# Associated Autoimmune Diseases in Systemic Sclerosis Define a Subset of Patients with Milder Disease: Results from 2 Large Cohorts of European Caucasian Patients

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*ABSTRACT*. ***Objective.*** To assess the prevalence and potential associations with the systemic sclerosis (SSc) phenotype of additional autoimmune diseases (AID).

***Methods.*** A multicenter study was performed in France and Italy to recruit consecutive European Caucasian patients with SSc systematically assessed for the coexistence of predefined AID known to occur with connective tissue diseases.

***Results.*** We recruited 585 French and 547 Italian patients with SSc. Specific AID were found in 114/585 (19%) French and 179/547 (33%) Italians with SSc ($p < 0.0001$). Sjögren's syndrome and thyroiditis were the predominant AID in both cohorts (12% for Sjögren's syndrome and 6% for thyroiditis in the combined populations). The frequency of myositis, primary biliary cirrhosis, rheumatoid arthritis, and systemic lupus erythematosus was low (< 4%) and similar in both cohorts. The coexistence of at least 1 of the AID in the whole cohort was associated in multivariate analysis with the limited cutaneous subtype, the presence of antinuclear antibodies, and a lower prevalence of digital ulcers.

***Conclusion.*** Our study shows that 21% of this large series of European Caucasian patients with SSc have developed at least 1 AID. This latter condition identified a subset of patients with milder disease. Thus, associations of AID and autoimmune background in SSc have to be considered for further therapeutic and biological investigations in SSc. (First Release Feb 1 2010; J Rheumatol 2010;37:608–14; doi:10.3899/jrheum.090815)

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Systemic sclerosis (SSc) is a severe connective tissue disorder characterized by alterations of the microvasculature, disturbances of the immune system, and the massive deposition of collagen in connective tissue[1]. Although the mechanisms that underlie these changes are not entirely clear, it has been suggested that immunological abnormalities play a key role in the pathogenesis of the disease, supported by the detection of various autoantibodies in the serum of patients with SSc. Autoantibody specificity may associate with disease phenotype, as anticentromere antibodies (ACA) are usually found in the limited cutaneous subtype and correlate positively with ischemic digital loss and development of pulmonary arterial hypertension. On the other hand, antitopoisomerase I antibodies are mainly detected in the diffuse cutaneous subtype, in association with fibrosing alveolitis and heart involvement[2,3].

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Some evidence also supports a potential causal role in the pathogenesis of the disease for antitopoisomerase I and platelet derived growth factor receptor (PDGFR) autoantibodies. Antitopoisomerase I antibodies are highly specific for SSc, are present in high titers extremely early in the disease process, and correlate with disease activity/severity[4]. Stimulatory autoantibodies against PDGFR also appear to be a specific hallmark of SSc and display biologic activity on fibroblasts[5].

Although scarce data are available, preliminary results suggest that SSc could be associated with other autoimmune diseases (AID)[6]. However, their precise frequency in a large cohort of patients and their effect on disease phenotype remain unclear. We previously assessed the prevalence of secondary Sjögren's syndrome (SS) in a prospective 2-center series of 133 patients with SSc[7]. SS was diagnosed in 14% of our patients and was much more common in the limited cutaneous form of SSc, and was associated with lower frequency of pulmonary fibrosis. However, in that study we did not evaluate overlap between SSc and other AID known to be associated with connective tissue diseases (CTD), such as autoimmune thyroiditis, myositis, primary biliary cirrhosis (PBC), rheumatoid arthritis (RA), or systemic lupus erythematosus (SLE)[6].

The aims of our study were to assess the prevalence of AID known to be associated with CTD in 2 large and consecutive populations of European Caucasian subjects with SSc from France and Italy, and to determine potential associations between the presence of AID and the phenotype of patients with SSc in the combined population.

## MATERIALS AND METHODS

A multicenter study was performed in France and Italy to recruit consecutive European Caucasian patients with SSc. A first set of successive French patients with SSc from 6 centers was included to design a primary cohort. A second set of consecutive Caucasian Italian patients with SSc from 5 centers was included to form a secondary cohort.

