



## Early View

Review

# Mortality and survival in idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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## **Mortality and survival in idiopathic pulmonary fibrosis: a systematic review and meta-analysis**

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### **Take-Home Message**

Mortality of IPF varied worldwide from approximately 0.5 to 12 per 100,000 population per year since 2000 and survival of IPF did not change before 2010, with then an improvement, which can be attributable to multiple factors.

## ABSTRACT

**Background:** There are substantial advances in diagnosis and treatment for idiopathic pulmonary fibrosis (IPF), but without much evidence available on recent mortality and survival trends.

**Methods:** A narrative synthesis approach was used to investigate the mortality trends, then meta-analyses for survival trends were carried out based on various time periods.

**Results:** Six studies reported the mortality data for IPF in 22 countries, and 62 studies (covering 63,307 patients from 20 countries) reported survival data for IPF. Age-standardised mortality for IPF varied from approximately 0.5 to 12 per 100,000 population per year after year 2000. There were increased mortality trends for IPF in Australia, Brazil, Belgium, Canada, Czech Republic, Finland, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Spain, Sweden, and UK, while Austria, Croatia, Denmark, Romania, and US showed decreased mortality trends. The overall 3-year and 5-year cumulative survival rates (CSRs) were 61.8% (95% CI, 58.7-64.9;  $I^2=97.1\%$ ) and 45.6% (95% CI, 41.5-49.7;  $I^2=97.7\%$ ), respectively. Prior to 2010, the pooled 3-year CSRs was 59.9% (95% CI, 55.8-64.1;  $I^2>95.8\%$ ), then not significantly ( $P=0.067$ ) increased to 66.2% (95% CI, 62.9-69.5;  $I^2=92.6\%$ ) in the 2010s decade. After excluding three studies in which no patients received antifibrotics after year 2010, the pooled 3-year CSRs significantly ( $P=0.039$ ) increased to 67.4% (95% CI, 63.9-70.9;  $I^2=93.1\%$ ) in the 2010s decade.

**Discussion:** IPF is a diagnosis associated with high mortality. There was no observed increasing survival trend for patients with IPF before year 2010, with then a switch to an improvement, which is probably multifactorial.

**Key Words:** antifibrotic medication; IPF; mortality; survival

## **Mortality and survival trends of IPF**

### **Background**

Idiopathic pulmonary fibrosis (IPF), although relatively uncommon, is a progressive interstitial lung disease, with poor prognosis and high mortality risk [1]. Since the affected population is largely over 65 years old with a male predominance, in the more elderly population more specifically the impact of IPF is considerably greater [2]. Estimated incidence rates of IPF showed increased trends ranging from approximately 3 to 9 per 100,000 population per year between 1998 and 2012 in Europe and North America [3]. Only a limited number of ecological studies [4] (i.e., at population level) of the mortality of IPF have been published worldwide.

A systematic review [3] reported only eight ecological studies and found that estimated mortality rates of IPF ranging from around 1 to 14 per 100,000 population per year in various countries between 1979 and 2012. However, the worldwide variation of mortality rates for IPF reported by Hutchinson et al. [3] in 2015 may have been influenced by widespread use of differing International Classification of Diseases (ICD) codes (such as ICD-8 517, ICD-9 515, ICD-9 516.3 and ICD-10 J84.1), death certificates using either IPF as underlying cause of death or as part of multi-cause deaths, and not differentiating between crude and age-standardised disease rates. Most recently, Khor et al. [5] in 2020 conducted a systematic review and meta-analysis of prognosis for patients with IPF in cohort studies or in the control arm of recent drug trials, followed for at least 12 months who were not treated with antifibrotic therapies. Although the mean survival time of patients with IPF has been estimated as 4 years from diagnosis [5], survival trends for IPF in various time periods are not well described.

Recently, management guidelines for diagnosis [6, 7] has been updated, and treatment of IPF now focus on the new antifibrotic medications (pirfenidone and nintedanib) [8, 9] that may slow progression of the disease but without much evidence available on mortality or any overall impact on survival rates. We aimed to update the last systematic review in 2015 [3] and investigate the recent mortality and survival trends for IPF.

### **Methods**

The protocol of this study was registered at PROSPERO (registration number: CRD 42020151288; <https://www.crd.york.ac.uk/Prospero/>) on 18 September 2019. During the manuscript review process, we were advised some valid changes to update the literature search, exclude conference abstracts, and conduct a meta-analysis of survival using various diagnostic criteria from the protocol. This systematic review was reported in accordance with the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10], and the PRISMA Checklist was presented in Table S1.

### ***Search strategy and databases***

The search strategy involved several combinations of “idiopathic pulmonary fibrosis”, “mortality”, “survival” and their synonyms. Detailed search strategy was outlined in Table S2. Databases including PubMed, EMBASE (via Ovid) and Scopus were searched for eligible studies. Non-English language papers were translated using Google translator platform. Further, a key word search of Google Scholar was performed to detect potential additional studies. The searches included all studies published on or before 1<sup>st</sup> November 2021. The reference lists from the included studies and two previous systematic reviews [3, 5] were reviewed.

### ***Study selection and eligibility***

Studies that met the following criteria were included based on “PICOS” algorithms:

- 1) Patients with the diagnosis of IPF: mortality statistics using ICD-10 J84.1 (other interstitial pulmonary diseases with fibrosis) as the diagnostic criteria and regarding IPF as the underlying cause of death (UCD); survival statistics using ICD codes or clinical guidelines as diagnostic criteria.
- 2) Interventions: no specific requirement.
- 3) Comparators: no specific requirement.
- 4) Outcomes: annual mortality rates for IPF at a population-based level; 3-year or 5-year cumulative survival rates (CSRs) for IPF.
- 5) Study designs: ecological studies for mortality rates; ecological or cohort studies, followed for at least 3 years for CSRs.
- 6) Without language limitations.

Exclusion criteria were listed as follows:

- 1) Participants did not represent the general population of patients with IPF (e.g., focused only on patients with IPF with acute exacerbations).
- 2) Studies without reporting the annual mortality rates or CSRs of IPF, or without required data to calculate these outcomes.
- 3) Survival time reported from onset of symptoms to death without reporting survival time from diagnosis, as used in many studies.
- 4) Duration of follow up less than 3 years.

- 5) Death certificates using IPF as part of multi-cause deaths.
- 6) Randomized controlled trials (RCTs), reviews, letters, commentaries, editorials, case reports, and conference abstracts.
- 7) Non-human studies.

The screening process for eligible studies was performed using the Covidence (Veritas Health Innovation, Melbourne, Australia; <https://www.covidence.org>). Firstly, all search results from the databases were imported into Covidence to remove the duplicates. Secondly, using just titles and abstracts of records, potentially eligible studies were assessed by two co-authors (QZ and IAC) independently, based on inclusion criteria. Thirdly, full text studies were further screened by the same two co-authors independently, based on exclusion criteria. All discrepancies were discussed with a third co-author (AJP) to obtain consensus.

### ***Quality assessment***

One co-author (QZ) assessed each included study according to the established tool, and the other co-author (IAC) independently validated the results. No validated study appraisal for evaluating quality of epidemiological studies of IPF exists, so we summarized the various criteria used by previous studies [3, 7, 11-15] and established a new tool with a total of 26 items for quality assessment, which includes two parts: criteria for case definition of IPF (13 items), and study methodology for epidemiological studies (13 items). Detailed method of quality assessment was presented in Table S3, and the outcomes of quality score were expressed as percentage with interquartile range (IQR).

### ***Data extraction***

For data extraction, one co-author (QZ) extracted all specific information including: first author, year of publication, median year studied where patients were included across multiple years, country, sample size, age, sex (percentage of males), ethnicity, smoking (percentage of patients with smoking history), pack-years of smoking, family history of interstitial lung diseases (ILDs), forced vital capacity (FVC) % predicted, diffusing capacity of the lung for carbon monoxide ( $D_{LCO}$ ) % predicted, body mass index (BMI), six minutes walking testing distance (6MWD), adequacy of case definition, percentage of patients without any therapy, percentage of patients with now recognised harmful therapies, percentage of patients with new antifibrotic therapies, source of data (such as from single centre, national registry, and national database), duration of follow-up, study design, annual country-specific mortality rates, and survival-related outcomes (3-year or 5-year CSRs). Table S4 shows development of diagnostic criteria

for IPF based on ICD codes. Although ICD-10 code J84.1 may include other idiopathic interstitial pneumonias (IIPs), it is the most specific code for IPF to present global mortality statistics in the study timeframe [3]. Therefore, we used the cut-off of year 2000 to show recent mortality trends for IPF. The cut-off of year 2010 was used to describe survival trends for IPF corresponding to substantial advances in diagnosis [7] and treatment [8, 9] for IPF after year 2010. Studies were either distributed to antifibrotics group if they reported participants explicitly taking antifibrotics, or to non-antifibrotics group if they reported other therapies. The classification of antifibrotics (effective therapies), and non-antifibrotics (no, ineffective, or harmful therapies) were determined according to Richeldi et al. study [2]. All data from individual studies were entered into a pre-designed Microsoft Excel Worksheet, and then were validated by another co-author (JAC). Again, all discrepancies were discussed and resolved with the third co-author (AJP) by consensus.

### *Statistical analyses*

STATA (STATA 16.1, Stata Corp, College Station, Texas, USA) was used for all data analyses and graphing. A narrative synthesis approach was used for the current mortality trends. The random-effects model was selected and applied to summarise the overall effective values of 3-year and 5-year CSRs considering the high between-studies heterogeneity (defined as Higgins's  $I^2 > 50\%$ ) [16]. Three-year or 5-year CSRs were reconstructed from Kaplan-Meier survival curves if studies not reported data directly [17]. If the 95% confidence intervals (CIs) of CSRs were not provided, the following formula was used for calculating:  $p \pm 1.96 * \sqrt{\left(\frac{p(1-p)}{n}\right)}$ , in which  $p$  was defined as CSRs in each included study and  $n$  represented the sample size [18]. Non-overlap of the 95% CIs between two subgroups indicates statistical significance, and meta-regression techniques based on random-effects models were used to further test the difference between subgroups if there is a small overlap of the 95% CIs [19].

