Prevalence and risk factors of systemic sclerosis-associated interstitial lung disease in East Asia: A systematic review and meta-analysis

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Abstract
Objective: Interstitial lung disease (ILD) is a common and potentially life-threatening complication for individuals with systemic sclerosis (SSc). The purpose of this study was to complete a systematic review and meta-analysis on prevalence and risk factors of SSc-ILD in East Asia.

Methods: Medline, EMBASE, and Cochrane Library were searched up to January 22, 2021. The Reporting of Observational Studies in Epidemiology (STROBE) statement was applied to access the methodological quality of the eligible studies. Study characteristics and magnitude of effect sizes were extracted. Then, we calculated the pooled prevalence, weighted mean differences (WMDs), pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs), and performed subgroup analysis, sensitivity analysis, and publication bias with Egger’s test.

Results: Twenty-seven of 1584 articles were eligible and a total of 5250 patients with SSc were selected in the meta-analysis. The pooled prevalence of SSc-ILD in East Asia was 56% (95% CI 49%-63%). The SSc-ILD prevalence was higher in China (72%) than in Japan (46%) and Korea (51%). Longer disease duration (WMD = 1.97, 95% CI 0.55-3.38), diffuse SSc (OR = 2.84, 95% CI 1.91-4.21), positive anti-topoisomerase I antibody (ATA) (OR = 4.92, 95% CI 2.74-8.84), positive anti-centromere body antibody (ACA) (OR = 0.14, 95% CI 0.08-0.25), positive anti-U3 ribonucleoprotein (RNP) antibody (OR = 0.17, 95% CI 0.04-0.66), and higher erythrocyte sedimentation rate (ESR) (WMD = 6.62, 95% CI 1.19-12.05) were associated with SSc-ILD in East Asia.

Conclusion: Through this systematic review and meta-analysis, we found that ILD occurs in up to approximately 56% of patients with SSc in East Asia. Longer disease duration, diffuse SSc, positive ATA, negative ACA, negative anti-U3 RNP antibody, and higher ESR were risk factors for SSc-ILD.

KEYWORDS
interstitial lung disease, meta-analysis, prevalence, risk factor, systemic sclerosis
1 | INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue, characterized by microvascular damage, immune dysfunction, and fibrosis of multiple organs.1 It is a rare disease, with an estimated global prevalence of 3-24 per 100,000.2 SSc is generally classified into two categories based on the extent of skin sclerosis: limited cutaneous SSc (lSSc) and diffuse cutaneous SSc (dSSc).3 The causes of death in individuals with SSc have dramatically changed over the past 30 years.4,5 Interstitial lung disease (ILD) is currently the leading causes of death in patients with SSc, but reported prevalence of ILD in patients with SSc ranges from 25% to 90%, depending on the subtype of SSc and the criteria used to define ILD in different countries.6 SSc-associated interstitial lung disease (SSc-ILD) has a heterogeneous clinical presentation and disease course, and providing a prognosis for SSc-ILD is challenging. High-resolution computed tomography (HRCT) is a high-sensitivity diagnostic method useful for early detection of ILD complications in patients with SSc, commonly finding nonspecific interstitial pneumonitis and usual interstitial pneumonitis. Furthermore, the risk factors in patients with SSc-ILD remain controversial. To address these issues, this systematic review and meta-analysis was performed to identify the prevalence and potential risk factors for SSc-ILD in East Asia.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines throughout this review.7 We searched Medline, EMBASE, and Cochrane databases, the Cochrane Library (the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials [CENTRAL]) through to January 22, 2021. Databases were searched and data were abstracted by two authors working independently. We used medical subject headings (MeSH) terms, EMBASE subject headings (EMTREE), and text words related to study population to finish the search. The search terms used in Medline were: (((systemic sclerosis[MeSH Terms]) AND (systemic sclerosis[Title/Abstract])) OR ((scleroderma[MeSH Terms]) AND (scleroderma[Title/Abstract]))) AND (((interstitial lung disease[MeSH Terms]) OR (diffuse parenchymal lung disease)) OR (interstitial pneumonia)) OR (interstitial pneumonitis))) AND ((incidence[Title/Abstract] OR prevalence[Title/Abstract] OR epidemiology[Title/Abstract]) OR (risk factor[Title/Abstract] OR predictor[Title/Abstract] OR relate[Title/Abstract] OR associate[Title/Abstract] OR correlation[Title/Abstract])). The search terms used in EMBASE were (((systemic sclerosis/exp OR ‘systemic sclerosis’) AND ‘systemic sclerosis’:ab,ti) AND ((‘interstitial lung disease’/exp OR ‘interstitial lung disease’) OR (‘diffuse parenchymal lung disease’/exp OR ‘diffuse parenchymal lung disease’) OR (‘interstitial pneumonia’/exp OR ‘interstitial pneumonia’)) AND (incidence OR prevalence OR epidemiology OR risk factor’ OR predictor OR relate OR associate OR correlation).

