]	Denmark	prospective cohort	ATS/ERS/JRS/ALAT	2011	2016.8-2018.3	150	122/28	72.9	87.2	KBILD SF-36 SGRQ-I	YES

Table 1 (continued)

Author, Year	Country	Study design	Diagnose standard	DS year	Study period	sample size	Male/ Female	Ages	FVC% predit	Measurement instrument	Ethic
Capparelli et al. 2018 [64]	Argentina	prospective cohort	ATS/ERS/JRS/ALAT	2011	2026.01-2017.01	23	18/5	71.9	68.9	SGRQ-I	YES
Mavroudi et al. 2018 [65]	Greece	case control	ATS/ERS	2000	2013.11-2015.11	19	11/8	69.8	75.6	SF-36	YES
Nolan et al. 2018 [66]	UK	prospective cohort	ATS/ERS/JRS/ALAT	2011	2015.01-2015.12	65	58/7	72.0	73.2	KBILD	YES
Wuyts et al. 2018 [67]	multi-country	prospective cohort	ATS/ERS/JRS/ALAT	2011	2013.10-2016.1	277	213/64	69.6	80.6	EQ-5D SGRQ	YES
Furukawa et al. 2017 [68]	Japan	Retrospective cohort	ATS/ERS/JRS/ALAT	2011	2007.5-2012.12	182	155/27	65.6	79.7	SGRQ	YES
Kreuter et al. 2017 [69]	Germany	prospective cohort	ATS/ERS/JRS/ALAT	2011	NR	623	481/142	69.6	67.5	EQ-5D SGRQ	YES
Magnani et al. 2017 [70]	Italy	prospective cohort	ATS/ERS/JRS/ALAT	2011	2015.1-2015.6	18	8/10	66.5	NR	PGWBI	NR
Matsuda et al. 2017 [71]	Japan	retrospective cohort	ATS/ERS/JRS/ALAT	2011	2009.4-2013.3	121	99/22	66.8	81.1	SGRQ	YES
Matsuda et al. 2017 [72]	Japan	cross-sectional	ATS/ERS/JRS/ALAT	2011	2011.7-2014.10	106	90/16	67.1	81.9	SGRQ	YES
Natalini et al. 2017 [73]	USA	cross-sectional	ATS/ERS/JRS/ALAT	2011	2010.3-2015.9	50	39/11	70.8	70.3	SF-36	YES
Sokai et al. 2017 [74]	Japan	prospective cohort	ATS/ERS/JRS/ALAT	2011	2013.4-2014.10	52	44/8	72.0	86.1	SF-36 SGRQ-I	YES
Wapenaar et al. 2017 [75]	multi-country	prospective cohort	ATS/ERS	2000	2013.12-2016.4	108	84/24	70.5	72.5	EQ-5D SGRQ KBILD	YES
Atkins et al. 2016 [76]	UK	cross-sectional	ATS/ERS/JRS/ALAT	2011	2012.9-2014.3	77	59/18	76.4	84.3	EQ-5D SGRQ KBILD	YES
Bahmer et al. 2016 [77]	Germany	prospective cohort	ATS/ERS/JRS/ALAT	2011	2013.1-2013.10	48	36/12	67.1	75.4	SGRQ SF-12	YES
Kotecha et al. 2016 [78]	UK	prospective cohort	ATS/ERS/JRS/ALAT	2011	2013.1-2014.3	75	58/17	76.4	83.6	SGRQ	YES

Table 1 (continued)

Author, Year	Country	Study design	Diagnose standard	DS year	Study period	sample size	Male/ Female	Ages	FVC% predit	Measurement instrument	Ethic
Lubin et al. 2014 [79]	USA	prospective cohort	ATS/ERS	2000	2010.1-2012.8	102	76/26	70.0	70.0	SF-36	YES
Nishiyama et al. 2012 [80]	Japan	retrospective cohort	ATS/ERS	2000	2000.4-2005.7	87	77/10	66.3	75	SGRQ	YES
Noth et al. 2012 [81]	USA	RCT	ATS/ERS/JRS/ALAT	22,011	2009.12-2011.4	145	106/39	66.9	58.79	EQ-5D SGRQ SF-36	YES
Swigris et al. 2012 [82]	USA	retrospective cohort	ATS/ERS	2005	NR	180	83/97	69.0	56.8	SGRQ SF-36	NR
Elfferich et al. 2011 [83]	Netherlands	cross-sectional	Medical records	NA	2007.10	49	31/18	63.1	82.9	WHOQOL-100	YES
King et al. 2011 [84]	multi-country	RCT	ATS/ERS	2000	2007.1-2008.10	407	296/111	63.8	74.9	EQ-5D SF-36	YES
Jones et al. 2011 [85]	UK	case control	ATS/ERS	2002	NR	27	17/10	71.7	80.4	LCQ	YES
Verma et al. 2011 [86]	Canada	cross-sectional	ATS/ERS	2000	2003.10-2008.3	137	90/47	59.4	61.7	SGRQ SF-36	YES
Han et al. 2010 [87]	USA	cross-sectional	ATS/ERS	2000	2003-2009.1	221	147/74	63.3	62.77	SGRQ SF-12	YES
Key et al. 2010 [88]	UK	cross-sectional	ATS/ERS	2002	2001–2007	19	14/5	70.8	78.5	LCQ	YES
Swigris et al. 2010 [89]	USA	prospective cohort	ATS/ERS	2000	NR	95	82/13	69.3	65	ATAQ-IPF	NR
Zisman et al. 2010 [90]	USA	RCT	ATS/ERS	2000	2007.9-2009.3	89	75/14	69.8	54.89	EQ-5D SGRQ SF-36	YES
Krishnan et al. 2008 [91]	USA	cross-sectional	ATS/ERS	2000	NR	41	22/19	67.7	68.9	SF-36	YES
Peng et al. 2008 [92]	China	cross-sectional	ATS/ERS	2000	2002.1-2007.5	68	54/14	64.0	66	SGRQ	YES
Tomioka et al. 2007 [93]	Japan	cross-sectional	ATS/ERS	2000	2000.3-2005.12	46	32/14	69.9	71	SF-36	YES
Zimmermann et al. 2007 [94]	Brazil	cross-sectional	ATS/ERS	2000	NR	20	12/8	61.5	70.4	SGRQ SF-36	NR

Table 1 (continued)

Author, Year	Country	Study design	Diagnose standard	DS year	Study period	sample size	Male/ Female	Ages	FVC% predit	Measurement instrument	Ethic
Nishiyama et al. 2005 [95]	Japan	prospective cohort	ATS/ERS	2000	2000.1-2002.12	41	35/6	64.0	76.6	SGRQ	NR
Tzanakis et al. 2005 [96]	Greece	cross-sectional	ATS/ERS	2000	1994.1-1999.7	25	21/4	66.0	68.8	SGRQ	YES
Baddini et al. 2002 [97]	Brazil	cross-sectional	Lung biopsy and CT	NA	NR	30	18/12	58.6	61.9	SF-36	YES
De Vries et al. 2001 [98]	Netherlands	cross-sectional	ATS/ERS	2000	NR	41	15/26	63.5	NR	WHOQOL-100	NR

