International Journal of
Rheumatic Diseases WILEY

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

Meihua Qiu[1] [ID] | Xueyuan Nian[2] | Lingling Pang[1] | Pengfei Yu[1] | Shenchun Zou[1]

[1]Department of Respiratory and Critical Care Medicine, Yantai Yuhuangding Hospital, Affiliated with the Medical College of Qingdao, Yantai, China

[2]Department of Gastroenterology, Yantai Yuhuangding Hospital, Affiliated with the Medical College of Qingdao, Yantai, China

Correspondence
Pengfei Yu and Shenchun Zou, Department of Respiratory and Critical Care Medicine, Yantai Yuhuangding Hospital, Affiliated with the Medical College of Qingdao, 20 Yuhuangding East Road, Yantai, Shandong 264200, China.
Email: huxi901013@163.com (P.Y); ytyhdpccm@163.com (S.Z)

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).

mp. (mp = title, abstract)). The search terms used in CENTRAL were (systemic sclerosis) [Title/Abstract/keyword] AND ((interstitial lung disease) or (interstitial pneumonia)).

The reference lists of eligible studies and relevant review articles were also hand-searched to find additional reports.

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 weighed 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.[9] 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.[10] 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).[11-36]
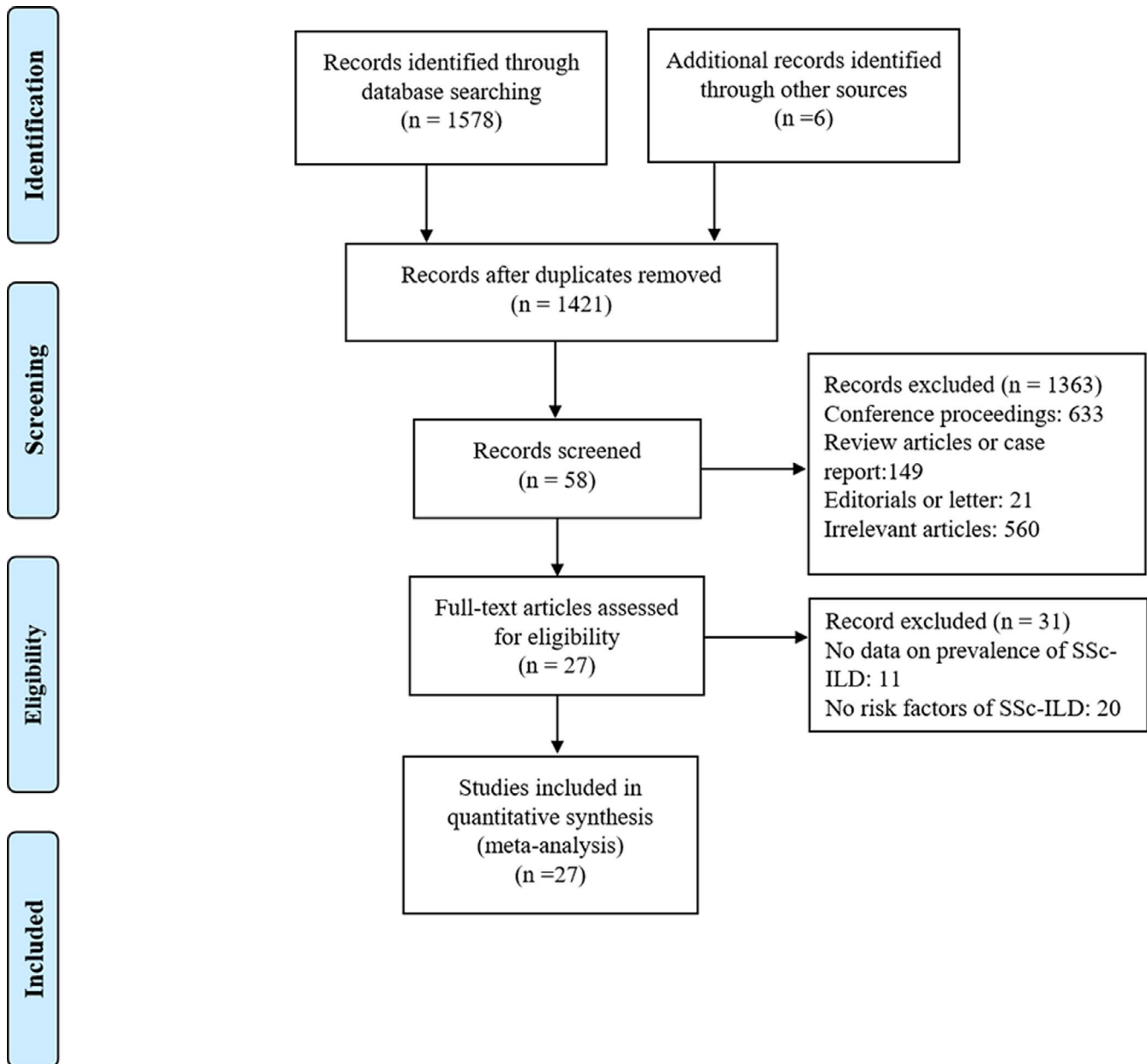