2.2 | Eligibility criteria

Two authors independently evaluated each study for eligibility, sequentially reviewing the title, abstract, and full text of each publication. The inclusion criteria were: (a) studies on SSc patients with ILD—variable criteria were used for the diagnosis of ILD, including findings on CT and/or HRCT; HRCT and pulmonary function tests; and a combination of clinical presentation, pulmonary function tests, and HRCT findings; (b) studies reporting or providing data for calculating the SSc-ILD prevalence, and/or investigating risk factors for SSc-ILD; (c) observational studies; (d) the sample size of study more than 30; and (e) the area of study belongs to East Asia. The exclusion criteria were: (a) case reports, editorials, letters, reviews articles, and conference proceedings; (b) irrelevant to study topic; and (c) duplicated publications. If SSc patients were overlapping between two studies, the study with the largest samples size was prioritized in the analysis. Any uncertainties or disagreements between two authors were resolved by discussions and consensus.

2.3 | Data extraction and study quality assessment

Two authors independently extracted data from included articles based on a predefined data extraction form. Extracted data included first author’s name, year of publication, study location, study design, number of SSc patients, number of ILD patients, demographic features of participants, SSc-ILD prevalence, classification criteria of SSc, the diagnostic method of ILD, risk factors for SSc-ILD. The methodological quality of study was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, with a checklist of 22 terms.8 Studies were of high quality if scores were 17 or more. Two investigators assessed the quality of the studies through consultations to reach consensus.

2.4 | Statistical analysis

All statistical analyses were performed using STATA software (version 13; StataCorp, College Station, TX, USA). The prevalence of SSc-ILD was log-transformed according to the Shapiro-Wilk test. Risk factors of ILD in SSc patients in more than one of the selected studies were quantified by weighted mean differences (WMDs) with 95% confidence intervals (CIs) for continuous variables and pooled odd ratios (ORs) with 95% CIs for categorical variables. The results from the fixed-effect model were presented only when there was no heterogeneity between studies; otherwise, the results from the
random-effects model were presented. Heterogeneity between studies was assessed using $I^2$ statistics and statistical significance was considered with a P value of less than 0.05. Forest plots were used to display the results from the individual studies and the pooled estimates. We also performed subgroup analysis stratified by region, study quality, publication year, and SSc criteria to investigate heterogeneity. Sensitivity analysis was conducted by sequentially omitting individual studies. The potential for publication bias was evaluated by Egger test if five or more studies were available for meta-analysis. If combining data were deemed inappropriate, the results were reported qualitatively (because of the small number of studies or substantial clinical or methodological diversity). $P$ values less than 0.05 were considered statistically significant.

3 RESULTS

3.1 Search strategy

A total of 1584 reports were identified through Medline, EMBASE, and Cochrane Central Register of Controlled Trials. After excluding 163 duplicates, 803 reports of ineligible types (consisting of 633 conference proceedings, 149 review articles or case reports, and 21 editorials or letters) and 560 irrelevant articles, the remaining 58 reports were screened as full texts. Out of these, 31 reports were excluded for no data on prevalence of SSc-ILD in 11 articles and no data on risk factors of SSc-ILD in 20 articles. Finally, 27 articles were eligible for this meta-analysis and review (Figure 1).

