Autoimmunity Reviews 24 (2025) 103922

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

Updated systematic literature review and meta-analysis to inform the Italian Society of Rheumatology Recommendations on the treatment of rheumatoid arthritis-associated interstitial lung disease

A. Fassio [a], M. Sebastiani [b,c], F. Pollastri [a,*], F. Cozzini [b], C. Crotti [d], N. Ughi [e,f], E. De Lorenzis [g], S. Mancuso [h], M. Radin [i], G. Carrara [f], G. Landolfi [f], D. Rozza [f], A. Manfredi [j,k]

[a] Rheumatology Unit, University of Verona, Italy
[b] Department of Medicine and Surgery, University of Parma, Parma, Italy
[c] Rheumatology Unit, AUSL Piacenza, Piacenza, Italy
[d] Bone Disease Unit, Department of Rheumatology and Medical Science, ASST-G.Pini-CTO, Milan, Italy
[e] Division of Rheumatology, Multispecialist Medical Department, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[f] Epidemiology Research Unit, Società Italiana di Reumatologia, Milan, Italy
[g] Department of Aging Diseases, Orthopedic and Rheumatology, Rheumatology Division, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[h] Rheumatology Unit, Department of Clinical, Internal, Anaesthesiologic and Cardiovascular, Sciences, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy
[i] Nephrology and Dialysis Unit and Center of Immuno-Rheumatology and Rare Diseases (CMID), Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital ASL Città di Torino and Department of Clinical and Biological Sciences, Turin, Italy
[j] University of Modena and Reggio Emilia, Italy
[k] Rheumatology Unit, AUSL-IRCCS Reggio Emilia, Italy

ARTICLE INFO

Keywords:
Rheumatoid arthritis
Interstitial lung disease
Italian recommendations
Metanalysis

ABSTRACT

Background: rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is a severe extra-articular manifestation of rheumatoid arthritis (RA). Despite recent guideline initiatives, no treatment recommendations specifically tailored to RA-ILD have been developed in Italy. This systematic literature review (SLR) and meta-analysis was conducted to inform the Italian Society of Rheumatology (SIR) national recommendations for the management of RA-ILD.

Methods: we conducted a systematic review and meta-analysis of studies evaluating pharmacological interventions for RA-ILD from inception up to October 2023, followed by an update up to April 2025, with a predefined protocol. Eligible studies included randomized controlled trials, cohort studies, and case series reporting pulmonary function outcomes, radiological progression, adverse events, and mortality. Meta-analyses were performed, and heterogeneity and publication bias were thoroughly assessed.

Results: sixty-nine studies encompassing 7879 RA-ILD patients were included. Treatments with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), rituximab (RTX), mycophenolate mofetil (MMF), abatacept (ABA), and Janus kinase inhibitors (JAKi) were associated with stabilization or improvement of forced vital capacity (FVC). Methotrexate (MTX) was associated with reduced risk of ILD progression and mortality. Antifibrotics, particularly nintedanib, demonstrated variable efficacy, while pirfenidone showed limited benefit. Safety profiles favored antifibrotics over csDMARDs/immunosuppressants regarding serious adverse events.

Conclusions: this SLR provides an updated synthesis of evidence on RA-ILD treatments, supporting the forthcoming SIR recommendations. Despite inherent limitations of observational studies and heterogeneity, the data highlight the safety of MTX and particularly support ABA, RTX, and nintedanib as promising options, while underscoring the need for further high-quality trials specifically in RA-ILD.

* Corresponding author at: Rheumatology Unit, University of Verona, Ospedale GB Rossi, Piazzale A. Scuro, 37134 Verona, Italy.
E-mail addresses: franpollastri@yahoo.it, francesco.pollastri@univr.it (F. Pollastri).

https://doi.org/10.1016/j.autrev.2025.103922
Received 16 June 2025; Received in revised form 21 August 2025; Accepted 25 August 2025
Available online 26 August 2025

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with an autoimmune pathogenesis, affecting approximately 0.5–1 % of the adult population in Western countries. It is estimated that at least 350,000 individuals in Italy have RA [1,2]. While joint inflammation represents the primary clinical manifestation, extra-articular involvement is not uncommon. The lungs are among the main extra-articular sites that can be affected, with interstitial lung disease (ILD) being the most frequent respiratory complication [3].

RA-associated interstitial lung disease (RA-ILD) is characterized by inflammation that may progress to fibrosis in the pulmonary interstitial spaces, potentially leading to respiratory failure and an increased risk of infections and cardiac complications [3]. ILD develops in at least 10–15 % of RA patients [4] and is associated with significantly increased morbidity and mortality rates compared to RA without pulmonary involvement. The condition also imposes substantial healthcare costs, both direct (related to pharmacological treatments and management of complications) and indirect (due to loss of work ability and reduced quality of life) [5].

The management of RA-ILD is particularly challenging due to the heterogeneity of its clinical presentation and disease course, which may range from subclinical or stable to slowly or rapidly progressive forms. This complexity is further compounded by the diversity of radiological patterns and histopathological subtypes, as well as the concurrent presence of joint and extra-articular RA manifestations, which themselves exhibit considerable heterogeneity. Therefore, key factors influencing treatment decisions include joint disease activity and severity, the histopathological and radiological pattern of ILD, and the extent and progression of pulmonary involvement [6,7].

In August 2024, the American College of Rheumatology (ACR) and the American College of Chest Physicians (ACCP) published guidelines for the treatment of ILD in patients with systemic autoimmune diseases [7]. These guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology; however, unlike the 2022 Spanish recommendations [6], they provide recommendations for ILD secondary to systemic autoimmune diseases such as systemic sclerosis, idiopathic inflammatory myopathies, mixed connective tissue disease, Sjögren's syndrome, and RA, without specifically addressing the treatment of joint involvement in this patient population. Furthermore, differences in drug indications between the United States and Italy limit the applicability of the American guidelines to the Italian clinical setting.

The numerous unmet needs in the routine management of RA-ILD patients, which remain unresolved by current evidence, highlight the necessity for shared treatment recommendations in this field. In the absence of national or European guidelines specifically addressing RA-ILD treatment, the Italian Society of Rheumatology (SIR) has undertaken the development of de novo national clinical practice guidelines for the management of patients with RA-ILD, in accordance with the requirements of the National Guideline System (SNLG) of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS).

As part of this effort, a systematic literature review (SLR) was conducted to evaluate treatment options for RA-ILD, with the aim of informing the 2024 SIR recommendations on the management of patients with this condition [8].

2. Methods

2.1. Eligibility criteria and literature search

To guide the literature search, pre-defined clinical questions were formulated and structured according to the PICO method (P: patient; I: intervention; C: comparator/control; O: outcome). The outcomes (direct, surrogate, indirect, and patient-reported) were identified, classified, and ranked by importance through consultation with panel members and stakeholders. The project was approved by the Steering Committee, and the final protocol for the development of the guidelines was approved by the panel (version 2.0, July 16, 2023 [8]).

Based on the formulation of structured PICO clinical questions (population, intervention, comparator, outcome), which were modified and adapted to the Italian context from the American College of Rheumatology (ACR) Project Plan [9], the disease-related outcomes were evaluated by the panel (October 9–23, 2023) and stakeholders (February 1–15, 2024). Outcomes rated as 'important and essential' (i.e., scoring $\geq$7 on a 9-point scale) by the expert panel ($n = 21$) were prioritized, following confirmation of high agreement (score ≥ 7) by stakeholders ($n = 32$). These outcomes were selected as primary endpoints to guide the systematic review of evidence.

The literature search was conducted using customized keywords and search strings (Supplementary appendix 1) developed specifically for this new systematic review. The following databases were searched: Medline (via Ovid), Embase (via Ovid), Cochrane Library (via Cochrane Central).

A de novo systematic review was conducted from the inception of each database up to October 20, 2023. Subsequently, an updated search was performed using the same protocol, covering the period from October 1, 2023 to April 1, 2025.

2.2. Data quality assessment

Publication bias was evaluated through funnel plot visualization and Egger's test when at least 10 studies were included in the meta-analysis [10].

The Risk of Bias (RoB) was evaluated using the following tools: Risk Of Bias In Non-randomized Study - of Interventions (ROBINS-I) [11], Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) [12] for treatment evaluation. The Quality in Prognosis Studies (QUIPS) tool was used to assess the risk of bias in prognostic studies [13]. Uncontrolled studies (including studies with before-and-after design as comparator) and case series were assigned a priori as having "High" RoB.

2.3. Study selection, data extraction and analysis

The selected primary 'important and essential outcomes' were: disease activity/progression defined by percent predicted forced vital capacity (%FVC), disease activity/progression defined by diffusion capacity for carbon monoxide (%DLCO), disease activity/progression defined by chest high-resolution computed tomography (HRCT) and disease activity/progression defined by composite outcomes including pulmonary function tests (PFTs)/HRCT/symptom worsening.

In addition, serious adverse events (SAEs) and mortality were addressed. SAEs were defined according to the European Medicines Agency [14]. The mortality risk was analyzed as a separate critical outcome and therefore not included within the SAEs data, unless the cause of death was adjudicated as a drug-related event.

The Evidence Review Team independently screened studies and extracted data (by at least two members). The following inclusion criteria were applied: studies published in English or Italian (or other languages if translation was available) with relevance to the structured clinical questions; due to the anticipated scarcity of high-quality evidence, and in agreement with the expert panel, non-randomized and uncontrolled cohort studies were also included. Case series were included if comprising at least five RA-ILD subjects.

The following exclusion criteria were applied: publications classified as recommendations, guidelines, or expert consensus, case reports with fewer than three subjects, studies in languages without available translation, lack of relevance to the structured clinical questions. When feasible, data from treatment subgroups reporting the outcomes of interest were extracted for analysis. In these studies reporting outcomes for multiple treatment arms or subgroups (e.g., different

immunosuppressive agents), each subgroup was included separately in the corresponding treatment-specific meta-analysis. Since the primary objective was to estimate treatment-specific pooled effects, and each subgroup received a distinct intervention, they were considered as independent units for the purpose of stratified meta-analysis. However, when subgroup analyses were conducted according to treatment class rather than individual treatments, a multilevel meta-analytic model with a random effect clustered by study identifier (PMID) was employed to account for the potential dependency among subgroups originating from the same study.

When appropriate, meta-analyses were performed. To assess the risk of worsening of the reported outcomes and the risk for SAEs in individuals treated and untreated with the intervention of interest, the odds ratios (ORs) and 95 % CIs were considered as the effect size for each eligible study. The OR for disease progression was analyzed separately based on %FVC and HRCT data, as well as in an aggregated manner including %FVC, HRCT, and the general term 'ILD progression' or similar definitions reported in the selected studies. Concerning this last outcome, when both %FVC and %DLCO data were reported, %FVC was preferred; when both %FVC and HRCT data were reported, the worse was preferred.

For continuous outcomes such as %FVC and %DLCO, the pre–post changes of the treated groups were meta-analyzed using raw mean differences (MRAW) and their corresponding standard deviations. When both treatment and control groups were available, treatment effects were assessed using between-group mean differences (MD), calculated as the between-group pre-post, together with their corresponding standard errors.

If the outcome measures of interest were reported in median, range, or 25th–75th per-centiles, the mean and SD values were estimated using validated formulas [15]. In addition, for continuous variables, if not available, SDs of the mean differences were estimated using the following formula: $SD = \sqrt{}$ [(SD pretreatment)2 + (SD posttreatment)2 − (2r × SD pre-treatment × SD post-treatment) [16]. Meta-analyses of the Incidence Rate (IR) per 100 patient-years (100PY) were performed using the incidence rate log-normal model, which accommodates studies with zero events. Pooled estimates for antifibrotics and disease modifying anti-rheumatic drugs (DMARDs)/Immunosuppressants were obtained under a random-effects model on the log scale and back-transformed for interpretation.

Visual inspection of the forest plot was used to assess statistical heterogeneity. This was also assessed with the I^2-statistics, which provides an estimate of the percentage of variability across eligible studies that is due to heterogeneity rather than chance alone. Heterogeneity was considered to be low if I^2 is <25 %, moderate if I^2 is between 25 % and 75 %, and high if I^2 is >75 % [15].

To identify potential outliers, we calculated the standardized distance of each study's effect size from the overall pooled estimate of the random-effects model. Studies were considered statistical outliers if their effect size differed by more than three between-study standard deviations (τ) from the pooled effect. Sensitivity analyses were performed by excluding identified outliers and re-estimating the pooled effect and heterogeneity to assess the robustness of the results.

A leave-one-out (LOO) sensitivity analysis was performed to assess the influence of individual studies on the pooled effect estimate. In each iteration, the meta-analysis was repeated omitting one study at a time, and changes in effect size and heterogeneity were evaluated.

In order to explore further possible sources of heterogeneity among the analyses, we conducted meta-regression analyses by mean age, duration of follow-up (months), proportion of males, proportion of usual interstial pneumonia (UIP), publication year and treatment by adopting abatacept (ABA) as reference. Meta-regressions were conducted adopting multilevel modelling, with a random intercept for study (clustered for PMID) to account for within-study correlation due to the presence of multiple subgroups from same studies.

To compare the incidence rates of SAEs between antifibrotics and DMARDs/Immunosuppressants, a meta-regression was performed with the class of treatment as a categorical moderator. Log-transformed IR/100PY were modelled assuming a log-normal distribution, with a random intercept for study (clustered for PMID). Pooled estimates for each group were obtained by back-transforming the model coefficients.

Data were analyzed with R-studio, using the 'meta'and 'metafor' packages.

3. Results

We identified 5611 potentially relevant papers in the first search from inception up to 09 October 2023 and 295 potentially relevant paper in the updated search up to 01 April 2025. A total of sixty-nine studies were considered eligible for the inclusion in this SLR and were assessed for quality; the flow of study selection is presented in Fig. 1, panel a and b.

After examining the full text of these articles, we excluded a total of thirty-three studies due to of unsatisfactory inclusion criteria or unsatisfactory outcome measures (supplementary table 1).

