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Systemic sclerosis and primary biliary cholangitis: Longitudinal data to determine the outcomes

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Abstract

Background: Several studies described the cross-sectional characteristics of systemic sclerosis patients and coexisting primary biliary cholangitis, but longitudinal prognostic data are lacking.

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Aims: To describe the systemic sclerosis–primary biliary cholangitis phenotype, including baseline characteristics and outcomes.
Methods: We performed a multicentre the European Scleroderma Trials and Research Group study of systemic sclerosis patients with primary biliary cholangitis or with primary biliary cholangitis–specific antibodies, matched with systemic sclerosis controls free from hepatobiliary involvement matched for disease duration and cutaneous subset. Data were recorded at baseline and at the last available visit.
Results: A total of 261 patients were enrolled (115 primary biliary cholangitis–systemic sclerosis, 161 systemic sclerosis). At baseline, systemic sclerosis–primary biliary cholangitis patients had a higher prevalence of anti-centromere antibodies ($p = 0.0023$) and a lower prevalence of complete absence of digital ulcers. The milder vascular involvement was confirmed at follow-up when crucial differences emerged in the percentage of patients experiencing digital ulcers; a significantly higher number of patients who never experienced digital ulcers were observed among primary biliary cholangitis–systemic sclerosis patients ($p = 0.0015$). Moreover, a greater incidence of pulmonary arterial hypertension ($p < 0.001$) and of conduction blocks ($p = 0.0256$) was observed in systemic sclerosis patients without primary biliary cholangitis. Patients with primary biliary cholangitis had higher levels of liver enzymes at baseline than systemic sclerosis patients; a significant decrease in liver enzymes was observed at follow-up. Out of 18 patients with cholangitis, one received a liver transplant at follow-up.
Conclusion: Our data show that systemic sclerosis–primary biliary cholangitis exhibit a mild systemic sclerosis and primary biliary cholangitis phenotype with outcomes being in general favourable.

Keywords
Systemic sclerosis, primary biliary cholangitis, outcomes, fibrotic diseases, overlap syndrome, autoimmunity

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Introduction

Systemic sclerosis (SSc) is a chronic complex autoimmune disease characterized by vasculopathy, immune dysregulation and tissue inflammation leading to skin and internal organ fibrosis.[1] Based on the extent of skin involvement, two subsets are recognized: the limited cutaneous systemic sclerosis (lcSSc) and the diffuse cutaneous systemic sclerosis (dcSSc).[2,3] However, this classification is probably insufficient to cover the entire SSc heterogeneity and to predict its morbidity and mortality.[3,4] In this context, organ damage, antibody profile and molecular classifications have an important role in the identification of subset of patients with a particular prognosis.[5,6] In addition, a specific attention has been paid on SSc-specific antibodies and on clinical features to early identify patients with SSc as also stated in the 2013 America Collage of Rheumatology (ACR) and the European League against Rheumatism (EULAR) classification criteria.[7] These classification criteria allow to enrol homogeneous groups of patients in clinical trials and multicentre studies also recognizing SSc patients in the early phase and not only those in the fibrotic stage of the disease.

SSc may be associated with other autoimmune disorders (AIDs),[8] including rheumatic diseases as Sjögren syndrome (SjS) and Systemic Lupus Erythematosus (SLE), and specific-organ diseases,[9] with thyroiditis being the most common one. The first association between SSc and hepatobiliary involvement (HBI) was reported in 1934.[10] Among autoimmune liver diseases leading to hepatic manifestations in SSc, primary biliary cholangitis (PBC) is that more frequently reported compared to autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC). PBC, previously known as primary biliary cirrhosis, was described in association with SSc for the first time by Murray-Lyon et al.[11] in 1970 and afterwards other studies confirmed PBC as the more frequent autoimmune liver disease in SSc.[12] PBC is a cholestatic disorder with a non-suppurative destructive cholangitis[13] caused by a typical chronic inflammation leading to duct destruction and fibroproliferative response.[14] Up to 95% of PBC patients had anti-mitochondrial antibodies (AMAs) which are rare outside this autoimmune liver disease. PBC-specific antinuclear antibodies (ANAs) are also anti-sp100 and anti-gp210 antibodies: often associated with a higher mortality. The diagnosis of PBC is mainly based on clinical and laboratory features, with abnormal liver enzymes (cholestatic enzymes) persisting for more than 6 months and the presence of PBC-specific antibodies highly increasing the probably of a PBC diagnosis. The diagnosis may be confirmed by liver biopsy, which, in clinical practice, seems confined to those cases needing to exclude other possible causes of cholestasis, such as in patients with abnormal liver enzymes but without PBC-specific antibodies.[14] Studies estimated the prevalence of PBC in SSc around 2%–3%, higher than in general population, but the prevalence of PBC-specific autoantibodies is even higher.[15–18] PBC seems more frequent in lcSSc than in dcSSc[19] and therefore associated with a higher frequency of limited skin involvement.[20] Previous studies suggest that the

presence of PBC may identify a group of SSc patients with a milder systemic disease.[15,21] Although, the phenotype of PBC in patients with SSc still remains debated, some studies reported a less aggressive course of the liver disease and the patients mortality rather linked to SSc complications than to liver progression.[22–24]

Given these data, the aim of this study was to describe clinical characteristics of two populations: PBC–SSc patients and of SSc patients with PBC-specific antibodies (first group) compared to a control SSc population free from HBI (second group), in order to evaluate not only cross-sectional data but also to determine the outcomes of such patients affected by two fibrotic conditions.

