Rheumatoid arthritis-associated interstitial lung disease: epidemiology, risk/prognostic factors, and treatment landscape

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ABSTRACT

Objective. *To summarise the epidemiology, risk and prognostic factors, and treatment landscape of rheumatoid arthritis-associated interstitial lung disease (RA-ILD).*

Methods. *Targeted and systematic literature reviews were conducted to characterise the epidemiology and treatment landscape associated with RA-ILD, respectively. MEDLINE®, Embase, and CENTRAL were searched via OvidSP in March 2019 and December 2018. The results were narratively summarised.*

Results. *A total of 24 and 20 publications were captured through targeted and systematic literature review, respectively. No randomised controlled trials were identified; publications were observational cohort studies, cross-sectional, or case-control. Unadjusted incidence of interstitial lung disease (ILD) ranged from 1.3/1,000 person-years for interstitial pneumonia-type ILD to 5.0/1,000 person-years for 'probable or definite ILD'. Prevalence of ILD ranged from 1.8% to 67% (median: 24.9%) and varied with case definition and sample size. Few publications identified the same risk and prognostic factors; age, male sex, duration of disease, and antibodies to cyclic citrullinated peptides were the most frequently reported risk factors for development of RA-ILD, and age was the most common predictor of mortality. Despite identification of a variety of pharmacotherapeutic interventions, assessment of the comparative efficacy and safety of the available treatments were difficult due to heterogenous reporting of outcomes and small sample size.*

Conclusion. *A wide range of estimates were identified for incidence and prevalence of RA-ILD. Further, there was no consensus on risk and prognostic factors. Sufficiently powered clinical trials are needed to confirm the findings of the observational studies with respect to efficacy and safety of current treatments.*

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease with systemic complications beyond the hallmark symptoms of joint pain and inflammation. Interstitial lung disease (ILD) is the most common lung manifestation of RA, involving progressive fibrosis of the lung parenchyma, and is the second leading cause of mortality in RA patients (1, 2). Despite high burden of comorbidity among individuals with RA, the epidemiology and natural history of ILD have been historically difficult to define: while radiological evidence of the disease has been observed in 19–67% of RA patients, prevalence estimates drop to 3–5% when only clinically significant cases are considered (3).

The determinants of RA-associated ILD (RA-ILD) are likewise poorly understood. Though RA is itself a known risk factor for ILD, only a subset of patients develop the disease (1), and determining the influence of environmental, serologic, clinical, genetic, and drug-related risk factors is challenging. Male sex, advanced age, smoking status, and various lab parameters, including rheumatoid factor (RF) positivity and antibodies to cyclic citrullinated peptides (ACPA), have all been suggested as putative risk factors (1). However, identification of factors independently associated with increased risk of RA-ILD requires careful examination through multivariable analysis, which has been infrequently performed in previous studies. Fewer RA-ILD prognostic factors have been identified,

and while presence of usual interstitial pneumonia (UIP) pattern is a well-established predictor of adverse clinical outcomes, its precise contribution to mortality is unknown (4).

To date, there are no approved pharmacotherapy options for RA-ILD, and as no randomised controlled trials (RCTs) are yet available, optimal therapeutic regimens remain unclear (1). Clinical management is currently empirical, relying on corticosteroids as first-line treatment. Some therapies have shown promise in stabilising or improving ILD, including abatacept (ABA) and rituximab (RTX) (3). Nevertheless, management of RA-ILD remains clinically challenging, as common therapies for RA such as methotrexate (MTX), leflunomide, and anti-tumour necrosis factor agents (anti-TNFs) have been implicated in both *ex novo* occurrence and acceleration of existing ILD (1, 5). Given the lack of consensus on optimal treatment strategy, an overview of existing therapies for RA-ILD is warranted to assess the available efficacy/effectiveness and safety of treatments currently used, as well as unmet needs and knowledge gaps in the management of patients with RA-ILD.

The objective of this study was to evaluate the existing literature on epidemiology and treatment landscape of ILD in the RA population. To this end, a targeted literature review (TLR) was conducted to summarise incidence, prevalence, and risk/prognostic factors of RA-ILD, in parallel with a systematic literature review (SLR) aimed at describing the published evidence on available treatment options.

Materials and methods

Targeted and systematic literature searches were undertaken in parallel. Primary searches were carried out in DOC Search™ (Doctor Evidence, LLC, Santa Monica, CA, USA), containing MEDLINE®, clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), European public assessment reports (EPAR), DailyMed, and RSS feeds for the targeted review, and in MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and Embase (via OvidSP) for the systematic review. Supplemental searches were conducted in Embase (via OvidSP) to capture conference proceedings published within the preceding two years (2016–2018) from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), as well as clinical trials registered on clinicaltrials.gov and clinicaltrialsregister.eu. All searches were performed on December 26, 2018; the targeted literature search was updated March 24, 2019. Search strategies are outlined in Suppplementary Tables S1–S7.

Following deduplication, separate screening criteria were applied to the targeted and systematic reviews. Two independent reviewers screened publications using a Population, Intervention, Comparator, and Outcome (PICO) framework (6). For both reviews, only studies of adults ≥18 years of age with RA-ILD were considered. For the targeted literature search, publications were included if they reported RA-ILD prevalence and incidence, patient characteristics/risk factors linked to disease occurrence, or patient characteristics/prognostic factors associated with clinical outcomes. Case reports/series and pre-clinical studies were excluded. For the systematic search, publications were included if they were RCTs, non-RCTs, or observational studies, and were assessed for the following efficacy/effectiveness and safety outcomes: American College of Rheumatology 20%, 50%, and 70% (ACR20/50/70) responses, Sharp Scores, Disease Activity Score 28 (DAS28), dyspnea, Modified Medical Research Council (MMRC) Dyspnea Scale, diffusing capacity for carbon monoxide (DLCO), forced vital capacity (FVC), forced expiratory volume (FEV1), FEV1/FVC, ILD exacerbation, total study withdrawal, study withdrawal due to adverse events (AEs), serious/severe AEs, or specific AEs.

