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Increased risk of mortality in systemic sclerosis-associated pulmonary hypertension: a systemic review and meta-analysis

Anji Xiong[1,2*†], Qingting Liu[1†], Jiaxun Zhong[1†], Yuzi Cao[1], Qilang Xiang[1], Ziyi Hu[1], Shifeng Zhou[1], Zhuoyao Song[1], Huini Chen[1], Yan Zhang[1], Hongxu Cui[1] and Shiquan Shuai[1,2]

Abstract

Background: Pulmonary hypertension (PH) is a frequent complication of systemic sclerosis (SSc) and is currently one of the primary causes of death in patients with this disease. We conducted a systematic review and meta-analysis to assess the association between PH and mortality in patients with SSc to verify trends in mortality in patients with SSc-associated PH.

Methods: We searched the PubMed and Embase databases for published studies on SSc-associated PH from inception to May 2021. All cohort studies in which mortality and/or survival for SSc-associated PH were reported were included in the analysis. The outcome parameters were pooled and analyzed using a random-effects model via generic inverse-variance weighting in conventional and cumulative meta-analysis.

Results: The literature search identified 1161 citations, and the full texts of 54 studies were examined. Sixteen articles, with a total of 7857 patients with SSc and 1140 patients with SSc-associated PH, were included in the meta-analysis. Patients with SSc-associated PH had a higher pooled risk of mortality than patients with SSc without PH (risk ratio = 3.12; 95% confidence interval: [2.44, 3.98]).

Conclusions: This meta-analysis revealed a higher mortality in patients with SSc-associated PH. PH was a significant predictor of death in patients with SSc. Thus, early diagnosis and treatment of PH are important in patients with SSc.

Keywords: Systemic sclerosis, Pulmonary hypertension, Early diagnosis, Mortality, Meta-analysis

Key messages

(1) SSc patients with PH had an increased pooled mortality risk than SSc patients without PH.
(2) Early diagnosis and treatment of PH are important in patients with SSc.

Introduction

Systemic sclerosis (SSc) is a multisystem disease characterized by fibrosis and excessive collagen deposition within the skin and internal organs, chronic inflammation, immune dysregulation, and microvascular

*Correspondence: xionganji@126.com
†Anji Xiong, Qingting Liu, and Jiaxun Zhong have contributed equally to this work
[1] Department of Rheumatology and Immunology, Nanchong Central Hospital, The Affiliated Nanchong Central Hospital of North Sichuan Medical College, 97 Renmin South Road, Shunqing District, Nanchong, Sichuan, China
Full list of author information is available at the end of the article

endothelial dysfunction [1, 2]. SSc is associated with high morbidity and mortality related to multiple organ complications. The risk of mortality is 4–5 times greater than that in an age- and sex-matched population [3]. There have been changes in the pattern of death in the last decade after the introduction of new therapies, with an important reduction in the number of deaths related to kidney involvement, and currently, pulmonary fibrosis is the leading cause of death in SSc patients, followed by pulmonary hypertension (PH) [4]. Pulmonary arterial hypertension (PAH) is the most common cause of SSc-associated PH [5]. In addition, myocardial fibrosis, left heart disease (LHD), interstitial lung disease (ILD), and pulmonary veno-occlusive (PVOD) are important causes of SSc-associated PH [6]. Furthermore, compared to PH from all connective tissue diseases, SSc-associated PH has the worst prognosis [7].

Prior to this meta-analysis, numerous observational studies have highlighted that patients with SSc and PH are at a higher risk of death [8–15]. However, owing to the small number of patients included, these observational studies had a low power for statistical analysis, resulting in lower reliability of these results. Because mortality is high in patients with SSc-associated PH, early diagnosis and treatment of PH may be important contributing factors for improved outcomes in patients with SSc [16]. Therefore, a large sample with a higher power for statistical analysis is crucial to determine whether PH represents an important risk factor for mortality. We conducted a systematic review and meta-analysis of cohort studies to assess the association between PH and mortality in patients with SSc.

Material and methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement protocol (Additional file 1: Material S1) [17].

