Seminars in Arthritis and Rheumatism 60 (2023) 152187

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Survival of adults with rheumatoid arthritis associated interstitial lung disease - A systematic review and meta-analysis

HJ Farquhar [a,*], N Beckert [a], L Beckert [a], AL Edwards [b], EL Matteson [c], C Frampton [a], LK Stamp [a]

[a] Department of Medicine, University of Otago, Christchurch, Christchurch, New Zealand
[b] Respiratory Department, Christchurch Hospital, Christchurch, New Zealand
[c] Division of Rheumatology and Department of Health Sciences Research, Mayo Clinic College of Medicine, Rochester, Minnesota

ARTICLE INFO

Keywords:
Rheumatoid arthritis
Interstitial lung disease
Survival
Systematic review
Meta-analysis

ABSTRACT

Background: Rheumatoid arthritis associated interstitial lung disease (RA-ILD) is associated with high levels of morbidity and mortality. The primary aim of this systematic review was to determine the duration of survival, from time of diagnosis of RA-ILD.

Methods: Medline (Ovid), Embase (OVID), CINAHL (EBSCO), PubMed, and the Cochrane Library were searched for studies that reported duration of survival from time of diagnosis of RA-ILD. Risk of bias of included studies was assessed based upon 4 domains of the Quality In Prognosis Studies tool. Results for median survival were presented by tabulation and discussed qualitatively. Meta-analysis of cumulative mortality at 1 year, >1y to ≤3 years, >3 years to ≤5 years, and >5 years to≤ 10 years was undertaken, for total RA-ILD population, and according to ILD pattern.

Results: 78 studies were included. Median survival for the total RA-ILD population ranged from 2 to 14 years. Pooled estimates for cumulative percentage mortality up to 1 year were 9.0% (95% CI 6.1, 12.5, I^2 88.9%), >1 to ≤3 years 21.4% (17.3, 25.9, I^2 85.7%), >3 to ≤ 5 years 30.2% (24.8, 35.9, I^2 87.7%), and > 5 to ≤ 10 years 49.1% (40.6, 57.7 I^2 85.0%). Heterogeneity was high. Only 15 studies were rated as low risk of bias in all 4 domains assessed.

Conclusion: This review summarises the high mortality of RA-ILD, however the strength of conclusions that can be made is limited by the heterogeneity of the available studies, due to methodological and clinical factors. Further studies are needed to better understand the natural history of this condition.

Introduction

Rheumatoid arthritis (RA) affects approximately 0.5–1% of the population. Clinically significant interstitial lung disease (ILD) occurs in approximately 5–10% of individuals with RA. The frequency of subclinical disease is much higher, with up to 58% of persons with RA having abnormalities consistent with ILD on one or more investigations [1–3]. Histologically, a usual interstitial pneumonia (UIP) pattern is more common in RA-ILD compared with ILD associated with other connective tissue diseases. A range of other patterns are also recognised including non-specific interstitial pneumonia (NSIP), organising pneumonia (OP), lymphocytic interstitial pneumonia (LIP), diffuse alveolar damage (DAD), and desquamative interstitial pneumonia (DIP) [4,5].

The aetiology of RA-ILD is incompletely understood, and is believed to be multifactorial with a combination of environmental and genetic risk factors. The risk of developing ILD has been reported to be higher in those with an older age at RA onset [1,6], in men [1,3,7,8], and amongst smokers [9,10]. Smoking has also been associated with a UIP pattern [11]. Increased articular disease activity has also been shown to be associated with an increased risk of RA-ILD; HR 2.22, 95% CI 1.28–3.82, for moderate/high disease activity compared to group with remission/low disease activity [12]. A variant in the promoter of MUC5B has been associated with RA-ILD, and in particular a UIP pattern of disease (adjusted OR 3.1, 95% CI 1.8, 5.4, for RA-ILD vs RA without ILD in

Abbreviations: CTD, connective tissue disease; DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; FVC, forced vital capacity; HRCT, high resolution computed tomography; ILD, interstitial lung disease; LIP, lymphocytic interstitial pneumonia; NSIP, non specific interstitial pneumonia; OP, organising pneumonia; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia; QUIPS, Quality In Prognosis Studies.

* Corresponding author.
E-mail address: hamish.farquhar@cdhb.health.nz (H. Farquhar).

https://doi.org/10.1016/j.semarthrit.2023.152187

Available online 9 March 2023

combined analysis of discovery population and multiethnic case series) [13].

Observational studies suggest potential benefit of a number of immunosuppressive therapies, but data from randomised controlled studies in RA-ILD are lacking [14]. Antifibrotic agents have been shown to slow deterioration in pulmonary function tests in some patients with RA-ILD. The INBUILD trial was a 52-week randomised double blind placebo-controlled trial of nintedanib in 663 patients with progressive fibrosing interstitial lung disease, that included 89 participants with RA-ILD, and reported a lower rate of annual decline in forced vital capacity (FVC) in patients who received nintedanib compared with placebo. Mortality was studied as a secondary endpoint, and was not found to differ significantly between the nintedanib group and the placebo group in the overall study, or in the subgroup of individuals with progressive autoimmune disease related ILDs [15,16]. TRAIL 1 was a phase 2 randomised controlled trial of pirfenidone in RA-ILD, that was stopped early due to slow recruitment and the COVID-19 pandemic. The available results did not demonstrate a statistically significant difference in the primary composite endpoint of decline from baseline in percent predicted FVC of 10% or greater or death during the 52-week treatment period; a statistically significant reduction in annual decline in FVC was reported [17].

Further research is required to better understand the natural history of RA-ILD. Duration of survival has not been a focus of previous systematic reviews. Understanding prognosis in terms of duration of survival can assist meaningful discussions with individuals with RA-ILD and may help serve as a baseline for future studies that have mortality as an outcome. Therefore, we undertook a systematic review to determine the duration of survival, from time of diagnosis of RA-ILD to death from any cause, regardless of treatments.

Materials and methods

Search strategy and selection criteria

A systematic review and meta-analysis of studies that report duration of survival of persons with RA-ILD was undertaken. The protocol was prospectively registered with the International Prospective Register of Reviews (PROSPERO CRD42020173714) [18].

