Prognostic Factors for Survival in Scleroderma Associated Pulmonary Arterial Hypertension

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ABSTRACT. ***Objective***. Identification of prognostic factors for survival in systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) is necessary for appropriate monitoring, interventions, and timely referral for lung transplantation. Our objectives were (1) to identify factors associated with survival in SSc-PAH and (2) to evaluate the methodologic quality of prognostic studies against current standards.

Methods. A systematic review was performed to identify studies evaluating factors associated with survival in SSc-PAH. The methodologic quality of each study was evaluated using a methodologic quality index.

Results. HLA-DRw6 (RR 54.52, p = 0.01), HLA-DRw52 (RR not reported, p = 0.02), initial systolic pulmonary artery pressure (sPAP) > 60 mmHg (HR 3.60, 95% CI 1.42, 9.15), elevated mean right atrial pressure (mRAP) (HR 20.7, p = 0.0001), and shorter time between SSc onset and observed PAH (5.24 vs 9.93 yrs, p < 0.01) were associated with decreased survival. Age > 50 years (HR 2.34, 95% CI 0.54, 10.2), male sex (HR 2.02, 95% CI 0.65, 6.20), limited subtype (HR 2.37, 95% CI 0.68, 8.20), pulmonary fibrosis [Kaplan-Meier (KM) curves, p = 0.3], change in pulmonary vascular resistance (KM curves, p = 0.8), anti-centromere (HR 1.67, 95% CI 0.66, 4.26) and anti-Scl-70 (HR 0.28, 95% CI 0.03, 1.99) antibodies were not definitively associated with survival. Attributes of participants, prognostic factors, and outcome measures were well reported. Study attrition, confounding, and analysis were not well reported.

Conclusion. HLA-DRw52 and -DRw6, initial sPAP > 60 mmHg, mRAP, and shorter time between SSc onset and observed PAH were associated with decreased survival; however, methodologic quality of study reporting was variable. Prognostic factor research is needed using current methodologic standards. (First Release July 1 2008; J Rheumatol 2008;35:1584–90)

Key Indexing Terms:
PROGNOSIS PULMONARY ARTERIAL HYPERTENSION SYSTEMIC SCLEROSIS SCLERODERMA REVIEW

Systemic sclerosis (SSc) is a multisystem disorder characterized by collagen deposition and fibrosis of the skin, blood vessels, and internal organs; with an incidence of 2 to 20 per million per year and a prevalence of 13 to 280 cases per million adults[1-3]. SSc predominantly occurs in females, with a peak incidence rate in the third to fifth decade of life and a 3:1 female to male ratio[1,3]. In a Canadian population of patients attending a scleroderma clinic, survival rates in SSc patients were reported to be 86% at 3 years, 76% at 6 years, and 61% at 9 years[4].

Pulmonary arterial hypertension (PAH) is a well-recognized and significant complication of both limited and diffuse SSc. The prevalence of SSc associated PAH (SSc-PAH) is estimated to be between 10 and 40% depending on the population studied and criteria used for diagnosis[2,5-12]. Within the SSc population, those with PAH have a significantly higher mortality rate than those without PAH[5,8,10,13]. Prior to the availability of epoprostenol and other therapies targeting pulmonary hypertension, the mortality in SSc-PAH patients was high. In a study of 20 patients by Stupi, *et al*[14] mortality of 60% at 2 years was reported, while a study by Koh, *et al* reported a median survival of 12 months in 17 patients with SSc-PAH[15]. Even with current medical therapy, survival remains poor. In a study by Mukerjee, *et al* that prospectively followed 794 patients with SSc-associated PAH from 1998 to 2002, survival was only 81% at 1 year, 63% at 2 years, and 56% at 3 years from the time of diagnosis of PAH[5]. Similarly, a retrospective study of 619 patients with scleroderma found that, compared to those without pulmonary disease, the mortality risk ratio for patients with isolated pulmonary hypertension was 2.9[10].