Search strategy

We searched the PubMed and Embase.databases for relevant studies published from inception until May 2021. The search included various combinations of the terms scleroderma OR sclerosis AND systemic, together with medical subject headings (MeSH). The search terms used for PubMed were as follows: ("scleroderma, systemic" [Mesh] OR "systemic, scleroderma" [Title/Abstract] OR "systemic sclerosis" [Title/Abstract] OR "sclerosis, systemic" [Title/Abstract]) AND ("hypertension, pulmonary" [Mesh] OR "pulmonary hypertension" [Title/Abstract]) AND ("mortality" [Mesh] OR "death" [Title/Abstract]). The following filters were used: species (humans). In addition, we searched the reference lists of relevant studies, reviews, and letters. In cases of incomplete reporting, the individual authors were contacted.

Selection criteria

Studies were included if they met the following criteria: (1) the study was a cohort study; (2) the patients included were adults with a diagnosis of SSc according to the American College of Rheumatology Criteria [18] and/or the Leroy and Medsger classification [19]; (3) PH was defined as mean pulmonary arterial pressure > 20 mmHg on right heart catheterization (RHC) [20]. (4) Risk ratios (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were provided or the exact number of patients in each group (deceased patients with SSc and deceased patients with SSc-associated PH) was reported, allowing the RR or OR to be calculated. Articles were excluded before full reading when they reported data related to diseases other than SSc or focused on preclinical data, such as animal studies. We also excluded articles that did not provide precise data on mortality rate or frequency of PH. The full texts of the remaining articles were analyzed to determine whether the articles contained relevant information.

Risk of bias assessment

Quality assessment of individual studies was performed independently by two authors using the Newcastle–Ottawa Scale for cohort studies. The scale allocates stars (maximum of nine) for quality of selection, comparability exposure, and outcome of study participants (Additional file 2: Material S2) [21]. Disagreements were resolved through a joint re-evaluation of the original article.

Data extraction

Data were extracted from the selected studies independently by two authors using a predefined standardized form. The data extracted for the meta-analysis included the number of deaths in patients with SSc with and without PH (Table 1). When the information available was incomplete, attempts were made to contact the corresponding authors of the studies for more details.

Data analysis

The primary outcome was mortality in patients with SSc with PH. The RR for mortality was estimated for each study included in the meta-analysis. The meta-analysis was carried out using the inverse variance approach, which assumes a random-effects model, to determine the weight given to each study. It provided a RR estimate with a 95% CI, taking the weight of the different samples into account. RRs and their 95% CIs are shown in a forest plot. Statistical heterogeneity among the selected studies

Table 1 Table of data extractions from 16 articles included in the study

Author	Year of publication	Study type	Localization	Study duration years	HR/RR	Number of patients in the cohort	Number of patients with PH	Number of deceased patients	Number of deceased patients with PH
Al-Dhaher, F. F	2010	Cohort	USA	10	2.70 [1.00, 7.29]	185	19	42	9
Chung, M. P	2020	Cohort	USA	10	2.33 [1.48, 3.68]	609	50	105	16
Hachulla, E	2009	Cohort	France	3	7.25 [4.00, 13.12]	546	47	47	20
Hashimoto, A	2011	Cohort	Japan	Retrospective	2.39 [1.65, 3.46]	405	65	86	27
Hesselstrand,R	2011	Cohort	Sweden	7	3.20 [1.80, 5.69]	180	30	-	-
Hissaria, P	2011	Cohort	Australia	15	2.17 [1.40,3.36]	786	65	331	-
Hoffmann-Vold	2013	Cohort	Norway	11	8.00 [3.40, 18.82]	312	34	43	8
Hsu, V. M	2019	Cohort	USA	4 (0.4–8.5)	2.99 [1.30, 6.88]	236	35	32	7
Hu, S	2018	Cohort	China	10	6.25 [2.86, 13.67]	448	78	40	22
Joven, B. E	2010	Cohort	Spain	8	2.20 [1.20, 4.03]	204	59	44	11
Moon, K. W	2018	Cohort	Korea	Retrospective	4.66 [2.57, 8.45]	751	102	57	-
Noviani, M	2020	Cohort	Singapore	8.8	2.39 [1.13, 5.06]	490	50	-	-
Panopoulos, S	2018	Cohort	Greece	8.5 ± 4	7.49 [1.70, 33.00]	115	16	23	6
Rubio-Rivas M	2018	Cohort	Spain	Retrospective	1.68 [1.29,2.19]	1625	311	277	43
Simeon-Aznar	2015	Cohort	Spain	Retrospective	2.69 [1.73, 4.17]	879	161	138	58
Trad, S	2006	Cohort	France	6	4.09 [1.47, 11.38]	86	18	17	9