Only two RTCs were included, namely a subgroup analysis of the INBUILD phase 3 trial on nintedanib [16], and a phase 2 study on pirfenidone (TRAIL1, prematurely discontinued due to slow recruitment and the impact of the COVID-19 pandemic) [17]. Of the remaining, thirteen were prospective [18–32] and fifty-two retrospective studies [33–81]. Forty-one studies included a comparator [16,17,19–30,34,38,41,42,44,46,47,49,51,53–56,59–62,64,65,67,68,70,77,78,82–84], most commonly consisting of individuals not exposed to the investigated drug. In seven of these studies, the comparator was the same cohort observed during a period preceding drug initiation (before-and-after design) [20,21,34,46,49,65,83].

The present systematic review included a total of 7879 individuals affected by RA-ILD, with a mean age 64.4 years (SD: 8.3), mean proportion of men 39 % (SD: 14 %), mean proportion of UIP 49 % (SD 18 %), with a mean follow-up time of 31.3 months (SD 30.2).

Twenty-one studies reported data on subjects treated with csDMARDs, including methotrexate (MTX) and leflunomide (LEF) [19,22,23,25–28,38,44,48,51,53,54,56,61,64,66,67,77,81], seventeen on Tumour Necrosis Factor-α inhibitors (TNFi) [25,27,28,30,31,41–44,51–54,63,68,78,84], twenty on ABA [23,28–30,36,37,41,44,53–55,57,61–63,68,71,74,76,81], twelve on anti-IL6R [23,27,28,30,33,41,44,53,58,63,68,72], eleven on Janus kinase inhibitors (JAKi) [23,30,40,44,50,54,61,68,74,76,80], sixteen on RTX [21,23,28,32,35,39–41,44,45,47,51,59,60,68,83], thirteen on immunosuppressants such as: cyclophosphamide (Cyc), mycophenolate mofetil (MMF), azathioprine (AZA) and tacrolimus (TAC) [21,22,26–28,30,38,44,46,56,59,66,79], thirteen on glucocorticoids (GCs) [19,25–28,30,38,44,53,56,61,64,77], one on intravenous immunoglobulins (IVIg) [70], eleven on antifibrotics (nintedanib, pirfenidone) [16–18,20,24,34,49,65,69,75,85].

Table 1 and Table 2 show the characteristics and RoB of the eligible studies and the characteristics of patients and controls (when available) included in the final document, respectively.

3.1. Differences in %FVC

The forest plot and pooled estimates in the **pre-post change in % FVC** divided according to the drug is reported in supplementary fig. 1, while supplementary fig. 2–6 report the forest plot and pooled estimates in the pre-post %FVC differences divided according to the drug class. Thirty-two studies were selected for the analysis [16–18,20,21,24,29,32,34–37,45–47,49,50,55,57,60,65,66,70,71,73–75,79–81,83,85]. The pooled estimates for most drugs were associated with stabilization or improvement (RTX, MMF, JAKi) of the %FVC; only pirfenidone was associated with worsening (−1.17 %, 95 %CI -2.16 to −0.18). Overall, high heterogeneity

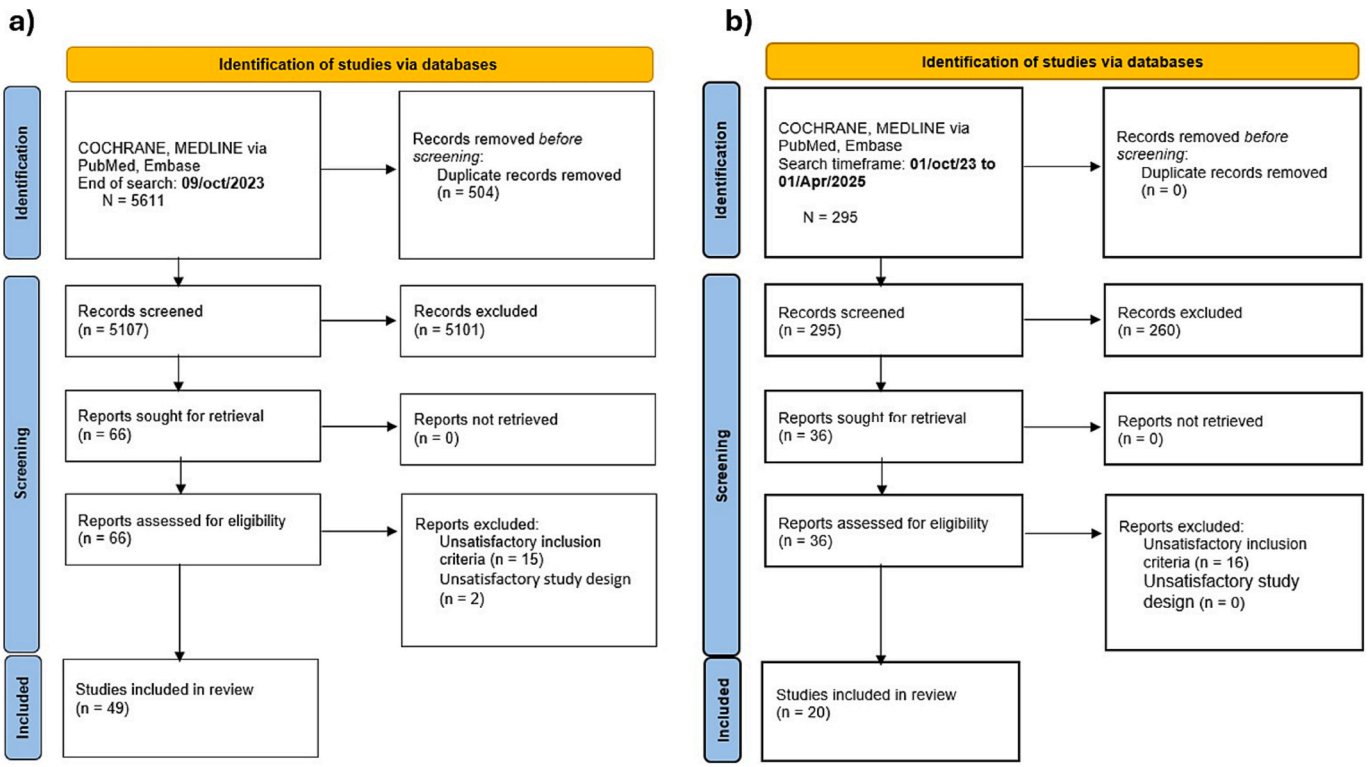

Fig. 1. PRISMA flow diagram for the present systematic review.

was observed across the included studies (I^2: 95.1 %).

The LOO analysis for studies including nintedanib confirmed the robustness of the pooled estimate of %FVC change, as no single study had a disproportionate influence on the overall effect size. Notably, the exclusion of the studies by Tekgoz E, 2025 [75] and Boutel M, 2023 [85]—both mixed cohorts in which RA-specific data were not extractable—led to modest reductions in heterogeneity (I^2 from 80.3 % to 61.7 % and 85.1 %, respectively), yet the overall effect remained non-significant across all iterations.

Shen X et al., 2022 [70], the only study investigating the effect of IVIg, resulted a significant outlier ($\tau = 3.47$), which is substantially higher than the average effect observed across the other included studies.

The forest plot and pooled estimates in the **between-group difference in %FVC change** (treated vs controls or non-users) divided according to the drug is reported in Fig. 2, while supplementary fig. 7–9 report the forest plot and pooled estimates in the between group difference in %FVC change, divided according to the drug class. Fifteen studies were selected for the analysis [16,17,20,21,24,29,34,46,47,49,55,60,65,70,83]. The pooled estimates for all treatments, except ABA, were associated with a positive difference when compared to non-users, however none were associated with a negative difference (namely worse than controls); high heterogeneity was observed across the included studies (I^2: 97.0 %).

We performed meta-regression analyses to explore potential sources of heterogeneity for the pre-post %FVC differences.

Treatment emerged as a significant moderator ($p < 0.001$, supplementary table 2). Meta-regressions for age, proportion of males, publication year, duration of follow-up (months), and proportion of UIP yielded non-significant results (data not shown).

Similarly, we performed meta-regression analyses to explore potential sources of heterogeneity for the between-group difference in %FVC changes. Meta-regression analyses for mean age, proportion of males, duration of follow-up, proportion of UIP and publication year yielded non-significant results (data not shown).

Treatment type was also a significant moderator ($p = 0.0056$, supplementary table 3).

The visual inspection of the funnel plot (supplementary fig. 10, panel a and b) and the Egger's test ($p = 0.0012$ for pre-post mean %FVC difference; $p = 0.0087$ for between-group pre-post %FVC differences) suggested the presence of publication bias for both analyses.

3.2. Differences in %DLCO

The forest plot and pooled estimates in the **pre-post change in % DLCO** divided according to the drug is reported in supplementary fig. 11, while supplementary fig. 12–15 report the forest plot and pooled estimates in the pre-post %DLCO differences grouped according to the drug class. Twenty-two studies were selected for the analysis [18,21,24,29,32,34–36,45–47,49,55,60,65,73,74,79,80,83,85,86]. The pooled estimates for all drugs were associated with stabilization or improvement (MMF) of the %DLCO. Overall, high heterogeneity was observed across the included studies (I^2: 89.4 %).

For RTX, LOO showed that, while the direction of the effect remained consistently positive across all iterations, statistical significance was observed when Eroglu DS, 2022 [45], or Md Yusof MdY, 2017 [60] were excluded, suggesting limited robustness of the estimate. Between-study heterogeneity remained high in all scenarios (I^2: 74–86 %). For ABA, LOO sensitivity analysis showed that the pooled estimate remained stable across all iterations.

The forest plot and pooled estimates in the **between-group difference in %DLCO change** (treated vs controls or non-users) divided according to the drug is reported in supplementary fig. 16, while supplementary fig. 17–19 report the forest plot and pooled estimates in the between-group difference in %DLCO change, divided according to the drug class. Nine studies were selected for the analysis [21,29,34,46,47,49,55,60,65]. Meta-analyses for ABA, MMF, nintedanib, and RTX showed no significant differences in %DLCO changes compared to non-users.

Only single studies reported between-group %DLCO differences for

Table 1
Characteristics and RoB of the eligible studies included in the final analysis.

Author (ref)	Publication year	Study type	Population or hospital based	Country	Overall RoB
Akiyama M [33]	2016	Retrospective	Hospital	Japan	High
Atienza-Mateo B [36]	2023	Retrospective	Hospital	Spain	High
Atienza-Mateo B [35]	2020	Retrospective	Hospital	Spain	High
Atienza-Mateo B [34]	2025	Retrospective	Hospital	Spain	High
Behera AK [18]	2024	Prospective	Hospital	India	High
Boutel M [85]	2023	Retrospective	Population	Greece	High
Cassone G [37]	2020	Retrospective	Hospital	ITA	High
Chai D [38]	2023	Retrospective	Hospital	China	Moderate
Chang S [19]	2023	Prospective	Hospital	Korea	High
Chartrand S [39]	2015	Retrospective	Hospital	USA	High
Cronin O [40]	2021	Retrospective	Hospital	Germany	High
Curtis JR [41]	2015	Retrospective	Population	USA	High
Dixon WJ [42]	2010	Retrospective	Population	UK	Moderate
Druce K [82]	2017	Retrospective	Population	UK	Low
Duarte AC [20]	2024	Prospective	Hospital	Portugal	High
England BR [84]	2025	Retrospective	Population	USA	Moderate
Ekici M [44]	2024	Retrospective	Hospital	Turkey	Moderate
Eroglu DS [45]	2022	Retrospective	Hospital	Turkey	High
Fernandez-Diaz C [81]	2020	Retrospective	Hospital	Spain	High
Fischer A [46]	2013	Retrospective	Hospital	USA	High
Fui A [47]	2020	Retrospective	Hospital	Italy	High
Izuka S [48]	2021	Retrospective	Hospital	Japan	High
Juge PA [49]	2024	Retrospective	Hospital	USA	High
Kalyoncu U [50]	2022	Retrospective	Hospital	Turkey	High
Kelly C [51]	2021	Retrospective	Population	UK	High
Kim J-W [26]	2023	Prospective	Hospital	Korea	Moderate
Kim K [27]	2022	Prospective	Hospital	Korea	Moderate
Koo BS [52]	2015	Retrospective	Hospital	Korea	High
Kurata I [53]	2019	Retrospective	Hospital	Japan	Moderate
Kurushima S [54]	2025	Retrospective	Hospital	Japan	Moderate
Lee K-A [55]	2024	Retrospective	Hospital	Korea	High
Liu L [56]	2022	Retrospective	Hospital	China	Moderate
Lopez-Maraver M [57]	2024	Retrospective	Hospital	Spain	High
Makino H [30]	2023	Retrospective	Population	Japan	High
Manfredi A [58]	2020	Retrospective	Hospital	Italy	High
Marcoux V [59]	2023	Retrospective	Hospital	Canada	Moderate
Matson SM [21]	2023	Prospective	Hospital	USA	High
Matsumoto T [31]	2018	Retrospective	Hospital	Japan	High
Matteson EL [32]	2012	Prospective	Hospital	USA	High
Matteson EL [16]	2023	RCT (post-hoc)	Hospital	Multicentric	Moderate
Md Yuzaiful Md Yusof [60]	2017	Retrospective	Hospital	UK	High
Mena-Vàzquez N [28]	2020	Prospective	Hospital	Spain	High
Mena-Vàzquez N [64]	2021	Retrospective	Hospital	Spain	Moderate
Mena-Vàzquez N [25]	2021	Prospective	Hospital	Spain	Moderate
Mena-Vàzquez N [29]	2022	Prospective	Hospital	Spain	Moderate
Mochizuki T [89]	2023	Retrospective	Hospital	Japan	Moderate
Mochizuki T [61]	2019	Retrospective	Hospital	Japan	High
Nakashita T [63]	2014	Retrospective	Hospital	Japan	High
Narvaez J [83]	2020	Retrospective	Hospital	Spain	High
Narvaez J [65]	2024	Retrospective	Hospital	spain	High
Nomura M [22]	2025	Prospective	Hospital	Japan	Moderate
Rojas-Serrano J [66]	2012	Retrospective	Hospital	Spain	High
Rojas-Serrano J [67]	2017	Retrospective	Hospital	Spain	Moderate
Rudi T [23]	2024	Prospective	Population	Germany	Low
Sebastiani M [68]	2023	Retrospective	Hospital	Italy	High
Sebastiani M [69]	2025	Retrospective	Hospital	Italy	Low
Shen X [70]	2023	Retrospective	Hospital	China	High
Shoda T [71]	2024	Retrospective	Hospital	Japan	High
Solomon JJ [17]	2022	RCT	Hospital	USA, UK	Moderate
Suzuki K [72]	2025	Retrospective	Hospital	Japan	High
Tardella M [73]	2021	Retrospective	Hospital	Italy	High
Tardella M [74]	2022	Retrospective	Hospital	Italy	High
Tekgoz E [75]	2025	Retrospective	Hospital	Turkey	High
Tsuji A [76]	2024	Retrospective	Hospital	Japan	High
Venerito V [80]	2023	Retrospective	Hospital	Italy	High
Venkat RK [77]	2024	Retrospective	Population	USA	Low
Wang J [24]	2022	Prospective	Hospital	China	High
Wolfe F [78]	2007	Retrospective	Population	USA	High
Yamano Y [79]	2018	Retrospective	Hospital	Japan	High

Table 2
Characteristics of the treated subjects and comparators (when available) enrolled in the studies included in the final analysis.