Inclusion criteria were: randomised controlled trials, cohort studies, or case control studies of persons with RA-ILD reporting overall survival/mortality, participants aged $\geq$ 18 years, with a diagnosis of RA-ILD (as defined by the investigators of the original studies), and study duration at least 12 months. Exclusion criteria were: studies that included participants with RA-ILD, but did not report survival for persons with RA-ILD separately, studies without a clear definition of RA-ILD, (e.g., studies that include drug reactions), review articles, case reports, and non-English language studies. Studies that reported survival according to an investigational prognostic factor but not overall survival were also excluded.

Medline (Ovid), Embase (Ovid), CINAHL (EBSCO), PubMed, and the Cochrane Library were searched from inception up until March 31st 2020. An updated search was performed on November 16th 2021. References lists of included studies and relevant review papers, and www.clinicaltrials.gov were also searched.

The search strategy was informed by previous systematic reviews of prognostic factors in RA-ILD and overall prognosis in idiopathic pulmonary fibrosis [19–21]. Medical subject headings and text words for RA, connective tissue disease (CTD), and ILD, were combined with search terms based upon a previously published strategy for identifying prognostic studies [22], and terms based on the Cochrane Highly Sensitive Search Strategy (sensitivity maximising version) for identifying randomised trials [23]. Additionally, studies focussed on RA rather than RA-ILD were searched by combining search terms for RA only, with terms based upon the sensitivity and precision maximising version of the Cochrane Highly Sensitive Search Strategy, in order to capture relevant data that may not be detected when searching for studies that focus on persons with RA-ILD or CTD-ILD. The MEDLINE search strategy is outlined in supplementary figure 1.

Articles identified from the database searches were managed using Covidence online software [24]. Two investigators independently screened titles and abstracts for inclusion (HF or LS plus one other investigator: NB, CS, or EL). Full texts were located using the automated article finding function in EndNote, online searching, and the University of Otago library catalogue. Full text reports were reviewed independently by two investigators (HF plus one other investigator: LS, NB, or LB) and assessed for inclusion in final review. Disagreements were resolved by discussion (HF plus one other investigator: LS, NB or LB). Multiple reports from the same study, or population (identified by location, institution, or research cohort) with RA-ILD were included if they reported unique data for duration of survival from the time of RA-ILD diagnosis, for example by ILD subtype. When there were multiple reports from the same study or population that did not have unique data relating to overall duration of survival, only the most comprehensive report was included.

Data extraction

Data from the included studies was independently extracted by two investigators (HF and LS) using a standardised form within Covidence. Disagreements were resolved by discussion until consensus was reached. Where multiple reports from the same study were included, data was extracted from each individual record and acknowledged in the results section of the review.

Data items relating to study characteristics included study funding source, year of publication, study design, population studied, classification criteria for RA, diagnostic criteria for RA-ILD, duration of follow-up, baseline characteristics of participants, and treatments received.

Risk of bias assessment

Risk of bias was assessed using pre-defined criteria, based upon modification of the Quality In Prognosis Studies (QUIPS) tool [25], and informed by previous systematic reviews of prognosis [26,27]. One modification to the tool included removing the domains “prognostic factor measurement” and “study confounding”. This approach has been endorsed by the researchers who developed the QUIPs tool, for the purpose of assessing studies of overall prognosis [25]. Additional adaptations were made to the remaining domains to prompt consideration of aspects important to the focus of this review. The tool used for this review is shown in supplementary Table 1.The risk of bias for the domains “study participation”, “study attrition”, “outcome measurement”, and “statistical analysis and reporting” was rated as low, moderate and high, by consensus between two reviewers, (HF and LS). A study was considered low risk of bias if it had a low risk of bias in all domains.

Outcomes

The primary outcome was overall duration of survival, from time of diagnosis of RA-ILD to death from any cause. Secondary outcomes included the cumulative percentage mortality at different time-points, duration of survival for persons with RA-ILD according to radiologic/histologic pattern, and the frequency of different causes of mortality for persons with RA-ILD.

Statistical analysis

A random effects meta-analysis of cumulative mortality up to 1 year, >1y to $\leq$3 years, >3 years to $\leq$5 years, and >5 years to $\leq$10 years was undertaken, for the total RA-ILD population (defined as persons with RA-ILD not restricted to a single radiological or histological pattern), UIP at any level of confidence, definite or typical (where authors

