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Serum inflammatory markers as predictors of therapeutic response in non-idiopathic pulmonary fibrosis fibrotic interstitial lung disease: a retrospective cohort analysis

Yanisa Kluanwan[1,2] and Teng Moua[2*]

Abstract

Background The role of chronic inflammation in non-idiopathic pulmonary fibrosis fibrotic interstitial lung disease (non-IPF f-ILD) remains unclear, with varied responses to anti-inflammatory or immunosuppressive therapy. A reliable predictor for guiding treatment response may enhance clinical decision-making and minimize adverse treatment effects. We hypothesized that elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be associated with improved treatment response.

Methods Our retrospective cohort study compared treatment response to anti-inflammatory therapy in patients with non-IPF f-ILD stratified by baseline CRP and ESR levels. Treatment response was defined as: (1) relative increase in percent predicted forced vital capacity (FVC%) ≥ 5% in 6 months or ≥ 10% in 12 months; or (2) no change or any increase in FVC% if FVC% decline was noted prior to treatment. Logistic regression was used to delineate outcome predictors with FVC% change over time assessed with linear mixed effects models.

Results Of 832 non-IPF f-ILD patients screened, 167 received anti-inflammatory therapy and baseline inflammatory marker testing stratified into high vs. low-to-normal groups (104 vs. 63, respectively). Median age was 64 years, and 57% were diagnosed with a systemic autoimmune rheumatic disease (SARD). Treatment response was greater in those with elevated inflammatory markers (56% vs. 35%; OR 2.45 [1.243–4.828] $P=0.010$) even after adjustment for a priori covariables. SARD diagnosis was associated with treatment response (OR 2.90 [1.45–5.81] $P=0.003$), independent of inflammatory marker level. A positive FVC% slope was observed in treated patients with initially elevated inflammatory markers ($P=0.003$).

Conclusion Patients with non-IPF f-ILD and elevated inflammatory markers appear to be more responsive to anti-inflammatory therapy with slower FVC decline over time. These findings suggest baseline serum ESR and CRP may be feasible and reliable predictors of treatment response in certain subgroups.

Keywords Interstitial lung disease, Lung fibrosis, Anti-inflammatory treatment, Immunosuppression

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Background

Pulmonary fibrosis is believed to result from inappropriate healing or repair of damaged lung tissue. Significant organ dysfunction with shortness of breath, cough, and fatigue, may progress if underlying disease is not controlled. The pathogenesis of pulmonary fibrosis in non-idiopathic pulmonary fibrosis (non-IPF) disease includes chronic inflammation, though specific pathways of lung injury and repair are multifaceted and complex. Prior reports [1–4] suggest potentially good responses to anti-inflammatory or immunosuppressive agents in non-IPF fibrotic interstitial lung disease (f-ILD), while others have suggested poor outcomes with related complications or adverse effects [5, 6]. Unique immunoregulatory environments in individual patients may explain why anti-inflammatory medications are effective in some but not others. Serum inflammatory markers, namely C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are commonly obtained laboratory tests that may reflect the extent of background inflammation. An association between elevated inflammatory markers and ILD progression, regardless of treatment, was first postulated by a large cohort study which noted significant deterioration in pulmonary function testing in patients with scleroderma (SSc) who had a two-fold higher elevation in both ESR and CRP [7]. Another observational study found any elevated CRP level was associated with forced vital capacity (FVC) decline in patients with SSc-ILD [4]; however, there is no robust data to demonstrate that baseline or serial inflammatory markers may be predictive of clinical or functional response to anti-inflammatory therapy. We hypothesize that elevated pre-treatment serum inflammatory markers CRP and ESR may be associated with greater likelihood of anti-inflammatory or immunosuppressive treatment response, as defined by lung function, and may help direct initial treatment.

Patients and methods

Institutional review board (IRB) approval was obtained before study initiation (IRB # 24-007082). We performed a retrospective cohort study of patients with fibrotic ILD due to systemic autoimmune rheumatic disease (SARD) (formerly known as connective-tissue disease including *rheumatoid arthritis (RA), SSc), mixed connective tissue disease (MCTD), undifferentiated connective tissue disease (UCTD), anti-synthetase syndrome (AsyS), systemic lupus erythematosus (SLE), dermatomyositis (DM), and polymyositis (PM)*), interstitial pneumonia with autoimmune features (IPAF), ANCA-associated vasculitis, fibrotic hypersensitivity pneumonitis (f-HP), drug or radiation-induced fibrosis, and unclassifiable ILD (uILD) with non-IPF clinical and radiologic findings. Eligible patients with non-IPF f-ILD were older than 18 years, with findings on high-resolution computed tomography (HRCT) compatible with chronic fibrosis, including reticular and ground-glass opacities (GGO), traction bronchiolectasis or bronchiectasis, and honeycombing. Patients with suspected IPF, non-fibrotic radiologic findings, missing CRP or ESR testing, concomitant acute exacerbation, pulmonary embolism, heart failure, or infection at the time of anti-inflammatory testing, loss to follow-up, or inadequate data to address clinical response to treatment, were excluded. A computer-assisted search of the electronic medical record was performed for non-IPF f-ILD patients seen from 1/1/2018 through 3/30/2024. Baseline demographics, pulmonary function testing, smoking history, and underlying f-ILD diagnoses were collected. Absolute CRP and ESR levels, along with positive cut-offs (defined as CRP greater than 5 mg/dL or ESR more than 20 mm/hr) obtained just before treatment, were collated, with enrolled patients stratified into two groups of high (either marker or both) vs. low-normal baseline inflammatory marker cut-offs. Anti-inflammatory treatment was defined as exposure to at least one or more of the following for at least three or more consecutive months: oral corticosteroids (CS; prednisone, dexamethasone, or methylprednisolone), azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), leflunomide (LFL), rituximab (RTX) or other biologic, and intravenous immunoglobulin (IVIG). Treatment response was defined by pulmonary function test (PFT) criteria as the following:

a. INCREASE in relative percent predicted forced vital capacity (FVC%) ≥ 5% at six months or ≥ 10% at twelve months, if FVC% was stable or unchanged prior to initiation of therapy, or:
b. STABLE or NO CHANGE in FVC% or relative INCREASE in FVC% ≥ 5% at six months or ≥ 10% at 12 months, if FVC% was declining or the patient met other clinical criteria for progressive pulmonary fibrosis (PPF) prior to therapy.

