

Phenotyping by persistent inflammation in systemic sclerosis associated interstitial lung disease: a EUSTAR database analysis

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ABSTRACT

Background Systemic sclerosis (SSc) is a heterogeneous disease with frequently associated interstitial lung disease (SSc-ILD). We aimed to determine the prognostic potential of phenotyping patients with SSc and SSc-ILD by inflammation and to describe disease trajectories stratified by inflammation and immunosuppressive treatment.

Methods Patients from the European Scleroderma Trials and Research (EUSTAR) group cohort were allocated to persistent inflammatory, intermediate and non-inflammatory phenotypes if C-reactive protein (CRP) levels were ≥ 5 mg/L at $\geq 80\%$, at 20–80% and at $< 20\%$ of visits, respectively. Cox regression models were used to analyse mortality risk and mixed effect models to describe trajectories of FVC and diffusing capacity for carbon monoxide (DLCO) %-predicted stratified by inflammation and immunosuppressive treatment.

Results 2971 patients with SSc and 1171 patients with SSc-ILD had at least three CRP measurements available. Patients with SSc-ILD with a persistent inflammatory phenotype had a 6.7 times higher risk of mortality within 5 years compared with those with a persistent non-inflammatory phenotype (95% CI 3 to 15). In the inflammatory phenotype, FVC %-predicted was declining without (−1.11 (95% CI −2.14 to −0.08)/year), but stable with immunosuppressive treatment (−0.00 (95% CI −0.92 to 0.92)/year). In the non-inflammatory phenotype, patients with and without immunosuppressive treatment had a significant decline in FVC %-predicted, which was more pronounced in those with immunosuppressive treatment (−1.26 (95% CI −1.87 to −0.64) and −0.84 (95% CI −1.35 to −0.33)/year, respectively).

Conclusions Phenotyping by persistent inflammation provides valuable prognostic information, independent of demographics, disease duration, cutaneous subtype, treatment and SSc-ILD severity. The findings from this study support early immunosuppressive treatment in patients with SSc-ILD with persistent inflammation.

INTRODUCTION

Systemic sclerosis (SSc) is a heterogeneous disease characterised by vasculopathy, fibrosis and autoimmunity. Affected individuals suffer from severe

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Preliminary studies in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD) suggest that C-reactive protein blood levels might be prognostically important.
- ⇒ Several randomised controlled trials demonstrate efficacy of immunosuppressive and antifibrotic drugs in the heterogeneous SSc-ILD population, however, strategies on phenotyping for treatment decisions are lacking.

WHAT THIS STUDY ADDS

- ⇒ This study shows that persistent inflammation is an important risk factor for early mortality in SSc-ILD, independent from demographics, time from disease onset, cutaneous phenotype, baseline pulmonary function and immunosuppressive treatment.
- ⇒ This study also describes patients with SSc-ILD with an inflammatory phenotype to show stable FVC trajectories with immunosuppression, whereas those with a non-inflammatory phenotype have declining FVC when treated with conventional immunosuppressive drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Phenotyping by persistent inflammation is a useful concept for clinical practice and might facilitate risk stratification and potentially treatment decisions in SSc-ILD.

organ manifestations which impact on patients' quality of life and survival.¹ Interstitial lung disease (ILD) is a frequent and severe SSc complication and approximately 40–50% of patients suffer from a progressive decline in pulmonary function, leading to a loss of physical functionality and early mortality.²

Management of SSc remains challenging, and several immunosuppressive drugs are used to treat organ manifestations with several randomised controlled trials demonstrating efficacy in patients with SSc-ILD.^{3–6} Cyclophosphamide,



mycophenolate mofetil, azathioprine and methotrexate are frequently used,^{3 4 7} and autologous stem-cell transplantation and biologicals are emerging treatment options in selected patients.^{5 6 8–10} Furthermore, nintedanib has been shown to reduce lung function decline and has recently been approved for the treatment of SSc-ILD.^{11 12}

The availability of immunosuppressive and antifibrotic SSc-ILD treatments emphasises the need for biomarkers to estimate response to therapy and facilitate treatment decisions in the individual patient. It is likely that not all patients with SSc benefit from immunosuppressive therapies, and predictors of treatment response are urgently needed.^{5 13 14} The concept of phenotyping patients with SSc by serum C-reactive protein (CRP) levels and corresponding inflammation has been suggested previously. Elevated serum CRP levels have been observed more frequently in the diffuse cutaneous subtype and have been associated with higher disease activity, poorer pulmonary function and shorter survival.^{15–17} To date, it is unclear whether consideration of multiple CRP values over time is more informative than single CRP values¹⁵ and whether patients with inflammatory SSc respond better to immunosuppressive therapy than patients with a non-inflammatory phenotype.

We hypothesised that patients with SSc with persistent inflammation are not only characterised by a more severe phenotype and higher mortality but also respond better to immunosuppressive therapy than patients with a non-inflammatory phenotype. To investigate this, we identified patients with persistent inflammation and assessed phenotype, overall survival and disease course with and without immunosuppressive treatment in the European Scleroderma Trials and Research group (EUSTAR) cohort.¹⁸

METHODS

Study design and patient population

This multicentre cohort study analysed data from patients with SSc included in the prospective EUSTAR database. The EUSTAR database is an international registry, established in 2004, which follows patients with SSc annually.^{18 19} At the time of data extraction, 19 115 patients had been included in EUSTAR. Inclusion criteria for this study were fulfilling the ACR/EULAR classification criteria for SSc,²⁰ and availability of CRP measurement at baseline (defined as first visit documented in the EUSTAR database) and at least two follow-up visits. EUSTAR demands entry of regular and not high-sensitivity CRP measurements. Patients with reports of infections and those treated with tocilizumab were excluded due to invalidity of CRP values for inflammatory phenotyping. Presence of SSc-ILD was considered in patients who were clinically labelled as having pulmonary fibrosis and/or had indication of radiological ILD characteristics on chest CT scans, including groundglass opacities, reticulations, traction bronchiectasis and/or honeycombing.