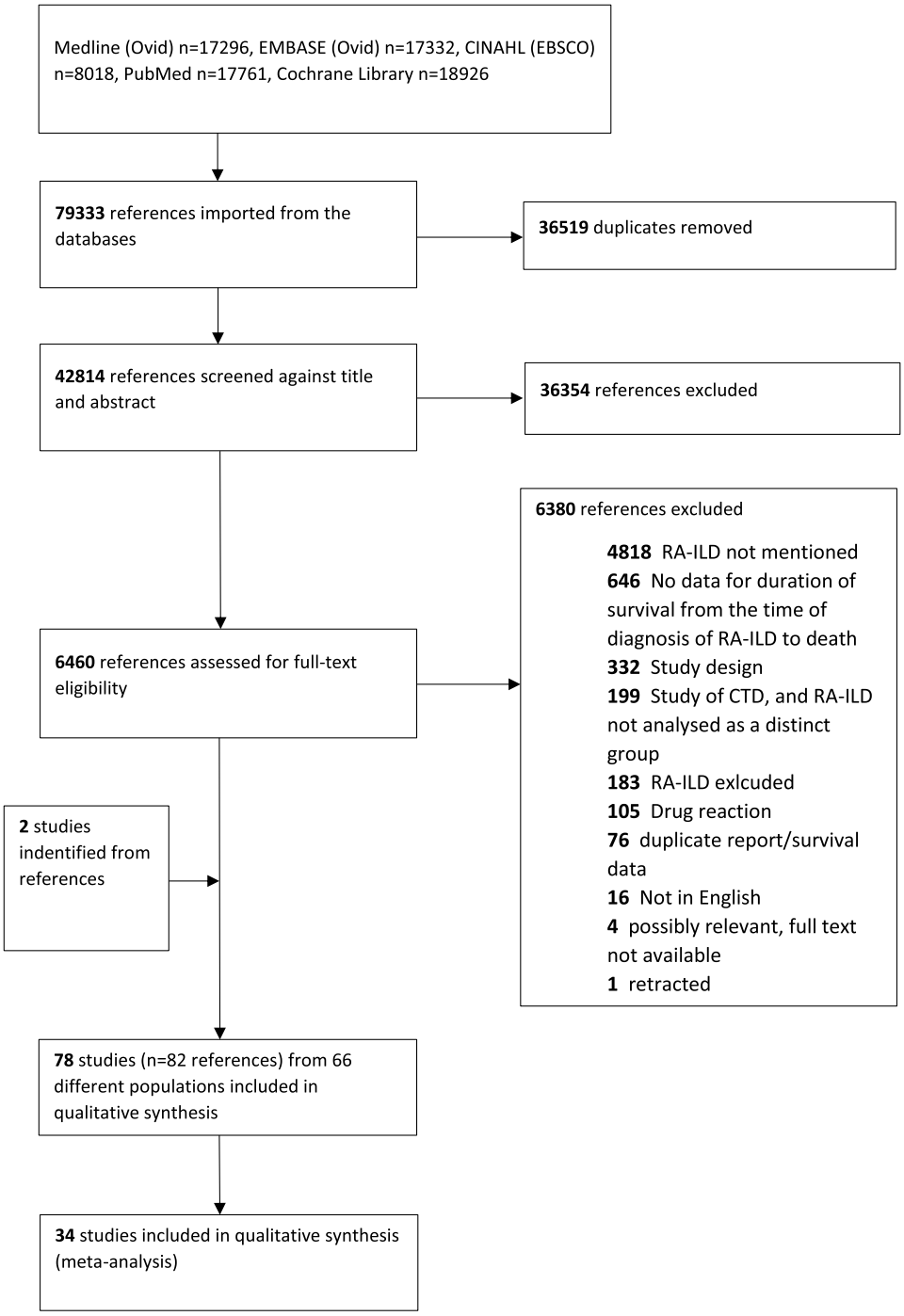

Fig. 1. Study selection.

specifically referred to participants as having this pattern) and/or biopsy proven UIP, and NSIP. Studies that grouped isolated bronchiectasis with ILD were not included in the meta-analysis. For each pattern, studies were considered for meta-analysis if they reported the cumulative percentage mortality at each time in the text of the article, or in a Kaplan Meier graph. If there were multiple studies from the same population, the study with the largest number of cases was included. In order to conduct calculations for the meta-analysis, the number of deaths was estimated using the reported percentage mortality and the number of subjects in the cohort at baseline. In order to minimise overestimation of the denominator from censoring not due to death, the following strategies were employed: If the number of persons at risk at the different time points was reported, then the number of deaths was calculated using the number of persons at risk at each time point, and the estimated number of deaths recalculated by multiplying this by the proportion mortality. If the actual number of deaths at each time-point was reported this process was undertaken using the actual reported number of deaths instead of calculated number of deaths. Statistical heterogeneity was measured by calculating the I^2 statistic [28].

In order to identify factors that could explain study heterogeneity in terms of median survival, we examined specific study characteristics including study aim, inclusion and exclusion criteria, method of diagnosis of RA-ILD, duration of follow-up and the population source. These associations were tested using non-parametric Wilcoxon summed rank tests.

Sensitivity analyses were undertaken restricting included studies to

Table 1
Summary of Included Studies ($n = 78$).

Characteristic	Summary
Number of participants with RA-ILD	Median (range) 48.5 (3, 3142)
Design	Prospective cohort - 10 Retrospective cohort - 61 Case control - 1 Case series −2 Non-randomised experimental study −1 Not reported - 2 Uncontrolled, open label, prospective study - 1
Location	North America - 19 South America - 2 Africa - 1 Europe - 27 Asia - 25 Multinational - 4
Population description	Single-centre - 47 Multi-centre - 18 Population-based - 5 Insurance database - 2 Unclear/not reported - 6
Criteria for RA[a]	1987 ACR criteria[b] - 29 2010 ACR/EULAR criteria[c] - 25 Disease codes[d] - 3 Physician diagnosis - 2 Not reported – 24 Other 5
Criteria used for determining ILD pattern[a]	2000 ATS/ERS[e] – 2 2002 ATS/ERS[f] – 11 2011 ATS/ERS/JRS/ALAT[g] – 13 2013 ATS/ERS[h] – 9 2018 ATS/ERS/JRS/ALAT[i] – 5 2018 Fleischner society diagnostic guidelines[j] - 1 Other – 16 Not reported −34

ACR = American College of Rehuamtology. ALAT = Latin American Thoracic Association. ATS = American Thoracic Society. ERS = European Respiratory Society. EULAR = European Alliance of Associations for Rheumatology. JRS = Japanese Respiratory Society.

[a] some studies utilise more than one criteria for classification.
[b] ACR 1987 revised criteria for the classification of rheumatoid arthritis [41].
[c] 2010 ACR/EULAR rheumatoid arthritis classification criteria [42].
[d] ICD codes and Readcodes.
[e] 2000 ATS/ERS International consensus statement for idiopathic pulmonary fibrosis [43].
[f] 2002 ATS/ERS International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias [44].
[g] 2011 ATS/ERS/ALAT statement for evidence based diagnosis and management of idiopathic pulmonary fibrosis [45].
[h] 2013 ATS/ERS update of the international multidisciplinary classification of the idiopathic interstitial pneumonias [46].
[i] 2018 ATS/ERS/JRS/ALAT clinical practice guideline for idiopathic pulmonary fibrosis [47].
[j] 2018 Fleischner Society white paper for idiopathic pulmonary fibrosis [48].

those that were: retrospective, prospective, included >20 persons with RA-ILD, low risk of bias in all domains, and not low risk of bias in all domains. The effect of adjusting for censoring not due to death was also examined by conducting the analysis using number at risk at baseline for all calculations. The potential effect of change in survival over time was examined by conducting the analysis for studies published in 2010 and earlier, and after 2010. Because no randomised controlled trials were included, and only two studies with $n<20$ for total RA-ILD were included in the primary analysis, further sensitivity analysis based upon study design, and $n<20$ were not performed. Analyses were performed using a random effects model with Medcalc® Statistical Software version 20.113.

Table 2
Median Survival.