Patients with ILD progression prior to treatment were defined by meeting either of two guideline criteria for progressive pulmonary fibrosis (PFF), the first characterized as having any 2 of the following three criteria: (1) worsening symptoms, (2) radiological progression, and (3) absolute FVC decline ≥ 5% or percent predicted diffusion capacity for carbon monoxide (DLCO%) decline ≥ 10% in the last 12 months [8], or according to the INBUILD study [9] meeting at least one of the following criteria: (1) relative FVC decline ≥ 10%, (2) relative FVC decline ≥ 5% with worsening symptoms or radiological progression, or (3) worsening symptoms and radiological progression, occurring within the prior 24 months. Serial FVC% and DLCO% were collected from treated and nontreated patients stratified by initial

positive or negative pre-treatment inflammatory markers. As follow-up inflammatory markers after treatment initiation were not protocolized and available variably in only a few patients, they were not collected or reviewed to assess subsequent marker response to treatment. Adverse treatment effects were collated for all treated groups.

The primary study endpoint was comparative frequency or incidence of treatment response in patients with initially high vs. low-normal inflammatory markers. Secondary outcomes included other predictors of treatment response as delineated on univariable and multivariable regression analysis, adjusted for a priori baseline covariables of age, sex, and pre-treatment FVC%. Comparisons of treatment adverse events, acute exacerbation, mortality, and lung transplantation were made between high vs. low-normal inflammatory marker groups. Moreover, disease progression in treated and untreated patients as stratified by high vs. low-normal baseline inflammatory markers was also assessed.

Statistical analysis

Continuous data were presented as mean with standard deviation or median with interquartile (25–75) range. Categorical data were presented as counts and percentages. Two-sample t-test or ANOVA was used to compare continuous variables with Chi-square used for count or categorical data. A logistic regression model was used to identify covariables associated with treatment response as stratified by initially high vs. low-normal inflammatory markers, adjusted for a priori covariables of age, sex, duration of treatment (months), pre-treatment FVC%, and presence of SARD. A linear mixed effects model for repeated measures was used for comparing change in FVC% while treated (fixed effects included baseline FVC%, time on treatment, and inflammatory marker status, with individual subjects as random effects) and for non-treated patients stratified by high vs. low-normal baseline inflammatory markers. *P*-values < 0.05 were considered statistically significant. Statistical analysis was completed with STATA version 16MP.

Results

A total of 832 patients were screened with 253 meeting study inclusion (167 treated with anti-inflammatory therapy and 86 non-treated) (Fig. 1). To assess differences in baseline characteristics that might lead to a greater likelihood of receiving treatment, treated and non-treated patients were compared, noting younger age, presence of SARD, lower baseline FVC%, and initially higher inflammatory markers in those receiving treatment. Baseline characteristics for the whole cohort and treated vs. non-treated are presented in supplementary Table S1.