Publications meeting inclusion criteria proceeded to data extraction, performed by two reviewers with discrepancies resolved through arbitration. For RA-ILD incidence and prevalence, values were either taken directly from the text or calculated, if possible. Risk and prognostic factor data were only collected from multivariable analyses. Bibliographic cross-referencing was performed to capture all pertinent literature. Quality of studies was assessed only for the systematic literature review using the Newcastle-Ottawa Scale (NOS) (7). Results for both reviews were reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). K is used to indicate number of included studies, while n indicates the number of included participants.

Results

Targeted Literature Review: epidemiology and risk/prognostic factors

The targeted literature review of RA-ILD epidemiology and risk/prognostic factors identified 24 observational studies: 20 cohort studies, three cross-sectional studies, and one case-control study (Fig. 1A).

Incidence and prevalence of RA-ILD

The incidence of RA-ILD was reported by two retrospective cohort studies among patients with RA in the United States (US; 1955–1994) (9) and Japan (2004–2006) (10) (Table I), as well as one retrospective cohort study among the US general population (2003–2014) (11). Among patients with RA, unadjusted incidence ranged from 1.3/1,000 person-years for interstitial pneumonia subtype ILD (10) to 5.0/1,000 person-years for "probable or definite ILD" (9). Within the US general population, yearly incidence ranged from 2.7 (95% confidence interval [CI] 2.5–2.9) to 3.8 (95% CI 3.5–4.0) cases per 100,000 people (11).

Ten observational studies reported prevalence of RA-ILD within the RA patient population (12-21), with estimates ranging between 1.8% (15) and 67% (18) (median: 24.9%; Table I). Among the US general population, a claims-based analysis estimated prevalence of RA-ILD at 3.2 (95% CI 3.0-3.4) to 6.0 (95% CI 5.7-6.2) cases per 100,000 people per year, noting an increase in RA-ILD prevalence over the ten-year study period, even as in-

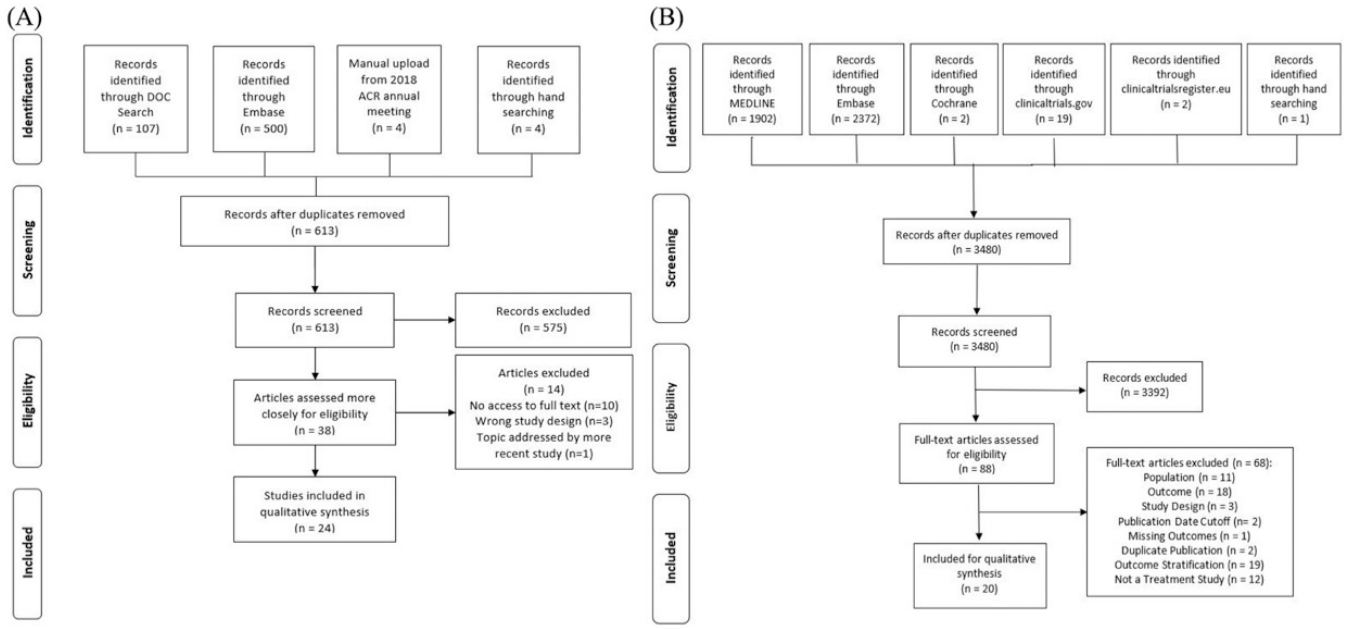

Fig. 1. PRISMA diagrams for (**A**) the TLR of RA-ILD epidemiology and (**B**) the SLR of RA-ILD treatment landscape.

cidence remained stable (11). Substantial variation in case definition was observed across studies: while most publications diagnosed RA according to ACR criteria, ILD was classified using International Classification of Diseases, 10th Revision (ICD-10) codes by one study (14), lung abnormalities present on chest scan in six studies (13, 15, 17-19, 21), and abnormalities identified through a combination of chest scan, pulmonary function tests, and/or lung biopsy in two studies (12, 16). One study did not describe how ILD was defined (20).