Study ID	Median Survival (years)			
	total RA-ILD pop	UIP	NSIP	Other pattern
Hakala [49]	3.5	na	na	na
Rajasekaran [50]	5	na	na	na
Park [51]	na	7.3[a]	na	na
Bongartz [1]	2.6	na	na	na
Del [52]	7.2	na	na	na
Koduri [6]	3	na	na	na
Kim [53]	5.0	3.2[b]	na	non-UIP: 6.6 indeterminate UIP/NSIP: 6.6
Navaratnam [54]	6.6	na	na	na
Tsuchiya [55]	na	3.9[c]	17.0	DAD: 0.2
Solomon [56]	3.7	3.3[a]	na	na
Song [57]	na	4.7[d]	na	na
Moua [58]	na	3.2[a]	na	na
Strand [59]	na	5.5[a]	na	na
Nakaya [39]	na	9.0[a]	na	na
Krause [60]	na	3.8[c]	na	without UIP: 3.6
Lee [30]	2	na	na	na
Nunez [61]	7.4	6[e]	na	non-UIP: 8.9
Solomon [62]	10.4	10.2[e]	13.6	na
Yunt[f] [63]	na	8.3[b] 6.1[g]	na	na
Nurmi [64]	8.9	7.7[b]	na	non-UIP 11.4
Zamora-Legoff [65]	6.6	5.7[c]	na	OP: 3.4
Hyldgaard [66]	6.6	na	na	na
Rojas-Serrano [32]	5.8	na	na	na
Jacob [67]	na	3.6[b]	na	Without definite UIP: 11.5
Raimundo [68]	7.8	na	na	na
Yamakawa [69]	na	6.8[b] 9.1[h]	7.8	NSIP/UIP: 8.6
Yamakawa [70]	8.6	na	na	na
Jacob [71]	na	2.6[i]	na	na
Fui [34]	na	7.9[c]	na	na
Huang [72]	11.3	na	na	na
Kim [73]	na	4.0[c]	na	na
Sueyasu [74]	4.7	na	na	na
Ekici [75]	12.1	10.8[c]	na	na
Nieto [76]	8.2	7.9[c]	na	na
Cano-Jimenez [77]	3.4	na	na	na
Chen [78]	14	na	na	na
Kelly [79]	1990–1995[j]: 2.8 1996–2002: 3 2003–2008: 4.2 2009–2015: 8.2			
Park [80]	9.7	na	na	na

DAD: diffuse alveolar damage. na: not available. na: not available. NSIP: non-specific intersitial pneumonia. OP: organizing pneumonia. RA-ILD: rheumatoid arthritis associated interstitial lung disease. UIP: usual interstitial pneumonia.

[a] diagnosed on biopsy.
[b] authors referred to as definite UIP.
[c] authors referred to as UIP without specific reference to a level of confidence.
[d] definite UIP, or biopsy.
[e] UIP or possible UIP.
[f] primary study.
[g] possible UIP.
[h] probable UIP.
[i] honeycombing occurring in a non IPF-like distribution.
[j] time period of diagnosis.

Results

Study selection

79,333 references were identified from the database searches and

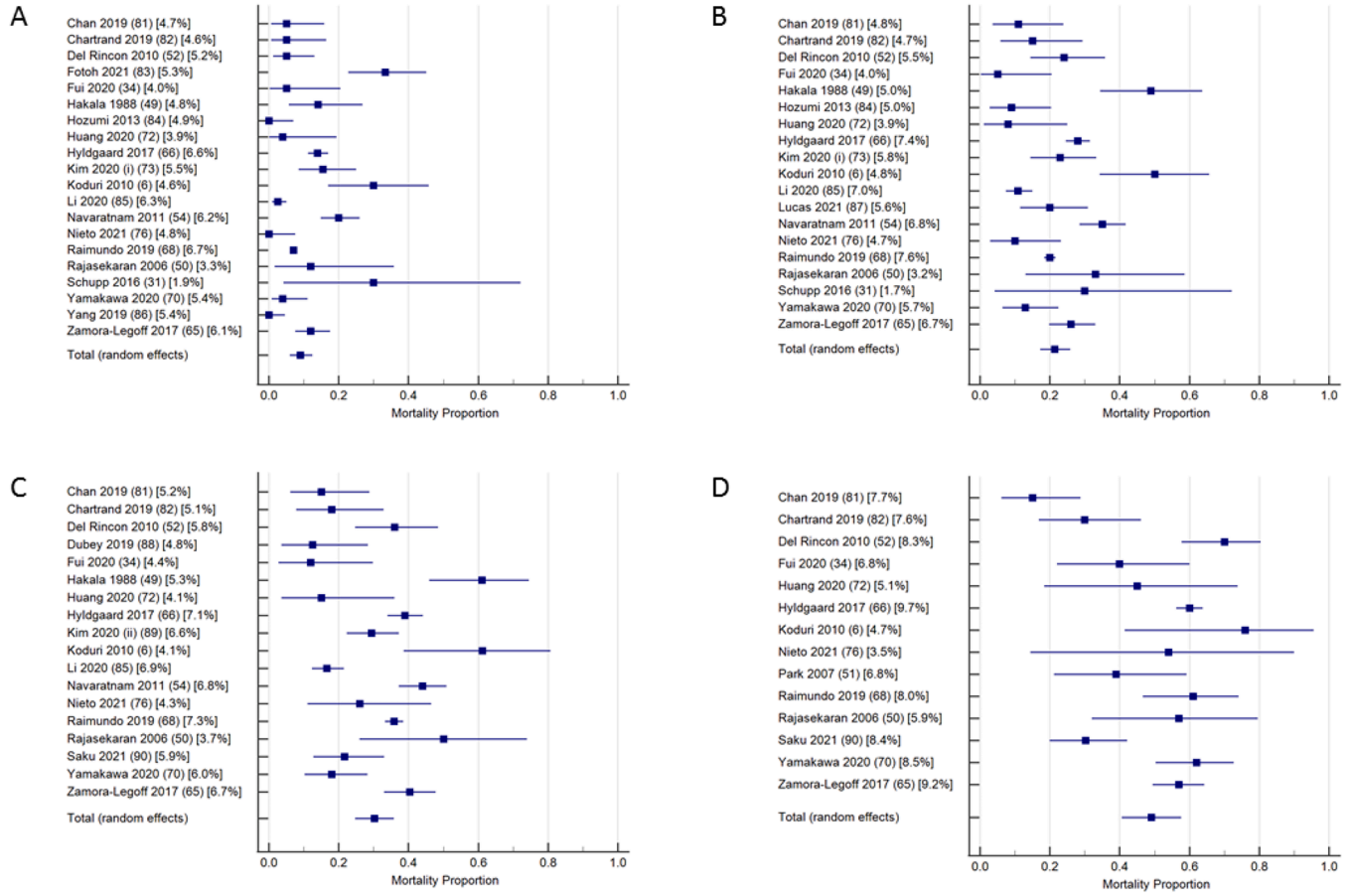

Fig. 2. Cumulative mortality for total RA-ILD population. Boxes represent proprotion mortality, and horizontal lines represent 95% confidence intervals. The reference for each study is in circular brackets, and the weighting is in square brackets. At A: 1 year, pooled estimate 9.0% (95% CI 6.1, 12.5), I^2 88.9% B: >1 to ≤3 years, pooled estimate 21.4% (17.3,25.9), I^2 85.7% C: >3 to ≤5 years, pooled estimate 30.2% (24.8,35.9), I^2 87.7% D: >5 to ≤10 years, pooled estimate 49.1% (40.6, 57.7), I^2 85.0%.

