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Background: Autoantibodies permit to classify and subgroup connective tissue diseases (CTD) in homogeneous groups of patients in terms of phenotype and prognosis. Anti PM-Scl antibodies have been associated with different CTD categories such as: idiopathic inflammatory myositis (IIM), systemic sclerosis (SSc), Sjögren's syndrome (SjS), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) or undifferentiated connective tissue disease (UCTD).

Objectives: To determine clinical spectrum of anti-PM-Scl associated disease and if it an homogenous condition.

Methods: This multicentric (four hospitals) observational and retrospective study included all consecutive patients with positive testing for anti PM-Scl antibodies on immunoblot assay and connective tissue disease (2011 -2020). Epidemiological, biological, clinical and radiological data were collected in standard form as well as patient's outcome.

Results: One hundred twenty height patients (female n=96;75%) were included. Median [quartiles] age at diagnosis was 50 [18;84] (IQR) and follow-up duration of 7 [3.75-12] years. Seventy-six (59.3%) patients were simple anti-PM-Scl positive, and 40.7% were associated with other antibodies: anti-SSA/Ro52 (n=13; 10.92%), SSc associated antibodies (n=21; 16.4%), anti-dsDNA for (n=9; 7%), anti-RNP (n=6; 4.7%) and anti-CCP antibodies (n=6; 4.7%). Most patients had cutaneous involvement (n=106; 83%) with skin thickening (n=47; 36%), mechanics hands (n= 28; 22%), calcinosis (n=26; 20.3%) and subcutaneous edema (n=20; 15.62%). Vascular involvement was frequent with Raynaud phenomenon (n= 89; 69%), telangiectasia (n=36; 28%), skin ulcers (n=27; 21%), pulmonary hypertension (n=8/120; 6.7%) and scleroderma renal crisis (n=2; 1.5%). A majority of patients also displayed an interstitial lung disease (ILD) (n=83; 65.8%); nonspecific interstitial pneumonia (92.7%) and/or organizing pneumonia (25.3%). ILD was characterized by a subacute onset in 37/81 (45.7%); median [quartiles] forced vital capacity (FVC) and total lung capacity (TLC) at diagnosis of 88% [73-105] and 79.5% [68.5-101] respectively. Sixty patients (47%) had muscular sign including myalgia (47%), elevated CPK (n=51; 40%) and muscular weakness (Medical Research Council score <4) (n=19/124;15%). Finally, fifty-three (41.7%) had gastroesophageal reflux. Thirty-nine patients (30.4%) experienced at least one muscular or ILD relapse and 6 (4.84%) died during follow-up (2 breast cancer, 1 pneumonia, 3 unknown etiology). Concerning patients' prognosis, relapses were associated with skeletal (n=29, 74.4% vs n=32, 35.96%, $p < 0.001$) or cardiac muscle involvement (n=7, 18.4% vs n=2, 2.5%, $p=0.007$), and subacute ILD (n=19, 65.5% vs n=18, 34.62%, $p=0.05$) with organized pneumonia pattern (n=11, 32.3% vs n=10, 13.9%, $p=0.05$). Strikingly, ILD occurred mainly in men (90.6% vs 57.2%, $p < 0.001$) and was associated with anti-Scl-70 positivity (n=14, 16.67% vs 0%, $p=0.01$). Muscle involvement was associated arthralgia (n=46, 76.67% vs n=34, 50.75%, $p=0.005$), respiratory signs at diagnosis: dyspnea NYHA ≥ 3 (n=46, 75.41% vs n=30, 44.78%, $p < 0.001$), sub-acute ILD (n=24, 61.54% vs n=13, 30.95%, $p=0.011$) with lower FVC (73% [64;88] vs 98 [76;105], $p < 0.001$). Ulcers were associated with Anti-Scl70 positivity (n=9, 33.33% vs n=5, 4.95%, $p < 0.001$), Raynaud phenomenon (n=27, 100% vs n=62, 61.39%, $p < 0.001$), digestive involvement (n=20, 74.07% vs n=34, 33.66%, $p < 0.001$), ILD with chronic onset (n=15, 78.95% vs n=29, 46.77%, $p=0.027$) and increased incidence of deaths (n=4, 16% vs n=2, 2.02%, $p=0.01$).

Conclusion: Conducted on the largest cohort of Anti-PM-Scl patients, this study highlights two main phenotypes that determine different outcome and prognosis. One was associated with muscular disease and subacute onset ILD with more frequent relapses. The second with a vascular phenotype associated with chronic ILD, digestive involvement, chronic evolution and increased incidence of death. This could lead to a reclassification of PM-Scl associated autoimmune diseases.

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POS0324

SMOKING HISTORY AND SCLERODERMA CLINICAL TRIALS CONSORTIUM DAMAGE INDEX (SCTC-DI) AS INDEPENDENT PREDICTORS OF MORTALITY IN SYSTEMIC SCLEROSIS IN A SINGLE-CENTRE ITALIAN COHORT

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Background: Systemic Sclerosis (SSc) is characterized by increased mortality and organ damage accrual. A composite SSc Damage Index was recently developed by the Scleroderma Clinical Trials Consortium (SCTC-DI) and was demonstrated as a predictor of mortality both in the Australian derivation cohort and in the Canadian validation cohort (1). Several independent predictors of mortality in SSc have been reported, but only limited data are available on the role of smoking.