FIGURE 1 The Study flow diagram [Colour figure can be viewed at wileyonlinelibrary.com]
| Study       | Design         | Country | No. of SSc patients | Age, y    | Female (%) | No. with ILD | SSc Classification criteria | ILD diagnosis methods                          | STROBE checklist |
|------------|---------------|---------|---------------------|-----------|-------------|--------------|-----------------------------|-----------------------------------------------|-----------------|
| Kim 2010   | Cohort study  | Korean  | 230                 | 43.7 ± 14 | 89.1        | 134          | 1980 ACR criteria           | Chest radiography or HRCT                      | 17/22           |
| Won-Moon 2018 | Cohort study | Korean  | 751                 | 48.9 ± 13.3 | 86.7        | 396          | 1980 ACR criteria           | Chest radiography or HRCT                      | 19/22           |
| Jung 2018  | Cross-sectional study | Korean  | 108                 | 50.1 ± 13.5 | 92.2        | 43           | 1980 ACR criteria           | HRCT                                           | 16/22           |
| Ooi 2003   | Cross-sectional study | China  | 45                  | 48.5 ± 13.4 | 88.9        | 39           | 1980 ACR criteria           | HRCT                                           | 15/22           |
| Mok 2008   | Cross-sectional study | China  | 43                  | 47.7 ± 13.0 | 88.4        | 37           | 1980 ACR criteria           | HRCT                                           | 14/22           |
| Wang 2013  | Cross-sectional study | China  | 419                 | NA        | 83.1        | 327          | 1980 ACR criteria or have at least three out of five CREST features | HRCT                                           | 17/22           |
| Hu 2018    | Cohort study  | China  | 448                 | 42.8 ± 12.1 | 90.4        | 382          | 2013 ACR/EULAR criteria    | HRCT                                           | 18/22           |
| Li 2018    | Cohort study  | China  | 201                 | 41.6 ± 13.5 | 91          | 148          | 1980 ACR criteria           | Chest X-ray and/or CT                         | 19/22           |
| Liu 2019   | Cross-sectional study | China  | 320                 | 48.2 ± 12.92 | 86.6        | 202          | 2013 ACR/EULAR criteria    | HRCT                                           | 15/22           |
| Zhang 2020 | Cross-sectional study | China  | 169                 | 58 ± 14.7 | 68.6        | 92           | 2013 ACR/EULAR criteria    | Pulmonary function tests and HRCT scans       | 19/22           |
| Zheng 2020 | Cross-sectional study | China  | 31                  | 51 ± 13    | 87          | 21           | 2013 ACR/EULAR criteria    | Chest radiography or HRCT                      | 20/22           |
| Zhou 2020  | Cross-sectional study | China  | 204                 | 52.8 ± 12.9 | 77.9        | 129          | 1980 ACR criteria or 2013 ACR/EULAR criteria | HRCT and pulmonary function                   | 18/22           |
| Ji 2018    | Cross-sectional study | China  | 71                  | 52.59 ± 12.77 | 91.5        | 45           | 1980 ACR criteria or 2013 ACR/EULAR criteria | HRCT                                           | 17/22           |
| Kuwana 1994 | Cohort study  | Japan  | 275                 | 41.7      | 88.7        | 151          | 1980 ACR criteria           | Chest radiogram                               | 15/22           |
| Sato 2000  | Cross-sectional study | Japan  | 45                  | 50        | 88.9        | 12           | 1980 ACR criteria           | Chest radiogram and HRCT                      | 15/22           |
| Hamaguchi 2007 | Cohort study | Japan  | 203                 | 46 ± 15   | 85          | 89           | 1980 ACR criteria           | Chest radiogram and HRCT                      | 19/22           |
| Ashida 2007 | Cohort study  | Japan  | 350                 | 52        | 72          | 117          | 1980 ACR criteria           | Chest radiogram and HRCT                      | 15/22           |
| Hashimoto 2011 | Cohort study | Japan  | 405                 | 47 ± 0.7  | 92.8        | 204          | 1980 ACR criteria           | Chest radiographs or by computed tomography   | 19/22           |