Risk factors for ILD in RA

Eight observational studies employed multivariable statistical analyses to identify risk factors of RA-ILD (Table II) (10, 13, 16, 17, 19, 21-23). The factors investigated included demographics, RA-related disease activity, disease-modifying antirheumatic drug (DMARD) use, genetic factors, and lab parameters. Advanced age was a risk factor in five publications (13, 17, 19, 21, 23) and was both a strong predictor of developing ILD in RA and poor prognosis in pre-existing RA-ILD (17, 21, 23). However, not all publications adjusting for age found it predictive of ILD. Male sex was a risk factor for RA-ILD in two publications (10, 16), including one in which it was the only factor independently associated with risk of interstitial pneumonia subtype ILD (female: odds ratio [OR] 0.23, 95% CI 0.07-0.75, p=0.01) (10). Duration of RA disease was identified as a predictor of ILD in three publications, with both longer (16, 19) and shorter (21) disease duration associated with increased risk of RA-ILD. Three publications reported ACPA positivity as an independent risk factor (17, 19, 22). Of the five publications including RA drug treatments as covariates, use of steroids (17), leflunomide (13), and prednisone (16) were identified as risk factors of ILD onset. Other risk factors identified included smoking (13, 21), rheumatoid factor (21, 22), and lactate dehydrogenase (LDH) levels (21).

Prognostic factors associated with ILD clinical outcomes

Nine cohort studies assessed predictors of RA-ILD morbidity or mortality through multivariable analyses (Table III) (24-32). Methotrexate use, ACPA positivity, and DLCO <45% were among factors independently associated with ILD morbidity (25, 28). Age was the most frequently identified predictor of mortality, reported by seven studies (24, 25, 27, 29-32), with hazard ratios (HR) ranging from 1.04 (per year variable) (27, 30) to 2.28 (per decade variable, 95% CI: 1.64–3.15) (24). Four publications included FVC in their adjusted models (25, 26, 29, 32), but only one identified some level of independent association with adverse clinical outcomes (29). Other factors of interest included smoking history, DLCO, DAS28, RA disease duration, male sex, presence of UIP pattern, and extent of fibrosis (based on either high-resolution computed tomography [HRCT] or histopathology).

Systematic Literature Review: RA-ILD treatment landscape

A total of 20 publications pertaining to 19 studies were included in the systematic literature review examining the treatment landscape of RA-ILD (Fig. 1B). The 19 studies included 16 cohort studies, two case-control studies, and one non-controlled clinical trial for a variety of therapies, either as combinations or monotherapies (Table IV).

Efficacy/effectiveness outcomes

Clinical outcomes reported across studies included DAS28, dyspnea, DLCO, FVC, FEV1, FEV1/FVC, and ILD exacerbation (Suppl. Table S8). With the exception of DAS28, few RA-related outcomes (such as ACR20/50/70) were recorded. As reporting of FEV1, FEV1/FVC, and ILD exacerbation was limited, these outcomes are described in the Supplementary file.

Disease Activity Score 28 (DAS28)

In total, 13 studies reported DAS28 outcomes following treatment for RA-ILD (Suppl. Table S9). High disease activity was generally considered DAS28 >5.1. Outcomes for DAS28 were most frequently available in studies evaluating ABA (k=4) (33-36) and RTX (k=4) (37-40); other treatments are listed in Supplementary Table S9.

Seven studies (33-35, 37, 38, 41, 42) reported mean or median DAS28 scores between 3 and 12 months of follow-up. Scores ranged from a mean of 2.2 (standard deviation [SD]): 1.1; tociliz-

Table I. Incidence and prevalence of ILD among individuals with RA.

Incidence: cohort studies				
Reference	**Incidence rate***	**Case definition**	**Cases/sample size**	**Study period**
Bongartz *et al.* 2010 (9)	5.0 per 1,000 person-years**	Probable or definite ILD	46/582**	Mean ± SD 16.4 years ± 10.5
Shidara *et al.* 2010 (10)	1.3 per 1,000 person-years	Interstitial pneumonia, a subtype of ILD	15/11,557.5 PY	April 2004-October 2006 (2.5 years)
Prevalence: cohort studies				
Reference	**Unadjusted Prevalence**	**Case definition**	**Cases/sample size**	**Study period**
Hyldgaard *et al.* 2017 (14)	2.2%	RA: ICD-10 code M05 or M06 (using ACR 1987 criteria until 2009 and ACR/EULAR criteria 2010-onwards) ILD: ICD-10 code J84 or M05.1c	679/31,333	January 2004 – July 2016 (151 months)
Kim ***et al.* 2017 (15)**	1.8% (95% CI 1.4-2.3%)¥	RA: Fulfilled 1987 ACR criteria ILD: Chest image reports such as "pulmonary fibrosis", "interstitial fibrosis", "interstitial pneumonia", "interstitial lung disease" and "ILD", in addition to descriptions of patterns of the lung disease *e.g.* "usual interstitial pneumonia"	64/3555	July 2009 – December 2012 (42 months)
Wang *et al.* 2017 (18)	Main set: 58.7%¥¥¥ Validation set: 67%¥¥¥	RA: Clinical diagnosis of RA in electronic medical record ILD or pulmonary fibrosis: presence of abnormalities on HRCT	364/620 146/218	January 2013 – December 2015 (36 months) January 2014 – December 2015 (24 months)
Zhang *et al.* 2017 (21)	43.1%	RA: Fulfilled 1987 or 2009 ACR criteria, or EULAR criteria ILD: Defined according to lung HRCT	237/550	January 2008 – June 2013 (66 months)
Chen *et al.* 2015 (12)	Chinese cohort: 31% US cohort: 57%	RA: Fulfilled 1987 ACR criteria ILD: Chest HRCT and pulmonary function testing tests contained radiographic and functional abnormalities indicative of ILD	41/133 49/86	July 2012 – March 2013 (9 months) October 2010 – June 2013 (33 months)
Wang *et al.* 2015 (17)	15.26%	RA: Fulfilled ACR 2006 criteria ILD: Presence of ILD abnormalities on HRCT	83/544	July 2006 – June 2011 (60 months)
Giles *et al.* 2014 (13)	32.2%	RA: Fulfilled 1987 ACR criteria ILD: Cardiac multidetector row CT scans that observed pulmonary parenchymal disease and presence of ILD features (*e.g.* ground glass opacities, honeycombing)	57/177	October 2004 – May 2006 (20 months)
Yin *et al.* 2014 (19)	24.9%	RA: Fulfilled ACR 1987 criteria ILD: Chest HRCT with presence of ILD abnormalities	71/285	January 2004 – October 2013 (118 months)

