The role of Inflammation in Systemic Sclerosis: A Comprehensive Analysis of CRP-Associated Phenotypes and Prognostic Implications

Cristiana Sieiro Santos 1, Miriam Retuerto-Guerrero1, Paula Pérez-García 1, Jose Ordas Martínez 1, Pedro Baenas González 1, Carolina Álvarez Castro 1, Carolina Díez 1, Ismael González Fernández 1, Ignacio González Fernández 1, Clara Moriano 1, Elvira Diez Álvarez 1

1 Servicio de Reumatología, Complejo Asistencial Universitario de León

Background

- Systemic sclerosis (SSc) manifests through a diverse **interplay of inflammatory, fibrotic, and vascular alterations**, intricately entwined in its pathogenesis, which encompasses immune system dysregulation, tissue fibrosis, and vascular dysfunction.
- While elevated C-reactive protein (CRP) levels in SSc have been associated with the early inflammatory phases of the disease, comprehensive data regarding the influence of CRP on SSc activity and severity remain limited.

Objectives

- This study aims to investigate the **significance of inflammatory phenotypes in clinical parameters among individuals with SSc** and to **assess the prognostic importance of baseline and persistent inflammatory phenotypes in SSc**

Methods

- A cross-sectional study involving **133 SSc patients meeting the 2013 ACR/EULAR criteria** was conducted. Patients were categorized into **inflammatory (CRP > 5 mg/l) and non-inflammatory (CRP < 5mg/l) phenotypes** at the first visit and additionally stratified into **persistent inflammatory/non-inflammatory phenotypes (CRP>5 mg/l for >80% of visits).** Cox regression models analysed **mortality risk and ILD development**. Logistic regression assessed **the risk of major organ involvement (ILD, PH, scleroderma renal crisis, heart involvement, peripheral vasculature involvement)** relative to inflammation at SSc onset, adjusting for conceptual confounders. .

Results

- Among 133 patients, **53 (39%) exhibited a persistent inflammatory phenotype**. The inflammatory phenotype was more frequently associated **with diffuse-cutaneous disease (p=0.02), anti-Scl-70 autoantibodies (p=0.02), ILD (p=0.02), lower diffusing capacity for carbon monoxide (p=0.01) and myositis (p=0.04)** (Table 1).
- **Higher serum levels of KL-6 (p=0.002) and IL-18 (p=0.04)** at baseline were observed in patients with an inflammatory phenotype. Those with persistent inflammation had a **4.6 times higher risk of all-cause mortality** (HR 4.61 [95% CI 1.2-15.2, p=0.04) and **5.6 times higher of ILD** (HR 5.41 [95%CI 2.4-16.4], p=0.02) compared to non-inflammatory patients (figure 1 and figure 2).

Cristiana Sieiro Santos
@cristianasieiro
cristysieirosantos@gmail.com

- Logistic regression linked **inflammation with mortality** (β=0.65, p=0.004), ILD (β=0.45, p=0.007), **arthritis** (β=0.40, p=0.04), **myositis** (β=0.23, p=0.04), **IL-18 concentration** (β=0.32, p=0.002) and **anti-Scl70 positivity** (β=0.21, p=0.04).

	Inflammatory phenotype	Non-inflammatory phenotype	P value
Age at diagnosis (mean ±SD)	66.6±17.5	59±14.5	0.16
Female (n, %)	37 (70%)	57 (72%)	0.86
Disease duration in years (mean ± SD)	3±2.1	6.5±7.5	**0.02**
Diffuse cutaneous (n, %)	13 (25%)	7 (9%)	**0.02**
Scl70 positivity (n, %)	16 (30%)	11 (14%)	**0.02**
mRSS (mean ± SD)	14±9.4	8+4.5	**0.02**
sPAP≥40 mmHg (n, %)	26 (49%)	21 (26%)	**0.008**
PH (n, %)	14 (26%)	12 (15%)	0.10
ILD (n, %)	28 (53%)	26 (33%)	**0.02**
%FVC<80 (n, %)	32 (60%)	29 (36%)	**0.007**
%FVC (mean ± SD)	76.5±11	79.8±14	0.16
%DLCO<75% (n, %)	37 (70%)	39 (49%)	**0.01**
%DLCO (mean ± SD)	60±23	72±23	**0.01**
Pericardial effusion	10 (19%)	14 (17.5%)	0.84
AV block (n, %)	9 (21%)	5 (6%)	**0.04**
Diastolic dysfunction (n, %)	32 (60%)	45 (56%)	0.63
Gastrointestinal involvement (n, %)	28 (53%)	42 (53%)	0.97
Renal crisis (n, %)	6 (11%)	11 (14%)	0.68
Myositis (n, %)	12 (23%)	8 (10%)	**0.04**
Arthritis (n, %)	15 (28%)	21 (26%)	0.79
Digital ulcers (n, %)	17 (32%)	28 (35%)	0.72
Late pattern in NFC (n, %)	33 (62%)	30 (38%)	**0.006**
KL-6 levels (median ±SD)	627,34±145	443,45±82	**0.002**
IL-18 levels (median ±SD)	256,45±102	102,49±24	**0.04**
Mortality (n, %)	20 (38%)	7 (9%)	**0.0002**
Prednisone>10mg/day	14 (26%)	10 (12.5%)	**0.04**
MMF (n, %)	30 (69%)	31 (39%)	**0.001**
RTX (n, %)	8 (15%)	10 (12.5%)	0.67
CYC (n, %)	9 (17%)	9 (11%)	0.34
MTX (n, %)	10 (19%)	25 (31%)	0.12

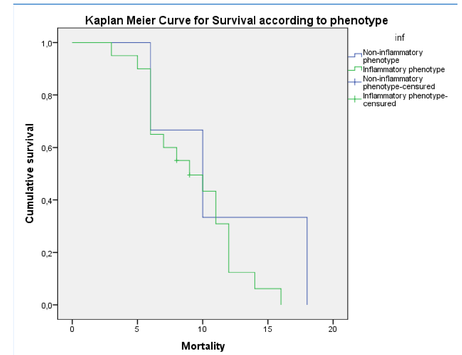

Figure 1: Kaplan-Meier survival curve comparing patients according to their inflammatory phenotype.

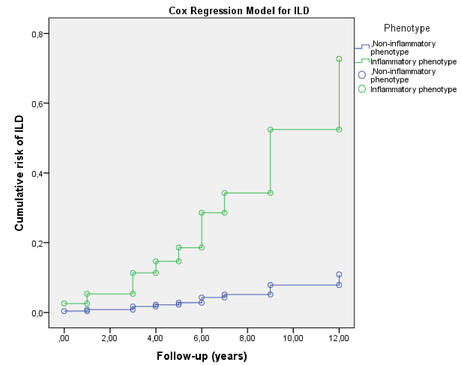

Figure 2: Cox Hazard Regression model for ILD in SSc patients according to their inflammatory phenotype

Conclusion

The study linked **persistent inflammation in SSc patients** to distinct clinical and immunological features. Importantly, patients with **persistent inflammation had substantially increased risks of all-cause mortality and ILD.** These findings highlight the prognostic value of recognizing and monitoring the inflammatory phenotype in SSc patients for more targeted management approaches.

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