Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis

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Substantial variability exists in interstitial lung disease prevalence, risk factors and computed tomography patterns across connective tissue disease subtypes. Further research is required to better understand the complex pathobiology of this disease. https://bit.ly/3QJXn4d

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Abstract

Introduction Interstitial lung disease (ILD) is a frequent manifestation of connective tissue disease (CTD) with substantial variability in prevalence and outcomes reported across CTD subtypes. This systematic review summarises the prevalence, risk factors and ILD patterns on chest computed tomography of CTD-ILD.

Methods A comprehensive search was performed in Medline and Embase to identify eligible studies. Meta-analyses were completed using a random effects model to determine the pooled prevalence of CTD-ILD and ILD patterns.

Results 11 582 unique citations were identified with 237 articles included. Pooled prevalence of ILD was 11% in rheumatoid arthritis (95% CI 7–15%), 47% in systemic sclerosis (44–50%), 41% in idiopathic inflammatory myositis (33–50%), 17% in primary Sjögren's syndrome (12–21%), 56% in mixed connective tissue disease (39–72%) and 6% in systemic lupus erythematosus (3–10%). Usual interstitial pneumonia was the most prevalent ILD pattern in rheumatoid arthritis (pooled prevalence of 46%), while nonspecific interstitial pneumonia was the most common ILD pattern in all other CTD subtypes (pooled prevalence range 27–76%). Across all CTDs with available data, positive serology and higher inflammatory markers were risk factors for development of ILD.

Discussion We identified substantial variability in ILD across CTD subtypes suggesting that CTD-ILD is too heterogenous to be considered a single entity.

Introduction

Interstitial lung disease (ILD) is a frequent complication of connective tissue disease (CTD), with a significant impact on morbidity and mortality [1]. Although ILD is reported in all CTDs, there is substantial variability across CTDs in both the prevalence and pattern of ILD subtypes [2, 3]. For example, there appears to be a lower prevalence of ILD in systemic lupus erythematosus (SLE) (range 4–13%) and a higher prevalence in systemic sclerosis (SSc) (up to 91% in some studies), with other CTDs having prevalence estimates between these extremes, including rheumatoid arthritis (RA), primary Sjögren's syndrome (pSS), idiopathic inflammatory myositis (IIM), mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD) [2, 3].

Previous studies have not comprehensively studied how ILD differs across all CTD subtypes, with particularly limited data on the variability of ILD patterns and the risk factors for both the presence of ILD

and for specific ILD patterns on chest computed tomography (CT). We therefore conducted a systematic review to better characterise ILD prevalence, risk factors for ILD, frequency of specific ILD patterns on CT and risk factors for these ILD patterns in patients with a wide variety of CTDs. Through this comprehensive summary of existing data, we aim to provide an evidence-informed understanding of the prevalence and risk factors for CTD-ILD that will help guide screening practices, disease monitoring and prognostication of patients with CTD and CTD-ILD. We further anticipate that this knowledge will serve as the foundation for future research in risk stratification and treatment trials across in this heterogenous disease classification.

Methods

Data sources and search strategy

We performed a comprehensive search of the literature using the Embase and Medline databases between 1 January 2000 and 29 June 2022 that was designed to retrieve all citations related to CTD-ILD, including its prevalence, ILD patterns on chest CT and ILD risk factors (supplemental table S1). The strategy was reviewed by a medical librarian prior to execution and the study protocol was registered with Research Registry (reviewregistry1029).

Study selection

Studies were eligible if they were original research, published in English, consecutively enrolled outpatients with CTD (as defined by study authors) and included ⩾10 patients with ILD as defined by presence on chest CT. Authors were contacted for clarification if the means of diagnosis was not specified and studies that defined ILD by only chest X-ray were excluded. We focused our review on RA, SSc, IIM, pSS, MCTD, SLE and UCTD. Interstitial pneumonia with autoimmune features was not included in this review. Studies focusing on overlap CTD were excluded, except for secondary Sjögren's syndrome that was included in analyses according to the primary CTD diagnosis. Conference abstracts were included if sufficient information was provided to satisfy eligibility assessment. Sequential review of titles, abstracts and full texts was completed by two independent reviewers and disagreements were resolved by a third reviewer.

