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Association of pulmonary hypertension with outcomes in patients with Systemic sclerosis and other connective tissue disorders: review and meta-analysis

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Abstract. *Background and aim:* Pulmonary hypertension (PH) is a frequent complication of connective tissue disorders (CTDs), with a major impact on the prognosis of the disease. The aim of our study was to perform a systemic review and meta-analysis of published literature evaluating survival function in patients with systemic sclerosis (SSc) with and without PH and to compare survival function between patients with SSc, systemic lupus erythematosus (SLE), other CTDs, and conditions associated with PH. *Methods:* The established protocol of the Cochrane Collaboration Steps and meta-analysis of observational studies in epidemiology recommendations (MOOSE) were used. *Results:* 7 studies, including 1470 SSc-PH patients and 1368 SSc patients without PH, and 4 studies, including 108 SLE-PH patients and 1288 SLE patients without PH, assessed survival function were selected. Six studies (including 777 SSc, 249 SLE, 90 idiopathic pulmonary arterial hypertension -IPAH (2 papers selected for the study with the old terminology of idiopathic pulmonary hypertension-IPH and idiopathic primary pulmonary hypertension IPP) and 29 primary Sjogren's syndrome patients) comparing survival function in different subgroups of patients with confirmed PH were included. SSc patients with PH showed the worst survival as compared to SSc patients without PH [OR (95% CI) 3.70 (2.42–5.67); p<0.00001]. The same pattern was observed in patients with SLE. SSc patients with PH were characterized by lower survival function compared to other reasons for PH, including SLE [OR (95% CI) 2.76 (1.95–3.91); p<0.00001]. *Conclusions*: Patients with SSc-PH are characterized by significantly lower survival function as compared to SSc patients without PH. Among the different entities of PH, SSc shows the worst survival, underlining prognostic significance of detection and evaluation of PH according to the currently established approach.

Key words: Pulmonary hypertension, Systemic Sclerosis, Systemic lupus erythematosus

Introduction

Pulmonary hypertension (PH) is characterized by a high prevalence and increased mortality in patients with connective tissue disorders (CTD). Pulmonary arterial hypertension (PAH) is the most progressive form of PH, but also other forms of PH occur and CTD patients often suffer from overlap of different forms of PH. CTD-associated PH and its survival rate remain high; however, this has changed significantly over the last few years, considering advanced therapies, improved diagnostic tools, and the implementation of a multi-step approach in the evaluation of pulmonary hypertension. PH is defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, according to the New European Society of Cardiology/European Respiratory Society

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(ESC/ERS) guidelines. This is supported by studies assessing the upper limit of normal pulmonary arterial pressure (PAP) in healthy subjects and by studies investigating the prognostic relevance of increased PAP (1).

Previously published few studies indicated that PAH associated with systemic sclerosis showed worst survival as compared to other entities of CTD(2, 3), however, data about true comparative survival among groups of CTDs is scarce. In patients with CTDs, the mechanism of pulmonary arterial hypertension (PAH) is complex and is characterized by a pulmonary arterial vasculopathy: abnormal proliferation, vasoconstriction, and thrombosis, leading to a subsequent increase in pulmonary vascular resistance (PVR), increased right ventricular (RV) afterload, and right heart failure. Patients with PAH are hemodynamically characterized by precapillary PH in the absence of other causes of pre-capillary PH, such as CTEPH and PH associated with lung diseases. From the 5 groups of pulmonary hypertensions underlined in the current 2022 European Society of Cardiology/ European Respiratory Society (ESC/ERS) guidelines,(1) in SSc patients, SSc-associated PAH (group 1) is more frequently observed, together with PH associated with lung disease or hypoxia (group 3). Patients with SSc may also develop other forms of PH, especially PH associated with left heart disease (SSc-PH-LHD) (group 2).

Systemic lupus erythematosus (SLE) is the second most common reason for CTD-associated PAH and accounts for approximately 5.8% of all patients in Group 1, while SSc-PAH is observed in almost 21% of these patients. In general, studies have shown that overall CTD-PAH is seen in 34% of all cases of Group 1 PAH.(4) Although prevalence of SLE-PAH is not high, it can be associated with poor prognosis (5, 6).