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Akiyama M [33]	66.7	78	–	60	11.8 (RA-ILD)	ANTI-IL6R	–	–	-	–	6/78 (7.7 %) 4.0 per 100 pt-y (overall observation periods 148.8 patient-years)
Atienza-Mateo B [36]	62.7	190	–	12	1.1 (ILD duration)	ABA +/− MTX/other csDMARDs	Pre-post %FVC difference: −2.6 % stabilization FVC 65.3 % (CI 95 %, 58.0–72.0)	Pre-post %DLCO difference: +3.11 %	stable 56.3 % worsened 29 % improved 14.7 %	0/190	–
Atienza-Mateo B [35]	58.3	26 (5 RA-ILD) #	–	24	3.4	RTX+/− csDMARDs	Pre-post %FVC difference (delta mean): +4.2 %	Pre-post %DLCO difference (delta mean) +10.6 %	stable 65.2 % worsened 21.7 % improved 13.1 %	–	–
Atienza-Mateo B [34]	**69.3**	74	74 (pre-treatment)	15	4.4	nintedanib	Pre-post %FVC difference (delta mean) in Nintedanib group: +1.04 % (at 12 months, 23 patients) +0.67 (at 24 months, 6 patientis) Pre-post %FVC difference (delta mean) in control group: − 6.69 (at 12 months; 49 patients) − 9.37 (at 24 months; 46 patients)	Pre-post % DLCO difference (delta mean) in Nintedanib group: +1 % (at 12 months) +2.9 % (at 24 months)	stable 47.4 %	9 (12.2 %)	0/74
Behera AK [18]	53.0	24/26 antifibrotics	–	6	–	nintedanib ($n = 14$), pirfenidone ($n = 10$)	Pre-post %FVC difference (delta median): +0.7 %	Pre-post % DLCO difference (delta mean): +2 %	–	–	0/24
Boutel M [85]	64	21 (5/21 RA-ILD) #		10	4.8	Nintedanib	Pre-post %FVC: +0.9	Pre-post % DLCO: +3.4	–	–	0/21
Cassone G [37]	65	44	–	26.5	7.4	ABA	Pre-post %FVC difference (delta mean) -3.55 % stabilization FVC 86.1 % (CI 95 % 70.5, 95.3)	Pre-post %DLCO difference (delta median) -1.9 % stabilization DLCO 88.9 % (CI 95 %, 73.9, 96.9)	stable 70.4 % worsened 18.2 % improved 11.4 %	–	1/44

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Chai D [38]	**67**	120 36 CYC 69 GCs 21 LEF 49 MTX	120 84 controls-CYC 51 controls-GCs 99 controls-LEF 71 controls-MTX	19	–	GCs ($n = 69$), CYC ($n = 36$), LEF (n = 21), MTX ($n = 49$), bDMARDs (n = 1), tsDMARDs (n = 1)	Pre-post %FVC difference (delta mean) +0.7 %	pre-post %DLCO difference (delta mean) +0.4 %	pre-post HRCT score (delta mean): +0.5 stable 35.7 % worsened 50.1 % improved 13.3 % risk factors of the progression of RA-ILD: OR MTX 0.72 (0.40, 0.1.30) OR GCs 2.58 (1.37, 4.86) aOR GCs 1.61 (0.81, 3.19	–	–
Chang S [19]	66.5	77 MTX 123 GCs	–	33.6	7.9	GCs ($n = 123$), MTX ($n = 77$)	FVC% over 3 years of FU: improved 7.9 % stable 38.4 % worsened 53.6 % Annual rate of change in FVC (mL), mean (95 % CI) 41.6 (50.6, 32.5) RR of rapidly declining predicted FVC% trajectory (95 % CI): no-MTX 7.45 (0.90, 61.89) GCs 0.18 (0.04, 0.82)	DLCO% over 3 years of FU: improved 8.0 % stable 48.9 % worsened 43.1 % Annual rate of change in predicted DLCO % 1.48 (1.78, 1.19)	–	12 (8.6 %)	–
Chartrand S [39]	62.9	15	–	50	11.6	RTX	Stability or improvement in FVC% 57,1 %	–	–	–	0/15
Cronin O [40]	69.5	28 (JAKi) 19 (RTX)	–	24	7.8	RTX, JAKI	–	–	0	2 JAKi 1 RTX (infection)	3/28 JAKI 3/19 RTX
Curtis JR [41]	60.8	232 TNFi 59 ANTI-IL6R 99 RTX 109 ABA	267 no-TNFi 440 no-ANTI-IL6R 400 no-RTX 390 no-ABA	7	–	TNFI ($n = 232$), ANTI-IL6R($n = 59$), RTX ($n = 99$), ABA ($n = 109$)	–	–	–	–	HR ANTI-IL6R 0.5 (95 % CI 0.1–2.1) HR RTX 1.6 (95 % CI 0.8–3.2) HR ABA 0.9 (95 % CI 0.4–2.1) TNFI 24/234 (fu 0.7y) ANTI-IL6R 8/59 (fu 0.6y) RTX 12/99 (fu 0.7y)

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
											ABA 12/109 (fu 0.7y)
Dixon WJ [42]	63.9	299 TNFi	68 DMARDs	72	12	TNFI, DMARDs	–	–	–	mortality Rate Ratio (CI 95 %) 0,74 (0.42, 1.33) aMRR (CI 95 %) to 0.81 (0.38, 1.73).	–
Druce K [82]	62.8	309 (anti-TNFI) (tot 352)	43 (RTX)	65	11.1	TNFI, RTX	–	–	–	HR 0.53 (0.26, 1.1) aHR 0.49 (0.23, 1.06)	–
Duarte AC [20]	70.9	40	20 (pre-treatment)	154.8	12	nintedanib, pirfenidone	Pre-post % FVC difference (delta mean) in antifibrotics group: +0.7 % (at 12 months) Pre-post % FVC difference (delta mean) in control group: −7.7 % (at 12 months)	Pre-post %DLCO difference (delta mean) in antifibrotics group: −2.9 % (at 12 months) Pre-post % DLCO difference (delta mean) in control group: −3.0 % (at 12 months)	–	4/40	–
Ekici M [44]	62.7	8 ABA 13 AZA 13 CYC 99 GCs 2 JAKI 80 LEF 87 MTX 27 RTX 24 TNFi 3 ANTI-IL6R	96 no-ABA 91 no-AZA 91 no-CyC 5 no-GCs 102 no-JAKi 24 no-LEF 17 no-MTX 77 no-RTX 80 no-TNFi 101 no-ANTI-IL6R	66	11.1	MTX, AZA, CYC, GCs, JAKi, LEF, RTX, TNFi, ANTI-IL6R	Pre-post %FVC difference (delta mean) total patients:− 2 % (group with radiographic progression) +9 % (group without radiographic progression)	% (n) of patients with ILD progression 7 % (3) ABA 19 % (8) AZA 11.9 % (5) CYC 40.4 % (40) GCs 0 JAKi 67.4 % (29) LEF 60.5 % (36) MTX 30.2 % (13) RTX 23.3 % (15) TNFi 0 ANTI-IL6R	–	28 death rate MTX (2.8, 0.3–25.9).	–
England BR [84]	68	237 TNFi	237 Non-users	3 years	6.9	TNFi				aHR (3-years) for non-users (TNFi as ref.) 1.15 (0.83–1.60) aHR (1-year) for non-users (TNFi as ref.) 1.25 (0.68–2.32)	
Eroglu DS [45]	61.4	26	–	28.8	10.1	RTX+/− csDMARDs	Pre-post %FVC difference (delta mean): +10 % (at 12 months)	Pre-post %DLCO difference (delta mean) -8 % (at 12 months)	stable 55.0 % worsened 35.0 % improved 10 %	1/26	0/26

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Fernandez-Diaz C [81]	64.6	263	–	12	9.74	ABA	Pre-post %FVC difference − 1.16 % stabilization FVC 87.7 % (CI 95 % 81.7, 92.3)	Pre-post %DLCO difference − 1.22 % stabilization DLCO 90.6 % (CI 95 %, 84.5, 96.9)	stable 57.8 % worsened 23.4 % improved 18.8 %	–	29/263
Fischer A [46]	60.4	125 (18/125 RA-ILD) #	127 (pre-treatment)	26	–	MMF	Pre-post %FVC difference (data mean) MMF group: +4.9 % (at 52 weeks) +6.1 % (at 104 weeks) +7.3 % (at 156 weeks) pre-post %FVC difference (data mean) control group: −0.8 % (at 52 weeks) -1.5 % (at 104 weeks) -2.3 % (at 156 weeks)	Pre-post %DLCO difference (data mean) MMF group: +6.3 % (at 52 weeks) +7.1 % (at 104 weeks) Pre-post %DLCO difference (data mean) control group: −3.6 % (at 52 weeks) -7.1 % (at 104 weeks) -10.7 % (at 156 weeks)	–	–	–
Fui A [47]	66.2	14	28	12	–	RTX	Pre-post %FVC difference (delta mean) RTX group: +5.90 % Pre-post %FVC difference (data mean) control group: −2.37 %	Pre-post %DLCO difference (delta mean) RTX group: +1.34 % Pre-post %DLCO difference (data mean) control group: +7.3 %	–	2/14	–
Izuka S [48]	74	99	66	14.5	1.21	MTX	–	–	–	HR MTX 0.16 (CI 95 %, 0.04, 0.72) (treatement and control 3/165) 4/74 lung transplant 26/74 deaths (17 ILD's contribution)	OR (current MTX use) 1.75 (CI 95 %, 0.76, 4.00)
Juge PA [49]	67.8	40 nintedanib 34 pirfenidone	40 (pre-treatment for nintedanib) 34 (pre-treatment for pirfenidone)	18	8.8	Nintedanib ($n = 40$), pirfenidone ($n = 34$)	Pre-post %FVC difference (delta mean) treatment group: +0.5 % per year (nintedanib) −1.5 % per year, (pirfenidone) Pre-post %FVC difference (delta mean) control group: −5.6 % per year (pre-nintedanib)	Pre-post %DLCO difference (delta mean) treatment group: −3.3 % per year, (nintedanib) −3.7 % per year, (pirfenidone) Pre-post %DLCO difference (delta mean) control group: −5.5 % per year (pre-nintedanib)	–	Data of Nintedanib + pirfenidone HR for lung transplant or mortality (pirfenidone) 0.94 (95 % CI 0.45, 1.96)	2/74 data of Nintedanib + pirfenidone