Definition of the inflammatory phenotypes

For the persistent inflammatory phenotype, ≥ 3 CRP values from consecutive visits were included in the evaluation. Patients were stratified as persistent inflammatory, if CRP values were ≥ 5 mg/L on $\geq 80\%$ of visits, intermediate, if CRP ≥ 5 mg/L at 20–80% of visits and persistent non-inflammatory if CRP ≥ 5 mg/L at $< 20\%$ of visits. This classification has been established in a previous study and has shown to be resistant to treatment with immunosuppressive drugs.¹⁵

For a sensitivity analysis, the baseline inflammatory phenotype was defined by the first available (baseline) CRP value.

Patients were stratified as baseline inflammatory versus non-inflammatory if CRP values were ≥ 5 mg/L and < 5 mg/L at baseline, respectively.

Definition of treatment groups

Patients were stratified to the treatment group if they had received any of the following immunosuppressive treatments within 5 years from baseline: cyclophosphamide, mycophenolate mofetil, methotrexate, azathioprine, rituximab or prednisone > 10 mg per day at any visit. The no treatment group consisted of the patients who had not received any immunosuppressive drugs.

Outcomes

Overall survival of the patients with inflammatory phenotypes was estimated by analysing time from the first available CRP measurement (baseline) to all-cause death or censoring within 5 years from baseline. Pulmonary function tests were performed in the individual centres using established protocols.

Statistical analysis

Patients' characteristics were described as number (percentage) or median (IQR). Kaplan-Meier curves were used to illustrate survival function for the inflammatory phenotypes. To examine the association between the inflammatory phenotypes and mortality, we used Cox proportional hazards models to estimate HR and its 95% CI. Models were adjusted for prespecified confounders with conceptual importance. Age, sex, ever smoking, years from onset of first non-Raynaud manifestation, diffuse vs limited cutaneous disease and immunosuppressive treatment were the confounders for the SSc-ILD subgroup, with addition of ILD for the entire SSc cohort.^{15–17 21–23} The proportional hazards assumption was verified using log-log plots of survival.

In patients with SSc-ILD, FVC %-predicted and diffusing capacity for carbon monoxide (DLCO) %-predicted mean trajectories with 95% CI were estimated for the persistent inflammatory phenotypes using mixed effect models with random intercepts accounting for repeated measurements per patient. An independent variance-covariance structure of the random effects was used and mixed effects models were adjusted for the respective baseline values of FVC and DLCO %-predicted. For the adjusted analyses, the following prespecified confounders were included in the models: age, sex, ever smoking, years from onset of first non-Raynaud manifestation, diffuse versus limited cutaneous disease and immunosuppressive treatments. Multiple imputation was performed using chained equations to impute covariates' missing values. Imputation models were based on all other covariates as well as the baseline inflammatory phenotype. In total, 50 imputed data sets were generated, which were analysed as described above using Rubin's rules to combine results across data sets.²⁴ A $p < 0.05$ indicated statistical significance for all comparisons. Data were analysed using Stata V.17.0 (Stata Corporation).

RESULTS

Study overview and patient characteristics by inflammatory phenotype

Of the 19 115 patients in the registry, 8852 with available CRP measurements were included in the study, with follow-up visits available in 5776. For stratification by persistent inflammation, at least three CRP values were needed and 2971 patients with SSc and 1171 with SSc-ILD were considered for these analyses (online supplemental figure S1, table 1). CT scans were available

Interstitial lung disease

Table 1 Patient characteristics stratified by persistent inflammatory phenotypes in all SSc and in patients with SSc-ILD