We carried out a complete evaluation of these patients based on the following data: age, sex, cutaneous SSc subtype as defined by LeRoy, *et al*[8], disease duration (date of first non-Raynaud symptom), duration of Raynaud's phenomenon, and digital ulceration. Systemic assessment was carried out as recommended[9]. We used computed tomography and respiratory function tests [forced vital capacity (FVC) and carbon monoxide diffusion capacity divided by alveolar volume (DLCO/AV)] to assess pulmonary fibrosis. An echocardiographically estimated systolic pulmonary arterial pressure (PAP) > 40 mm Hg was used as a screening threshold for suspicion of pulmonary arterial hypertension (PAH). Patients identified by this preliminary screening were offered right-heart catheterization. Confirmed PAH was defined as a resting mean PAP ≥ 25 mm Hg with a pulmonary capillary wedge pressure of ≤ 15 mm Hg, measured by right-heart catheterization[10]. The following biological tests were carried out: routine blood tests, serological testing for antinuclear antibodies (ANA) or ACA (immunofluorescence on HEp-2 cells), and antitopoisomerase I/anti-U1 ribonucleoprotein antibodies (counter immunoelectrophoresis and/or immunodiffusion).

Patients with SSc were systematically assessed for the coexistence of AID known to be associated with CTD in order to compare their respective frequencies among these 2 groups. Then the 2 cohorts were combined to build a large series of patients allowing determination of the disease phenotype influence of AID. These latter were defined in accord with standard international criteria (Table 1). SS was defined by the revised American-European consensus classification criteria for SS[11]; SLE and RA were defined by the revised classification criteria from the American College of Rheumatology[12,13]. Autoimmune thyroiditis[14], PBC[15], and myositis[16,17] were diagnosed as reported following clinical, biological, and histological criteria (Table 2).

All patients gave informed consent for all procedures, which were carried out with local ethics committee approval. The study was conducted in accord with the recommendations of the Helsinki Declaration and all investigations were those routinely required to evaluate the patients.

*Statistical analysis*. All data are presented as mean (standard deviation, SD) for continuous variables and numbers and percentages for categorical variables, unless stated otherwise. Data were statistically analyzed using chi-squared tests for differences in frequency and parametric Student's t-test for comparison between 2 normally distributed continuous variables. Although considered very conservative, we applied a Bonferroni correction for multiple comparisons. We divided 0.05 by the number of disease characteristics tested (13 sets of variables). P value ≤ 0.004 was considered statistically significant.

A multivariate stepwise logistic regression analysis was also performed to determine whether the presence of AID was associated with the various phenotypes of SSc. We included in our multivariate model all variables identified with a corrected p value < 0.1 univariately[18], with calculation of OR estimates and 95% confidence intervals (CI) for significant variables (OR and p value were not provided by the software when not significant). In this model, p value < 0.05 was considered statistically significant.

## RESULTS

*Study population*. We included 547 patients with SSc from Italy and 585 from France. The mean age was 57 ± 14 years in the French cohort and 63 ± 14 years in the Italian cohort (p < 0.0001). The mean disease duration was 11 ± 9 years in the French cohort and 13 ± 8 years in the Italian cohort (p < 0.0001). These measures were significantly higher in the Italian cohort: the frequency of the limited cutaneous subtype (75% vs 67%; p = 0.004), ANA (99% vs 86%; p < 0.0001), ACA (50% vs 33%; p < 0.0001), altered DLCO (DLCO/AV < 75%: 52% vs 32%; p < 0.0001), and PAH (13.5% vs 8%; p = 0.001). A description of the French and Italian cohorts is provided in Table 1.