FIGURE 1 The Study flow diagram [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of the studies for the prevalence of SSc-ILD

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 radiograph	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)

TABLE 1 (Continued)

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 SSc[38] 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).[11-37] 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
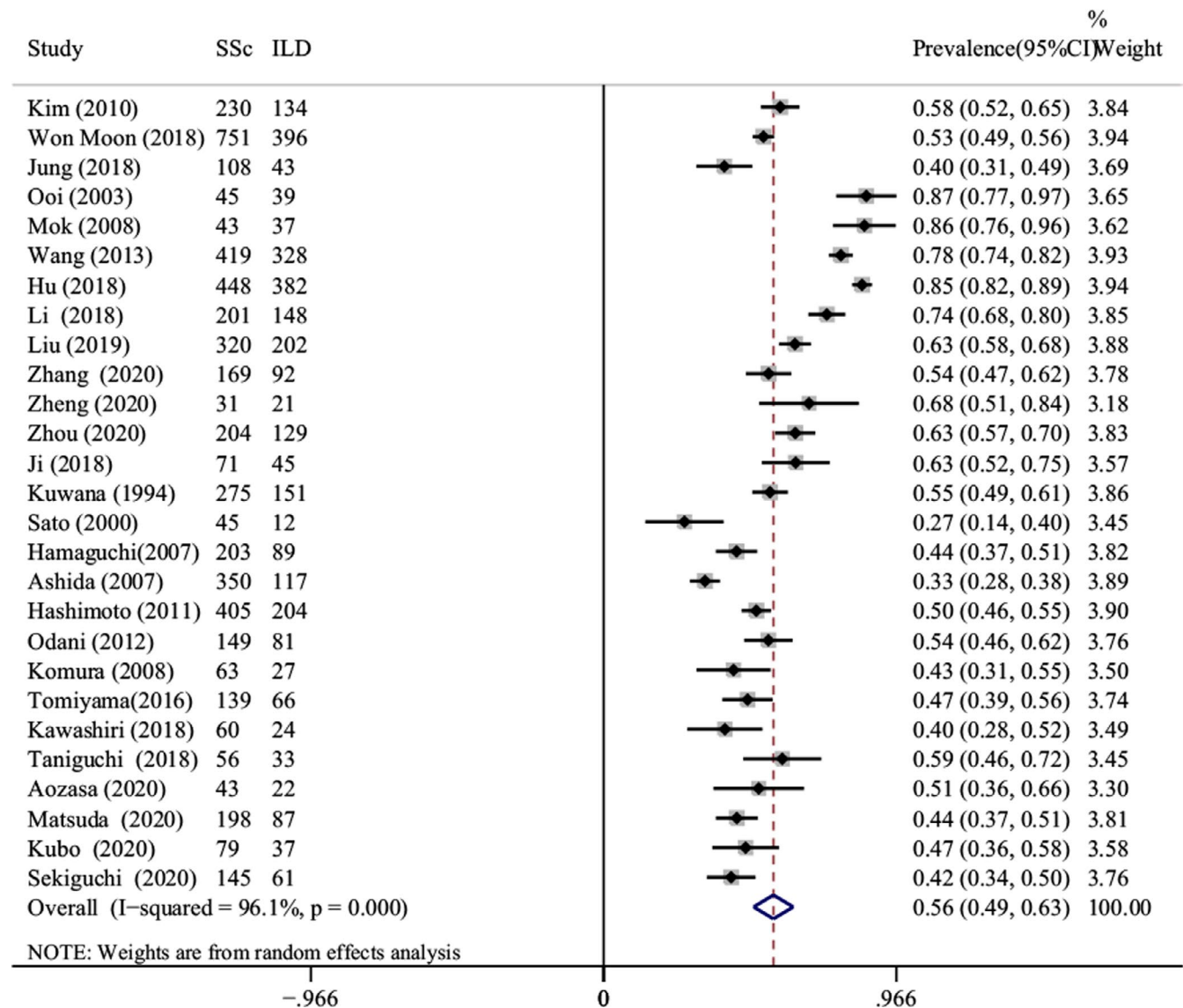
Study	SSc	ILD		Prevalence(95%CI)	Weight
Kim (2010)	230	134		0.58 (0.52, 0.65)	3.84
Won Moon (2018)	751	396		0.53 (0.49, 0.56)	3.94
Jung (2018)	108	43		0.40 (0.31, 0.49)	3.69
Ooi (2003)	45	39		0.87 (0.77, 0.97)	3.65
Mok (2008)	43	37		0.86 (0.76, 0.96)	3.62
Wang (2013)	419	328		0.78 (0.74, 0.82)	3.93
Hu (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 (I−squared = 96.1%, p = 0.000)				0.56 (0.49, 0.63)	100.00