HR: Hazard ratio, RR: Risk Ratio, PH: pulmonary hypertension

was quantified using the Q-test (Chi-2), using a level of significance of 0.05, and were reported using I^2 statistics, in which high values indicate high heterogeneity. Heterogeneity values of 25%, 50%, and 75% were designated as low, moderate and high, respectively [22]. Computation was performed using the Revman 5.3.5 software package developed by the Cochrane Collaboration (The Nordic Cochrane Center, Copenhagen). *P*-values less than 0.05 were considered as significant.

Sensitivity analysis was performed to evaluate whether any individual study influenced the overall results in order to confirm the stability and reliability of the meta-analysis. Predefined subgroup analyses were performed between low- and high-quality studies (i.e., studies with quality scores under and over the median), recent and older studies, and studies with shorter or longer duration, to identify possible sources of heterogeneity.

Results

Selection of studies

Our search of the PubMed and Embase databases from inception to May 2021 retrieved 1161 citations. After the titles and abstracts were evaluated, 1107 reviews and articles did not meet the inclusion criteria. The full texts of the remaining 54 studies were examined, and the exclusion criteria were applied. Finally, 16 articles, with a total of 7857 patients with SSc and 1140 patients with SSc-associated PH, were selected for data extraction (Fig. 1) [8–11, 13, 15, 23–32]

