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Manuscript Title:

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

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Table of content:

Supplement 1 PRISMA 2009 checklist

TABLE S1 PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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
RESULTS			
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
DISCUSSION			

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
FUNDING			
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

Embase (Ovid):

1. idiopathic pulmonary fibrosis.tw.
2. cryptogenic fibrosing alveolitis.tw.
3. usual interstitial pneumonitis.tw.
4. usual interstitial pneumonia.tw.
5. fibrosing alveolitis.tw.
6. IPF.tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. mortality.tw.
9. survival.tw.
10. 8 or 9
11. 7 and 10
12. limit 11 to (human and yr="1950 - 2021")

PubMed:

(((((((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.

Scopus:

((TITLE-ABS-KEY ("MORTALITY") OR TITLE-ABS-KEY ("SURVIVAL")) AND PUBYEAR > 1959 AND PUBYEAR < 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")))

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
Exclusion of other causes of ILDs	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
Clinical characteristics	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
	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_{CO}, 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
High-resolution computerised tomography (HRCT)	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
Histopathological confirmation	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
Characteristics of IPF subjects	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_{CO}: 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]

Element	Quality assessment criteria	Items
Population	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
Data collection	Were standardised data collection methods/protocols used?	M4
	Was the methodology described insufficient detail?	M5
	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
Data analysis	Were appropriate statistical methods used for analysis? Did the analysis methods take into consideration the sampling methods?	M9
	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
ICD-8		1968-1978	[8]
517	Other chronic interstitial pneumonia		
ICD-9		1979-1998	[9]
515	Postinflammatory pulmonary fibrosis		
516.3	Idiopathic fibrosising alveolitis		
ICD-10		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, unspecificed		
ICD-11			
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

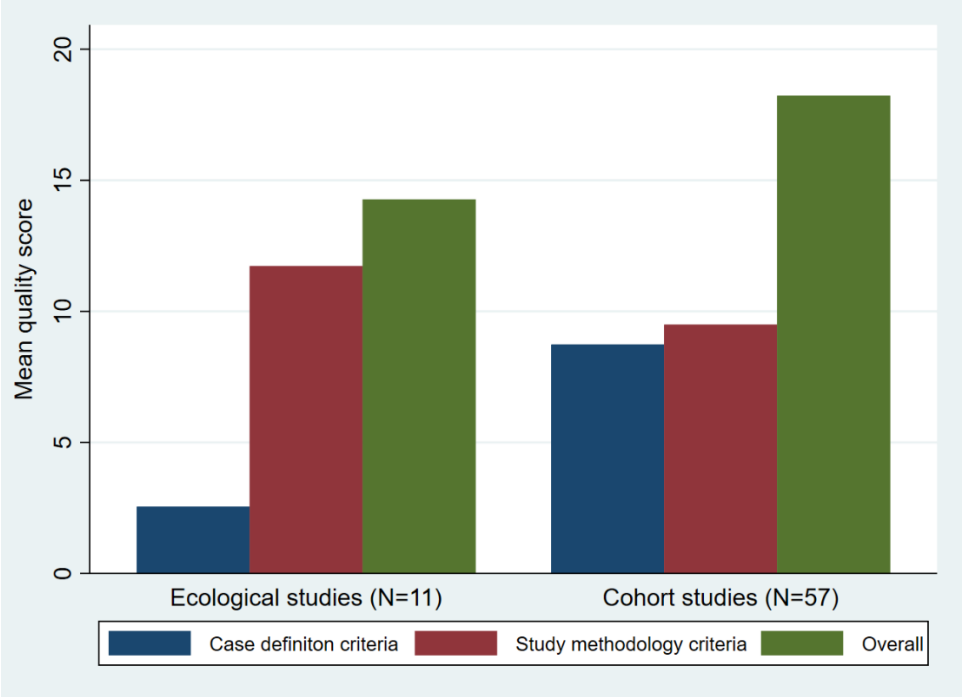
TABLE S5 A detailed scoring for both case definition and study methodology criteria for each study