NOTE: Weights are from random effects analysis

−.966   0   .966

FIGURE 2 Forrest plots of SSc-ILD prevalence. SSc-ILD, systemic sclerosis-associated interstitial lung disease [Colour figure can be viewed at wileyonlinelibrary.com]
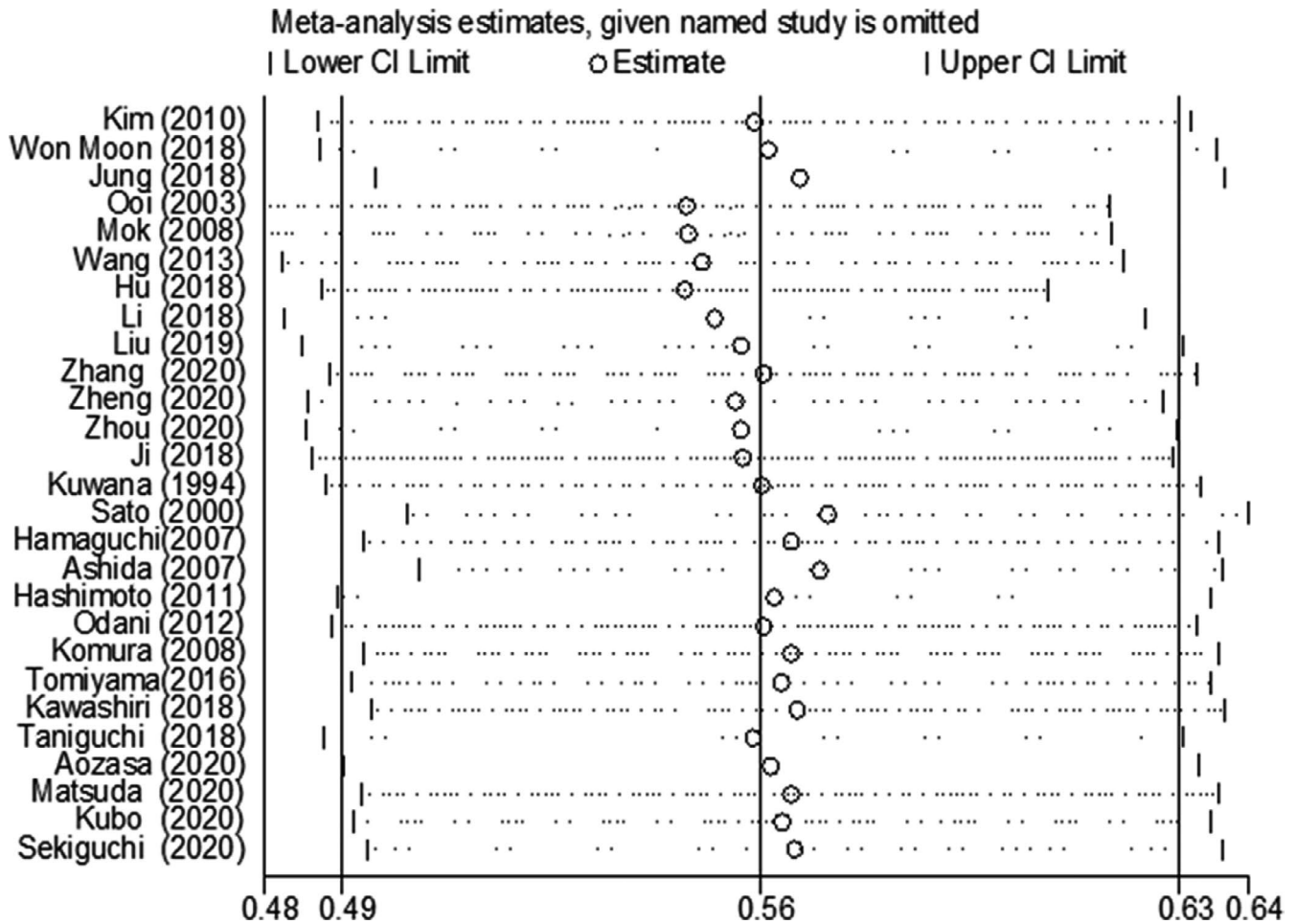
FIGURE 3   Sensitivity analysis of SSc-ILD prevalence. SSc-ILD, systemic sclerosis-associated interstitial lung disease