*Prevalence of associated AID in both cohorts*. AID were found in 87/585 (15%) of patients with SSc in the primary French cohort and 152/547 (28%) of patients in the Italian cohort (p < 0.0001) (Table 3). SS and thyroiditis were the predominant AID in both cohorts but with higher prevalence in the Italian (17% vs 7.5%, p < 0.0001, for SS and 8.5% vs 4%, p = 0.025, for thyroiditis). The prevalence of myositis, PBC, RA, and SLE was similar in both cohorts.

*Relationship between AID and SSc features*. Table 4 gives the results of multiple corrected chi-squared analyses for each AID.

SS (137/1132, 12%) was associated in multiple stepwise logistic regression analysis with the limited cutaneous subtype (OR 2.7, 95% CI 1.4–5.3).

The presence of autoimmune thyroiditis (70/1132, 6%) was associated with a lower frequency of pulmonary fibrosis (OR 0.3, 95% CI 0.1–0.7; Table 4).

*Table 1.* Characteristics of study participants: French and Italian Caucasian patients with SSc.

| Characteristics | SSc Patients from France (n = 585) | SSc Patients from Italy (n = 547) | p | Combined population |
|---|---|---|---|---|
| Sex (women/men) | 498/87 | 491/56 | 0.06 | 989/143 |
| Age (yrs), mean ± SD | 57 ± 14 | 63 ± 14 | < 0.0001 | 60 ± 14 |
| Cutaneous subtype (L/D), n (%) | 394 (67)/191 (33) | 411 (75)/136 (25) | 0.004 | 805 (71)/327 (29) |
| Disease duration (yrs), mean ± SD | 11 ± 9 | 13 ± 8 | < 0.0001 | 12 ± 8 |
| History of digital ulcers, n (%) | 224 (38) | 193 (35) | 0.32 | 417 (37) |
| Pulmonary arterial hypertension, n (%) | 45 (8) | 74 (13.5) | 0.001 | 119 (11) |
| Pulmonary fibrosis on CT scan, n (%) | 220 (38) | 175 (32) | 0.04 | 395 (35) |
| Scleroderma renal crisis, n (%) | 9 (1) | 10 (2) | 0.25 | 19 (2) |
| Antinuclear antibodies (> 1/160), n (%) | 503 (86) | 543 (99) | < 0.0001 | 1046 (92) |
| Antitopoisomerase I antibodies, n (%) | 149 (25) | 136 (24) | 0.75 | 285 (25) |
| Anticentromere antibodies, n (%) | 193 (33) | 276 (50) | < 0.0001 | 469 (41) |
| Anti-RNP antibodies | 31 (5) | 13 (2) | 0.01 | 44 (4) |
| Decreased FVC (< 75% of normal value), n (%) | 80 (13) | 86 (16) | 0.18 | 166 (15) |
| Decreased DLCO/AV (< 75% normal value), n (%) | 189 (32) | 284 (52) | < 0.0001 | 473 (42) |
| Immunosuppressive drugs, n (%) | 141 (24) | 131 (24) | 0.94 | 272 (24) |

SSc: systemic sclerosis; L/D: limited/diffuse; CT: computed tomography; RNP: ribonucleoprotein; FVC: forced vital capacity; DLCO/AV: carbon monoxide diffusion capacity divided by alveolar volume.

Myositis was associated in multivariate analysis with the use of immunosuppressive drugs (OR 11.5, 95% CI 5.1–25.7). PBC (31/1132, 3%) was associated in multivariate analysis with the limited cutaneous subtype (OR 2.1, 95% CI 1.5–2.8) and the presence of ACA (OR 6.2, 95% CI 2.3–16.5).

The number of patients with RA and SLE was too low to perform accurate chi-squared tests to find disease phenotype associations.

In multiple logistic regression analysis, the coexistence of at least 1 AID (239/1132, 21%) in the whole cohort of SSc was associated independently with the limited cutaneous subtype (OR 3.3, 95% CI 2.1–5.3), the presence of ANA (OR 8.6, 95% CI 2.1–35.9), and a lower prevalence of digital ulcers (OR 0.6, 95% CI 0.4–0.9).