First author (year) Ref.	Score for case definition	Score for study methodology	Total score	Quality index (%)	Quality level
Mortality statistics (n=6)					
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
Survival statistics (n=62)					
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)

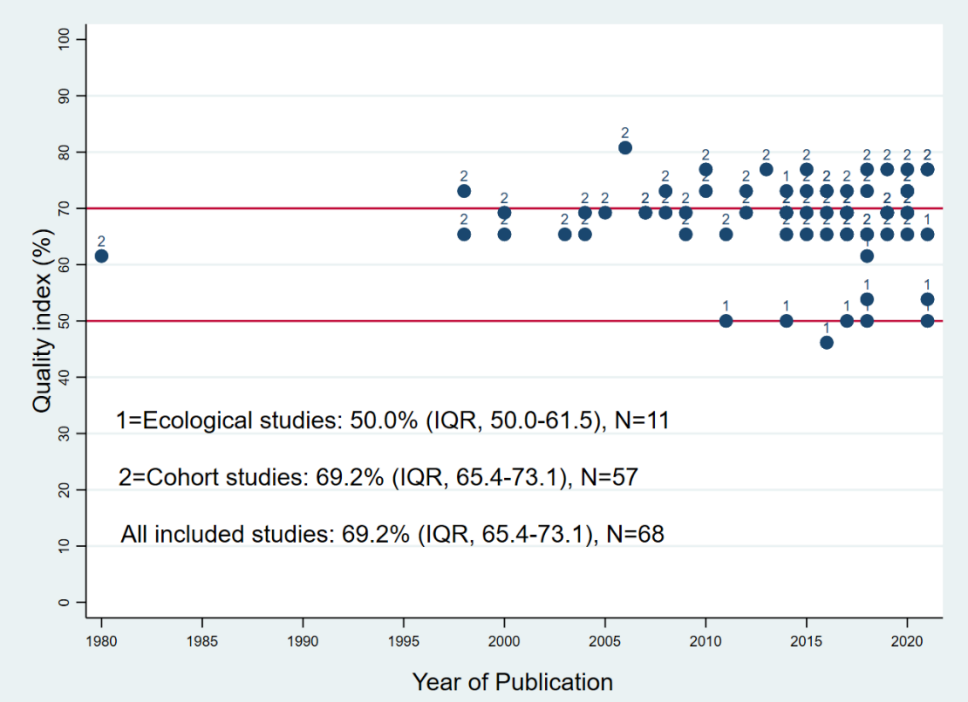
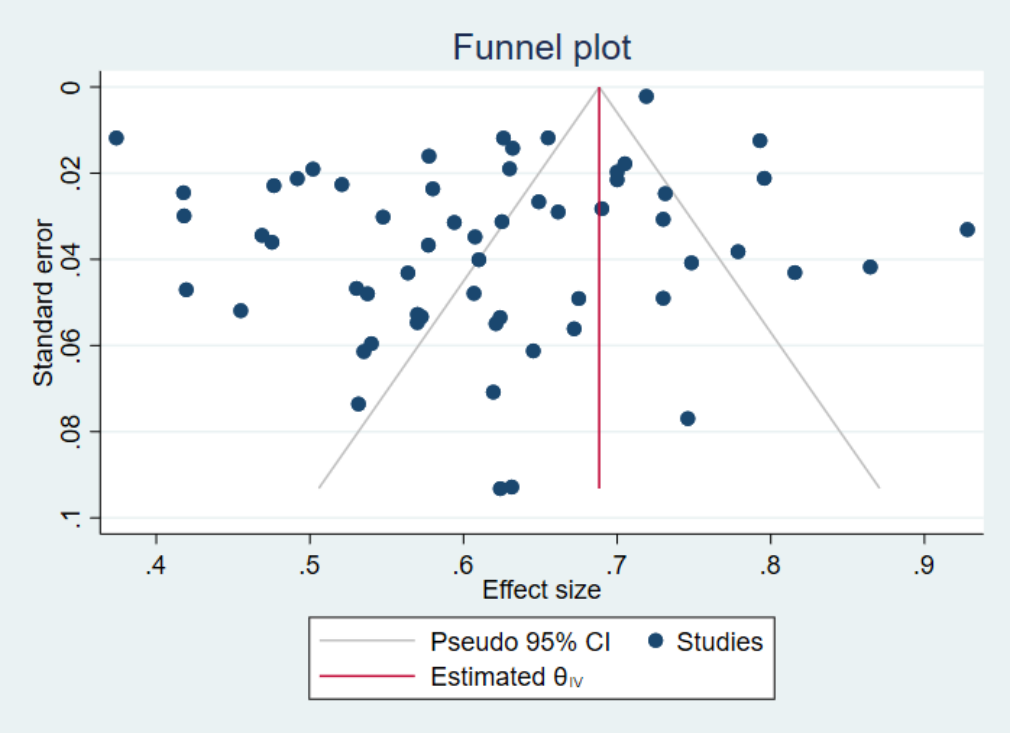