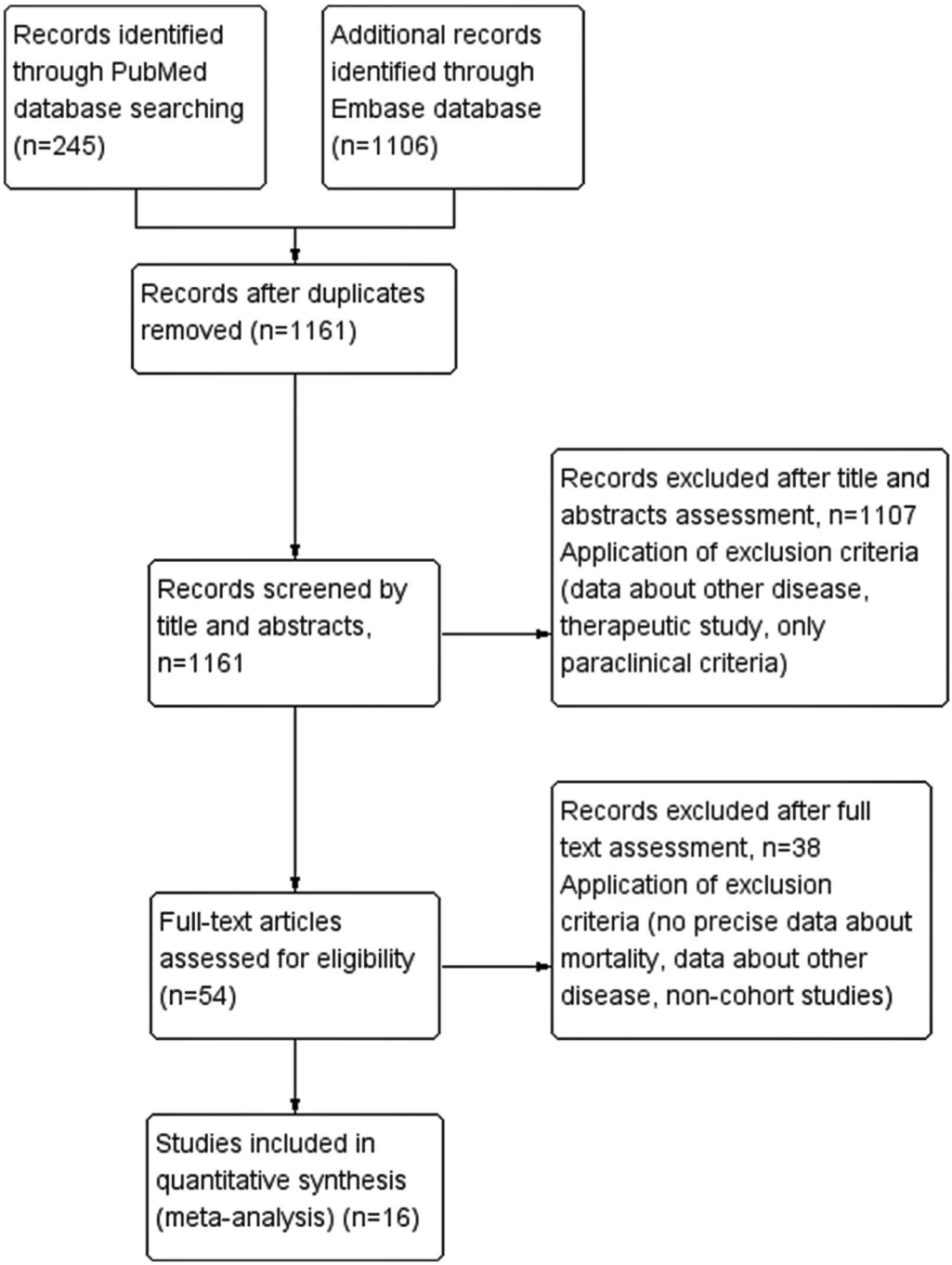

Fig. 1 Flow chart of study selection showing strategy used to include publications

Clinical results

A total of 16 studies were included in the meta-analysis (Table 1). No study was excluded because of the quality assessment. The meta-analysis included 7857 patients with SSc, including 1140 with SSc-associated PH. Six studies showed significant correlation between mortality and PH [8, 9, 11, 12, 25, 26]. Meta-analysis of the pooled outcomes showed a higher mortality in patients with PH than in those without. The pooled RR was 3.12 (95% CI [2.44, 3.98], $I^2 = 64\%$) (Fig. 2), which indicated moderate heterogeneity among the studies. Similar effects were consistently observed in the sensitivity and subgroup