The coexistence of at least 2 AID associated with SSc was associated only with the limited cutaneous subtype (p = 0.04).

## DISCUSSION

Our main results from these large series of consecutive patients, performed in centers accustomed to the systematic evaluation of patients with SSc, show that about a quarter of European Caucasian patients with SSc have developed 1 or more AID known to be associated with CTD. Moreover, the presence of these AID was associated with a subset of patients with milder disease, defined by the predominance of the limited cutaneous subtype, and a lower frequency of digital ulceration.

Our study shows differences between the French and Italian cohorts. Italian patients were significantly older, their disease duration was significantly longer, and we found a higher percentage of patients with the limited cutaneous subtype. Positive ACA were detected more frequently in Italian patients, which may explain the higher frequency of the limited cutaneous subtype and PAH, as these antibodies are usually detected in limited pattern in the disease and are positively correlated with development of PAH[3,6,19]. These data are in accord with a recent study, performed by the EULAR Scleroderma Trials and Research group (EUSTAR), that assessed the geographic variation of disease manifestations in SSc[20].

Although they were more frequent in the French population, the frequency of antiribonucleoprotein antibodies was low in both cohorts and was not associated with any SSc characteristics. This raises the question of the role of these antibodies as biomarkers or agents of disease pathogenesis.

We found that the prevalence of associated AID was 15% in France and 28% in Italy. The difference between these 2 cohorts may partly be explained by the higher frequency of AID in older patients (the Italian patients were older than the French ones) and the association, within the multivariate analysis, between coexistence of at least 1 AID with SSc and the limited cutaneous subtype, significantly more prevalent in the Italian cohort.

Our data show that 21% of this large series of patients developed at least 1 specific AID, with higher occurrence of SS (12%) and autoimmune thyroiditis (6%) than in the general European population (1% to 4% for SS, 1% to 2% for autoimmune thyroiditis)[21,22]. This supports the hypothesis that SSc may be commonly associated with AID. This prevalence is consistent with those of a recent genetic study, which investigated the autoimmune candidate gene and found that the association between an AID with SSc was 22% in a population of 659 European Caucasians with SSc[23]. These data are also close to those of a previous

*Table 2*. Standard international criteria for the diagnosis of autoimmune diseases.

| Disease | International Classification Criteria |
|---|---|
| Sjögren's syndrome | Four of 6 criteria are necessary for diagnosis:<br>1. Ocular symptoms<br>2. Oral symptoms<br>3. Ocular signs — objective evidence of ocular involvement defined as positive result for at least Schirmer's test or rose Bengal score/other ocular dye score<br>4. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis evaluated by an expert histopathologist<br>5. Salivary gland involvement: objective evidence defined by a positive result<br>6. Autoantibodies: presence in the serum of the following autoantibodies [antibodies to Ro (SSA) or La (SSB) antigens, or both] |
| Autoimmune thyroiditis | Graves-Basedow's disease: criteria 1 + 2 or 1 + 3 or 2 + 3<br>1. Hyperthyroidism<br>2. Exophthalmos<br>3. Positive Tsh-receptor antibodies<br>Hashimoto's thyroiditis: criteria 1 or 2 + 3<br>1. Hypothyroidism<br>2. Goiter<br>3. Positive antithyroid peroxidase antibodies |
| Primary biliary cirrhosis | Two of 3 criteria are necessary for diagnosis:<br>1. Clinical fatigue, pruritus, or jaundice<br>2. Presence of antimitochondrial antibodies, which are specific markers of the disease<br>3. Histological evidence of nonsuppurative inflammation of the liver |
| Systemic lupus erythematosus | Four of 11 criteria are necessary for diagnosis:<br>1. Malar rash<br>2. Discoid rash<br>3. Photosensitivity<br>4. Oral ulcers: includes oral and nasopharyngeal ulcers, observed by physician<br>5. Nonerosive arthritis<br>6. Serositis<br>7. Renal disorder (proteinuria > 0.5 g/24h)<br>8. Neurologic disorder (seizures without other cause or psychosis without other cause)<br>9. Hematologic disorders: hemolytic anemia or leukopenia (< 4000/$mm^3$) or lymphopenia (< 1500/$mm^3$) or thrombocytopenia (< 100,000/$mm^3$) in the absence of offending drugs<br>10. Immunologic disorder: anti-dsDNA, anti-Sm, and/or anti-phospholipid<br>11. Antinuclear antibodies |
| Rheumatoid arthritis | Four criteria are necessary for diagnosis:<br>1. Morning stiffness<br>2. Arthritis of 3 or more joint areas<br>3. Arthritis of hand joints<br>4. Symmetric arthritis<br>5. Rheumatoid nodules<br>6. Serum rheumatoid factor<br>7. Radiographic changes |
| Myositis | Definite polymyositis = all first 4; probable polymyositis = 3 of first 4; possible polymyositis = 2 of 4.<br>Definite dermatomyositis = rash + 3 other; probable dermatomyositis = rash + 2 other; possible dermatomyositis = rash + 1 other:<br>1. Symmetrical weakness, usually progressive, of the limb-girdle muscles<br>2. Muscle biopsy evidence of myositis<br>3. Elevation of serum levels of muscle-associated enzymes<br>4. Electromyographic triad of myopathy<br>5. Characteristic rashes of dermatomyositis |