All SSc	Non-inflammatory (n=1048)	Intermediate (n=1499)	Inflammatory (n=424)
Sex, women	920 (88%)	1253 (84%)	337 (79%)
Age, years	56 (46–64)	57 (48–66)	57 (49–66)
Race, white	960 (92%)	1295 (86%)	314 (74%)
Body mass index, kg/m ²	24 (21–27)	24 (22–27)	25 (22–29)
Ever smoker	272 (26%)	352 (23%)	136 (32%)
Time from SSc onset, years	8.4 (3.7–15)	8.8 (3.5–15)	7.4 (2.7–13)
Cutaneous subset			
Diffuse	228 (22%)	416 (28%)	145 (34%)
Limited	612 (58%)	800 (53%)	195 (46%)
mRSS	4 (1–9)	4 (1–10)	6 (2–13)
Puffy fingers	624 (60%)	908 (61%)	248 (58%)
Joint synovitis	320 (31%)	522 (35%)	146 (34%)
Digital ulcers, ever	419 (40%)	719 (48%)	182 (43%)
Tendon friction rubs	40 (3.8%)	80 (5.3%)	23 (5.4%)
Serum markers			
Anti-topoisomerase	276 (26%)	489 (33%)	153 (36%)
Anti-centromere	374 (36%)	492 (33%)	121 (29%)
Anti-RNA polymerase III	40 (3.8%)	57 (3.8%)	17 (4.0%)
CRP, mg/L	1.0 (0.5–2.2)	2.7 (0.1–5.7)	11 (7.3–21)
Comorbidities, symptoms and treatment			
Arterial hypertension	220 (21%)	369 (25%)	120 (28%)
Pulmonary hypertension	76 (7.3%)	146 (10%)	46 (11%)
Renal crisis	13 (1.2%)	15 (1.0%)	10 (2.4%)
Oesophageal symptoms	612 (58%)	896 (60%)	257 (61%)
Any immunosuppression*	350 (33%)	556 (37%)	186 (44%)
SSc-ILD (n, % of all SSc)	Non-inflammatory (n=390, 37%)	Intermediate (n=604, 40%)	Inflammatory (n=177, 42%)
Time from ILD diagnosis, years	4.6 (1.4–9)	4.4 (1.4–11)	3.4 (1.1–8)
CRP, mg/L	1.1 (0.5–2.2)	2.7 (1.0–6.4)	11 (7.3–18)
TLC, %-predicted	91 (79–105)	90 (76–102)	86 (69–95)
FVC, %-predicted	90 (79–105)	88 (73–102)	79 (67–95)
DLCO, %-predicted	64 (51–75)	60 (47–73)	55 (40–68)
6 min walk distance	510 (435–564)	483 (410–560)	470 (380–545)
Ground glass opacities	144 (37%)	225 (37%)	70 (40%)
Reticulations	94 (24%)	121 (20%)	60 (34%)
Traction bronchiectasis	51 (13%)	103 (17%)	45 (25%)
Honeycombing	40 (10%)	70 (12%)	27 (15%)
Treatment in SSc-ILD			
Any immunosuppression*	152 (39%)	278 (46%)	96 (54%)
Cyclophosphamide	21 (5%)	38 (6%)	14 (8%)
Mycophenolate mofetil	14 (4%)	26 (4%)	8 (5%)
Methotrexate	30 (8%)	51 (8%)	33 (19%)
Azathioprine	45 (12%)	75 (12%)	12 (7%)
Rituximab	1 (0.3%)	3 (0.5%)	3 (1.7%)
Prednisone >10 mg/d	8 (2%)	16 (3%)	4 (2%)

Data presented as median (IQR) or number (percentage).
 *Within 5 years from baseline.
 DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; mRSS, modified rodnan skin score; mRSS, modified Rodnan skin score; NYHA, New York Heart Association functional classification; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis associated interstitial lung disease; TLC, total lung capacity.

in 810 (69%) of the patients with SSc-ILD, FVC %-predicted in 1131 (97%) and DLCO %-predicted in 1085 (93%).

Of the entire SSc cohort, 424 patients (14%) had a persistent inflammatory, 1499 (50%) an intermediate and 1048 (35%) a persistent non-inflammatory phenotype. Patients with a persistent inflammatory phenotype were less frequently women (79% vs 88%) and white (74% vs 92%), more frequently smokers (32% vs 26%) and presented more often with a diffuse cutaneous phenotype (34% vs 22%) compared with patients with a persistent non-inflammatory phenotype. The median time from onset of first non-Raynaud's symptoms was 1 year shorter in persistent inflammatory compared with non-inflammatory patients (median 7.4 vs 8.4 years). The persistent inflammatory phenotype was also associated with more severe skin disease (median (IQR) modified Rodnan Skin Score 6 (2–13) and 4 (1–9) in inflammatory and non-inflammatory patients, respectively). Joint synovitis and digital ulcers were more frequently present in the persistent inflammatory phenotype (34% vs 31% and 43% vs 40%, respectively). Autoantibodies similarly showed a distinct pattern in the inflammatory phenotypes with anti-topoisomerase positivity being more common and anti-centromere positivity less common in persistent inflammatory compared with non-inflammatory patients (36% vs 26% and 29% vs 36%, respectively). Pulmonary hypertension was reported in 11% of the persistent inflammatory and 7% of the persistent non-inflammatory SSc patients. In the entire SSc cohort, persistent inflammatory patients were more often treated with immunosuppressive drugs compared with non-inflammatory patients (any immunosuppression in 44% vs 33%).

Compared with patients with persistent non-inflammatory SSc-ILD, patients with persistent inflammatory SSc-ILD had poorer lung function (median (IQR) FVC 79 (67–95) vs 90 (79–105) %-predicted and DLCO 55 (40–68) vs 64 (51–75) %-predicted, respectively) and shorter 6 min walk distances (median (IQR) 470 (380–545) vs 510 (435–564) metres). Furthermore, CT scans showed more frequent reticulations and traction bronchiectasis (34% vs 24% and 25% vs 13%). Overall, immunosuppression was more common in the SSc-ILD subgroup compared with the entire SSc population, and among patients with SSc-ILD, those with persistent inflammation were more often treated with immunosuppression compared with those with a non-inflammatory phenotype (54% vs 39%) (table 1).

Phenotyping by persistent versus baseline inflammation for mortality risk stratification

Over a median (IQR) follow-up time of 3.5 (2.4–5) years, 373 of the 5776 patients (6.4 %) with SSc and 207 of the 2100 patients with SSc-ILD (9.9 %) died.