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The identification of factors that prognosticate survival for those with SSc-PAH is necessary for optimal care of these patients to facilitate appropriate monitoring, timing of therapeutic intervention, and optimal timing for lung transplantation. Screening recommendations are difficult unless population subsets at higher risk can be identified. Knowledge of factors that portend a worse outcome for patients with SSc-PAH may have significant clinical utility. To determine whether prognostic factors have clinical utility or before additional research is undertaken, a review of the current state of knowledge and methodologic rigor is warranted.

We set as our study objectives (1) to systematically review the medical literature to identify factors that prognosticate survival in SSc-PAH and (2), since methodological standards for prognostic studies have changed, to evaluate the methodologic quality of published prognostic studies against current standards[16,17].

MATERIALS AND METHODS

Data sources and searches. Two investigators (JS, SJ) and an information specialist (MS) through the University Health Network Library Services independently performed the literature search. The following keywords with mapping of term to subject heading were used in the database search: (scleroderma or systemic sclerosis) and (pulmonary hypertension or pulmonary arterial hypertension) and (prognosis or prognostic factors or predictor or risk factors). The search was limited to human studies but not limited to English language. The results of the 3 independent searches were compared to ensure completeness.

Ovid Medline (1950 to September, week 2, 2007), EMBASE (1974 to week 37, 2007, inclusive), and Cochrane Database of Systematic Reviews (inception to 2007) were searched. The reference list of selected articles was hand searched for relevant publications.

Study selection. Titles and abstracts were screened to identify studies that evaluate prognostic factors related to survival or mortality in SSc-PAH. Survival or mortality must have been specified as an outcome. Studies that did not report survival or mortality as an outcome and studies that did not evaluate SSc-PAH patients were excluded.

Data extraction and quality assessment. A standardized form was used to abstract author names, citation, population definition, case definition, source population (location and time period), sample size, followup period, outcomes reported, mortality/survival results, study design (case series, retrospective or prospective cohort study, or randomized controlled trial), prognostic factors, and quantitative measure of risk (relative risk, hazard ratio, univariable or multivariable analysis).

All articles included in this study were evaluated for methodologic quality using a critical appraisal index. This index has been specifically developed and validated for the evaluation of the methodologic quality of prognostic studies[16,17]. Each article was evaluated on the reporting of the following domains: study participants, study attrition, prognostic factor measurement, outcome measurement, confounding measurement, and analysis with a Yes/No response option. Two independent reviewers (JS, SJ) used a standardized form for data abstraction. The "category of evidence" as a measure of the strength of evidence was evaluated using the EULAR standardized operating procedures[18].

Data synthesis and analysis. Descriptive statistics were used to characterize the quality of the studies. Inter-rater reliability was evaluated using the kappa statistic. SAS for Windows, version 8.0 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

RESULTS

Search results. Using the same search strategy, the 2 independent investigators identified the same eligible citations: 91 citations in Medline and 2 citations in Embase. Using a more sensitive screening filter, the library services information specialist identified 353 eligible citations: 106 citations in Medline and 247 citations in Embase. No additional citations were identified using the Cochrane Database of Systematic Reviews or hand searching of reference lists. The 353 citations identified by the information specialist included the 93 citations identified by the investigators. Thus the search strategy identified a total of 353 eligible citations. Screening of titles and abstracts resulted in the exclusion of 333 citations, and left 20 articles for full review. Citations were excluded because they were review articles, evaluated prognosis in SSc patients but not SSc-PAH patients, did not include survival as an outcome, or did not evaluate prognostic factors. Of the 20 articles that underwent full review, 15 were excluded that did not identify factors associated with survival in patients with SSc-PAH. Any discrepancies in the exclusion of articles were resolved through consensus. Five publications identified 5 factors that prognosticate survival in SSc-PAH.

Factors associated with survival in SSc-PAH (Table 1). In a retrospective cohort study of patients seen at a tertiary center scleroderma clinic (Toronto, Canada) between 1979 and 1989, human leukocyte antigen (HLA) -DRw52 was associated with poor survival in patients with SSc-PAH ($p = 0.02$, relative risk (RR) not reported)[19]. HLA-DRw6 was also associated with poor survival RR = 54.52, $p = 0.01$[19].