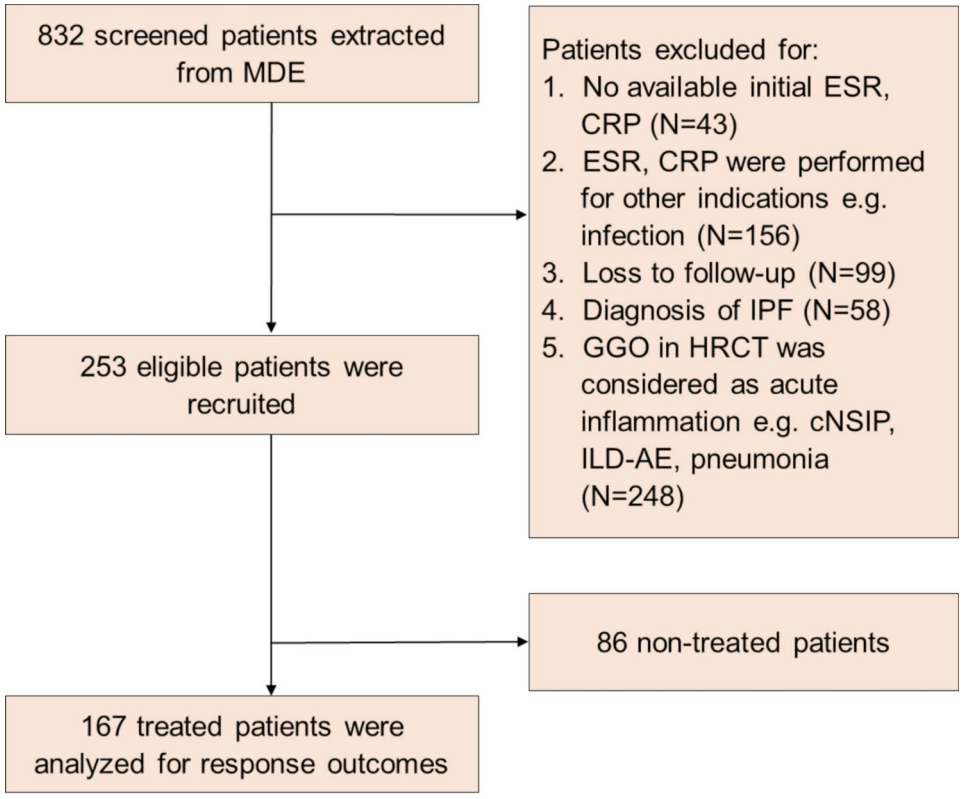

Fig. 1 Patient recruitment flow diagram

Of 167 treated patients with baseline inflammatory markers, 104 were elevated and 63 were low-normal prior to treatment (Table 1). Median age for the whole cohort was 64 years, with SARDs diagnosed in 96 (57%) and the majority being rheumatoid arthritis (18%). Other f-ILD included uILD in 17%, f-HP in 16%, and IPAF in 8%, respectively. Baseline characteristics were similar except for greater female sex in the high inflammatory marker group (64% vs. 46%, $P=0.024$). Anti-inflammatory treatment regimens were also similar between those with high vs. low-normal inflammatory markers, with the two most common medications being CS (58.7% vs. 65.1%, $P=0.513$) and MMF (44.2% vs. 54%, $P=0.264$), respectively. (Table 2). The use of anti-fibrotic agents in combination with anti-inflammatory therapy was also similar between groups (12.5% vs. 9.5%, $P=0.624$). Duration of treatment with anti-inflammatory agents was similar (8.1 vs. 6 months, $P=0.401$) along with incidences of acute exacerbation (AE) after treatment initiation ($N=13$ vs. 6, $P=0.626$), lung transplantation ($N=8$ vs. 11, $P=0.07$), and death ($N=13$ vs. 8 $P=1$). Treatment-related adverse events occurred more frequently in those with low-normal inflammatory markers (50.8% vs. 33.7%, $P=0.035$), dominated by anemia and hepatic injury. Treatment cessation occurred in only three cases for the whole study cohort (Table 2).

Treatment response was significantly higher in patients with any elevated inflammatory marker (combined effect) (55.8% vs. 34.9%, $P=0.011$) (Table 3). After adjustment for age, sex, baseline FVC%, and treatment duration, this remained true for the whole cohort (OR 2.45 [1.24–4.83], $P=0.010$) and non-SARD f-ILD subgroup (OR 3.49 [1.136–10.705], $P=0.029$). Treatment response appeared to be higher in patients with SARD and elevated inflammatory markers, however, this did not reach statistical significance (OR 2.05 [0.81–5.14], $P=0.125$). (Table 3). When stratified by specific inflammatory marker, elevated CRP appeared to be the primary predictor of positive treatment response for the general cohort (Table 4). Elevated ESR was not predictive unless concordant with elevated CRP ($N=95$ after excluding discordant cases, univariable OR 2.35 [1.02–5.39], $P=0.045$; multivariable OR 2.78 [1.06–7.29] $P=0.038$). Elevated CRP with or without concordant ESR was independently associated with treatment response (multivariable OR 2.68 [1.27–5.67] $P=0.010$). The presence of SARD was predictive of treatment response on unadjusted (univariable OR 2.23 [1.19–4.17] $P=0.013$) and adjusted (multivariable OR 2.9 [1.45–5.81] $P=0.003$) analyses, with similar baseline frequencies of high vs. low-normal inflammatory markers (60% vs. 54%, $P=0.520$) prior to treatment in those with SARD (Table 1). Lastly, higher baseline FVC% was independently associated with a decreased likelihood of treatment response (multivariable OR 0.98 [0.96–0.99] $P=0.015$).

To assess if elevated inflammatory markers remained predictive of positive treatment response across disease subtypes, subgroup analyses restricted to patients with SARD and non-SARD f-ILD are presented in Tables 5 and 6, respectively. Among patients with SARD ($N=96$), individual inflammatory markers (CRP or ESR) were not predictive of treatment response, whether concordant or not, with no other associated clinical, functional, or radiologic predictors on univariable regression (Table 5). In patients with non-SARD f-ILD ($N=71$), positive CRP on unadjusted analysis (univariable OR 3.5 (1.13–10.83) $P=0.030$) was predictive of treatment response while UIP CT pattern was associated with a decreased likelihood of treatment response on adjusted analysis (OR 0.12 [0.02–0.92) $P=0.041$) (Table 6). Absolute values for CRP and ESR were not predictive of treatment response for both cohort and subgroup analyses, likely due to underpowering and a non-linear relationship between absolute values and dichotomous study outcomes (data not shown). Lastly, concomitant use of antifibrotics was not associated with treatment response for the whole cohort or for any subgroup.

FVC% slope while on treatment appeared to trend positively in patients with initially elevated inflammatory markers ($P=0.003$) (Fig. 2). When comparing treated vs. non-treated patients ($N=253$) (Fig. 3a) stratified by high ($N=141$) vs. low-normal baseline inflammatory markers ($N=112$), FVC% slope was less negative in those with low-normal inflammatory markers receiving treatment (Fig. 3c) and trended upwards in those with elevated marker levels (Fig. 3b).

Discussion

Our findings suggest that non-IPF f-ILD patients with initially elevated inflammatory markers may respond better to anti-inflammatory therapy than those with initially low-normal levels, particularly if CRP is elevated. FVC% slope in those with elevated baseline markers trended towards positive or were less negative while on treatment.

Prior studies have reported elevated inflammatory markers being associated with disease progression [1–4]. Our findings suggest for the first time potentially greater treatment response in a broad spectrum of non-IPF f-ILD. Additional subgroup analyses demonstrated better treatment response in those with SARD regardless of initial inflammatory marker level or CT pattern. Only unadjusted elevated CRP was associated with treatment response in patients with non-SARD f-ILD when stratified by specific marker, while the combined effect of any elevated inflammatory marker was robustly predictive.