Phenotyping by persistent inflammation showed that the intermediate phenotype had double the risk of mortality compared with the persistent non-inflammatory phenotype with HR 1.99 (95% CI 1.10 to 3.61, $p<0.001$) in the entire SSc population and HR 1.93 (95% CI 0.86 to 4.32, $p=0.11$) in patients with SSc-ILD. The persistent inflammatory phenotype was associated with a six times higher risk for mortality in the entire SSc population HR 6.45 (95% CI 3.45 to 12.05) and in the SSc-ILD subpopulation HR 6.74 (95% CI 2.95 to 15.4) compared with the persistent non-inflammatory phenotype. This association remained largely unchanged and statistically significant with adjustment for confounding factors including age, sex, disease duration, diffuse versus limited cutaneous disease, ILD (or FVC %-predicted for the SSc-ILD population), and immunosuppressive treatment (figure 1A,B, table 2).

Phenotyping by the baseline inflammatory phenotype (baseline CRP ≥ 5 mg/L) showed that patients with SSc with a baseline inflammatory phenotype had a 2.6 times (95% CI 2.11 to 3.18) higher risk of mortality compared with those with a non-inflammatory phenotype. Similarly, in the SSc-ILD subgroup, the baseline inflammatory phenotype showed a significant association with mortality risk HR 2.54 (95% CI 1.93 to 3.34). These findings remained largely unchanged and statistically significant in the adjusted analyses (figure 1C,D, table 2).

Trajectories of pulmonary function stratified by persistent inflammatory phenotype in SSc-ILD

The median (IQR) number of FVC %-predicted and DLCO %-predicted follow-up measurements were 4 (3–5) and 3 (3–4) with median (IQR) time intervals of 372 (279–481) and 378 (289–499) days between measurements, respectively.

Over 5 years from baseline, the persistent inflammatory phenotype had a non-significant annual decline in FVC %-predicted (-0.51 (95% CI -1.19 to 0.18 , $p=0.148$)), whereas average patients with an intermediate phenotype had significant (-0.79 (95% CI -1.14 to -0.44), $p<0.001$) and patients with a persistent non-inflammatory phenotype larger FVC declines (-1.01 (95% CI -1.40 to -0.62 , $p<0.001$, respectively)). On average, the persistent inflammatory phenotype had a significant annual decline in DLCO %-predicted (-1.06 (95% CI -1.81 to -0.30), $p=0.006$) and average patients with an intermediate phenotype had also significant but smaller DLCO declines (-0.50 (95% CI -0.88 to -0.12), $p=0.01$). Patients with a persistent non-inflammatory phenotype did not have a significant decline in DLCO %-predicted (-0.29 (95% CI -0.72 to 0.13 , $p=0.177$) (figure 2, online supplemental table S1).

The estimated FVC %-predicted and DLCO %-predicted trajectories remained robust when models were adjusted for differences in age, sex, smoking, disease duration, diffuse versus limited cutaneous disease and immunosuppressive treatment as confounders (online supplemental table S1).

Trajectories of pulmonary function in SSc-ILD patients with and without immunosuppressive treatment

Any immunosuppressive treatment was used in 526 patients with SSc-ILD (45%) and 645 (55%) had not received any immunosuppressive treatment. Over a mean (SD) follow-up time of 3.0 (1.6) and 4.2 (1.8) years, patients with a persistent inflammatory and non-inflammatory phenotype were on immunosuppressive treatment for a mean (SD) of 2.1 (1.5) and 2.8 (1.6) years, respectively.

Among patients with a persistent inflammatory phenotype, those without immunosuppressive treatment had a significant annual decline in FVC %-predicted of -1.11 (95% CI -2.14 to -0.08 , $p=0.034$), whereas those with immunosuppressive treatment had stable FVC %-predicted (-0.00 , 95% CI -0.92 to 0.92 , $p=0.996$). Among patients with a persistent non-inflammatory phenotype, those without immunosuppressive treatment also had a significant annual decline in FVC %-predicted of -0.84 (95% CI -1.35 to -0.33 , $p=0.001$), which was more pronounced in those with immunosuppressive treatment (-1.26 , 95% CI -1.87 to -0.64 , $p=0.001$). The persistent non-inflammatory patients with immunosuppressive treatment represented the group with the largest mean annual FVC decline, which was significantly larger than the FVC decline in persistent inflammatory patients with immunosuppressive treatment (interaction $p=0.027$). Interaction terms for immunosuppressive treatment were not statistically significant.