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
							−4.4 % per year (pre-pirfenidone) Data of 27 patients (nintedanib) Data of 22 patients (pirfenidone) Pre-post %FVC (delta mean) +2.95 % worsening of FVC% by >5 %: 11.1 %	−5.9 % per year (pre-pirfenidone) Data of 27 patients (nintedanib) Data of 22 patients (pirfenidone)		aHR 1.03 (95 % CI 0.46, 2.29)	
Kalyoncu U [50]	68	47	–	15	10.7	JAKI (TOFA)	–	–	–	–	–
Kelly C [51]	**65**	240 150 MTX 61 LEF 54 AZA 42 MMF 21 CYC 40 TNFI 37 RTX		84	12	AZA, MTX, LEF, CYC, MMF, TNFI, RTX	–	–	–	RR (all patients) 1.55 (1.01, 2.4) RR (MTX) 1.25 (0.86, 1.81) RR (LEF) 1.23 (0.74–2.04) RR (AZA) 1.42 (0.7–2.8) RR (MMF) 0.65 (0.2–2.0) RR (CYC) 1.65 (0.7–3.8) RR (TNFI) 2.09 (1.1–4.0) RR(RTX) 0.52 (0.2–2.0)	–
Kim JW [26]	66.3	143 MTX 61 LEF 26 TAC 56	143 MTX 82 LEF 117 TAC 87	36	6.3	MTX ($N = 61$), LEF ($N = 26$), TAC ($N = 56$), bDMARDs or tsDMARDs ($N = 47$), GC ($N = 125$)	HR for of decrease FVC (CI 95 %): MTX 0.84 (0.51, 1.39) LFN 1.86 (1.05, 3.28) TAC 0.66 (0.39, 1.12) MTX- aHR 1.06 (0.59, 1.89) LEF-aHR 1.75 (0.88, 3.46) TAC- aHR 0.94 (0.52, 1.72)	–	–	–	–
Kim K [27]	64	125 MTX 79 LEF 62 TAC 56	controls MTX 64 controls LEF 81 controls TAC 87 controls TNFI 126	51	4.3	MTX ($N = 79$) LEF ($N = 62$) TAC ($N = 56$) ANTI-IL6R ($N = 20$) TNFI ($N = 17$)	OR of decreased FVC ⩾10 % (CI 95 %): MTX 0.27 (0.10,	–	–	Survival: MTX-HR 0.169 (CI 95 %, 0.059, 0.486)	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
		TNFI 17 ANTI-IL6R 20	controls ANTI-IL6R 123 (tot 125)			JAKI ($N = 11$) ABA ($N = 4$) RTX (N = 4) AZA (N = 2) MMF (N = 2) GC ($N = 145$)	0.74) LEF 0.89 (0.37, 2.15) TAC 1.75 (0.74–4.14) TNFI 1.24 (0.31, 4.92) ANTI-IL6R 1.486 (0.48, 4.61) aOR MTX 0.27 (0.09, 0.77)			MTX-aHR 0.284 (CI 95 %, 0.091, 0.880)	
Koo BS [52]	62.6	24	–	111	9	TNFI	–	–	–	25 % deaths (6/24)	–
Kurata I [53]	64.1	49 30 TNFi 12 ABA 7 ANTI-IL6R 15 MTX 31 GC	19 no-TNFi 37 no-ABA 42 no-ANTI-IL6R	17.4	9.4	TNFI (30), ABA (12), ANTI-IL6R (7)	–	–	14/30 TNFi 1/12 ABA 3/7 ANTI-IL6R 6/15 MTX 11/31 GC	–	–
Kurushima S [54]	**71**	36 JAKi 30 ABA 33 MTX 27 TNFi	57 no-JAKi 63 no-ABA 39 no-MTX 66 no-TNFi	14	9	JAKI, MTX, ABA, TNFI	–	–	worsening CT score: 19.4 % (7) JAKi 22.2 % (6) TNFi	–	–
Lee K-A [55]	**66**	59 ABA	64 csDMARDs	21	2.3	ABA, csDMARDs (LEF, AZA, HCQ, SSZ, MTX)	Pre-post %FVC difference (delta median): +0.4 % ABA +3 % csDMARDs FVC% stable or improved: 86.7 % ABA 88.2 % csDMARDs FVC% worsened 13.3 % ABA 11.8 % csDMARDs	pre-post %DLCO difference (delta median): +7 % ABA +9.25 % csDMARDs DLCO% stable or improved: 80.0 % ABA 84.4 % csDMARDs DLCO% worsened 20.0 % ABA 15.6 % csDMARDs	stable or improved: 88.9 % ABA 82.4 % csDMARDs worsened: 11.1 % ABA 17.6 % csDMARDs	–	–
Liu L [56]	67	105 3 AZA 56 CYC 138 GCs 88 LEF 12 MTX	198 no-AZA 145 no-CYC 63 no-GCs 113 no-LEF 189 no-MTX	38	8	CyC	Decrease in FVC of 15 % or a decline in FVC of 10 % combined with a DLCO of 15 % from the baseline: OR 0.245 (0.095, 0.632)	–	–	15/105	–
Lopez-Maraver M [57]	**66**	399		24	0.9 (ILD duration)	ABA	Pre-post %FVC difference (delta mean):− 1 %	Pre-post %DLCO difference (delta mean):− 3 %	stable: 56.92 % worsened: 33.36 %	–	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
									improved: 9.72 %		
Makino H [30]	70	312 MTX 115 ABA 28 JAKi 1 TNFi 31 ANTI-IL6R 15 TAC 49	197 no-MTX 284 no-ABA 311 no-JAKi 281 no-TNFi 297 no-ANTI-IL6R 263 no-TAC	24	6.5	MTX, ABA, JAKi, TNFi, TAC, ANTI-IL6R	–	–	–	OR of respiratory death 4.42 (CI 95 %, 0.99, 19,80) MTX 2/115 ABA 1/28 JAKI 0/1 TNFI 1/31 ANTI-IL6R 1/15 TAC 3/49	–
Manfredi A [58]	64	28	–	30	11.5	ANTI-IL6R	Pre-post %FVC difference (delta mean): −3 % FVC remained stable 56 % of patients, improved in 20 % and worsened in 24 %.	Pre-post %DLCO difference: −1.5 % DLCO stable 56 % improved: 20 % worsened 24 %	stable 89.3 % worsened 7.1 % improved 3.6 %	–	0/28
Marcoux V [59]	64	104 37 AZA 39 MMF 24 RTX 4 CYC	57 (no-treatment)	48	4	AZA (n = 37),MMF (n = 39), RTX (n = 24), CYC(n = 4)	mean annual decline in FVC%: untreated NSIP -1.0 ± 0.6, untreated UIP -1.4 ± 0.6 treated NSIP- 0.4 ± 1.1, treated UIP -2.4 ± 0.8	mean annual decline in DLCO %: untreated NSIP-1.2 ± 0.6, untreated UIP-2.8 ± 0.6 treated NSIP -1.4 ± 1.0, treated UIP -2.5 ± 0.7	17/104 (treatment group) 13/57 (control group)	–	–
Matson SM [21]	63.5	92 AZA 77 MMF 43 RTX tot 212	92 AZA pre-treatment 77 MMF pre-treament 43 RTX pre-treatment	24	2.21	AZA (N = 92) MMF(N = 77) RTX (N = 43)	Overall mean FVC % predicted after 12 months of treatment +3.9 % (95 % CI, 1.95–5.84) pre-post %FVC (delta mean) treatment group: MMF +4.55 % AZA + 3.84 % RTX + 3.3 % pre-post %FVC (delta mean) control group: pre-treatment	Overall mean FVC % predicted after 12 months of treatment +4.53 % (95 % CI, 2.12–6.94) pre-post %DLCO (delta mean) treatment group: MMF +3.67 % AZA + 1.93 % RTX + 6.73 % pre-post %DLCO (delta mean) control group: pre-treatment	–	–	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
							AZA −10 % pre treatment MMF -7 % pre-treatment RTX −8.5 %	AZA −5 % pre treatment MMF -4.5 % pre-treatment RTX −7 %			
Matsumoto T [31]	67.4	29	–	88.8	18.4	TNFi	–	–	–	–	3/29 HR of TNFi group for ILD events 0.58 (0.17–2.02)
Matteson EL [32]	64.7	10	–	12	13.8	RTX	Pre-post %FVC difference (delta mean) +2.4 %	Pre-post %DLCO difference (delta mean) +11.6 %	worsened 14 % (1/7) stable 71 % (5/7) improved 14 % (1/10)	2/10	–
Matteson EL [16]	66.9	42	47	12	9.9	nintedanib	pre-post %FVC difference (delta mean) nintedanib group −3.2 % pre-post %FVC difference (delta mean) control group −8 % OR Absolute decline in FVC >10 % 0.31 (0.10, 1.02))	–	–	HR nintedanib0.87 (0.46, 1.62) 7/43 (nintedanib) 9/47 (controls)	0/42 (nintedanib) 0/47 (controls)
Md Yuzaiful Md Yusof [60]	64	56	10	12	10	RTX	pre-post% FVC median difference (delta mean) RTX group +1.5 % pre-post% FVC median difference (delta mean) control group −2.4 %	Pre-post %DLCO median difference (delta mean) RTX group −1.3 % Pre-post %DLCO median difference (delta mean) control group −4.4 %	improved 7 % stable 42 % worsened 50 %	9/56	12/33
Mena-Vàzquez N [28]	68.8	70 31 MTX 8 ABA 1 AZA 10 LEF 5 MMF 10 RTX 7 TNFi 4 ANTI-IL6R 39 GCs	70 39 no-MTX 862 no-ABA 69 no-AZA 60 no-LEF 65 no-MMF 60 no- RTX 63 no-TNFi 66 no-ANTI-IL6R 31 no- GCs	13.4	24	MTX, LEF, AZA, MMF, RTX, TNFi, ANTI-IL6R, ABA, GCs	pre-post %FVC difference (delta mean) total patients −4.5 %	pre-post % DLCO difference (delta mean) total patients −6.1 %	worsened 8.6 % stable 60.8 % improved 30.4 % OR bDMARD (Variables independently associated with progression of lung disease in RA-ILD patients) 0.235 0.054–1.025 OR non anti-TNFi (Multivariate analysis, variables independently associated with	1/70	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Mena-Vàzquez N [64]	**69.2**	123 105 csDMARDs 14 TNFi 57 bDAMARDs 15 immunosoppressants 88 GCs	123 18 no-csDMARDs 66 no-bDMARDs 108 no-immunosoppresants 35 no-GCs	56	12.1	csDMARDs (MTX, LEF, SSZ, HCQ), bDMARDs (TNFi, ABA, RTX), immunosoppresants (MMF, CYC, AZA), GCs	pre-post %FVC difference (delta mean) total patients −7.7 %	pre-post %DLCO difference (delta mean) total patients −4.0 %	progression of lung disease in RA-ILD patients) 0.102 (0.015, 0.686) stable 60 % worsened 48 % improved 15 % + HR (progression of ILD or mortality) (95 % CI): HR csDMARDs 1.08 (0.59, 1.96) HR bDMARDs 0.74 (0.40, 1.35) HR immunosuppressive. 0.94 (0.52, 1.66) HR GCs 1.43 (0.76, 2.08)	19/123	–
Mena-Vàzquez N [25]	**68.3**	116 100 csDMARDs 34 bDMARDs (no TNFi) 16 TNFi 11 immunosoppresants 69 GCs	16 no-csDMARDs 62 no-bDMARDs (no TNFi) 100 no-TNFi 105 no-immunosoppresants 47 no-GCs total 116	60	12.4	csDMARDs (MTX, LEF, SSZ, HCQ), bDMARDs (TNFi, ANTI-IL6R, ABA, RTX), immunosoppresants (MMF, AZA), GCs	pre-post %FVC difference (delta mean) total patients −4.5 %	pre-post %DLCO difference (delta mean) total patients −4.4 %	stable 66.4 % worsened 27.6 % improved 6 % HR (progression ILD or mortality) (95 % CI): HR csDMARDs 0.66 (0.22, 1.93) HR bDMARS (no TNFi) 0.62 (0.36, 0.89) HR TNFi 2.69 (1.02, 7.87) HR immunosuppressive. 0.66 (0.16, 2.64) HR GCs 1.60 (0.71, 3.57)	18 0.03 py (incidence of mortality)	40/116 (34.4 %) 0.08 py (incidence of sAE)
Mena-Vàzquez N [29]	67.7	57	57	12	10	ABA	pre-post %FVC difference (delta mean) ABA group −0.8 % pre-post %FVC difference (delta mean) control group −3.9 %	pre-post %DLCO difference (delta mean) ABA group −2.8 % pre-post %DLCO difference (delta mean) control group −5.9 %	stable 68.6 % worsened 19.6 % improved 11.7 %	0/57 (12 months) 3/57 (end of follow-up, 27.3 months)	–
Mochizuki T [89]	71.1	48 ABA 36 (JAKI)	36 no-ABA 48 no-JAKi	12	14.7	ABA, JAKI	–	-	worsened: 4.2 % (2) ABA 5.6 % (2) JAKI	–	–
Mochizuki T [61]	67.9	85 ABA 76 MTX 64 GCs	46 no-ABA 55 no-MTX 67 no-GCs	47.8	10.7	ABA, MTX, GCs	–	–	Treatment group: stable 77.1 % worsened 8.4 % improved 14.5 % Control group: stable or improved	–	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
									71.4 % worsened 28.6 %		
Nakashita T [63]	66.1	58 46 TNFI 3 ABA 9 ANTI-IL6R	–	12	11.2	TNFI	–	–	–	–	–
Narvaez J [83]	61	31	31 (pre-treatment)	24	4	RTX	Pre-post %FVC difference (delta mean) RTX group: +8.06 % (at 1 year; 31 patients) +11.2 % (at 2 years; 25 patients) Pre-post %FVC difference (delta mean) pre-treatment group: −16.5 % (at 1 year)	Pre-post %DLCO difference (delta mean) RTX group: +12.7 % (at 1 year; 31 patients) + 14.8 % (at 2 years; 25 patients) re-post %DLCO difference (delta mean) pre-treatment group: −19.7 % (at 1 year)	QUILD score: worsened 33 % improved 11 % stable 56 %	2/31	0
Narvaez J [65]	**67**	27	27 (pre-treatments)	24	5.9	nintedanib ($n = 25$), pirfenidone (n = 2)	pre-post% FVC difference (delta mean) antifibrotic group: +1.2 % (at 6 months; 24 patients) +4.7 % (at 12 months; 18 patients) + 7.7 % (at 24 months; 9 patients) pre-post% FVC difference (delta mean) control group: −8.9 % (at 12 months; 27 patients) %FVC predicted after 12 months of antifibrotics: worsened 11.1 % improved 22.2 % stable 66.7 %	Pre-post %DLCO difference (delta mean) antifibrotic group: +3.9 % (at 6 months; 24 patients) −3.8 % (at 12 months; 18 patients) −2.2 % (at 24 months; 9 patients) Pre-post %DLCO difference (delta mean) control group: −14.8 % (at 12 months; 27 patients) %DLCO predicted after 12 months of treatment: worsened 27.7 % improved 11.1 % stable 61.2 %	–	4/27	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Nomura M [22]	**74.1**	47 MTX 18 TAC 10	10 TAC 18 MTX	60	–	MTX, TAC	–	–	–	3/47	18.7 sAE incidence rates per 100 py
Rojas-Serrano J [66]	58.5	40	–	6	5.3 (64 mesi)	MTX (n = 18), AZA (n = 10), LEF (n = 12)	pre-post% FVC difference (delta mean) total patients +11 %	–	–	–	–
Rojas-Serrano J [67]	57.8	52	26	6	–	MTX	–	–	–	aHR 0.063 (CI 95 %, 0.150, 0.470) 97/381 28/114 TNFi aHR csDMARDs 0.9 (95 % CI 0.42, 1.94, 10 deaths) aHR Anti-IL6R 0.62 (95 % CI 0.26, 1.51, 6 deaths) aHR T-cell 0.74 (95 % CI 0.36, 1.53, 11 deaths) aHR B-cell 0.56 (95 % CI 0.28, 1.12, 14 deaths) aHR JAKi 0.78 (95 % CI 0.28, 2.19, 4 deaths) aHR no-DMARD 2.85 (95 % CI 1.62, 5.01, 28 deaths)	–
Rudi T [23]	58.9	114 TNFi 61 csDMARDs 33 Anti-IL6R 60 T-cell 64 B-cell 19 JAKi 30 no DMARD	267	31.2	10.1	csDMARDs, TNFi, Anti-IL6R, RTX, JAKi	–	–	–		–
Sebastiani M [68]	**72**	134 89 MTX 43 ABA 42 TNFi 27 JAKI 23 RTX 20 Anti-IL6R (23.1 % non-fibrosing nonprogressive; 3 % non-fibrosing progressive, 37.3 % fibrosing non progressive, 36.6 % fibrosing progressive)	134 45 no-MTX 91 no-ABA 92 no-TNFi 107 no-JAKi 111 no-RTX 114 no-anti-IL6R	24	10	MTX (n = 84), ABA (n = 43), TNFi (n = 43), JAKi (n = 27), RTX (n = 23), Anti-IL6R (n = 20)	pre-post% FVC difference (delta mean) -5.5 % (total) Median FVC change: 0 (−1.5, 3) non-fibrosing nonprogressive 14 (8.5, 41) Non-Fibrosing Progressive 0 (−5, 2) Fibrosing Nonprogressive 12 (7, 22) Fibrosing Progressive	pre-post% DLCO difference (delta mean) -8 % Median DLCO change: −1 (−11, 1.25) non-fibrosing nonprogressive 9.1 (5.55–12.55) non-Fibrosing Progressive −1 (−6.5, 5.25) Fibrosing Nonprogressive 9 (2, 15) Fibrosing Progressive	association of progressive fibrosis with therapy OR MTX 0.64 (95 % CI 0.30,1.36) OR ABA 0.78 (95 % CI 0.36,1.70) OR TNFi 1.59 (95 % CI 0.74,3.39) OR JAKi 1.05 (95 % CI 0.43, 2.55) OR RTX 1.82 (95 % CI 0.72,4.58) OR Anti-IL6R 0.95 (95 % CI 0.35, 2.65)	–	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Sebastiani M [69]	71	65	–	9	7	nintedanib	–	–	–	0	0/65
Shen X [70]	51.5 (IVIg)	40	40	12	–	IVIg	pre-post% FVC difference (IVIg group) +21.5 % pre-post% FVC difference (control group) +7.9 %	–	pre-post HRCT score (IVIg group) -3.5 pre-post HRCT score (control group) -1.6	–	–
Shoda T [71]	**73**	38 (10 ABA+MTX, 22 ABA+ TAC, 13 ABA+ GCs)	38 ABA alone	12	3.4	ABA, TAC, MTX, GCs	–	–	total GGO score (ABA) improved from 11 to 5.33 points total fibrosis score (ABA) improved from 5.67 to 3.33 points OR GGO reduction in ABA+MTX/TAC/GCs groups: ABA+MTX 1.27 (95 % CI 0.24, 6.70) ABA+TAC 1.46 (95 % CI 0.32, 6.46) ABA+GCs 1.52 (95 % CI 0.32, 7.15) aOR GGO reduction: ABA+MTX 1.71 (95 % CI 0.26, 11.2) ABA+TAC 1.89 (95 % CI 0.36, 9.80) ABA+GCs 2.88 (95 % CI 0.33, 24.85)	–	–
Solomon JJ [17]	67.7	63	60	12	–	pirfenidone	Pre-post %FVC difference (delta mean) pirfenidone group: −1.02 % Pre-post %FVC difference (delta mean) control group: −3.21 % OR decline in FVC by 10 % or more 0.52 (0.14, 1.90)	–	–	OR mortality and decline of FVC% 0.67 (0.22, 2.03)	OR 1.10 (0.39, 3.10)
Suzuki K [72]	**56**	21	–	24	1.3	Anti-IL6R	–	–	stable 85.7 % worsened 4.8 % improved 9.5 %	–	–
Tardella M [73]	59.1	44	–	18	7.5	ABA + csDMARDs	Pre-post %FVC difference (delta mean) -1.05 %	Pre-post %DLCO difference (delta mean) +2.57 %	stable 72.6 % worsened 11.4 % improved 16.0 %	–	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Tardella M [74]	59.5	75 44 ABA 31 JAKI	–	18	7.4	ABA, JAKI	Pre-post %FVC difference (delta mean): −1.05 % (ABA) - 1.59 % (JAKI)	Pre-post %DLCO difference (delta mean): +2.57 % (ABA) +3.03 % (JAKI)	stable: 72.6 % (ABA), 64.5 % (JAKI) worsened: 11.4 % (ABA), 16.1 % (JAKI) improved: 16.0 % (ABA), 19.4 % (JAKI)	–	–
Tekgoz E [75]	62.2	36 (9/36 RA-ILD) #	–	6	5.2	nintedanib	Pre-post %FVC difference (delta mean): +9.5 %	–	improved or stable 61,1 % worsened 38.9 %	5/36	0/36
Tsuji A [76]	74	71 45 ABA 26 JAKi	–	13	10	ABA, JAKi	–	–	–	–	5/45 ABA 3/26 JAKI
Venerito V [80]	68.9	43	–	19.1		JAKi	Pre-post %FVC difference (delta mean): +3.39 % FVC remained stable in 78.57 % of patients improved in 10.71 % and worsened in 10.71 %.	Pre-post %DLCO difference + 3.44 % DLCO stable 72 % improved 8 % worsened 20 %	stable 86.0 % improved 4.7 % worsened 9.3 %	1/43	0/43
Venkat RK [77]	62.2	172 (97 GCs, 54 MTX, 29 RTX or MMF, 45 bDMARD or JAKi)	75 no-GCs 117 no-MTX 63 no-RTX or MMF 63 no-bDMARD or JAKi	78	RA duration. 0 to 2 years 44 % (*n* = 75) 2 to 10 years 24 % (*n* = 41) >10 years 33 % (*n* = 56)	MTX, GCs, RTX (n = 20), MMF (*n* = 9), JAKi (n = 3),bDMARD (*n* = 42)	OR for %FVC decline by>10 % within 24 months (95 % CI): OR MTX use 0.66 (0.35, 1.27) OR GC use 0.66 (0.36, 1.22) OR RTX or MMF 0.70 (0.27, 1.86) OR bDMARDs or JAKi 0.64 (0.41, 2.16)	-	–	HR (lung transplant or ILD-related death) (95 % CI): HR MTX 0.68 (0.42, 1.11) HR GCs 1.37 (0.88, 2.13) HR RTX or MMF 1.04 (0.47,2.31) HR bDMARDs or JAKi 0.50 (0.26, 0.96)	–
Wang J [24]	56.1	10 (nintedanib) 7 (pirfenidone)	–	6	5	–	Pre-post %FVC difference (delta mean) pirfenidone group: −4 % Pre-post %FVC difference (delta mean) control group: −3 % HR −2.68 (−9.28, 3.61)	Pre-post %DLCO difference (delta mean) pirfenidone group: +10 % Pre-post %DLCO difference (delta mean) control group: −6 % HR −1.32 (−8.19, 5.54)	–	1/10 (nintedanib) 0/7 (pirfenidone)	–

