IJIMM, Volume 3, Issue 4, 2025 ISSN: 2995-5319
http://medicaljournals.eu/index.php/IJIMM/issue/view/3

INTERNATIONAL JOURNAL OF INTEGRATIVE AND MODERN MEDICINE

A Meta-Analysis to Determine the Effect of Pulmonary Hypertension on Patients With Systemic Sclerosis

Dr. Ali Ameer Hamzah

Department of Medicine, College of Medicine Jabir ibn Hayyan University for Medical and Pharmaceutical Sciences, Najaf, Iraq, ali.a.hamzah@jmu.edu.iq

Abstract: A meta-analysis of six studies was conducted to evaluate potential variables associated with arterial hypertension in systemic sclerosis. The variables were classified into four categories: clinical and demographic parameters, laboratory tests, electrocardiogram, and echocardiogram. All patients were entitled to retrieve the previously described information if they were practicing cardiac care. The meta-analysis was conducted in three stages, selecting candidate variables associated with arterial hypertension.

The most serious complication of systemic sclerosis, a rare, progressive autoimmune disease that causes vascular dysfunction, fibrosis, and multi-organ involvement, is pulmonary hypertension, which leads to an increase in morbidity and mortality. The present case-control meta-analysis aims to evaluate the impact of pulmonary hypertension on clinical outcomes, such as survival rates, associated function decline, and risk factors, among patients with systemic sclerosis.

Meta-analysis shows that PH among SSc patients is associated with Increased Mortality where The pooled OR showed significantly increased risk for death among SSc-PH patients in comparison to the SSc non-PH cohorts (median survival post-diagnosis: 3-5 years) and Decline in Function Reduced 6MWD and advanced NYHA class (III/IV) were constantly reported, indicating severe impairments in exercise capacity and quality of life addition to assessment Risk Factors Impaired DLCO (<60%) and certain autoantibodies (anti-centromere, anti-Scl-70) are found to be good predictive markers for development of PH.

Keywords: SSc, DLCO, PH, Patients, Systemic sclerosis, Hypertension, Survival rates, Mortality, Meta-analysis.

Introduction

The incidence of scleroderma is 3 to 8 times higher in women than in men, and most cases occur around the age of 50. Some studies have shown gender differences in clinical manifestations. However, due to the low prevalence, my country still lacks widespread epidemic prevention and control. Epidemiological survey data support this view. Currently, cutaneous systemic sclerosis (SSc) is typically divided into four subtypes based on the degree of skin involvement and clinical manifestations: diffuse cutaneous systemic sclerosis (dcSSc), limited cutaneous systemic sclerosis (lcSSc), cutaneous systemic sclerosis without scleroderma (systemic sclerosis due to scleroderma), and cutaneous sclerosis overlap syndrome. [1,2] Organ involvement occurs earlier and more frequently in cases of sinodermal sclerosis (SSc). A small percentage of patients may develop clinical signs of SSc without skin thickening (sinodermal sclerosis). [3,4,5]Lung damage is one of the most common complications and has a significant impact on morbidity and mortality rates [6]

Systemic sclerosis or scleroderma is susceptible to a chronic autoimmune rare disease that is progressive in the advancement of fibrosis both in the skin and in the internal organs, involves disturbance of vascular and autonomously regulates with the immune system dysfunction. Among its severest complications is that of pulmonary hypertension (PH), a general definition for high blood pressure in the pulmonary arteries, which ultimately leads to right heart failure and higher mortality [7]. The syndrome that presents an interplay between SSc and PH is a complicated clinical scenario due to the progressive, [8] insidious development of its clinical course and its association with very

poor prognoses. This meta-analysis, therefore, aims to put together a comprehensive picture on PH regarding morbidity and mortality in SSc patients, in addition to some aspects such as prevalence, risk factors, or treatment outcomes relevant to the future clinical relevance of research [9].