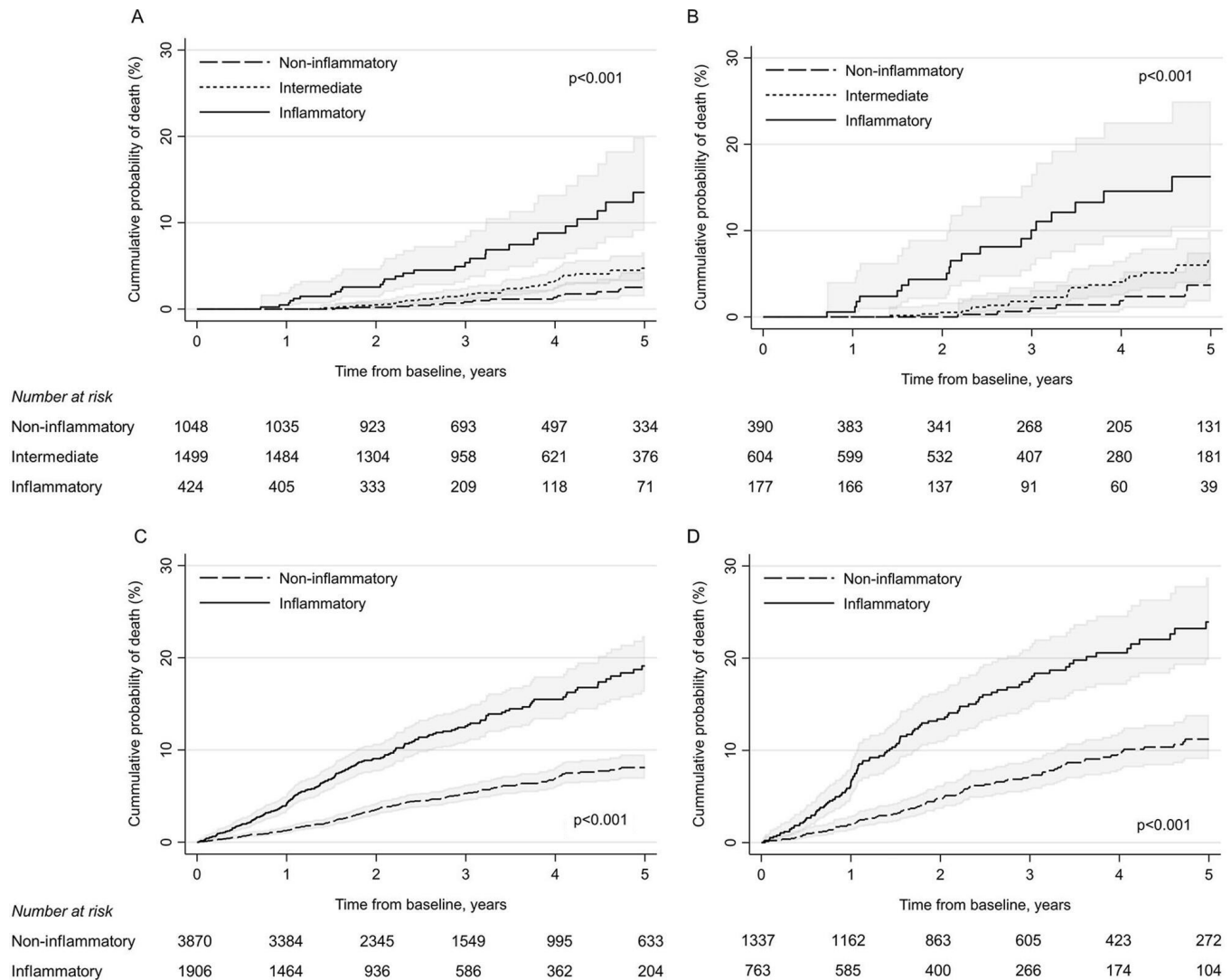


Figure 1 Survival by persistent (A), (B) and baseline (C), (D) inflammatory phenotype in all SSc (A), (C) and SSc-ILD (B), (D) patients. SSc, systemic sclerosis; ILD, interstitial lung disease.

After adjustment for age, sex, smoking, disease duration and diffuse versus limited cutaneous disease, these findings remained unchanged (figure 3, table 3).

Among patients with a persistent inflammatory phenotype, those without immunosuppressive treatment had a non-significant annual decline in DLCO %-predicted of -0.96 (95% CI -2.11 to 0.19 , $p=0.10$), whereas those with immunosuppressive treatment had a significant decline in DLCO %-predicted (-1.11 , 95% CI -2.12 to -0.11 , $p=0.029$). Patients with a persistent non-inflammatory phenotype had stable DLCO %-predicted with (-0.42 , 95% CI -1.08 to 0.24 , $p=0.21$) and without (-0.20 , 95% CI -0.76 to 0.35 , $p=0.48$) immunosuppressive treatment. With adjustment for age, sex, smoking, disease duration and diffuse versus limited cutaneous disease, these findings remained unchanged (figure 3, table 3).

DISCUSSION

Patients with SSc with a persistent inflammatory phenotype characterised by persistently elevated CRP levels showed features of more severe ILD and had a six times higher risk of mortality within 5 years from baseline. With stratification by immunosuppressive treatment, we observed the largest FVC decline in patients with non-inflammatory SSc-ILD who were

treated with immunosuppressive drugs, whereas the inflammatory phenotype showed stable FVC %-predicted when treated with immunosuppressive drugs. These findings should stimulate discussions whether traditionally used immunosuppressive therapies are equally beneficial in patients with persistent inflammatory and non-inflammatory SSc-ILD. This simple approach to inflammatory phenotyping demonstrates the benefit of repeatedly measuring CRP values for risk stratification and potentially also for treatment decisions in SSc-ILD.

This is the largest cohort study ever to show that SSc and specifically patients with SSc-ILD with a persistent inflammatory phenotype had a substantially higher risk of early mortality compared with those with a persistent non-inflammatory phenotype—independent from demographics, time from disease onset, cutaneous phenotype, baseline pulmonary function and immunosuppressive treatment. We also explored stratification by a single CRP measurement at baseline but found that the risk of mortality was roughly three times higher in the persistent versus the baseline inflammatory phenotype. Consequently, stratification by persistent inflammation outperforms consideration of single CRP measurements for the estimation of mortality risk within the next 5 years. A few previous studies have shown that CRP blood levels might be prognostically important in SSc,

Table 2 Mortality risk within 5 years from baseline by persistent inflammatory and baseline inflammatory phenotypes in the entire SSc population and in the subgroup with SSc-ILD