Survival trends for IPF were carried out based on various time periods (before 2010, and 2010s). Subgroup analyses for survival outcomes of IPF by various diagnostic criteria (2011 ATS/ERS/JRS/ALAT guideline, 2000 or 2002 ATS/ERS guideline, and other criteria) and treatment (non-antifibrotics, and antifibrotics) were conducted to show diagnostic and therapeutic advances, respectively. Sensitivity analyses for survival outcomes by excluding the studies with extreme data were also performed. In addition, univariate meta-regression was used to investigate the association between age at diagnosis and median year studied.

Publication bias and small study effects were explored by using funnel plots and Egger's test [20].

## **Results**

### ***Eligible studies***

A total of 14,170 records were retrieved from database searching and hand searching (Figure 1). After excluding duplicates, 9,588 potentially relevant studies remained for further title and abstract screening. N=348 studies were included and assessed for eligibility, and 68 studies [21-88] were finally included in the qualitative analyses. However, only 62 studies [27-88] with sufficient data were eligible for the meta-analyses.

### ***Study characteristics and quality assessment***

Table 1 summarises the characteristics of included studies reported mortality for IPF. Six studies [21-26] reporting mortality of IPF between 2000 and 2019 were all ecological studies from 22 different countries, with 82% (n=18) from Europe (Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Romania, Spain, Sweden, and UK), two from North America (USA and Canada), one from Oceania (Australia), and one from South America (Brazil). Data on mortality statistics for IPF were from national statistics agencies [21-23, 26], WHO mortality database [25], and regional statistics agencies [24], respectively.

Table 2 shows the characteristics of included studies reported survival outcomes for IPF. The 62 studies [27-88] reporting survival outcomes of IPF between 1964 and 2017 (these dates indicating the median year of the studies being undertaken) covering 63,307 patients with IPF from 20 different countries, with 90% (n=56) of these studies conducted in Japan (n=9), Korea (n=8), Europe (n=19) and North America (n=20). Most of all survival studies (n=58) were cohort studies. One study [68] including two independent cohorts reported survival outcomes of IPF.

In terms of quality assessment, a detailed scoring for each study has been provided in the Online Supplement (Table S5). The median index of quality score for cohort studies (69.2%) was higher than ecological studies (50.0%) due to cohort studies had robust case definition criteria (clinical guidelines) compared to ecological studies (ICD codes). Median index of the quality score was 69.2% (IQR, 65.4-73.1) for all included studies (Figure S1). Only one study [46]



was low quality, while 68% (n=46) and 31% (n=21) of all included studies were ranked as moderate and high level of quality, respectively.

### ***Mortality trends for IPF in various countries***

There were 6 ecological studies reporting mortality rates of IPF since the year of 2000 used a relatively narrower case definition of IPF (ICD-10 J84.1) and regarded IPF as the UCD. These data suggested that crude mortality rates have increased from 2 to 7 per 100,000 population per year in five regions (England and Wales, Australia, Canada, Spain, and USA) between 2000 and 2012 (Table 1). Age-standardised mortality for IPF varied from approximately 0.5 to 12 per 100,000 population per year in 22 different countries, being lowest in Brazil, Croatia, Czech Republic, Lithuania, Poland, and Romania, while being highest in UK. There were increased mortality trends for IPF in Australia, Brazil, Belgium, Canada, Czech Republic, Finland, France, Germany, Hungary, Italy (males aged  $\geq 85$  years only), Lithuania, Netherlands, Poland, Portugal, Spain, Sweden, and UK, while Austria (males only), Croatia (males only), Denmark, Romania (females only), and US (between 2004 and 2017) showed decreased mortality trends.

### ***Survival trends for IPF in various time periods***

The overall 3-year CSRs (based on 59 studies with 62,069 patients) and 5-year CSRs (based on 50 studies with 56,774 patients) were 61.8% (95% CI, 58.7-64.9;  $I^2=97.1\%$ ), and 45.6% (95% CI, 41.5-49.7;  $I^2=97.7\%$ ), respectively (Table 3). Prior to 2010, the pooled 3-year and 5-year CSRs were 59.9% (95% CI, 55.8-64.1;  $I^2>95.8\%$ ) and 44.1% (95% CI, 39.9-48.3;  $I^2>93.7\%$ ), then increased to 66.2% (95% CI, 62.9-69.5;  $I^2=92.6\%$ ) and 49.3% (95% CI, 42.7-55.9;  $I^2=97.7\%$ ), in the 2010s decade, respectively. However, test for difference between two subgroups (before 2010 vs. 2010s) was not statistically significant ( $P=0.067$  for 3-year CSRs and  $P=0.203$  for 5-year CSRs). After excluding three studies [44, 60, 61] in which no patients received antifibrotics after year 2010, the overall 3-year and 5-year CSRs remained consistent, while the pooled 3-year CSRs significantly increased to 67.4% (95% CI, 63.9-70.9;  $I^2 = 93.1\%$ ) in the 2010s decade after test for difference between two subgroups ( $P=0.039$ ). Figure 2 presents the pooled 3-year and 5-year CSRs remained consistently low before 2010, with then an improvement in the 2010s decade.

### ***Subgroup analysis by various treatment and diagnostic criteria***

Figure 3 presents the outcomes of the pooled 3-year and 5-year CSRs by the various pharmaceutical regimens. Patients taking antifibrotics (67.4%, [95% CI, 63.9-70.9];  $I^2 = 93.1\%$ )

had significantly ( $P=0.032$ ) higher pooled 3-year CSRs than those taking non-antifibrotics (59.8%, [95% CI, 59.8-63.8];  $I^2=95.5\%$ ). Similar trend was found for the 5-year CSRs (patients taking antifibrotics: 51.4% [95% CI, 44.1-58.7;  $I^2=97.9\%$ ] vs. those taking non-antifibrotics: 43.9% [95% CI, 39.9-47.8;  $I^2=93.4\%$ ]) ( $P=0.084$ ). In addition, there were no significant associations between various diagnostic criteria and CSRs, and those associations remained consistent after exclusion of 16 studies [27, 32, 39, 40, 43, 49, 50, 52, 55, 66, 68, 71, 74, 85, 86, 88] in which patients received antifibrotics (Table 4).

#### ***Association between mean age at diagnosis and median year studied***

There were 51 studies reporting mean (standard deviation, SD) age at diagnosis that significantly ( $P=0.002$ ) increased by 0.26 year (95% CI, 0.10-0.41) for each 1-year increase in the median year studied between 1980 and 2020. This association did not change dramatically after removing four outlier studies [31, 36, 84, 88] (the orange markers in Figure 4) in a sensitivity analysis.

#### ***Publication Bias***

Funnel plots (Figure S3) for assessing the influence of each included study on the overall meta-analysis estimates identified several outliers, but Egger's test found no evidence for publication bias for the 3-year CSRs (bias = 0.25,  $P=0.854$ ) or 5-year CSRs (bias = -0.67,  $P=0.591$ ).

#### **Discussion**

We found that the age-standardised mortality rates for IPF ranged from 0.5 to 12 per 100,000 population per year after year 2000, carrying a burden as severe as several cancers including those of oesophagus, pancreas, and prostate, but without the same prominence in screening, management, surveillance, research, and disease control [89]. Our data suggest no increased survival trend for patients with IPF up to year 2010, while there might be an increase thereafter. Patients with IPF taking antifibrotics had significantly higher long-term survival compared to those not on antifibrotics, which reinforces the beneficial messages from drug-development studies, but this should be interpreted in the context of high heterogeneity.

The lack of age adjustment for much of mortality data has proved to be significant limitation. Therefore, we described the age-standardised mortality rates for IPF based on a narrower definition (ICD-10 J84.1) and UCD across various countries different from the previous systematic review [3]. We found that age-standardised mortality for IPF varied worldwide from various countries since 2000. There were increased mortality trends for IPF in Brazil [21],

Australia [22], Canada [22], and many European countries (Belgium, Canada, Czech Republic, Finland, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Spain, Sweden, and UK) with the exceptions of Austria, Denmark, Croatia, and Romania [24-26]. Hutchinson et al. [22] reported that there was an increased mortality trend (age adjusted for 2013 European population) in US ranging from 5.62 to 6.16 per 100,000 population per year between 2000 and 2010, while a more recent study [23] found a decreased mortality trend (age adjusted for 2000 US population) ranging from 4.22 to 3.64 per 100,000 population per year between 2004 and 2017, which may contribute to a decline in smoking or changes in other environmental and genetic factors.

Recently, Khor et al. [5] conducted a systematic review reporting a mortality of 69% beyond 5 years for patients with IPF without taking antifibrotics based on 170 included studies, and 34 of them were also included in current study. We had different study aims compared with Khor et al. because: 1) we summarized annual mortality rates for IPF based on population-based studies and presented the changing trends in various countries; and 2) we investigated survival trends over various time periods including both patients with and without antifibrotics.

The lack of evidence for the improvement in the survival trends of IPF up to year 2010 might be explained by two main causes. Firstly, the advanced populations and higher age at diagnosis were used in that earlier era. Nearly 90% of included studies reporting survival outcomes were from countries with ageing populations, with a mean age at diagnosis of IPF significantly increased over the past six decades. Secondly, routinely used immunosuppressive combination drugs were used for IPF in that earlier era. Cortisone was first used to treat IPF in 1948 [90] and several subsequent studies [91-93] purported to demonstrate that corticosteroids might improve lung function and prolong survival, so that it became the first-line therapy for IPF essentially from the 1950s. In 2012, multi-centre RCTs suggested the significant harmful effects and decreased survival on patients with IPF using the combination of prednisone, azathioprine and N-acetylcysteine compared to those using placebo [94]. Since then, the usage of steroid/immunosuppressive drug combinations rapidly reduced.