(*continued on next page*)

Table 2 (*continued*)

Author	Mean age	N, treatment	N, controls	Median follow-up (months)	Disease duration (years)	Treatment adopted	Results - FVC	Results - DLCO	Results - CT	Results - mortality	Results - SAEs
Wolfe F [78]	66.4	100	17,498	186.3	15.3	IFX (TNFi), ETN (TNFi), CYC, LEF, AZA, MTX	–	–	–		HRs for hospitalisation (95 % CI): HR IFX (TNFi) 0.7 (0.4,1.3) HR ETN 0.9 (TNFi) (0.4, 1.7) HR CYC 1.5 (0.1, 16.4) HR LEF 1.3 (0.7,2.3), HR AZA 0.9 (0.3, 2.9), HR MTX 1.2 (0.7, 1.9)
Yamano Y [79]	63	26 (11/26 RA-ILD) #	–	12	0.1	TAC	Pre-post %FVC difference + 16.8 %	Pre-post % DLCO difference + 9 %	–	0	0

ABA, abatacept; AZA, azathioprine; bDMARD, biologic disease-modifying antirheumatic drug; csDMARDs, conventional synthetic DMARDs; CT, computed tomography; CTD, connective tissue disease; CYC, cyclophosphamide; DLCO, diffusion of carbon monoxide; ETN, etanercept; FVC, forced vital capacity; GCs, glucocorticoids; HR, hazard ratio; IFX, infliximab; ILD, interstitial lung disease; IVIg, intravenous immunoglobulins; JAKi, Janus kinases inhibitors; MMF, mycophenolate mofetil; MTX, methotrexate; OR, odds ratio; RA, rheumatoid arthritis; RTX, rituximab; SAEs, severe adverse events TAC, tacrolimus; TNFi, tumour necrosis factor-alpha inhibitors; tsDMARDs, targeted synthetic DMARDs.

Data extraction from the overall CTD-ILD cohort not feasible.

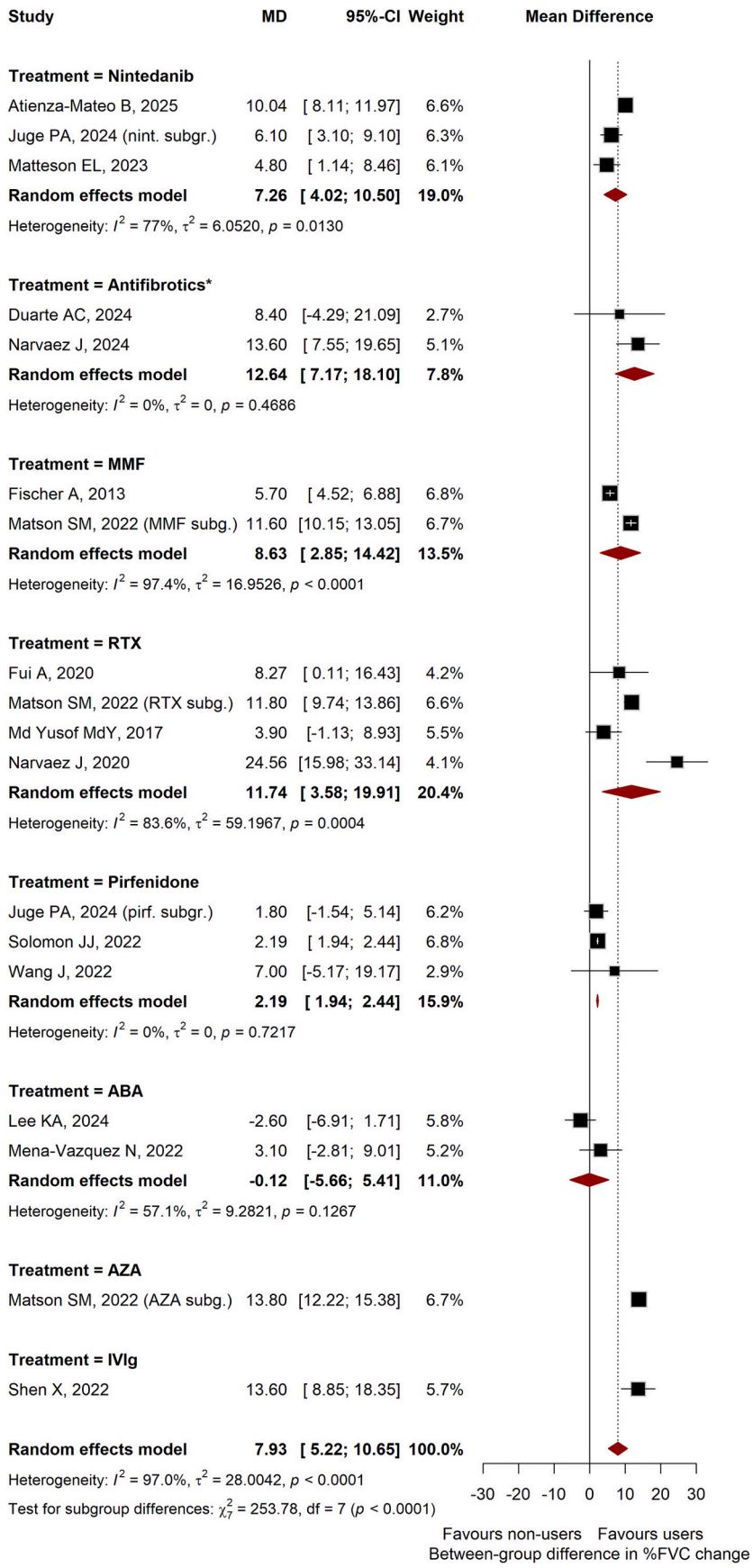

Fig. 2. Pooled and treatment-specific subgroup estimates of the between-group difference in %FVC change (treatment users vs. non-users).

AZA [21], pirfenidone [49] and one study including mixed cohort of antifibrotic [65]. High heterogeneity was observed across the included studies (I^2: 89.8 %). Treatment with MMF was associated with a between-group difference in DLCO change favouring treatment (8.97 %, 95 % CI 7.32 to 10.36 with moderato heterogeneity for MMF, I^2: 52.7 %).

We performed meta-regression analyses to explore potential sources of heterogeneity for the pre-post %DLCO differences.

Meta-regressions for age, proportion of males, publication year, duration of follow-up (months), and proportion of UIP and treatment yielded non-significant results (data not shown).

Similarly, we performed meta-regression analyses to explore potential sources of heterogeneity for the between-group difference in % DLCO. Meta-regressions for age, proportion of males, publication year, duration of follow-up (months), and proportion of UIP and treatment yielded non-significant results (data not shown).

3.3. Risk for RA-ILD progression

When considering the OR for **%FVC progression** (defined as >%10 FVC decline), seven studies were included [16,17,26,27,55,65,77]. The forest plot and the pooled estimates for the OR %FVC progression are reported in Fig. 3. Only treatment with MTX was associated with a reduced OR pooled estimate for progression (0.40, 95 %CI 0.17 to 0.91, moderate heterogeneity for MTX subgroup, I^2: 74.1 %). The OR for the other drugs were non-statistically significant. The overall heterogeneity was moderate (I^2: 47.3 %).

After univariate meta-regression of proportion of UIP, proportion of males, age, duration of follow-up (months), treatment, and year of publication, no moderator yielded statistically significant results (data not shown).

When considering the OR for **%DLCO progression**, only two studies could be retrieved, one including antifibrotics (data extraction for individual agents not feasible) [65] and one including ABA [55], the OR for %DLCO progression was non-significant for both (supplementary fig. 20).