Data extraction and risk of bias assessment

Data were extracted using a standardised data collection tool designed in Excel that included information on study design, CTD population characteristics, ILD prevalence and patterns, and risk factors for both ILD as a whole and specific ILD pattern. ILD patterns of interest included usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organising pneumonia (OP), lymphoid interstitial pneumonia (LIP) and pleuroparenchymal fibroelastosis [4]. We focused on fibrotic ILD and therefore excluded other diffuse lung diseases (*e.g.* bronchiolitis obliterans and follicular bronchiolitis). Definite and probable or possible UIP were included as UIP where this distinction was made. The Newcastle Ottawa Scale (NOS) was applied for risk of bias assessment [5], which included evaluation of patient selection, comparability of groups and ascertainment of exposure or outcome. Studies were assigned between zero and nine points for each component of the NOS, with scores 0–3, 4–6 and 7–9 considered low, moderate and high quality, respectively. All abstracted data were independently verified by a second reviewer.

Data synthesis and statistical analysis

Data are reported as mean±standard deviation, median (interquartile range) or number (percent), unless otherwise specified. Pooled prevalence is reported as prevalence (95% confidence interval). A random-effects meta-analysis of pooled prevalence of CTD-ILD and ILD pattern was completed using Freeman–Tukey transformation given the heterogeneity of data [6], which was reported using the I^2 statistic. A meta-regression was completed to explore heterogeneity of prevalence data if ⩾10 eligible studies were available for a given population of interest (*e.g.* for a given CTD subtype). Data analysis was performed using Stata/BE 17.0 (StataCorp LLC 2021. College Station, TX).

Results

Search results and study characteristics

The search identified 11 582 unique citations, with 3162 reviewed in full text (figure 1). The final analysis consisted of 237 articles (86 RA, 85 SSc, 44 IIM, 25 pSS, nine MCTD, seven SLE, three UCTD), including 51 abstracts (supplemental table S2). Population characteristics of included studies are provided in supplemental table S3. All studies were observational in their design, with 1.7% scored as low quality, 24.5% as moderate quality and 73.8% as high quality by the NOS (supplemental table S4).