Shortly after the “downfall” of the established steroid/immunosuppressant era, in 2014, a substantial breakthrough was made for two antifibrotic drugs that had been confirmed to be effective in treating IPF through several multi-centres RCTs [8, 9]. In 2017, Costabel et al. [39] provided the long-term safety evidence for pirfenidone after following an open-label extension study of RCTs. We found that there may be potentially beneficial effects of antifibrotic therapy

on the long-term survival outcomes of patients with IPF, which was in accordance with the finding of a systematic review [95] including 8 RCTs and 18 cohort studies reported antifibrotic treatment might reduce the risk of all-cause mortality in IPF. However, we found such an association was not detected between diagnostic criteria and long-term survival outcomes of patients with IPF.

We can draw several clinical observations from our review. First, IPF carries mortality burdens as bad as several cancers, but with less attention being given to it in general, perhaps because it affects largely a more elderly population and is more insidious and less dramatic at onset. Second, our summaries for the mortality and survival of IPF internationally might help stimulate future studies to consider the issues about surveillance, disease control and development of new therapies. Third, the likely impact at a population level of harmful but widely used treatments in the past for IPF emphasises the vital importance of adequately powered RCTs in guiding IPF therapy. Further, there might be some signals emerging for an improvement in long-term survival related to the relatively newly available antifibrotic drugs for IPF.

Our study however is not without limitations. First, although ICD-10 code J84.1 is the most specific code for IPF to present mortality statistics in the study timeframe [3], it may be inherently inaccurate due to the inclusion of other IIPs. Future studies report mortality statistics for IPF should use stricter and narrower ICD codes (e.g., ICD-11 CB03.4). Second, patients who were misdiagnosed with IPF may have superior survival due to diagnostic inaccuracies (e.g., ICD codes), which may influence the survival trend for IPF in various time periods. Further, a review with such inherent heterogeneity due to drawing together various types of work worldwide (with different data sources, study designs, and study methodologies) makes our conclusions rather provisional. Lastly, studies showing favourable effects of antifibrotic drugs were more likely to be published in recent years, while there might be reporting biases that better holistic management of patients with IPF might contribute to improved survival.

In conclusion, IPF is a diagnosis associated with high mortality, similar to that seen in several cancers, though there is much less recognition of IPF in the population, press or research funding agendas. Lack of improvement of survival trends for IPF worldwide before 2010 may be related to changing age profiles at diagnosis or the prevailing therapeutic regimens which were since proven to have negative effects. Substantial therapeutic advances after 2010 might have contributed to the increased survival trends. Further, there might be some signals

emerging for an improvement in long-term survival related specifically to the newly available antifibrotic drugs.

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## **Declaration of interests**

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## **Author contribution**

IAC, QZ, DB, and AJP worked on protocol development. QZ, IAC and JAC collected data. QZ, EHW, QX, PO, IAC, and AJP analysed and interpreted data. QZ wrote the draft of manuscript. All authors contributed to review and agreed the manuscript.

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**TABLE 1** Summary characteristics of included studies related to mortality for IPF using various ICD codes

First author (year) [ref.]	Country/region	Year studied	Data sources	Standard population	Incidence (per 100, 000)	Mortality trends
Algranti (2017) [21]	Brazil	2000-2014	National statistics agencies	2010 Brazilian population	Overall: 0.46-1.10 <sup>†</sup>	Increased
Hutchinson (2014) [22]	England and Wales	2001-2012	National statistics agencies	2013 European population	Overall: 4.33-6.90 <sup>*</sup> ; 6.09-8.28 <sup>†</sup>	Increased
	Australia	2000-2011			Overall: 2.56-3.47 <sup>*</sup> ; 4.23-5.08 <sup>†</sup>	Increased
	Canada	2000-2011			Overall: 3.06-4.60 <sup>*</sup> ; 5.09-6.38 <sup>†</sup>	Increased
	Spain	2000-2012			Overall: 2.78-4.09 <sup>*</sup> ; 3.51-4.64 <sup>†</sup>	Increased
	USA	2000-2010			Overall: 3.48-4.12 <sup>*</sup> ; 5.62-6.16 <sup>†</sup>	Increased
Jeganathan (2021) [23]	USA	2004-2017	National health statistics	2000 US population	Overall: 4.22-3.64 <sup>†</sup>	Decreased
Marcon (2021) [24]	Italy	2008-2019	Regional statistics agencies	2013 European population	Males: 2.80 <sup>†</sup> ; Females: 1.70 <sup>†</sup>	Increased in males aged ≥ 85 years.
Marshall (2018) [25]	Austria	2002-2013	WHO mortality database	2013 European population	Males: 2.56-2.34 <sup>†</sup> ; Females: 0.96-1.29 <sup>†</sup>	Decreased (males only)
	Belgium	2001-2013			Males: 2.63-4.15 <sup>†</sup> ; Females: 1.43-1.88 <sup>†</sup>	Increased
	Croatia	2001-2013			Males: 0.51-0.39 <sup>†</sup> ; Females: 0.13-0.49 <sup>†</sup>	Decreased (males only)
	Czech Republic	2001-2013			Males: 0.77-2.13 <sup>†</sup> ; Females: 0.46-1.16 <sup>†</sup>	Increased
	Denmark	2001-2013			Males: 3.28-1.73 <sup>†</sup> ; Females: 1.39-0.63 <sup>†</sup>	Decreased
	Finland	2001-2013			Males: 4.43-7.36 <sup>†</sup> ; Females: 2.92-3.62 <sup>†</sup>	Increased
	France	2001-2013			Males: 2.63-3.97 <sup>†</sup> ; Females: 1.27-1.68 <sup>†</sup>	Increased
	Germany	2001-2013			Males: 2.80-4.46 <sup>†</sup> ; Females: 1.43-2.08 <sup>†</sup>	Increased
	Hungary	2001-2013			Males: 1.72-2.66 <sup>†</sup> ; Females: 0.97-1.39 <sup>†</sup>	Increased
	Lithuania	2001-2013			Males: 0.24-0.85 <sup>†</sup> ; Females: 0.10-0.24 <sup>†</sup>	Increased
	Netherlands	2001-2013			Males: 3.56-4.81 <sup>†</sup> ; Females: 1.61-1.82 <sup>†</sup>	Increased
	Poland	2001-2013			Males: 0.75-1.28 <sup>†</sup> ; Females: 0.44-0.68 <sup>†</sup>	Increased
	Portugal	2002-2013			Males: 2.11-4.77 <sup>†</sup> ; Females: 1.35-2.25 <sup>†</sup>	Increased
Romania	2001-2013	Males: 0.60-0.64 <sup>†</sup> ; Females: 0.34-0.25 <sup>†</sup>	Decreased (females only)			

	Spain	2001-2013			Males: 4.81-6.06 <sup>†</sup> ; Females: 3.02-3.35 <sup>†</sup>	Increased
	Sweden	2001-2013			Males: 4.61-6.46 <sup>†</sup> ; Females: 2.11-2.59 <sup>†</sup>	Increased
	UK	2001-2013			Males: 8.16-12.01 <sup>†</sup> ; Females: 3.61-5.63 <sup>†</sup>	Increased
Navaratnam (2011) [26]	UK	2000-2008	National statistics agencies	2008 UK population	Overall: 4.40-5.10 <sup>†</sup>	Increased

\*: Crude mortality rate; †: Age-standardised rate; WHO: World Health Organization; ICD-n: International Classification of Diseases, nth Revision; Case definition was based on the ICD-10 J84.1 (other interstitial pulmonary diseases with fibrosis) and underlying causes death in all included studies.

**TABLE 2** Summary characteristics of included studies related to survival outcomes in IPF

First author (year) [ref.]	Country/ Region	N	Year studied	Time periods	Diagnostic criteria	Treatment	Age (years)	3-year CSRs (%)	5-year CSRs (%)
Adegunsoye (2020) [27]	US	240	2010-2019	2010s	2011 guideline	Antifibrotics	NA	62.5	NA
Aggarwal (2017) [28]	US	81	1985-2014	2000s	2011 guideline	Non-antifibrotics	63 (8.4)	<b>81.6</b>	59.0
Akyil (2016) [29]	Turkey	92	2005-2013	2000s	2011 guideline	Non-antifibrotics	63.5 (10.0)	<b>45.5</b>	<b>30.7</b>
Alakhras (2007) [30]	US	197	1994-1996	1990s	Other criteria	Non-antifibrotics	71.4 (8.9)	<b>60.8</b>	NA
Alhamad (2008) [31]	Saudi Arabia	61	1996-2005	2000s	2002 guideline	Non-antifibrotics	54.7 (15.2)	<b>92.8</b>	<b>73.7</b>
Antonίου (2020) [32]	Greece	244	2013-2018	2010s	2011 guideline	Antifibrotics	71.8 (7.5)	59.4	<b>58.0</b>
Araki (2003) [33]	Japan	86	1978-1997	Before 1990	Other criteria	Non-antifibrotics	80.5 (6.6)	<b>57.3</b>	<b>35.2</b>
Bando (2014) [34]	Japan	321	2006-2010	2000s	2011 guideline	Non-antifibrotics	NA	<b>73.1</b>	<b>59.3</b>
Barlo (2009) * [35]	Netherlands	113	1998-2007	2000s	2002 guideline	Non-antifibrotics	69 (12.7)	<b>74.8</b>	<b>27.1</b>
Bjoraker (1998) [36]	US	104	1967-1985	Before 1990	Other criteria	Non-antifibrotics	61.7 (10.6)	<b>60.7</b>	<b>42.0</b>
Cai (2014) [37]	China	210	1999-2007	2000s	2002 guideline	Non-antifibrotics	64 (10.0)	<b>46.9</b>	39.0
Collard (2004) [38]	US	82	1984-2002	1990s	2000 guideline	Non-antifibrotics	66.5 (7.4)	<b>62.4</b>	<b>42.8</b>
Costabel (2017) [39]	US	1058	2008-2015	2010s	2011 guideline	Antifibrotics	68.5 (7.5)	<b>79.3</b>	<b>60.5</b>
Doubkova (2017) [40]	Czech Republic	118	2012-2016	2010s	2011 guideline	Antifibrotics	NA	<b>77.9</b>	<b>62.6</b>
Douglas (2000) [41]	US	487	1994-1996	1990s	Other criteria	Non-antifibrotics	NA	<b>52.1</b>	NA
Fernández Pérez (2010) [42]	US	47	1997-2005	2000s	2002 guideline	Non-antifibrotics	73.5 (7.9)	<b>61.9</b>	<b>32.5</b>
Gao (2021) [43]	Sweden	540	2014-2020	2010s	2011 guideline	Antifibrotics	72.7 (7.5)	70.0	52.0
Guiot (2018) [44]	Belgium	82	2009-2017	2010s	2011 guideline	Non-antifibrotics	71.1 (9.4)	<b>57.0</b>	<b>38.6</b>
Hamada (2007) [45]	Japan	61	1991-2004	1990s	2000 guideline	Non-antifibrotics	62.0 (8.0)	<b>64.5</b>	<b>47.1</b>
Hopkins (2016) [46]	Canada	1151	2007-2011	2000s	Other criteria	Non-antifibrotics	68.1 (11.1)	63.2	NA
Jacob (2017) [47]	UK	272	2007-2011	2000s	2011 guideline	Non-antifibrotics	NA	<b>41.8</b>	<b>22.5</b>
Jeon (2006) [48]	Korea	88	1996-2002	1990s	2000 guideline	Non-antifibrotics	60.3 (7.5)	57.0	41.0
Jo (2017) [49]	Australia	647	2012-2016	2010s	2011 guideline	Antifibrotics	70.9 (8.5)	63.0	NA
Kang (2020) [50]	Korea	948	2004-2017	2010s	2011 guideline	Antifibrotics	65.8 (8.3)	<b>57.8</b>	<b>39.0</b>
Kärkkäinen (2017) [51]	Finland	132	2002-2012	2000s	Other criteria	Non-antifibrotics	70.5 (9.8)	<b>56.4</b>	<b>36.7</b>
Kaunisto (2019) [52]	Finland	453	2011-2015	2010s	2011 guideline	Antifibrotics	73.0 (9.0)	70.0	45.0
Kim (2012) [54]	Korea	67	1996-2007	2000s	2011 guideline	Non-antifibrotics	69.9 (9.9)	<b>86.5</b>	<b>78.3</b>