Pulmonary artery pressure (PAP) was associated with survival from time of diagnosis in 2 studies. In a retrospective cohort study of SSc patients attending a tertiary connective tissue disease clinic (London, England) between 1992 and 1997, MacGregor, *et al* demonstrated that an initial systolic PAP > 60 mmHg on echocardiogram conferred a hazard ratio (HR) for death of 3.60 (95% CI 1.42, 9.15)[8]. In a second cohort study from the same center conducted between 1998 and 2002, Mukerjee, *et al* separated patients into 3 groups based on mean PAP, and reported the 3-year survival in patients with a mean PAP < 32 mmHg, 32–44 mmHg, > 45 mmHg as 75%, 61%, and 33%, respectively[5]. An elevated mean right atrial pressure on cardiac catheterization was also associated with poor survival: HR = 20.7, $p = 0.0001$ (95% CI not reported)[5]. The manner in which mean right atrial pressure was categorized in the analysis was not specified.

In a retrospective cohort study of patients with SSc, lupus, and mixed connective tissue disease evaluated at 21 centers in Japan (accrual and followup time period not specified), a shorter mean period of time between onset of SSc and observed PAH was associated with poor prognosis, where non-survivors had a time interval of 5.24 years versus 9.93 years in survivors, $p < 0.01$[20]. "Onset of SSc" was

Table 1. Factors that are and are not associated with survival in SSc-PAH.

Factors	Study Design	Sample Size	Point Estimate	Reference
Factors associated with survival in SSc-PAH				
HLA-DRw52	Retrospective cohort, 1979–1989	16	Association with death in patients with PAH (p = 0.02)	Langevitz[19]
HLA-DRw6	Retrospective cohort, 1979–1989	16	RR = 54.52, p = 0.01	Langevitz[19]
PAP	Prospective cohort, 1998–2002	148	3-yr survival in patients with mPAP < 32 mmHg, 32–44 mmHg, > 45 mmHg was 75%, 61% and 33%. Significant difference between each group (p < 0.01) using Kaplan-Meier curves.	Mukerjee[5]
	Retrospective cohort, 1992–1997	152	Initial sPAP > 60 mmHg HR = 3.60 (95% CI 1.42, 9.15)	MacGregor[8]
mRAP	Prospective cohort, 1998–2002	148	HR = 20.7, p = 0.0001	Mukerjee[5]
Mean period, SSc onset to observed PAH	Retrospective cohort, time period not specified	14	5.24 yrs of non-survivors versus 9.93 yrs for survivors (p < 0.01)	Kasukawa[20]
Factors not definitively associated with survival in SSc-PAH				
Age > 50	Retrospective cohort, 1992–1997	152	HR = 2.34 (95% CI 0.54, 10.2)	MacGregor[8]
Male sex	Retrospective cohort, 1992–1997	152	HR = 2.02 (95% CI 0.65, 6.20)	MacGregor[8]
Limited subtype	Retrospective cohort, 1992–1997	152	HR = 2.37 (95% CI 0.68, 8.20)	MacGregor[8]
	Retrospective cohort, 1975–1992	74	Limited and diffuse SSc subtypes have equally poor survival: 10–20% at 5 yrs. Measure of statistical significance not reported.	Sacks[23]
Pulmonary fibrosis	Prospective cohort, 1998–2002	148	No difference in Kaplan-Meier curves in SSc-PAH patients with and without fibrosis. (p = 0.3)	Mukerjee[5]
	Retrospective cohort	17	No difference in median survival in SSc-PAH with and without fibrosis: 55 (95% CI 3–58) mo versus 11.5 (95% CI 4–26) mo; log rank p = 0.20	Koh[15]
Change in PVR	Prospective cohort, 1998–2002	148	No difference in Kaplan-Meier curves in patients with ΔPVR < 20%, 20–34%, ≥ 35%; p = 0.8	Mukerjee[5]
Rising PAP	Retrospective cohort, 1992–1997	152	HR = 5.36 (95% CI 0.4, 37.8)	MacGregor[8]
ACA positive	Retrospective cohort, 1992–1997	152	HR = 1.67 (95% CI 0.66, 4.26)	MacGregor[8]
Scl-70 positive	Retrospective cohort, 1992–1997	152	HR = 0.28 (95% CI 0.03, 1.99)	MacGregor[8]