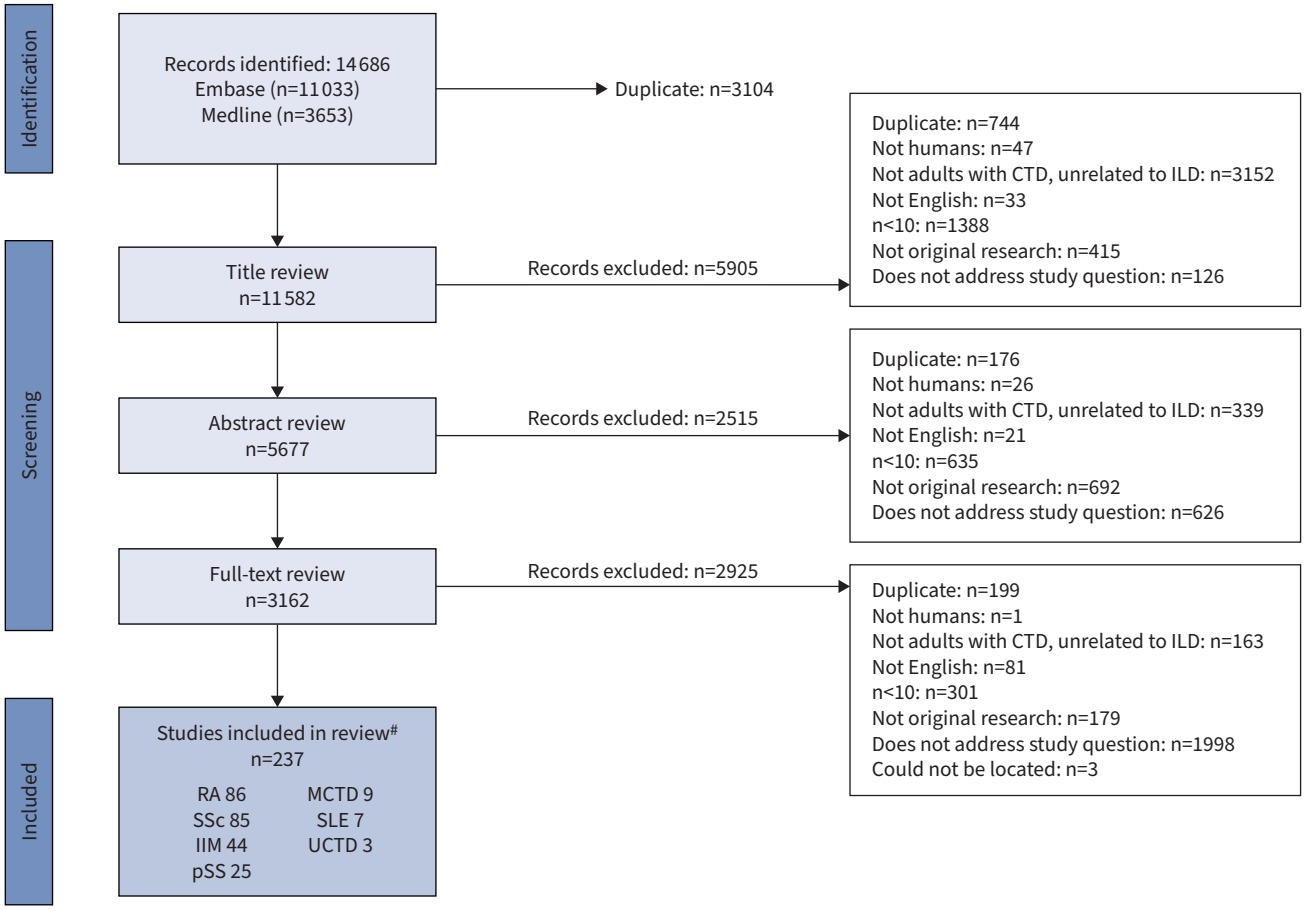

FIGURE 1 Identification of studies flow diagram. #: Some studies addressed more than one connective tissue disease (CTD). IIM: idiopathic inflammatory myositis; ILD: interstitial lung disease; MCTD: mixed connective tissue disease; pSS: primary Sjögren's syndrome; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; UCTD: undifferentiated connective tissue disease.

Prevalence of ILD by CTD subtype

The prevalence of ILD by CTD subtype was addressed in 139 studies that included a total of 65 008 patients. The pooled prevalence of ILD was 11% in RA (95%CI 7–15%), 47% in SSc (44–50%), 41% in IIM (33–50%), 17% in pSS (12–21%), 56% in MCTD (39–72%) and 6% in SLE (3–10%) (figure 2). No studies addressed the prevalence of ILD in UCTD. There was significant heterogeneity in ILD prevalence across studies within all CTD subtypes as demonstrated by the I^2 statistic (supplemental figure S1a–f).

Risk factors for ILD by CTD subtype

Risk factors for CTD-ILD were addressed in 108 studies that included 43 978 patients (table 1), with wide variability in the number and quality of studies for each CTD. In RA, risk factors associated with the presence of ILD in ⩾5 studies included male sex, older age, longer RA duration, older age of RA onset, smoking history, rheumatoid factor positivity and titre, anti-cyclic citrullinated peptide positivity and titre, higher c-reactive protein, and higher erythrocyte sedimentation rate (ESR). In SSc, diffuse SSc subtype, positive anti-Scl70 antibody and negative anti-centromere antibody were consistent risk factors for ILD (identified in ⩾5 studies).