study[6], which reported that approximately one-third of patients affected by SSc developed 1 or more additional AID. That study included additional AID (as celiac disease or vitiligo) and was not restricted to Caucasian patients, as compared to our study, which may account for the difference from our results. All these results emphasize that patients with SSc should be carefully evaluated both at onset and during followup for the possible coexistence of other autoimmune disorders. However, the reasons why AID occur together remains unknown, and shared pathophysiological mechanisms remain to be identified. In Caucasian patients, these diseases show a frequent association with HLA-B8, -DR3, and/or -DR4 compared with the general population. Natural killer T cell counts are relatively low in

*Table 3.* Prevalence of SSc-associated autoimmune disease (AID) in French and Italian cohorts.

| Disease [n (%)] | SSc Patients from France, n = 585 | SSc Patients from Italy, n = 547 | p | Combined Population, n = 1132 |
|---|---|---|---|---|
| Sjögren's syndrome | 44 (7.5) | 93 (17) | < 0.0001 | 137 (12) |
| Autoimmune thyroiditis | 23 (4) | 47 (8.5) | 0.025 | 70 (6) |
| Myositis | 19 (3) | 16 (3) | 0.86 | 35 (3) |
| Primary biliary cirrhosis | 14 (2) | 17 (3) | 0.37 | 31 (3) |
| Rheumatoid arthritis | 8 (1) | 3 (0.5) | 0.53 | 11 (1) |
| Systemic lupus erythematosus | 6 (1) | 3 (0.5) | 0.53 | 9 (1) |
| At least 1 AID associated with SSc | 87 (15) | 152 (28) | < 0.0001 | 239 (21) |
| At least 2 AID associated with SSc | 16 (3) | 14 (2.5) | 0.74 | 30 (3) |
| At least 3 AID associated with SSc | 2 (0.3) | 2 (0.3) | 0.59 | 4 (0.3) |

patients with AID and this may also be true for multiple AID[24]. In animals, it was reported that thymectomy alone produced multiorgan-specific AID, suggesting that some kind of common immunologic pathway exists[25].

The presence of at least 1 AID was associated with the limited cutaneous subtype, ANA, and a lower frequency of digital ulceration, defining a subset of patients with milder disease. This suggests that the limited cutaneous subtype of SSc has a distinct pathogenesis with a greater autoimmune background, and may have implications for the research and trials in a disease in which there is no specific treatment[26], although this will require further studies.