Persistent inflammatory phenotype					
Intermediate vs non-inflammatory					
	Events/ patients	HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
All SSc	84/2971	1.99 (1.10 to 3.61)	0.023	1.85 (1.02 to 3.36)	0.043
SSc-ILD	50/1171	1.93 (0.86 to 4.32)	0.11	1.89 (0.84 to 4.24)	0.12
Inflammatory vs non-inflammatory					
All SSc	84/2971	6.45 (3.45 to 12.05)	<0.001	5.66 (3.01 to 10.64)	<0.001
SSc-ILD	50/1171	6.74 (2.95 to 15.41)	<0.001	5.57 (2.39 to 13.02)	<0.001
Baseline inflammatory phenotype					
Inflammatory vs non-inflammatory					
	Events/ patients	HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
All SSc	373/5776	2.59 (2.11 to 3.18)	<0.001	2.29 (1.86 to 2.82)	<0.001
SSc-ILD	207/2100	2.54 (1.93 to 3.34)	<0.001	1.90 (1.43 to 2.52)	<0.001

*Adjusted for age, sex, smoking status (ever smoking), years from onset of first non-Raynaud manifestation, diffuse vs limited cutaneous disease, ILD and immunosuppressive treatment for all SSc. Adjusted for age, sex, smoking status (ever smoking), years from onset of first non-Raynaud manifestation, diffuse vs limited cutaneous disease, FVC %-predicted and immunosuppressive treatment for SSc-ILD.

FVC, forced vital capacity; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

however, mortality risk was not adjusted for confounders and no dedicated analyses for SSc-ILD were performed.^{16 23}

While patients in the persistent inflammatory subgroup had a higher risk of mortality and a larger decline in DLCO %-predicted compared with non-inflammatory patients, the

decline in FVC %-predicted was smaller in this subgroup. There are several potential reasons for this observation. Although respiratory failure remains the primary cause of death in SSc, it is noteworthy that 80–90% of patients die of non-respiratory causes.^{25 26} Cardiovascular diseases and cancer contribute significantly to mortality rates,²⁶ and there is a well-studied relationship between inflammation, cardiovascular and cancer mortality.²⁷ In contrast to FVC, DLCO decline is less specific for ILD progression, but can decline also due to cardiovascular disease, particularly pulmonary hypertension. Some studies demonstrate that change in DLCO is the stronger predictor of long-term survival compared with change in FVC.^{28–30} Furthermore, analyses from the scleroderma lung studies suggest that despite the positive effect of treatment on FVC, there is no difference in long-term survival in patients who had been randomised to receive cyclophosphamide, mycophenolate or placebo.²⁶ The latter leads us to suspect that differences in FVC % trajectories we observe between patients treated with and without immunosuppressive drugs might not have translated to overall survival.

Furthermore, our analyses showed no impact of immunosuppressive treatment on DLCO trajectories, which might partially be explained by the more frequent pulmonary hypertension in the inflammatory compared with the non-inflammatory phenotype (11% vs 7%), which has been described previously,³¹ and further links DLCO trajectories to mortality risks in SSc-ILD. The retrospective design of the current study limits our ability to draw definite conclusions regarding the interplay of these factors.

Our study has several other limitations. Inherent to observational studies, no definite inference on cause and effect can be drawn from the observed associations. For example, we observed that patients with immunosuppression were followed-up slightly more closely. We cannot completely exclude that missingness of data is not at random and that there is residual confounding in the comparison between patients with and without immunosuppression. We choose linear mixed models for our analysis because of their well-established performance in the context of missing data, variable follow-up observations per patients and variable follow-up intervals.³² The survival and repeated measures models were adjusted for prespecified confounders

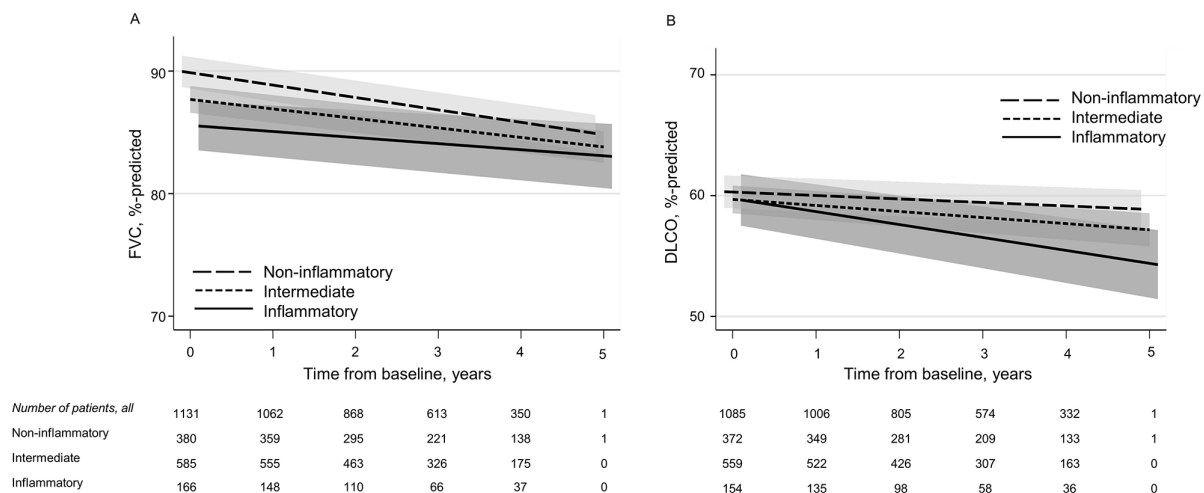


Figure 2 Trajectories of FVC %-predicted (A) and DLCO %-predicted (B) stratified by persistent inflammatory phenotype in patients with SSc-ILD. Average slopes in FVC and DLCO %-predicted are adjusted for baseline FVC (respectively, DLCO %-predicted), age, sex, smoking status, years from onset of first non-Raynaud manifestation, diffuse vs limited cutaneous disease and immunosuppressive treatment. The grey shaded bands illustrate 95% CIs. The number of patients is indicated for follow-up times ≥ 0 to 4 years and exactly 5 years, as follow-up time was limited to 5 years. DLCO, diffusing capacity for carbon monoxide; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