Fewer studies addressed risk factors for ILD in IIM, pSS and MCTD. Clinical and serologic risk factors for IIM-ILD identified in at least one study included black race, mechanic's hands, arthritis, lateral hip erythema, anti-synthetase antibodies, anti-melanoma differentiation-associated gene 5 antibodies, antinuclear antibody (ANA), anti-Sjögren's syndrome type B (anti-SSB), anti-Ro52 and higher inflammatory markers (ESR, c-reactive protein (CRP)). Polymyositis, anti-NXP2, anti-Tiff and anti-Mi2 were associated with lower ILD prevalence in IIM. Risk factors for pSS-ILD included older age, older age

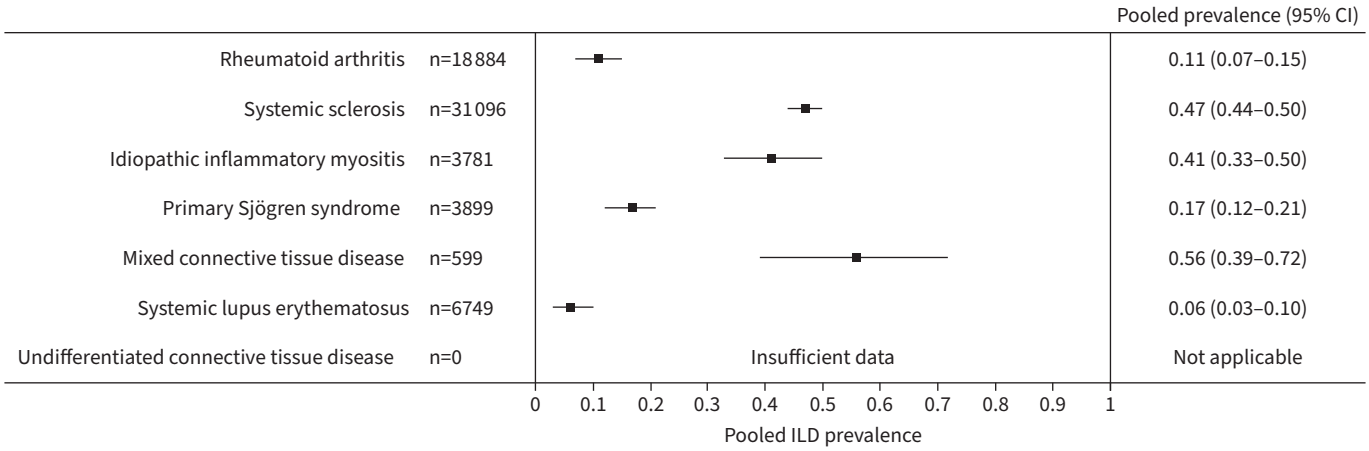

FIGURE 2 Pooled prevalence of interstitial lung disease (ILD) in patients with connective tissue disease.

of CTD onset, male sex, longer CTD duration, seropositivity (ANA, anti-SSA, anti-SSB, anti-Ro52) and higher inflammatory markers (ESR, CRP). Clinical features associated with pSS-ILD included Raynaud's phenomenon, oral ulcers and salivary gland biopsy focus score ⩾4.

Meta-regression was completed where sufficient data were available (figure 3). There was higher ILD prevalence in patients with SSc who were younger, had diffuse cutaneous involvement and were anti-centromere negative. ILD prevalence was lower in patients with IIM who had polymyositis.