The association between AID and the limited cutaneous disease subset, with this autoimmune propensity, may be explained by the distinct expression of the diseases in various ethnic groups, depending on genetic and environmental factors that could predispose to autoimmunity in general, and to certain clinical manifestations of each disease in particular[27]. The clinical course of patients with SSc may be modified by the previous damage produced by the associated AID. This strongly suggests shared autoimmunity, a common genetic background that would drive predominant autoimmunity within the same family or the same patient. This is highlighted by 3 recent studies. The first[23] showed an association between the *PTPN22* 1858T allele and SSc, indicating that *PTPN22*, a shared genetic factor of multiple autoimmune diseases, also contributes to the genetic background of SSc. The second study found an association between *STAT4* tagging polymorphism and AID[28], suggesting that *STAT4* is a novel common risk factor for AID. The third study showed that *IRF5* rs2004640 polymorphism, identified as a susceptibility gene of SLE and SS, was associated with SSc[29]. Thus, some immune gene may be shared by different diseases. This shared autoimmunity, within the analysis of polymorphisms and mutations of genes linked to autoimmunity in several ethnic groups, should offer an excellent tool for understanding the physiopathology of AID.

AID aggregation has already been assessed in families with primary SS[30]. A recent study examined the aggregation of AID among first-degree relatives of patients with primary SS. Their results indicate that diseases with immune disturbances (such as autoimmune thyroiditis, SLE, or SSc) cluster within families of patients with primary SS. This familial aggregation of AID suggests that diseases with distinct phenotypes might share a common susceptibility gene.

Our study had some limitations. Disease phenotype associations have to be considered cautiously as the study was cross-sectional. Moreover, this design did not allow us to determine if AID occurred before or after the diagnosis of SSc and the potential effect of this sequence on the disease phenotype. It was not possible to assess in the whole cohort the segregation of specific autoantibodies, i.e., antimitochondrial antibodies, antithyroid peroxydase antibodies, or anti-Ro/SSA antibodies, as this was done in routine care only in patients with the respective suspected AID. We focused only on European Caucasian patients with SSc; further studies are thus needed to confirm these results in other ethnic groups. Patients were from tertiary centers; this may mean that they experienced more active and severe disease than patients followed in routine care centers. However, all centers involved in this project are highly active in the field of SSc clinical research, a fact that markedly increases the quality and accuracy of the data collected. We also chose to concentrate on a restricted panel of AID known to occur with CTD and which were commonly and systematically assessed in all 11 centers. Further studies are now warranted to assess the coexistence of other AID (e.g., diabetes mellitus or vitiligo) with SSc.

Our study shows that 21% of this large series of European Caucasian patients with SSc has developed 1 or more AID known to occur with CTD. The presence of at least 1 of these AID was associated with the presence of ANA, the limited cutaneous subtype, and lower frequency of digital ulceration. This defines a subset of patients with a milder disease, probably associated with weaker fibrotic or vascular propensities. This strongly suggests that genetic background would drive predominant autoimmunity. Therefore the association of AID in SSc has to be considered for investigations in SSc and in particular for genetic, immune, or therapeutic studies.

*Table 4*. Associations between AID and systemic sclerosis features.