Studies have reported that in patients with primary Sjögren's syndrome (pSS), right heart catheterization shows worse hemodynamic profiles compared to SSc and SLE; however, outcomes in pSS are less commonly associated with PAH (7).

Idiopathic pulmonary hypertension (IPH) and primary pulmonary hypertension (PPH) present in the literature prior to the new guidelines, are no longer used and today referred as idiopathic pulmonary arterial hypertension (IPAH), are also common reasons for PAH.

Aim of our study was to perform review and meta-analysis of published literature evaluating association of PH with outcomes in patients with SSc and SLE, also to perform comparative assessment of PH-associated pooled survival/outcomes among different conditions, previously known to be associated with PH.

Methods

Based on the fact that it is a review and meta-analysis of already published data, new patients were not recruited for the analysis, informed consent was not required, as well as institutional review board's approval was not necessary. Objectives of the study, methods of statistical analysis, literature search strategy, inclusion and exclusion criteria, outcome measurements were defined according to Cochrane Collaboration steps (8). including recommendations for meta-analysis of observational studies in epidemiology (MOOSE) (9). PRISMA flow diagram was used to depicts the flow of information through the different phases of a systematic review.

Literature search criteria

Electronic databases of PubMed MEDLINE, Cochrane Library, and MD Consult were used to obtain sources of published data. A literature search was performed in July 2022, including articles from all regions in English. The search criteria included the following search terms in all possible combinations: "Pulmonary hypertension in SSc", "Pulmonary hypertension in SLE," or "Pulmonary hypertension in CTDs" from January 1, 1995, to March 10, 2022.

Inclusion and exclusion criteria

Inclusion criteria for the studies were defined as follow: (1) original studies with case-control (not case matched) design that compared overall survival function in patients with SSc and SLE with and without PH; (2) original studies with case-control design that compared PH associated survival function between SSc and SLE patients and also between SSc and other CTDs.

The exclusion criteria for the meta-analysis included (1) studies with incomplete general information about PH causes; (2) studies without original

data of measured PH parameters; (3) studies that are published in non- English journals.

In addition, the reference lists of all retrieved articles were manually reviewed. Retrieved citations were screened independently by two authors using the title and keywords of the articles, followed by a full-text review for the final inclusion.

Data extraction and outcomes of interest

The data included in this study were extracted and summarized by two independent authors. Studies were carefully analyzed for survival function in SSc and SLE patients with and without PH, also PH-associated survival function was compared between SSc and other entities. As a primary analysis, we evaluated survival function in SSc and SLE patients with and without PH in reported studies and, as a next step, analyzed PH-associated survival function between SSc, SLE, and other conditions with PH.

Quality assessment and statistical analysis

All the meta-analyses were performed using Review Manager 5.0 (Cochrane Collaboration, Oxford, UK) and SPSS for Windows version 23.0 (IBM, Armonk, New York). The standard mean difference and odds ratio (OR) were used to compare continuous and dichotomous variables, respectively. All results were reported with 95% confidence intervals (CIs). Statistical heterogeneity between studies was formally assessed using the chi-square test with significance set at $p < 0.10$, and heterogeneity was quantified using the inconsistency index (I2) statistic. Heterogeneity (a lack of homogeneity) was considered to be significant with an $I^2 \geq 50\%$. The random-effects model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was adopted (10, 11). Sensitivity analysis was performed using both models. Publication bias was performed by Egger's test and the significance was considered if $p < 0.05$ was achieved.

Results

A total of 2114 papers were collected according to our searching criteria. Of those, 2097 publications were unrelated to our purpose of meta-analysis and therefore excluded from the study. The flow diagram of the selection process is shown in Figure 1. Finally, from selected 17 studies, 7 studies including 1470 SSc patients with PH and 1368 SSc patients without PH, also 4 studies including 108 SLE patients