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.[12,17,20,21,23,24,30,31,37,40] 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% CI 0.55-3.38).[12,21,23] Diffuse SSc (OR = 2.84, 95% CI 1.91-4.21),[12,20,21,23,30] positive ATA (OR = 4.92, 95% CI 2.74-8.84),[12,17,20,21,23,24,30,31,37,40] positive ACA (OR = 0.14, 95% CI 0.08-0.25),[12,17,20,21,23,24,30,31,37] positive anti-U3 RNP antibody (OR = 0.17, 95% CI 0.04-0.66),[23,37] and higher ESR (WMD = 6.62, 95% CI 1.19-12.05)[12,21,23] 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% CI −1.54 to 8.31),[12,20,21,23,30] male sex (OR = 1.31, 95% CI 0.83-2.06),[12,20,21,23,30] Raynaud phenomenon (OR = 0.68, 95% CI 0.30-1.54),[12,21,23,30] digital ulcer (OR = 1.79, 95% CI 1.00-3.20),[12,29] CRP (WMD = 0.98, 95% CI 0.00-1.95),[12,23] positive ANA (OR = 1.6, 95% CI 0.62-4.17),[12,20,21] positive anti-U1 RNP antibody (OR = 0.98, 95% CI 0.69-1.40),[17,21,23,24,30,31,37] positive anti-Th/To antibody (OR = 0.35, 95% CI 0.09-1.31),[23,37] and positive anti-RNAP (OR = 0.49, 95% CI 0.23-1.03)[17,23,31,37] 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% 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

Subgroups	No. studies	ILD/total patients	I^2 (%)	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[a]	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.

[a]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.

higher ESR. The knowledge of risk factors for ILD, which are composed of clinical information that is easily accessible in daily clinical practice, will be of great help in the management of individuals with SSc.

