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Survival in systemic sclerosis–pulmonary arterial hypertension by serum autoantibody status in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Registry

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Abbreviations: PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; ANA, antinuclear antibodies; PH, pulmonary hypertension; WHO, World Health Organization; PHAROS, Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma; NYHA, New York Heart Association; DLCO, diffusion capacity for carbon monoxide; RHC, right heart catheterization; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; HRCT, high-resolution computed tomography of the lungs; PFT, pulmonary function tests; AC, anticentromere; NUC, isolated nucleolar ANA; Scl-70, anti-topoisomerase I; RNA pol, RNA polymerase III; FVC, forced vital capacity % predicted; mRSS, modified Rodnan skin score; ILD, interstitial lung disease; sPAP, systolic pulmonary artery pressure; HR, hazard ratio; CI, 95% confidence interval; REVEAL, Registry to Evaluate Early and Long-term Disease Management.

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ABSTRACT

Objective: To determine the association between serum autoantibodies and survival in patients with incident systemic sclerosis (SSc)–pulmonary arterial hypertension (PAH) enrolled in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) Registry.
Methods: Patients with definite PAH diagnosed by right heart catheterization within 6 months of registry enrollment were studied. Serum autoantibodies were assayed at each participating institution's clinical laboratory. Mortality data were collected from electronic medical records and/or the Social Security Death Index. Kaplan – Meier survival estimates were reported for five autoantibody groups (anticentromere/AC, nucleolar ANA/NUC, anti-topoisomerase/Scl-70, overlapping or non-specific autoantibodies/other, and a combined group with similar survival consisting of RNA polymerase III, U1RNP, and autoantibody-negative patients). Cox proportional hazards models permitted examination of the association between autoantibody groups and overall survival, controlling for age, sex, race, and SSc disease duration.
Results: In all, 162 subjects had PAH, and serum autoantibody and survival information; 60 (37%) had AC, 39 (24%) NUC, 11 (7%) Scl-70, 28 (17%) had other, 9 (6%) RNA pol, 8 (5%) U1RNP autoantibodies, and 7 (4%) had negative antibodies; 32 (20%) subjects died over a median follow-up time of 2.1 years (range: 0.01–6.8); 1- and 3-year survival estimates were, respectively, 94% and 78% for AC, 94% and 72% for NUC, 89% and 63% for Scl-70, 92% and 79% for the other group, and 100% and 93% for the combined group. Unadjusted and adjusted hazard ratios revealed no statistically significant association between risk of death and autoantibodies.
Conclusion: Anticentromere and NUC autoantibodies are prevalent in SSc-PAH patients. An association between serum autoantibodies and survival in patients with SSc-PAH was not identified in the PHAROS cohort.

Pulmonary arterial hypertension (PAH) is one of the most serious complications occurring in systemic sclerosis (SSc), with a cumulative incidence of 15% over 15 years of follow-up [1]. Patients with SSc-PAH have worse outcomes than patients with idiopathic PAH and other connective tissue disease associated PAH [2]. Anticentromere and antinuclear antibodies (ANAs) with a nucleolar pattern (anti-Th/To antibodies, anti-U3-ribonucleoprotein, and anti-B23) have been associated with an increased risk for the development of PAH in SSc patients, but the mortality risk associated with specific serum autoantibodies in patients with definite SSc-PAH is unknown [3].

SSc-specific autoantibodies are directed against ubiquitously expressed antigens and yet are associated with unique clinical phenotypes including PAH. Studies suggest that the pathogenesis of SSc-associated complications such as PAH may involve a complex interplay between target tissue damage (to release and/or modify intercellular antigens) and autoimmune responses (antigen-specific cytotoxic T-lymphocyte expansion) [4]. Numerous data have shown that SSc-specific autoantigens including CENPs B and C (centromere antigens) that are associated with SSc-PAH undergo structural changes during T-lymphocyte-mediated immune responses [4]. We postulate that SSc patients who develop PAH incur pulmonary vasculature endothelial cell damage that leads to the presentation of centromere antigens to activated immune cells. Thus, we hypothesize that patients expressing specific serum autoantibodies, such as anticentromere antibodies, may demonstrate unique clinical features or experience higher mortality rates.

A revised pulmonary hypertension (PH) classification scheme was published in 2009 [5]. Patients with SSc are at increased risk for developing World Health Organization (WHO) Group 1 PAH, Group 2 pulmonary hypertension secondary to left-sided heart disease, and Group 3 pulmonary hypertension due to interstitial lung disease and/or hypoxemia [6]. The multicenter, observational Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) patient registry was created in 2006 in order to prospectively follow-SSc patients at high risk for developing, or with newly diagnosed, SSc-associated PH [6]. The 3-year survival of this cohort of patients was recently reported to be 75%, which is better than those of other historical cohorts of SSc-PAH patients [7]. Factors associated with poor survival in the PHAROS cohort include New York Heart Association (NYHA) Functional Class IV status at PAH diagnosis, male gender, diffusing capacity of carbon monoxide (DLCO) $<39\%$ predicted, and age >60 years [8]. The purpose of this study was to examine whether specific serum autoantibodies were associated with worse survival in patients enrolled in the PHAROS Registry with right heart catheterization (RHC)-confirmed SSc-PAH. The ability to identify SSc-PAH patients at highest risk for death will help inform development of rational PAH-specific treatment protocols.

Patients and methods

The Institutional Review Board at each of the 22 participating US centers approved the PHAROS protocol and patients provided written informed consent prior to enrollment in the study. All subjects fulfilled American College of Rheumatology criteria for SSc or the LeRoy definitions of limited or diffuse cutaneous SSc [6]. Only patients with incident WHO Group 1 PAH were included in the analysis. Specifically, patients had to have undergone an RHC within 6 months of registry enrollment that demonstrated an elevated mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and a normal pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. Subjects with significant pulmonary fibrosis were excluded.

Clinical features and laboratory assessments including autoantibody profiles were performed as previously described [6]. High-resolution thoracic computed tomography (HRCT) scans, RHC, pulmonary function tests (PFTs), 2-dimensional echocardiograms with tissue Doppler, and 6-minute walk distance test were performed at baseline and repeated annually or as clinically indicated as determined by the site investigator. Local electronic health records or the Social Security Death Index was queried to