Prevalence: cross-sectional studies				
Reference	**Unadjusted prevalence**	**Case definition**	**Cases/sample size**	**Study period**
Restrepo *et al*. 2015 (16)	8.8%¥¥	Probable ILD: chest x-ray or CT scan contained "pulmonary fibrosis," "fibrosis changes," "fibrosis," "RA lung," and "fibrosing alveolitis," and the treating physician used diagnostic terms associated with ILD Definitive ILD: diagnosed by a pulmonologist, in the presence of two of the following three criteria: ILD observed in chest radiograph or chest CT, restrictive pattern observed on pulmonary function test, and bronchoscopy or surgical lung biopsy compatible with ILD	69/779	January 1996 – April 2000 (52 months)
Prevalence: case-control studies				
Reference	**Unadjusted prevalence**	**Case definition**	**Cases/sample size**	**Study period**
Yuvienco *et al*. 2018 (20)	6.4%	Unknown: Analysis of medical records used to find patients with ILD, who were also diagnosed with RA, and *vice versa*.	34/528	January 2013 - May 2017 (53 months)

Timepoints for prevalence estimates have been converted to months for ease of comparison.
* Unadjusted. ** In order to make the reported cumulative incidence of Bongartz *et al*. comparable to the incidence rate of Shidara *et al*., the incidence was calculated using the formula:
IR = -log(1-CI)/time [derived from CI = 1 - exp(-IR*time)]; this formula is an estimate and assumes that incidence remained constant over the study period.
¥ Based on CXR and/or CT images. When estimated using CXR alone or CT alone, prevalence was 1.2% (95% CI 0.9%-1.6%).
¥¥ Includes both probable and definite cases of ILD.
¥¥¥ Based on HRCT, "diagnosed as complicated with ILD"(18).
ACR: American College of Rheumatology; CI: confidence interval; CT: computed tomography; EULAR: European League Against Rheumatism; HRCT: high-resolution computed tomography; ICD: International Classification of Diseases; ILD=interstitial lung disease; PY: person-years; RA: rheumatoid arthritis; SD: standard deviation.

umab [TOC] at 120 weeks) (41) to 4.4 (SD: 1.8; TOC at 24 weeks) (41). Among publications reporting multiple timepoints, DAS28 scores tended to decrease over time (33, 38, 41, 42).

Mean (SD) DAS28 with C-reactive protein (DAS28-CRP) was reported in one study, decreasing from 3.70 (1.19) at 3 months to 2.89 (0.93) at 12 months in patients treated with RTX + methylprednisolone (MPS) (39). DAS28 with erythrocyte sedimentation rate (DAS28-ESR) was reported in five studies (35, 36, 40, 43, 44), with scores ranging from a mean (SD) of 2.54 (1.12; DMARDs at 1 year) (44) to 4.22 (1.5; MTX + hydroxychloroquine [HCQ] at 1 year) (43). Few to no patients treated with ABA, ABA ± DMARDs, ABA ± immunosuppressor, anti-TNFs, DMARDs, MTX + HCQ, RTX, RTX + MPS ± DMARDS, RTX + MPS, TOC, or TOC ± DMARDs reported high disease activity (DAS28 >5.1) during follow-up.

Dyspnea

Dyspnea outcomes were reported in seven studies investigating ABA (k=4) (33-35, 45), RTX (k=3) (38, 39, 45), and TOC (k=2) (42, 45), all of which used the MMRC scale (Suppl. Table S10). Worsening dyspnea ranged from 0% (ABA ± immunosuppressor at 6 months (33); RTX + MPS ± DMARDs at 3, 6 and 12 months (38, 39); TOC ± DMARDs at 3 months (42); ABA at 3, 6, and 12 months (35)) to 23.1% (ABA at 12 months) (46). The percentage of patients who experienced stable dyspnea ranged from 53.8% (ABA at 12 months) (35) to 100% (TOC ± DMARDs at 3 months) (42). Improvement in dyspnea ranged from 0% (TOC ± DMARDs at 3 and 6 months) (42) to 41.67% (RTX + MPS ± DMARDs at 6 months) (39) of patients. In addition to MMRC scale outcomes, one publication (n=19) reported grade 1 (mild) dyspnea in a patient (5.26%) following ABA treatment after 9.4 months (35).

Diffusing capacity for carbon monoxide (DLCO)

DLCO outcomes were reported as percent change, percent predicted using the single breath technique, and DLCO improvement, stabilisation, or worsening. The most common treatments among publications reporting DLCO were RTX (k=5) (37-40, 45) and ABA (k=4) (33-35, 45) (Suppl. Tables S11–S12).

One study (40) reported absolute change in DLCO (mean: 7.93; RTX at 12–71 months follow-up), while another (37) reported percent change in DLCO (median: -1.3, interquartile range [IQR]: -8.7 to 6.4; RTX + MPS at 12 months). Two studies (43, 47) reported DLCO percent predicted using the single breath technique at one year, ranging from a mean (SD) of 69% (SD: 10%; penicillamine + prednisone) (47) to 79.56% (SD: 54.97%; MTX ± HCQ) (43).

Eight studies reported DLCO worsening, stabilisation, or improvement at 3-, 6-, and 12-month intervals for a variety

Table II. Risk factors of RA-ILD, after adjustment for covariates.