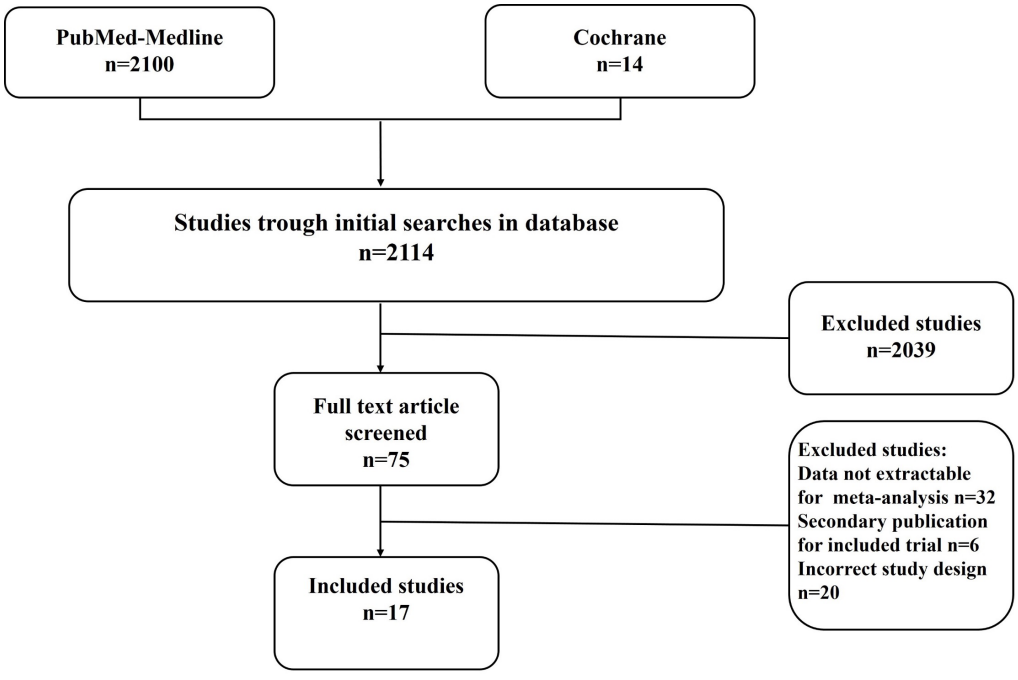

Figure 1. Flow diagram of studies identified, included, and excluded.

with PH and 1288 SLE patients without PH and assessed survival function were selected. We also performed meta-analysis of 6 studies (including 777 SSc, 249 SLE, 90 IPAH (41 idiopathic PH (25), 49 primary PH patients (26)) and 29 primary Sjogren's syndrome patients), comparing PH- associated survival function in different subgroups of patients. Selected studies met the predefined inclusion criteria and were used for this systemic review. All studies in our meta-analysis were case-control studies (level of evidence 3b) with high quality (quality score above 6). Firstly, we performed meta-analysis for following abnormalities: compared prevalence of outcomes in the groups of SSc and SLE patients with and without PH. Then we compared PH-associated outcomes between SSc and different entities, previously known with high prevalence of PH.

Meta-analysis for SSc, SLE and other entities were heterogeneous (I^2 > 50 %). Thus, a random model was used for the analysis.

Survival function in SSc and SLE patients with and without pulmonary hypertension

PH Survival function in SSc patients were reported in 7 papers including 1470 SSc patients with PH and 1368 patients without PH. Median follow-up time was 5 years (IQR: 4-6). The rate of mortality in SSc patients with PH was 21.4% (315/1470) vs. 11.5% (158/1365) in SSc patients without PH and showed 3.7 times higher risk in SSc-PH patients as compared to SSc patients without PH (OR (95% CI) 3.70 (2.42–5.67); p < 0.00001). (Figure 2). Prevalence of PH associated survival function in SLE patients was explored in 4 studies including 108 patients with PH and 1288 SLE patients without PH. Median follow-up time was 8 years (IQR: 4-10). The rate of mortality in SSc patients with PH was 23% (25/108) vs. 2.1% (26/1288) and showed 7 times higher risk of developing outcomes in SLE-PH patients as compared to SLE patients without PH (OR