(Continues)
| Study           | Design         | Country | No. of SSc patients | Age, y          | Female (%) | No. with ILD | SSc Classification criteria | ILD diagnosis methods | STROBE checklist |
|-----------------|----------------|---------|---------------------|-----------------|------------|-------------|-----------------------------|-----------------------|-----------------|
| Odani 2012      | Cohort study   | Japan   | 149                 | 51 ± 13.6/41 ± 12 | 85.9       | 81          | 1980 ACR criteria            | HRCT                  | 19/22           |
| Komura 2008     | Cross-sectional study | Japan  | 63                  | 55              | 85.7       | 27          | 1980 ACR criteria            | Chest radiogram and HRCT | 15/22           |
| Tomiyama 2016   | Cohort study   | Japan   | 139                 | 49.1 ± 15.1     | 81.3       | 66          | 2013 ACR/EULAR criteria     | HRCT                  | 17/22           |
| Kawashiri 2018  | Cohort study   | Japan   | 60                  | 64 (57-69)      | 93.3       | 24          | 2013 ACR/EULAR criteria     | HRCT                  | 17/22           |
| Taniguchi 2018  | Cross-sectional study | Japan  | 56                  | 59 (51.5-69)    | 92.9       | 33          | 2013 ACR/EULAR criteria     | HRCT                  | 17/22           |
| Aozasa 2020     | Cohort study   | Japan   | 43                  | 57 (45-71)      | 88.4       | 22          | 2013 ACR/EULAR criteria     | NA                    | 15/22           |
| Matsuda 2020    | Cohort study   | Japan   | 198                 | 55.4 ± 15.5     | 89.4       | 87          | 2013 ACR/EULAR criteria     | HRCT                  | 20/22           |
| Kubo 2020       | Cross-sectional study | Japan  | 79                  | 61.4 ± 18.4     | 88.6       | 37          | 1980 ACR criteria or 2013 ACR/EULAR criteria | CT                   | 16/22           |
| Sekiguchi 2020  | Cohort study   | Japan   | 145                 | 63.1 ± 1        | 83.4       | 61          | 2013 ACR/EULAR criteria     | Clinical symptoms, physical examination findings and HRCT findings | 17/22           |

Abbreviations: ACR, American College of Rheumatology; CREST, calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; EULAR, European league against rheumatism; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.
3.2 | Study characteristics

The characteristics of the included study are shown in Table 1. The 27 studies included 14 retrospective cohort studies and 13 cross-sectional studies. The studies were from three different countries (Japan, Korea, and China). The majority of studies took place in Japan (n = 14),24-37 followed by China (n = 10),14-23 and Korea (n = 3).11-13 Fourteen studies only used the 1980 American College of Rheumatology (ACR) diagnosis of SSC38 and 10 studies only used the 2013 ACR/European League Against Rheumatism (EULAR) diagnosis criteria of SSC.39 Three studies used the 1980 ACR or 2013 ACR/EULAR diagnosis criteria.22,35 In one study, SSC patients either met the 1980 ACR criteria or had at least three out of five CREST features (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) with sclerodactyly being mandatory.17 The methodological quality of each included study was assessed by the STROBE criteria. Sixteen studies were generally of good quality with a score of at least 17.

3.3 | Meta-analysis of SSc-ILD prevalence

There was a total of 5250 individuals with SSC in the included studies, with 3007 SSc-ILD patients. The prevalence of SSc-ILD ranged from 26.7% to 86%. The pooled SSc-ILD prevalence was 56% (95% CI 49-63) (Figure 2), which was stable in the sensitivity analysis (Figure 3). Heterogeneity across studies was high ($I^2 = 96.1\%$). There were significant differences in the prevalence of SSc-ILD for subgroups stratified by region, study quality, SSC classification criteria, and publication year (Table 2). The SSc-ILD prevalence was higher in China (72%) than in Japan (46%) and Korea (51%). There was a higher SSc-ILD prevalence in studies with STROBE checklist score of at least 17 than in those with a STROBE checklist score below 17. Further, SSc-ILD prevalence was higher in studies using two criteria than in those only using 1980 ACR criteria and only using 2013 ACR/EULAR criteria. Furthermore, SSc-ILD prevalence was lower in studies published before 2013 than in those published before 2013.