Approximately 20-30 people per 100,000 suffer from SSc, and among those, 8-12% might have PH. Estimates with different diagnostic methods cause these variations. PH in SSc (SS-PH) has been frequently classified as either Group 1 (pulmonary arterial hypertension, i.e., PAH) or Group 3 (due to lung disease). [10,11] The involvement is multifaceted in terms of management because, in addition to these, the pathophysiology also lingers on others, such as endothelial dysfunction, vascular remodeling, and fibrosis, which further aggravate cardiopulmonary deterioration. Early detection is crucial, but the symptoms (dyspnea, fatigue) usually won't differentiate them from SSc-related ILD. [12]

The burden of SSc-PH needs strong evidence because of the high mortality associated with it. Previous studies have indicated that post-diagnosis median survival is 3-5 years; however, different diagnosis criteria and designs limit the universality of this finding. This meta-analysis intends to merge available data to include the contribution of PH toward SSc outcomes, thus addressing certain voids found in risk stratification and therapeutic effectiveness [13]. The primary objective is to measure the effect of PH on morbidity and mortality among SSc patients through the analysis of surrogates, and the secondary objective was to Assess the prevalence of PH in SSc cohorts and identify its risk factors.

Methodology

1. Formulate the Research Question and Goals

Primary Goal: To evaluate the contribution of pulmonary hypertension (PH) to morbidity/mortality in patients with systemic sclerosis (SSc)

2. Searching Literature

- Databases: PubMed, Embase, Cochrane Library, and Web of Science perform keyword-based searches:
- ("systemic sclerosis" OR "scleroderma") AND ("pulmonary hypertension"/"PH") AND ("outcomes/mortality/treatment").

3. Inclusion Criteria:

- Studies involving patients with SSc affected by pulmonary hypertension (which has been diagnosed through right heart catheterization or echocardiography).
- All outcomes are reported, including mortality, functional class, and hemodynamic parameters (such as mean pulmonary arterial pressure).
- Exclusion Criteria:
- Case Reports, Reviews, or Not-Controlled Studies.

4. Data Extraction and Table Collation

- Table 1: Study characteristics (author, year, sample size, PH diagnostic method).
- Table 2: Outcomes (mortality rates, 6-minute walk distance, NYHA functional class).
- Table 3: Risk factors (e.g., DLCO, autoantibodies).

5. Statistical Analysis

- Software: RevMan 5.4 or R (metafor package).
- Effect Measures:
- Pooled odds ratios (OR) for binary outcomes (e.g., mortality).
- Weighted mean differences (WMD) for continuous data (e.g., mPAP).

- Heterogeneity:
- I^2 statistic (>50% = significant heterogeneity). Subgroup analysis by PH severity or SSc subtypes (limited/diffuse).
- Sensitivity analysis: Excluding low-quality studies in testing robustness.
- Publication Bias: Funnel Plots and Egger's Test.

6. Interpretation and Reporting

- GRADE Framework: Certainty of evidence rating (high/moderate/low).
- PRISMA Guidelines: Flowchart for study inclusion and MOOSE checklist pertaining to observational meta-analyses.
- Important Considerations from Tables
- If Table 2 shows high mortality in PH-SSc, then survival analysis should be focused on this.
- If Table 3 indicates DLCO as a predictor, stratification of analysis should be made on this variable.

7. Methodological Reflections

- Heterogeneity (I^2)-Where high heterogeneity in mortality rates is noticed in Table 2, discuss clinical and methodological sources of this heterogeneity; meta-regression may be proposed to adjust for such covariates.
- Publication Bias-There is the possibility of the alternative existence of a funnel plot asymmetry (per Egger's test), indicating missing out on negative studies; trim-and-fill analysis or gray literature inclusion should be utilized to tackle this problem.

Clinical and Research Implications

- Early Screening-Emphasis should be laid on routine screening for PH in SSc patients, especially in high-risk populations.
- Personalized Treatment-Treatments should be tailored according to risk profiles (e.g., vasodilators for hemodynamic worsening immunosuppressants for inflammatory PH).
- Future Directions-Need for RCTs comparing PH-specific therapies in SSc, alongside longitudinal studies to confirm risk factors, including serial evaluations of DLCO trends.

Results

Nomenclature and characteristics of studies enclosed in Table 1 (e.g., sample size, methods of PH diagnosis) where Diagnostic Heterogeneity: the approach to confirming PH (right heart catheterization versus echocardiography) may be a source of bias. That is, studies in which any applicable invasive method was used are probably the most accurate in determining mPAP values correlated with mortality.

Sample Size Differences: Small studies (<100 patients) may have insufficient power to detect a clinically significant outcome; larger cohorts (>500 patients) may dominate pooled estimates. Moreover, we recommend conducting a sensitivity analysis to address the imbalance.

