CCL24 serum concentration predicts both vascular and fibrotic complications in systemic sclerosis

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Background:

- CCL24 is a novel target that was found to play a dual role in advancing **pro-inflammatory and pro-fibrotic processes** in systemic sclerosis (SSc).
- Previous studies reported that skin and serum CCL24 levels are elevated in SSc and that blocking of CCL24 was effective in preventing and attenuating experimental-induced fibrosis in murine models as well as interfering with **endothelial cell activation**.

Aims of the study

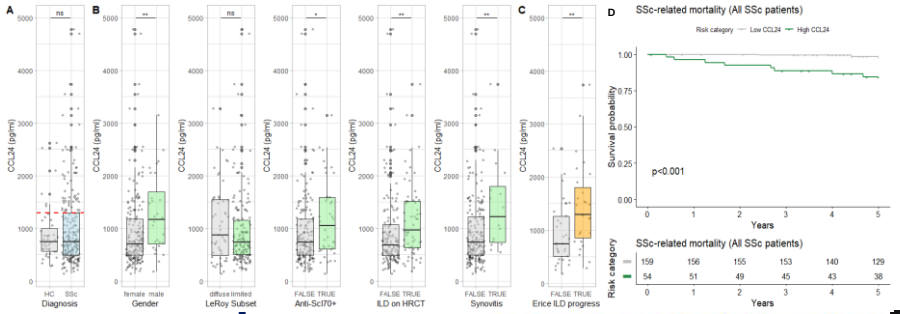
- To investigate the relationship of serum CCL24 to **disease features** in SSc.
- To investigate the ability of serum CCL24 to **predict clinical pulmonary progression in patients with interstitial lung disease (ILD)**
- To investigate the ability of serum CCL24 to **predict 5-year SSc-related mortality**.

Methods

- Consecutive SSc patients from a single-centre **observational cohort** were enrolled in this analysis and compared with age- and gender- matched healthy controls (HCs).
- Clinical data were collected according to the **EUSTAR minimal essential data set**.
- Serum Concentration of CCL24 was measured by **Luminex assay** (Myriad RBM) and a **High CCL24 status** was defined for serum values one standard deviation above the log-transformed mean in the HC group.
- **Progressive ILD** was defined as previously described, according to **Erice's criteria** within 24 months after CCL24 assessment.

Table 1: Overall patient characteristics and associations with CCL24 status

	Overall, N = 213	Low CCL24, N = 159	High CCL24, N = 54	p-value
Age, years, mean±SD	54.2±12.4	53.9±12.6	55.2±12.0	0.5
Body Mass Index, kg/m², mean±SD	26.4±5.3	26.7±5.1	25.6±5.7	0.2
Male gender, n	28 (13.1%)	17 (10.7%)	11 (20.4%)	0.069
Diffuse LeRoy, n	51 (23.9%)	33 (20.8%)	18 (33.3%)	0.061
Duration, years, median (IQR)	6.0 (3.0, 14.0)	7.0 (3.0, 14.0)	5.0 (2.0, 13.0)	0.2
Anti-Centromere positive, n	110 (51.6%)	86 (54.1%)	24 (44.4%)	0.2
Anti-Scl70 positive, n	38 (17.8%)	24 (15.1%)	14 (25.9%)	0.072
Active or late capillaroscopy, n	110 (67.9%)	81 (65.9%)	29 (74.4%)	0.3
Late capillaroscopy, n	54 (33.1%)	37 (30.1%)	17 (42.5%)	0.15
mRSS, median (IQR)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	3.0 (2.0, 4.8)	**0.048**
ILD on HR Computed Tomography, n	61 (28.6%)	39 (24.5%)	22 (40.7%)	**0.023**
PAH on Right Heart Catheterism, n	18 (8.5%)	12 (7.5%)	6 (11.1%)	0.4
Baseline FVC, %, mean±SD	103.9±22.0	104.6±22.1	101.7±21.7	0.4
Baseline DLco, %, mean±SD	64.7±15.5	66.2±15.6	60.2±14.5	**0.015**
Digital ulcers, n	100 (46.9%)	68 (42.8%)	32 (59.3%)	**0.036**
Skin calcinosis, n	117 (54.9%)	81 (50.9%)	36 (66.7%)	**0.045**
Telangiectasias, n	137 (64.3%)	96 (60.4%)	41 (75.9%)	**0.039**
Synovitis, n	16 (7.5%)	8 (5.0%)	8 (14.8%)	**0.032**
Myositis, n	18 (8.5%)	13 (8.2%)	5 (9.3%)	0.8
Immunosuppressants, n	59 (27.7%)	36 (22.6%)	23 (42.6%)	**0.005**
Vasoactive treatment, n	141 (66.2%)	103 (64.8%)	38 (70.4%)	0.5
CCL24, pg/ml, mean±SD	996.4±756.4	646.6±264.9	2,026.4±794.7	**<0.001**



Results

- Serum CCL24 did not differed in the overall SSc population compared to HCs but the 27.7% presented a high CCL24 status (Fig. A)
- Higher serum CCL24 levels were associated with **male gender, anti-Scl70 positivity, evidence of ILD on computed tomography, and history of arthritis** (Fig. B)
- High CCL24 status was also associated with **digital ulcers, skin calcinosis, skin telangiectasias, lower lung diffusion of CO (DLco), and higher modified Rodnan Skin Score** (Tab. 1)
- ILD progression was associated with higher baseline serum CCL24 (Fig. C) and the **high CCL24 status was associated with a three-fold increased risk ILD progression** in the following 2 years (OR 3.36, 95% IC 1.12 - 10.08).
- Lung functional deterioration measured by **relative FVC reduction** correlated with serum CCL24 levels at baseline (R = -0.430, p<0.001=
- A high CCL24 status at baseline was associated with an **shorter 5-year SSc-related survival time** (Fig D).

Conclusions:

- We show here that within the context of an observational cohort of unselected patients, **higher CCL24 serum concentrations reflect a more severe SSc disease and predict its prognosis**.
- These results informed the rationale for a **target-enriched basket randomized controlled trial** to test the biological and clinical effect of CCL24 inhibition in SSc across cutaneous disease subsets.

Mor A et al. Ann Rheum Dis. 2019, George P et al. Lancet Resp Med 2020

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