| AID | Disease Phenotype Associations in Univariate Analysis | Patients with AID, n (%) vs Patients without AID, n (%) | p* | Multivariate Stepwise Logistic Regression Analysis OR (95% CI) | p** |
|---|---|---|---|---|---|
| Sjögren's syndrome, (n = 137) | Female, n (%) | 127/137 (92) vs 862/995 (87) | 0.07 | | NS |
| | Age, mean ± SD, yrs | 65 ± 15 vs 62 ± 13 | 0.5 | | NI |
| | Disease duration, yrs | 14 ± 10 vs 12 ± 8 | 0.02 | | NS |
| | Limited cutaneous subtype, n (%) | 115/137 (84) vs 690/995 (69) | 0.002 | 2.7 (1.4–5.3) | 0.003 |
| | History of digital ulcers, n (%) | 40/137 (29) vs 377/995 (38) | 0.06 | | NS |
| | PAH, n (%) | 9/137 (7) vs 110/995 (11) | 0.04 | | NS |
| | Pulmonary fibrosis on CT scan, n (%) | 38/137 (27) vs 357/995 (36) | 0.07 | | NS |
| | ANA (> 1/160), n (%) | 134/137 (98) vs 912/995 (92) | 0.008 | | NS |
| | Anti-topo, n (%) | 21/137 (15) vs 254/995 (26) | 0.02 | | NS |
| | ACA, n (%) | 79/137 (58) vs 390/995 (39) | 0.001 | | NS |
| | Decreased forced vital capacity, n (%) | 10/137 (7) vs 156/995 (16) | 0.001 | | NS |
| | Decreased DLCO/AV, n (%) | 64/137 (47) vs 409/995 (41) | 0.6 | | NI |
| | Immunosuppressive drug, n (%) | 33/137 (24) vs 239/995 (24) | 0.9 | | NI |
| Autoimmune thyroiditis, (n = 70) | Female, n (%) | 68/70 (97) vs 921/1062 (87) | 0.04 | | NS |
| | Age, mean ± SD, yrs | 62 ± 13 vs 62 ± 13 | 0.9 | | NI |
| | Disease duration, yrs | 11 ± 9 vs 12 ± 9 | 0.5 | | NI |
| | Limited cutaneous subtype, n (%) | 55/70 (78) vs 750/1062 (71) | 0.2 | | NI |
| | History of digital ulcers, n (%) | 15/70 (22) vs 402/1062 (38) | 0.03 | | NS |
| | PAH, n (%) | 7/70 (10) vs 112/1062 (10) | 0.25 | | NI |
| | Pulmonary fibrosis on CT scan, n (%) | 13/70 (18) vs 382/1062 (36) | 0.001 | 0.3 (0.1–0.7) | 0.004 |
| | ANA (> 1/160), n (%) | 66/70 (94) vs 980/1062 (92) | 0.06 | | NS |
| | Anti-topo, n (%) | 14/70 (20) vs 271/1062 (25) | 0.4 | | NI |
| | ACA, n (%) | 41/70 (58) vs 428/1062 (40) | 0.02 | | NS |
| | Decreased forced vital capacity, n (%) | 8/70 (11) vs 158/1062 (15) | 0.3 | | NI |
| | Decreased DLCO/AV, n (%) | 27/70 (39) vs 446/1062 (42) | 0.3 | | NI |
| | Immunosuppressive drug, n (%) | 7/70 (10) vs 265/1062 (25) | 0.03 | | NS |
| Myositis, (n = 35) | Female, n (%) | 31/35 (88) vs 958/1097 (87) | 0.9 | | NI |
| | Age, mean ± SD, yrs | 64 ± 16 vs 62 ± 13 | 0.8 | | NI |
| | Disease duration, yrs | 11 ± 7 vs 12 ± 8 | 0.4 | | NI |
| | Limited cutaneous subtype, n (%) | 25/35 (71) vs 780/1097 (71) | 0.9 | | NI |
| | History of digital ulcers, n (%) | 11/35 (31) vs 406/1097 (37) | 0.6 | | NI |
| | PAH, n (%) | 3/35 (10) vs 116/1097 (11) | 0.6 | | NI |
| | Pulmonary fibrosis on CT scan, n (%) | 17/35 (49) vs 378/1097 (35) | 0.09 | | NS |
| | ANA (> 1/160), n (%) | 32/35 (91) vs 1014/1097 (92) | 0.8 | | NI |
| | Anti-topo, n (%) | 9/35 (26) vs 276/1097 (25) | 0.9 | | NI |