Materials and methods

Following a request disseminated to the whole European Scleroderma Trials and Research Group (EUSTAR) network, a total of 20 EUSTAR centres participated in the recruitment of patients with SSc and PBC and SSc controls. All patients had an SSc diagnosis according to the 2013 ACR/EULAR classification criteria. We asked investigators to fulfil additional forms dedicated to this study on top of the common data collected through EUSTAR database. Each participating centre provided data about available PBC–SSc patients (according to the local hepatologist diagnosis) or patients with PBC-specific abs and data of at least one SSc control for each PBC–SSc patient. Controls had to be matched for cutaneous subset and disease duration with the corresponding SSc patient. Each EUSTAR centre was approved by the local ethics committee, and a written informed consent was locally acquired for registered patients. Data were retrospectively collected as follows: demographics, clinical non SSc features, SSc clinical manifestations (disease subset, history/presence of digital ulcers (DUs) or gangrene, presence of arrhythmia and/or conduction block, gastrointestinal involvement, pulmonary arterial hypertension (PAH) proven by right heart catheterization (RHC)), radiology and instrumental assessments (nailfold videocapillaroscopy (NVC) pattern,[25] ejection fraction (EF), estimated systolic pulmonary arterial pressure (sPAP), parameters of pulmonary function tests (PFTs), presence of interstitial lung disease (ILD) at high-resolution computed tomography (HRCT)), serological tests (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, alanine and aspartate transaminase, alkaline phosphatase (AP), γGT, positivity for ANA, anti-topoisomerase I antibodies (ATA), anti-centromere antibodies (ACAs), anti-RNA polymerase III antibodies (ARA), AMA, anti-sp100 and anti-gp210 antibodies (these last three only for PBC–SSc patients)) and data on current treatment (immunosuppressive and/or immunomodulatory therapy (and which), prednisone (and what dosage)).

Arrhythmia, heart conduction block, PAH and ILD on HRCT were defined present according to the local clinical report which was entered in the database under the related field. All patients had also a follow-up evaluation through their last available visit, and all above-mentioned SSc clinical manifestations, radiology and instrumental assessments (except for NVC pattern) and serological tests (except for ESR, CRP, creatinine and autoantibodies positivity) were recorded also at the follow-up.

The baseline evaluation corresponded to the time of PBC diagnosis (±6 months) in PBC–SSc patients; centres were asked to provide SSc controls with the same disease duration at baseline assessment than PBC–SSc patients. For both populations (PBC–SSc and SSc alone), the follow-up evaluation corresponded to the last available clinical assessment.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD), while categorical ones as absolute and relative frequencies. In order to evaluate the distribution difference in continuous variables between groups, a T-test, the Satterthwaite T-test or the Mann–Whitney test was used according to the Shapiro–Wilk test and F-test results for normality and homoscedasticity, respectively. In order to evaluate the association between categorical variables and groups, the chi-square or the Fisher exact test were used. To evaluate the difference in incidence of major SSc complications (vascular, lung and heart involvement) between groups, the proportions and their 95% confidence interval were reported, and the z-test approximation was used. To evaluate the difference in continuous variables between baseline and follow-up, the unpaired t-test or the Wilcoxon signed-rank test according to the Shapiro–Wilk test for normality was used.

Results

A total of 276 patients (115 with PBC–SSc and 161 SSc controls) were enrolled by 20 EUSTAR centres. The mean age at SSc diagnosis (54.5 ± 12.5 years in the PBC–SSc population and 52.7 ± 13.1 in the SSc-only group) and the mean age of Raynaud's onset (42.5 ± 16.0 and 45.5 ± 14.5, respectively) were similar as requested for the enrolment (Table 1). In addition, the two populations were well-matched regarding the distribution of cutaneous subsets, as requested: 102 PBC–SSc patients (90.3%) and 149 (92.5%) controls had an lcSSc, and 4 PBC–SSc subjects (3.5%) and 6 (3.7%) SSc patients had a dcSSc.

Data at baseline

PBC–SSc patients presented a statistically higher prevalence of patients ACA positive compared to SSc controls ($p = 0.0023$) (Table 2). No significant difference was found in lung involvement (ILD at HRCT, PFTs parameters) at baseline. The evaluation of heart involvement at baseline showed a significant difference in sPAP mean, being

Table 1. Demographic, organ involvement and therapy of enrolled patients.