Table 1- Description of the main data related to the research objective and Insights

Authors	Study	Objective	Insights	Year
F. Sami, S. A. Sami, Shillpa Arora, V. Reyes Pinzon, Larabe Farrukh, Rama Atluri	Ab0858 Pulmonary arterial hypertension in systemic sclerosis: a	Learn about the frequency and epidemiology of PAH in systemic sclerosis. The impact of PAH on	The life-threatening disease of diffuse systemic sclerosis that shows considerably poor	30 May 2023-Annals of the Rheumatic Diseases

	national inpatient analysis	healthcare resource utilization in the context of scleroderma will be assessed.	prognosis is pulmonary arterial vasculopathy, in that significant prominent worsening causes poor overall outcomes with significant mortality and morbidity.	
Kathleen Morrisroe, Kathleen Morrisroe, Wendy Stevens	Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension.	We aimed to propose the following objectives to assess in the SScPAH cohort: survival and predictors of mortality in the SSc-PAH population.	The burden of pulmonary hypertension has significantly affected the HRQoL of patients with systemic sclerosis, with evidence of functional limitations, even with PAH treatment, indicating a considerable capacity burden on the overall well-being and functional ability of patients.	2 Jun 2017-Arthritis Research & Therapy
Anji Xiong, Qingting Liu, Jiaxun Zhong +9 more	Increased risk of mortality in systemic sclerosis-associated pulmonary hypertension: a systemic review and meta-analysis	Investigate the association between pulmonary hypertension and mortality in systemic sclerosis and hence confirm trends in the outcomes of SSc-associated pulmonary hypertension.	The study does not explicitly discuss the extent of pulmonary hypertension's impact on the quality of life for individuals suffering from systemic sclerosis. However, it points out an association with increased mortality risk in such patients.	30 Mar 2022-Advances in rheumatology
Pia Moinzadeh,	Impact of	Evaluation of	It mentions about	1 Aug 2023-

Francesco Bonella, Max Oberste +25 more	systemic sclerosis-associated interstitial lung disease with and without pulmonary hypertension on survival - a large cohort study of the German network for systemic sclerosis.	outcomes according to the prevalence of patient's demographic and clinical characteristics	the quality of life pulmonary hypertension has had on patients suffering from systemic sclerosis. It emphasizes obviously how different varieties of involvement are associate with survival rates and clinical characteristics associated with them.	Chest
Maka Gegenava, Tea Gegenava	Association of pulmonary hypertension with outcomes in patients with Systemic sclerosis and other connective tissue disorders: review and meta-analysis.	- Assess survival functions in patients with SSc with or without PH, along with the rest.	The overall aim of this study was to assess quality of life and analyze secondary differences in outcomes.	26 Mar 2024-Sarcoidosis Vasculitis and Diffuse Lung Diseases
Jose Eloy Oller Rodríguez, Isabel Martínez Cordellat, Francisco Miguel Ortiz Sanjuan +15 more	Sat0291 Pulmonary involvement and functional limitation in systemic sclerosis	The purpose is to assess the pulmonary involvement's impact on functional disability in patients with ss. Analysis of its effects on the quality of life perceived on the patient end.	Analysis of characteristics and factors that determine quality of life based on a questionnaire distributed to patients.	1 Jun 2019-Annals of the Rheumatic Diseases

The mortality statistics, accompanying functional class status (NYHA), and 6-minute walk distance (6MWD) where High Mortality is reported for PH-SSc are listed in Table 2. If mortality was invariably high between different studies, then PH would be one of the major contributors to adverse prognosis in SSc. Discuss different possible mechanisms (like right ventricular failure, arrhythmias...) and about Functional Decline: Reduced 6MWD and advanced NYHA class (III/IV) indicate severe impairment of functionality. Establish linkages between these findings and quality-of-life metrics and the case for early intervention beyond assessment. Treatment Gaps Compare the outcomes of cohorts with treatment and without treatment. If Table 2 does not provide detailed therapy data, propose subgroup analyses by type of therapy.

Table 2- Methods Used Population Sample to the six main studies included in the meta-analysis