HLA: Human leukocyte antigen; PAH: Pulmonary arterial hypertension; HR: Hazard ratio; CI: Confidence interval; ACA: Anti-centromere antibody; PVR: Pulmonary vascular resistance; PAP: Pulmonary artery pressure; mRAP: Mean right atrial pressure; RR: relative risks.

defined as a diagnosis made by a physician using the 1980 criteria of Masi, *et al*[21]. A patient was classified as having "observed PAH" if 3 of 5 clinical findings (exertional dyspnea, easy fatigue, sternal pain, systolic pulsation left of the sternum, or increased second pulmonic heart sound) and 2 of 4 laboratory findings (dilation of pulmonary arteries on radiograph recognized by 3 different senior physicians, right ventricular hypertrophy on electrocardiogram defined as a R/S ratio > 2 in lead V1, and R/S ratio > 1 in lead V6, or a mean pulmonary artery pressure > 25 mmHg on right heart catheterization).

Factors not definitively associated with survival in SSc-PAH (Table 1). MacGregor, *et al* reported that age > 50 years had a HR = 2.34 (95% CI 0.54, 10.2) and male sex had a HR = 2.02 (95% CI 0.65, 6.20)[8]. The limited subtype of systemic sclerosis[22] was not found to be associated with SSc-PAH prognosis in 2 studies. In a single center, retrospective cohort study conducted from 1975 to 1992 of SSc-PAH patients, Sacks, *et al* reported that both limited and diffuse subtypes have similarly poor outcomes with 10–20% cumulative survival at 5 years (statistical significance not specified)[23]. MacGregor, *et al* reported that the limited subtype of SSc had a HR = 2.37 (95% CI 0.68, 8.20)[8]. Mukerjee, *et al* reported no significant difference in survival (p = 0.3) between SSc-PAH patients with or without pulmonary fibrosis[5]. Koh, *et al* similarly reported no significant difference in survival between SSc-PAH patients with pulmonary fibrosis (median survival 55 mo, 95% CI 3, 58) and SSc-PAH without pulmonary fibrosis (median survival 11.5 mo, 95% CI 4, 26; log rank p = 0.20)[15]. Change in pulmonary vascular resistance (PVR) after iloprost challenge was not found to prognosticate survival[5]. Using Kaplan-Meier survival curves, Mukerjee, *et al* divided patients into 3 groups based on the change in PVR during a vasodilator challenge (change in PVR < 20%, 20–34% or ≥ 35%). No difference in survival between the 3 groups was found (p = 0.8)[5]. The presence of anti-centromere antibodies (ACA) and anti-Scl-70 antibodies was also not found to prognosticate survival in SSc-PAH. MacGregor, *et al* reported the presence of ACA and anti-Scl-70 antibodies had a HR = 1.67 (95% CI 0.66, 4.26) and HR = 0.28 (95% CI 0.03, 1.99), respectively[8].

Methodologic quality assessment. A methodologic quality assessment was performed on the 5 studies that evaluated factors potentially associated with survival in SSc-PAH. The methodologic quality was evaluated independently by 2 raters (JS, SJ), with substantial[24] inter-rater agreement

(kappa = 0.76). Any disagreement was resolved through consensus. For each study, the evaluation of study participants, study attrition, prognostic factor measurement, outcome measurement, confounding measurement, and analysis is reported in Table 2. Using the EULAR Categories of Evidence, all studies we identified attained category 3 since all were observational studies. None of the studies were randomized or controlled, or quasi-experimental.

Table 2. Quality assessment.