Objectives: To evaluate smoking history and SCTC-DI as independent predictors of mortality in SSc in a single centre Italian cohort.

Methods: A retrospective analysis was performed on patients prospectively followed in our centre from 1989 to 2019, with at least 2 evaluations and/or cause of death available. Organ damage was evaluated through the SCTC-DI (0-55 scale; severe damage>12), while comorbidities through the Charlson Comorbidity Index (CCI). Survival analysis was performed with Kaplan-Meier curves and with Log-rank test to compare different subsets. Cox-regression analysis was performed to identify baseline independent predictors of mortality.

Results: 648 SSc patients were 99% Caucasian, 90% female and had a median age at diagnosis of 55.5 years (IQR: 45.0-65.6); 19% had diffuse cutaneous involvement. ACA was positive in 52%; anti-Topol in 22% and anti-RNA Polymerase III in 5%.

Median SCTC-DI at diagnosis was 2 (0-4) (n=560); ever smokers were 27%. During the follow-up 240 patients died after a median period of 10.2 years (4.9-16.8). The cause of death was related to SSc in 41% (n=65; most frequent causes pulmonary arterial hypertension (n=35) and interstitial lung disease (n=30)) and to other diseases in 40% (n=95; most frequent cause cancer (n=40)), while was indeterminate in 19%.

Overall survival at 5, 10, 15, 20 years was 87.8% (SE 1.3%), 75.6% (1.9), 63.8% (2.3), 47.7% (2.8), respectively and was higher in females vs. males ($p < 0.0001$) and in ACA+ vs ACA- ($p=0.005$), but did not differ between cutaneous subsets. 111 patients were lost at follow-up (17%).

In the Cox-regression analysis smoking history and severe organ damage at diagnosis (score>12) were identified as independent predictors of death, while age at diagnosis, female gender, diffuse cutaneous subsets, ACA positivity and CCI were not (Table 1).

Conclusion: Smoking history and severe organ damage were independent predictors of death in a large Italian single centre SSc cohort. SCTC-DI was confirmed as a useful tool to predict mortality at every timepoint

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Characteristics	P-value	Hazard ratio	Confidence interval 95%
Female gender	0.9726	0.992	0.619-1.590
Diffuse cutaneous subset	0.7407	1.036	0.729-1.366
Ever smoker	0.0005	1.545	1.211-1.972
SCTC-DI at diagnosis >12 (severe damage)	0.0353	3.450	1.089-10.929
ACA positivity	0.7407	1.046	0.801-1.366
Age at diagnosis	0.4961	1.005	0.991-1.018
Charlson Comorbidity Index (age excluded)	0.1555	1.094	0.966-1.238

Table 1. Cox-regression analysis for any cause of death.

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POS0325

RADIOMIC BIOMARKER OF PULMONARY VASCULAR RELATED STRUCTURES PREDICTS MORTALITY IN SYSTEMIC SCLEROSIS

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Background: Quantitative computed tomography (QCT) extracts features from high-resolution CT scans and quantifies lung parenchymal and vascular abnormalities which may not be discernable by qualitative review. The threshold values

of individual parenchymal abnormalities and vascular features measured by QCT methods which associate with mortality in systemic sclerosis (SSc) are currently unknown.

Objectives: To determine whether QCT measures, specifically pulmonary parenchymal abnormalities and pulmonary vascular related structures (PVRS), can predict mortality in SSc and to determine the optimal quantitative thresholds for those parameters.

Methods: A total of 133 subjects (76% women) meeting 2013 ACR/EULAR classification criteria for SSc with a baseline CT within 3 years of diagnosis were retrospectively identified for inclusion. CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) was used to quantitatively measure volume of ground glass opacities (GGO), reticular densities, and honeycombing (HC). Total interstitial lung disease (ILD) was the summation of these features. PVRS was also quantified using CALIPER. Values for each feature were expressed as a percentage of total lung volume. Cox models evaluated the hazard ratio (HR) for mortality for each parameter adjusting for age at SSc diagnosis, sex, diffuse SSc subtype, and history of smoking. The optimal thresholds for mortality prediction for each parameter were determined using consensus between 4 methods: Contal and O'Quigley Method, Cox Model Hazard Ratio, Cox Model Wald P-value, and False Discovery Rate. The c-statistic was used to assess each models' ability to predict mortality.