Kim (2015) [53]	Korea	268	2005-2009	2000s	2011 guideline	Non-antifibrotics	65.9 (9.6)	69.0	<b>53.9</b>
Ko (2021) [55]	Korea	42777	2006-2016	2010s	Other criteria	Antifibrotics	64.6 (13.8)	71.9	62.9
Kondoh (2005) [56]	Japan	27	1991-1998	1990s	2000 guideline	Non-antifibrotics	56 (10.9)	<b>62.4</b>	<b>40.8</b>
Koo (2016) [57]	Korea	1663	2003-2007	2000s	2002 guideline	Non-antifibrotics	NA	62.6	49.2
Kreuter (2016) [58]	Germany	272	2004-2012	2000s	2011 guideline	Non-antifibrotics	68.5 (9.0)	<b>54.8</b>	<b>40.8</b>
Kurashima (2010) [59]	Japan	362	1997-2006	2000s	Other criteria	Non-antifibrotics	72.9 (8.1)	<b>79.6</b>	<b>69.4</b>
Lai (2019) [60]	Taiwan	114	2006-2016	2010s	2011 guideline	Non-antifibrotics	77.8 (9.4)	<b>53.0</b>	37.5
Lassenius (2019) [61]	Finland	266	2005-2017	2010s	Other criteria	Non-antifibrotics	74.3 (8.5)	<b>66.2</b>	47.0
Le Rouzic (2015) [62]	France	66	2000-2010	2000s	2000 guideline	Non-antifibrotics	NA	<b>53.5</b>	<b>34.9</b>
Lindell (2015) [63]	US	404	2000-2012	2000s	Other criteria	Non-antifibrotics	71.5 (9.2)	<b>41.8</b>	<b>31.0</b>
Mancuzo (2018) [64]	Brazil	70	1993-2017	2000s	2011 guideline	Non-antifibrotics	71.9 (6.4)	<b>67.2</b>	<b>41.4</b>
Mapel (1998) [65]	US	209	1988-1992	1990s	Other criteria	Non-antifibrotics	71.7 (12.3)	73.0	64.0
Margaritopoulos (2018) [66]	Greece	82	2011-2016	2010s	2011 guideline	Antifibrotics	74.9 (11.0)	73.0	<b>54.7</b>
Mejia (2009) [67]	Mexico	110	1996-2006	2000s	2000 guideline	Non-antifibrotics	63.0 (10.0)	<b>42.0</b>	NA
Moon (2021) <sup>†</sup> [68]	Korea	689	2000-2008	2000s	2000 guideline	Non-antifibrotics	68.0 (9.0)	50.2	NA
Moon (2021) <sup>†</sup> [68]	Korea	656	2010-2018	2010s	2011 guideline	Antifibrotics	68.0 (8.0)	70.5	NA
Mura (2012) [69]	Italy	70	2005-2007	2000s	2000 guideline	Non-antifibrotics	67.0 (8.0)	54.0	NA
Nadrous (2004) [70]	US	476	1994-1996	1990s	Other criteria	Non-antifibrotics	70.6 (9.0)	<b>47.7</b>	NA
Nathan (2020) [71]	US	436	2007-2016	2010s	2011 guideline	Antifibrotics	67.0 (8.9)	<b>58.0</b>	<b>34.4</b>
Natsuizaka (2014) [72]	Japan	553	2003-2007	2000s	2000 guideline	Non-antifibrotics	70.0 (9.0)	<b>49.2</b>	<b>33.4</b>
Nicholson (2000) [73]	US	78	1978-1989	Before 1990	Other criteria	Non-antifibrotics	57.2 (7.1)	<b>62.1</b>	<b>41.3</b>
Ogawa (2018) [74]	Japan	46	2009-2014	2010s	2011 guideline	Antifibrotics	NA	<b>53.2</b>	NA
Reid (2015) [75]	Germany	27	2005-2009	2000s	2000 guideline	Non-antifibrotics	NA	<b>63.1</b>	<b>33.5</b>
Ryerson (2013) [76]	US	192	2000-2012	2000s	2011 guideline	Non-antifibrotics	69.9 (8.7)	<b>47.5</b>	<b>24.1</b>
Shin (2008) [77]	US	108	1996-2004	2000s	Other criteria	Non-antifibrotics	63.0 (7.4)	NA	<b>54.1</b>
Strand (2014) [78]	US	321	1985-2011	1990s	2000 guideline	Non-antifibrotics	66.1 (9.1)	<b>64.9</b>	<b>44.9</b>
Strongman (2018) [79]	UK	555	2000-2012	2000s	Other criteria	Non-antifibrotics	NA	NA	32.0
Su (2011) [80]	US	148	2002-2009	2000s	2002 guideline	Non-antifibrotics	68.6 (12.1)	61.0	53.0
Sugino (2014) [81]	Japan	108	2003-2010	2000s	2000 guideline	Non-antifibrotics	71.4 (6.7)	<b>53.8</b>	<b>31.6</b>
Tarride (2018) [82]	Canada	1,673	2006-2011	2000s	Other criteria	Non-antifibrotics	76.8 (12.0)	37.4	NA
Tran (2020) [83]	Europe	1620	1996-2008	2000s	2011 guideline	Non-antifibrotics	67.6 (8.9)	65.5	46.4
Turner-warwick (1980) [84]	UK	181	1955-1973	Before 1990	Other criteria	Non-antifibrotics	57.6 (11.3)	<b>57.7</b>	<b>43.8</b>

Vietri (2020) [85]	Italy	91	2011-2013	2010s	2011 guideline	Antifibrotics	68.5 (7.7)	67.5	NA
Watanabe (2019) [86]	Japan	32	2008-2018	2010s	2011 guideline	Antifibrotics	NA	<b>74.6</b>	<b>49.8</b>
Zhang (2016) [87]	China	192	2001-2013	2000s	2011 guideline	Non-antifibrotics	66.0 (8.5)	NA	<b>55.5</b>
Zurkova (2019) [88]	Czech Republic	383	2012-2017	2010s	2011 guideline	Antifibrotics	NA	NA	<b>47.1</b>

\*: Non-English (Netherlandish) study; †: one study including two independent cohorts; IPF: idiopathic pulmonary fibrosis; 2000 guideline: 2000 ATS/ERS guideline; 2002 guideline: 2002 ATS/ERS guideline; 2011 guideline: 2011 ATS/ERS/JRS/LATA guideline; Other criteria: all other diagnostic criteria combined (such as clinical, radiographic, and biopsy criteria); ATS: American Thoracic Society; ERS: European Respiratory Society; JRS: Japanese Respiratory Society; LATA: Latin American Thoracic Association; N: number of participants; NA: not applicable; CSRs: cumulative survival rates; Age values were presented as mean (standard deviation); Data were extracted from Kaplan-Meier curves in bold.