NOTE Abbreviations: AQoL-8D: Assessment of Quality of Life- eight-dimension; ATS/ERS: American Thoracic Society/European Respiratory Society: ATS/ERS/JRS/ALAT: American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society; ATAQ-IPF: A Tool to Assess Quality of life in IPF; CRQ: Chronic Respiratory Questionnaire; CQLQ:, cough quality of life questionnaire; DS: Diagnose standard; EQ-5D: EuroQoL Five Dimensions Questionnaire; HSUs: Health state utilities; IPF: Idiopathic pulmonary fibrosis; KBILD: King's Brief Interstitial Lung Disease; LCQ: Leicester Cough Questionnaire; NA: Not appliable; NR: Not reported; PESaM: = Patient Experiences and Satisfaction with Medication questionnaire; PGWBI: Psychological General Well-Being Index; QoL-RIQ: Quality of Life for Respiratory Illness Questionnaire; RCT: Random control study; SF-12: 12-item short-form health survey; SF-36: Short Form-36; SGRQ: St. George's Respiratory Questionnaire; SGRQ-I: IPF specific version of SGRQ; WHOQoL-100: World Health Organization Quality of Life assessment 100; 15D: The 15-Dimension Questionnaire

Results

Identification of studies

In total, 4418 relevant studies were retrieved from the initial examination. After removing duplicates, primary screenings and double screenings, 68 studies [31–98] were utimately included, of which 20 reported HSUV and 67 reported QoL. Among these studies, 59 were employed in the quantitative synthesis (meta-analysis). The literature screening process and results are shown in Fig. 1. The detailed reasons for excluding studies from the full text are reported in Supplement Table 2.

Study characteristics

All included studies were published after 2001, and half of the studies (50%) were published within the last 6 years (Fig. 2). The participants of the included studies ranged from 13 to 1009, with a total sample size of 10,929. There were 27 studies with fewer than 60 participants (40%), 14 studies with IPF patients ranging from 60 to 100 (20%), and 27 studies with more than 100 subjects (40%). According to the WHO regional classification, the majority of studies were distributed in Europe (43%), the western Pacific region (24%) and the Americas region (28%). Many studies on HRQoL have been conducted in the United States, Japan, Germany and the Netherlands. In terms of World Bank income levels, the majority of countries (84%) have high incomes. Fifty-five studies explicitly reported passing the ethical review, whereas the remaining studies did not report ethical information. According to the Journal Citation Reports Quartile, most studies (72%) belong to Q1 or Q2. The basic characteristics of the included studies are shown in Table 1. Information on country distribution is depicted in Fig. 3.

IPF diagnostic criteria in 61 (90%) studies referred to international consensus, and 7 studies were confirmed on the basis of medical records, high-resolution CT, or biopsy. Most of the studied IPF patients (97%) were predominantly male. Forty-three studies recorded smoking information, of which 42 studies included more smokers than never smokers among patients with IPF. With respect to disease severity, 31 (46%) studies included mild IPF patients, and 33 (49%) studies included moderate IPF patients. A total of 34(50%) studies reported the treatment of IPF, most of which focused on antifibrosis agents, such as pirfenidone or nintedanib, and immunosuppressants. In addition, 22 studies documented information on oxygen therapy, with most patients requiring long-term maintenance oxygen therapy.

HRQoL measurement instruments

There were eighteen instruments for HRQoL in our study, including four measuring tools for the HSUV. Among them the EQ-5D was the most commonly used instrument for HSUV (90%). There were fourteen instruments involving QoL, of which the generic instruments included the SGRQ, the SF-36 and the King's Brief Interstitial Lung Disease Questionnaire (KBILD). The disease-specific scales used were the SGRQ-I and ATAQ-IPF. Detailed information about the instruments is shown in Supplement Fig. 1.

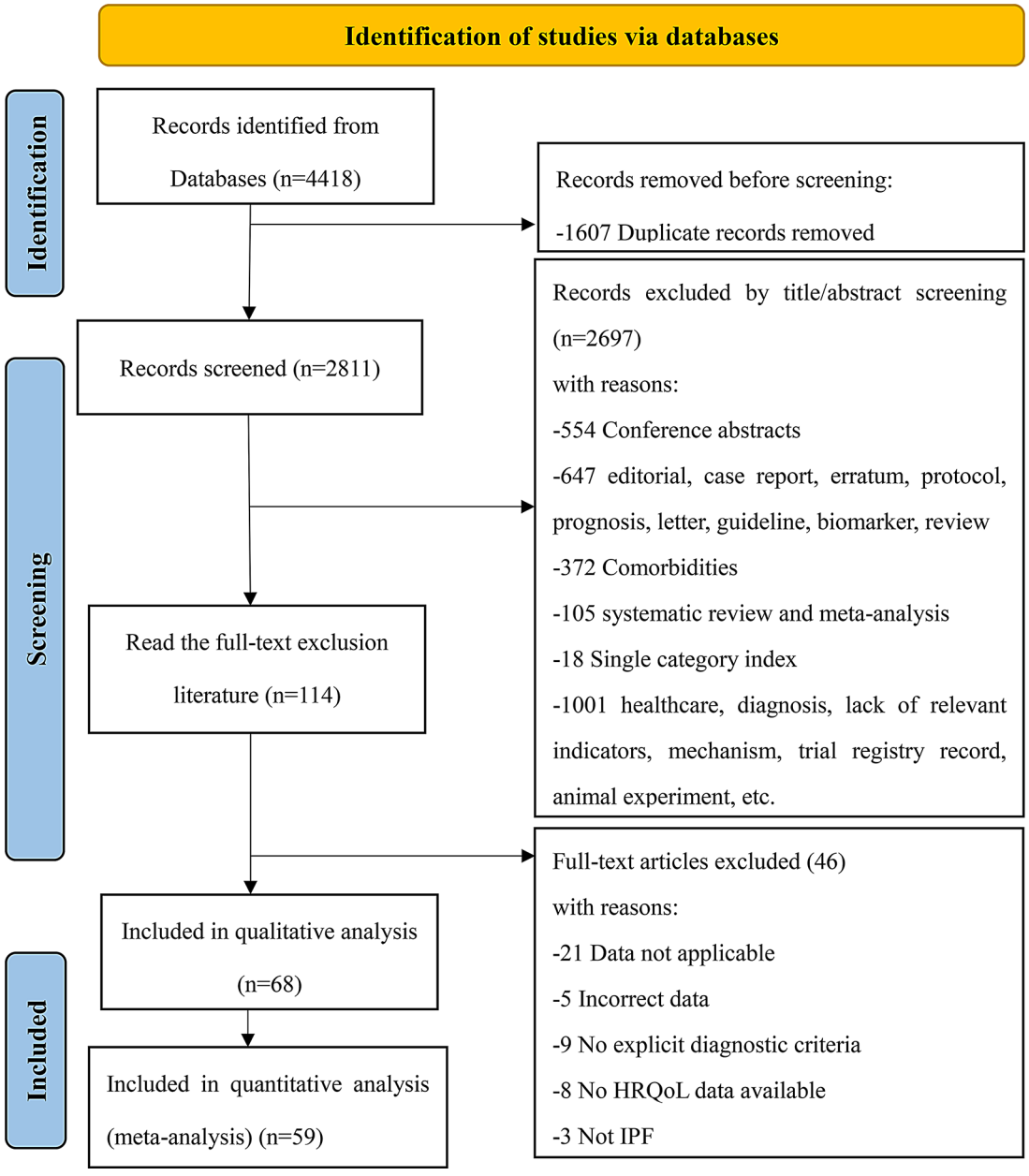

Fig. 1 Flowchart of literature screening

We conducted quantitative analysis on the instruments that reported more than twice, including the EQ-5D, SGRQ, SF-36, KBILD, IPF specific version of the SGRQ (SGRQ-I), the Leicester Cough Questionnaire (LCQ), the University of California San Diego Shortness of Breath Questionnaire (USCD-SOBQ), the 12-item short-form health survey (SF-12), the World Health Organization Quality of Life assessment 100 (WHOQoL-100) and the Tool to Assess Quality of Life in IPF (ATAQ-IPF). Studies involving instruments included in the meta-analysis are shown in Supplement Table 3.