Results: Mean $\pm$ SD for age at SSc diagnosis was 61 ± 13 years and length of follow-up was 4.7 ± 3.0 years. There were 32 deaths (24%). A Cox model including age (HR 1.05, 95% CI: 1.01-1.09), female sex (HR 0.49, 95% CI: 0.22-1.08), diffuse SSc subtype (HR 1.50, 95% CI: 0.69-3.30), and history of smoking (HR 2.09, 95% CI: 0.97-4.53) (Model 1) significantly predicted mortality (C-statistic 0.72, 95% CI: 0.63-0.81). Adjusting for Model 1, reticular densities% (HR 1.19, 95% CI: 1.05-1.35), total ILD% (HR 1.02, 95% CI: 1.00-1.03), and PVRS% (HR 1.19, 95% CI: 1.05-1.35) were associated with mortality on univariable analyses; GGO% (HR 1.01, 95% CI: 0.98-1.04) was not significantly associated with mortality. The optimal thresholds for mortality prediction were then determined and were as follows: GGO $\geq$ 20%, reticular densities $\geq$ 8%, total ILD $\geq$ 20%, and PVRS $\geq$ 5%. While the risk of mortality was significantly increased in subjects with GGO $\geq$ 20% (HR 2.70, 95% CI: 1.21-6.05), reticular densities $\geq$ 8% (HR 4.64, 95% CI: 1.68-12.81), and total ILD $\geq$ 20% (2.59, 95% CI: 1.12-5.99), these baseline thresholds did not improve upon mortality prediction when added individually to Model 1 (C-statistic 0.73 for each). PVRS $\geq$ 5%, which had an over six-fold increase in mortality (HR 6.42, 95% CI: 2.60-15.88), did improve mortality prediction when added to Model 1 (C-statistic 0.78, 95% CI: 0.70-0.86).

Conclusion: PVRS strongly associates with early mortality in patients with SSc and represents a novel radiomic biomarker that provides prognostic information on mortality beyond pulmonary parenchymal abnormalities. CALIPER derived PVRS quantifies CT data through a function that defines connected tubular branching structures. This extracts pulmonary arteries and veins from the adjacent parenchyma but could potentially also include regions of adjoining of fibrosis.¹ Larger studies examining the association between PVRS and progression of cardiopulmonary disease are warranted.

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Systemic sclerosis, myositis - etiology, pathogenesis and animal models

POS0326

ROLE OF THE IL-25 / IL-17RB AXIS IN TH9 POLARIZATION IN PATIENTS WITH PROGRESSIVE SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is an inflammatory connective tissue disease leading to chronic and progressive fibrosis, typically affecting the skin and internal organs. The alteration of both innate and adaptive immune responses plays a pivotal role in SSc pathophysiology, although it has not yet been fully elucidated [1].

Recent findings have demonstrated interleukin (IL)-9 overexpression and significant group 2 innate lymphoid cells (ILC2) expansion in patients with SSc. Th9-ILC2-mast cells axis seems to be involved in SSc tissue damage and in the induction of fibrosis [2]. Activation and production of IL-9 by Th9 cells are promoted by transforming growth factor (TGF)- β , thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. Thus, the IL-25 / IL-17RB pathway would act as a key player in SSc.

Objectives: The purpose of this study was to evaluate the role of the IL-25 / IL-17RB axis as a driver in Th9 polarization and ILC2 expansion and polarization in SSc patients.

Methods: 26 patients were enrolled in this study. Peripheral blood and skin biopsy specimens were obtained from SSc patients. PBMCs were isolated and incubated with and without recombinant (r)IL-25 for 24-48-72 hours and the frequencies of Th9 cells, Th17 cells and ILC2 were assessed by flow cytometry analysis. Moreover, the *ex vivo* expression of IL-17RB in ILC2 was also assessed. Immunofluorescence analysis was performed on biopsy skin samples to evaluate IL-17RB expression in ILC2.

Results: In SSc samples, Th9 cells frequency progressively increased after stimulation with rIL-25, compared to healthy controls in which IL-9 frequency decreased over time regardless of rIL-25.

Simultaneously, we evaluated the role of the IL-25 / IL-17RB axis in Th17 cells. In the SSc pool, the initially low rate of IL-17 increased at 72 hours after stimulation with rIL-25. In unstimulated SSc samples, the initially higher IL-17 rate decreased at 72 hours; conversely, it was consistently low in healthy controls, at both baseline and stimulated conditions.

Our results confirmed the presence of IL-25-dependent clonal ILC2 expansion, suggesting a greater and progressive expansion over time in patients with SSc, compared to controls.

Interestingly, increased IL-17RB expression was found in circulating ILC2 from SSc patients supporting the characterization of ILC2 inflammatory phenotype. Consistently, immunofluorescence on the skin of SSc patients showed a marked infiltrate of CD3⁺GATA3⁺ IL-17RB⁺ cells, confirming the presence of the activated inflammatory phenotype ILC2, absent in skin biopsies of healthy controls (Figure 1).

Conclusion: These preliminary data suggest an active role of the IL-25/IL-17RB axis in SSc. It results in Th9 polarization and Th17 clonal expansion, inducing the production of IL-9 and, to a lesser extent, IL-17. Moreover, in addition to promoting Th9-mediated ILC2 differentiation, IL-25 directs the polarization of ILC2 towards the inflammatory phenotype.

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Figure 1. Immunofluorescence on biopsy skin samples of SSc patients (top) and healthy control (bottom).

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