Cohort studies

Reference	Sample size [n]‡	Independent risk factors (and risk estimates, 95% CI, *p*-value)	Variables adjusted for in multivariable model
Zhang *et al.* 2017 (21)	237	Age (OR 1.599, $p<0.001$) RA duration (>10 years *vs.* 1 year; OR 0.368, $p=0.001$) Smoking (yes *vs.* no; OR 2.116, $p=0.001$) RF (positive *vs.* negative; OR 1.693 $p=0.043$) LDH (elevated *vs.* normal; OR 7.369, $p<0.001$)	Age, RA duration (Time 1 (1–5 years *vs.*1 year), Time 2 (5–10 years *vs.* 1 year), Time 3 (>10 years *vs.* 1 year), smoking, RF positive, LDH
Wang *et al.* 2015 (17)	83	Age (OR 2.20, 95% CI 1.04–4.65, $p=0.040$) Age at RA onset (OR 2.55, 95% CI 1.11–5.90, $p=0.028$) Positive ACPA (OR 2.47, 95% CI 1.19–5.17, $p=0.016$) Steroid use (OR 1.83, 95% CI 1.04–3.20, $p=0.035$)	Age, sex, age at RA onset, RA duration, ACPA, steroid use, RF, CRP, smoking, hepatitis B surface antigen, *Tripterygium wilfordii*
Giles *et al.* 2014 (13)	57	Age, per year (β*=0.034, $p=0.035$) High level ACPA (≥ 7; β=0.79, $p=0.055$) Ever smoking (β=0.78, $p=0.010$) Square Root DAS28 (β=1.35, $p=0.013$) Current leflunomide use (β=1.20, $p=0.007$)	Age, sex, ever smoking, current smoking, high level ACPA (groups: 0, 1 or 2, 3-6, ≥7), RF seropositivity, square root DAS28 (per unit), Log Sharp-van der Hiejde Score, rheumatoid nodules, HAQ, current prednisone, MTX, leflunomide, biologics use
Yin *et al.* 2014 (19)	71	Age (OR 1.06, 95% CI 1.03–1.08, $p<0.001$) RA duration (OR 1.04, 95% CI 1.01–1.07, $p=0.02$) Positive ACPA (OR 3.50, 95% CI 1.52–8.04, $p<0.001$)	Age, RA duration, ACPA (groups: seropositive, low positive, moderate positive, high positive), RF (groups: seropositive, low positive, moderate positive, high positive)
Shidara *et al.* 2010 (10)	132	Female (OR 0.23, 95% CI 0.07–0.75, $p=0.01$)	Age, sex, smoking, RA duration, joint health accounts questionnaire (J-HAQ) score, Global-Visual analogue scale (VAS), Pain-VAS, Physician-VAS, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), RF, MTX dose, prednisolone dose

Cross-sectional studies

Reference	Sample size [n]‡	Independent risk factors (and risk estimates, 95% CI, *p*-value)	Variables adjusted for in multivariable model
Wang *et al.* 2016 (23)	28	Age (OR 1.06, 95% CI 1.02–1.11), p=NR Higher Carbohydrate Antigen 125 (OR 1.03, 95% CI 1.01–1.05)	
Restrepo *et al.* 2015 (16)	69	Male (OR 3.38, 95% CI 1.96–5.84, $p\leq0.001$) RA duration (per 5 years; OR 1.29 95% CI 1.12–1.49, $p\leq0.001$) DAS28 (OR 1.49, 95% CI 1.23–1.80, $p\leq0.001$) Age at RA onset (per 5 years; OR 1.24, 95% CI 1.10–1.40, $p\leq0.001$) Prednisone use (OR 1.90, 95% CI 1.10–3.29, $p=0.02$) Reported significant but no data: ACPA, log RF, ESR	Age of onset, sex, RA duration, DAS28, HLA-DRB1 SE (gene), prednisone use, log RF, log ACPA, ESR
Rocha-Muñoz *et al.* 2015 (22)	39	Positive ACPA (OR 1.06 95 % CI 1.02–1.10, $p=0.003$) RF (positive *vs.* negative; OR 28.58, 95% CI 3.31–246.95, $p=0.002$)	Age, RA duration, smoke exposure, DAS28, HAQ-Di, ESR, ACPA titres, positive RF, MTX treatment duration

‡Sample size (n) represents number of patients with RA-ILD.
*β coefficients represent the average change in the square root of the expert read Interstitial Lung Disease Score associated with a 1-unit higher value of the characteristic of interest.
ACPA: anti-citrullinated protein/peptide antibody; CI: confidence interval; CRP: C-reactive protein; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HLA-DRB1 SE: human leukocyte antigen DR beta 1 shared epitope; HR: hazard ratio; J-HAQ: joint health accounts questionnaire; HAQ: health accounts questionnaire; LDH: lactate dehydrogenase; MTX: methotrexate; NR: not reported; RA: rheumatoid arthritis; RF: rheumatoid factor; VAS: visual analogue scale.

of treatments, including ABA, ABA ± DMARDs, ABA ± immunosuppressor, RTX, RTX + MPS ± DMARDs, TOC, and TOC ± DMARDs (33-35, 38-40, 42, 45). Between 0–50% of patients experienced DLCO worsening, 33–100% experienced no change, and 0–56% experienced DLCO improvement, with seven studies defining clinical worsening or improvement as change ≥10%. Importantly, proportions varied between treatments and timepoints.

Forced vital capacity (FVC)

FVC was reported by 13 studies as percent predicted, absolute change, percent change, or FVC improvement/stabilisation/worsening (Suppl. Tables S13–S14). Among reporting publica-

Table III. Predictors of RA-ILD morbidity and mortality, after adjustment for covariates.