### Table 1: Study characteristics

| Study         | SSc | ILD | Prevalence (95% CI) | Weight |
|---------------|-----|-----|---------------------|--------|
| Kim (2010)    | 230 | 134 | 0.58 (0.52, 0.65)   | 3.84   |
| Won Moon (2018) | 751 | 396 | 0.53 (0.49, 0.56)   | 3.94   |
| Jung (2018)   | 108 | 43  | 0.40 (0.31, 0.49)   | 3.69   |
| Ooi (2003)    | 45  | 39  | 0.87 (0.77, 0.97)   | 3.65   |
| Mok (2008)    | 43  | 37  | 0.86 (0.76, 0.96)   | 3.62   |
| Wang (2013)   | 419 | 328 | 0.78 (0.74, 0.82)   | 3.93   |
| Hu (2018)     | 448 | 382 | 0.85 (0.82, 0.89)   | 3.94   |
| Li (2018)     | 201 | 148 | 0.74 (0.68, 0.80)   | 3.85   |
| Liu (2019)    | 320 | 202 | 0.63 (0.58, 0.68)   | 3.88   |
| Zhang (2020)  | 169 | 92  | 0.54 (0.47, 0.62)   | 3.78   |
| Zheng (2020)  | 31  | 21  | 0.68 (0.51, 0.84)   | 3.18   |
| Zhou (2020)   | 204 | 129 | 0.63 (0.57, 0.70)   | 3.83   |
| Ji (2018)     | 71  | 45  | 0.63 (0.52, 0.75)   | 3.57   |
| Kuwana (1994) | 275 | 151 | 0.55 (0.49, 0.61)   | 3.86   |
| Sato (2000)   | 45  | 12  | 0.27 (0.14, 0.40)   | 3.45   |
| Hamaguchi(2007)| 203 | 89  | 0.44 (0.37, 0.51)   | 3.82   |
| Ashida (2007) | 350 | 117 | 0.33 (0.28, 0.38)   | 3.89   |
| Hashimoto (2011)| 405 | 204 | 0.50 (0.46, 0.55)   | 3.90   |
| Odani (2012)  | 149 | 81  | 0.54 (0.46, 0.62)   | 3.76   |
| Komura (2008) | 63  | 27  | 0.43 (0.31, 0.55)   | 3.50   |
| Tomiyama(2016)| 139 | 66  | 0.47 (0.39, 0.56)   | 3.74   |
| Kawashiri (2018) | 60 | 24  | 0.40 (0.28, 0.52)   | 3.49   |
| Taniguchi (2018)| 56 | 33  | 0.59 (0.46, 0.72)   | 3.45   |
| Aozasa (2020) | 43  | 22  | 0.51 (0.36, 0.66)   | 3.30   |
| Matsuda (2020) | 198 | 87  | 0.44 (0.37, 0.51)   | 3.81   |
| Kubo (2020)   | 79  | 37  | 0.47 (0.36, 0.58)   | 3.58   |
| Sekiguchi (2020)| 145 | 61  | 0.42 (0.34, 0.50)   | 3.76   |
| Overall (1-squared = 96.1%, p = 0.000) | | | 0.56 (0.49, 0.63) | 100.00 |

**NOTE:** Weights are from random effects analysis

**FIGURE 2** Forrest plots of SSc-ILD prevalence. SSc-ILD, systemic sclerosis-associated interstitial lung disease [Colour figure can be viewed at wileyonlinelibrary.com]
during 2013-2020. There was no publication bias among the 27 studies by the Egger test \((t = -1.84, P = 0.08)\) (Figure S1A).