**TABLE 3** Subgroup analyses for pooled analyses of survival by various time periods

	Baseline analyses			Sensitivity analyses *		
	N	CSRs (95% CIs)	<i>I</i> <sup>2</sup>	N	CSRs (95% CIs)	<i>I</i> <sup>2</sup>
<b>3-year CSRs</b>						
Overall	59	61.8 (58.7, 64.9)	97.1%	56	61.9 (58.7, 65.1)	97.2%
Before 2010	41	59.9 (55.8, 64.1)	95.8%	41	59.9 (55.8, 64.1)	95.8%
2010s	18	66.2 (58.7, 64.9)	92.6%	15	67.4 (63.9, 70.9)	93.1%
Test for difference †:		<i>P</i> = 0.067			<i>P</i> = 0.039	
<b>5-years CSRs</b>						
Overall	50	45.6 (41.5, 49.7)	97.7%	47	45.9 (41.6, 50.1)	97.8%
Before 2010	36	44.1 (39.9, 48.3)	93.7%	36	44.1 (39.9, 48.3)	93.7%
2010s	14	49.3 (42.7, 49.7)	97.7%	11	51.4 (44.1, 58.7)	93.9%
Test for difference †:		<i>P</i> = 0.203			<i>P</i> = 0.106	

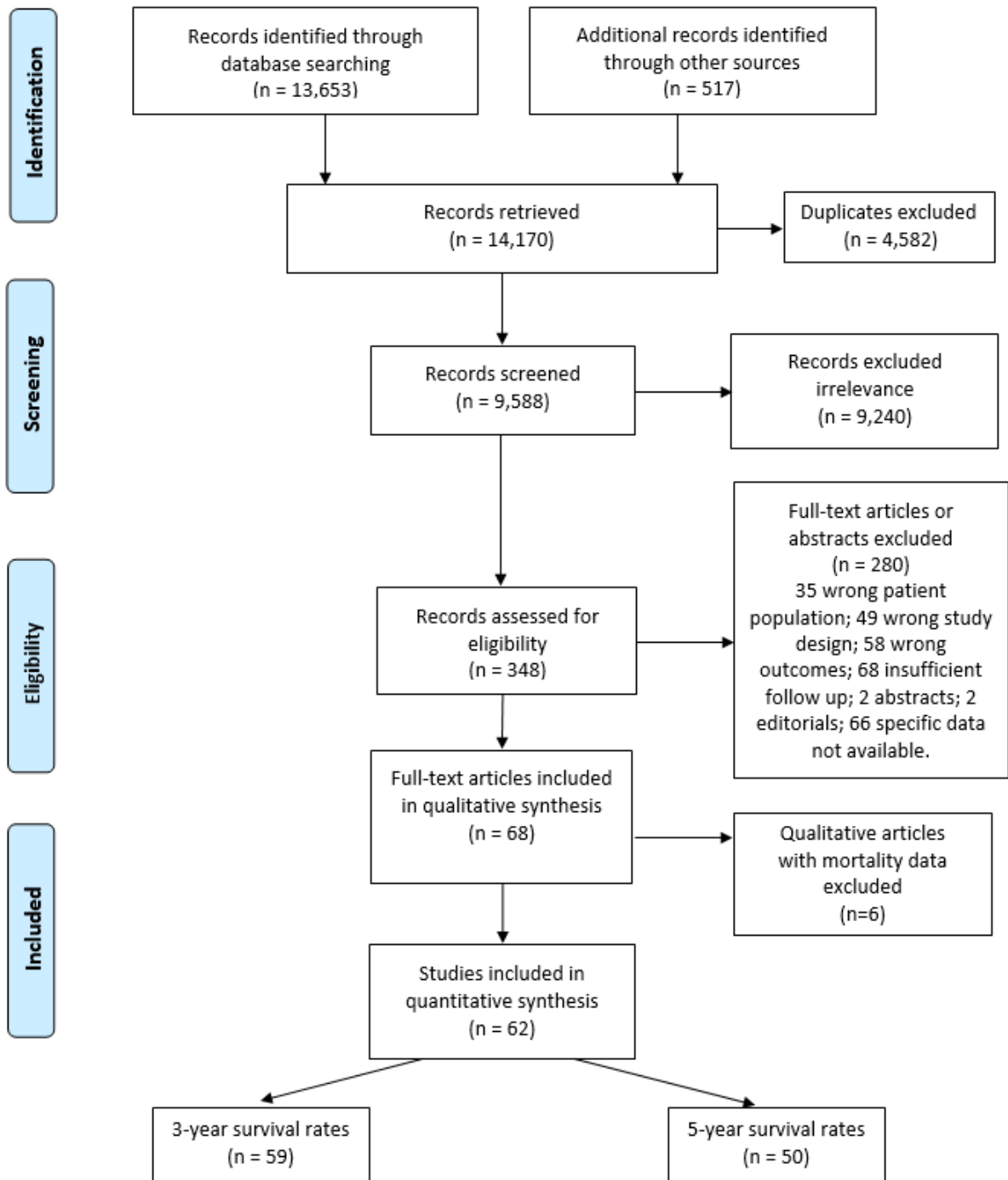
\*: Exclusion of 3 studies in which no patients received antifibrotics after year 2010; †: Test for difference between subgroups (before 2010 vs. 2010s); IPF: idiopathic pulmonary fibrosis; N: number of included studies; CSRs: cumulative survival rates; CIs: confidence intervals. *I*<sup>2</sup> > 50% represents high between-studies heterogeneity.

**TABLE 4** Subgroup analyses for pooled analyses of survival by various diagnostic criteria

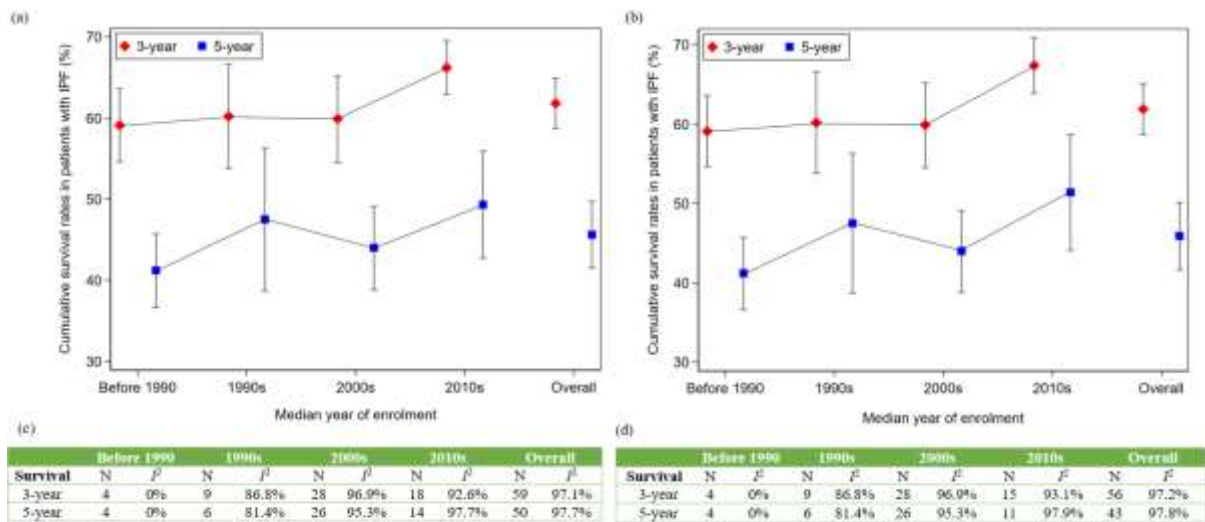
	Baseline analyses			Sensitivity analyses *		
	N	CSRs (95% CIs)	<i>I</i> <sup>2</sup>	N	CSRs (95% CIs)	<i>I</i> <sup>2</sup>
<b>3-year CSRs</b>						
Overall	59	61.8 (58.7, 64.9)	97.1%	44	59.8 (55.9, 63.8)	95.5%
2011 guideline	26	64.7 (60.8, 68.6)	93.2%	12	61.9 (55.0, 63.8)	93.5%
2000 or 2002 guideline	17	60.4 (54.6, 66.3)	91.0%	17	60.4 (54.6, 66.3)	91.0%
Other criteria	16	58.6 (50.7, 66.5)	98.9%	15	57.6 (50.4, 64.9)	97.1%
Test for difference †:		<i>P</i> = 0.105			<i>P</i> = 0.360	
<b>5-years CSRs</b>						
Overall	50	45.6 (41.5, 49.7)	97.7%	39	43.9 (39.9, 47.8)	93.4%
2011 guideline	23	47.3 (42.3, 52.2)	94.7%	13	45.1 (37.5, 52.7)	94.9%
2000 or 2002 guideline	15	41.8 (36.4, 47.2)	87.5%	15	41.8 (36.4, 47.2)	87.5%
Other criteria	12	46.7 (37.2, 56.2)	98.1%	11	45.2 (36.0, 54.4)	95.6%
Test for difference †:		<i>P</i> = 0.421			<i>P</i> = 0.991	

\*: Exclusion of 16 studies in which patients received antifibrotics; †: Test for difference between subgroups; 2000 guideline: 2000 ATS/ERS guideline; 2002 guideline: 2002 ATS/ERS guideline; 2011 guideline: 2011 ATS/ERS/JRS/LATA guideline; Other criteria: all other diagnostic criteria combined (such as clinical, radiographic, and biopsy criteria); ATS: American Thoracic Society; ERS: European Respiratory Society; JRS: Japanese Respiratory Society; LATA: Latin American Thoracic Association; IPF: idiopathic pulmonary fibrosis; N: number of included studies; CSRs: cumulative survival rates; CIs: confidence intervals. *I*<sup>2</sup> > 50% represents high between-studies heterogeneity.