Morbidity			
Reference	**Sample size [n]‡**	**Independent prognostic factors (and risk estimates, 95% CI, *p*-value)**	**Variables included in the model**
Fu *et al.* 2018 (25)	266	Positive ACPA (OR 4.03, 95% CI 1.04–15.69, p=0.04) DLCO %< 45% (OR 8.31, 95% CI 2.17–31.75, p<0.01)	Advanced age (>60 years old), ILD within 10 years of RA diagnosis, ever-smoker, ACPA high titre positivity, UIP pattern on HRCT, cyclophosphamide, MTX, FVC, DLCO
Mochizuki *et al.* 2018 (28)	55 (baseline)	MTX use (OR 12.75, 95% CI 1.09–148.77, p=0.042)	MTX use*, KL6*
Mortality			
Reference	**Sample size [n]‡**	**Independent prognostic factors (and risk estimates, 95% CI, *p*-value)**	**Variables included in the model**
Fu *et al.* 2018 (25)	266	Advanced age (>60 years old; HR 2.32, 95% CI 1.27–4.25, p=0.01) Lung involvement >30% on HRCT	Advanced age (>60 years old), sex, ever-smoker, high RF titre, ILD within 10 years of RA diagnosis, ACPA high titre positivity, UIP pattern on HRCT, lung involvement >30% on HRCT, cyclophosphamide, MTX, *Tripterygium wilfordii*
Yang *et al.* 2017 (31)	77	Age at ILD diagnosis (OR 1.08, 95% CI 1.02–1.15, p=0.012)	Age at ILD diagnosis (older), sex, history of smoking, high RF titre (≥3 ULN), ESR, CRP, UIP pattern on HRCT, Nonspecific interstitial pneumonia (NSIP) on HRCT
Zamora-Legoff *et al.* 2017 (32)	181	Age (HR 2.27, 95% CI 1.61–3.21, p<0.001) RA disease duration (HR 1.81, 95% CI 1.16–2.83, p=0.009) DLCO <=40% (HR 2.67, 95% CI 1.61–3.21, p<0.001) DLCO >40% (HR1.35, 95% CI 1.08–1.69, p=0.009)	Age, sex, RA duration, diffusion capacity of the lung for carbon monoxide (DLCO), FVC, CRP
Solomon *et al.* 2016 (29)	137	Age (HR 1.07, 95% CI 1.03–1.11, p=0.0002) Ever-smoker (HR 2.15, 95% CI 1.08–4.31, p=0.02) FVC 10% decline (HR 2.57, 95% CI 1.79–3.70, p<0.0001) FVC 10% lower than 68.7% at baseline (HR 1.46, 95% CI 1.23–1.73, p<0.0001)	Age, sex, ever-smoker, UIP pattern on HRCT, FVC 10% decline, FVC 10% lower than 68.7% at baseline
Solomon *et al.* 2011 (30)	48	Age (HR 1.04, p<0.01) Fibrosis on histopathology (HR 2.1, p<0.02)	TLC, FVC, DLCO, age, sex, presence of Fibrosis
Dixon *et al.* 2010 (24)	367	Age (per decade) (HR 2.28, 95% CI 1.64–3.25) DAS28 (HR 1.43, 95% CI 1.11–1.85)	Sex, RA duration, Calendar year of entry, HAQ, COPD/asthma, steroid use, MTX
Kim *et al.* 2010 (26)	82	UIP pattern (HR 2.34, p=0.05) DLCO % predicted (HR 0.96, p=0.003) Female sex (HR 0.3, p=0.008)	Baseline FVC% predicted
Koduri *et al.* 2010 (27)	52	Age (HR 1.04, 95% CI 1.0–1.09)	ESR, pain at baseline, HAQ, SES

All studies reporting prognostic factors were cohort studies.
‡Sample size (n) represents number of patients with RA-ILD.
*Factors were not specified in the publication but implied by the tables present.
ACPA: anti-citrullinated protein/peptide antibody; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DAS28: Disease Activity Score-28; DLCO: diffusion capacity of the lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; FVC%: forced vital capacity percent; HAQ: health assessment questionnaire; HR: hazard ratio, HRCT: high-resolution computed tomography; ILD: interstitial lung disease, KL6: Krebs von den Lungen-6 antigen; MTX: methotrexate; NR: not reported; NSIP: nonspecific interstitial pneumonia; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor; SES: socioeconomic status; TLC: total lung capacity; UIP: usual interstitial pneumonia; ULN: upper limit of normal.

tions, RTX (k=6) (37-40, 45, 48) and ABA (k=4) (33-35, 45) were the most common therapeutic agents.

Absolute and percent change in FVC were each reported by one study, both evaluating RTX treatment regimens (37, 40). Percent predicted FVC was reported by four studies assessing anti-TNFs, mycophenolate mofetil (MMF), MMF + prednisone, and MTX ± HCQ (43, 48-50). The lowest mean FVC percent predicted was 60% following treatment with MMF at 6 months (49), while the highest was 88.48% (SD: 19.93%), achieved through anti-TNF + MTX combination therapy at 1 year (43).

FVC worsening, stabilisation, and improvement were the most common FVC outcomes, reported in nine studies investigating ABA, ABA ± DMARDs, ABA ± immunosuppressor, RTX, RTX ± DMARDs, RTX + MPS ± DMARDs, TOC, and TOC ± DMARDs (33-35, 38-40, 42, 45, 48). Generally, greater

Table IV. Therapies assessed in the SLR of RA-ILD treatment landscape.

Interventions	Number of studies reporting	Study design	Citation(s)
ABA monotherapy	5	5 Retrospective Cohort	(33-36, 45)
RTX monotherapy	3	2 Retrospective Cohort	(45, 48)
		1 Prospective Cohort	(40)
TOC monotherapy	3	2 Retrospective Cohort	(42, 45)
		1 Case-Control	(41)
MTX monotherapy	3	2 Prospective Cohort	(43, 44)
		1 Case Control	(70)
RTX + MPS	3	3 Retrospective Cohort	(37-39)
ABA + cDMARDs*	2	2 Retrospective Cohort	(34, 35)
RTX + MPS + cDMARDs†	2	2 Retrospective Cohort	(38, 39)
anti-TNF monotherapy	2	2 Retrospective Cohort	(36, 71)
anti-TNF + MTX	1	Prospective Cohort	(43)
ABA + immunosuppressor	1	Prospective Cohort	(33)
DMARDs‡	1	Prospective Cohort	(44)
LEF monotherapy	1	Prospective Cohort	(44)
LEF + infliximab	1	Prospective Cohort	(44)
MTX + etanercept	1	Prospective Cohort	(44)
MTX + hydroxychloroquine	1	Prospective Cohort	(43)
MMF monotherapy	1	Retrospective Cohort	(49)
MMF + prednisone	1	Retrospective Cohort	(50)
Penicillamine + prednisone	1	Non-Controlled Clinical Trial	(47)
Sulfasalazine monotherapy	1	Prospective Cohort	(44)
TOC + cDMARDs#	1	Prospective Cohort	(42)