uploaded to Covidence. Following removal of duplicates, 42,814 references underwent title and abstract screening, and 6460 full texts were assessed for eligibility. Finally, 78 studies were included in the systematic review (Fig. 1). A summary of study characteristics, based upon the primary studies is shown in Table 1. Fifty-nine of the studies were full texts, 17 were abstracts, and 2 were letters. Most of the studies were retrospective, and single centre in design. Of studies that reported a median duration of follow-up, most were less than 5 years duration. Twenty-seven studies reported median follow-up duration (< 5 years n = 20, ≥ 5 years n = 7). Eighteen studies reported mean follow-up (<5 years n = 10, ≥ 5 years n = 8). Twenty studies did not report duration of follow-up and 13 reported follow-up using a different measure. Only 15 studies were rated as low risk of bias in all 4 domains. Nine studies stated that one of their primary objectives was evaluation of a specific therapy in persons with RA-ILD [29–37]. Indications for investigating subjects for ILD were inconsistently reported, however no study reported that participants were included on the basis of screening for ILD using HRCT. Further detail regarding risk of bias and characteristics of the individual studies is reported in supplementary Tables 2 and 3.

Mean age at ILD diagnosis ranged from 52 to 72 years (n = 32 studies). The percentage of female participants ranged from 0% to 87% (median 54%, n = 61 studies). Twenty-two studies reported use of DMARDs at any time during the course of RA or without specific reference to the timing of ILD diagnosis, 17 reported use of DMARDs prior to ILD diagnosis, and 37 reported treatments following ILD diagnosis. Three studies only included subjects diagnosed with ILD prior to the onset of RA [38–40], and the remainder either included participants who initially developed RA, or developed either manifestation first. Detailed participant characteristics for the individual studies are reported in supplementary Table 4.

Median survival for persons with RA-ILD

Median survival for the total RA-ILD population ranged from 2 to 14 years (n = 25 studies) (Table 2). Median survival for persons with a UIP pattern ranged from 2.6 (group categorised as honeycombing occurring in a non IPF-like distribution according to a modification of the Fleischner Society IPF guidelines) to 10.8 years (n = 20 studies). Three studies reported median survival of NSIP ranging from 7.8 to 17.0 years. Additional data relating to overall survival, including studies that do not report median survival, are shown in supplementary Table 5.

As noted above there was a wide range in median survival. Specific study characteristics that may have influenced overall median survival, including study aim, inclusion and exclusion criteria, method of diagnosis of RA-ILD, duration of follow-up and the population source are outlined in supplementary Table 6. Of these there was sufficient variability in population source (tertiary vs other), duration of follow-up (mean/median <5years vs ≥5 years) and method of RA-ILD diagnosis (biopsy vs HRCT vs multidisciplinary assessment). We explored the associations between these factors and median survival to determine whether these study characteristics influenced survival estimates. Only, duration of follow-up showed any statistically significant association with a median survival in those with follow-up <5 years of 7.6 years compared with 4.7 years in those with longer follow-up (p = 0.023). There was no association between population source and survival (median survival tertiary population 7.0 years vs other population 6.6 years;