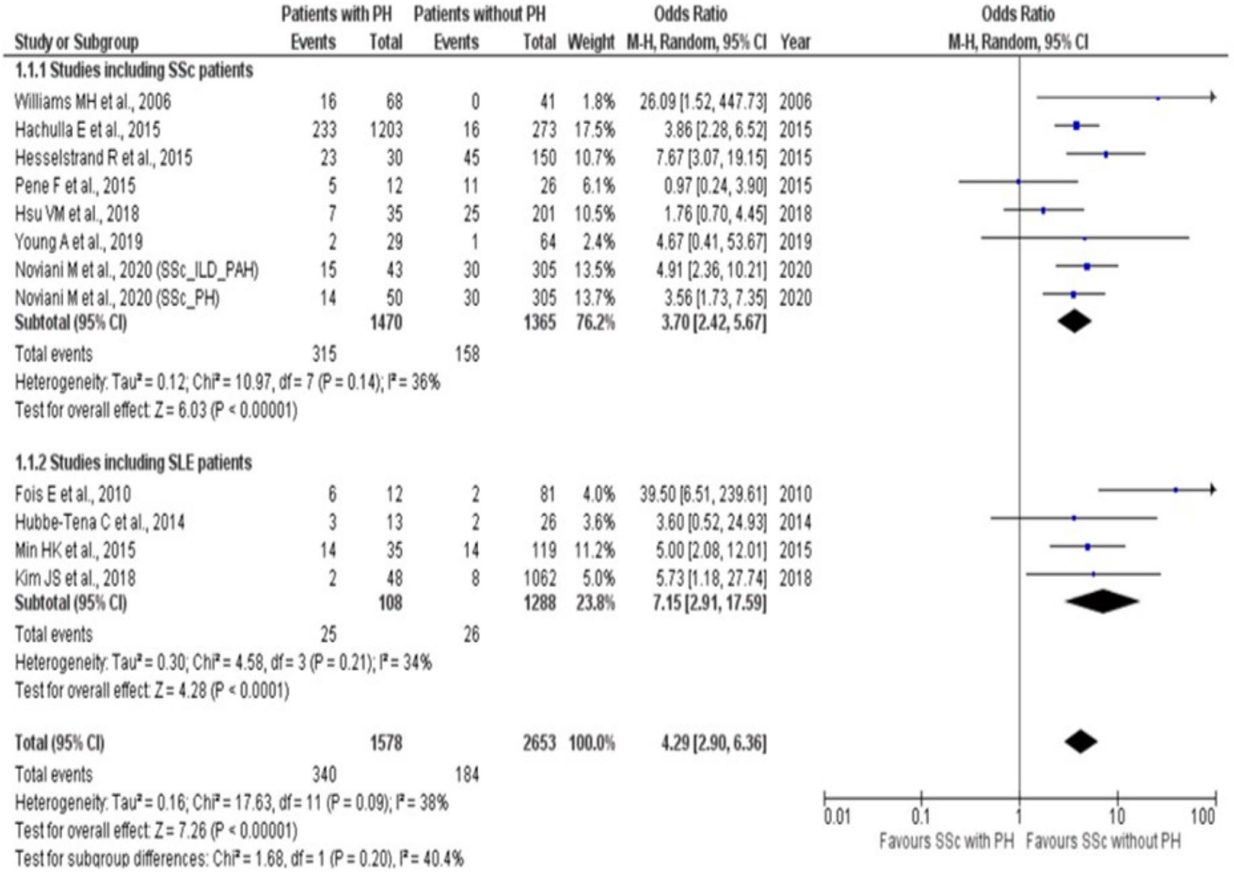

Figure 2. Forest plot and meta-analysis of pulmonary hypertension (PH)-associated survival function in patients with Systemic Sclerosis (SSc) and Systemic Lupus Erythematosus (SLE). *PH, pulmonary hypertension; SLE, Systemic lupus erythematosus; SSc, Systemic sclerosi*

(95% CI) 7.15 (2.91–17.59); p < 0.0001) (Figure 2). Overall, in SSc and SLE patients with PH survival function is low and shows 4.29 times higher risk of worst outcomes compared to SSc and SLE patients without PH (Figure 2).

Comparative assessment of PH associated survival function between SSc and other entities

We performed meta-analysis of 3 studies comparing PH-associated survival function between SSc and SLE patients (the median follow up time 3 years (IQR: 2-4,5)) and observed that PH associated event rate in SSc patients was 33.5% (237/708) vs. 23.6% (59/249) in SLE patients and shows 2.44 times higher risk of worst outcomes in SSc-PH patients as compared to SLE-PH patients (OR (95% CI) 2.44 (1.59–3.77); p < 0.0001) (Figure 3).