Table 1 Baseline characteristics of treated patients stratified by high vs. low-to-normal inflammatory markers (*N* = 167)

Baseline characteristics (All patients who were treated with anti-inflammatory agents)	**High inflammatory markers group (*N* = 104)**	**Low to normal inflammatory markers group (*N* = 63)**	***p*-value**
Age (year, median [IQR1 to IQR3])	64 [52.5 to 72]	64 [56 to 74]	0.609
Gender			0.024
• Male (%)	37 (35.6%)	34 (54%)	
• Female (%)	67 (64%)	29 (46%)	
Diagnosis of ILD			
SARDs	**62 (59.6%)**	**34 (54%)**	**0.520**
• SSc (%)	14 (13.5%)	6 (9.5%)	0.624
• IIM (%)	4 (3.9%)	2 (3.2%)	1.000
• RA (%)	18 (17.3%)	12 (19.1%)	0.836
• SLE (%)	2 (1.9%)	0 (0%)	0.527
• MCTD (%)	11 (10.6%)	3 (4.8%)	0.254
• UCTD (%)	1 (0.96%)	4 (6.4%)	0.068
• AsyS (%)	9 (8.7%)	2 (3.2%)	0.211
• pSS (%)	1 (0.96%)	4 (6.4%)	0.068
• GPA/EGPA (%)	4 (3.9%)	3 (4.8%)	1.000
• Overlapped disease (%)	2 (1.9%)	2 (3.2%)	0.633
Non-SARDs	**42 (40.4%)**	**29 (46%)**	**0.520**
• IPAF (%)	7 (6.7%)	7 (11.1%)	0.391
• Fibrotic HP (%)	13 (12.6%)	13 (20.6%)	0.190
• Unclassifiable ILD (%)	23 (22.1%)	6 (9.5%)	0.056
Underlying other medical history			
• GERD (%)	58 (55.8%)	33 (52.4%)	0.749
• Pulmonary hypertension (%)	25 (24%)	15 (23.8%)	1.000
• OSA (%)	30 (28.9%)	12 (19.1%)	0.198
Smoking history			0.876
• Non-smoker (%)	67 (64.4%)	38 (60.3%)	
• Former smoker (%)	36 (34.6%)	24 (38.1%)	
• Current smoker (%)	1 (0.96%)	1 (1.6%)	
- Amount of smoking exposure (packyear, median [IQR1 to IQR3])	22.5 [11.5 to 38.8]	15 [11.3 to 24]	0.229
Baseline inflammatory marker level			
• ESR (*N* = 123, median [IQR1 to IQR3])	30 [21 to 50]	7.5 [4 to 14]	< 0.001
• CRP (*N* = 148, median [IQR1 to IQR3])	10.9 [7.3 to 22]	3 [3 to 3]	< 0.001
Baseline PFT			
• FVC (%predicted, median [IQR1 to IQR3)	61 [49 to 77]	64 [51 to 77]	0.494
• DLCO (%predicted, median [IQR1 to IQR3])	42.5 [35 to 56]	48 [35 to 61]	0.488
Meet any PPF criteria (total *N* = 167)	40 (38.5%)	19 (30.2%)	0.318
• PPF by ATS/ERS/JRS/ALAT 2022 (total *N* = 35)	**26 (25%)**	**9 (14.3%)**	**0.118**
- Declined FVC or DLCO with HRCT progression	10 (38.5%)	3 (33.3%)	1.000
- Declined FVC or DLCO with worsened symptom	9 (34.6%)	1 (11.1%)	0.235
- Worsened symptoms with HRCT progression	4 (15.4%)	5 (55.6%)	0.030
- Worsened FVC or DLCO / CT / symptom	3 (11.5%)	0 (0%)	0.553
• PF-ILD by INBUILD criteria (total *N* = 57)	**39 (37.5%)**	**18 (28.6%)**	**0.312**
- Declined FVC ≥ 10%	30 (76.9%)	11 (61.1%)	0.341
- Declined FVC ≥ 5 with HRCT progression	4 (10.3%)	2 (11%)	1.000
- Decline in FVC ≥ 5% with worsened symptoms	1 (2.6%)	0 (0%)	1.000
- Worsened symptoms with HRCT progression	4 (10.3%)	5 (27.8%)	0.124
Baseline HRCT			
• Typical UIP (%)	34 (32.7%)	17 (27%)	0.491
• Probable UIP (%)	62 (59.6%)	39 (61.9%)	0.871
• Indeterminate UIP (%)	5 (4.8%)	2 (3.2%)	0.711
• fNSIP (%)	4 (3.9%)	5 (7.9%)	0.300

Table 2 Treatment type, outcome responses, and adverse events stratified by high vs. low inflammatory markers in those receiving anti-inflammatory therapy (*N* = 167)

Outcomes	High inflammatory markers group (*N* = 104)	Low to normal inflammatory markers group (*N* = 63)	*p*-value
Prescribed medications			
• Anti-inflammatory agents			
- Corticosteroid (%)	61 (58.7%)	41 (65.1%)	0.513
- AZA (%)	10 (9.6%)	4 (6.4%)	0.572
- MMF (%)	46 (44.2%)	34 (54%)	0.264
- RTX (%)	21 (20.2%)	7 (11.1%)	0.141
- Biologics, other than RTX (%)	7 (6.8%)	1 (1.6%)	0.261
- HCQ (%)	15 (14.4%)	4 (6.4%)	0.136
- IVIg (%)	3 (2.9%)	2 (3.2%)	1.000
- MTX (%)	1 (0.96%)	1 (1.6%)	1.000
• Concomitant antifibrotics	13 (12.5%)	6 (9.5%)	0.624
Duration of treatment at response evaluation (months, median [IQR1 to IQR3])	8.1 [4.8 to 14.6]	6 [3.4 to 13.5]	0.401
ILD-AE	13 (12.5%)	6 (9.7%)	0.626
Death during course of treatment	13 (12.5%)	8 (12.7%)	1.000
Proceed to rescue lung transplantation	8 (7.7%)	11 (17.5%)	0.077
Response to treatment	58 (55.8%)	22 (34.9%)	0.011
Adverse events from treatment	35 (33.7%)	32 (50.8%)	0.035
• Leukemia	7 (6.7%)	3 (4.8%)	0.744
• Neutropenia	2 (1.9%)	3 (4.8%)	0.367
• Anemia	22 (21.2%)	21 (33.3%)	0.101
• Thrombocytopenia	7 (6.7%)	8 (12.7%)	0.264
• Hepatic injury	12 (11.5%)	8 (12.7%)	0.811
• Nausea-vomiting	4 (3.9%)	1 (1.6%)	0.651
• Diarrhea	1 (0.96%)	2 (3.2%)	0.557
• Pneumonia	2 (1.9%)	3 (4.8%)	0.367
• Other infection	2 (1.9%)	2 (3.2%)	0.633
• Osteoporosis	1 (0.96%)	1 (1.6%)	1.000
Adverse events leading to treatment discontinuation	2 (1.9%)	1 (1.6%)	1.000
Adverse events leading to death	0 (0%)	0 (0%)	-