Clinical features	PBC–SSc patients ($n=115$)	SSc patients ($n=161$)	p-value
Age at Raynaud's onset in years (mean ± SD)	42.5 ± 16.0	45.5 ± 14.5	0.1150
Age at SSc diagnosis in years (mean ± SD)	54.5 ± 12.5	52.7 ± 13.1	0.2540
Smoking (past or present), *n* (%)	25 (24.7)	34 (22.1)	0.6819
Fibrosis at HRCT, *n* (%)	18 (16.8)	29 (20.0)	0.5390
FVC <80%, *n* (%)	10 (11.2)	10 (7.3)	0.3086
FVC% (mean ± SD)	104.2 ± 22.4	102.9 ± 17.2	0.6421
DLCO <80%, *n* (%)	42 (47.7)	77 (57.5)	0.1548
DLCO% (mean ± SD)	76.8 ± 18.7	76.7 ± 17.4	0.9581
DLCO/VA <80%, *n* (%)	35 (49.3)	62 (50.0)	0.9246
DLCO/VA (mean ± SD)	78.8 ± 18.2	78.9 ± 18.3	0.9620
sPAP >45 mm Hg, *n* (%)	9 (10.1)	5 (3.8)	0.0605
sPAP (mm Hg) (mean ± SD)	**33.0 ± 15.7**	**27.7 ± 9.6**	**0.0128**
EF <40%, *n* (%)	3 (3.2)	3 (2.1)	0.6865
PAH, *n* (%)	7 (6.6)	3 (2.0)	0.0984
Presence of arrhythmia, *n* (%)	5 (4.9)	5 (3.3)	0.5241
Presence of conduction block, *n* (%)	7 (7.1)	7 (4.6)	0.4128
Portal hypertension	6 (5.7)	–	–
DUs, *n* (%):			
Past	10 (8.9)	24 (15.7)	0.0988
Current	5 (4.4)	13 (8.5)	0.1912
Current and past	9 (8.0)	15 (9.8)	0.6048
Never	**82 (78.9)**	**101 (66.0)**	**0.0257**
Gangrene, *n* (%)			
Past	2 (1.8)	4 (2.6)	1.0000
Current	1 (0.9)	0	0.4226
Current and past	0	1 (0.7)	1.0000
Never	101 (96.2)	148 (96.7)	1.0000
Presence of GERD, *n* (%)	56 (54.4)	93 (64.6)	0.1057
Malabsorption, *n* (%)	3 (3.0)	6 (4.0)	1.0000
Anorectal incontinence, *n* (%)	1 (1%)	4 (2.6)	0.6510
Concomitant comorbidities, *n* (%):			
Pernicious anaemia	1 (0.9)	3 (2.0)	0.6412
Graves' or Basedow's disease	1 (0.9)	1 (0.7)	1.0000
Hashimoto thyroiditis (or history of hypothyroidism)	**15 (13.5)**	**7 (4.6)**	**0.0250**
Capillaroscopic pattern, *n* (%):			
Unspecific	15 (16.0)	26 (19.1)	0.5382
Early	33 (34.7)	55 (40.4)	0.3797
Active	31 (33.0)	33 (24.3)	0.1471
Late	15 (16.0)	23 (16.9)	0.8481
Therapy, *n* (%):			
Immunosuppressant therapy	**20 (17.5)**	**43 (28.9)**	**0.0331**
Methotrexate	4	16	
Azathioprine	3	4	
Cyclophosphamide	4	4	
Chloroquine/hydroxychloroquine	7	11	
Mycophenolate	1	5	
Cyclosporine	1	1	
Rituximab		1	
Leflunomide		1	
Corticosteroids	27 (23.9)	28 (11.9)	0.3288
Deoxycholic acid	84 (75.0)	–	–

PBC: primary biliary cholangitis; SSc: systemic sclerosis; SD: standard deviation; HRCT: high-resolution computed tomography; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; DLCO/VA: diffusing capacity for carbon monoxide/alveolar volume; sPAP: systolic pulmonary artery pressure; DUs: digital ulcers; EF: ejection fraction; PAH: pulmonary arterial hypertension; GERD: gastroesophageal reflux disease.
Bold values: values with statistical significance.

Table 2. Laboratory and antibodies profile of enrolled patients.

	PBC–SSc patients ($n=115$)	SSc patients ($n=161$)	p-value
Laboratory findings:			
ESR mm/h (mean ± SD)	27.1 ± 18.8	20.7 ± 16.5	**0.0049**
ESR >25 mm/h, *n* (%)	36 (40.1)	42 (30.4)	0.1063
CRP mg/L (mean ± SD)	9.0 ± 17.1	4.2 ± 6.9	**0.0003**
CRP >15 mg/L, *n* (%)	13 (13.1)	6 (4.3)	**0.0134**
Creatinine mmol/L (mean ± SD)	70.6 ± 22.5	70.8 ± 15.6	0.9469
Alanine transaminase U/L (mean ± SD)	48.2 ± 54.5	23.0 ± 14.4	<**0.0001**
Alanine transaminase >45 U/L, *n* (%)	25 (24.5)	8 (6.0)	<**0.0001**
Aspartate transaminase U/L (mean ± SD)	56.8 ± 103.9	24.6 ± 12.4	<**0.0001**
Aspartate transaminase >45 U/L, *n* (%)	28 (27.2)	6 (4.7)	<**0.0001**
Alkaline phosphatase U/L (mean ± SD)	221.7 ± 176.1	81.4 ± 52.7	<**0.0001**
Alkaline phosphatase >150 U/L, *n* (%)	48 (50.5)	9 (6.8)	<**0.0001**
γGT U/L (mean ± SD)	180.2 ± 271.8	31.5 ± 46.2	<**0.0001**
γGT >50 U/L, *n* (%)	80 (80.8)	14 (11.6)	<**0.0001**
Antibodies positivity, *n* (%):			
ANA	111 (98.2)	151 (99.3)	0.5771
Anti-topoisomerase I	**1 (0.9)**	**14 (9.2)**	**0.0052**
Anti-centromere	**94 (84.7)**	**103 (68.2)**	**0.0023**
Anti-RNA polymerase-III	1 (1.1)	5 (3.3)	0.41
AMA	85 (87.6)	–	–
Anti-gp210	8 (13.6)	–	–
Anti-sp100	9 (15.3)	–	–

PBC: primary biliary cholangitis; SSc: systemic sclerosis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SD: standard deviation; γGT: gamma-glutamyl transferase; ANA: antinuclear antibody; AMA: anti-mitochondrial antibody.
Bold values: values with statistical significance.

higher in PBC–SSc patients than in SSc group (33.0 ± 15.7 mm Hg vs 27.7 ± 9.6 mm Hg, respectively, $p=0.0128$). However, the two populations did not significantly differ in the prevalence of PAH (Table 1). The prevalence of gastrointestinal involvement and of different NVC patterns was similar in the two populations; however, regarding vascular involvement, there was a significant difference in the history of DUs. In particular, PBC–SSc population presented a greater number of patients without history of DUs (78.9% vs 66.0%, $p=0.0257$) (Table 1).

In PBC–SSc population, AMA was the most frequent PBC-specific antibody (87.6%), followed by anti-sp100 and anti-gp210 abs (15.3% and 13.6%, respectively). At baseline, out of 115 PBC–SSc subjects, only 6 patients (5.7%) suffered from portal hypertension. As expected, the laboratory evaluation of the two populations at baseline revealed major differences in the liver enzymes levels (alanine and aspartate transaminase, AP and γGT): all were statistically higher in PBC–SSc group ($p<0.001$) (Table 2).