Interstitial lung disease was a common complication in SSc patients. In our meta-analysis, the SSc-ILD prevalence was 56% in East Asia. However, the SSc-ILD prevalence remains controversial, which is probably due to the discrepancies in study region, SSc classification criteria, and publication year. The SSc-ILD prevalence was stable in sensitivity analysis, suggesting that the conclusion is robust. There was great variation in reported prevalence estimates in this meta-analysis. A significantly higher SS-ILD prevalence was reported in China than in Japan and Korea. The same phenomenon occurs outside East Asia; African Americans are more likely to develop SSc than Caucasians and experience worse pulmonary disease and greater morbidity.[40] A previous study found that African American ethnicity was associated with worse lung function in SSc patients.[40] It is not clear what contributes to the differences, but lineages, ethnicities, and genetic factors may have important impacts.[41]

In our meta-analysis, we confirmed that longer disease duration, dSSc subtype, and higher ESR were risk factors for ILD in SSc patients. In the UK, individuals with dSSc have a high incidence of ILD, renal crisis, and gastrointestinal involvement whereas individuals with lSSc frequently develop pulmonary hypertension.[42] As previously demonstrated, clinically significant ILD was twice as common among dSSc patients as among lSSc patients.[43] As expected, the presence of dSSc in East Asia was associated with ILD in our meta-analysis. Several previous studies have described variables

that predict clinically significant pulmonary fibrosis development, including greater age at onset.[42] 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.[44] 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.[45] ACA are the most frequently seen autoantibodies in SSc patients and their presence is highly specific in distinguishing SSc
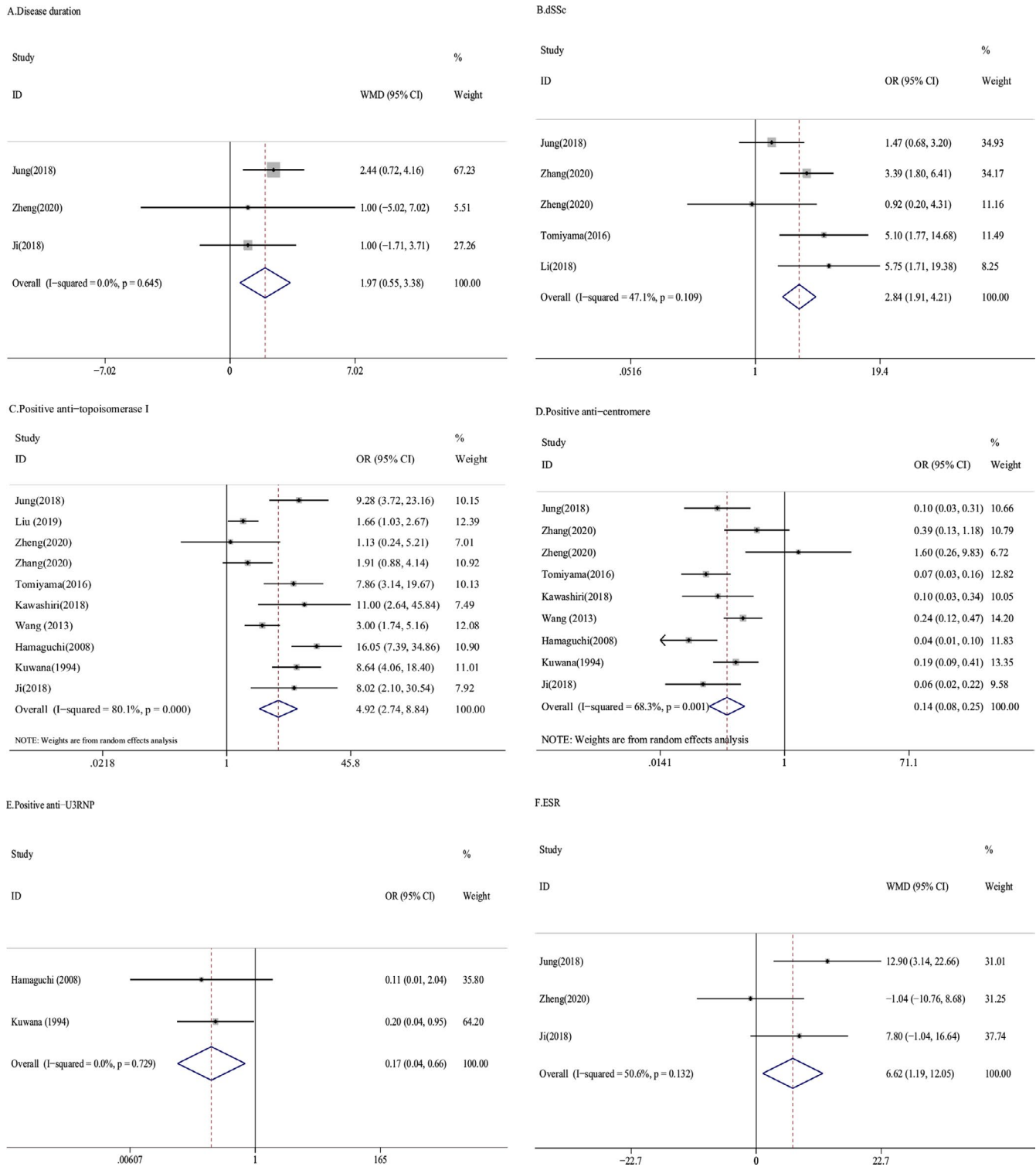
FIGURE 4 Forrest plots of risk factors of SSc-ILD. (A) Pooled WMDs for correlation of disease duration with SSc-ILD; (B) pooled ORs for correlation of dSSc with SSc-ILD; (C) pooled ORs for correlation of positive ATA with SSc-ILD; (D) pooled ORs for correlation of positive ACA with SSc-ILD; (E) pooled ORs for correlation of positive anti-U3 RNP antibody with SSc-ILD; (F) pooled WMDs for correlation of ESR with SSc-ILD. Abbreviations: ACA, anti-centromere antibody; ATA, anti-topoisomerase I antibody; dSSc, diffuse systemic sclerosis; ESR, erythrocyte sedimentation rate; ORs, odd ratios; SSc-ILD, systemic sclerosis-associated interstitial lung disease; U3 RNP, anti-U3 ribonucleoprotein; WMDs, weighted mean differences [Colour figure can be viewed at wileyonlinelibrary.com]