When considering the OR for **HRCT progression**, eight studies could be retrieved [29,34,44,53–55,61,62]. The forest plot and the pooled estimates for the OR HRCT progression are reported in supplementary fig. 21.

Only treatment with ABA was associated with a reduced OR pooled estimate for progression (0.43, 95 %CI 0.27 to 0.69, with low heterogeneity for ABA subgroup, I^2: 0.0 %). The OR for the other drugs were non-statistically significant. The overall heterogeneity was moderate (I^2: 49.2 %).

After univariate meta-regression of proportion of UIP, proportion of males, age, duration of follow-up (months), treatment, and year of publication, only treatment yielded significant results: in particular treatment with JAKi, AZA, RTX and TNFi were associated with a higher estimate for HRCT progression than ABA (supplementary table 4).

When considering the OR for **progression including all possible definitions** ("disease activity/progression defined by composite outcomes including pulmonary function tests (PFTs)/HRCT/symptom worsening), twenty-one studies were included [16,17,19,22,26–29,34,36,38,44,53–55,60,61,65,68,77,87]. The forest plot and the pooled estimates for the resulting OR are reported in supplementary fig. 22. Reduced pooled estimates for OR were observed for MTX (0.52, 95 % 0.37 to 0.73, moderate heterogeneity for MTX subgroup ^{2}: 33.9 %) and for ABA (0.45, 95 % 0.26 to 0.79, moderate heterogeneity for ABA subgroup ^{2}: 43.5 %), while for all the other treatments the resulting pooled estimates were non statistically significant. The overall heterogeneity was moderate (I^2: 59.0 %).

After univariate meta-regression of proportion of UIP, proportion of males, age, duration of follow-up (months), treatment, and year of publication, only treatment yielded significant results: in particular, treatment with AZA, GCs, JAKi, LEF, MMF and TNFi was associated with a higher estimate for all possible definitions for progression than ABA (supplementary table 5).

The visual inspection of the funnel plot (supplementary fig. 23) did not suggested evidence for publication bias, and the Egger's test did not support the hypothesis of publication bias for progression, all definitions ($p = 0.517$).

3.4. Incidence rate for SAEs and OR for mortality

When considering the **SAEs IR/100PY**, data of eight studies including antifibrotics [16–18,34,49,65,69,75], and fourteen for DMARDs/Immunosuppressants [25,31,33,37,39–41,45,58,60,76,79,81,83]. The forest plot and pooled estimate of the SAEs IR/100PY for antifibrotics is reported in supplementary fig. 24, panel a, and estimated as 0.36, 95 %CI 0.03 to 4.84. The forest plot and pooled estimate of the SAEs IR/100PY for csDMARDs/Immunosuppressants is reported in supplementary fig. 24, panel b, and estimated as 4.40, 95 %CI 2.12 to 9.13. Compared with antifibrotics, csDMARDs/immunosuppressants were associated with a significantly higher incidence rate ($p < 0.001$).

Finally, when considering **mortality**, ten studies were included [16,17,30,42–44,51,59,67,84].

The forest plot and the pooled estimates for the resulting OR are reported in Fig. 4. Reduced pooled estimates for OR were observed for MTX (0.24, 95 %CI 0.06 to 0.94, heterogeneity for MTX subgroup I^2: 89.9 %), while for all the other treatments the resulting pooled estimates were non statistically significant. The overall heterogeneity was moderate (I^2: 63.3 %). No outliers were observed.

LOO analysis for studies evaluating MTX showed that the exclusion of Kelly et all, 2021(MTX subgr.) [51] notably strengthen the protective effect of MTX (resulting OR 0.11 95 %CI 0.05 to 0.23), while also reducing heterogeneity to zero (I^2: 0 %), indicating that the study attenuated the pool effect size, although the direction of the association remained consistent.

Similarly, LOO analysis for RTX did not identify any single study that significantly influenced the overall effect estimate, but omitting Kelly et all, 2021 (RTX subgr.) [51] was associated with a complete resolution of heterogeneity (I^2: 0 %).

3.5. Risk of bias

The RoB assessment with the complete ROB-2, ROBINS-I and QUIPS tables are reported in Supplementary table 6. As already mentioned, uncontrolled studies and case series were a priori considered to be at high risk of bias.

Of the remaining thirty-four studies, ten were classified as having "high" RoB [24,30,41,47,51,55,60,61,70,78], twenty were classified as having "moderate" RoB [17,19,22,25,26,28,29,38,42,44,53,54,56,59,62,64,67,68,84], and four "low" RoB [16,23,77,82].

4. Discussion

This systematic literature review and meta-analysis provides an updated and comprehensive synthesis of the available evidence on the treatment of RA-ILD, supporting the development of the Italian Society of Rheumatology (SIR) national recommendations [8]. Our findings underline the complexity of therapeutic decision-making in RA-ILD, a disease characterized by clinical heterogeneity, variable radiological patterns, and a progressive course that substantially impacts morbidity and mortality [8].

Overall, treatments such as RTX, MMF, and JAKi were associated with stabilization or improvement in %FVC over time when considering within-group (pre-post) changes. However, the interpretation of pre-post data alone is limited by the absence of comparator groups and potential biases inherent to observational designs. More robust insights are provided by the between-group analyses, which compared %FVC

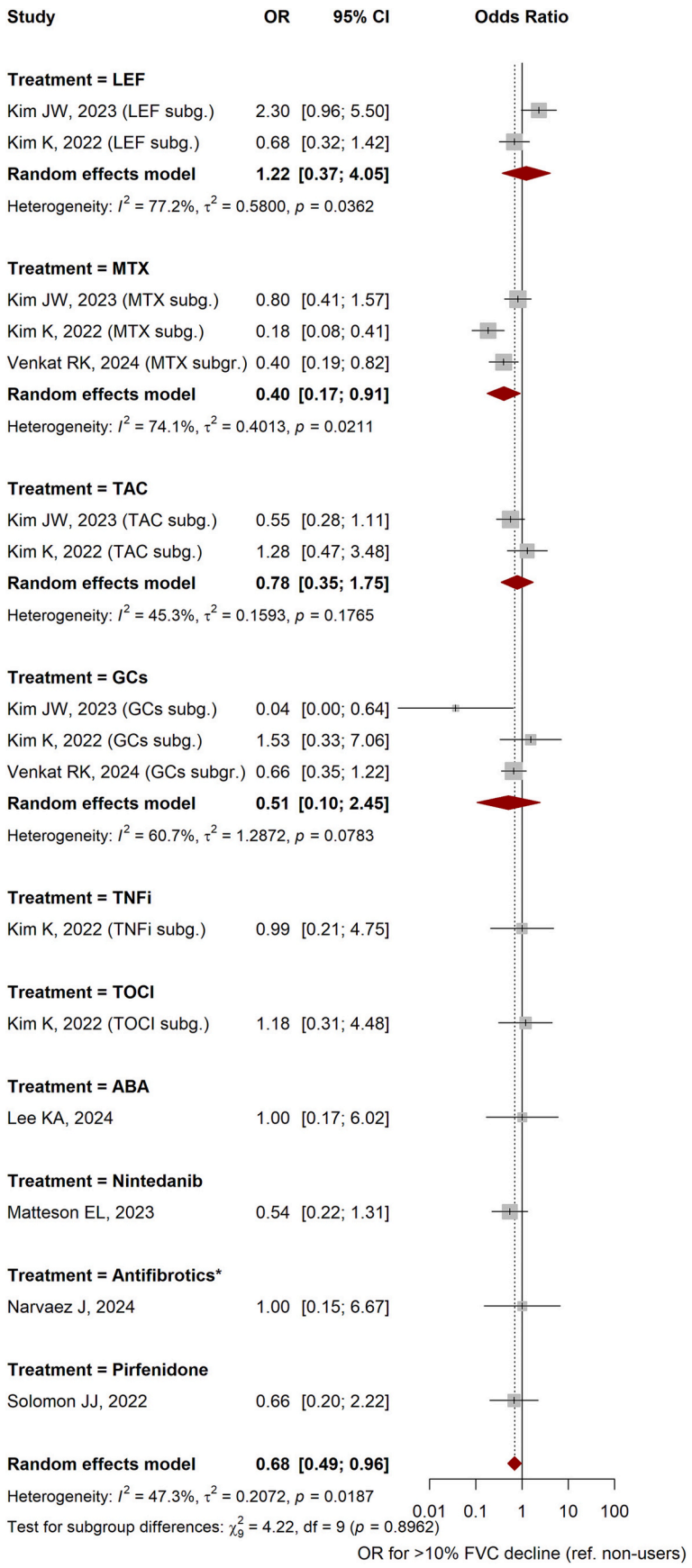

Fig. 3. Pooled and treatment-specific subgroup estimates for the ORs for progression according to %FVC (decline ≥10 %).

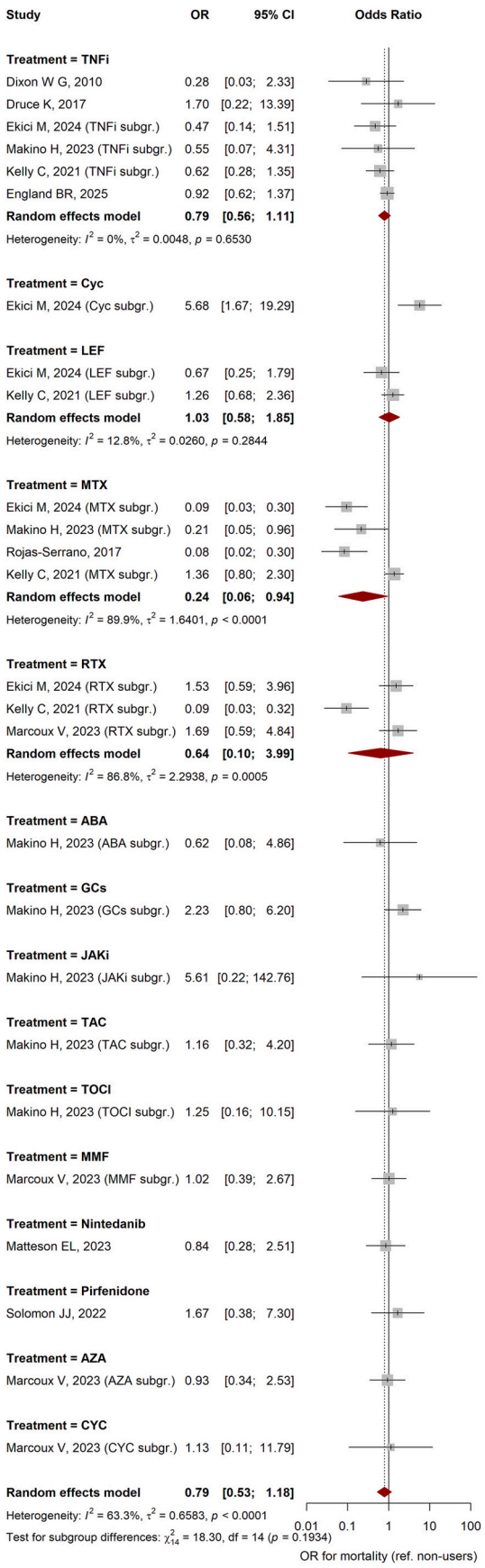

Fig. 4. Pooled and treatment-specific subgroup estimates for the ORs for mortality.

changes in treated patients versus non-users. In this context, most treatments, including RTX, MMF, and JAKi, demonstrated beneficial effects, with positive between-group differences compared to controls, suggesting a potential true treatment effect beyond the natural course of RA-ILD. Notably, no treatment was associated with a negative between-group difference relative to controls. High heterogeneity was observed across studies, but the consistency of direction across treatment classes strengthens the reliability of these findings.

Interestingly, MTX, a compound historically approached with caution in the setting of RA-ILD due to concerns about pulmonary toxicity and potential worsening of ILD, has emerged as a treatment associated with a reduced risk of disease progression and mortality. This observation is consistent with emerging data suggesting a protective rather than harmful effect [27,44], not only among patients with established RA-ILD but also in the broader RA population regarding the risk of developing interstitial lung disease. These findings reinforce a growing body of evidence that MTX may be safely used in selected RA-ILD patients with appropriate monitoring [8]. However, given the observational design of most included studies and the limited availability of detailed inclusion criteria, the possibility of confounding by indication cannot be ruled out. It remains plausible that MTX was preferentially prescribed to patients perceived to be at lower risk of pulmonary complications. While the direction of the association appeared consistent across several studies, this speculation might represent a hypothesis-generating observation that warrants further investigation in prospective, controlled settings.

ABA demonstrated encouraging effects on both pulmonary function and radiological progression, supporting its role as a potentially safer biologic option in RA-ILD [28,71]. In contrast, TNFi were associated with an increased risk of disease progression, as shown in the pooled analysis encompassing all available definitions of worsening (including pulmonary function tests, HRCT, and clinical deterioration) in Supplementary Fig. 22. Although the association narrowly reached statistical significance (OR 1.87, 95 % CI 1.00–3.51), the consistent direction of effect across studies reinforces the need for caution when considering TNFi in patients with RA-ILD.

Regarding antifibrotic agents, nintedanib showed variable effects across studies. While its efficacy in slowing FVC decline was confirmed in a subset of RA-ILD patients enrolled in the INBUILD trial [16], real-world data were heterogeneous, possibly reflecting differences in patient selection, comorbidities, and concomitant immunosuppression [34,65]. Pirfenidone, evaluated mainly in a prematurely interrupted RCT [17], appeared less effective, with an observed trend toward worsening FVC, although limitations in study power preclude definitive conclusions. The results of our analysis are consistent with recent literature, particularly with the recently published findings of Narváez et al. [88], who focused specifically on the efficacy and safety of antifibrotic agents in connective tissue disease–associated ILD, including RA-ILD.

The only study evaluating IVIg was identified as a statistical outlier in terms of effect size and was also assessed as having a high risk of bias. Although it was retained in the analysis based on the predefined inclusion criteria, its findings should be interpreted with extreme caution due to severe methodological limitations and the implausibility of the observed effect size.

The analysis of %DLCO changes showed overall stabilization across most treatments, with MMF particularly associated with a between-group improvement in DLCO. However, the robustness of these findings was limited by the relatively small number of studies available for this outcome and by significant between-study heterogeneity.