EQ-5D

Twenty-three studies have reported data concerning the EQ-5D, which comprises a descriptive system and a visual analogue scale (VAS) [99]. The data specifically reported in this study encompassed either EQ-5D utility scores, EQ-5D VAS scores, or both. The EQ-5D value is anchored at 1 (full health) and 0 (a state as bad as being dead). In some cases, values less than 0 represent health states considered worse than death. The EQ-5D VAS value ranges from 100 ('the best imaginable health state' or 'the best health state you can imagine') to 0 ('the worst imaginable health state' or 'the worst health you can imagine').

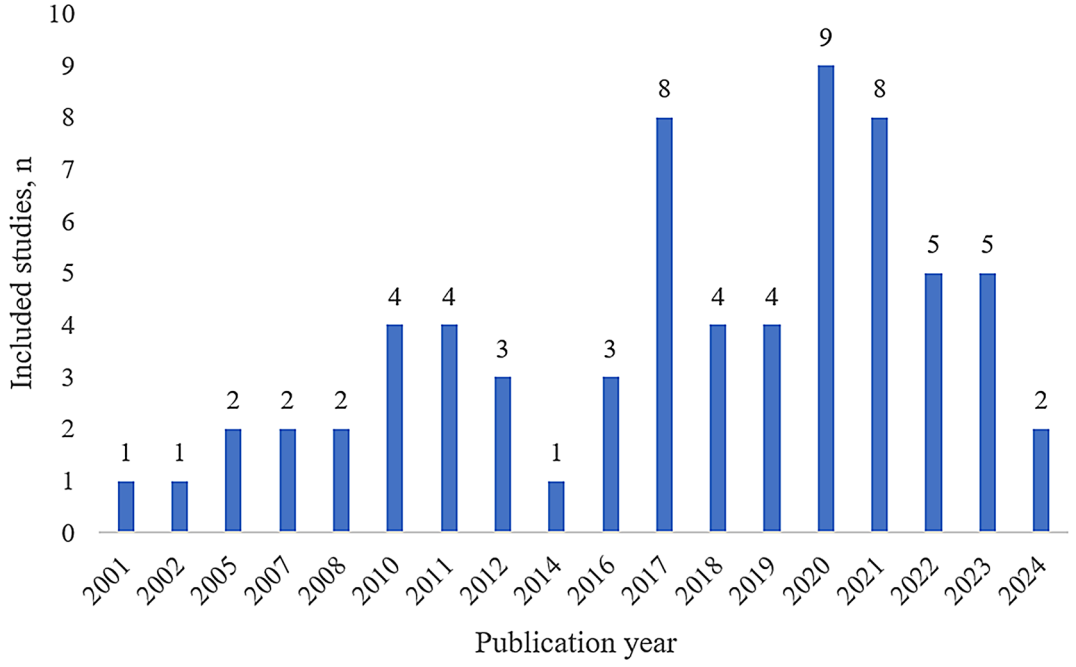

Fig. 2 The distribution of publication years of included studies

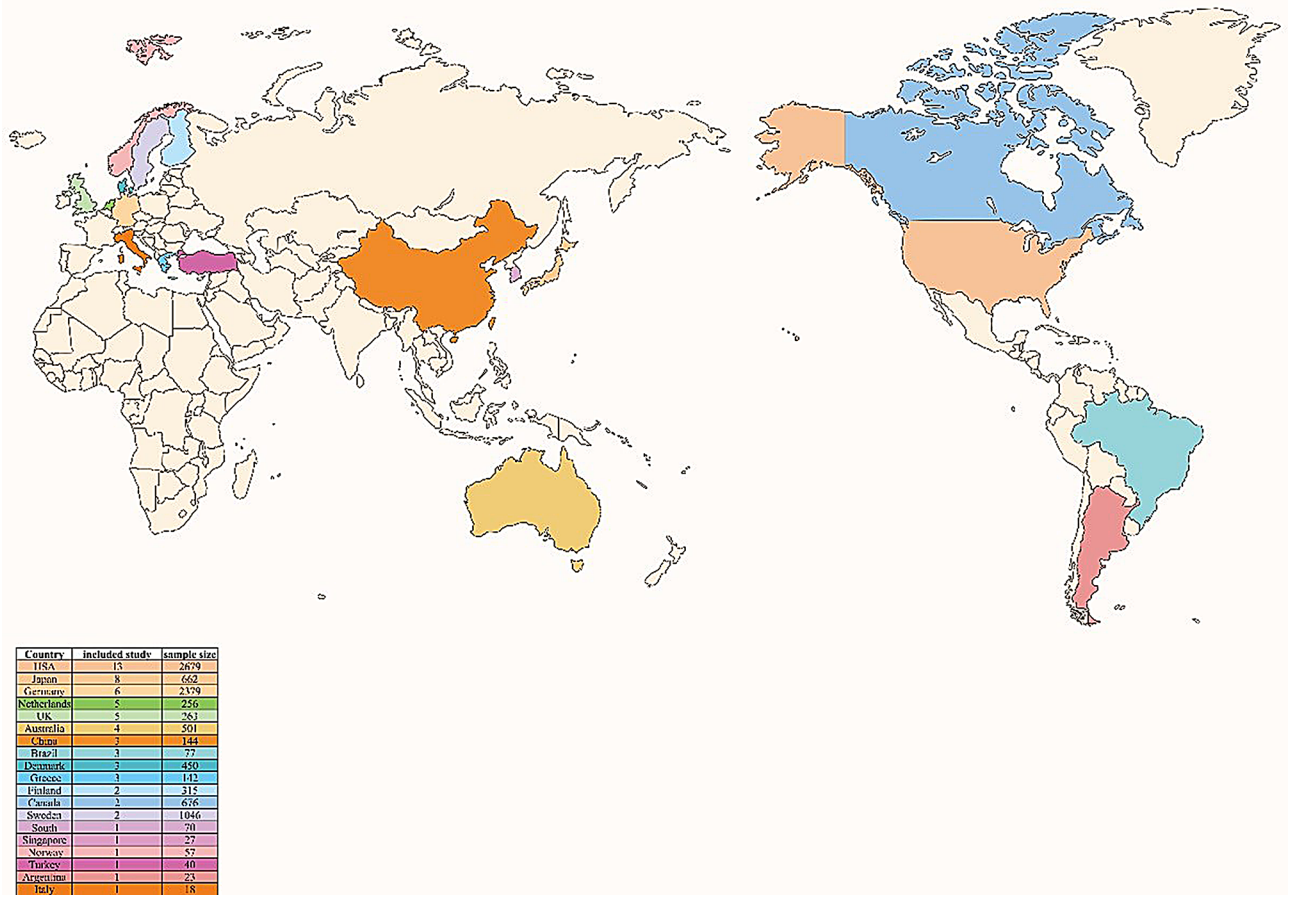

Fig. 3 The distribution of countries of included studies

SGRQ

The SGRQ is the most widely used HRQoL instrument for respiratory diseases. A total of thirty-five studies reported the SGRQ, which is divided into three domains: symptoms, activity and the impact of the disease on daily life, where a higher its score, indicates a worse the QoL of patients [100].