*including leflunomide, leflunomide + cyclosporine, sulfasalazine, methotrexate, methotrexate + leflunomide, hydroxychloroquine, hydroxychloroquine + leflunomide, azathioprine, chloroquine, and cyclosporine.
†including leflunomide, sulfasalazine, methotrexate, hydroxychloroquine, azathioprine, and mycophenolate mofetil.
‡including monotherapy or combination therapy with methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, mycophenolate mofetil, rituximab, abatacept, etanercept, infliximab, adalimumab, and tocilizumab.
#methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, and gold salts.
ABA: abatacept; anti-TNF: tumour necrosis factor inhibitor; cDMARDs: conventional disease-modifying anti-rheumatic drugs; DMARDs: disease-modifying anti-rheumatic drugs; LEF: leflunomide; MMF: mycophenolate mofetil; MPS: methylprednisolone; MTX: methotrexate; RTX: rituximab; TOC: tocilizumab.

proportions of patients exhibited stable FVC than FVC worsening or improvement following RA-ILD therapy. Stable FVC was observed in 8.33–100% of patients following treatment, while in contrast, 0–28.6% exhibited worsening and 0–57.1% exhibited improvement in FVC.

Safety outcomes

Three publications reported safety outcomes of interest (Suppl. Table S15) (35, 37, 40). One publication reported total study withdrawal in 11 (17.46%) participants and withdrawal due to AEs in seven (11.11%) participants following ABA treatment (follow-up: 12 months) (35), while a study of RTX therapy reported withdrawal due to AEs in three (13%) participants (follow-up: 71 months) (40). Severe AEs occurred in 33 (59%) patients treated with RTX + MPS combination therapy (follow-up: 6–12 months) (37) and 23 (13%) patients treated with RTX monotherapy (follow-up: 12–71 months) (40). One publication documented injection site reaction in one of 62 (1.59%) patients receiving ABA therapy (follow-up: 12 months) (35). No publications reported serious AEs, abdominal pain, diarrhoea, dizziness, headache, leukopenia, nausea, pruritus, rash, or upper respiratory tract infection.

Study quality assessment

Study quality assessments were conducted for all included studies using the NOS. Overall, studies were of low or moderate quality (Suppl. Table S16).

Discussion

The present targeted and systematic reviews summarise the existing literature on epidemiology and treatment landscape of ILD in the RA population. Given that many commonly prescribed RA drugs have been linked to worsening disease in patients with existing RA-ILD and *ex novo* occurrence in those without pre-existing RA-ILD (1), it is imperative to identify risk factors contributing to RA-ILD susceptibility, prognostic factors affecting the course of disease, and optimal treatment regimens for RA-ILD.

RA-ILD incidence estimates varied across included publications, in part due to differences in case definition. While Bongartz *et al*. (9) defined cases as any patient with 'probable or definite ILD,' Shidara *et al*. (10) included only participants with a definitive diagnosis of interstitial pneumonia subtype ILD. Prevalence estimates similarly differed with ILD case definition, as well as study sample size. Due to insufficient information on patient baseline characteristics, it was not possible to compare populations. However, in line with our findings, prior reviews have noted substantial heterogeneity in prevalence reporting, with values between 1.8% and 60% (1, 2, 51). In an evaluation of real-world data from RA patients (n=8,963) published after our literature searches, Zhuo *et al*. sought to resolve existing incongruities in ILD prevalence estimates by employing well-defined participant inclusion criteria (ICD diagnosis codes or provider indication in the JointMan record). By their estimate, ILD was present among 3.8% of patients with RA (52). Disparities in RA-ILD prevalence have also been attributed to differences in diagnostic procedures. Methods range from clinical data and spirometry-based pulmonary function tests, HRCT and x-ray imaging results, bronchoalveolar lavage, and tissue biopsy, each associated with detection thresholds which could potentially skew the number of ILD cases detected (53). Diagnosis based on lung pathology and imaging results are further subject to inter-rater variability, providing some explanation of the heterogeneity observed across studies using similar diagnostic methods. Artificial intelligence shows great promise in streamlining diagnostic processes and reducing variability within methods: deep learning algorithms are currently in development to aid diagnosis of ILD subtypes on HRCT (54), while machine

learning approaches have been used to identify RA patient subgroups and predict treatment response based on genetic and serum biomarkers (55). While wide-spread adoption of computer-aided diagnosis at the point of patient care presents with certain challenges (54), the advancement of machine learning approaches may help to achieve greater standardisation across ILD case definitions and diagnostic methods necessary to characterise RA-ILD epidemiology.

Although 24 studies met the PICO inclusion criteria for the targeted review, only eight studies employed multivariable analyses for assessment of ILD risk factors, and nine studies used multivariable analyses to identify prognostic factors. No two publications identified the same set of factors. Advanced age was the most frequently reported predictor of ILD onset and prognosis, though a number of studies adjusting for age failed to confirm this. The contribution of sex in RA-ILD is unclear: although women are at higher risk of developing RA, some studies have described RA-ILD as a male skewed pathology, necessitating further research. The inconsistencies observed across risk factors were likely due to study design, particularly the extent of heterogeneity within patient populations and analytical methods. For example, two publications (25, 28) had disproportionately small sample sizes, resulting in wide confidence intervals. Greater consistency may be achieved with larger samples sizes and increased homogeneity among participants. A previous systematic review from Assayag *et al*. (56) captured four publications included in the present targeted review (24, 26, 27, 30). The review identified male sex, DAS28, diminished pulmonary function, presence of UIP pattern, and extent of fibrosis as the only statistically significant factors predicting mortality in multivariable analyses. As factors such as lung pathology and HRCT characteristics are identified by clinicians, the impact of inter-rater variability may impact the strength of these characteristics as predictive factors for mortality. Our review provides an update to that of Assayag *et al*., finding additional evidence of DLCO and FEV as risk factors for mortality in RA-ILD. As both are measured through instruments rather than clinician evaluation, they offer the advantage of being unbiased, objective indicators of disease outcome.