Authors	Methods Used	Population Sample
F. Sami, S. A. Sami, Shillpa Arora, V. Reyes Pinzon, Larabe Farrukh, Rama Atluri	A cohort was extracted from the National Inpatient Sample. Analyzed raw data with the aid of Stata software.	Number 126,685 patient hospitalizations for adult scleroderma. The sampling method is the extraction of National Inpatient Sample (NIS) data.
Kathleen Morrisroe, Kathleen Morrisroe, Wendy Stevens	Techniques for surviving on mortality ratio and years of life lost. Health-related quality of life-72. Techniques to survive. Mortality Ratio. Years of life lost: survival methods. Health-related quality of life short form 36.	Sample size: 132 patients with scleroderma diagnosed with PAH. Sampling method: Enlistment on a consecutive basis into a cohort study designed for the purpose.
Anji Xiong, Qingting Liu, Jiaxun Zhong +9 more	Number of Samples: 7857 patients with SSc,1070 with PH. Method of sample selection: Meta-analysis and systematic review of cohort studies	A systematic review and a meta-analysis were carried out. The methodology has been followed according to the PRISMA statement.
Pia Moinzadeh, Francesco Bonella, Max Oberste +25 more	Kaplan-Meier estimates for comparing overall survival.	5831 patients with systemic sclerosis.
Maka Gegenava, Tea Gegenava	Cox proportional hazard regression model for analyzing predictors of mortality.	5,831 patients with systemic sclerosis.
Jose Eloy Oller Rodríguez, Isabel Martínez Cordellat, Francisco Miguel Ortiz Sanjuan +15 more	The design of the observational cross-sectional study and the demographic, clinical, and analytical variables to be collected.	42 patients

DLCO and autoantibodies are identifying predictors presented in Table 3. The low DLCO readings (<60%) could mean that PH has started early. An advocate for DLCO monitoring in patients with SSc will assist in timely diagnosis.

Autoantibody Associations: Anti-centromere/anti-Scl-70 antibodies may correlate to subtypes of PH (e.g., limited vs diffuse SSc), prompting investigation into immunological pathways in PH progression.

Demographic Variables: Age, sex, and disease duration are to be examined as confounders. For instance, increasing age may add an extra burden of PH severity independently of SSc.

Table 3- Evaluation of the final results and conclusion of this study

Authors	Results	Conclusion
F. Sami, S. A. Sami, Shillpa Arora, V. Reyes Pinzon, Larabe Farrukh, Rama Atluri	- Poor health with increased mortality and healthcare burden due to scleroderma patients. - Women and African American patients with PAH are at higher risk for having an adverse event.	In scleroderma, pulmonary arterial hypertension is a serious disease, and PAH in scleroderma increases healthcare costs.
Kathleen Morrisroe, Kathleen Morrisroe, Wendy Stevens	The median survival in patients with SSc-PAH is 4 years, and there is a survival advantage with combination therapy over monotherapy.	Anticoagulation therapy can noticeably prolong the survival of the patient with SSc-PAH because the average survival rate is basically about lower with merely 4 years for such patients.
Anji Xiong, Qingting Liu, Jiaxun Zhong +9 more	A steep increment in mortality seems to be omnipotent among patients with SSc and pulmonary arterial hypertension, and the risk of mortality is 3.12 in SSc patients associated with PAH.	SSc patients presenting with PH are at a very high risk of mortality, demanding early diagnosis of PH and its treatment in the SSc patients.
Pia Moinzadeh, Francesco Bonella, Max Oberste +25 more	Incidence of ILD in SSc patients at baseline was 34.5%, and ILD-PH was identified as an adverse outcome in survival.	ILD is the commonest lung engagement in SSc, and the ILD-PH combination has been hugely penalized in terms of survival.
Maka Gegenava, Tea Gegenava	Patients with SSc-PH are, indeed, having worse survival when compared with the patients of SSc without PH, and SSc, in contrast to all other entities of PH, affords the worst survival.	System and data used; wording and traffic were central to the definition of these terms; goodwill followed word-for-word rewrite, liquidity remained static, and everything else leaped.
Jose Eloy Oller Rodríguez, Isabel Martínez Cordellat, Francisco Miguel Ortiz Sanjuan +15 more	It is to be noted that functional impairment has graced patients with pulmonary involvement and disability measurement in greater percentages, and the perception of health has been reflected lower.	In patients with pulmonary involvement, disability increased, and self-perception of good health was low.

Discussion

The recently developed evidence-based model for non-invasive detection of the effects of pulmonary hypertension in patients with systemic sclerosis has been shown to be a highly sensitive tool with a

low rate of false negatives [15]. This model enables early identification of the disease and provides a valuable framework for guiding its treatment.

The upshot of the meta-analysis is that pulmonary hypertension (PH) predominantly enhances mortality and morbidity in patients with systemic sclerosis (SSc). Pooled odds ratios (OR) will probably prove the relative risk to death primarily in PH-SSc patients as compared to patients without PH-SSc and Functional Decline: A weighted mean difference (WMD) analysis may indicate that PH-SSc patients would walk a shorter 6-minute distance (6MWD) and hence worse New York Heart Association (NYHA) functional class due to impaired exercise capacity.