Interestingly, the number of patients with autoimmune-specific organ diseases other than hepatic disorders was greater in PBC–SSc group than in the SSc one, presenting a higher percentage of patients with Hashimoto thyroiditis (13.5% vs 4.6%, $p=0.0250$).

As reported in Table 1, the proportion of patients treated with immunosuppressant and/or immunomodulatory therapies was greater in the SSc population without PBC compared to PBC–SSc. In the latter group, there were more subjects treated with steroids, although this difference was not significant.

Data at follow-up

Table 3 reports the characteristics of the two populations at follow-up of about 10 years. SSc patients without PBC presented a higher prevalence of cardiac involvement with a greater number of subjects with conduction block: out of PBC–SSc subjects, 5 presented this complication compared to 20 patients from the SSc group ($p=0.0383$). In addition, SSc patients presented a higher prevalence of ILD and PAH compared to PBC–SSc subjects at follow-up, however, without reaching the statistical significance.

During the follow-up, SSc patients without PBC experienced more vascular complications (overall history of DU in SSc–PBC 77.2% vs 58% in SSc controls, $p=0.0015$). A statistically significant difference was found in the incidence of new DUs from baseline to the last follow-up evaluation in the two groups (SSc controls 30.1% vs PBC–SSc 15.6%; $p=0.0052$).

Table 3. Populations' characteristics at follow-up (last available visit).

Demographical and clinical feature at follow-up	PBC–SSc patients ($n=115$)	SSc patients ($n=161$)	p-value
Follow-up duration in years (mean ± SD)	10.5 ± 7.5	10.4 ± 6.4	0.863
Fibrosis at HRCT, *n* (%)	22 (22.7)	44 (29.5)	0.236
FVC <80%, *n* (%)	10 (10.6)	18 (12.2)	0.7042
FVC% (mean ± SD)	103.3 ± 20.8	102.6 ± 21.2	0.8024
DLCO <80%, *n* (%)	69 (74.2)	106 (72.6)	0.7866
DLCO% (mean ± SD)	67.4 ± 20.4	68.6 ± 20.3	0.6358
DLCO/VA <80%, *n* (%)	50 (65.0)	82 (64.1)	0.8995
DLCO/VA (mean ± SD)	73.2 ± 17.8	74.1 ± 18.5	0.7233
sPAP >45 mm Hg, *n* (%)	13 (14.1)	13 (9.0)	0.2082
sPAP (mm Hg) (mean ± SD)	33.0 ± 13.8	31.7 ± 13.7	0.4811
EF <40%, *n* (%)	4 (4.1)	6 (4.0)	1
PAH, *n* (%)	8 (8.0)	18 (11.7)	0.3434
Portal hypertension, *n* (%)	11 (11.3)	–	–
Presence of arrhythmia, *n* (%)	8 (8.0)	6 (3.9)	0.1576
Presence of conduction block, *n* (%)	**5 (5.0)**	**20 (12.9)**	**0.0383**
DUs, *n* (%):			
Past from the first visit	**17 (15.6)**	**48 (30.1)**	**0.0052**
Current	1 (0.1)	5 (3.2)	0.4058
Current and past from the last visit	6 (5.5)	13 (8.3)	0.3873
Never or not new	**78 (77.2)**	**91 (58.0)**	**0.0015**
Gangrene, *n* (%)			
Past from the first visit	2 (1.8)	6 (3.8)	0.4776
Current	1 (0.9)	0	0.4098
Current and past from the last visit	1 (0.9)	1 (0.6)	1
Never or not new	98 (97.0)	150 (95.5)	0.7445
Presence of GERD, *n* (%)	55 (56.1)	92 (62.6)	0.3118
Malabsorption, *n* (%)	6 (6.3)	10 (6.8)	0.8759
Anorectal incontinence, *n* (%)	7 (7.3%)	8 (5.4)	0.549
Laboratory findings:			
Alanine transaminase U/L (mean ± SD)	**29.7 ± 22.3**	**21.8 ± 11.1**	**<0.0001**
Alanine transaminase >45 U/L, *n* (%)	**9 (9.1)**	**3 (2.3)**	**0.0339**
Aspartate transaminase U/L (mean ± SD)	**30.0 ± 16.9**	**23.8 ± 7.9**	**0.0002**
Aspartate transaminase >45 U/L, *n* (%)	5 (5.0)	3 (2.0)	0.2714
Alkaline phosphatase U/L (mean ± SD)	**150.3 ± 137.7**	**77.1 ± 57.2**	**<0.0001**
Alkaline phosphatase >150 U/L, *n* (%)	**24 (27.0)**	**4 (3.4)**	**<0.0001**
γGT U/L (mean ± SD)	**97.8 ± 110.7**	**37.8 ± 42.0**	**<0.0001**
γGT >50 U/L, *n* (%)	**52 (55.3)**	**17 (15.5)**	**<0.0001**

PBC: primary biliary cholangitis; SSc: systemic sclerosis; SD: standard deviation; HRCT: high-resolution computed tomography; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; DLCO/VA: diffusing capacity for carbon monoxide/alveolar volume; sPAP: systolic pulmonary artery pressure; EF: ejection fraction; PAH: pulmonary arterial hypertension; DUs: digital ulcers; GERD: gastroesophageal reflux disease; γGT: gamma-glutamyl transferase.
Bold values: values with statistical significance.

Incidence of major SSc complications at follow-up

The incidence of SSc complications in the follow-up in the two populations is reported in Table 4. Data from this study clearly showed a higher percentage of SSc complications in SSc patients without PBC than in PBC–SSc subjects. A higher percentage of new cases of ILD at HRCT ($p=0.0048$) and of cardiac involvement was detected. In fact, although PBC–SSc patients presented at baseline higher percentage of PAH and conduction block (Table 1), in SSc patients without PBC, there was a greater incidence of PAH than in PBC–SSc subjects ($p<0.001$) and of new cases of conduction block ($p=0.0256$) at follow-up. In addition, PBC–SSc patients presented a lower incidence of DUs from baseline to follow-up compared to SSc population (10.3% vs 22.5%, $p=0.0112$).