Criteria	Kasukawa[20]	Koh[15]	Langevitz[19]	MacGregor[8]	Mukerjee[5]
Research question clearly stated	Y	Y	Y	Y	Y
Study participants					
Source population clearly defined	N	Y	Y	Y	Y
Inclusion criteria specified	Y	Y	Y	N	Y
Exclusion criteria specified	N	N	N	N	N
Baseline comparability of groups reported	Y	Y	Y	Y	N
Recruitment period specified	N	Y	Y	Y	Y
Place of recruitment specified	Y	Y	Y	Y	Y
Study attrition					
Participation rate reported	N	N	Y	N	Y
Followup reported, explained and reasonable	N	N	Y	Y	Y
Lost to followup equal in both groups	N/S	Y	N/S	N/S	N/S
Lost to followup patients characterized	N/S	N/A	N/S	N/S	N/S
Lost to followup patients significantly different than study completers	N/S	N/A	N/S	N/S	N/S
Prognostic factor measurement					
All aspects of the factor measured	N	Y	Y	Y	Y
Factor measured at baseline and followup	Y	Y	Y	Y	Y
Regular followup periods maintained	N/S	N/S	Y	N/S	N/S
Other factors measured	Y	N	Y	Y	Y
Time zero specified	N	Y	Y	Y	Y
Cutoffs for continuous variables specified	Y	Y	N/A	Y	Y
Adequate proportion of sample had complete data for factor	N/S	N/A	Y	N/S	Y
Method and setting of factor measurement the same for all participants	N	Y	Y	Y	Y
Methods used to account for missing data	N	Y	N/S	N/S	N/S
Outcome measurement					
Duration of followup adequate	N/S	Y	Y	Y	Y
Outcome defined and measurable	N	N	N	Y	Y
Valid outcome	Y	Y	Y	Y	Y
Blinded outcome assessment	N/S	N/S	N/S	N/S	N/S
Same data collection used for all participants	N	N/S	Y	Y	Y
Methods to account for missing confounder data	N/S	N/S	N/S	N/S	N/S
Confounding measurement and account					
Confounding variables defined	N	Y	N	Y	N
Adjustment for confounders in analysis	N	N	Y	Y	Y
Confounding variables measured, valid and reliable	N/S	N/S	N/S	Y	N/S
Similar confounding variable measurement in all study participants	N/S	Y	N/S	Y	N/S
Confounding variables accounted for in study design	N/S	N/S	N/S	Y	N/S
Analysis					
Pre-planned sample size with adequate power	N/S	N	N/S	N/S	N/S
Appropriate statistical analysis	Y	Y	Y	Y	Y
Verifiable results from the data	Y	Y	Y	Y	N
Appropriate strategy for model building based on a conceptual framework	N	N	N	N	N
Selected model is adequate for the study design	Y	Y	Y	Y	Y
Selective reporting of results	N/S	N	N/S	N/S	N/S

N/S: Not specified; N/A: Not applicable.

DISCUSSION

In this systematic review, we identified 5 factors (2 genetic, 2 hemodynamic, and 1 time related) associated with survival in SSc-PAH. The relationship between an abnormal PAP and poor survival is the strongest prognostic factor as it is supported by plausibility (there is a credible mechanism to explain the association), coherence (the association is consistent with the natural history of the disease), consistency (the relationship was independently demonstrated by 2 groups of investigators)[5,8], and biological gradient (increasing PAP is associated with a decreasing survival time)[5]. In contrast, the relationship between mPAP and survival remains controversial among patients with idiopathic PAH (IPAH). Our systematic review of prognostic factors for survival among patients with IPAH found 12 publications that supported this relationship, and 19 publications that did not definitively support it. The prognostic value of mPAP may change through the course of disease, where initially an elevated mPAP indicates disease severity. However, as the right ventricle progressively fails, it is unable to generate an elevated mPAP. Thus a lower mPAP may also be indicative of a poor prognosis as the result of incipient right heart failure.

A shorter mean period of time between onset of SSc and diagnosed PAH was also a statistically significant prognostic factor[20]. This finding may be representative of a subset of patients with more aggressive disease. In this regard, one could speculate that early screening and possible early intervention may improve prognosis. However, the validity and generalizability of this notion may be threatened by important biases. Screening for PAH may produce the effect of lead time bias, with a resultant improvement in outcome from time of diagnosis.