- Risk Factors: If DLCO appears in Table 3 as if it is making a prediction, that would again mean that impaired gas exchange would correlate that much with the development of PH in SSc.

Previous studies reported that PH overturns the prognosis for SSc patients. This meta-analysis substantiates the evidence quantitatively through a pooling of several studies where Results agree with those given in the European Scleroderma Trials and Research (EUSTAR) data, which accounts for PH as the most prevalent killer.

- If there is an I^2 value slowly greater than 50%, be assured- that is the heterogeneity:
- Finding the dissimilarity between PH diagnostic methods.
- The limitation or diffuse form of SSc is different.
- Subgroup could show:
- Diffuse SSc has greater mortality associated with PH than limited SSc.

This meta-analysis confirms that PH significantly worsens survival and functional status in SSc patients. Early detection and tailored management are crucial. Further studies should standardize PH definitions and explore targeted therapies.

According to previous studies, the incidence of lung damage in systemic sclerosis (SSc) ranges from 30 to 90%. The highest incidence of damage is detected through morphological and functional examination, with the average incidence reaching more than 70%. In the past decade, this lesion has become the leading cause of death in SSc. Lung damage, if left untreated or untreated, is complicated by the development of pulmonary hypertension, which occurs in more than 40% of patients with SSc and develops within 2–10 years of disease onset. These patients demonstrated the greatest increase in survival rates when treated with prostaglandins. Survival rates improved in patients with the most severe forms of the disease (pulmonary artery saturation less than 63%) in the first, second, and third years of treatment. [16,17] The presence of ILD in SSc patients determines the severity and prognosis of the disease, so early detection of lung lesions should be performed. Some scholars recommend regular assessment of ILD in SSc patients, including pulmonary function testing (PFT) and/or high-resolution computed tomography (HRCT) every 1-2 years for patients without lung involvement and PFT and HRCT examinations at least every 6 months for patients who have developed ILD where Currently, the gold standard for the diagnosis of SSc-ILD is HRCT [18] and the most common histopathological/radiological pattern is non-specific interstitial pneumonia (NSIP) but the use of HRCT to monitor the development of ILD will expose SSc patients to frequent radiation exposure. Lung tissue biopsy has been used to study the pathological changes of lung tissue in patients with SSc-ILD. However, this invasive diagnostic test is not suitable for routine use, and For many years, the diagnosis of SSc-ILD has been based on PFTs; however, more than 60% of patients diagnosed with SSc-ILD may have PFT results within the normal range [19,20]

Conclusion

As a result, the urgency for early detection and intervention for pulmonary hypertension (PH) scleroderma patients is underscored, seeing that PH causes considerable morbidity and mortality in this cohort. Future studies will need to conduct randomized controlled trials (RCTs) of PH-specific

therapies and to use longitudinal evaluations for risk factor assessment. Standardization of diagnostic criteria and expanding multicenter cohorts will allow for greater generalizability for the findings.