Interstitial lung disease

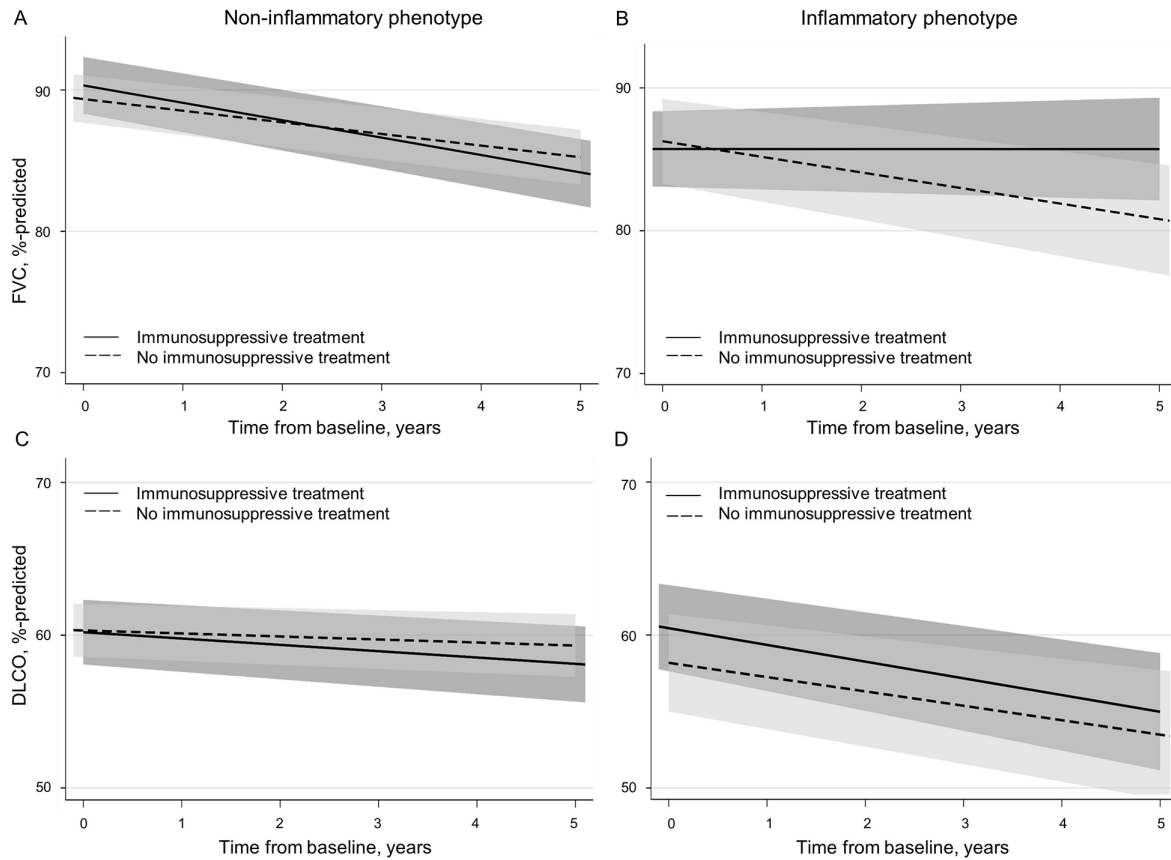


Figure 3 Trajectories of FVC %-predicted (A), (B) and DLCO %-predicted (C), (D) by immunosuppressive treatment in non-inflammatory (A), (C) and inflammatory (B), (D) SSc-ILD. Average slopes in FVC and DLCO %-predicted are adjusted for baseline FVC (respectively DLCO %-predicted), age, sex, smoking status, years from onset of first non-Raynaud manifestation, and diffuse vs limited cutaneous disease. The grey shaded bands illustrate 95% CIs. DLCO, diffusing capacity for carbon monoxide; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

Table 3 Annual change in pulmonary function by immunosuppressive treatment and persistent inflammatory phenotypes in SSc-ILD