In this context, a composite index for major SSc complications (development of DU in patients without history of DU *OR* appearance of ILD *OR* new diagnosis of PAH) was analysed in the two populations, and the incidence of patients that experimented at least one of the above SSc

Table 4. Cumulative incidence of SSc complications in the two populations at the follow-up.

Feature	Incidence in PBC–SSc patients, *n* (%)	Incidence in SSc patients, *n* (%)	Difference in incidence (%, confidence limits)	*p*-value
Appearance of fibrosis at HRCT	**3 (4.0)**	**17 (15.6)**	**−11.6 (19.75; −3.55)**	**0.0048**
Appearance of FVC <80%	3 (4.6)	6 (5.2)	−0.60 (−7.12; 5.92)	0.8564
Appearance of DLCO <80%	18 (51.4)	23 (46.0)	5.43 (−16.14; 26.99)	0.6217
Appearance of DLCO/VA <80%	12 (48.0)	17 (30.4)	17.64 (−5.35; 40.63)	0.1326
Appearance of PAPs >45 mm Hg	4 (5.88)	8 (6.8)	−0.9 (−8.1; 6.3)	0.8070
Appearance of EF <40%	1 (1.3)	6 (4.6)	−3.35 (−7.72; 1.02)	0.1329
Appearance of PAH	**0 (0)**	**14 (9.9)**	**−9.86 (−14.76; −4.96)**	**<0.0001**
Appearance of arrhythmia	4 (4.4)	4 (2.9)	1.54 (−3.50; 6.57)	0.5493
Appearance of conduction block	**2 (2.3)**	**12 (8.7)**	**−6.42 (−12.06; −0.78)**	**0.0256**
Past DUs from baseline to follow-up	**10 (10.3)**	**29 (22.5)**	**−12.17 (−21.58; −2.76)**	**0.0112**
Incidence of DUs	1 (1.0)	3 (2.2)	−1.23 (−4.35; 1.90)	0.4417
Past gangrene from baseline to follow-up	1 (1.0)	2 (1.40)	−0.43 (−3.08; 2.23)	0.7527
Current gangrene in the follow-up	1 (1.0)	0 (0)	0.95 (−0.91; 2.81)	0.3150
Appearance of GERD	13 (32.5)	10 (20.8)	11.67 (− 6.84; 30.18)	0.2167
Appearance of malabsorption	2 (2.3)	5 (3.8)	− 1.46 (−5.97; 3.05)	0.5259
Appearance of anorectal incontinence	4 (4.4)	4 (2.9)	1.50 (− 3.61; 6.62)	0.5648
Composite outcome	**5 (8.5)**	**26 (34.6)**	**−26.19 (−39.1; −13.29)**	**<0.0001**

PBC: primary biliary cholangitis; SSc: systemic sclerosis; HRCT: high-resolution computed tomography; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; DLCO/VA: diffusing capacity for carbon monoxide/alveolar volume; EF: ejection fraction; PAH: pulmonary arterial hypertension; PAP: pulmonary artery pressure; DUs: digital ulcers; GERD: gastroesophageal reflux disease.
Bold values: values with statistical significance.

complications during the follow-up was significant greater in SSc patients without PBC (34.6%) compared with PBC–SSc (8.5%; $p < 0.0001$) (Table 4).

PBC disease in the follow-up

Data at follow-up regarding liver disease identified five new cases of portal hypertension, with an incidence of this PBC complication of 5.8%. As reported in Table 1, 75% of PBC–SSc patients were treated with deoxycholic acid and the trend of liver enzymes at follow-up indicated a moderate control of the hepatic disorder (Table 3). In the PBC–SSc group, a significant decrease in alanine and aspartate transaminase, AP and γGT was reported from baseline to follow-up ($p < 0.0001$). The decrease from baseline to follow-up of alanine transaminase was −19.9 U/L (confidence limits −32.3 and −7.5), of aspartate transaminase −29.0 (confidence limits −52.6 and −5.5), of AP −75.9 (confidence limits −117.9 and −33.9) and of γGT −97.3 (confidence limits −149.3 and −45.2). In addition, among PBC–SSc patients with altered alanine transaminase at baseline, 20 (87%) presented a normalization of this enzyme at follow-up. The same analysis regarding aspartate transaminase showed a normalization of this parameter in 23 (92%) of PBC–SSc patients. The percentages of normalization of AP and γGT were lower (53.9% and 33.9%, respectively). However, the mean value of liver enzymes was still significant higher in PBC–SSc population compared to SSc one (Table 3). Nevertheless, the percentages of new cases of alteration of these enzymes (normal value at baseline and higher the upper limit at follow-up) were lower than the percentages of normalization (Table 5).

Liver biopsy was performed in 44/115 (38.2%) of PBC–SSc subjects at baseline. The anatomopathological reports were different depending on the centre that provided the datum. Reports can be summarized in 5 groups: in 18/44 patients with signs of cholangitis were described (9 of which with nodules or micronodules and in one patient with signs of overlap with AIH), 13/44 patients presented bile duct alteration (in 8 with associated periportal inflammation), in 11/44 patients liver biopsy was compatible with PBC, in one patient it was normal and in another one patient was only reported the absence of signs of cirrhosis.

Out of 18 patients with signs of cholangitis, 1 patient was subjected to liver transplantation during the follow-up. Out of PBC–SSc patients, two patients were subjected to liver biopsy during the follow-up (with signs of active cholangitis in one patient and normal liver architecture in the other one).