FIGURE S1 Quality assessment for all included studies; (a) mean quality scores for ecological and cohort studies according to various criteria (case definition and study methodology criteria); (b) quality index for ecological and cohort studies based on various years of publication.

Supplement 6 Publication bias

(a)



(b)

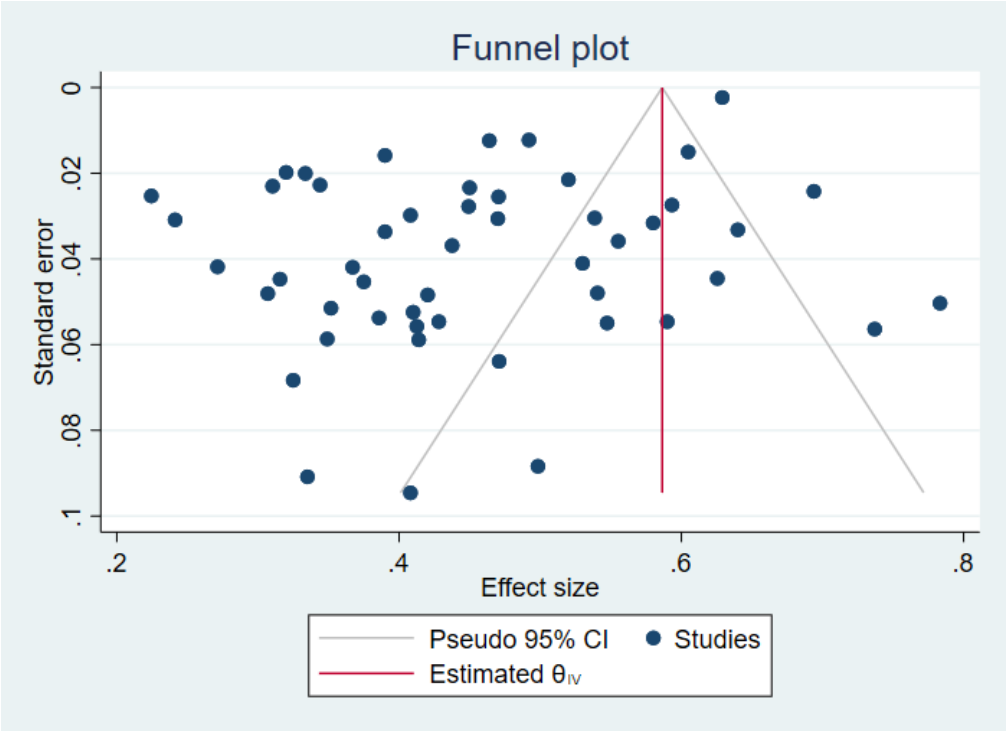


FIGURE S2 Funnel plots for cumulative survival rates. a): 3-year survival rates; b): 5-year survival rates.

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