Prevalence of ILD patterns by CTD subtype

ILD pattern on chest CT was addressed in 122 studies that included 8266 patients (figure 4, supplemental table S5 and supplemental figure S2). UIP was the most common ILD pattern in RA (pooled prevalence of 46%), while NSIP was the most common ILD pattern in all other CTD subtypes (range of pooled prevalence from 27 to 76%). LIP was more common in pSS (pooled prevalence 7%, 95% CI 2–15%) than in other CTDs (no summary statistic available due to low prevalence). OP was still infrequent but was most common in IIM (pooled prevalence 16%, 95% CI 9–25%).

Risk factors for ILD patterns by CTD subtype

Risk factors for specific ILD patterns on chest CT were addressed in 11 studies across all CTD subtypes, including a total of 1827 patients. Eight studies addressed risk factors for specific ILD patterns in RA, with few predictors of ILD pattern identified. One study reported that a UIP pattern was more common with a longer duration of RA (p=0.03) [7], while another reported that patients with a UIP pattern were older (p<0.05) and had a higher pack-year history of smoking (p<0.001) compared to those with an NSIP pattern [8]. In IIM, an NSIP pattern was more frequent in patients with positive anti-synthetase antibodies compared to those that were anti-synthetase antibody negative (p=0.03) [9]. In pSS, UIP was associated with male sex (OR 8.4, 95% CI 1.7–40.5, p=0.008) and older age at disease onset (OR 1.1 95% CI 1.1–1.2, p=0.04) [10]. In UCTD, age <60 years predicted an ILD pattern inconsistent with UIP (OR 11.53, 95% CI 2.7–47.69, p<0.01) [11].

Discussion

This comprehensive systematic review provides precise summary data on the overall prevalence of ILD, risk factors for ILD, frequency of specific ILD patterns on chest CT and risk factors for these patterns. Consistent with previous reviews, we confirm that ILD is a common extra-articular manifestation in CTD, although with significant variability in ILD prevalence and pattern across CTD subtypes. We further summarise the relatively sparse data available on risk factors for both ILD as a whole and for specific ILD patterns, identifying the need for further research to better understand and learn from the differences that exist across CTD subtypes. Together, these data may inform screening practices and clinical management of patients with CTD and will further provide a comprehensive framework for future research in this area.

Our meta-analysis identified three CTD subgroups that have relatively distinct ILD prevalence. ILD prevalence was highest in SSc, IIM and MCTD (pooled prevalence ranging from 41 to 56%), moderate in RA (pooled prevalence 11%) and pSS (pooled prevalence 17%), and lowest in SLE (pooled prevalence 6%).

TABLE 1 Risk factors for development of interstitial lung disease (ILD)

	Demographic	Clinical	Serologic
RA	*Older age*[#] *Older age of RA onset*[#] *Male sex*[#] Female sex[#] *Longer RA duration* Shorter RA duration[#]	Morning stiffness Erosive arthritis DAS28 score[#] BMI >30 kg·m^{-2}[#] *Smoking history*[#]	*RF positive*[#] *RF titre*[#] *Anti-CCP positive*[#] *Anti-CCP titre*[#] *ESR*[#] *CRP* LDH[#]
SSc	Older age Male sex Female sex Black race[#] Longer SSc duration[#] Shorter SSc duration	*Diffuse cutaneous subtype*[#] Higher MRSS Digital ulcers[#] History of renal crisis GI system involvement[#] Myopathy Ever smoker (lower ILD)	*Anti-Scl70*[#] *Anti-centromere absent*[#] Anti-SSA positive ESR[#] CRP Hb <13.0 g·dL^{-1}
Idiopathic inflammatory myositis	Black race	Polymyositis (lower ILD) Anti-synthetase syndrome Clinically amyopathic Mechanic's hands[#] Absence of malignancy Arthralgia/arthritis Lateral hip erythema[#]	Anti-synthetase antibody Anti-Jo1 Anti-PL7/12 Anti-MDA5[#] ANA Anti-SSA Anti-Ro52 Anti-NXP2, Tiff, Mi2 (lower ILD) ESR[#] CRP Lower Hb
Primary Sjögren syndrome	Older age[#] Older age of onset Male sex[#] Longer disease duration	Raynaud's phenomenon Oral ulcer Salivary gland biopsy focus score ⩾4[#]	ANA Anti-SSA Anti-SSB Anti-Ro52 ANCA positive ESR CRP
Mixed connective tissue disease		Raynaud's phenomenon[#] Dysphagia[#] Never arthritis	Anti-U1 RNP >200