### 3.4 Meta-analysis of risk factors for SSc-ILD

We evaluated the potential risk factors for SSc-ILD in 10 studies with 1795 SSc patients in East Asia. The following 15 risk factors appearing in more than one study were selected in the meta-analysis: disease duration, dSSc, anti-topoisomerase I antibody (ATA), anti-centromere body antibody (ACA), anti-U3 ribonucleoprotein (RNP) antibody, digital ulcer, age, male sex, antinuclear antibody (ANA), anti-U1 RNP antibody, anti-Th/To antibody, Raynaud phenomenon, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anti-ribonucleic acid polymerases (RNAP). SSc-ILD patients had a longer disease duration than SSc patients without ILD \((WMD = 1.97, 95\% \text{ CI } 0.55-3.38)\). Diffuse SSc \((OR = 2.84, 95\% \text{ CI } 1.91-4.21)\) and positive ATA \((OR = 4.92, 95\% \text{ CI } 2.74-8.84)\) were associated with ILD in SSc patients (Figure 4A-F). There was no publication bias among studies about dSSc by Egger test \((t = 0.29, P = 0.79)\), about ATA by Egger test \((t = 1.39, P = 0.20)\), or about ACA by Egger test \((t = 1.45, P = 0.19)\) (Figure S1B-D). However, age \((WMD = 3.39, 95\% \text{ CI } -1.54 \text{ to } 8.31)\), male sex \((OR = 1.31, 95\% \text{ CI } 0.83-2.06)\) Raynaud phenomenon \((OR = 0.68, 95\% \text{ CI } 0.30-1.54)\) digital ulcer \((OR = 1.79, 95\% \text{ CI } 1.00-3.20)\), CRP \((WMD = 0.98, 95\% \text{ CI } 0.00-1.95)\) were not associated with ILD in SSc patients (Figure S2A-I). There was no publication bias in the studies about age by the Egger's test \((t = -0.43, P = 0.70)\), about male sex by the Egger's test \((t = 1.55, P = 0.33)\), and about anti-U1 RNP by the Egger's test \((t = 1.35, P = 0.24)\) (Figure S3A-C).

### 4 DISCUSSION

To our knowledge, this is the first meta-analysis of the prevalence and risk factors in SSc patients in East Asia. We showed that the pooled SSc-ILD prevalence was 56\% \((95\% \text{ CI } 49\%-63)\). Moreover, we identified six risk factors associated with SSc-ILD: longer disease duration, dSSc, positive ATA, negative ACA, negative anti-U3 RNP antibody, and
Several previous studies have described variables that predict clinically significant pulmonary fibrosis development, including greater age at onset. However, we reported no difference in age between SSc-ILD and non-ILD patients (WMD = 3.39, 95% CI -1.54 to 8.31); SSc-ILD patients had longer disease duration and higher ESR than the SSc patients without ILD in our study. A potential explanation for age difference was a geographical difference or an introduced bias. Moreover, we speculated that SSc patients with longer disease duration were more likely to have ILD. Disease in SSc-ILD patients tends to be more severe and there is higher disease activity with higher ESR than in SSc patients.

The significance of autoantibodies in SSc remains unclear, although a variety of autoantibodies are not just markers of disease, but also have a role in pathogenesis. The presence of ANA is most frequently a representative feature of the immunological abnormalities in SSc patients, and more than 90% of SSc patients are positive for ANA. The common serum ANAs in SSc patients include anti-ATA (anti-topo I, formerly termed anti-Scl-70), ACA, anti-U1 RNP antibody, anti-RNAP antibody, anti-Th/To antibody, and anti-U3 RNP antibody. This meta-analysis showed that positive ATA, negative ACA, and negative anti-U3 RNP were risk factors for ILD in SSc patients. It has been demonstrated that ATA themselves display anti-fibroblast antibody activity by reacting with determinants at the fibroblast surface. Anti-fibroblast antibodies induce a pro-inflammatory phenotype in fibroblasts and are strongly correlated with ATA and pulmonary fibrosis in patients with SSc. ACA are the most frequently seen autoantibodies in SSc patients and their presence is highly specific in distinguishing SSc.