patients from healthy individuals or study participants with other connective tissue diseases. ACA positivity is strongly associated with the occurrence of lSSc 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

ACA-positive participants.[46,47] Anti-U3 RNP antibody is frequently detected in patients with dSSc with a low frequency of pulmonary involvement,[48] 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.[49] Anti-Th/To antibody is associated with lSSc and a low frequency of severe internal organ involvement.[50] Anti-RNAP antibody is often detected in patients with dSSc and is associated with a high frequency of renal disease.[51] 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.

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.

ORCID
Meihua Qiu https://orcid.org/0000-0001-6803-5582

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103): 1685-1699.
2. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. *Autoimmun Rev*. 2010;9(5):A311-318.
3. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*. 1988;15(2):202-205.
4. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med*. 2005;118(1):2-10.
5. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis*. 2007;66(7):940-944.
6. White B. Interstitial lung disease in scleroderma. *Rheum Dis Clin N Am*. 2003;29(2):371-390.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, w264.
8. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelin es for reporting observational studies. *Lancet*. 2007;370(9596):1453-1457.
9. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systemati c Reviews of Interventions. *Cochrane database syst rev*. 2019;10:Ed000142.
10. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109): 629-634.
11. Kim J, Park SK, Moon KW, et al. The prognostic factors of systemic sclerosis for survival among Koreans. *Clin Rheumatol*. 2010;29(3):297-302.
12. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with interstitial lung disease. *Arch Rheumatol*. 2018;33(3):322-327. https://doi.org/10.5606/ArchRheumatol. 2018.6630
13. Moon KW, Lee SS, Lee YJ, et al. Clinical and laboratory characteristics and mortality in Korean patients with systemic sclerosis: A nationwide multicenter retrospective cohort study. *J Rheumatol*. 2018;45(9):1281-1288. https://doi.org/10.3899/jrheum.171443
14. Ooi GC, Mok MY, Tsang KW, et al. Interstitial lung disease in systemic sclerosis. *Acta Radiol* (Stockholm, Sweden: 1987). 2003;44(3):258-264.
15. Mok MY, Fung PCW, Ooi C, et al. Serum nitric oxide metabolites and disease activity in patients with systemic sclerosis. *Clin Rheumatol*. 2008;27(3):315-322. https://doi.org/10.1007/s10067-007-0708-9
16. Low AH, Johnson SR, Lee P. Ethnic influence on disease manifestations and autoantibodies in Chinese-descent patients with system ic sclerosis. *J Rheumatol*. 2009;36(4):787-793.
17. Wang J, Assassi S, Guo G, et al. Clinical and serological features of systemic sclerosis in a Chinese cohort. *Clin Rheumatol*. 2013;32(5):617-621.
18. Hu S, Hou Y, Wang Q, Li M, Xu D, Zeng X. Prognostic profile of systemic sclerosis: Analysis of the clinical EUSTAR cohort in China. *Arthritis Res Ther*. 2018;20(1):235. https://doi.org/10.1186/s13075-018-1735-4
19. Li X, Qian YQ, Liu N, et al. Survival rate, causes of death, and risk factors in systemic sclerosis: a large cohort study. *Clin Rheumatol*. 2018;37(11):3051-3056. https://doi.org/10.1007/s10067-018-4291-z
20. Zhang M, Zhang L, Linning E, et al. Increased levels of HE4 (WFDC2) in systemic sclerosis: a novel biomarker reflecting interstitial lung disease severity? *Ther Adv Chronic Dis*. 2020;11:1-11. https://doi.org/10.1177/2040622320956420

21. Zheng JN, Li Y, Yan YM, Yu Y, Shao WQ, Wang Q. Increased serum calpain activity is associated with HMGB1 levels in systemic sclerosis. *Arthritis Res Ther*. 2020;22(1):110. https://doi.org/10.1186/s13075-020-02195-y

22. Zhou M, Jiang L, Nie L, et al. Myopathy is a risk factor for poor prognosis of patients with systemic sclerosis: A retrospective cohort study. *Medicine*. 2020;99(33):e21734. https://doi.org/10.1097/MD.0000000000021734

23. Ji LL, Wang H, Zhang XH, Zhang ZL. Correlation between nailfold capillaroscopic findings and presence of interstitial lung disease in systemic sclerosis patients. *J Peking Univ Health Sci*. 2018;50(3):501-506. http://xuebao.bjmu.edu.cn/EN/Y2018/V50/I3/501

24. Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. *Arthritis Rheum*. 1994;37(1):75-83.

25. Sato S, Nagaoka T, Hasegawa M, Nishijima C, Takehara K. Elevated serum KL-6 levels in patients with systemic sclerosis: Association with the severity of pulmonary fibrosis. *Dermatology (Basel, Switzerland)*. 2000;200(3):196-201. https://doi.org/10.1159/000018382

26. Ashida R, Ihn H, Mimura Y, et al. Clinical features of scleroderma patients with contracture of phalanges. *Clin Rheumatol*. 2007;26(8):1275-1277. https://doi.org/10.1007/s10067-006-0490-0

27. Komura K, Fujimoto M, Hasegawa M, et al. Increased serum interleukin 23 in patients with systemic sclerosis. *J Rheumatol*. 2008;35(1):120-125.

28. Hashimoto A, Tejima S, Tono T, et al. Predictors of survival and causes of death in Japanese patients with systemic sclerosis. *J Rheumatol*. 2011;38(9):1931-1939.

29. Odani T, Yasuda S, Ota Y, et al. Up-regulated expression of HLA-DRB5 transcripts and high frequency of the HLA-DRB5*01:05 allele in scleroderma patients with interstitial lung disease. *Rheumatology*. 2012;51(10):1765-1774. https://doi.org/10.1093/rheumatology/kes149

30. Tomiyama F, Watanabe R, Ishii T, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. *Tohoku J Exp Med*. 2016;239(4):279-305. https://doi.org/10.1620/tjem.239.297

31. Kawashiri SY, Nishino A, Igawa T, et al. Prediction of organ involvement in systemic sclerosis by serum biomarkers and peripheral endothelial function. *Clin Exp Rheumatol*. 2018;36 Suppl 113(4);102-108.