Safety profiles emerged as a critical determinant for therapeutic choices. As expected, antifibrotics were associated with a significantly lower incidence of SAEs compared to csDMARDs/immunosuppressants, although the confidence intervals were wide and influenced by a small number of studies. Regarding mortality, MTX again demonstrated a protective effect, while no other treatment showed a statistically

significant reduction.

Several limitations must be acknowledged. First, the overall quality of evidence was moderate to low, driven by the predominance of observational studies and the inherent biases associated with non-randomized designs. Only two randomized controlled trials were available. Second, significant heterogeneity was observed across most meta-analyses, only partially explained by treatment type. Differences in patient populations, ILD patterns (e.g., UIP versus nonspecific interstitial pneumonia, NSIP), disease severity, and concomitant therapies likely contributed to this variability. Third, despite attempts to mitigate publication bias, the asymmetry of funnel plots and significant Egger's tests for key outcomes suggest a potential for reporting bias favouring positive results.

Nevertheless, the strengths of this work include a comprehensive search strategy, rigorous data extraction, application of meta-analytic techniques accounting for subgroup dependency, and extensive sensitivity analyses. This SLR provides the best currently available synthesis of the efficacy and safety of treatments for RA-ILD, offering critical insights for clinicians and informing evidence-based national recommendations.

Future research efforts should prioritize high-quality prospective cohorts and randomized controlled trials specifically designed for RA-ILD, with harmonized outcome measures and stratification by radiological patterns and severity. Moreover, the role of combination therapies—balancing immunosuppression and antifibrotic effects—remains a promising yet underexplored area.

5. Conclusions

In this updated systematic review and meta-analysis, we identified that treatments such as RTX, MMF, ABA, MTX, and nintedanib are associated with stabilization or improvement in pulmonary outcomes in patients with RA-ILD. MTX and ABA, in particular, were associated with reduced risk of disease progression (MTX and ABA) and mortality (MTX). Treatment decisions in RA-ILD should consider both joint and pulmonary disease activity, radiological patterns, and safety profiles. Despite the limitations of the available evidence, this review provides a robust foundation for the development of the Italian Society of Rheumatology's national recommendations and underscores the urgent need for further high-quality research focused specifically on RA-ILD.

Funding

The Authors declare that no financial support was received for the research and/or publication of this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Professor Marco Sebastiani has received consultancy fees, and/or speaker fees from Boehringer Ingelheim, outside the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2025.103922.

Data availability

Data will be made available on request.

References

[1] Salaffi F, De Angelis R, Grassi W, MArche Pain Prevalence, INvestigation Group (MAPPING) Study. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. Clin. Exp. Rheumatol. 2005;23:819–28.
[2] Rossini M, Rossi E, Bernardi D, Viapiana O, Gatti D, Idolazzi L, et al. Prevalence and incidence of rheumatoid arthritis in Italy. Rheumatol. Int. 2014;34:659–64. https://doi.org/10.1007/s00296-014-2974-6.
[3] Juge P-A, Crestani B, Dieudé P. Recent advances in rheumatoid arthritis-associated interstitial lung disease. Curr. Opin. Pulm. Med. 2020;26:477–86. https://doi.org/10.1097/MCP.0000000000000710.
[4] Samhouri BF, Vassallo R, Achenbach SJ, Kronzer VL, Davis JM, Myasoedova E, et al. Incidence, risk factors, and mortality of clinical and subclinical rheumatoid arthritis-associated interstitial lung disease: a population-based cohort. Arthritis Care Res. 2022;74:2042–9. https://doi.org/10.1002/acr.24856.
[5] Raimundo K, Solomon JJ, Olson AL, Kong AM, Cole AL, Fischer A, et al. Rheumatoid arthritis-interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. J. Rheumatol. 2019;46:360–9. https://doi.org/10.3899/jrheum.171315.
[6] Narváez J, Díaz Del Campo Fontecha P, Brito García N, Bonilla G, Aburto M, Castellví I, et al. SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 2: Treatment. Reumatol Clin (Engl Ed) 2022;18:501–12. https://doi.org/10.1016/j.reumae.2022.03.004.
[7] Johnson SR, Bernstein EJ, Bolster MB, Chung JH, Danoff SK, George MD, et al. 2023 American College of Rheumatology (ACR)/American College of CHEST Physicians (CHEST) guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic diseases. Arthritis Rheum. 2024;76:1182–200. https://doi.org/10.1002/art.42861.
[8] Le raccomandazioni della Società Italiana di Reumatologia sul trattamento del paziente con artrite reumatoide e interstiziopatia polmonare. 2024.
[9] Interstitial Lung Disease Clinical Practice Guidelines. https://rheumatology.org/interstitial-lung-disease-guideline; 2025 (accessed September 27, 2024).
[10] Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane handbook for systematic reviews of interventions. Cochrane Database Syst. Rev. 2019;10:ED000142. https://doi.org/10.1002/14651858.ED000142.
[11] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.
[12] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.
[13] Hayden JA, Côté P, Steenstra IA, Bombardier C, QUIPS-LBP Working Group. Identifying phases of investigation helps planning, appraising, and applying the results of explanatory prognosis studies. J. Clin. Epidemiol. 2008;61:552–60. https://doi.org/10.1016/j.jclinepi.2007.08.005.
[14] Serious Adverse Reaction. European Medicines Agency (EMA). https://www.ema.europa.eu/en/glossary-terms/serious-adverse-reaction; 2025 (accessed March 29, 2025).
[15] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat. Med. 2002;21:1539–58. https://doi.org/10.1002/sim.1186.
[16] Matteson E, Aringer M, Burmester G, Mueller H, Moros L, Kolb M. Effect of nintedanib in patients with progressive pulmonary fibrosis associated with rheumatoid arthritis: data from the INBUILD trial. Clin. Rheumatol. 2023;42:2311–9. https://doi.org/10.1007/s10067-023-06623-7.
[17] Solomon JJ, Danoff SK, Woodhead FA, Hurwitz S, Maurer R, Glaspole I, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Respir. Med. 2023;11:87–96. https://doi.org/10.1016/S2213-2600(22)00260-0.
[18] Behera AK, Kumar V, Sharma P, Ganga R, Meher J, Pati S, et al. Antifibrotics in the Management of Rheumatoid Arthritis-Associated Interstitial Lung Disease: prospective real-world experience from an interstitial lung disease Clinic in India. Cureus 2024;16:e63518. https://doi.org/10.7759/cureus.63518.
[19] Chang SH, Lee JS, Ha Y-J, Kim MU, Park CH, Lee JS, et al. Lung function trajectory of rheumatoid arthritis–associated interstitial lung disease. Rheumatology 2023;62:3014–24. https://doi.org/10.1093/rheumatology/kead027.
[20] Duarte AC, Marques Gomes C, Correia M, Mendes B, Mazeda C, Guimarães F, et al. Antifibrotics in rheumatoid arthritis-associated interstitial lung disease - real-world data from a nationwide cohort. ARP Rheumatol 2024;3:182–8. https://doi.org/10.63032/POPM9413.
[21] Matson SM, Baqir M, Moua T, Marll M, Kent J, Iannazzo NS, et al. Treatment outcomes for rheumatoid arthritis-associated interstitial lung disease: a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest 2023;163:861–9. https://doi.org/10.1016/j.chest.2022.11.035.
[22] Nomura M, Sugihara T, Baba H, Hosoya T, Kamiya M, Ishizaki T, et al. Long-term outcome of a treat-to-target strategy in late-onset rheumatoid arthritis with chronic lung disease: 5-year results of a prospective observational study. Arthritis Res Ther 2025;27:22. https://doi.org/10.1186/s13075-025-03491-1.
[23] Rudi T, Zietemann V, Meissner Y, Zink A, Krause A, Lorenz H-M, et al. Impact of DMARD treatment and systemic inflammation on all-cause mortality in patients with rheumatoid arthritis and interstitial lung disease: a cohort study from the German RABBIT register. RMD Open 2024;10:e003789. https://doi.org/10.1136/rmdopen-2023-003789.

[24] Wang J, Wang X, Qi X, Sun Z, Zhang T, Cui Y, et al. The efficacy and safety of pirfenidone combined with immunosuppressant therapy in connective tissue disease-associated interstitial lung disease: a 24-week prospective controlled cohort study. Front. Med. 2022;9:871861. https://doi.org/10.3389/fmed.2022.871861.

[25] Mena-Vázquez N, Rojas-Gimenez M, Romero-Barco CM, Manrique-Arija S, Francisco E, Aguilar-Hurtado MC, et al. Predictors of progression and mortality in patients with prevalent rheumatoid arthritis and interstitial lung disease: a prospective cohort study. J. Clin. Med. 2021:10. https://doi.org/10.3390/jcm10040874.

[26] Kim J-W, Chung SW, Pyo JY, Chang SH, Kim MU, Park CH, et al. Methotrexate, leflunomide and tacrolimus use and the progression of rheumatoid arthritis-associated interstitial lung disease. Rheumatology (Oxford) 2023;62:2377–85. https://doi.org/10.1093/rheumatology/keac651.

[27] Kim K, Woo A, Park Y, Yong SH, Lee SH, Lee SH, et al. Protective effect of methotrexate on lung function and mortality in rheumatoid arthritis-related interstitial lung disease: a retrospective cohort study. Ther. Adv. Respir. Dis. 2022;16. https://doi.org/10.1177/17534666221135314. 17534666221135314.

[28] Mena-Vázquez N, Godoy-Navarrete FJ, Manrique-Arija S, Aguilar-Hurtado MC, Romero-Barco CM, Ureña-Garnica I, et al. Non-anti-TNF biologic agents are associated with slower worsening of interstitial lung disease secondary to rheumatoid arthritis. Clin. Rheumatol. 2021;40:133–42. https://doi.org/10.1007/s10067-020-05227-9.

[29] Mena-Vázquez N, Rojas-Gimenez M, Fuego-Varela C, García-Studer A, Perez-Gómez N, Romero-Barco CM, et al. Safety and effectiveness of abatacept in a prospective cohort of patients with rheumatoid arthritis-associated interstitial lung disease. Biomedicines 2022:10. https://doi.org/10.3390/biomedicines10071480.

[30] Makino H, Kotani T, Hata K, Nishioka D, Yamamoto W, Yoshikawa A, et al. Prognostic factors affecting respiratory-related death in patients with rheumatoid arthritis complicated by interstitial lung disease: an ANSWER cohort study. Mod. Rheumatol. 2023;33:928–35. https://doi.org/10.1093/mr/roac115.

[31] Matsumoto T, Iwano S, Takahashi N, Asai S, Watanabe T, Asai N, et al. Association between chest computed tomography findings and respiratory adverse events in rheumatoid arthritis patients undergoing long-term biological therapy. Int. J. Rheum. Dis. 2019;22:626–35. https://doi.org/10.1111/1756-185X.13434.

[32] Matteson EL, Dellaripa PF, Ryu JH, Crowson CS, Hartman TE, Bongartz T. Open-label, pilot study of the safety and clinical effects of rituximab in patients with rheumatoid arthritis-associated interstitial pneumonia. Arthritis Care Res. 2011;63.

[33] Akiyama M, Kaneko Y, Yamaoka K, Kondo H, Takeuchi T. Association of disease activity with acute exacerbation of interstitial lung disease during tocilizumab treatment in patients with rheumatoid arthritis: a retrospective, case-control study. Rheumatol. Int. 2016;36:881–9. https://doi.org/10.1007/s00296-016-3478-3.

[34] Atienza-Mateo B, Serrano-Combarro A, Loarce Martos J, Vegas-Revenga N, Martín López M, Castañeda S, et al. Real-world evidence of the antifibrotic nintedanib in rheumatoid arthritis-interstitial lung disease. National multicenter study of 74 patients. Semin. Arthritis Rheum. 2025;72:152710. https://doi.org/10.1016/j.semarthrit.2025.152710.

[35] Atienza-Mateo B, Remuzgo-Martínez S, Prieto-Peña D, Mora Cuesta VM, Iturbe-Fernández D, Llorca J, et al. Rituximab in the treatment of interstitial lung disease associated with autoimmune diseases: experience from a single referral Center and literature review. J. Clin. Med. 2020:9. https://doi.org/10.3390/jcm9103070.

[36] Atienza-Mateo B, Fernández-Díaz C, Vicente-Rabaneda EF, Melero-González RB, Ortiz-Sanjuán F, Casafont-Solé I, et al. Abatacept in usual and in non-specific interstitial pneumonia associated with rheumatoid arthritis. Eur J Intern Med 2023. https://doi.org/10.1016/j.ejim.2023.08.025. S0953-6205(23)00309-6.

[37] Cassone G, Manfredi A, Atzeni F, Venerito V, Vacchi C, Picerno V, et al. Safety of abatacept in Italian patients with rheumatoid arthritis and interstitial lung disease: a multicenter retrospective study. J. Clin. Med. 2020:9. https://doi.org/10.3390/jcm9010277.

[38] Chai D, Sun D, Wang Y, Song Y, Wu N, Ye Q. Progression of radiographic fibrosis in rheumatoid arthritis-associated interstitial lung disease. Front. Med. 2023;10:1265355. https://doi.org/10.3389/fmed.2023.1265355.

[39] Chartrand S, Swigris JJ, Peykova L, Fischer A. Rituximab for the treatment of connective tissue diseaseassociated interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2015;32:296–304.

[40] Cronin O, McKnight O, Keir L, Ralston SH, Hirani N, Harris H. A retrospective comparison of respiratory events with JAK inhibitors or rituximab for rheumatoid arthritis in patients with pulmonary disease. Rheumatol. Int. 2021;41:921–8. https://doi.org/10.1007/s00296-021-04835-1.

[41] Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study. Arthritis Res Ther 2015;17:319. https://doi.org/10.1186/s13075-015-0835-7.

[42] Dixon WG, Hyrich KL, Watson KD, Lunt M, BSRBR Control Centre Consortium, Symmons DPM, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology biologics register. Ann. Rheum. Dis. 2010;69:1086–91. https://doi.org/10.1136/ard.2009.120626.