Table 3 Adjusted and unadjusted treatment response stratified by the whole cohort, SARD, and non-SARD subgroups

Outcomes	High inflammatory markers group	Low to normal inflammatory markers group	*p*-value
All treated patients (*N* = 167), N (%); OR [95% CI]	58 (55.8%)	22 (34.9%)	0.011
	OR 2.35 [1.23–4.48]		0.010
	OR* 2.45 [1.24–4.83]		0.010
Treated patients with underlying SARDs (*N* = 96), N (%); OR [95% CI]	38 (61.2%)	16 (47%)	0.202
	OR 1.78 [0.77–4.15]		0.181
	OR* 2.05 [0.81–5.14]		0.125
Treated patients without underlying SARDs (*N* = 71), N (%); OR [95% CI]	20 (47.6%)	6 (20.7%)	0.026
	OR 3.48 [1.18–10.3]		0.024
	OR* 3.49 [1.14–10.71]		0.029

*Adjusted odd ratio with age, sex, duration of treatment at response evaluation, and baseline FVC (%predicted)

A consistent or probable UIP CT pattern was associated with decreased response in those with non-SARD f-ILD.

Current treatments for non-IPF f-ILD include anti-inflammatory or immunosuppressive agents, with first-line therapies being oral CS or steroid-sparing agent (SSA). The exception is SSc-ILD, where high-dose CS are often avoided. Several SSAs, including MMF, AZA, MTX, and cyclophosphamide, are commonly used for the treatment of suspected inflammatory ILD whereas rituximab, tocilizumab, IVIG, and other biologics (including

Table 4 Univariate and multivariate logistic regression for predictors of treatment response (*N* = 167)

Factors	Unadjusted (Univariate Analysis)		Adjusted* (Multivariate Analysis)	
	Odds ratio (95% confidence interval)	*P*-value	Odds ratio (95% confidence interval)	*P*-value
Baseline inflammatory marker level				
ESR status (Cut-off level: High vs. Low-normal)				
• Total *N* = 123	1.54 (0.76–3.14)	0.234	1.63 (0.75–3.55)	0.217
• Exclude discordant with CRP **N* = 95	2.35 (1.02–5.39)	0.045	2.78 (1.06–7.29)	0.038
CRP status (Cut-off level: High vs. Low-normal)				
• Total *N* = 148	2.38 (1.21–4.67)	0.012	2.68 (1.27–5.67)	0.010
• Exclude discordant with ESR **N* = 120	2.35 (1.11–4.97)	0.025	2.68 (1.17–6.17)	0.020
Age	1.01 (0.98–1.03)	0.660	1.02 (0.99–1.05)	0.133
Gender	0.91 (0.49–1.68)	0.757	1.03 (0.53–1.99)	0.934
Duration of anti-inflammatory treatment (at response evaluation)	0.99 (0.96–1.01)	0.240	0.98 (0.96–1.01)	0.190
Antifibrotics in combination with anti-inflammatory treatment	1.57 (0.60–4.14)	0.357	1.25 (0.44–3.53)	0.671
Baseline PFT				
FVC (%predicted) **N* = 166	0.98 (0.96–0.99)	0.024	0.98 (0.96-1.00)	0.015
DLCO (%predicted) **N* = 149	0.99 (0.98–1.01)	0.396	1.01 (0.97–1.03)	0.434
Progression before initiating treatment				
Meet any of the criteria	1.48 (0.78–2.80)	0.227	1.21 (0.61–2.41)	0.588
PPF by ATS/ERS/JRS/ALAT 2022	0.97 (0.37–1.64)	0.502	0.62 (0.28–1.39)	0.245
PF-ILD by INBUILD criteria	1.48 (0.78–2.82)	0.228	1.27 (0.63–2.53)	0.502
Baseline HRCT				
• UIP pattern (typical & probable UIP)	0.52 (0.18–1.49)	0.225	0.43 (0.14–1.32)	0.139
• Indeterminate UIP	1.47 (0.32–6.79)	0.619	2.26 (0.49–11.43)	0.323
• fNSIP	2.27 (0.55–9.39)	0.258	2.24 (0.49–10.05)	0.293
Diagnosis				
SARDs related (exclude IPAF, fHP, unclassifiable ILD)	2.23 (1.19–4.17)	0.013	2.90 (1.45–5.81)	0.003

*Adjusted for age, gender, duration of treatment at response evaluation, baseline FVC%, and presence of SARDs

Janus kinase (JAK) and tumor necrosis factor (TNF) inhibitors) are reserved for those with more progressive disease refractory to first-line agents [10]. However, evidence for the treatment of SARD-related ILD is limited except in SSc-ILD where several controlled trials have demonstrated efficacy of MMF in slowing FVC decline [11]. Suggested therapeutic approaches in patients with SLE, UCTD, and IPAF remain limited. Evidence for anti-inflammatory therapy in these diseases include case reports [12] and observational studies [13], with extrapolation from one randomized controlled trial involving a broad cohort of connective tissue diseases [14]. Lastly, comparative evidence for treatment approaches in non-SARD non-IPF f-ILD is also lacking. CS and SSAs such as MMF or AZA are often considered in f-HP based on an early RCT involving CS in more acute disease [15] and several retrospective cohort studies [16, 17]. A better understanding of potential treatment response may improve clinical use as well as design of future comparative studies that are powered for detecting efficacy and determining effect sizes in heterogeneous populations.

