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ORIGINAL RESEARCH

Peripheral Levels of Selected Biomarkers in Patients with Post-Sarcoidosis Chronic Fatigue Syndrome

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Introduction: Chronic fatigue syndrome (CFS) is characterized by persistent fatigue and multiple symptoms such as cognitive impairment and muscle pain, often linked to immune-inflammatory dysfunction. Sarcoidosis, a granulomatous disease with systemic inflammation, commonly causes fatigue, even during remission. This study examined whether fatigue and depressive symptoms in sarcoidosis remission relate to residual inflammation or oxidative stress. Recent studies highlight parallels between post-infectious fatigue syndromes, including Long COVID, and sarcoidosis-related fatigue, emphasizing IL-6 mediated pathways. Theoretical frameworks of immune–metabolic interactions further support the hypothesis that residual inflammation drives persistent fatigue in remission.

Materials and methods: Seventy-one sarcoidosis patients were divided into three groups: remission with fatigue (RS/CFS, n=22), remission without fatigue (R/S, n=23), and active sarcoidosis (A/S, n=26). Fatigue was assessed with the Fatigue Assessment Scale (FAS), depressive symptoms with the Beck Depression Inventory (BDI), and quality of life with PHQ-9. Pulmonary function tests measured FEV_1 and FVC. Serum biomarkers (hsCRP, IL-6, TNF-α, total antioxidant status, and 8-isoprostanes) were measured by ELISA.

Results: RS/CFS and A/S groups showed significantly higher fatigue, and depressive scores compared to R/S (P <0.05). HsCRP and IL-6 levels were elevated in fatigued patients (RS/CFS and A/S) versus non-fatigued (R/S) (P <0.05). IL-6 correlated moderately with fatigue and depression scores (r =0.33). No significant differences were found in TNF-α or oxidative stress markers. Pulmonary function was slightly reduced in fatigued patients and weakly correlated with mental fatigue (r = –0.26).

Conclusion: Our data support a role for low-grade systemic inflammation, especially elevated hsCRP and IL-6, in fatigue and depressive symptoms during sarcoidosis remission. Further research integrating inflammatory, oxidative, metabolic, and neuroendocrine pathways is needed to elucidate fatigue pathogenesis and develop targeted interventions. IL-6 may represent a potential biomarker of fatigue in sarcoidosis. These findings highlight the importance of persistent low-grade inflammation and may guide the development of future therapeutic strategies.

Plain Language Summary: Fatigue is one of the most common and disabling symptoms in patients with sarcoidosis, even when the disease appears to be in remission. In this study, we compared three groups of patients with sarcoidosis – those in remission with fatigue, those with active disease, and those in remission without fatigue. We measured blood markers of inflammation and oxidative stress, as well as symptoms of fatigue and depression. We found that patients with fatigue had higher levels of inflammation, especially interleukin-6 (IL-6). This suggests that low-grade inflammation may play a role in persistent fatigue, and IL-6 might become a potential treatment target in the future.

Keywords: sarcoidosis, chronic fatigue syndrome, inflammation, oxidative stress

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Introduction

Chronic fatigue syndrome (CFS) is a complex, multifactorial illness defined by persistent, unexplained fatigue that fails to improve with rest and severely limits day-to-day functioning.[1] Although definitions differ, most require at least six consecutive months of incapacitating fatigue plus four or more accompanying symptoms—post-exertional malaise, unrefreshing sleep, cognitive difficulties (memory or concentration problems), myalgia, polyarthralgia, sore throat, tender lymph nodes, or new-onset headaches.[2] Its precise cause remains uncertain; nonetheless, immune-inflammatory disturbances and altered cytokine profiles are strongly implicated,[3] with many abnormalities linked to activation of nitro-oxidative pathways.[4]

Sarcoidosis, a systemic granulomatous disease of unknown origin, is characterised by non-caseating granulomas that can involve multiple organs and markedly reduce quality of life.[5] Inflammation is central to its pathogenesis, and treatments attempt to suppress macrophage and T-cell activity along with their cytokines—TNF-α, IL-1β, IFN-γ, and IL-6.[6] Oxidative stress likewise contributes to sarcoidosis development and progression.[7]

CFS is increasingly recognized as a severe, prevalent condition within the broader spectrum of immune-inflammatory and oxidative-stress-related disorders.[8] In sarcoidosis, fatigue is often the most debilitating symptom and can persist during both active disease and periods of clinical and radiological remission.[8] Such enduring fatigue in remission may signal ongoing subclinical processes and therefore warrants closer study. Epidemiological studies indicate that fatigue affects approximately 60–70% of patients with sarcoidosis and is considered one of the most disabling symptoms of the disease.