[43] Druce KL, Iqbal K, Watson K, Symmons DPM, Hyrich KL, Kelly C. Mortality in patients with rheumatoid arthritis and interstitial lung disease treated with tumour necrosis factor inhibitor or rituximab. Rheumatology 2017;56. https://doi.org/10.1093/rheumatology/kex062.001. ii127–8.

[44] Ekici M, Baytar Y, Akdoğan A, Durhan G, Arıyürek M, Kalyoncu U. Prognostic factors for interstitial lung disease progression in rheumatoid arthritis: May methotrexate protect against progression? Scand. J. Rheumatol. 2024;53:371–9. https://doi.org/10.1080/03009742.2024.2371658.

[45] Sahin Eroglu D, Colaklar A, Baysal S, Torgutalp M, Baygul A, Yayla ME, et al. Rituximab experience from a single Centre for patients with rheumatoid arthritis-related interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis 2022;39:e2022029. https://doi.org/10.36141/svdld.v39i3.12337.

[46] Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J. Rheumatol. 2013;40:640–6. https://doi.org/10.3899/jrheum.121043.

[47] Fui A, Bergantini L, Selvi E, Mazzei MA, Bennett D, Pieroni MG, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. Intern. Med. J. 2020;50:330–6. https://doi.org/10.1111/imj.14306.

[48] Izuka S, Yamashita H, Iba A, Takahashi Y, Kaneko H. Acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: clinical features and prognosis. Rheumatology (Oxford) 2021;60:2348–54. https://doi.org/10.1093/rheumatology/keaa608.

[49] Juge P-A, Hayashi K, McDermott GC, Vanni KMM, Kowalski E, Qian G, et al. Effectiveness and tolerability of antifibrotics in rheumatoid arthritis-associated interstitial lung disease. Semin. Arthritis Rheum. 2024;64:152312. https://doi.org/10.1016/j.semarthrit.2023.152312.

[50] Kalyoncu U, Bilgin E, Erden A, Satış H, Tufan A, Tekgöz E, et al. Effectiveness and safety of tofacitinib in rheumatoid arthritis-associated interstitial lung disease: TReasure real-life data. Clin. Exp. Rheumatol. 2022;40(11):2071–7. https://doi.org/10.55563/clinexprheumatol/9h6dtb.

[51] Kelly CA, Nisar M, Arthanari S, Carty S, Woodhead FA, Price-Forbes A, et al. Rheumatoid arthritis related interstitial lung disease – improving outcomes over 25 years: a large multicentre UK study. Rheumatology 2021;60:1882–90. https://doi.org/10.1093/rheumatology/keaa577.

[52] Koo BS, Hong S, Kim YJ, Kim Y-G, Lee C-K, Yoo B. Mortality in patients with rheumatoid arthritis-associated interstitial lung disease treated with an anti-tumor necrosis factor agent. Korean J Intern Med 2015;30:104. https://doi.org/10.3904/kjim.2015.30.1.104.

[53] Kurata I, Tsuboi H, Terasaki M, Shimizu M, Toko H, Honda F, et al. Effect of biological disease-modifying anti-rheumatic drugs on airway and interstitial lung disease in patients with rheumatoid arthritis. Intern. Med. 2019;58:1703–12. https://doi.org/10.2169/internalmedicine.2226-18.

[54] Kurushima S, Koga T, Umeda M, Iwamoto N, Miyashita R, Tokito T, et al. Impact of Janus kinase inhibitors and methotrexate on interstitial lung disease in rheumatoid arthritis patients. Front. Immunol. 2024;15:1501146. https://doi.org/10.3389/fimmu.2024.1501146.

[55] Lee K-A, Kim BY, Kim SS, Cheon YH, Lee S-I, Kim S-H, et al. Effect of abatacept versus conventional synthetic disease modifying anti-rheumatic drugs on rheumatoid arthritis-associated interstitial lung disease. Korean J Intern Med 2024;39:855–64. https://doi.org/10.3904/kjim.2023.207.

[56] Liu L, Fang C, Sun B, Bao R, Zhang H. Predictors of progression in rheumatoid arthritis-associated interstitial lung disease: a single-center retrospective study from China. Int. J. Rheum. Dis. 2022;25:795–802. https://doi.org/10.1111/1756-185X.14351.

[57] López-Maraver M, Serrano-Combarro A, Atienza-Mateo B, Del Val N, Casafont-Solé I, Melero-Gonzalez RB, et al. Subcutaneous vs intravenous abatacept in rheumatoid arthritis-interstitial lung disease. National multicentre study of 397 patients. Semin. Arthritis Rheum. 2024;68:152517. https://doi.org/10.1016/j.semarthrit.2024.152517.

[58] Manfredi A, Cassone G, Furini F, Gremese E, Venerito V, Atzeni F, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicentre retrospective study. Intern. Med. J. 2020;50:1085–90. https://doi.org/10.1111/imj.14670.

[59] Marcoux V, Lok S, Mondal P, Assayag D, Fisher JH, Shapera S, et al. Treatment of rheumatoid arthritis-associated interstitial lung disease in a multi-center registry cohort. J Thorac Dis 2023;15:2517–27. https://doi.org/10.21037/jtd-22-1820.

[60] Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single Centre. Rheumatology (Oxford) 2017;56:1348–57. https://doi.org/10.1093/rheumatology/kex072.

[61] Mochizuki T, Ikari K, Yano K, Sato M, Okazaki K. Long-term deterioration of interstitial lung disease in patients with rheumatoid arthritis treated with abatacept. Mod. Rheumatol. 2019;29:413–7. https://doi.org/10.1080/14397595.2018.1481566.

[62] Mochizuki T, Yano K, Ikari K, Okazaki K. Combination treatment with Janus kinase inhibitor and nintedanib for rheumatoid arthritis with progressive interstitial lung disease: a case report. Mod Rheumatol Case Rep 2023;7:350–3. https://doi.org/10.1093/mrcr/rxad021.

[63] Nakashita T, Ando K, Kaneko N, Takahashi K, Motojima S. Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis. BMJ Open 2014;4:e005615. https://doi.org/10.1136/bmjopen-2014-005615.

[64] Mena-Vázquez N, Rojas-Gimenez M, Romero-Barco CM, Manrique-Arija S, Hidalgo Conde A, Ríos Arnedo Díez De Los, et al. Characteristics and predictors of progression interstitial lung disease in rheumatoid arthritis compared with other autoimmune disease: a retrospective cohort study. Diagnostics 2021;11:1794. https://doi.org/10.3390/diagnostics11101794.

[65] Narváez J, Aguilar-Coll M, Vicens-Zygmunt V, Alegre JJ, Bermudo G, Molina-Molina M. Real-world clinical effectiveness and safety of antifibrotics in progressive pulmonary fibrosis associated with rheumatoid arthritis. J. Clin. Med. 2024;13:7074. https://doi.org/10.3390/jcm13237074.

[66] Rojas-Serrano J, González-Velásquez E, Mejía M, Sánchez-Rodríguez A, Carrillo G. Interstitial lung disease related to rheumatoid arthritis: evolution after treatment.

Reumatología Clínica 2012;8:68–71. https://doi.org/10.1016/j.reuma.2011.12.008.
[67] Rojas-Serrano J, Herrera-Bringas D, Pérez-Román DI, Pérez-Dorame R, Mateos-Toledo H, Mejía M. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): methotrexate and the severity of lung disease are associated to prognosis. Clin. Rheumatol. 2017;36:1493–500. https://doi.org/10.1007/s10067-017-3707-5.
[68] Sebastiani M, Venerito V, Laurino E, Gentileschi S, Atzeni F, Canofari C, et al. Fibrosing progressive interstitial lung disease in rheumatoid arthritis: a multicentre Italian study. J. Clin. Med. 2023;12:7041. https://doi.org/10.3390/jcm12227041.
[69] Sebastiani M, Lepri G, Iannone C, Bozzalla Cassione E, Guggino G, Lo Monaco A, et al. Nintedanib in rheumatoid arthritis-related interstitial lung disease: real-world safety profile and risk of side effects and discontinuation. J. Rheumatol. 2025. https://doi.org/10.3899/jrheum.2024-0976. jrheum.2024–0976.
[70] Shen X, Wang F. The additional treatment value of immunoglobulin for the treatment of rheumatoid arthritis complicated with interstitial lung disease: a propensity score-matched pilot study. Int. J. Rheum. Dis. 2023;26:1745–50. https://doi.org/10.1111/1756-185X.14808.
[71] Shoda T, Kotani T, Koyama M, Yoshikawa A, Wada Y, Makino H, et al. The therapeutic efficacy of abatacept for rheumatoid arthritis-associated interstitial lung disease: insights from a 12-month trial using semi-quantitative chest high-resolution computed tomography imaging. JCM 2024;13:5871. https://doi.org/10.3390/jcm13195871.
[72] Suzuki K, Akiyama M, Kaneko Y. Long-term efficacy of sarilumab on the progression of interstitial lung disease in rheumatoid arthritis: the KEIO-RA cohort and literature review. Clin. Exp. Rheumatol. 2024. https://doi.org/10.55563/clinexprheumatol/pc2kq1.
[73] Tardella M, Di Carlo M, Carotti M, Giovagnoni A, Salaffi F. Abatacept in rheumatoid arthritis-associated interstitial lung disease: short-term outcomes and predictors of progression. Clin. Rheumatol. 2021;40:4861–7. https://doi.org/10.1007/s10067-021-05854-w.
[74] Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. Inflammopharmacology 2022;30:705–12. https://doi.org/10.1007/s10787-022-00936-w.
[75] Tekgoz E, Colak SY, Gunes EC, Ocal N, Cinar M, Yilmaz S. Nintedanib and its combination with immunosuppressives in connective tissue disease-related interstitial lung diseases. Ir. J. Med. Sci. 2025;194:391–7. https://doi.org/10.1007/s11845-024-03848-6.
[76] Tsujii A, Isoda K, Yoshimura M, Nakabayashi A, Kim D-S, Tamada T, et al. Janus kinase inhibitors vs. abatacept about safety and efficacy for patients with rheumatoid arthritis-associated interstitial lung disease: a retrospective nested case-control study. BMC Rheumatol 2024;8:4. https://doi.org/10.1186/s41927-024-00374-x.
[77] Venkat RK, Hayashi K, Juge P-A, McDermott G, Paudel M, Wang X, et al. Forced vital capacity trajectories and risk of lung transplant and ILD-related mortality among patients with rheumatoid arthritis-associated interstitial lung disease. Clin. Rheumatol. 2024;43:2453–66. https://doi.org/10.1007/s10067-024-07028-w.
[78] Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand. J. Rheumatol. 2007;36:172–8. https://doi.org/10.1080/03009740601153774.
[79] Yamano Y, Taniguchi H, Kondoh Y, Ando M, Kataoka K, Furukawa T, et al. Multidimensional improvement in connective tissue disease-associated interstitial lung disease: two courses of pulse dose methylprednisolone followed by low-dose prednisone and tacrolimus. Respirology 2018;23:1041–8. https://doi.org/10.1111/resp.13365.
[80] Venerito V, Manfredi A, Carletto A, Gentileschi S, Atzeni F, Guiducci S, et al. Evolution of rheumatoid-arthritis-associated interstitial lung disease in patients treated with JAK inhibitors: a retrospective exploratory study. J. Clin. Med. 2023:12. https://doi.org/10.3390/jcm12030957.
[81] Fernández-Díaz C, Castañeda S, Melero-González RB, Ortiz-Sanjuán F, Juan-Mas A, Carrasco-Cubero C, et al. Abatacept in interstitial lung disease associated with rheumatoid arthritis: national multicenter study of 263 patients. Rheumatology (Oxford) 2020;59:3906–16. https://doi.org/10.1093/rheumatology/keaa621.
[82] Druce KL, Iqbal K, Watson KD, Symmons DPM, Hyrich KL, Kelly C. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. RMD Open 2017;3:e000473. https://doi.org/10.1136/rmdopen-2017-000473.
[83] Narváez J, Robles-Pérez A, Molina-Molina M, Vicens-Zygmunt V, Luburich P, Yañez MA, et al. Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. Semin. Arthritis Rheum. 2020;50:902–10. https://doi.org/10.1016/j.semarthrit.2020.08.008.
[84] England BR, Baker JF, George MD, Johnson TM, Yang Y, Roul P, et al. Advanced therapies in US veterans with rheumatoid arthritis-associated interstitial lung disease: a retrospective, active-comparator, new-user, cohort study. Lancet Rheumatol 2025;7:e166–77. https://doi.org/10.1016/S2665-9913(24)00265-0.
[85] Boutel M, Boutou A, Pitsiou G, Garyfallos A, Dimitroulas T. Efficacy and safety of Nintedanib in patients with connective tissue disease-interstitial lung disease (CTD-ILD): a real-world single Center experience. Diagnostics (Basel) 2023;13:1221. https://doi.org/10.3390/diagnostics13071221.
[86] Fernandez-Diaz C, Castaneda S, Melero R, Loricera J, Ortiz-Sanjuan F, Juan-Mas A, et al. Abatacept in combination with metotrexate in patients with rheumatoid arthritis associated to interstitial lung disease: national multicenter study of 263 patients. Ann. Rheum. Dis. 2020;79:972. https://doi.org/10.1136/annrheumdis-2020-eular.1630.
[87] Liu Y, Liu S, Liu L, Gong X, Liu J, Sun L, et al. Fine comparison of the efficacy and safety between GB242 and infliximab in patients with rheumatoid arthritis: a phase III study. Rheumatology and Therapy 2022;9:175–89. https://doi.org/10.1007/s40744-021-00396-8.
[88] Narváez J, Aguilar-Coll M, Roig-Kim M, Palacios-Olid J, Maymó-Paituvi P, de Daniel-Bisbe L, et al. Efficacy, safety, and tolerability of antifibrotic agents in rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. Autoimmun. Rev. 2025;24:103804. https://doi.org/10.1016/j.autrev.2025.103804.
[89] Mochizuki T, Yano K, Ikari K, Okazaki K. Radiological evaluation of interstitial lung disease in patients with rheumatoid arthritis treated with abatacept or JAK inhibitors for 1 year. Respir. Investig. 2023;61:359–63. https://doi.org/10.1016/j.resinv.2023.02.007.