Indeed, the complement to predicting treatment response and maximizing positive outcomes is minimizing or avoiding adverse treatment effects in those not expected to improve. In our study, adverse treatment effects occurred more frequently in those with low-normal inflammatory marker levels, with complications in three patients severe enough to discontinue therapy. Despite increased treatment complications and a lower likelihood of treatment response, our findings also suggest those with low-normal inflammatory marker levels and underlying SARD may still benefit from anti-inflammatory therapy. A recent meta-analysis found empiric CS may reduce FVC decline across a broad spectrum of patients with non-IPF f-ILD [18]. Our study demonstrated FVC% slope was less negative in those receiving any anti-inflammatory therapy compared to those who were untreated, perhaps driven by underlying SARD, but independent of baseline inflammatory marker level (Fig. 3). Avoiding treatment in those with lower likelihood of treatment response and background comorbidities or advanced disease seems reasonable, except perhaps in SARD where treatment response may still be possible independent of inflammatory marker levels or other baseline characteristics.

Table 5 Subgroup analysis for predictors of treatment response in patients with SARDs (*N* = 96)

Factors	Unadjusted Odds Ratio (Univariate Analysis)		Adjusted Odds Ratio* (Multivariate Analysis)	
	95% confidence interval	*p*-value	95% confidence interval	*p*-value
Baseline inflammatory marker level				
ESR status (Cut-off level: High vs. Low-normal)				
• Total *N* = 80	1.45 (0.59–3.52)	0.413	1.60 (0.60–4.25)	0.346
• Exclude discordant case to CRP *N = 61	1.94 (0.69–5.51)	0.212	3.00 (0.82–10.96)	0.097
CRP status (Cut-off level: High vs. Low-normal)				
• Total *N* = 87	1.81 (0.75–4.33)	0.187	2.50 (0.92–6.79)	0.073
• Exclude discordant case to ESR *N = 68	1.87 (0.69–5.01)	0.215	2.26 (0.75–6.81)	0.148
Age	1.02 (0.99–1.05)	0.182	1.03 (0.99–1.06)	0.133
Gender	0.83 (0.36–1.89)	0.656	1.02 (0.41–2.50)	0.967
Duration of anti-inflammatory treatment (at response evaluation)	0.98 (0.95–1.01)	0.140	0.98 (0.95–1.01)	0.268
Antifibrotics in combination with anti-inflammatory treatment	1.41 (0.39–5.20)	0.601	1.08 (0.26–4.42)	0.971
Baseline PFT				
FVC (%predicted) *N = 95	0.98 (0.96-1.00)	0.064	0.98 (0.95–0.99)	0.048
DLCO (%predicted) *N = 85	0.99 (0.97–1.01)	0.359	1.01 (0.98–1.04)	0.581
Progression before initiate treatment				
Meet any of the criteria	1.94 (0.81–4.65)	0.139	1.43 (0.56–3.65)	0.451
PPF by ATS/ERS/JRS/ALAT 2022	1.35 (0.50–3.63)	0.555	1.13 (0.39–3.19)	0.822
PF-ILD by INBUILD criteria	2.04 (0.83–4.99)	0.120	1.57 (0.61–4.03)	0.352
Baseline HRCT				
• UIP pattern (typical & probable UIP)	1.03 (0.26–4.12)	0.965	0.90 (0.214–3.78)	0.884
• Indeterminate UIP	1.58 (0.14-18)	0.714	2.49 (0.20–30.5)	0.476
• f-NSIP	0.76 (0.15–3.99)	0.751	0.73 (0.13–4.10)	0.719

*Adjusted for age, gender, duration of treatment at response evaluation, and baseline FVC (%predicted)

Table 6 Subgroup analysis for predictors of treatment response in non-SARD patients (*N* = 71)

Factors	Unadjusted Odds Ratio (Univariate Analysis)		Adjusted Odds Ratio* (Multivariate Analysis)	
	95% confidence interval	*p*-value	95% confidence interval	*p*-value
Baseline inflammatory marker level				
ESR status (Cut-off level: High vs. Low-normal)				
• Total *N* = 43	1.64 (0.45–5.94)	0.451	1.78 (0.46–6.95)	0.404
• Exclude discordant case to CRP *N = 34	2.72 (0.62–12.04)	0.187	3.48 (0.62–19.44)	0.156
CRP status (Cut-off level: High vs. Low-normal)				
• Total *N* = 61	3.50 (1.13–10.83)	0.030	3.13 (0.97–10.05)	0.056
• Exclude discordant case to ESR *N = 52	3.40 (0.996–11.602)	0.051	3.45 (0.95–12.59)	0.061
Age	1.00 (0.956–1.051)	0.917	1.01 (0.96–1.06)	0.700
Gender	0.93 (0.354–2.461)	0.889	1.11 (0.40–3.06)	0.844
Duration of anti-inflammatory treatment (at response evaluation)	0.96 (0.885–1.043)	0.343	0.96 (0.88–1.05)	0.412
Antifibrotics in combination with anti-inflammatory treatment	1.86 (0.42–8.18)	0.410	1.45 (0.30–6.94)	0.639
Baseline PFT				
FVC (%predicted) *N = 71	0.98 (0.951–1.009)	0.163	0.98 (0.95–1.01)	0.167
DLCO (%predicted) *N = 64	0.99 (0.963–1.025)	0.667	1.01 (0.97–1.05)	0.565
Progression before initiate treatment				
Meet any of the criteria	1.13 (0.42–3.07)	0.807	1.01 (0.35–2.88)	0.989
PPF by ATS/ERS/JRS/ALAT 2022	0.23 (0.05–1.12)	0.069	0.20 (0.04-1.00)	0.050
PF-ILD by INBUILD criteria	1.13 (0.41–3.07)	0.807	1.01 (0.35–2.88)	0.989
Baseline HRCT				
• UIP pattern (typical & probable UIP)	0.20 (0.04–1.09)	0.063	0.12 (0.02–0.92)	0.041
• Indeterminate UIP	1.79 (0.24–13.54)	0.572	2.39 (0.25–23.44)	0.453
• fNSIP	1	-	1	-