Meta-analysis of 3 more studies comparing PH associated survival in between SSc and other entities, commonly known with high prevalence of PH (two studies compared survival in between SSc-PH and idiopathic pulmonary arterial hypertension IPAH groups (included papers selected for the study with the old terminology of IPH and PPH), third study compared SSc-PH survival with primary Sjogren syndrome-pSS associated PH survival), showed that event rate in SSc PH group was 55.4% (66/119) vs. 28.5% (34/119) in non SSc group with almost 3.43 times higher risk of bad outcomes compared to other entities (OR (95% CI) 3.43 (1.92–6.13); p < 0.0001). The median follow-up time for this group was 3 years (IQR: 2-3).

Overall, our analysis shows, that SSc-PH associated survival function is lower than in other groups commonly known to be associated with pulmonary hypertension (OR (95% CI) 2.76 (1.95–3.91); p < 0.00001) (Figure 3).

Discussion

In this study we performed complex meta-analysis of overall 3665 SSc patients, 1645 SLE patients and 119 patients with the other conditions, commonly characterized with PH. We investigated PH- associated survival in SSc and SLE patients,

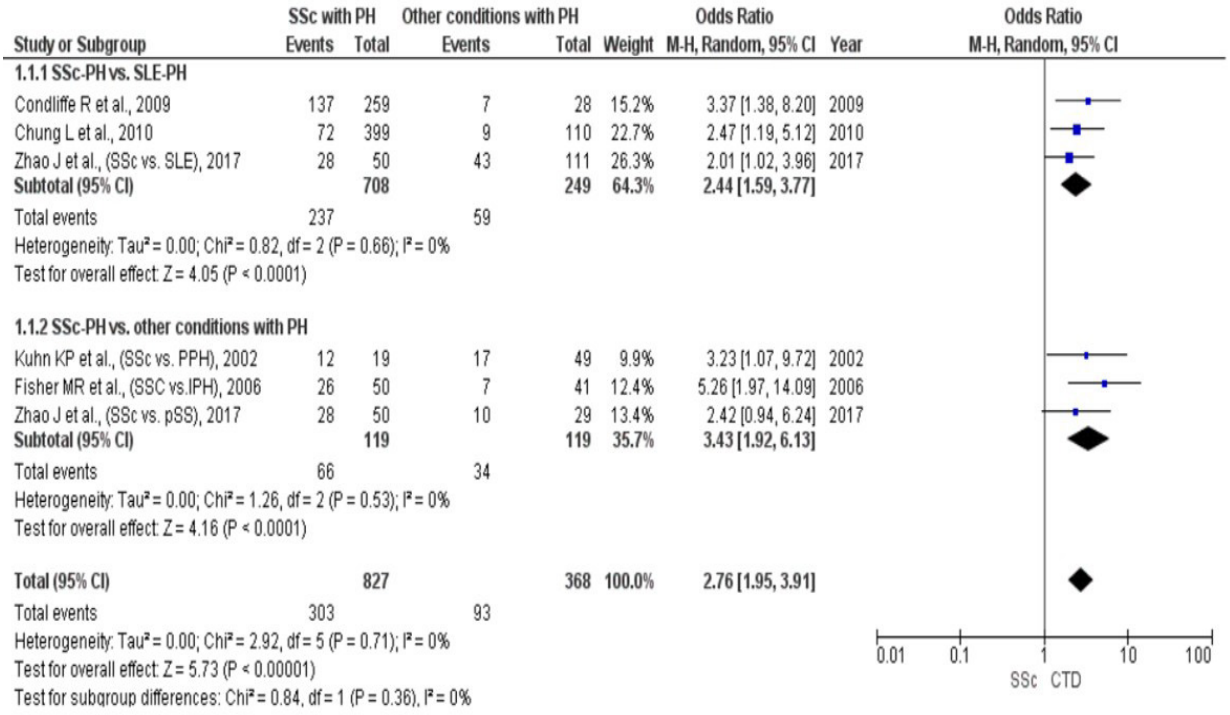

Figure 3. Forest plot and meta-analysis of comparison of pulmonary hypertension (PH)-associated survival function in between patients with Systemic Sclerosis (SSc), other Connective Tissue Disorders (CTDs) and conditions associated with PH. *CTDs, connective tissue disorders; IPH, idiopathic pulmonary hypertension (currently called idiopathic pulmonary arterial hypertension IPAH); PH, pulmonary hypertension; PPH, primary pulmonary hypertension; SSc, systemic sclerosis*

also compared PH associated survival function in between SSc and SLE, also between SSc and other conditions known to be characterized with PH. To the best of our knowledge, it is the first meta-analysis performing comparative assessment of PH-associated survival function within SSc group and between SSc and other conditions commonly characterized with PH. Our study showed that SSc and SLE patients with PH are characterized with worse survival function as compared to SSc and SLE patients without PH. PH associated survival function was lower in SSc patients compared to SLE and other conditions characterized with PH.