SF-36

Fifteen studies reported SF-36 scores. It is widely used to assess the QoL of patients with different diseases [101, 102], and is also an effective tool for evaluating the QoL of patients with IPF [103]. It consists of 8 domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Among them, PF, GH, RP, and BP are classified as physical component summary (PCS), VT, SF, RE, and MH are classified as mental component summary (MCS). The score range of each domain is 0 to 100, with higher scores indicating better QoL.

KBILD

Fourteen studies reported KBILD scores, which include the Psychological, Breathlessness/Activities, and Chest Symptoms domains, scores range from 0 to 100, with higher scores indicating better QoL [104].

SGRQ-I

The SGRQ-I, a disease-specific questionnaire fof IPF, was reported by five studies. Like the SGRQ, the SGRQ-I is also divided into three domains, with higher scores in each domain indicating worse QoL [105, 106].

Other instruments

Four studies reported the LCQ, which mainly evaluates the degree of cough in patients. It covers three physiological, psychological and social domains. Each domain score ranges from 1 to 7, with a higher score indicating better health of patients [107]. Five studies reported the UCSD-SOBQ, which consists of 24 items across two domains, with scores ranging from 0 to 120. The higher the score is, the more severe the degree of shortness of breath. Four studies reported the SF-12, which like the SF-36, also includes 8 domains, with scores ranging from 0 to 100, and health status was positively correlated with the score [108]. Two studies reported the WHOQoL-100, which includes 6 domains and 24 aspects, namely the physical, psychological, independence, social relations, environment, and spiritual/religious/personal beliefs domains, and the score in each domain is positively related to the QoL [109]. Two studies reported ATAQ-IPF scores, which included 74 items in 13 domains, with higher scores indicating poorer QoL in patients with IPF [89].

Quality assessment

The overall quality of the literature was excellent for studies reporting HSUV, whereas a sample size less than 100 and failure to describe follow-up were the major downgrading factors. A total of twenty-nine studies with cohort or case-control studies used the NOS to evaluate literature quality, with twenty-four and five studies classified as high quality and medium quality, respectively. Nineteen cross-sectional studies used AHRQ, of which seventeen were of high quality and the others were of medium quality. The quality of the included studies was generally high. Detailed information about the quality assessment is shown in Supplement Table 4.

Results of the meta-analysis

EQ-5D

A total of sixteen studies involving 4705 participants analyzed the HSUV of IPF patients, with an overall estimated mean utility of 0.75 (95% confidence interval [CI]: 0.72–0.79) (Fig. 4). Seventeen studies covering 6044 patients performed a pooled analysis of the EQ-5D VAS scores, which was 66.88 (95% CI: 63.75–70.01) (Fig. 5).

Owing to significant heterogeneity between studies($I^2 \geq 50\%$), we conducted subgroup analyses on the basis of disease severity, region and country (Figs. 4 and 5), which revealed that none of the above factors were sources of heterogeneity. We adopted sensitivity analysis to verify the robustness of the study, which demonstrated that our results had considerable credibility (Supplementary Fig. 8).

SGRQ

Thirty-one studies including 6150 patients reported total SGRQ scores, with the pooled mean score estimated through random effects model meta-analysis being 45.28 (95% CI: 41.10-49.47) (Fig. 6). Twenty studies involving 4875 patients reported QoL in the symptom domain, with a meta-analysis result of 50.99 (95% CI: 47.72–54.26); 21 studies involving 5055 individuals described QoL in the activity domain, with a pooled scores of 60.59 (95% CI: 55.84–65.33); and 20 studies covering 4875 invalid patients recorded the QoL in the impact domain, with a random effects pooled analysis result of 38.55 (95% CI: 34.17–42.92) (Supplemental Table 5).

Subgroup analysis of each SGRQ domain was conducted according to disease severity, income level, region, and country. The results revealed that the QoL score of patients with moderate IPF, upper-middle income levels and Chinese ethnicity were relatively lower in terms of all domains and total SGRQ scores (Supplement Table 5). The sensitivity analysis was conducted via a one-by-one

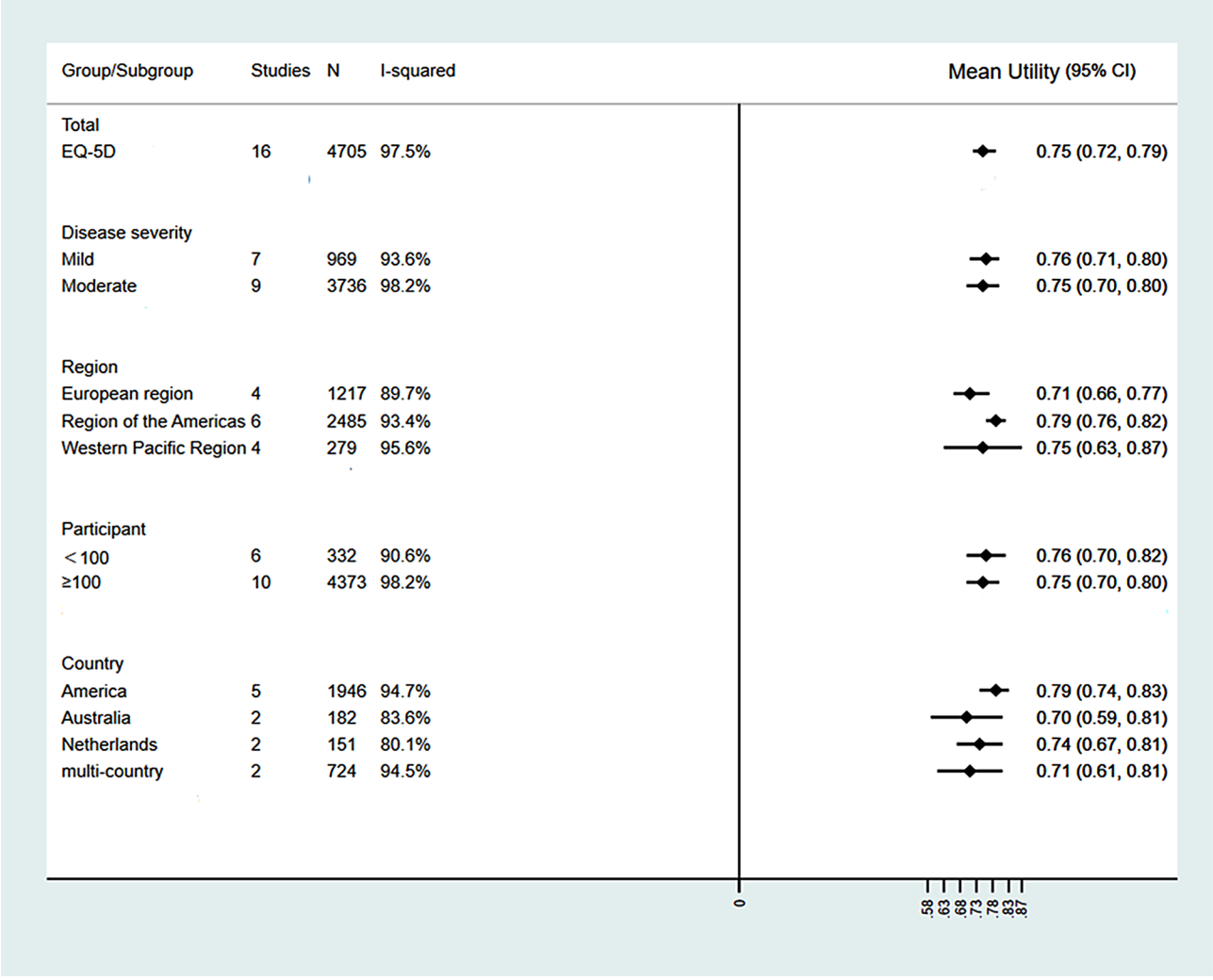

Fig. 4 Forest plot of mean utility, using the EQ-5D

exclusion method. The results revealed that the effect size of each domain and the total SGRQ score were similar, indicating that the results were stable (Supplementary Fig. 8).