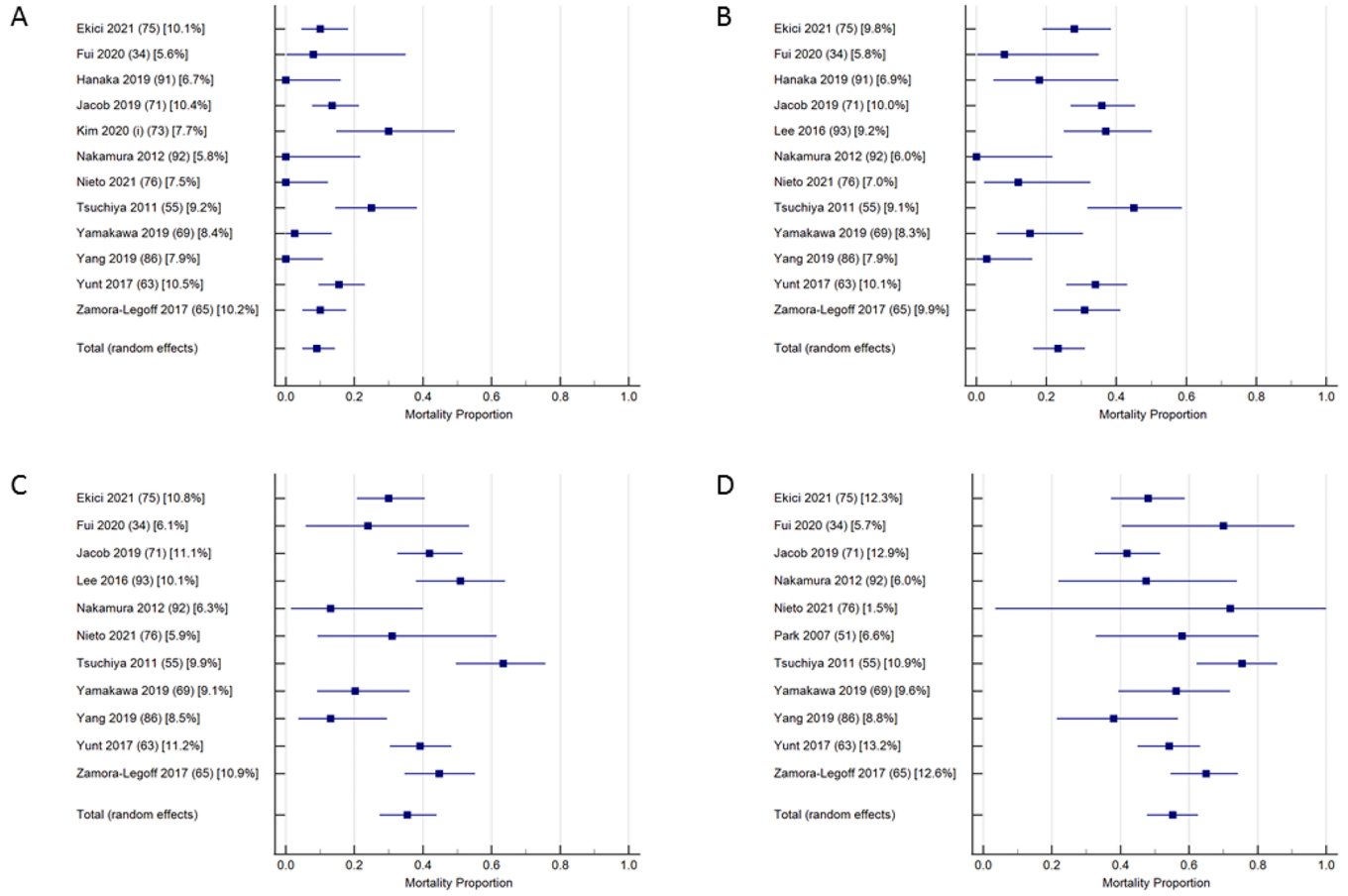

Fig. 3. Cumulative mortality for UIP pattern (any level of confidence). A: 1 year, pooled estimate 9.1% (95% CI 4.9, 14.3), I^2 75.9% B: >1 to ≤3 years, pooled estimate 23.3% (16.4, 31.1), I^2 79.6% C: >3 to ≤5 years, pooled estimate 35.5% (27.4, 44.0), I^2 78.3%, D: >5 to ≤10 year,s pooled estimate 55.3% (47.7, 62.7), I^2 65.8%. (See reference [91]).

$p = 0.40$). Likewise, there was no association between method of RA-ILD diagnosis and survival (median survival biopsy ($n = 1$ study) 3.7 years, HRCT 7.4 years and multidisciplinary 6.6 years; $p = 0.45$). For studies that reported median survival for UIP ($n = 21$) none of these three factors influenced median survival ($p>0.44$ for all).

Cumulative mortality at different timepoints

The pooled estimates for cumulative mortality at different time points for the total RA-ILD population, UIP (any level of confidence), and NSIP are shown in Figs. 2–4 respectively. A further analysis using only those studies which contributed data for all time points in the primary analysis for the total RA-ILD population indicated no profound difference in the pooled estimates for all studies vs. this restricted group (supplementary figure 2).

The results of the meta-analyses are summarised in Table 3. High values for I^2 indicate a high level of heterogeneity. The cumulative percentage mortality for a total RA-ILD population at 1 year was 9.0% (95% CI 6.1, 12.5), >1 to ≤3 years 21.4% (17.3, 25.9), >3 to ≤5years 30.2% (24.8, 35.9), >5 ≤ 10 years 49.1% (40.6, 57.7). Subgroup analyses for UIP (any level of confidence) and definite or typical or biopsy proven UIP showed cumulative percentage mortality at >5 to ≤10 years of 55.3% (47.7, 62.7), and 56.9% (48.3, 65.3) respectively. Sensitivity analysis restricting the included studies to those published in 2010 or earlier showed cumulative percentage mortality at >3 ≤ 5 years 49.9% (37.5, 62.3). Undertaking the analysis using baseline number at risk for all calculations rather than using number at risk at the different time points where reported showed the percentage mortality at >3 ≤ 5 years was 30.5% (25.5, 35.7) indicating the results have a low sensitivity to these calculations. Further data regarding percentage mortality as reported in the text, or x-axis divisions of Kaplan-Meier graphs are presented in supplementary Table 7. Causes of death are shown in supplementary Table 8.

Discussion

This systematic review included 78 studies reporting duration of survival of persons with RA-ILD. Median survival of the total RA-ILD population, ranged from 2 to 14 years. Pooled estimates for the cumulative percentage of mortality at 1 year, >1 to ≤3 years, >3 to≤5 years, and >5 to ≤10 years were 9.0%, 21.4%, 30.2%, and 49.1% respectively. Whilst this study did not directly compare mortality rates in different patterns of disease, subgroup analysis showed higher pooled estimates for cumulative mortality for individuals with a UIP pattern.

These results assist with better understanding the natural history of RA-ILD based upon current evidence and build upon previous systematic reviews of prognostic factors [20,21,95]. A systematic review of prognosis in IPF without anti-fibrotic therapy reported pooled percentages of mortality 1–2 years, 2–5 years, and ≥ 5 years of 12%, 38%, and 69% [96]. Whilst IPF and RA-ILD are different diseases, and the time periods analysed are different, these results are of interest given the two conditions are recognised to share certain clinical and genetic features in common [97].

Mortality in RA-ILD has been shown to have reduced over time potentially due earlier diagnosis and improved treatments [79]. When the sensitivity analysis was run to only include studies published prior to