HLA-DRw52 and HLA-DRw6 haplotypes are non-modifiable, genetic factors that have been associated with survival. The clinical relevance of this cohort study has been questioned due to the small sample size of 16 patients. It may be useful if a patient happens to have one of these HLA types. Indeed identification of persons with specific genotypes or HLA classes may aid practitioners regarding timing of referral for transplant and counseling. The validity and reproducibility of the prognostic utility of HLA type should be further evaluated.

Other factors (age > 50 yrs, male sex, limited subtype of SSc, pulmonary fibrosis, change in PVR, presence of ACA or anti-Scl-70) have been evaluated as potential prognostic factors. Although many of the factors have a hazard ratio > 1 (increased risk of death), the confidence interval associated with this finding includes values < 1 (decreased risk of death). Thus there is currently insufficient evidence to conclude that these factors confer a poor survival[25]. Inadequate power, loss-to-follow-up/dropouts, or presence of time-dependent factors may have affected these findings. These limitations are not insurmountable, and support the notion that additional research needs to be completed to re-evaluate the importance of these factors in patients with SSc-PAH. Studies using appropriate inclusion criteria (using consistent and well accepted criteria for the diagnosis of PAH), appropriate sample size, and rigorous followup will be able to ascertain whether these factors are associated with survival.

The methodologic quality of the prognostic studies in SSc-PAH is variable. Studies that identified factors associated with survival in SSc-PAH were of comparable methodologic quality to studies that did not definitively identify factors associated with survival. Study participants were well reported in all studies, with over 80% fulfilling each of the requirements. The significant weakness was the lack of reporting of exclusion criteria in all studies. Attributes of study attrition were also poorly reported where most studies did not report participation rate or characterize patients who were lost to followup. Inadequate sample size, description of study participants, and study attrition limit the generalizability and validity of the study findings as they may be adversely affected by bias. Attributes of prognostic factor and outcome measurement were largely well reported in all studies.

The use of variable inclusion criteria is also a threat to the validity and generalizability of the study findings. In particular, studies used variable definitions for classification of PAH. Two studies used echocardiographic measures of pulmonary artery pressures in the range of 30-40 mmHg as criteria for PAH[5]. Another study used a combination of clinical findings and laboratory findings as criteria for PAH[20]. These thresholds for classification and the lack of diagnostic confirmation using cardiac catheterization have limited the validity and generalizability of the findings. Future investigators should use standardized criteria, such as the World Health Organization criteria for the diagnosis of PAH, to improve study validity and generalizability[26].

The most significant issues affecting methodologic quality of the prognostic studies were those related to confounding measurement and analysis. Confounding variables are factors that may affect the relationship between the disease, the prognostic factor, and survival. If unaccounted for, a false relationship between a purported prognostic factor and survival may be identified. At best, an under- or over-representation of the strength of association may be reported; at worst, an errant attribution of an association may be reported. Some studies did not clearly specify how factors were categorized in the analysis. For example, although an elevated mean right atrial pressure (mRAP) was found to be a prognostic factor, it is uncertain whether the risk of death is related to an incremental rise in pressure or increases once an individual crosses a threshold value for mRAP.

A limitation to analysis noted in all the studies was a lack of a conceptual framework on which to base the analytic model. The conceptual model outlines the theoretical underpinning for the relationship between disease, survival, and prognostic factors. Simply stated, statistical analyses are not

clinically useful if they are not supported by a biologically plausible framework.

Based on the findings of our study, we propose a conceptual framework outlining the relationship between the identified prognostic factors and survival in SSc-PAH (Figure 1). This conceptual framework is an explicit specification of the clinical characteristics or factors that prognosticate the relationship between SSc-PAH and survival. More recently, investigators have reminded the rheumatology scientific community to use conceptual frameworks to guide our thinking[27,28]. Such frameworks provide a formal basis on which construct and content validity can be tested. The conceptual framework is not static, but rather serves to lay the groundwork for debate and modification as further insights are gained and our construct of relationships changes. An explicitly stated framework will be useful as future investigators face the challenge of identifying prognostic factors in a setting where new therapies are being developed and applied.