SF-36

Fifteen studies covering 1866 patients were pooled, limited by high heterogeneity, and pooled mean scores of the PCS and MCS estimated via random effects model meta-analysis were 36.70 (95% CI: 32.98–40.41) and 48.99 (95% CI: 47.44–50.55), respectively (Fig. 7). The scores of the eight domains are recorded in Supplement Table 6.

On the basis of the basic characteristics of the included studies, we performed subgroup analyses for disease severity and region. Combining the analysis results of all the domains, we found that moderate IPF patients generally had low QoL, especially in the PH and RP domains, and the PCS. With the aggravation of disease, patients have different degrees of deterioration in various indicators (Supplemental Table 6). Sensitivity analysis revealed that studies influencing the effect size had the commonality of small sample sizes and mild patients, but the overall effect size did not change significantly (Supplementary Fig. 8).

KBILD

The pooled analysis of the total KBILD score was 58.31 (95% CI: 55.43–61.19) for 1489 patients in thirteen studies (Fig. 8). The QoL scores in the psychological, breathlessness/activities, and chest symptoms domains were 57.00(95% CI: 52.87–61.12), 43.82(95% CI: 39.19–48.45) and 70.11(95% CI: 65.60-74.61), respectively. These results also proved that patients with IPF have significantly restricted in breath.

Subgroup analysis of each domain according to disease severity and region revealed that patients with moderate IPF and those in the European region had poor QoL, which was consistent with the results of other analyses

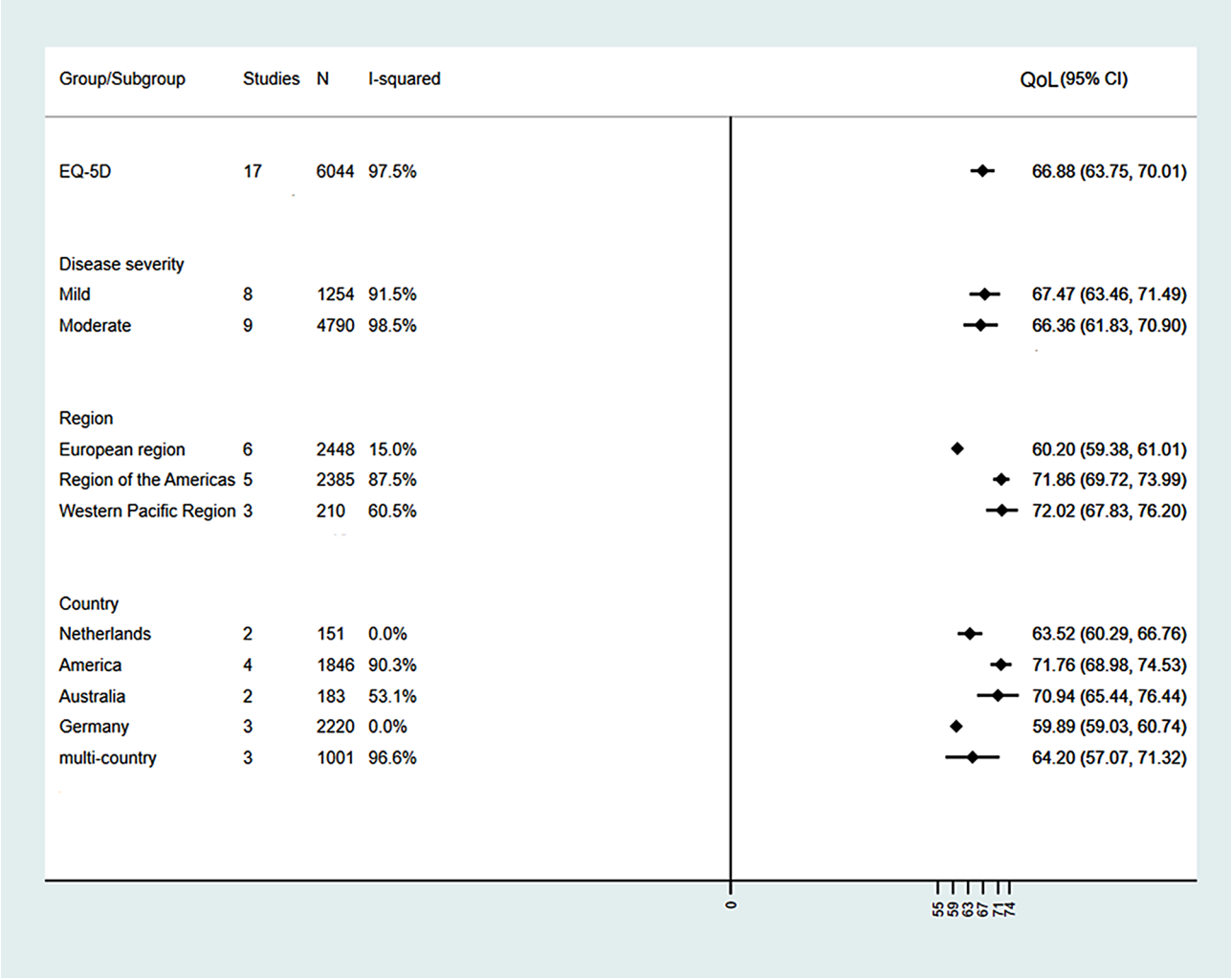

Fig. 5 Forest plot of QoL, using the EQ-5D VAS instrument

(Supplemental Table 7). Sensitivity analysis revealed that all studies were roughly distributed on both sides of the vertical line, with little impact on the total pooled effect size, and the analysis results were robust and reliable (Supplementary Fig. 8).

SGRQ-I

Three studies involving 225 patients with IPF were included in the quantitative analysis, and the results revealed that the total score of SGRQ-I was 40.38 (95% CI: 28.81–51.96). The pooled score for the symptom, activity, and inactive domains were 49.10 (95% CI: 42.34–55.86), 59.63 (95% CI: 47.51–71.76) and 28.40 (95% CI: 17.63–39.16), respectively (Supplemental Fig. 2).