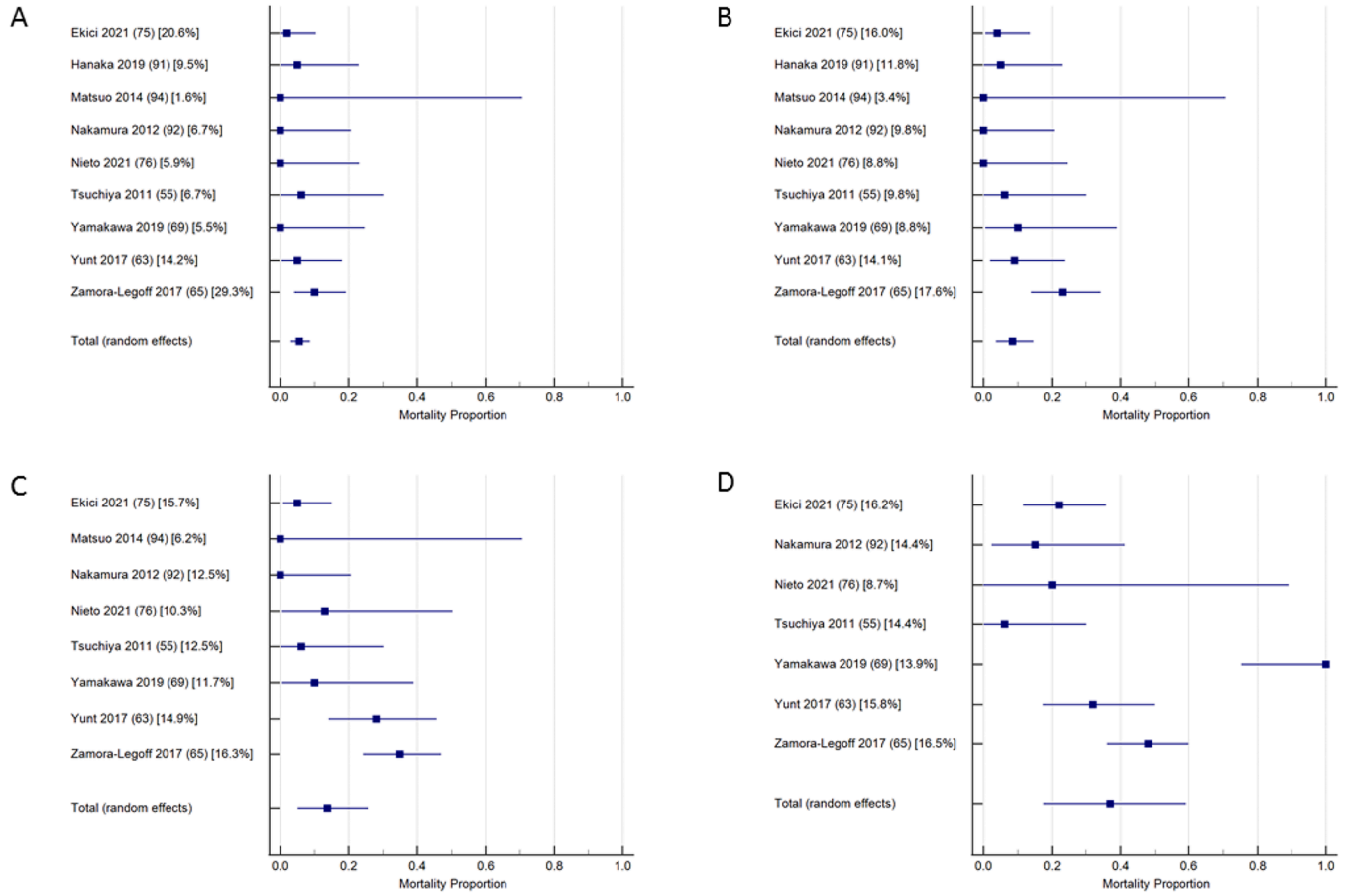

Fig. 4. Cumulative mortality for NSIP pattern. A: 1 year, pooled estimate 5.6% (3.1, 8.8), I^2 0.0% B: >1 to ≤3 years, pooled estimate 8.4% (3.8, 14.7), I^2 53.3% C: >3 to ≤5 years, pooled estimate 13.7% (5.1, 25.6), I^2 77.1% D: >5 to ≤10 years, pooled estimate 37.1% (17.5, 59.2), I^2 89.3%. (See references [91] and [94]).

and including 2010, it yielded somewhat higher percentage mortality results than the primary analysis and provides some evidence in support of this. However, the strength of conclusions that can be drawn from this analysis are limited. The year of publication is an imprecise measure of when persons were diagnosed with RA-ILD; some of the included studies had enrolment periods spanning several years.

The main limitation of this systematic review is the heterogeneity of the results, which limits confidence in the pooled estimates. It is likely that clinical diversity in the included subjects contributes to this. Sources of heterogeneity could include differences in study objectives, as well as the criteria used for RA-ILD diagnosis and classification. It is also possible that some of the observed differences may relate to differences in survival of the underlying populations from which participants were drawn. Differences in the stage of disease, and severity at baseline are also likely to have occurred, for reasons including study methodology and regional variation in practice. The indications for investigating a person for RA-ILD are likely to have varied for reasons including availability of appropriate diagnostic testing procedures and local practice. At the present time, screening for RA-ILD with HRCT is not standard practice in most parts of the world. It therefore seems likely that most of the study participants would be considered to have clinically significant RA-ILD. Importantly we examined a number of these variables to look for associations with median survival. It is very apparent from this that unlike RCTs where there are specific inclusion and exclusion criteria based on a range of patient demographic and clinical features including disease severity, for these observational studies the inclusion criteria were predominantly based simply on presence of RA-ILD, and the exclusion criteria focussed on excluding other forms of ILD. Therefore, further analysis based on eligibility is not possible. Of the three factors where there was sufficient variability only duration of follow-up was associated with median survival. Of note populations sourced from National or tertiary referral centers, where one might anticipate those individuals with more severe or rapidly progressive disease might be seen was not associated with shorter median survival. These data suggest that prospective studies of sufficient duration and with well defined populations will be required if the sources of variability in survival are to be elucidated more clearly.

A further limitation is the difficulty in accounting for censored data in the meta-analysis of proportion of mortality at different time-points. Considering this, the number of persons at risk at each time point were used in calculations when reported. Sensitivity analysis not using this method to account for censoring did not meaningfully affect the results. Additionally, because this review focussed on duration of survival from time of ILD diagnosis, studies that report mortality using a different measure were not included.

A strength of this systematic review is the comprehensive search strategy. A broad approach was taken, as it was felt possible that data to answer the review aims may be contained within studies focussed on persons with RA. However, none of the included studies were trials focussed on RA and therefore it is unlikely that a significant number of relevant studies have been missed.

In conclusion, this study provides a comprehensive review of the duration of survival of persons with RA-ILD. It supports the substantial impact on mortality of this condition. It also highlights the diverse nature of both the condition itself and the related research. Further studies are required to better understand the pathogenesis and natural history of RA-ILD, in order to help understand the effects it has on persons with RA, and evaluate the benefit of new therapeutic strategies. In particular,

Table 3
Summary results of random effects meta-analysis.