### Table 2: Subgroup analysis for the prevalence of SSc-ILD

| Subgroups | No. studies | ILD/patients | I² (%) | P value | Prevalence (%) | 95% CI |
|-----------|-------------|--------------|--------|---------|----------------|--------|
| Overall prevalence | 27 | 3007/5250 | 96.1 | <0.05 | 56 | 49-63 |
| Region | | | | | | |
| Korea | 3 | 573/1089 | 80.8 | <0.05 | 51 | 43-59 |
| China | 10 | 1424/1951 | 92.2 | <0.05 | 72 | 65-79 |
| Japan | 14 | 1011/2210 | 77 | <0.05 | 46 | 41-50 |
| STROBE checklist | | | | | | |
| Score ≥17 | 17 | 2374/3819 | 96.3 | <0.05 | 58 | 50-65 |
| Score <17 | 10 | 633/1342 | 95.1 | <0.05 | 53 | 41-65 |
| Classification criteria | | | | | | |
| 1980 ACR criteria | 13 | 1478/2868 | 94.7 | <0.05 | 54 | 46-52 |
| 2013ACR/EULAR criteria | 10 | 990/1609 | 96.7 | <0.05 | 55 | 43-68 |
| 1980 ACR or other | 4 | 539/773 | 92.2 | <0.05 | 64 | 50-77 |
| Publication year | | | | | | |
| Before 2013 | 10 | 891/1808 | 94.7 | <0.05 | 54 | 44-64 |
| 2013-2020 | 17 | 2116/3442 | 95.9 | <0.05 | 56 | 49-63 |

Abbreviations: ACR, American College of Rheumatology; CI, confidence intervals; EULAR, European league against rheumatism; ILD, interstitial lung disease; SSc-ILD, systemic sclerosis-associated interstitial lung disease; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

© Other criteria: have at least out of five CREST features or the 2013 ACR/EULAR criteria; CREST: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.
patients from healthy individuals or study participants with other connective tissue diseases. ACA positivity is strongly associated with the occurrence of ISSc and has been described as conferring relative protection from SSc-associated pulmonary fibrosis.37,46,47 Some studies have even reported that ATA-positive patients have a considerably higher incidence of digital ulcers compared with...
ANTI-RNP antibody is frequently detected in patients with dSSc with a low frequency of pulmonary involvement, whereas anti-U1 RNP antibody is generally found in overlap syndrome, especially mixed connective tissue disease, and is associated with isolated pulmonary arterial hypertension and arthritis. Anti-Th/To antibody is associated with ISSc and a low frequency of severe internal organ involvement. Anti-RNAP antibody is often detected in patients with dSSc and is associated with a high frequency of renal disease. Likewise, we showed that anti-U1 RNP antibody, anti-Th/To antibody, and anti-RNAP antibody are not associated with SSC-ILD in this meta-analysis.

Our study has several limitations. First, as no eligible studies were found for North Korea and Mongolia, the pooled result may be not totally representative of the prevalence of SSC-ILD in East Asia. Second, the study design, methodology quality, sample size, study population, and ILD diagnostic methods might result in significant heterogeneities of SSC-ILD prevalence in the identified studies. A random model was used in calculating the pooled SSC-ILD prevalence, and the sensitivity analysis confirmed that the result was stable. Third, all studies were observational studies, which makes it difficult to determine the causal relationship of risk factors.

5 | CONCLUSION

In conclusion, this meta-analysis showed that ILD occurs in up to 56% of patients with SSC in East Asia. Longer disease duration, dSSc, positive ATA, negative ACA, negative anti-U3 RNP antibody, and higher ESR were risk factors for ILD in SSC patients. However, the data should be interpreted cautiously because of the methodological differences and the limitations inherent in observational studies.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

AUTHORS CONTRIBUTIONS

MHQ, SCZ, and PFY designed the study. MHQ and XYN conducted the literature search and data extraction. MHQ, XYN, and LLP conducted the meta-analysis. MHQ and XYN interpreted the data and wrote the draft of the manuscript. SCZ and PFY critically revised the manuscript. All authors approved submission of the final version of the manuscript. MHQ and XYN contributed equally to this work and are co-first authors. PFY and SCZ contributed equally to this work and are co-correspondence authors.

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