All risk factors are reported as the state associated with an increased risk of ILD (*e.g.* "Older age" indicates higher ILD prevalence with older age). Some studies reported opposite effects (*e.g.* male and female sex were each identified as a risk factor for ILD in different studies of rheumatoid arthritis (RA)). Insufficient data were available for systemic lupus erythematosus and undifferentiated connective tissue disease. Italic: ⩾5 studies. [#]: adjusted analysis. ANA: antinuclear antibody; ANCA: antineutrophil cytoplasmic antibody; BMI: body mass index; CCP: cyclic citrullinated peptide; CRP: c-reactive protein; DAS: disease activity score; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; Hb: haemoglobin; LDH: lactate dehydrogenase; MDA5: melanoma differentiation-associated gene 5; MRSS: modified Rodnan skin score; RF: rheumatoid factor; RNP: ribonucleoprotein; SSA/B: Sjögren's syndrome type A/B; SSc: systemic sclerosis.

This wide variability is based on data from thousands of patients and this therefore likely represents true differences in prevalence; however, sampling bias may still affect prevalence estimates due to different practices by country or centre, by date of publication, or by suspicion of ILD by CTD subtype given the lack of standardised guidelines. Additional studies are needed to better define the potential health systems, genetic and environmental factors that contribute to this varying prevalence, which may have implications for screening approaches as well as further impact on clinical management and drug development.

Seropositivity and higher inflammatory markers were relatively consistent risk factors for development of ILD. An exception to this was SLE, in which ILD is uncommon despite frequent abnormal autoimmune serologies; however, there were no identified studies specifically addressing risk factors for development of ILD in SLE [12]. RA and pSS has similar demographic risk factors for development of ILD, including older age, longer duration of CTD, later onset of CTD and male sex. These risk factors (older males) are similar to those of idiopathic pulmonary fibrosis (IPF), potentially relating to the higher frequency of UIP in these CTDs compared to other ILD patterns. Apart from these findings, there were limited and typically inconsistent demographic and clinical risk factors for development of ILD, as well as few studies addressing risk factors for development of specific ILD patterns. Large, well-designed studies are required