Group	1 year			>1 ≤ 3 year			>3 ≤ 5 year			>5 ≤ 10 year		
	sample size (n)	% mortality (95% CI)	I^2 (%) (95% CI)	sample size (n)	% mortality (95% CI)	I^2 (%) (95% CI)	sample size (n)	% mortality (95% CI)	I^2(%)(95% CI)	sample size (n)	% mortality (95% CI)	I^2 (%) (95% CI)
Total RA-ILD pop	5144	9.0 (6.1, 12.5)	88.9 (84.4, 92.2)	4357	21.4 (17.3, 25.9)	85.7 (79.1, 90.3)	3039	30.2 (24.8, 35.9)	87.7 (82.0, 91.5)	1322	49.1 (40.6, 57.7)	85.0 (76.4, 90.5)
UIP	657	9.1 (4.9, 14.3)	75.9 (57.8, 86.2)	683	23.3 (16.4, 31.1)	79.6 (65.1, 88.1)	653	35.5 (27.4, 44.0)	78.3 (61.6, 87.7)	597	55.3 (47.7, 62.7)	65.8 (35.1, 81.9)
Definite/typical/ biopsy proven UIP[a]	232	15.4 (8.9, 23.3)	51.1 (0.0, 80.6)	276	33.1 (21.1, 46.4)	78.8 (53.6, 90.4)	276	43.2 (31.9, 54.8)	71.1 (32.8, 87.6)	232	56.9 (48.3, 65.3)	35.7 (0.0, 74.3)
NSIP	244	5.6 (3.1, 8.8)	0.0 (0.0, 53.6)	243	8.4 (3.8, 14.7)	53.3 (0.8, 78.0)	216	13.7 (5.1, 25.6)	77.1 (54.6, 88.5)	206	37.1 (17.5, 59.2)	89.3 (80.4, 94.1)
Sensitivity analyses for total RA-ILD pop												
Retrospective[b]	4390	6.6 (4.0, 9.8)	85.4 (77.4, 90.5)	3589	19.9 (15.6, 24.6)	83.1 (73.4, 89.3)	2604	28.2 (22.2, 34.6)	88.7 (82.8, 92.6)			
Prospective[c]	679	15.6 (8.2, 25.0)	66.1 (0.5, 88.4)	768	28.1 (14.1, 44.7)	84.9 (62.5, 93.9)	435	39.1 (22.8, 56.8)	81.3 (51.1, 92.8)			
$N > 20$[d]	5119	8.6 (5.6, 12.1)	89.9 (85.6, 92.9)	4332	20.9 (16.7, 25.4)	87.1 (80.9, 91.3)	3021	29.5 (24.0, 35.2)	88.2 (82.7, 92.0)			
LROB in all domains[e]	4082	9.6 (5.2, 15.2)	91.3 (84.7, 95.1)	3373	23.7 (17.9, 30.0)	87.2 (75.8, 93.2)	2162	35.3 (30.4, 40.3)	69.6 (33.3, 86.2)			
Not LROB in all domains[f,g]	1136	10.9 (5.8, 17.3)	88.9 (83.4, 92.6)	1058	22.7 (15.6, 30.6)	87.2 (80.3, 91.7)	1007	30.4 (21.1, 40.6)	90.5 (85.6, 93.7)			
Using baseline n	5233	9.0 (6.1, 12.5)	89.2 (84.7, 92.3)	5155	21.4 (17.4, 25.8)	85.9 (79.3, 90.4)	5198	30.5 (25.5, 35.7)	88.8 (83.8, 92.2)			
Published 2010 or earlier[h]	253	19.2 (9.9, 30.6)	77.8 (50.9, 90.0)	253	40.0 (29.1,51.4)	70.6 (31.3, 87.4)	232	49.9 (37.5, 62.3)	72.4 (36.3, 88.0)			
Published after 2010[i]	4965	8.0 (4.9, 11.6)	90.2 (85.8, 93.3)	4178	18.2(14.4, 22.4)	84.4 (75.7, 90.0)	2881	25.8 (20.4, 31.6)	88.3 (82.2, 92.4)			

LROB = low risk of bias. NSIP = non-specific interstitial pneumonia. RA-ILD = rheumatoid arthritis associated interstitial lung disease. UIP = usual interstitial pneumonia.

[a] includes data from [51,58,63,69,71,92,93].
[b] includes data from [31,49,52,54,65,68,70,72,73,76,81,82,84-90].
[c] includes data from [6,34,50,66].
[d] includes data from [6,34,49,52,54,65,66,68,70,72,73,76,81-90].
[e] includes data from [6,51,65,66,68,76,84,89,90].
[f] includes data from [1,31,34,49,50,52,54,70,72,73,81-83,85-88].
[g] Data from Kim (i) [73] and Yamakawa [73] included in this analysis although primary studies were rated LROB in all domains.
[h] includes data from [1,6,49-52].
[i] includes data from [31,34,54,65,66,68,70,72,73,76,81-90].

standardisation of criteria for classifying RA-ILD, and measuring outcomes will assist comparisons of different populations as well as help in the development of evidence-based management guidelines.

Funding

HJF receives funding from scholarship grants via the University of Otago, to support PhD studies. These are funded by Canterbury Arthritis Support Trust and the Bannan bequest administered via the Foundation Trust University of Otago.

CRediT authorship contribution statement

HJ Farquhar: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. **N Beckert:** Investigation, Data curation. **L Beckert:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Supervision. **AL Edwards:** Writing – review & editing. **EL Matteson:** Writing – review & editing. **C Frampton:** Methodology, Formal analysis, Writing – review & editing. **LK Stamp:** .

Declaration of Competing Interest

LKS has received grants or contracts to from Health Research Council of New Zealand paid to their institution, royalties or licenses from UpToDate, and consulting fees from Pharmac paid to them and their institution. ELM has received royalties or licenses from UpToDate, consulting fees from Beohringer-Ingelheim and Alvotech Inc, Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Practice Point Communications/ Simply Speaking, Beohringer-Ingelheim, Novartis, Participation on a Data Safety Monitoring Board or Advisory Board for Horizon Therapeutics and National Institute of Health USA, Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid The American College of Rheumatology.

Acknowledgements

The authors would like to thank Charlotte Skelton, from The University of Otago, Christchurch, and Emma Lynch, from Christchurch Hospital, for their assistance screening titles and abstracts, Elizabeth Goddard, from the University of Otago, Christchurch, for assistance with locating full text articles, and Richard German, from the Health Sciences Library, University of Otago, Dunedin, for assistance with search strategy and protocol development, as well as staff from the University of Otago Canterbury Medical Library who provided support when the protocol was in development.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152187.

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