## Figures

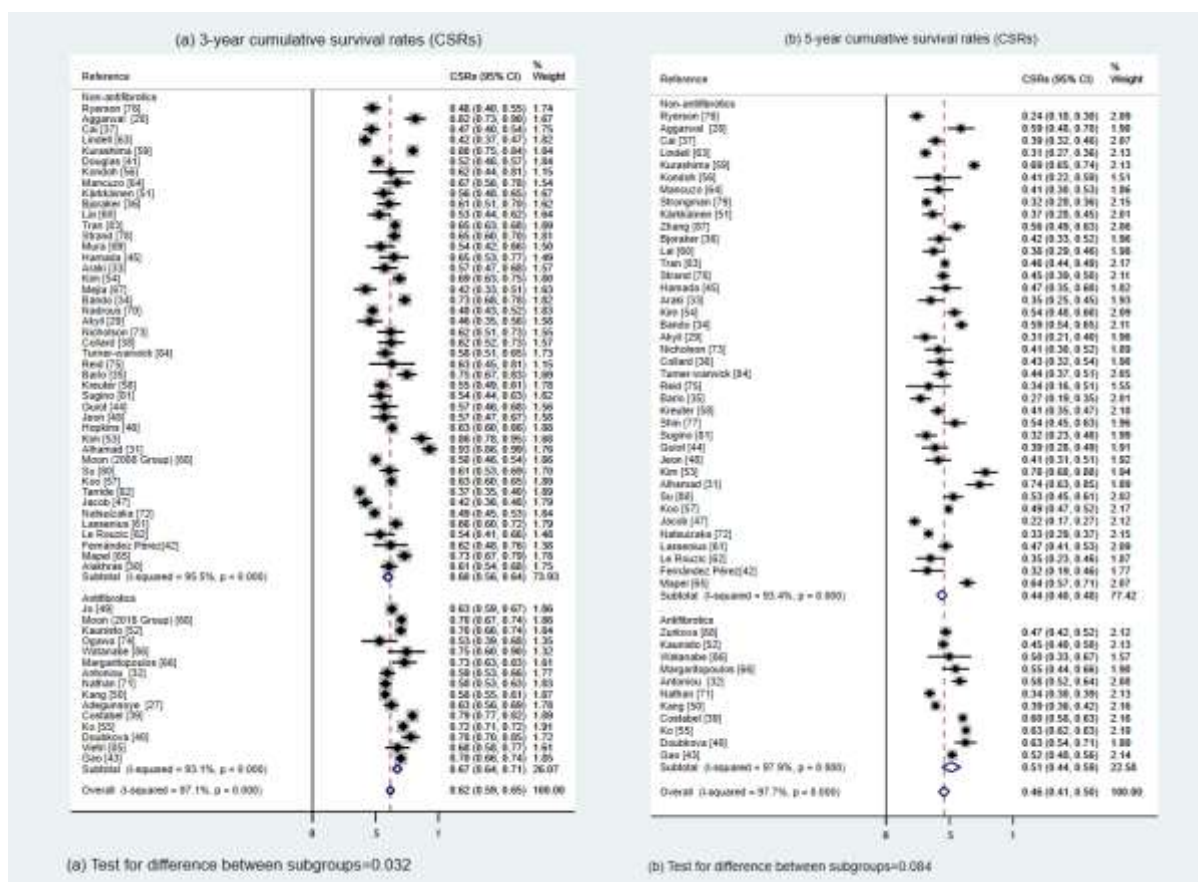


**FIGURE 1** Flow diagram of search progress, informed by PRISMA guidelines.

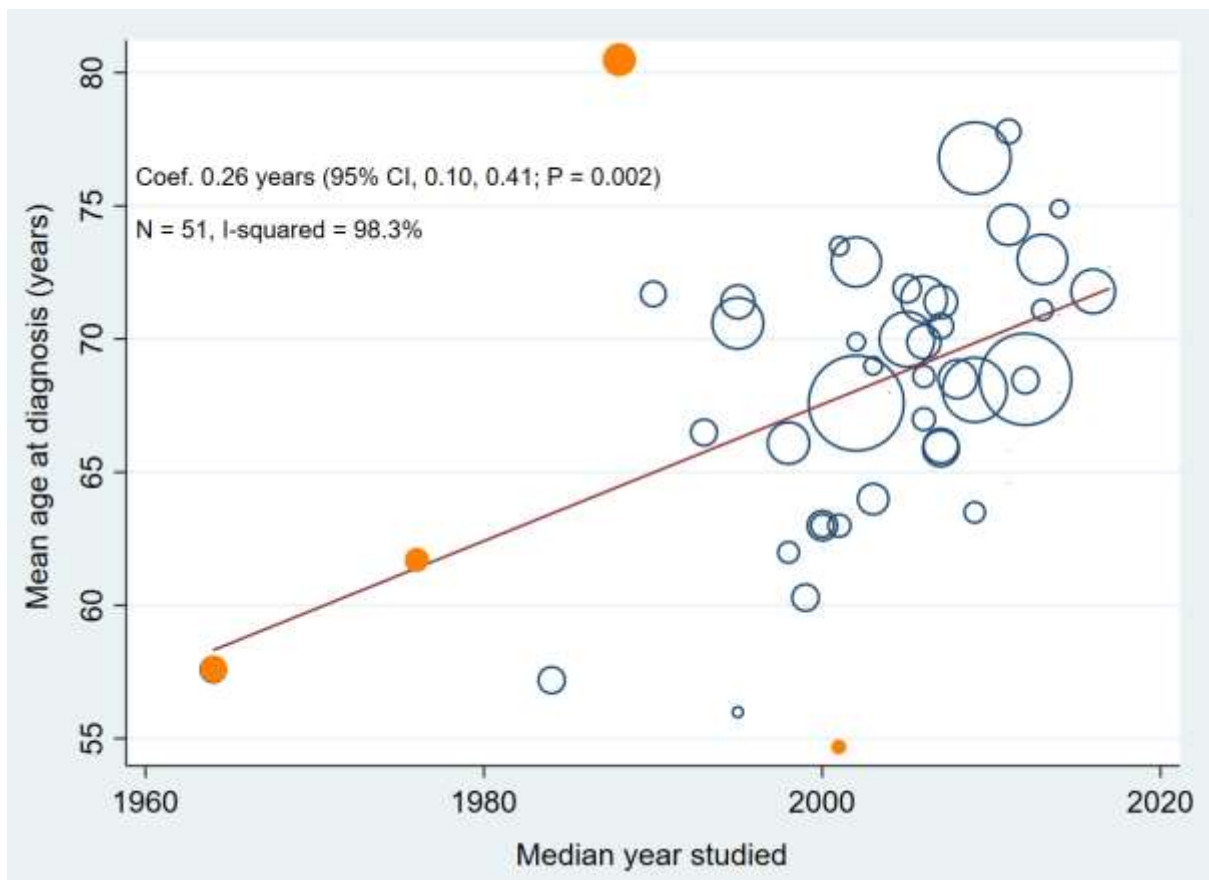


**FIGURE 2** Subgroup analyses for survival rates by various time periods in (a) and (c); after exclusion of 3 studies in which no patients received antifibrotics after year 2010 in (b) and (d). IPF: idiopathic pulmonary fibrosis; N: number of included studies;  $I^2 > 50\%$  represents high between-studies heterogeneity.

**FIGURE 2** Subgroup analyses for survival rates by various time periods in (a) and (c); after exclusion of 3 studies in which no patients received antifibrotics after year 2010 in (b) and (d). IPF: idiopathic pulmonary fibrosis; N: number of included studies;  $I^2 > 50\%$  represents high between-studies heterogeneity.



**FIGURE 3** Subgroup analyses for cumulative survival rates (CSRs) by various pharmaceutical regimens. (a) 3-year CSRs; (b) 5-year CSRs.



**FIGURE 4** Association between mean age at diagnosis and median year studied between 1960 and 2020 by using univariate meta-regression. Each size of the bubble depends on the weights in the random-effects models. Orange markers show studies removed for sensitivity analysis with extreme data points or before year 1980.

## **Online Supplement:**

### **Manuscript Title:**

Mortality and survival in idiopathic pulmonary fibrosis: a systematic review and meta-analysis

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<b>Supplement 4. Diagnostic criteria.....</b>	<b>9</b>
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## Supplement 1 PRISMA 2009 checklist

**TABLE S1** PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6



Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9
<b>DISCUSSION</b>			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review.	12-13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

## Supplement 2 Database search strategy

**TABLE S2** Database search strategy for mortality and survival in IPF

<p><b>Embase (Ovid):</b></p> <ol style="list-style-type: none"><li>1. idiopathic pulmonary fibrosis.tw.</li><li>2. cryptogenic fibrosing alveolitis.tw.</li><li>3. usual interstitial pneumonitis.tw.</li><li>4. usual interstitial pneumonia.tw.</li><li>5. fibrosing alveolitis.tw.</li><li>6. IPF.tw.</li><li>7. 1 or 2 or 3 or 4 or 5 or 6</li><li>8. mortality.tw.</li><li>9. survival.tw.</li><li>10. 8 or 9</li><li>11. 7 and 10</li><li>12. limit 11 to (human and yr="1950 - 2021")</li></ol>
<p><b>PubMed:</b></p> <p>(((((((((idiopathic pulmonary fibrosis[MeSH Terms]) OR (idiopathic pulmonary fibrosis[Text Word])) OR (cryptogenic fibrosing alveolitis[Text Word])) OR (usual interstitial pneumonitis[Text Word])) OR (usual interstitial pneumonia[Text Word])) OR (fibrosing alveolitis[Text Word])) OR (IPF[Text Word])) AND (((Mortality[MeSH Terms]) OR (Mortality[Text Word])) OR ((Survival[MeSH Terms]) OR (Survival[Text Word])))) AND (("1900/01/01"[Date - Publication] : "2021/11/01"[Date - Publication])) Filters: Humans.</p>
<p><b>Scopus:</b></p> <p>((TITLE-ABS-KEY ("MORTALITY") OR TITLE-ABS-KEY ("SURVIVAL")) AND PUBYEAR &gt; 1959 AND PUBYEAR &lt; 2022) AND ((TITLE-ABS-KEY (" IDIOPATHIC PULMONARY FIBROSIS") OR TITLE-ABS-KEY ("CRYPTOGENIC FIBROSING ALVEOLITIS") OR TITLE-ABS-KEY ("USUAL INTERSTITIAL PNEUMONITIS") OR TITLE-ABS-KEY ("USUAL INTERSTITIAL PNEUMONIA") OR TITLE-ABS-KEY ("FIBROSING ALVEOLITIS") OR TITLE-ABS-KEY ("IPF"))))</p>

### Supplement 3 A tool for quality assessment

There are a total of 26 items for quality assessment and each of them has been evaluated as one of three responses (yes, no, and not mentioned/not applicable) based on the description of study characteristics. When the item only responses to yes, one point adds to this study. Total quality score of each study is the summary of each item. The formula used for calculating the index ( $Q$ ) of quality for each study is  $Q = \frac{x}{26} * 100\%$ , in which  $x$  indicates the total scores of each study. We defined quality of studies as three levels: low, moderate, and high when  $Q \leq 50\%$ ,  $50\% < Q \leq 70\%$ , and  $Q > 70\%$ , respectively. The outcomes of quality score were expressed as percentage with interquartile range (IQR).