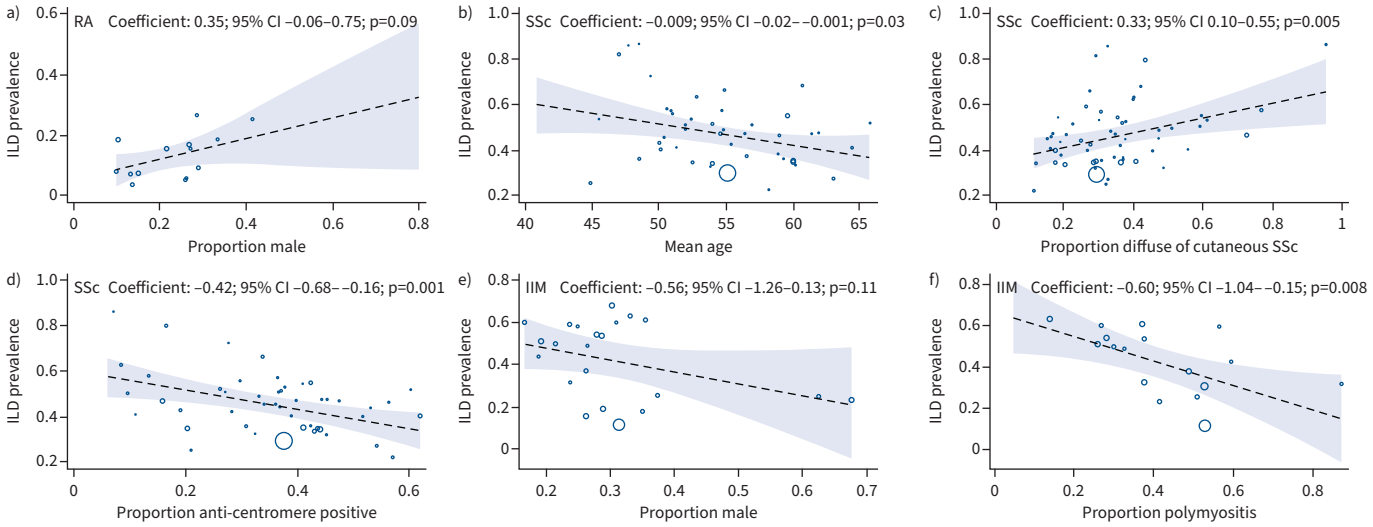

FIGURE 3 Metaregression of potential factors influencing heterogeneity of reported prevalence of interstitial lung disease (ILD) within each connective tissue disease. a) Rheumatoid arthritis (RA), b–d) systemic sclerosis (SSc), e–f) idiopathic inflammatory myositis (IIM). There were insufficient data to support meta-regression for primary Sjögren's syndrome, systemic lupus erythematosus, mixed connective tissue disease and undifferentiated connective tissue disease.

to clarify risk factors for development of CTD-ILD as well as specific ILD patterns, with the goal of using better morphological characterisation to provide greater insights into underlying disease biology.

The prevalence of specific ILD patterns varied substantially by CTD subtype, with overall trends that in part reflected the risk factors for development of ILD within each CTD. Specifically, RA had the highest prevalence of UIP (pooled prevalence 46%), coinciding with older age, male sex, and smoking being risk factors for ILD in patients with RA, similar to major risk factors for IPF (*i.e.* idiopathic UIP). All other CTDs were more frequently associated with a pattern of NSIP, with OP having the highest prevalence in IIM, corroborating the classic but relatively uncommon initial presentation of IIM-ILD. Importantly, the presence of OP in IIM can be associated with a rapidly progressive form of ILD that is often refractory to immunosuppressive therapy, carrying a high mortality rate of up to 51% in hospitalised patients [13, 14]. Taken together, the substantial variability in patterns across CTDs and the different risk factors for these