Mortality rates

A total of eight deaths were observed among 276 enrolled patients. Seven deaths occurred in PBC–SSc patients with a mortality rate of 6.1% while a single death was reported in the control group. However, in three out of seven patients, death was not related to SSc (one dementia, one suicide, one COPD), and in two out of seven cases, the

Table 5. Trend of liver enzymes in PBC–SSc patients.

Laboratory data	Incidence in PBC–SSc patients, *n* (%)
Appearance of alanine transaminase alteration (>45 U/L)	5 (7.7)
Return to normal levels of alanine transaminase	20 (87.0)
Appearance of aspartate transaminase alteration (>45 U/L)	2 (3.1)
Return of normal levels of aspartate transaminase	23 (92.0)
Appearance of AP alteration (>150 U/L)	4 (10.5)
Return of normal levels of AP	21 (53.9)
Appearance of γGT alteration (>50 U/L)	3 (16.7)
Return of normal levels of γGT	22 (33.9)

PBC: primary biliary cholangitis; SSc: systemic sclerosis; AP: alkaline phosphatase; γGT: gamma-glutamyl transferase.

relationship was not sure (one sudden death and one sepsis with multiorgan failure).

Discussion

Systemic sclerosis and primary biliary cholangitis are two fibrotic disorders that can co-occur. Although the prevalence of PBC in SSc varies according to different studies, ranging from 2% to 3%,[20,26,27] it is undoubtedly higher in SSc than in general population where it represents a rare cholestatic disease. Although it widely differs within geographic regions, the prevalence in Europe and North America is estimated to be 300–450 per million in general population.[28]

It is established that the prevalence of PBC is different among the two cutaneous SSc subsets, being more frequent in lcSSc than in dcSSc[19,21] and a strong association between ACA positivity and PBC was reported by different authors.[24,27,29]

Compared to PBC frequency in SSc, the prevalence of PBC-specific antibodies seems to be even higher in SSc patients. Imura-Kumada et al.[30] reported the presence of AMA in more than 15% of 225 Japanese SSc patients (anti-sp100 and anti-gp201 had a prevalence of 5.8% and 1.3%, respectively) and confirmed the association of AMA and ACA with PBC in SSc patients.

Our project aimed at determining the phenotype of SSc–PBC patients with emphasis on the outcomes of these patients. Indeed, we enrolled for each PBC–SSc patients at least one SSc control matched for disease subset and disease duration. Given these premises, to investigate the prevalence of PBC or PBC-specific antibodies and to analyse the association between SSc disease subset and PBC were not objectives of this study. Our data agree with previous studies, confirming a significant higher prevalence of ACA in PBC–SSc patients compared to subjects with SSc alone. This datum seems to be in accordance with results from a recent study of Florin et al.[31] that showed a strong correlation of different PBC-specific antibodies and ACA and not with the limited cutaneous subset.

These data suggest a probable crucial role of ACA in autoimmune disease. In fact, although these antibodies are characteristics of SSc, ACA may be present also in other AIDs, as SjS, SLE or PBC. Their significance in patients with only PBC has recently been investigated suggesting that these antibodies may predict the development of a connective tissue disease (CTD), in particular SSc.[32] However, the role of ACA in patients with only PBC remains debated as they may also represent a marker of a specific subset of PBC.[33] Given these data, patients with PBC and ACA have to be investigated to exclude the presence of signs and/or symptoms suggestive of CTD, particularly of SSc, and ACA positivity hires a crucial role in the patient's management. At the same time, PBC-specific autoantibodies may be found in SSc patients also in the absence of cholestatic liver enzyme elevations probably preceding PBC development.[31]

Another interpretation of these findings is that the link between SSc and PBC relates more strongly with autoimmunity rather with the severity of fibrosis as demonstrated by the association with the limited cutaneous subset and not with the diffuse one. This could give clues to some pathomechanisms involved in SSc–PBC subphenotype. According to this interpretation, SSc and PBC could share common pathogenic features not only involving fibrogenic or fibroproliferative pathways but also immune and inflammatory ones.[34] In this context, Ikawa et al.,[35] analysing 67 SSc patients and 20 controls, showed an association of C-C motif ligand 20 (CCL20), a homeostatic and inflammatory chemokine, with cardiopulmonary involvement, AMA titres and PBC suggesting autoimmunity and inflammatory pathways as probable link between SSc and PBC.

Our project focused on the description of SSc baseline presentation of PBC–SSc patients versus subjects with SSc free of HBI, and our results seem to agree with previous ones suggesting a milder systemic disease.[21] This datum would be consistent with previous results demonstrating that SSc, when associated with other AIDs, may be characterized by a weaker fibrotic or vascular propensity.[21] However, many studies comparing the PBC phenotype in

SSc patients to PBC alone suggested a slower liver disease progression in the first group of patients.[24] Unfortunately, PBC may evolve to liver cirrhosis also when associated with SSc; however, in patients with these both diseases, the main causes of death seem to be led by SSc organs involvement than by PBC complications.[22,23]

Already at baseline, in the cross-sectional analyses, we observed some differences in SSc phenotype in the two populations. Although NVC patterns did not differ among the two groups of patients, PBC–SSc subjects seem to present a less severe vascular involvement characterizing by a higher percentage of patients who never experienced DUs. In addition, a significant higher mean of sPAP values in PBC–SSc patients was reported, probably associated with the higher percentage of ACA in this population, as these antibodies are known as risk factors in PAH development.[21,36,37] However, the percentages of patients with an sPAP >45 mm Hg and with PAH proven by RHC were not statistically different in the two groups of patients, suggesting a similar cardiac involvement at baseline in the two populations without major organ complications. Interestingly, in the longitudinal part, our results detected a greater percentage of SSc complications and organ damages in SSc patients without PBC. Comparing the two populations at follow-up, crucial differences emerged in the percentage of patients experiencing DUs from baseline to follow-up. In addition, a significant higher number of patients who never experienced DUs were observed among PBC–SSc patients than SSc controls. A more severe vascular involvement seems not to be the only SSc complication with a greater incidence in SSc patients compared to PBC–SSc subjects. The percentage of patients with diagnosis of conduction block at follow-up was higher in SSc population compared to PBC–SSc one, and the incidence of PAH was significant higher in SSc population compared to PBC–SSc group. However, this last datum may be influenced by the greater percentage of PAH patients in the PBC–SSc population at baseline. This datum gives interesting insights remembering that patients with SSc and PBC may have different and synergistic risk factors of developing pulmonary hypertension because of both ILD, vascular involvement (PAH) and liver disease with possible porto-pulmonary hypertension.[26]