LCQ

Four studies with 171 participants were included in the analysis, and the pooled total LCQ score was 16.09 (95% CI: 15.45–16.74). Two studies reported physical, psychological and social domain scores, and the QoL scores of the meta-analysis were 5.24 (95% CI: 4.99–5.49), 5.14 (95% CI: 4.80–5.48) and 5.67 (95% CI: 5.37–5.96), respectively. (Supplemental Fig. 3)

Other instruments

Two studies reported scores in each domain of the ATAQ-IPF, with the results indicating that patients had the worst QoL in the dyspnea, emotional well-being, and finance domains (Supplemental Fig. 4). Two studies reported WHOQoL-100 scores, and the quantitative analysis revealed low scores in all the fields (Supplemental Fig. 5). The results of the SF-12 analysis were similar to those of the SF-36, and the patients' comprehensive scores in the PF domain and PCS were lower (Supplemental Fig. 6). The pooled result of the total UCSD-SOBQ score was 45.05(95% CI: 41.56–48.55) (Supplemental Fig. 7).

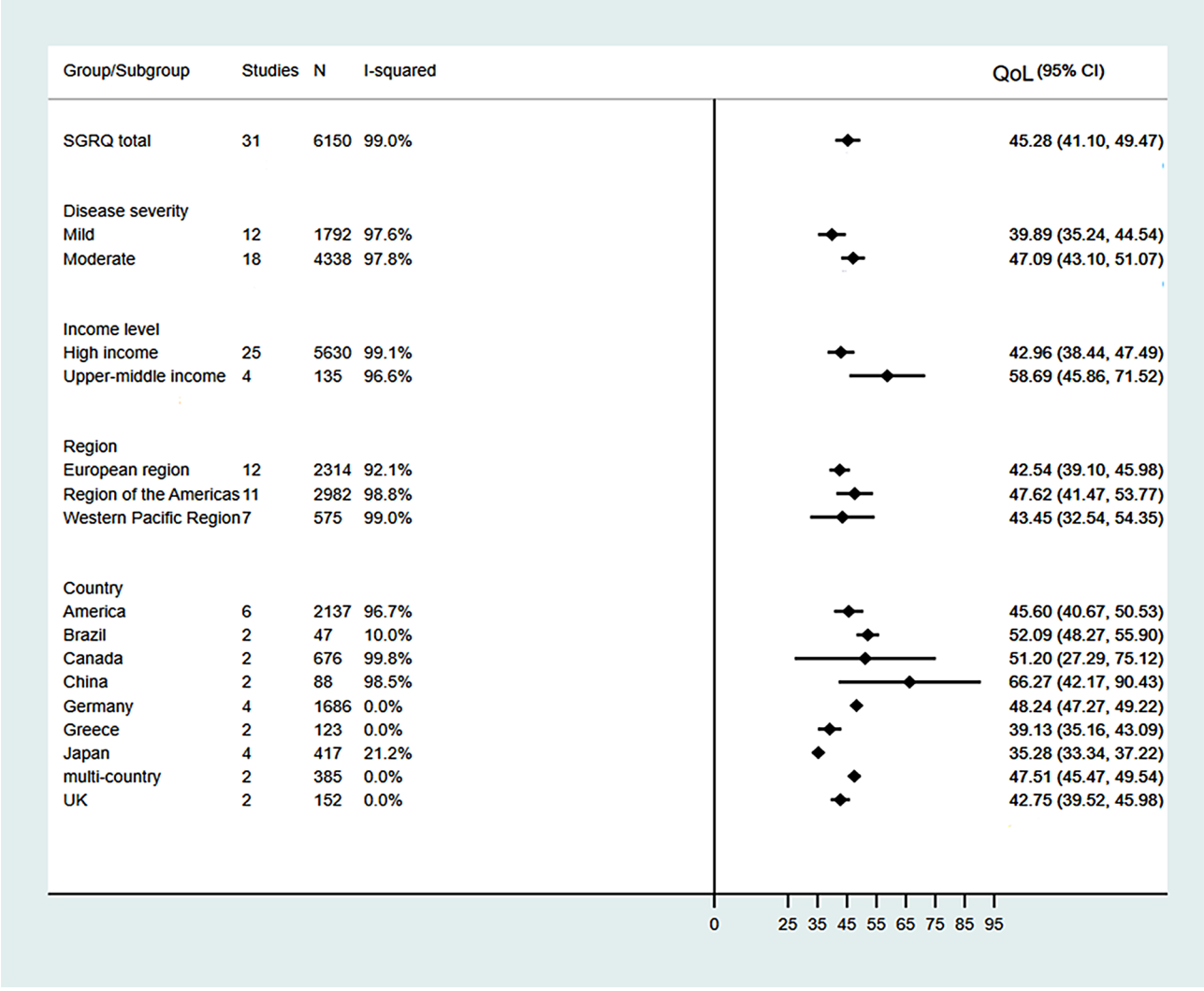

Fig. 6 Forest plot of QoL, using the SGRQ instrument

Publication bias

Funnel plots and Egger's tests were used to evaluate publication bias for the outcome indicators with more than 10 studies included, including the EQ-5D score, SGRQ total score and each domain, the PH domain of the SF-36, and the KBILD total score. Although the results showed that the funnel plot had some visual asymmetry, all the outcome indicator Egger's test results were greater than 0.05 except for the total SGRQ score (t=2.80, P=0.009) (Supplementary Fig. 9). For the studies with publication bias, there was no significant change in the results after correction via the trimming and filling method, which further demonstrated that our analysis results were statistically reliable.

Discussion

Our systematic review and meta-analysis of HRQoL and HSUV in patients with IPF revealed that the pooled estimates of HRQoL and HSUV in IPF patients were generally poor [110, 111], whether in the domains of symptoms, activity, or psychology, and that the HRQoL of patients relatively decreased with the deterioration of the disease. Compared with those in high-income populations or developed countries, HRQoL and HSUV are worse in patients with upper-middle income levels or in developing countries. In addition, there are diverse instruments for measuring HRQoL and HSUV in IPF patients, and different HRQoL and HSUV measurement tools may lead to uncertainty in the results, which demonstrates the importance of standardized HRQoL and HSUV assessment tools. Our study confirms that IPF significantly affects the HRQoL and HSUV of patients, providing comprehensive data support and information