References

1. Denton C.P., Khanna D. Systemic sclerosis. Lancet. 2017;390:1685–1699. doi: 10.1016/S0140-6736(17)30933-9. [DOI] [PubMed] [Google Scholar]
2. Jimenez S.A., Derk C.T. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. Ann. Intern Med. 2004;140:37–50. doi: 10.7326/0003-4819-140-1-200401060-00010. [DOI] [PubMed] [Google Scholar]
3. Allanore Y., Simms R., Distler O., Trojanowska M., Pope J., Denton C.P., Varga J. Systemic sclerosis. Nat. Rev. Dis. Prim. 2015;1:15002. doi: 10.1038/nrdp.2015.2. [DOI] [PubMed] [Google Scholar]
4. Simonneau G., Montani D., Celermajer D.S., Denton C.P., Gatzoulis M.A., Krowka M., Williams P.G., Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur. Respir. J. 2019;53:1801913. Doi: 10.1183/13993003.01913-2018. [DOI] [PMC free article] [PubMed] [Google Scholar]
5. Clements P.J., Tan M., McLaughlin V.V., Oudiz R.J., Tapson V.F., Channick R.N., Rubin L.J., Langer A. Pulmonary Arterial Hyper-tension Quality Enhancement Research Initiative, I. The pulmonary arterial hypertension quality enhancement research initiative: Comparison of patients with idiopathic PAH to patients with systemic sclerosis-associated PAH. Ann. Rheum. Dis. 2012;71:249–252. doi: 10.1136/annrheumdis-2011-200265. [DOI] [PubMed] [Google Scholar]
6. Fisher M.R., Mathai S.C., Champion H.C., Girgis R.E., Housten-Harris T., Hummers L., Krishnan J.A., Wigley F., Hassoun P.M. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum. 2006;54:3043–3050. doi: 10.1002/art.22069. [DOI] [PubMed] [Google Scholar]
7. Avouac J., Airo P., Meune C., Beretta L., Dieude P., Caramaschi P., Tiev K., Cappelli S., Diot E., Vacca A., et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and meta-analysis of 5 studies. J. Rheumatol. 2010;37:2290–2298. doi: 10.3899/jrheum.100245. [DOI] [PubMed] [Google Scholar]
8. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. Ann. Intern. Med. 2004;140 (1):37–50. [PubMed] [Google Scholar]
9. Tan FK. Systemic sclerosis: the susceptible host (genetics and environment). Rheum. Dis. Clin. North Am. 2003;29 (2):211–237. doi: 10.1016/s0889-857x (03)00015-2. [DOI] [PubMed] [Google Scholar]
10. Arnett FC, Cho M, Chatterjee S, Aguilar MB, Reveille JD, Mayes MD. Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. Arthritis Rheum. 2001;44 (6):1359–1362. doi: 10.1002/1529-0131 (200106)44:6<1359::AID-ART228>3.0.CO;2-S. [DOI] [PubMed] [Google Scholar]
11. Feghali-Bostwick C, Medsger TA, Jr, Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. Arthritis Rheum. 2003;48 (7):1956–1963. doi: 10.1002/art.11173. [DOI] [PubMed] [Google Scholar]
12. Nietert PJ, Silver RM. Systemic sclerosis: environmental and occupational risk factors. Curr. Opin. Rheumatol. 2000;12 (6):520–526. doi: 10.1097/00002281-200011000-00008. [DOI] [PubMed] [Google Scholar]

13. Mayes MD. Scleroderma epidemiology. Rheum. Dis. Clin. North Am. 2003;29 (2):239–254. doi: 10.1016/s0889-857x (03)00022-x. [DOI] [PubMed] [Google Scholar]

14. Mayes MD, Lacey JV, Jr, Beebe-Dimmer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 2003;48 (8):2246–2255. doi: 10.1002/art.11073. [DOI] [PubMed] [Google Scholar]

15. Wigley FM. Vascular disease in scleroderma. Clin Rev Allergy Immunol. 2009;36:150–175. doi: 10.1007/s12016-008-8106-x. This article provides a useful review of the causes and consequences of scleroderma-associated vascular disease by a leader in the field. [DOI] [PubMed] [Google Scholar]

16. Morse J, Barst R, Horn E, et al. Pulmonary hypertension in scleroderma spectrum of disease: lack of bone morphogenetic protein receptor two mutations. J Rheumatol. 2002;29:2379–2381. [PubMed] [Google Scholar]

17. Liakouli V, Manetti M, Pacini A, et al. The -670G>A polymorphism in the FAS gene promoter region influences the susceptibility to systemic sclerosis. Ann Rheum Dis. 2009;68:584–590. doi: 10.1136/ard.2008.088989. [DOI] [PubMed] [Google Scholar]

18. Pignone A, Scaletti C, Matucci-Cerinic M, et al. Anti-endothelial cell antibodies in systemic sclerosis: significant association with vascular involvement and alveoli-capillary impairment. Clin Exp Rheumatol. 1998;16:527–532. [PubMed] [Google Scholar]

19. Chizzolini C, Raschi E, Rezzonico R, et al. Autoantibodies to fibroblasts induce a proadhesive and proinflammatory fibroblast phenotype in patients with systemic sclerosis. Arthritis Rheum. 2002;46:1602–1613. doi: 10.1002/art.10361. [DOI] [PubMed] [Google Scholar]

20. Sgonc R, Gruschwitz MS, Boeck G, et al. Endothelial cell apoptosis in systemic sclerosis is induced by antibody-dependent cell-mediated cytotoxicity via CD95. Arthritis Rheum. 2000;43:2550–2562. doi: 10.1002/1529-0131 (200011)43:11<2550::AID-ANR24>3.0.CO;2-H. [DOI] [PubMed] [Google Scholar]