**TABLE S3a** Case definition criteria for IPF subjects [1, 2]

Element	Quality assessment criteria	Items
<b>Exclusion of other causes of ILDs</b>	Have other potential causes of ILDs or pulmonary fibrosis been excluded in the subjects? (environmental/domestic/occupational exposures, connective tissue disease, drug toxicity, radiation)	C1
	Did the author specify if the clinical diagnosis was made by a multi-disciplinary team?	C2
	Was the diagnosis made based on the classic signs, symptoms, and physical examination characteristics of IPF?	C3
<b>Clinical characteristics</b>	Is there any FVC tests done for the subjects?	C4
	Are there any other respiratory physiology tests mentioned if an FVC was not done? (Spirometry, TLC, DL <sub>CO</sub> , FEV, etc)	C5
	Was timing of onset symptoms recorded? i.e., is there indication of when disease process was first evident, rather than when diagnosed?	C6
<b>High-resolution computerised tomography (HRCT)</b>	Was the diagnosis in subjects made based on HRCT?	C7
	Was the pattern consistent with the American Thoracic Society guidelines for usual interstitial pneumonia (UIP)?	C8
	Is there mention of the diagnosis being made by two radiologists?	C9
<b>Histopathological confirmation</b>	If diagnosis was not made by HRCT in subjects, was there mention of histopathological confirmation?	C10
	Was the pattern consistent with the ATS guidelines?	C11
	Is there mention of the diagnosis being made by two pathologists?	C12
<b>Characteristics of IPF subjects</b>	Does the article adequately report participant characteristics? (Such as age distribution, sex distribution, and race/ethnicity)	C13

IPF: idiopathic pulmonary fibrosis; ILDs: interstitial lung diseases; HRCT: High-resolution computerised tomography; ATS: American Thoracic Society; UIP: usual interstitial pneumonia; FVC: forced vital capacity; DL<sub>CO</sub>: diffusing capacity of the lung for carbon monoxide; FEV: forced expiratory volume; TLC: total lung capacity.

**TABLE S3b** Study methodology criteria for epidemiological studies [3-7]

<b>Element</b>	<b>Quality assessment criteria</b>	<b>Items</b>
<b>Population</b>	Were the sampling methods described? What sampling methods were used (prevalence studies or population-based studies)?	M1
	Is the sample representative of the target population?	M2
	Does the paper make mention of inclusion and exclusion criteria?	M3
	Were standardised data collection methods/protocols used?	M4
	Was the methodology described in sufficient detail?	M5
<b>Data collection</b>	Was the timeframe for data collection specified in the paper?	M6
	Did the study directly sample the population or were medical records, databases and registries used for data collection?	M7
	If medical records, databases/ registries were used, was standardised/up to date terminology or codes used for IPF, e.g., ICD coding?	M8
	Were appropriate statistical methods used for analysis? Did the analysis methods take into consideration the sampling methods?	M9
<b>Data analysis</b>	Was the denominator for the population specified?	M10
	Were survival rates, mortality reported in standardised formats (per 100 000/population/specified timeframe)?	M11
	Did the reports include confidence intervals?	M12
	Was there mention of how missing data were managed?	M13

ICD: International Classification of Diseases.

## Supplement 4 Diagnostic criteria

For global mortality statistics, Table S4 shows the development of International Classification of Diseases (ICD) codes for IPF. We summarize annual mortality rates of IPF from included studies based on the ICD codes, because it is routinely used to calculate mortality statistics worldwide. There are various ICD codes (such as ICD-8 517, ICD-9 515, ICD-9 516.3 and ICD-10 J84.1) to record the death certificate of people with IPF [8-10]. Although ICD-10 code J84.1 may include other idiopathic interstitial pneumonias (IIPs) (such as nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonia), it is the most specific code for IPF to present global mortality statistics in the study timeframe [3]. Future studies report mortality statistics for IPF should use stricter and narrower ICD codes (e.g., ICD-11 CB03.4) [10].

In terms of survival statistics for IPF worldwide, the 2000 ATS/ERS guideline [12] on IPF represented a first platform for diagnostic criteria. The 2002 ATS/ERS guideline [13] on IIPs represented disease classification for IIPs and suggested the final diagnosis of IPF should be rendered only after the multidiscipline team (MDT) including pulmonologist, radiologist, and pathologist. Despite this remarkable progress, the latest 2011 ATS/ERS/JRS/ALAT guideline [1] had dramatically changed the criteria for IPF diagnosis in both radiological and histological aspects.

**TABLE S4** Development of diagnostic criteria for IPF based on ICD codes.

ICD codes	Case definition	Years Covered	Reference
<b>ICD-8</b>		1968-1978	[8]
517	Other chronic interstitial pneumonia		
<b>ICD-9</b>		1979-1998	[9]
515	Postinflammatory pulmonary fibrosis		
516.3	Idiopathic fibrosing alveolitis		
<b>ICD-10</b>		1999-2018	[10]
J84	Other interstitial pulmonary disease		
J84.0	Alveolar and parieto-alveolar conditions		
J84.1	Other interstitial pulmonary diseases with fibrosis		
J84.8	Other specified interstitial lung disease		
J84.9	Interstitial pulmonary disease, unspecified		
<b>ICD-11</b>			
CB03.4	Idiopathic pulmonary fibrosis	2019-present	[11]

ICD-n: International Classification of Disease nth Revision; IPF: Idiopathic Pulmonary Fibrosis.

## Supplement 5 Results of quality assessment

**TABLE S5** A detailed scoring for both case definition and study methodology criteria for each study

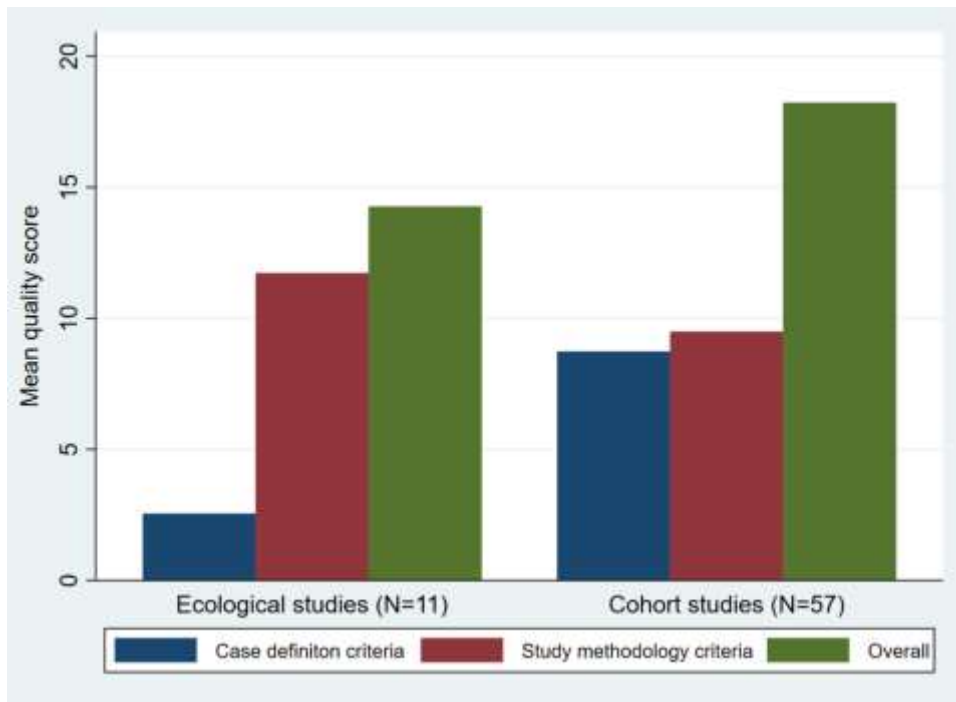
First author (year) Ref.	Score for case definition	Score for study methodology	Total score	Quality index (%)	Quality level
<b>Mortality statistics (n=6)</b>					
Algranti (2017) [21]	1	12	13	50.0	Moderate
Hutchinson (2014) [22]	1	12	13	50.0	Moderate
Jeganathan (2021) [23]	2	12	14	53.8	Moderate
Marcon (2021) [24]	1	12	13	50.0	Moderate
Marshall (2018) [25]	1	12	13	50.0	Moderate
Navaratnam (2011) [26]	1	12	13	50.0	Moderate
<b>Survival statistics (n=62)</b>					
Adegunsoye (2020) [27]	8	10	18	69.2	Moderate
Aggarwal (2017) [28]	8	9	17	65.4	Moderate
Akyil (2016) [29]	9	10	19	73.1	High
Alakhras (2007) [30]	8	10	18	69.2	Moderate
Alhamad (2008) [31]	9	10	19	73.1	High
Antoniou (2020) [32]	9	11	20	76.9	High
Araki (2003) [33]	8	9	17	65.4	Moderate
Bando (2014) [34]	9	9	18	69.2	Moderate
Barlo (2009) * [35]	9	9	18	69.2	Moderate
Bjoraker (1998) [36]	10	9	19	73.1	High
Cai (2014) [37]	9	9	18	69.2	Moderate
Collard (2004) [38]	8	10	18	69.2	Moderate
Costabel (2017) [39]	8	9	17	65.4	Moderate
Doubkova (2017) [40]	9	9	18	69.2	Moderate
Douglas (2000) [41]	8	9	17	65.4	Moderate
Fernández Pérez (2010) [42]	9	11	20	76.9	High
Gao (2021) [43]	10	10	20	76.9	High
Guiot (2018) [44]	10	10	20	76.9	High
Hamada (2007) [45]	8	10	18	69.2	Moderate
Hopkins (2016) [46]	1	11	12	46.2	Low
Jacob (2017) [47]	9	9	18	69.2	Moderate
Jeon (2006) [48]	11	10	21	80.8	High
Jo (2017) [49]	9	10	19	73.1	High
Kang (2020) [50]	9	10	19	73.1	High
Kärkkäinen (2017) [51]	9	9	18	69.2	Moderate
Kaunisto (2019) [52]	11	9	20	76.9	High
Kim (2012) [54]	8	10	18	69.2	Moderate
Kim (2015) [53]	9	10	19	73.1	High
Ko (2021) [55]	5	12	17	65.4	Moderate
Kondoh (2005) [56]	9	9	18	69.2	Moderate
Koo (2016) [57]	8	9	17	65.4	Moderate
Kreuter (2016) [58]	9	10	19	73.1	High
Kurashima (2010) [59]	10	9	19	73.1	High
Lai (2019) [60]	9	9	18	69.2	Moderate
Lassenius (2019) [61]	8	10	18	69.2	Moderate
Le Rouzic (2015) [62]	10	10	20	76.9	High
Lindell (2015) [63]	8	10	18	69.2	Moderate
Mancuzo (2018) [64]	9	10	19	73.1	High
Mapel (1998) [65]	7	10	17	65.4	Moderate
Margaritopoulos (2018) [66]	8	9	17	65.4	Moderate
Mejia (2009) [67]	8	9	17	65.4	Moderate
Moon (2008) † [68]	10	10	20	76.9	High
Mura (2012) [69]	10	9	19	73.1	High
Nadrous (2004) [70]	8	9	17	65.4	Moderate