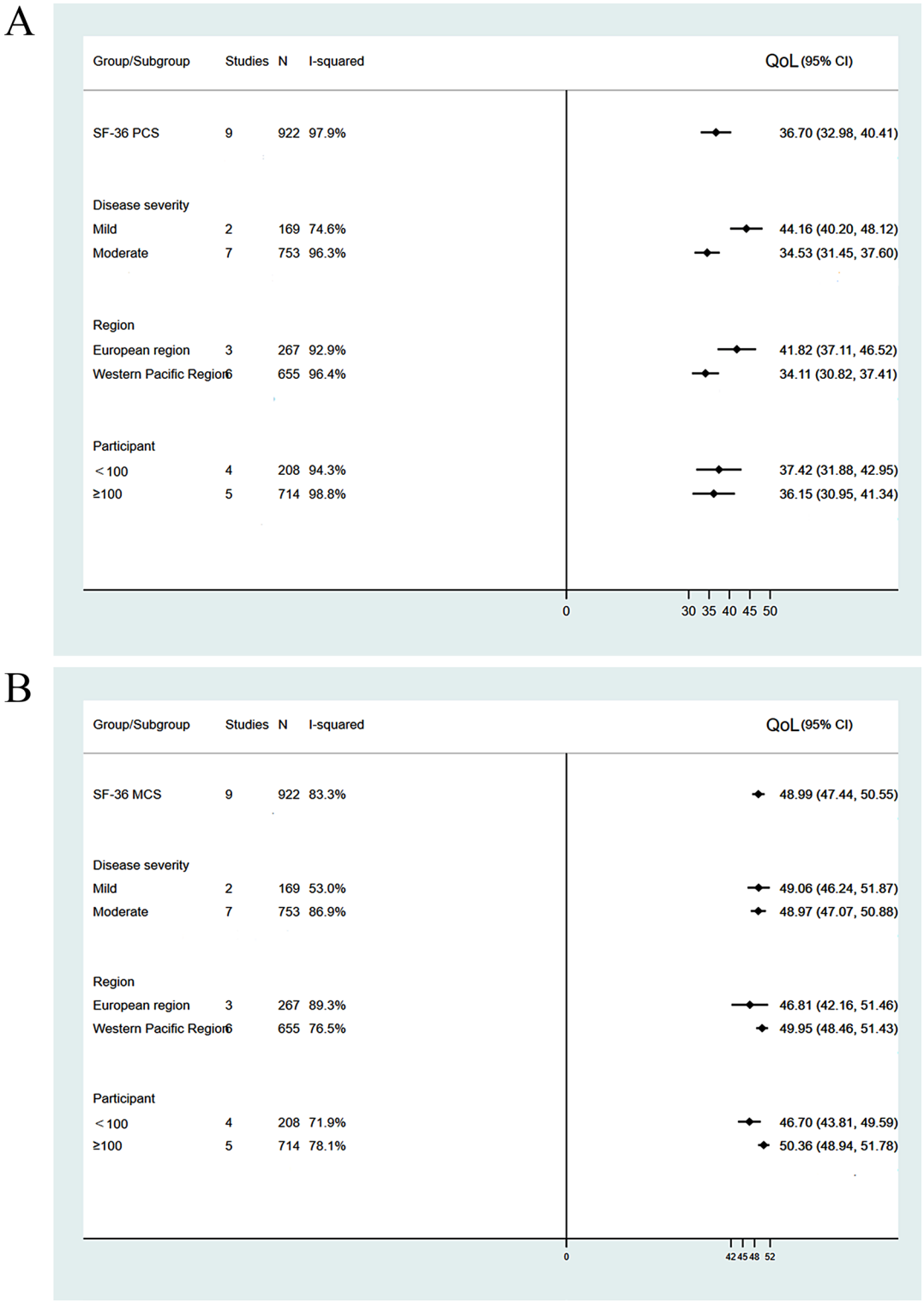

Fig. 7 (**a**) Forest plot of QoL, using the SF-36 PCS, (**b**)Forest plot of QoL, using the SF-36 MCS

sources that can be used to guide clinical and economic evaluation in the future.

The quantity and quality of the included studies in our analysis were high, and most of them were published in the past decade, which is closely related to the increasing number of patients and attention given to IPF. At present, the treatment for IPF is extremely limited [12], as IPF is an incurable disease, improving patients' HRQoL has

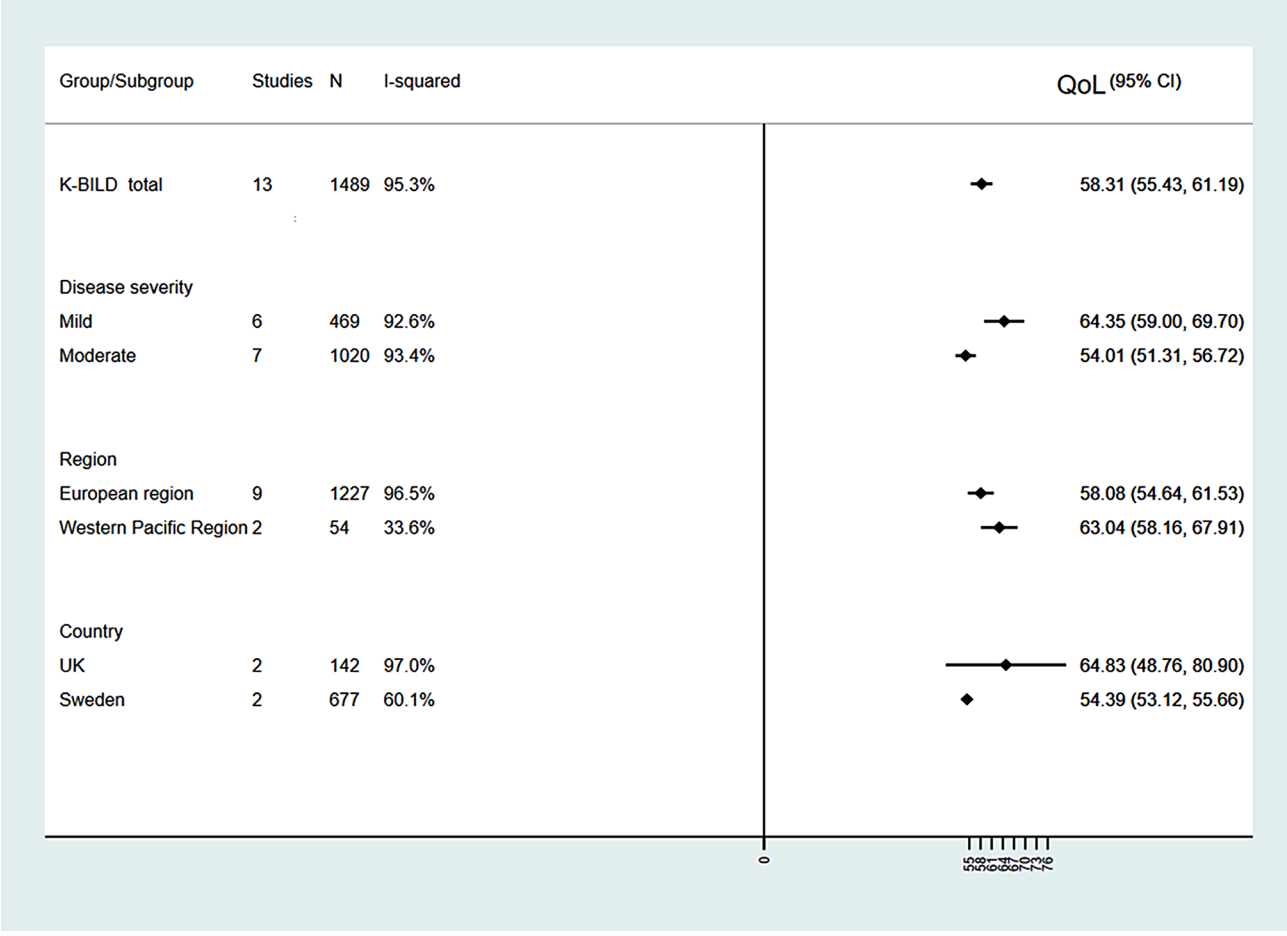

Fig. 8 Forest plot of QoL, using the KBILD instrument

become an important clinical goal. We summarized and analyzed existing HRQoL studies, indicting that HRQoL plays a crucial role in the comprehensive management of IPF patients. Our study revealed that a generic instrument is the primary method for measuring HRQoL in IPF patients, with the SGRQ, EQ-5D, SF-36 and KBILD being common, and the EQ-5D is a major measurement tool for the HSUV. As a generic instrument widely used worldwide, quantitative analysis of the EQ-5D provides basic data support for the pharmacoeconomic evaluation and health technology evaluation of IPF-related treatments in the future.