| | ACA, n (%) | 5/35 (14) vs 464/1097 (42) | 0.002 | | NS |
| | Decreased forced vital capacity, n (%) | 6/35 (17) vs 160/1097 (14) | 0.9 | | NI |
| | Decreased DLCO/AV, n (%) | 15/35 (43) vs 458/1097 (42) | 0.9 | | NI |
| | Immunosuppressive drug, n (%) | 27/35 (77) vs 245/1097 (22) | < 0.0001 | 11.5 (5.1–25.7) | < 0.0001 |
| Primary biliary cirrhosis, (n = 31) | Female, n (%) | 28/31 (91) vs 961/1101 (87) | 0.7 | | NI |
| | Age, mean ± SD, yrs | 65 ± 13 vs 62 ± 12 | 0.7 | | NI |
| | Disease duration, yrs | 16 ± 10 vs 12 ± 9 | 0.008 | | NS |
| | Limited cutaneous subtype, n (%) | 30/31 (97) vs 775/1101 (70) | 0.002 | 2.1 (1.5–2.8) | 0.02 |
| | History of digital ulcers, n (%) | 6/31 (21) vs 411/1101 (37) | 0.06 | | NS |
| | PAH, n (%) | 2/31 (7) vs 117/1101 (11) | 0.8 | | NI |
| | Pulmonary fibrosis on CT scan, n (%) | 5/31 (16) vs 390/1101 (35) | 0.04 | | NS |
| | ANA (> 1/160), n (%) | 28/31 (91) vs 1014/1101 (92) | 0.9 | | NI |
| | Anti-topo, n (%) | 1/31 (3) vs 284/1101 (26) | 0.008 | | NS |
| | ACA, n (%) | 23/31 (74) vs 446/1101 (40) | 0.0003 | 6.2 (2.3–16.5) | 0.003 |
| | Decreased forced vital capacity, n (%) | 1/31 (3) vs 165/1101 (15) | 0.08 | | NS |
| | Decreased DLCO/AV, n (%) | 12/31 (39) vs 461/1101 (42) | 0.2 | | NI |
| | Immunosuppressive drug, n (%) | 9/31 (29) vs 263/1101 (24) | 0.6 | | NI |
| At least 1 AID, (n = 239) | Female, n (%) | 220/239 (92) vs 769/893 (86) | 0.02 | | NS |
| | Age, mean ± SD, yrs | 63 ± 15 vs 59 ± 13 | 0.01 | | NS |
| | Disease duration, yrs | 13 ± 10 vs 12 ± 10 | 0.1 | | NI |
| | Limited cutaneous subtype, n (%) | 194/239 (81) vs 611/893 (68) | < 0.0001 | 3.3 (2.1–5.3) | < 0.0001 |
| | History of digital ulcers, n (%) | 64/239 (27) vs 353/893 (40) | 0.0007 | 0.6 (0.4–0.9) | 0.02 |
| | PAH, n (%) | 19/239 (8) vs 100/893 (11) | 0.3 | | NI |
| | Pulmonary fibrosis on CT scan, n (%) | 64/239 (27) vs 331/893 (37) | 0.006 | | NS |
| | ANA (> 1/160), n (%) | 229/239 (96) vs 817/893 (91) | 0.002 | 8.6 (2.1–35.9) | 0.004 |
| | Anti-topo, n (%) | 43/239 (18) vs 242/893 (27) | 0.003 | | NS |
| | ACA, n (%) | 117/239 (49) vs 372/893 (41) | 0.002 | | NS |
| | Decreased forced vital capacity, n (%) | 26/239 (11) vs 140/893 (16) | 0.006 | | NS |
| | Decreased DLCO/AV, n (%) | 105/239 (44) vs 367/893 (41) | 0.09 | | NS |
| | Immunosuppressive drug, n (%) | 26/239 (30) vs 246/893 (27) | 0.07 | | NS |

AID: autoimmune diseases; PAH: pulmonary arterial hypertension; ANA: antinuclear antibodies; Anti-topo: antitopoIsomerase I antibodies; ACA: anticentromere antibodies; CT: computed tomography; DLCO/AV: carbon monoxide diffusion capacity divided by alveolar volume; NS: not significant. NI: not included. * Significant if $p < 0.004$. ** Significant if $p < 0.05$.

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