*Adjusted for age, gender, duration of treatment at response evaluation, and baseline FVC (%predicted)

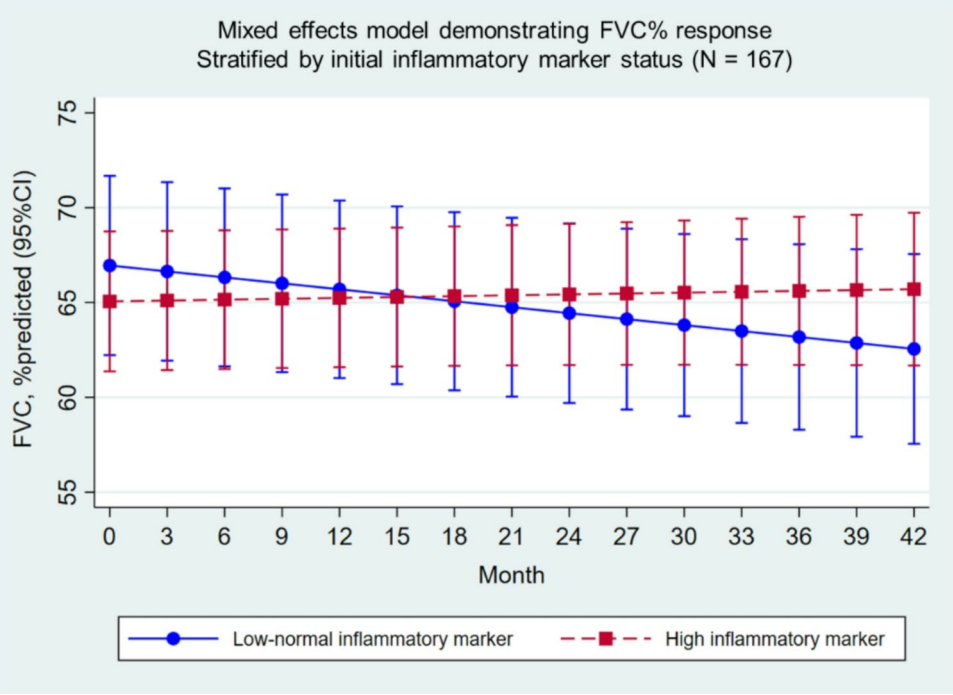

Fig. 2 Mixed model for repeated measures demonstrating FVC% response over time while treated, stratified by initial high vs. low-to-normal inflammatory markers. Fixed effects were FVC%, time on treatment, and inflammatory marker status, with individual patients as random effects. FVC% appears to be improving over time in treated patients with initially high inflammatory markers vs. declining in those with low-to-normal markers ($P = 0.003$)

Other investigations associated with pulmonary inflammation may be helpful for predicting treatment response and initiating therapy. Ground-glass or consolidative opacities on CT have historically suggested potential inflammation or active injury and were recently suggested as potentially helpful findings for initiating CS therapy in f-ILD [19]. While a UIP-like CT pattern in our study was associated with lower likelihood of treatment response in those with non-SARD f-ILD, many SARD and non-SARD patients demonstrated treatment response with typical UIP CT patterns or findings on imaging. Serum biomarkers have been shown to predict the course of certain f-ILD, including elevated CRP with lower FVC [4] and leukocyte telomere length with disease progression in f-HP and uILD [5]. Theoretically, non-pulmonary or systemic inflammation may also contribute to elevated inflammatory marker levels and not reflect lung-specific injury and therefore predict lung-related treatment response [7]. We found similarly elevated inflammatory markers in those with and without SARD (65% vs. 59%, respectively), with SARD still more likely to respond to treatment independent of inflammatory marker level.

Our study has several limitations. A retrospective design may not account for missingness or varied timing of events, along with selection or treatment bias based on presenting characteristics. We adjusted for factors that may potentially confound treatment response though cannot account for unknown confounders or differences in treated versus non-treated patients and those with high vs. low-normal inflammatory markers. In addition, a retrospective approach may not entirely exclude coinciding or undocumented causes of elevated inflammatory markers, including occult infection, thromboembolic disease, trauma, or extra-pulmonary inflammation due to other organ damage, especially in those with SARDs. Secondly, several characteristics including female sex, prior ILD progression, and UIP-like CT patterns, were more frequent in our cohort than observed in a recent cohort [20]. However, age, smoking status, and baseline FVC% were similar. Generalizability may be limited with other centers having varied clinical or disease severities and underlying diagnoses, suggesting additional studies are needed to confirm or support our findings in varied settings and patient subgroups. Lastly, our sample size was limited by a retrospective approach with non-protocolized testing which resulted in greater exclusions and lower study enrollment. We were therefore likely underpowered for detecting the association of individual inflammatory markers (CRP vs. ESR) and treatment response in some subgroups despite the robustness of the combined effect across the whole cohort.