This study revealed that the HSUV of IPF patients was 0.75, which is similar to previous meta-analysis results, indicating that IPF can affect the HSUV of patients [18]. We also performed subgroup analyses for disease severity, and regional, and country factors and reported that the HSUV decreased with disease severity. This is different from the analysis results of Cox IA et al. [18], who provided opposite evidence. This could be attributed to the fact that they included fewer studies with mild IPF (only two studies were analyzed), which affected the stability and reliability of the synthetic results. Furthermore, they mixed the data of HSUV from other interstitial lung diseases, which also interfered with the power of the test. Moreover, subgroup analysis revealed that the HSUV of IPF patients in Australia was lower, which was associated with the fact that IPF patients included in the analysis were older (over 70 years) and had multiple comorbidities [112]. Moreover, the HSUV confidence range obtained in our meta-analysis was more concentrated, which also indicates that our results are accurate.

EQ-5D VAS analysis revealed that patients with IPF had worse HRQoL than did those with other diseases [111]. Subgroup analysis revealed a lower overall HRQoL in Germany, possibly because only moderate IPF patients were included in the analysis. However, there is no direct evidence that the measurement properties of the EQ-5D are related to IPF [113], thus, the use of the EQ-5D to measure the HRQoL of IPF patients may not be the best choice. Moreover, our study revealed that the EQ-5D was mostly used simultaneously with other generic assessment instruments such as the SGRQ and SF-36.

A suitability evaluation of the SGRQ and SF-36 in IPF patients revealed remarkable sensitivity, which indicated that these two scales are powerful tools for evaluating HRQoL in patients with IPF [103, 114, 115]. The generic SGRQ instrument was used to evaluate the QoL of patients in three domains, and the results confirmed that the symptom and activity domains of patients were relatively limited. With the deterioration of disease, the QoL scores of patients decreased in all domains, which was similar to previous results [42, 57]. Progressive worsening dyspnea affects all aspects of patients' prognosis [116]. Restrictive ventilation dysfunction can lead to hypoxemia or respiratory failure, which is a crucial cause of acute exacerbation/death in patients. Our subgroup analysis also revealed that IPF patients with upper-middle income levels had relatively lower QoL scores than did those with high income levels, which was comparable to the results of the analysis by country classification (China and Brazil had lower QoL scores in all domains). An analysis on the clinical efficacy and cost-effectiveness of IPF showed that compared with best supportive care, drug therapy greatly increases the cost [117], and the enormous financial burden makes it difficult to maintain medication for IPF patients in less developed regions/countries [11]. A previous study revealed that the risk of hospitalization of patients with IPF was 134% greater (48.7% vs. 20.8%) than that of non-IPF patients of the same age, and the annual treatment cost for IPF patients was as high as 2 billion dollars [118]. The SF-36 is divided into eight domains, which can be classified into the PCS and the MCS. Compared with COPD [119] and asthma [120] patients, IPF patients had lower scores in all domains, which also indicated that IPF patients had worse HRQoL. The results of the subgroup analysis were similar to those of the SGRQ, further confirming that disease severity and income level affect patients' HRQoL. KBILD is the first clinical evaluation tool developed to evaluate disease-specific symptoms in patients with pulmonary interstitial disease [36, 63]. Our analysis revealed that IPF patients had lower scores in the breathlessness/activities domain, which is consistent with typical disease symptom.

Disease-specific assessment tools have high sensitivity to diseases and can reflect minute changes in HRQoL in patients more accurately and comprehensively [69]. The IPF disease-specific measurement tools used for quantitative synthesis in our study include the SGRQ-I and ATAQ-IPF. The results of the SGRQ-I analysis were similar to those of the SGRQ, but the SGRQ-I is more instructive in the evaluation of HRQoL in IPF patients [50]. ATAQ-IPF analysis revealed particularly low scores in the dyspnea, emotional well-being, cough, and finance domains. This questionnaire is based on various aspects of an individual's QoL evaluation, and there is a significant correlation between its scores and other indicators [121], which enhances the reliability of the questionnaire to some extent. Unfortunately, owning to the limited number of included studies, the results should be treated with caution. Nevertheless, on the basis of the the analysis results of the above measurement tools, we can still obtain conclusive evidence that IPF affects various aspects of patient HRQoL.

This study quantitatively analyzed HRQoL in IPF patients, the number of included studies was large, the sample size was substantial, the quality of the literature was high, the subgroup information was relatively complete, the data analysis was comprehensive, and the results were reliable. Despite its strengths, our review also has the following limitations. First, given that other measurement tools for HSUV were applied fewer than twice and could not be used for quantitative analysis, our study analyzed only the EQ-5D. Second, the heterogeneity among the included studies was high, and subgroup analysis also failed to reduce the differences, which affected the stability of the results. Third, owing to incomplete/missing reports on comorbidities, smoking status, age, time since disease diagnosis, medication treatment, sex and other information in the included studies, our study failed to clarify its impact on HRQoL. Finally, most of the studies were conducted in developed countries, and insufficient attention has been given to HRQoL in developing countries, which may have exaggerated the results.

Conclusion

This study systematically evaluated sixty-nine studies on HRQoL and HSUV in IPF patients, providing pooled estimates of HRQoL and HSUV in IPF patients, and revealed that HRQoL and HSUV are significantly lower than population norms. Disease severity and income level may be factors affecting patients' overall HRQoL and HSUV, suggesting that attention should be given to the comprehensive management of disease. In addition, diverse HRQoL measurement tools lead to uncertainty in the results, and research on the optimal evaluation tool for disease should be strengthened in the future. Our study provides high-quality comprehensive evidence for the HRQoL and HSUV of IPF patients, which can be used to guide clinical and economic evaluations in the future.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12955-024-02326-y.

Supplementary Material 1: Appendix 1 Relevant information and table results. Supplementary Table 1: Search strategies. Supplementary Table 2: Citations of excluded full texts.Supplementary Table 3: Studies involving instruments included in the meta-analysis. Supplementary Table 4: Results of quality assessment. Supplementary Table 5: Results of each domain of QoL in SGRQ. Supplementary Table 6: Results of each domain of QoL in SF-36. Supplementary Table 7: Results of each domain of QoL in KBILD.

Supplementary Material 2: Appendix 2 Relevant information and figure results. Supplementary Fig. 1: Summary of HRQoL instruments used in studies. Supplementary Fig. 2: Forest plot of QoL, using the SGRQ-I instrument. Supplementary Fig. 3: Forest plot of QoL, using the LCQ instrument. Supplementary Fig. 4: Forest plot of QoL, using the ATAQ-IPF instrument. Supplementary Fig. 5: Forest plot of QoL, using the WHOQoL instrument. Supplementary Fig. 6: Forest plot of QoL, using the SF-12 instrument. Supplementary Fig. 7: Forest plot of QoL, using the UCSD-SOBQ instrument. Supplementary Fig. 8: Sensitivity analysis using the leave-one-out method of instruments adopted in quantitative analysis. Supplementary Fig. 9: Funnel plot showing the effect of instruments used in more than ten studies.

Supplementary Material 3: Appendix 3 PRISMA Checklist. PRISMA-checklist was adopted to normalize the report of this overview, in which the page numbers of the content were detailed.

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Author contributions
GX Z and SY L contributed to study conception, literature retrieval, bias assessment and interpretation. GX Z wrote the main manuscript. GX Z and Y L contributed to data extraction and analysis. Y L and ZZ F contributed to interpretation of data and chart production. SY L and JS L contributed to critical review and substantive revised it. All the authors reviewed the manuscript and approved it its submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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