Phenotypes	Unadjusted analysis				Adjusted analysis*			
	Mean annual change (95% CI)		Mean annual change (95% CI)		Mean annual change (95% CI)		Mean annual change (95% CI)	
	No immunosuppression	P value	Immunosuppression	P value	No immunosuppression	P value	Immunosuppression	P value
FVC, %-predicted					FVC, %-predicted			
Inflammatory	1.11 (-2.14 to -0.08)†	0.034	0.00 (-0.92 to 0.92)‡ ^a	0.996	1.09 (-2.11 to -0.06)†	0.039	0.01 (-0.93 to 0.91)† ^b	0.987
Intermediate	0.62 (-1.10 to -0.14)	0.012	0.98 (-1.49 to -0.46)	<0.001	0.60 (-1.08 to -0.12)	0.014	0.97 (-1.48 to -0.46)	<0.001
Non-inflammatory	0.84 (-1.35 to -0.33)	0.001	1.26 (-1.87 to -0.64) ^a	<0.001	0.84 (-1.35 to -0.32)	0.001	1.27 (-1.88 to -0.65) ^b	<0.001
DLCO, %-predicted					DLCO, %-predicted			
Inflammatory	0.96 (-2.11 to 0.19)	0.101	1.11 (-2.12 to -0.11)	0.029	0.97 (-2.11 to 0.18)	0.098	1.13 (-2.13 to -0.13)	0.027
Intermediate	0.67 (-1.20 to -0.14)	0.014	0.32 (-0.87 to 0.23)	0.256	0.68 (-1.21 to -0.14)	0.013	0.32 (-0.87 to 0.23)	0.258
Non-inflammatory	0.20 (-0.76 to 0.35)	0.477	0.42 (-1.08 to 0.24)	0.210	0.20 (-0.76 to 0.35)	0.475	0.41 (-1.07 to 0.25)	0.226

Mean annual change for individuals with average baseline values as derived from mixed effect models over 5 years from baseline. Negative/positive changes indicate decline/increase, respectively.

Interaction terms for immunosuppressive treatment had non-significant p values in all models. In the persistent inflammatory phenotype, the p values for immunosuppression were 0.115[†] and 0.126[‡]. Within the immunosuppression group, mean annual changes of FVC %-predicted was statistically different between the inflammatory and the non-inflammatory phenotype (^ap=0.027, ^bp=0.026).

*Adjusted for: age, sex, smoking status (ever smoking), years from onset of first non-Raynaud manifestation, diffuse vs limited cutaneous disease.

DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

between the relationship of inflammation, immunosuppressive treatment and outcomes. This approach accounts for the most important reasons for medication prescription (eg, patients with more severe ILD are more likely to be treated with immunosuppressive drugs). We did not take treatment duration into account for our analyses, which differed only marginally between patients with the persistent inflammatory and non-inflammatory phenotype. However, overall residual confounding cannot be completely excluded. Pulmonary function testing is dependent on qualifications of technicians and strict adherence to established protocols. While EUSTAR sites are generally recognised as interdisciplinary centres of excellence, there may still be some degree of local variability in the performance of pulmonary function testing. Inflammatory phenotyping was based on a previous study describing a distinct, severe clinical SSc phenotype with repeatedly positive CRP values that were robust to long-term follow-up and unchanged with conventional immunosuppression.¹⁵ However, previously other CRP cut-offs have been used,¹⁶ and there is a possibility that other CRP cut-offs or CRP as a continuous parameter, with or without splines, might be valid in this and other populations. For this study, 115 patients treated with tocilizumab (2% of the study population) were excluded, due to the effect of tocilizumab on CRP levels that would have interfered with our phenotyping approach. It is unlikely that observations from these few patients would have influenced our findings, however based on a recent clinical trial,⁵ inclusion of these patients might have led to a more pronounced benefit from immunosuppression in the inflammatory phenotype.

This study supports the concept of personalised management and phenotyping for monitoring and treatment decisions in SSc. The high mortality and disease progression in the inflammatory phenotype suggest close monitoring and potentially early immunosuppressive therapy in these patients. On the contrary, the largest FVC decline with immunosuppressive treatment observed in the non-inflammatory phenotype questions the effectiveness of immunosuppressive treatment in patients with SSc-ILD without signs of inflammation, particularly if extrapulmonary manifestations are mild or stable. A post hoc analysis of the scleroderma lung study I⁴ showed a greater treatment response in patients with severe cutaneous disease and pulmonary fibrosis.¹⁴ As the extend of skin and lung fibrosis is associated with elevated CRP levels,^{15–17} a reason for the more favourable response in the severe subgroup might be an underlying inflammatory phenotype. Furthermore, a recent phase 3 study investigating the efficacy of tocilizumab in patients with SSc with a set of inflammatory features showed a large FVC decline in the SSc-ILD placebo group and stabilisation in the tocilizumab group, which confirm the progressive nature and likely favourable immunosuppressive treatment response of the inflammatory SSc-ILD phenotype.⁵ On the contrary, antifibrotic drugs are effective for the treatment of idiopathic pulmonary fibrosis (IPF),³³ other types of progressive ILDs¹² and SSc-ILD.¹¹ Since the publication of the PANTHER trial showing a deleterious effect of a treatment regimen including azathioprine in patients with IPF, immunosuppressive treatment is prohibited in IPF.³⁴ Our findings are likely to stimulate further discussions and might encourage clinicians to carefully consider the potential benefits and harms of using immunosuppressive drugs in their patients with SSc-ILD who have minimal extrapulmonary SSc activity and show no signs of an inflammatory phenotype.

In summary, findings from the large, prospective, multicentre EUSTAR cohort support phenotyping of patients with SSc by the persistent inflammatory phenotype based on its prognostic importance and potential impact for management decisions.

While baseline CRP measurements provide some prognostic information, the impact of persistent inflammation on survival is clearly larger. The stable FVC in inflammatory but declining FVC trajectories in the patients with non-inflammatory SSc-ILD who are treated with immunosuppressive drugs might prompt clinical trials to specifically investigate the potential harm of immunosuppression in patients with a non-inflammatory SSc-ILD phenotype. Clinical trials might enrich not only for participants with inflammatory but depending on the drug target also for patients with SSc-ILD with a non-inflammatory phenotype. Overall, phenotyping by persistent inflammation might contribute to improve personalised treatment approaches in SSc-ILD.

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