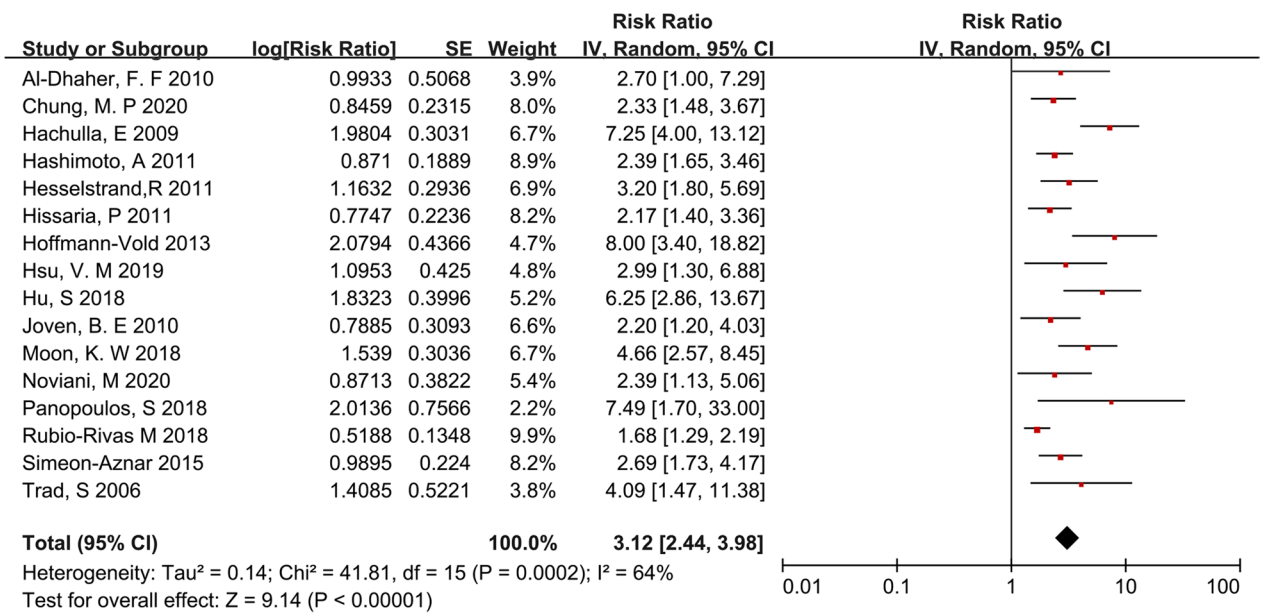

Fig. 2 Systemic sclerosis associated pulmonary hypertension: forest plot showing the pooled risk-ratio

Table 2 Subgroup of different causes of death in cohort of SSc-PH patients

Subgroup	No. of studies	Number of patients	Number of patients with PH	Pooled RR
Year of publication				
Before 2011 (10 years ago)	4	1021	143	3.71 (1.97, 7.00) *
After 2011 (10 years later)	12	6836	997	2.93 (2.27, 3.78) *
Study duration, years				
Less than 10 years	7	1857	255	3.55 (2.43, 5.17) *
More than 10 years	5	2340	246	3.42 (2.08, 5.62) *
Retrospective	4	3660	639	2.51 (1.71, 3.68) *
Quality score				
High-quality studies (QS > 8)	8	5264	765	2.91 (2.04, 4.13) *
Low-quality studies (QS ≤ 8)	8	1674	375	3.38 (2.48, 4.60) *

RR: Risk Ratio, PH: pulmonary hypertension, QS: quality score. Data are presented as RR (95% CI). *$P < 0.05$

analyses (Table 2), which confirmed the robustness of our results. Furthermore, the moderate heterogeneity reduced to 49% if we excluded the study by Rubio-Rivas (2018) [24] (Fig. 3). This may be attributed to the larger sample size (a multicenter, nationwide, retrospective study involving 28 referral centers for diagnosis and management of SSc from 1995 to 2015), which was different from that of other studies.

Discussion

Most articles included in the meta-analysis highlighted that PH has an important impact on the mortality in patients with SSc. In particular, four studies showed significant correlations between mortality and PH, with PH increasing the RR for mortality in patients with SSc by more than fivefold [9, 11, 12, 25]. Recent studies, including the EUSTAR registry, reported 5-year and 10-year survival rates of 90% and 84%, respectively [16]. However, the 3-year and 5-year survival rates in patients with SSc-associated PH are between 31% and 62.5% [33–36], and < 50%, respectively [34]. Our findings support the significant impact of this complication on mortality