Nathan (2020) [71]	8	10	18	69.2	Moderate
Natsuizaka (2014) [72]	8	11	19	73.1	High
Nicholson (2000) [73]	9	9	18	69.2	Moderate
Ogawa (2018) [74]	8	9	17	65.4	Moderate
Reid (2015) [75]	8	9	17	65.4	Moderate
Ryerson (2013) [76]	10	10	20	76.9	High
Shin (2008) [77]	9	9	18	69.2	Moderate
Strand (2014) [78]	8	10	18	69.2	Moderate
Strongman (2018) [79]	2	12	14	53.8	Moderate
Su (2011) [80]	8	9	17	65.4	Moderate
Sugino (2014) [81]	8	9	17	65.4	Moderate
Tarride (2018) [82]	5	11	16	61.5	Moderate
Tran (2020) [83]	10	9	19	73.1	High
Turner-warwick (1980) [84]	7	9	16	61.5	Moderate
Vietri (2020) [85]	8	9	17	65.4	Moderate
Watanabe (2019) [86]	8	9	17	65.4	Moderate
Zhang (2016) [87]	9	9	18	69.2	Moderate
Zurkova (2019) [88]	8	10	18	69.2	Moderate

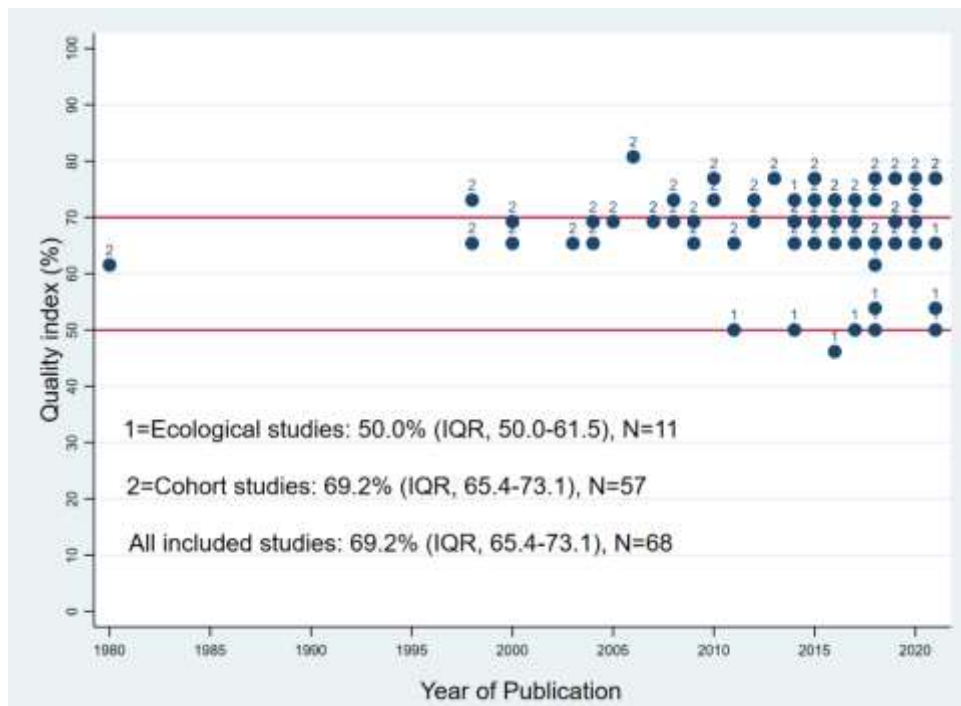
\*: Non-English (Netherlandish) study; †: one study including two independent cohorts.



(a)



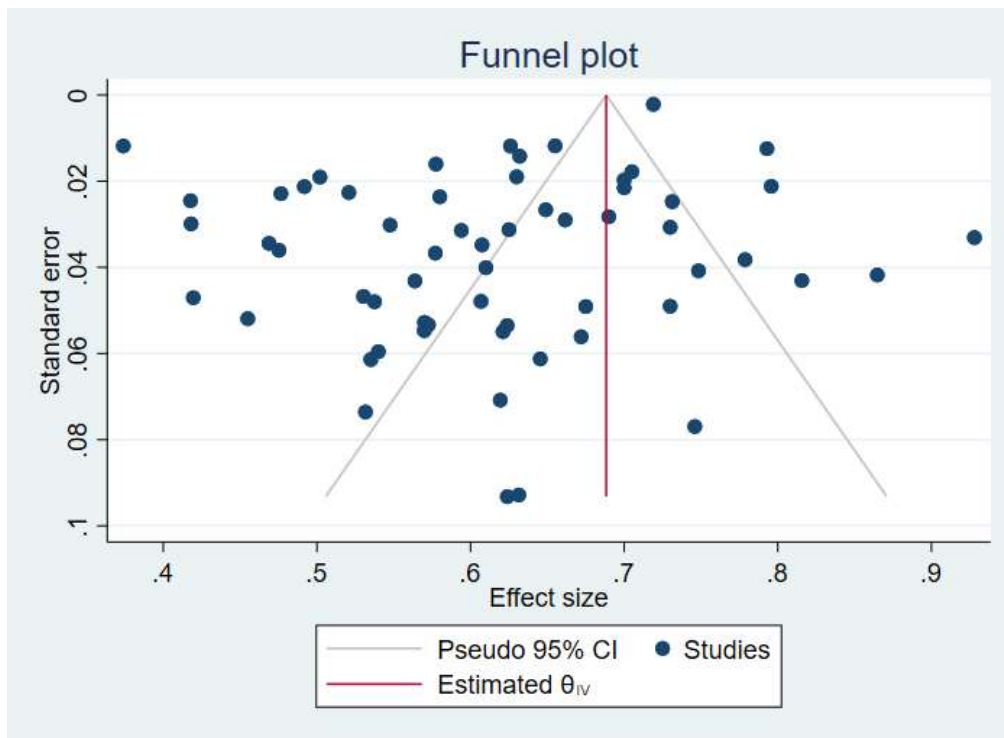
(b)



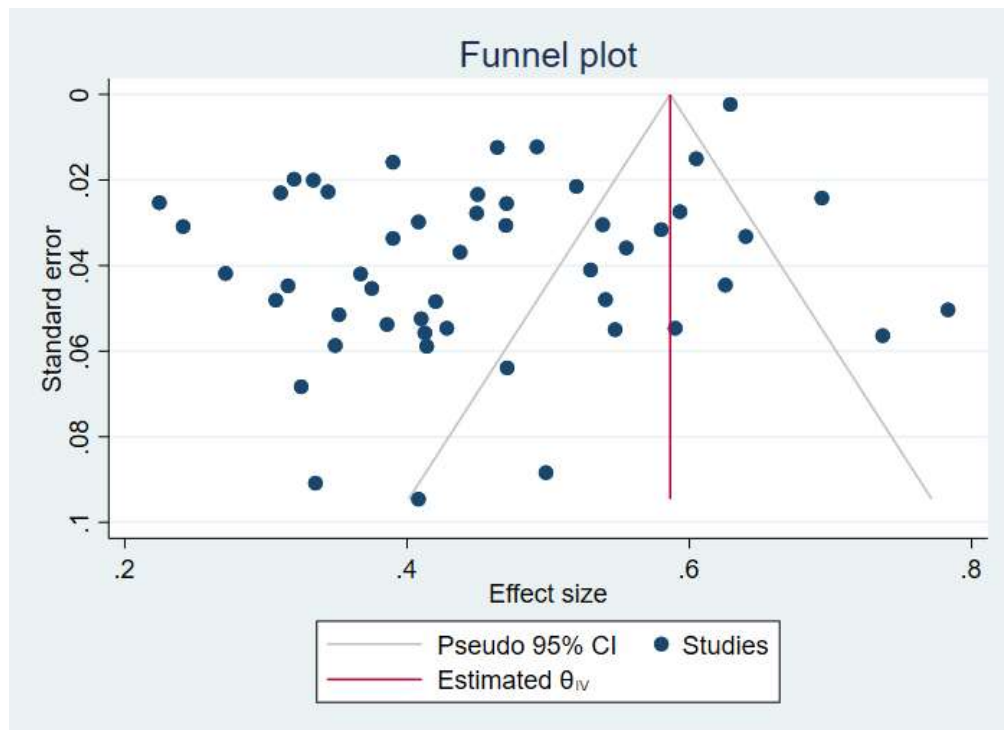
**FIGURE S1** Quality assessment for all included studies; (a) mean quality scores for ecological and cohort studies according to various criteria (case definition and study methodology criteria); (b) quality index for ecological and cohort studies based on various years of publication.

## Supplement 6 Publication bias

(a)



(b)



**FIGURE S2** Funnel plots for cumulative survival rates. a): 3-year survival rates; b): 5-year survival rates.

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