Our data also suggested a greater risk of pulmonary complication in SSc patients compared to PBC–SSc ones showing a significant higher incidence of pulmonary fibrosis at follow-up in the first group of subjects. This datum probably also reflects the autoantibodies profile of enrolled populations with a higher prevalence of ACA in PBC–SSc patients and of topoisomerase I in SSc alone.

As expected, our PBC–SSc patients were characterized at baseline by significant higher mean value of liver enzymes compared to SSc populations. A total of 75% of PBC–SSc patients were treated with deoxycholic acid with a good control of liver disorder as attested by the significant decrease in liver enzymes levels at follow-up assessment in PBC–SSc population. Furthermore, out of 115 PBC–SSc patients, only 47 patients were subjected to liver biopsy, and this datum may lead to several reflections. First, the access to this procedure differs significantly depending on the centre in which some limitations in performing this invasive examination may be present (patient safety, patient decision, facilities). In addition, our datum may confirm that this examination is probably confined to those cases requiring the exclusion of other possible cholestatic causes or when patients present persistent abnormal liver enzymes without specific antibodies, according to what already reported.[14]

This study also showed a significant higher percentage of autoimmune diseases (particularly Hashimoto thyroiditis) in PBC–SSc patients. This datum is in agreement with previous reports indicating autoimmune thyroiditis as the more frequent specific-organ disorders and suggesting SSc polyautoimmunity as a frequent condition in SSc population.[9] In addition, in our PBC–SSc patients, AMAs were the most common antibodies and a previous study indicated that SSc patients with AMA positivity may present an overlap syndrome with more than one CTDs. This result might suggest SSc patients with AMA as a real crossroad of polyautoimmunity.[9,19]

This study also presents some limitations. PBC–SSc population is composed by patients with diagnosis of PBC and also by patients with a probable diagnosis of PBC (with abnormal liver enzymes levels and PBC-specific antibodies). PBC–SSc population may be less homogeneous due to this enrolment bias; however, it may influence particularly the evolution and progression of liver disease. Another limitation of this study is represented by the different duration of follow-up for each patient. At time of study design, the last assessment was decided to coincide with the last available SSc evaluation, for this reason, patients from the same population may present a different duration of follow-up. However, the mean duration of follow-up was similar in the two populations allowing a valid comparative analysis of the results between the two groups. In addition, at baseline and at the follow-up evaluation, possible missing data regarding clinical, laboratoristic and instrumental features were present. In fact, both at baseline and at follow-up, patients were screened by different instrumental examinations only according to the clinical indications in each centre. This limitation reflects the retrospective design of the study and involves both PBC–SSc patients and SSc controls.

Conclusion

The pathogenesis of SSc and PBC is still unknown; however, both diseases are characterized by a fibrogenic response that in SSc patients leads to fibrosis of skin and internal organ and in PBC to bile duct fibrosis, but we

highlight herein some data raising that autoimmunity is probably also a link between the two conditions. PBC–SSc patients may be considered a real crossroad of polyautoimmunity that seem to alleviate the SSc phenotype. However, but in the same direction, PBC–SSc patients seem to have also a milder PBC phenotype rarely leading to major PBC complications. All together these data might also suggest the possible identification of a peculiar SSc phenotype when the systemic disease is associated with other AIDs. This should be known by the clinicians and contribute to the risk-stratification of these patients. Nevertheless, at the individual level, longitudinal careful follow-up is still mandatory because although less common than in the whole SSc and PBC populations, some complications or progressions may be unfortunately responsible of patient's exitus.

Authors' note

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References

1. Varga J, Trojanowska M and Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. *J Scleroderma Rel Disord* 2017; 2(3): 137–152.
2. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15(2): 202–205.
3. Leclair V, Hudson M, Proudman SM, et al. Subsets in systemic sclerosis: one size does not fit all. *J Scleroderma Relat Disord* 2016; 1(3): 298–306.
4. Frantz C, Huscher D, Avouac J, et al. Outcomes of limited cutaneous systemic sclerosis patients: results on more than 12,000 patients from the EUSTAR database. *Autoimmun Rev* 2020; 19(2): 102452.
5. Sobanski V, Giovannelli J, Allanore Y, et al. Phenotypes determined by cluster analysis and their survival in the prospective European Scleroderma Trials and Research cohort of patients with systemic sclerosis. *Arthritis Rheumatol* 2019; 71(9): 1553–1570.
6. Johnson SR, Hinchcliff M and Asano Y. Controversies: molecular vs. Clinical systemic sclerosis classification. *J Scleroderma Relat Disord* 2016; 1(3): 277–285.
7. van Den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65(11): 2737–2747.
8. Caramaschi P, Biasi D, Volpe A, et al. Coexistence of systemic sclerosis with other autoimmune diseases. *Rheumatol Int* 2007; 27(4): 407–410.
9. Elhai M, Avouac J, Kahan A, et al. Systemic sclerosis at the crossroad of polyautoimmunity. *Autoimmun Rev* 2013; 12(11): 1052–1057.
10. Milbradt W. Atypische diffuse sklerodermia mit Oslerschem syndrome und leberstorung. *Dermatol Monatsschr* 1934; 99: 973–979.
11. Murray-Lyon IM, Thompson RP, Ansell ID, et al. Scleroderma and primary biliary cirrhosis. *Br Med J* 1970; 3(5717): 258–259.
12. Marí-Alfonso B, Simeón-Aznar CP, Guillén-Del Castillo A, et al. Hepatobiliary involvement in systemic sclerosis and the cutaneous subsets: characteristics and survival of patients from the Spanish RESCLE registry. *Semin Arthritis Rheum* 2018; 47(6): 849–857.
13. Engel B, Taubert R, Jaeckel E, et al. The future of autoimmune liver diseases – understanding pathogenesis and improving morbidity and mortality. *Liver Int* 2020; 40(Suppl. 1): 149–153.
14. Kumagi T and Heathcote EJ. Primary biliary cirrhosis. *Orphanet J Rare Dis* 2008; 3: 1.
15. Lepri G, Bellando-Randone S, Matucci-Cerinic M, et al. Systemic sclerosis and primary biliary cholangitis: an overlapping entity. *J Scleroderma Relat Disord* 2019; 4(2): 111–117.