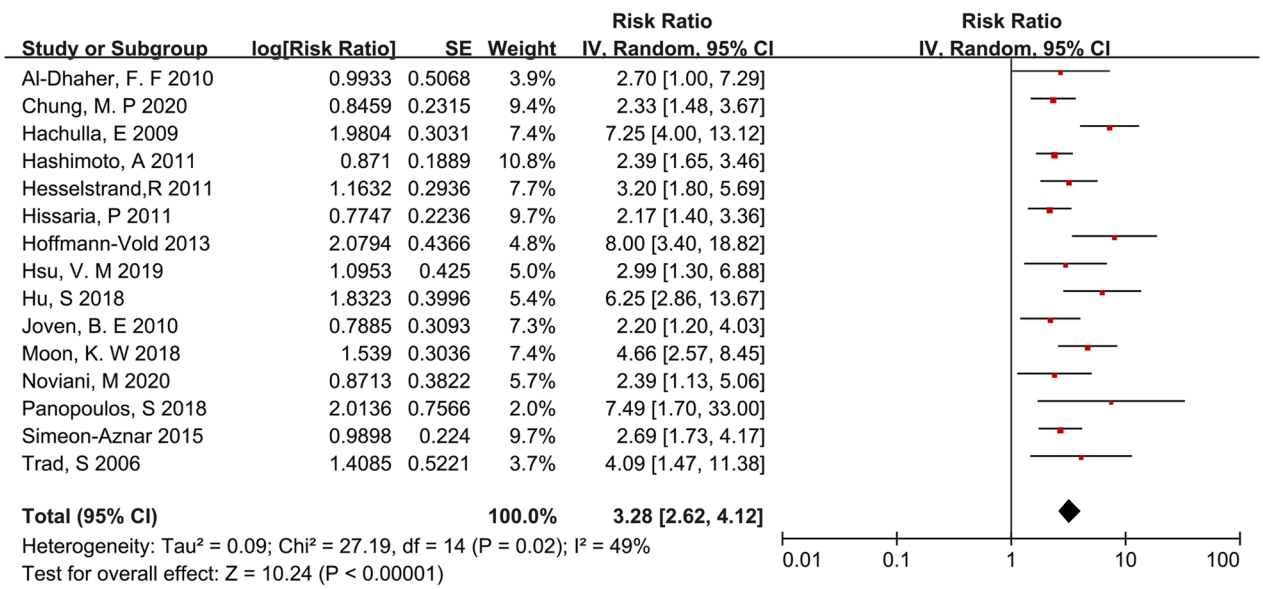

Fig. 3 Systemic sclerosis associated pulmonary hypertension: forest plot showing the pooled risk-ratio when we excluded Rubio-Rivas, M 2018

in patients with SSc. SSc with PH was associated with higher mortality than SSc without PH (RR = 3.12; 95% CI [2.44, 3.98]) in this meta-analysis. Moreover, a comparison of our results with those of the meta-analysis by Komocsi [37] on mortality in patients with SSc-associated PH showed that the RR for mortality in patients with SSc-associated PH was similar between the studies. This revealed a poor prognosis in patients with SSc-associated PH. The primary cause of death in patients with SSc-associated PH may be PH itself, that is, acute right ventricular failure leading to biventricular failure [38–40]. Fortunately, early diagnosis and treatment may improve long-term outcomes in patients with SSc-associated PH [41].

PH is hemodynamically defined as a mean pulmonary artery pressure > 20 mmHg at rest on RHC [20], and it has a highly heterogeneous etiology [42]. PH can be classified as: Group 1, PAH; Group 1-bis', PVOD and/or pulmonary capillary haemangiomatosis; Group 2, PH due to LHD; Group 3, PH due to lung disease and/or hypoxia; Group 4, chronic thromboembolic pulmonary hypertension (CTEPH); and Group 5, PH due to unclear multifactorial mechanisms [5].

The time from symptom onset to diagnosis of PH is often long, which can delay initiation of treatment and contribute to worse outcomes [43]. A recent study found that the incidence of early-onset PH was similar to that of late-onset PH (0.7 per 100 person-years), with a mean disease duration at the time of PH diagnosis of 2.2 years for early-onset PH and 9.3 years for late-onset PH [14]. Thus, patients diagnosed with SSc should be closely monitored and screened for PH, particularly during the first 2 years of onset [14]. However, early symptoms of PH are non-specific [5], and early diagnosis of PH is easily overlooked by physicians. A recent retrospective observational study showed that patients with SSc with early diagnosis of PH through screening before symptom onset had a better prognosis compared to patients identified after symptom onset [16]. However, PH is typically recognized in the late stage, when patients present with severe symptoms, hemodynamic deterioration, and poor prognosis [44]. However, considering the higher mortality in patients with SSc-PH, physicians should pay attention to the early diagnosis of PH in patients with SSc. Current guidelines recommend comprehensive screening for PH to enable early and correct diagnosis [5]. Echocardiography is the first step in the analysis process. Echocardiography is currently the most important noninvasive method for the diagnosis of PH [45] and is known to identify PH with high sensitivity [46]. When echocardiography reveals a tricuspid regurgitation velocity between 2.9 m/s and 3.4 m/s, there is an intermediate probability of PH. If the value is > 3.4 m/s, there is a high probability of PH [47]. Echocardiography is widely available and allows the estimation of pulmonary artery systolic pressure (PASP), cardiac output, and with some limitations also pulmonary artery wedge pressure (PAWP) [45]. The threshold of PASP ≥ 45 mmHg is associated with PH at catheterization in 97% of cases [48]. The poor prognosis of patients with SSc-associated PH emphasizes the need for physicians to follow the most recent guidelines, and echocardiographic screening for the detection of PH