Pulmonary hypertension and survival in SSc and SLE patients

PH is a major cause of mortality in SSc and in other CTDs and in general is associated with poor prognosis (12-18). Pulmonary arterial obstructive proliferative vasculopathy and interstitial lung disease associated hypoxia can be a reason of increased precapillary PH in SSc (13, 19) and also in SLE, PH associated with pulmonary veno occlusive disease can be seen in CTDs, thromboembolic complications can be also associated with a precapillary PH, while left heart disease commonly is associated with postcapillary PH (12, 20).

Reported survival function in SSc patients with PH ranges between 40-63%, Including the PHAROS registry, which showed higher overall and 5-year survival (63%) than other SSc-PH cohorts. (21) SSc-PH 5-year survival in REVEAL study was as low as 40%.(22) Our meta-analysis of 7 studies (8 groups) confirmed that in patients of SSc-PH risk of worse outcomes is 3.7 times greater than in SSc patients without PH. In every reported study, including patients with SSc suspected PH on echocardiography was confirmed by the right heart catheterization (RHC).

Age, sex, mixed venous oxygen saturation, and World Health Organization functional class were independent predictors of survival in isolated SSc-PAH (23). R Hesselstrand (15) reported that limited skin involvement, low diffusing capacity of the lung for carbon monoxide (DLCO), high N-terminal pro-brain natriuretic peptide (NTProBNP), increased estimated systolic pulmonary arterial pressure, and the presence of telangiectasias, severe peripheral vascular disease requiring treatment during follow-up was associated with an eightfold increased risk of PAH.

Pulmonary hypertension in SLE patients usually is not clinically severe but can be associated with poor prognosis (24), survival function in SLE-PH is significantly better than in SSc-PH (23) and worse than in idiopathic PAH (4). Our meta-analysis of 4 studies including 1396 SLE patients showed that survival function in SLE-PH patients is inferior compared to SLE patients with no PH. In our study comparing 708 SSc-PH patients to 249 SLE-PH patients (4 studies), we confirmed that survival function is lower in SSc-PH patients and this group is characterized 2.44 times higher risk of poor outcomes compared to SLE-PH patients.

In our study comparing PH associated survival function of IPAH and pSS patients with SSc we showed, that the risk of worse outcome is still higher in SSc-PH patients. Study by Zhao J et al showed that PH associated survival in pSS patients is better than in a SSc-PH group, but worse than in the SLE-PH group.(7) Studies show that PAH associated prognosis in IPAH patients is poor, however has been improved with the implementation of new diagnostic and treatment methods (25). Fisher et al showed that 3 years PH associated survival in SSc was lower than in IPH (currently called IPAH) 48.9% vs. 83.6%. Patients with SSc-PAH were 3.06 times more likely to die than were patients with IPH (IPAH0 (26), left heart disease was more common in SSc patients but was not a predictive of unfavourable outcome in these patients.

Some limitations of this meta-analysis must be acknowledged. All studies included in the present study were case-control studies (not a case-matched), though most of them were of high quality. Studies have shown heterogeneity >50%, this is likely that the significant between-study heterogeneity may be associated with the included studies involving different ages, sexes, races, disease courses, and disease activities of SSc, SLE and other conditions associated with CTDs. Adopting the random effects model may reduce the effect of heterogeneity, but it does not prevent it totally. RHC for the confirmation of PH was performed after the echocardiographic screening for suspected PH in every study including SSc patients and in some selected SLE patients.

Conclusions

Patients with SSc associated PH are characterized with significantly lower survival function as compared to SSc patients without PH. Among different entities of PH, SSc shows worst survival, underlining prognostic significance of detection and evaluation of PH according to the currently established approach.

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Conflict of Interest: Dr. Maka Gegenava and Dr Tea Gegenava do not have commercial associations that might pose a conflict of interest in connection with the submitted article.

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