16. Cavazzana I, Ceribelli A, Taraborelli M, et al. Primary biliary cirrhosis-related autoantibodies in a large cohort of Italian patients with systemic sclerosis. *J Rheumatol* 2011; 38(10): 2180–2185.
17. Norman GL, Bialek A, Encabo S, et al. Is prevalence of PBC underestimated in patients with systemic sclerosis? *Dig Liver Dis* 2009; 41(10): 762–764.
18. Skare TL, Nisihara RM, Haider O, et al. Liver autoantibodies in patients with scleroderma. *Clin Rheumatol* 2011; 30: 129–132.
19. Wielosz E, Majdan M, Koszarny A, et al. Presence of organ specific antibodies in patients with systemic sclerosis. *Pol Arch Med Wewn* 2016; 11: 862–869.
20. Assassi S, Fritzler MJ, Arnett CF, et al. Primary biliary cirrhosis (PBC), PBC autoantibodies, and hepatic parameter abnormalities in a large population of systemic sclerosis patients. *J Rheumatol* 2009; 36(10): 2250–2256.
21. Avouac J, Airò P, Dieude P, et al. Associated autoimmune diseases in systemic sclerosis define a subset of patients with milder disease: results from 2 large cohorts of European Caucasian patients. *J Rheumatol* 2010; 37(3): 608–614.
22. De Santis M, Crotti C and Selmi C. Liver abnormalities in connective tissue diseases. *Best Pract Res Clin Gastroenterol* 2013; 27(4): 543–551.
23. Rigamonti C, Bogdanos DP, Mytilinaiou MG, et al. Primary biliary cirrhosis associated with systemic sclerosis: diagnostic and clinical challenges. *Int J Rheumatol* 2011; 2011: 976427–976412.
24. Rigamonti C, Shand LM, Feudjo M, et al. Clinical features and prognosis of primary biliary cirrhosis associated with systemic sclerosis. *Gut* 2006; 55(3): 388–394.
25. Ruaro B, Sulli A, Smith V, et al. Advances in nailfold capillaroscopic analysis in systemic sclerosis. *J Scleroderma Relat Disord* 2018; 3(2): 122–131.
26. David C, Chaigne B, Hollande C, et al. Primary biliary cholangitis and systemic sclerosis (Reynolds syndrome): a case-control study. *Autoimmun Rev* 2021; 20(7): 102842.
27. Jacobsen S, Halberg P, Ullman S, et al. Clinical features and serum antinuclear antibodies in 230 Danish patients with systemic sclerosis. *Br J Rheumatol* 1998; 37(1): 39–45.
28. Zeng N, Duan W, Chen S, et al. Epidemiology and clinical course of primary biliary cholangitis in the Asia-Pacific region: a systematic review and meta-analysis. *Hepatol Int* 2019; 13(6): 788–799.
29. Powell FC, Schroeter AL and Dickson ER. Primary biliary cirrhosis and the CREST syndrome: a report of 22 cases. *Q J Med* 1987; 62(237): 75–82.
30. Imura-Kumada S, Hasegawa M, Matsushita T, et al. High prevalence of primary biliary cirrhosis and disease-associated autoantibodies in Japanese patients with systemic sclerosis. *Mod Rheumatol* 2012; 22(6): 892–898.
31. Florin L, Rubben K, Vanhaecke A, et al. Evaluation of the primary biliary cholangitis-related serologic profile in a large cohort of Belgian systemic sclerosis patients. *Clin Chem Lab Med* 2020; 58(3): 416–423.
32. Marasini B, Gagetta M, Rossi V, et al. Rheumatic disorders and primary biliary cirrhosis: an appraisal of 170 Italian patients. *Ann Rheum Dis* 2001; 60(11): 1046–1049.
33. Liberal R, Grant CR, Sakkas L, et al. Diagnostic and clinical significance of anti-centromere antibodies in primary biliary cirrhosis. *Clin Res Hepatol Gastroenterol* 2013; 37(6): 572–585.
34. Pienkos S, Gallego N, Condon DF, et al. Novel TNIP2 and TRAF2 variants are implicated in the pathogenesis of pulmonary arterial hypertension. *Front Med* 2021; 8: 625763.
35. Ikawa T, Miyagawa T, Fukui Y, et al. Association of serum CCL20 levels with pulmonary vascular involvement and primary biliary cholangitis in patients with systemic sclerosis. *Int J Rheum Dis* 2021; 24(5): 711–718.
36. Nunes JPL, AC Cunha, Meirinhos T, et al. Prevalence of auto–antibodies associated to pulmonary arterial hypertension in scleroderma – a review. *Autoimmun Rev* 2018; 17(12): 1186–1201.
37. Miyawaki S, Asanuma H, Nishiyama S, et al. Clinical and serological heterogeneity in patients with anticentromere antibodies. *J Rheumatol* 2005; 32(8): 1488–1494.