is recommended for patients with SSc without symptoms of PH. The second step is to identify the clinical group. An electrocardiogram (ECG) may provide supportive evidence of PH, but a normal ECG does not exclude the diagnosis. An abnormal ECG is more likely in severe rather than mild PH. ECG abnormalities may include P pulmonale, right axis deviation, right ventricular (RV) hypertrophy, RV strain, right bundle branch block, and QTc prolongation [5]. If echocardiography is suggestive of PH, it is possible to evaluate left heart involvement using an ECG in order to confirm the diagnosis of Group 2 PH [47]. Chest radiographs in patients with PH reveal central pulmonary arterial dilatation, which contrasts with 'pruning' (loss) of the peripheral blood vessels. A chest radiograph may assist in the differential diagnosis of PH by revealing signs suggestive of lung disease (Group 3) or pulmonary venous congestion due to LHD (Group 2) [5]. Pulmonary function tests identify the presence of airway or parenchymal lung disease. Usually, patients with PAH (Group 1) have a reduced diffusion capacity of the lungs for carbon monoxide (DLCO, 40–80% [predicted]) and mild-to-moderate reduction in lung volumes with normal left heart function [47]. DLCO is probably one of the most important parameters to be evaluated in patients with SSc because it can represent a marker of PAH. A reduced DLCO with a conserved forced vital capacity is suggestive of pulmonary vascular disease, and the probability is especially high in patients with SSc-associated PH [49]. An annual lung function test with DLCO is recommended for patients with SSc [5]. High-resolution computed tomography (HRCT) provides detailed views of the lung parenchyma and facilitates the diagnosis of ILD (Group3) [50]. Moreover, HRCT may also be very helpful when there is a clinical suspicion of PVOD (Group1). Characteristic changes such as interstitial edema with diffuse central ground-glass opacification and thickening of the interlobular septa support the diagnosis of PVOD [5]. A ventilation/perfusion (V/Q) lung scan will allow identification of CTEPH (Group4). The V/Q scan is the screening method of choice for CTEPH because of its higher sensitivity to chronic pulmonary obstruction compared with computed tomography pulmonary angiogram [5]. The last procedure is the RHC, which is mandatory in all patients with suspected PH to confirm the diagnosis and determine disease severity [43].

PH is the hallmark manifestation of microvasculopathy in SSc, and rapid evolution of vasculopathy occurs in the initial years [51]. Therefore, once PH is diagnosed via RHC, it should be treated aggressively. Careful phenotyping of SSc-associated PH is important, as the treatment for each specific underlying condition is different. For patients with SSc in Group 1, the initial therapy includes the following general measures: physical activity and supervised rehabilitation, avoiding pregnancy, infection prevention, psychosocial support, and supportive therapy, in particular, oxygen and diuretics [47]. In addition, high doses of calcium channel blockers are recommended in patients with IPAH (idiopathic pulmonary arterial hypertension), HPAH (heritable pulmonary arterial hypertension) and PAH associated with drugs and toxin use who respond to acute vasoreactivity testing [5]. However, as reported before, patients with SSc-associated PAH do not respond to calcium channel blockers therapy, so it is important to begin the treatment with specific vasodilators as soon as possible [47]. The main goal in the treatment of Group 2 PH is to optimize the underlying left heart condition [52]. This includes repair of valvular heart disease when indicated, and aggressive therapy for heart failure with reduced systolic function [5]. Currently, there is no specific therapy for PH associated with lung diseases (Group 3). Long-term O2 administration has been shown to partially reduce the progression of PH. Thus, patients with lung disease and PH who are hypoxemic should receive long-term O2 therapy [5]. Treatment with conventional vasodilators such as calcium channel blockers is not recommended because they may impair gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction [53] and because of their lack of efficacy after long-term use [54]. Further, the use of drugs approved for PAH is not recommended for patients with PH due to lung disease [5]. Pulmonary endarterectomy is the treatment of choice for CTEPH (Group 4) [5]. Moreover, treatment of CTEPH necessitates a true bilateral endarterectomy through the medial layer of the pulmonary arteries, which is performed under deep hypothermia and circulatory arrest without the need for cerebral perfusion [55]. PH with unclear and/or multifactorial mechanisms (Group 5) includes several disorders with multiple pathologies [5]. A common feature of these diseases is that the mechanisms of PH are poorly understood. The axiom should be 'Treat the lung, not the pressure [5]. Meanwhile, treatments for SSc-associated PH are complex and best accomplished by a multidisciplinary team [43].