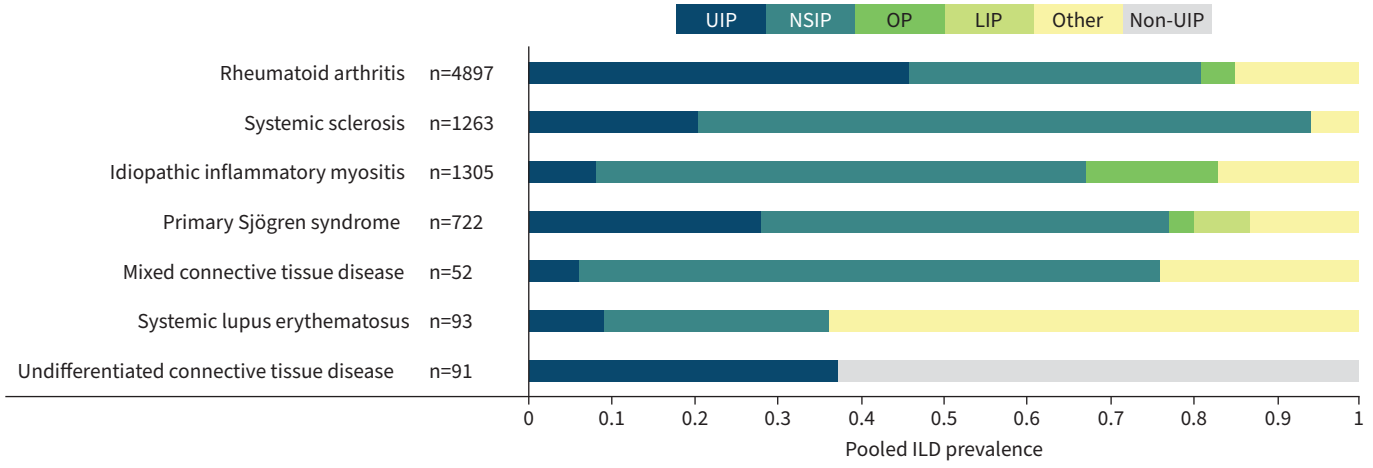

FIGURE 4 Pooled prevalence of interstitial lung disease patterns by connective tissue disease. Insufficient data were available to support subdivision of non-usual interstitial pneumonia (UIP) patterns in undifferentiated connective tissue disease. LIP: lymphocytic interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; other: other and undifferentiated; OP: organising pneumonia.

patterns suggest the potential of clinically important biological differences among these populations that should be further explored.

Limitations

The main limitation of this systematic review is the significant variability in prevalence of both ILD and CT patterns seen across studies, and the inability to fully explore the reasons for these differences. The widest range of prevalence was seen in SSc-ILD (22–87%) and IIM-ILD (11–68%). While some variability may be explained by biologic factors such as genetics, race or difference in representation of disease subsets (limited *versus* diffuse, polymyositis *versus* anti-synthetase syndrome), there are certainly other sources of bias that could not be quantified. This could include tertiary referral centre cohorts representing a more severe or progressive disease subset, variation in ILD definitions or differences in study design. Significant heterogeneity is also seen across CT pattern data, likely with similar factors at play. In addition to these factors, the definition of ILD patterns (*i.e.* UIP) have evolved with guideline updates, which may account for some variability. Many of these CTD-ILD cohorts were from respiratory tertiary referral centres, which would place further emphasis on the sampling bias of severe or progressive forms of ILD which may skew data towards certain ILD patterns (UIP) compared to others (OP).

A second limitation is that many population-based studies were excluded based particularly on identification of ILD using International Classification of Disease (ICD) ninth revision codes (*i.e.* without confirmation by chest CT), reflecting our desire to ensure our focus on well-characterised populations. Third, many studies were of low quality; however, the large sample size helps to minimise the impact of potential outliers on our pooled estimates. Despite these limitations, the large number of studies and patients included in this comprehensive systematic review still provides the most robust data available for this important topic, setting the stage for future studies that are needed to better characterise the biological basis for the variable manifestations of these diseases.

Future directions

In summary, this comprehensive and rigorous systematic review summarised data from over 65 000 patients within 237 studies to provide the most robust data on the prevalence of ILD within common CTD subtypes and the frequency of specific ILD patterns in these populations. Beyond providing summary data that can be helpful to patients and clinicians, we show the significant variability that exists across studies and populations that can be further studied to advance our biological understanding of these complex diseases. Importantly, our findings suggest that CTD-ILD is too heterogenous to be combined as a single entity for clinical or research purposes and that additional classification approaches are necessary, for example, based on disease behaviour, ILD pattern or ideally other more objective and reproducible biomarkers. The current systematic review sets the stage for this next generation of studies with highly characterised CTD-ILD populations that are needed to better understand the complex biology of these heterogeneous diseases.

Questions for future research

- Identification of causes for variability in ILD prevalence and ILD pattern across populations of patients with CTD.
- Identification of objective or reproducible biomarkers that predict risk of developing ILD, the pattern of ILD and the clinical course of ILD in patients with CTD.
- Development of clinical practice guidelines for ILD screening and monitoring in patients with CTD.

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