32. Taniguchi T, Miyagawa T, Toyama S, et al. CXCL13 produced by macrophages due to Fli1 deficiency may contribute to the development of tissue fibrosis, vasculopathy and immune activation in systemic sclerosis. *Exp Dermatol*. 2018;27(9):1030-1037. https://doi.org/10.1111/exd.13724

33. Matsuda KM, Yoshizaki A, Kuzumi A, et al. Skin thickness score as a surrogate marker of organ involvements in systemic sclerosis: A retrospective observational study. *Arthritis Res Ther*. 2019;21(1):129. https://doi.org/10.1186/s13075-019-1919-6

34. Aozasa N, Hatano M, Saigusa R, et al. Clinical significance of endothelial vasodilatory function evaluated by EndoPAT in patients with systemic sclerosis. *J Dermatol*. 2020;47(6):609-614. https://doi.org/10.1111/1346-8138.15334

35. Kubo S, Siebuhr AS, Bay-Jensen AC, et al. Correlation between serological biomarkers of extracellular matrix turnover and lung fibrosis and pulmonary artery hypertension in patients with systemic sclerosis. *Int J Rheum Dis*. 2020;23(4):532-539. https://doi.org/10.1111/1756-185X.13804

36. Sekiguchi A, Inoue Y, Yamazaki S, et al. Prevalence and clinical characteristics of earlobe crease in systemic sclerosis: Possible association with vascular dysfunction. *J Dermatol*. 2020;47(8):870-875. https://doi.org/10.1111/1346-8138.15400

37. Hamaguchi Y, Hasegawa M, Fujimoto M, et al. The clinical relevance of serum antinuclear antibodies in Japanese patients with systemic sclerosis. *Br J Dermatol*. 2008;158(3):487-495. https://doi.org/10.1111/j.1365-2133.2007.08392.x

38. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum*. 1980;23(5):581-590.

39. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72(11):1747-1755.

40. Greidinger EL, Flaherty KT, White B, Rosen A, Wigley FM, Wise RA. African-American race and antibodies to topoisomerase I are associated with increased severity of scleroderma lung disease. *Chest*. 1998;114(3):801-807.

41. Ramos PS, Silver RM, Feghali-Bostwick CA. Genetics of systemic sclerosis: recent advances. *Curr Opin Rheumatol*. 2015;27(6):521-529.

42. Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol*. 2014;66(6):1625-1635.

43. Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. *QJM*. 2010;103(2):109-115.

44. Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in systemic sclerosis. *Nat Rev Rheumatol*. 2010;6(2):112-116.

45. Hénault J, Tremblay M, Clément I, Raymond Y, Senécal J-L. Direct binding of anti-DNA topoisomerase I autoantibodies to the cell surface of fibroblasts in patients with systemic sclerosis. *Arthritis Rheum*. 2004;50(10):3265-3274.

46. Walker UA, Tyndall A, Czirjak L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis*. 2007;66(6):754-763.

47. Hachulla E, Carpentier P, Gressin V, et al. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study. *Rheumatology* (Oxford). 2009;48(3):304-308.

48. Okano Y, Steen VD, Medsger TA. Autoantibody to U3 nucleolar ribonucleoprotein (fibrillarin) in patients with systemic sclerosis. *Arthritis Rheum*. 1992;35(1):95-100.

49. Jacobsen S, Halberg P, Ullman S, et al. Clinical features and serum antinuclear antibodies in 230 Danish patients with systemic sclerosis. *Br J Rheumatol*. 1998;37(1):39-45.

50. Kuwana M, Kimura K, Hirakata M, Kawakami Y, Ikeda Y. Differences in autoantibody response to Th/To between systemic sclerosis and other autoimmune diseases. *Ann Rheum Dis*. 2002;61(9):842-846.

51. Okano Y, Steen VD, Medsger TA. Autoantibody reactive with RNA polymerase III in systemic sclerosis. *Ann Intern Med*. 1993;119(10):1005-1013.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.