Additional RA-ILD risk and prognostic factors have been proposed since our search. In an investigation of serum biomarkers, Avouac *et al*. observed elevated concentrations of circulating Krebs von den Lungen-6 glycoprotein (KL-6) in RA-ILD patients vs. unaffected RA patients (57), finding the diagnostic capability of KL-6 to be superior compared to other markers assessed (57). In an examination of RA-ILD patients' clinical and radiological characteristics, Fui *et al*. observed an increased mortality rate in participants with radiological UIP pattern compared to those with other radiological patterns (58), garnering additional support for UIP pattern as a predictor of mortality (26). Recent observations of interstitial pneumonia as a common feature of coronavirus disease 2019 (COVID-19)-related deaths have led to renewed interest in and comparison with interstitial pneumonia associated with RA. While the underlying pathophysiology of both conditions are largely unknown, common pathogenic mechanisms have been speculated, including activation of toll-like receptors, involved in initiation of innate immune responses (59). Intriguingly, variations in expression of toll-like receptors and other alterations in innate immunity have been observed across ILD phenotypes (*i.e*. UIP and nonspecific interstitial pneumonia) (60, 61) and have been proposed as an additional source of heterogeneity across patients. Smoking status and RA inflammatory activity (as measured by DAS28) were recently found to be associated with ILD progression in RA patients (62), both of which were identified in our review as prognostic factors of mortality (24, 29). Importantly, smoking and other respiratory exposures have been separately suggested as risk factors for development of RA, implicating the lung as an autoimmunity initiation site (55) and further complicating identification of ILD-specific factors. A number of recent studies have explored the effects of RA treatment on ILD risk and prognosis. Non-anti-TNF DMARDs were found to reduce the risk of lung disease progression in 90% of patients with RA-ILD (62). In a recent case-control study, not only was antecedent MTX exposure associated with reduced odds of ILD in RA patients, but use of the drug was further linked to delayed disease onset (63). This is in contrast to results from Mochizuki *et al*., captured in the present review, which identified MTX use as a predictor of ILD deterioration in a cohort of RA patients both with and without pre-existing ILD (28). These discrepancies are likely due to differences in study design and statistical methodology, underscoring a substantial lack of high-quality evidence to guide MTX treatment regimens. While many recently identified clinical and biochemical markers are in line with the targeted review, there is a persistent lack of consensus among studies as to which therapies are predictive of or protective against RA-ILD onset and progression.

Across publications included in the systematic review, ABA monotherapy was the most frequently assessed treatment strategy, investigated in five studies, followed by monotherapy with RTX and TOC. DMARDs, nonbiologic DMARDs, glucocorticoids, and immunosuppressive drugs were assessed either as monotherapies or combination therapies. The SLR found that many patients with RA-ILD responded to a wide variety of treatments for lung-related outcomes such as DAS28, dyspnea, and DLCO. In a previous SLR, Roubille *et al*. reviewed case reports and case series to assess cDMARDs and biologic agents in inducing or exacerbating ILD in RA patients (5). While MTX, leflunomide, anti-TNFs, RTX, and TOC were linked to onset or worsening of pneumonitis and ILD, improvement in RA-ILD was highlighted following treatment with anti-TNFs, and no cases of ILD onset or worsening were reported following treatment with anakinra or HCQ (5). Importantly, the case reports/series captured by Roubille *et al*. included a mixture of patients with and without pre-existing RA-ILD. The present SLR excluded case reports/series and included patients with RA-

ILD only, identifying only two studies reporting on exacerbation of ILD. Despite these differences in protocol, both Roubille *et al*. and the results reported herein suggest that a definitive causal relationship between RA therapies and exacerbation of ILD cannot be made with the available evidence.

There is a shortage of efficacy and safety data for current RA-ILD therapeutic options, due in large part to a lack of RCTs and inconsistent use of diagnostic methods across studies. Three previous reviews have documented similar gaps in reporting from clinical trials (1, 2, 51). The present assessment of treatment landscape confirms that while observational evidence on this topic continues to accumulate, high-quality data from RCTs remains persistently scarce. A multicenter RCT investigating the tyrosine kinase inhibitor nintedanib in participants with ILD has only recently concluded (64), with results for a subpopulation of patients with autoimmune disease-related ILD published after our literature search (65). A search on clinicaltrials.gov revealed two RCTS currently in the recruiting phase (66, 67), while a search of the European Union Clinical Trials Register revealed no additional trials. While there have been recent developments in the treatment of RA, particularly with respect to Janus Kinase (JAK) inhibitors (68), efficacy and safety of this relatively new class of drugs in RA-ILD has not yet been established, though an RCT comparing the JAK inhibitor tofacitinib to MTX in RA-ILD is expected to begin patient recruitment shortly (69). Nearly all publications included in the systematic review were observational studies, and publications reporting outcomes for multiple groups often did not provide statistical significance, reducing our ability to compare outcomes across available treatment options. Finally, the overall quality of the included studies was low, limiting the generalisability of our findings and underscoring the critical need for well-designed RCTs to assess treatment strategies in RA-ILD.

This review describes the current state of published evidence on the epidemiology and treatment landscape of RA-ILD. A wide range of estimates were reported for incidence/prevalence, with no consensus between publications on risk and prognostic factors. Qualitative assessment of the evidence showed that most available therapeutic regimens have moderate to good effectiveness in terms of disease activity, dyspnea, and lung function impairments in patients with RA-ILD. However, the current treatment landscape is largely founded on evidence from observational studies. Robust clinical data from RCTs are warranted to fully assess optimal treatment efficacy and safety of RA-ILD therapies.

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