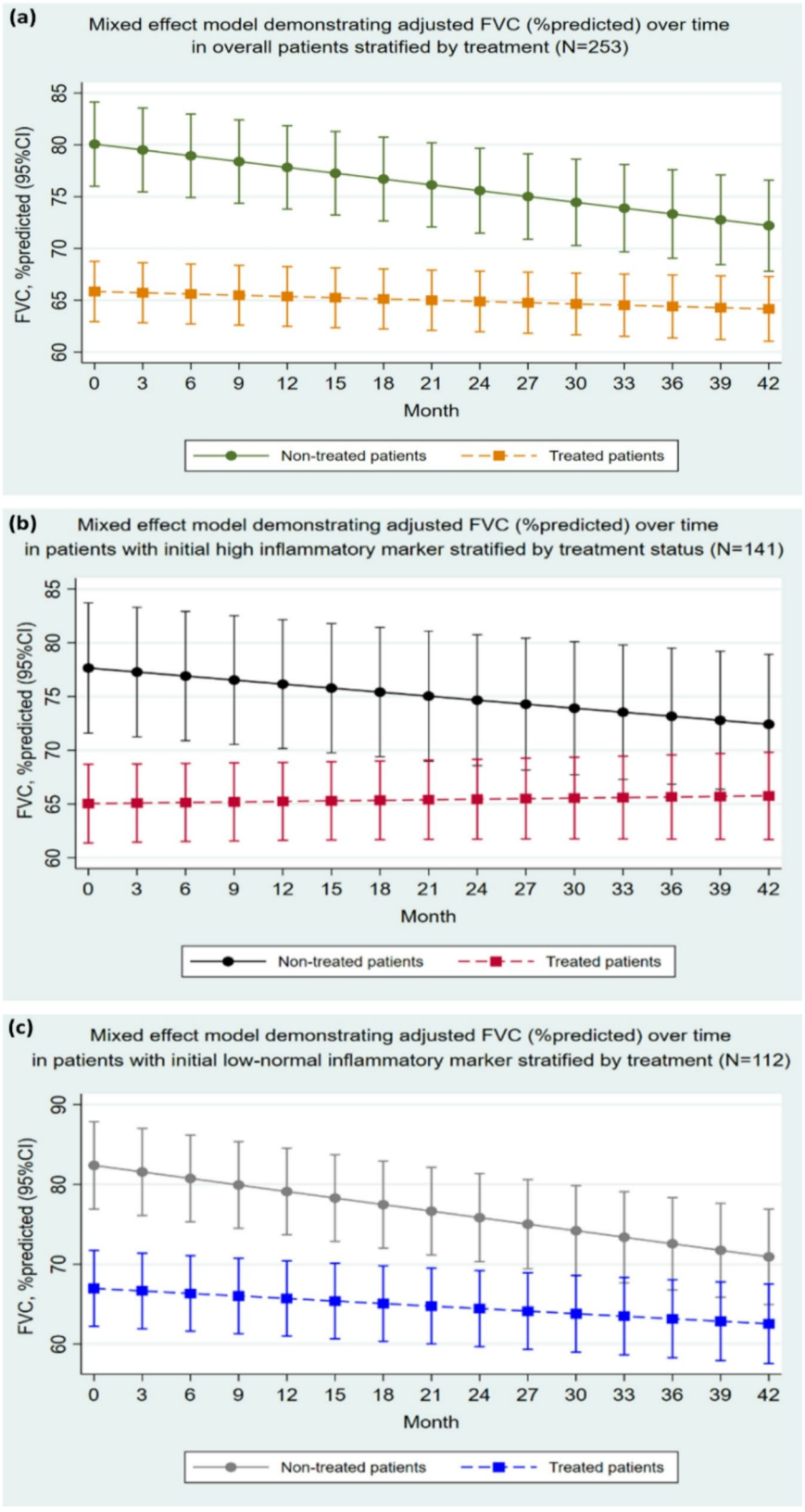

Fig. 3 Linear mixed effects models for change in FVC% over time in non-IPF f-ILD patients, showing slower FVC decline in treated vs. non-treated group: (**a**) across the whole cohort, with FVC% slope in the treated group being less negative ($P < 0.001$); (**b**) among the patients with initially high inflammatory marker status, where FVC% slope in the treated group turned positive ($P = 0.004$); and (**c**) among the patients with initially low-to-normal inflammatory marker status, where FVC% slope in the treated group was less negative ($P = 0.001$)

Conclusion

Patients with non-IPF f-ILD and elevated inflammatory markers, particularly elevated CRP, appear to be more responsive to anti-inflammatory therapy with slower FVC decline while on treatment. Underlying SARD was also associated with better treatment response, independent of baseline inflammatory marker level or CT pattern in this subgroup.

Abbreviations

AE	Acute exacerbation.
AsyS	Anti-synthetase syndrome.
AZA	Azathioprine.
CRP	C-reactive protein.
CS	Corticosteroid.
DLCO%	Percent predicted diffusion capacity for carbon monoxide.
DLCO	Diffusion capacity for carbon monoxide.
DM	Dermatomyositis.
ESR	Erythrocyte sedimentation rate.
f-HP	Fibrotic hypersensitivity pneumonitis.
f-ILD	Fibrotic interstitial lung disease.
FVC%	Percent predicted forced vital capacity.
FVC	Forced vital capacity.
GGO	Ground glass opacity.
HRCT	High resolution computed tomography.
IPAF	Interstitial pneumonia with autoimmune features.
IPF	Idiopathic pulmonary fibrosis.
IRB	Institutional review board.
IVIG	Intravenous immunoglobulin.
JAK	Janus kinase.
LFL	Leflunomide.
MCTD	Mixed connective tissue disease.
MMF	Mycophenolate mofetil.
MTX	Methotrexate.
Non-IPF	Non-idiopathic pulmonary fibrosis.
Non-SARD	Non-systemic autoimmune rheumatic disease.
OR	Odd ratio.
PFT	Pulmonary function test.
PM	Polymyositis.
PPF	Progressive pulmonary fibrosis.
RA	Rheumatoid arthritis.
RCT	Randomized controlled trial.
RTX	Rituximab.
SARD-ILD	Systemic autoimmune rheumatic disease related interstitial lung disease.
SARD	Systemic autoimmune rheumatic disease.
SLE	Systemic lupus erythematosus.
SSA	Steroid-sparing agent.
SSc-ILD	Scleroderma-related interstitial lung disease.
SSc	Scleroderma.
TNF	Tumor necrosis factor.
u-ILD	Unclassifiable interstitial lung disease.
UCTD	Undifferentiated connective-tissue disease.

Supplementary Information

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Supplementary Material 1

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Author contributions

Both authors, Yanisa Kluanwan and Teng Moua, contributed equally to the conceptualization, data acquisition, data analysis, manuscript writing, and review of this submitted work.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Study approval was obtained by Mayo Clinic Institutional Review Board before initiation; all included study participants completed broad consent forms to have their clinical and personal information anonymized and reviewed for research purposes.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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