Our study had several limitations: The meta-analysis included observational studies, which are usually unbalanced with regard to the baseline clinical characteristics of the patients. Thus, outcome parameters were pooled with logarithmic transformation according to a random-effects model via generic inverse-variance weighting, which is a more appropriate method for observational studies. Four studies included were published more than ten years ago [8, 9, 31, 32], seven studies had a short follow-up of less than 10 years [8, 9, 13, 15, 25, 30, 31], suggesting a potential bias. To address these potential

limitations, we conducted subgroup analyses. Similar effects were consistently observed in the subgroup analyses, which confirmed the stability and reliability of our studies. Despite these limitations, our meta-analysis revealed an increased risk of mortality in patients with SSc with PH. A further limitation is that PH has been classically considered the main cause of death in patients with the limited cutaneous systemic sclerosis (lcSSc), but not in patients with diffuse cutaneous SSc (dcSSc). However, some studies have shown that this pulmonary vascular complication is a frequent clinical manifestation in all SSc subsets [31, 32, 56]. Unfortunately, most articles included in our study did not provide precise data on mortality rate or frequency of lcSSc-PH and dcSSc-PH in each group, so we could not compare the mortality between lcSSc-PH and dcSSc-PH. Finally, lead-time bias may have affected the results. Therefore, further studies are required to resolve these issues.

Conclusion

The results of this meta-analysis confirm that patients with SSc and PH have a higher risk for poor outcomes. PH should be seen as a red flag for an increased risk of mortality and physicians should strive to diagnose SSc-associated PH early, so that early treatment may be initiated.

Abbreviations

PH: Pulmonary hypertension; SSc: Systemic sclerosis; PAH: Pulmonary arterial hypertension; PAWP: Pulmonary artery wedge pressure; LHD: Left heart disease; ILD: Interstitial lung diseases; PVOD: Pulmonary veno-occlusive disease; CTEPH: Chronic thromboembolic pulmonary hypertension; RHC: Right heart catheterization; PRISMA: Preferred Reporting Items for Systemic Reviews and Meta-Analyses; MeSH: Medical subject headings; RR: Risk ratio; OR: Odds ratio; CI: Confidence interval; PAP: Pulmonary artery pressure; RV: Right ventricular; DLCO: Diffusing capacity of the lungs for carbon monoxide; ECG: Electrocardiogram; HRCT: High-resolution computed tomography; V/Q: Ventilation/Perfusion; lcSSc: Limited cutaneous systemic sclerosis; dcSSc: Diffuse cutaneous systemic sclerosis.

Supplementary Information

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Additional file 1: Material S1. PRISMA 2009 checklist. PRISMA checklist.

Additional file 2: Material S2. Results of quality assessment using the Newcastle–Ottawa Scale for cohort studies. Newcastle–Ottawa Scale.

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Author contributions

AX: Conceptualization (lead); review and editing (equal). QL: writing—original draft (lead); review and editing (equal). JZ: review and editing (equal); writing—original draft (supporting). YC: review and editing (equal). QX: review and editing (equal). ZH: review and editing (equal). SZ: review and editing (equal). ZS: review and editing (equal). HC: review and editing (equal). YZ: review and editing (equal). HC: review and editing (equal). SS: review and editing (equal). All authors read and approved the final manuscript.

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Availability of data and materials

All data are fully available without restriction.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Rheumatology and Immunology, Nanchong Central Hospital, The Affiliated Nanchong Central Hospital of North Sichuan Medical College, 97 Renmin South Road, Shunqing District, Nanchong, Sichuan, China. [2]Inflammation and Immunology Key Laboratory of Nanchong, Nanchong, Sichuan, China.

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