Our model suggests that in an individual, genetics may predispose a patient with SSc to the development of PAH and/or may potentiate the disease. Once SSc-PAH occurs, other factors can contribute to an individual's survival. We currently classify these factors as potentially modifiable (rising PAP, right heart abnormalities, pulmonary fibrosis) or non-modifiable (age, sex, scleroderma subtype). One may speculate that environmental factors, co-existing disease, or socioeconomic status may also be prognostic factors for survival in this framework; however, these factors need to be investigated. In the setting of new therapies, the effect of all prognostic factors will need to be re-evaluated. Are factors independent of treatment? Is a factor a confounder? For example, immunosuppression may improve survival by decreasing SSc disease activity that subsequently affects the presence of serologic markers. As insights are gained, our construct of the relationship between disease, prognostic factors, interventions, and survival will be refined.

To pragmatically utilize prognostic factors in the clinical setting, much research is needed. Such research should use current standards of methodologic quality to identify additional prognostic factors. Also research into prognostic factors should investigate the nature of their relationship to survival. Discrimination of factors that indicate "distance," i.e., time to death, and those indicating "velocity," i.e., speed of approaching death, will have important clinical utility. Finally, research is needed on the relationship of therapeutic interventions and prognostic factors. Together, these results will build prognostic indices to assist in patient monitoring, interventions, and resource allocation in lung transplantation. Indeed, multicenter, multidisciplinary, collaborative, longitudinal research endeavors such as the Pulmonary Hypertension Registry of Scleroderma (PHAROS) or the Canadian Scleroderma Research Group national database are uniquely positioned to address these important issues.

In conclusion, HLA-DRw52 and HLA-DRw6 haplotypes, initial sPAP > 60 mmHg, elevated mRAP, and shorter mean period of time between onset of SSc and observed PAH were associated with decreased survival; however, there was variable methodologic quality in study reporting. Additional research on prognostic factors in SSc-PAH is needed using modern methodologic standards.

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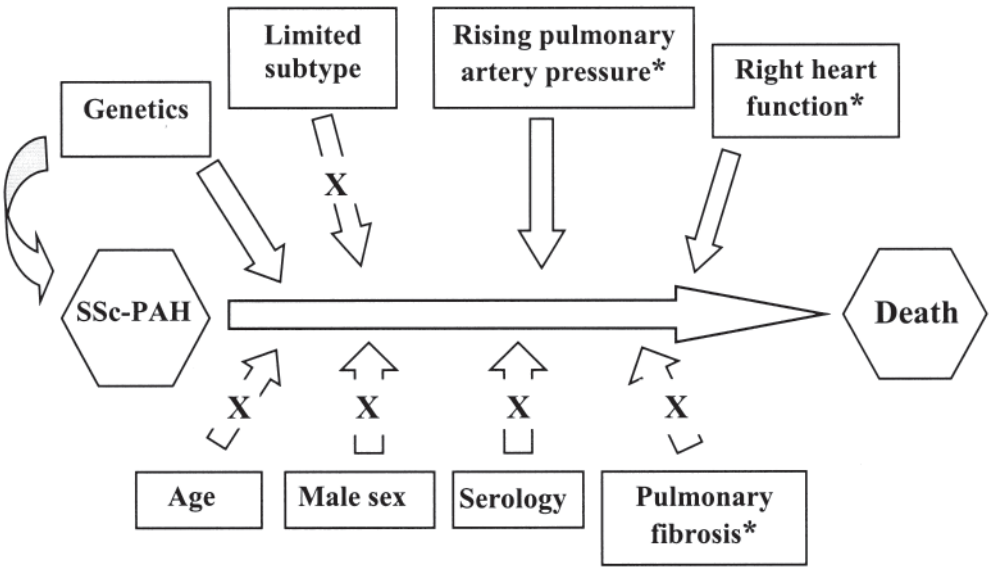

Figure 1. Conceptual model of prognostic factors for survival in scleroderma-pulmonary artery hypertension. *Modifiable factors; X: there is currrently insufficient evidence to support this relationship.

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