The mechanisms underpinning CFS in active sarcoidosis remain incompletely defined but likely involve chronic low-grade inflammation, sustained cytokine release, and immune-inflammatory signaling pathways common to sarcoidosis, together with possible contributions from impaired pulmonary function. For instance, fatigue severity measured by the Fatigue Assessment Scale (FAS) has been correlated with reduced forced expiratory volume in one second (FEV_1).[9] Conversely, the pathophysiology of CFS observed during sarcoidosis remission is still obscure, making identification of its drivers crucial—especially in the absence of validated diagnostic tools or targeted therapies. Chronic low-grade inflammation is a plausible contributor.

Given the role of inflammation in both sarcoidosis and CFS, examining key mediators such as IL-6, TNF-α, and high-sensitivity C-reactive protein (hsCRP) may reveal shared pathways. Oxidative-stress markers and their interplay with immune-inflammatory factors might also sustain CFS symptoms in patients with sarcoidosis in remission. Fatigue affects up to 60–70% of patients with sarcoidosis and is considered the most disabling symptom.[10] Depressive symptoms are also frequent and may share inflammatory mechanisms with fatigue, justifying their combined analysis. Accordingly, this study assessed fatigue severity, depressive symptoms, and other mental-health parameters in individuals with sarcoidosis. The primary aim was to determine whether these symptoms during remission associate with residual inflammation and/or oxidative stress—evaluated via hsCRP, IL-6, TNF-α, total antioxidant status (TAS), and 8-isoprostanes—and to explore their relationship with pulmonary function.

Depressive symptoms are also common in sarcoidosis and may share inflammatory pathways with fatigue, particularly involving IL-6 and TNF-α. Including depressive symptoms in the analysis may therefore provide additional insight into the role of systemic inflammation.

Methods

Study Design and Participants

This cross-sectional study included 71 patients diagnosed with sarcoidosis based on the American Thoracic Society/World Association for Sarcoidosis and Other Granulomatous Disorders (ATS/WASOG) criteria. Before being enrolled in the study, patients completed two informed consent forms based on previously issued approvals numbered RNN/99/08/KE and RNN 182/12/KE by the Bioethics Committee of the Medical University of Lodz. This study was conducted in accordance with the Declaration of Helsinki. Patients were recruited from the Outpatient Clinic and the Department of Pneumology at the University Hospital No 1 in Łódź, Poland. From this population, a subgroup of patients in clinical and radiological remission who met diagnostic criteria for chronic fatigue syndrome (CFS) was preselected (R/CSF – remission + fatigue).

Table 1 Study Cohorts

Code	n	Clinical Definition	Fatigue Criterion*
RS/CFS (remission + fatigue)	22	Complete clinical and radiological remission	FAS ≥ 22
A/S (active sarcoidosis)	26	Active pulmonary sarcoidosis (Scadding stage I–III)	Not applicable
R/S (true remission)	23	Complete clinical and radiological remission	FAS ≤ 21

Notes: *Fatigue was assessed exclusively with the Fatigue Assessment Scale (FAS); no subjective, non-standardised fatigue ratings were used.

This group was compared with two control groups: (1) patients with sarcoidosis in remission but without fatigue (R/S – true remission), and (2) patients with active sarcoidosis, regardless fatigue presence and intensity (A/S – active sarcoidosis). Remission was defined as the absence of clinical symptoms and complete radiological resolution of previous abnormalities (Scadding stage 0). All patients in remission had a prior diagnosis of sarcoidosis confirmed by biopsy and had previously demonstrated abnormal radiological findings consistent with Scadding stage I–III. The diagnosis of CFS was based on a Fatigue Assessment Scale score ≥22, after systematic exclusion of alternative causes of fatigue (eg, thyroid dysfunction, anaemia, ongoing infection). Although no formal matching technique was employed, the three groups did not differ significantly in terms of age or sex. The clinical definitions of the three study cohorts are summarized in Table 1.

Inclusion and Exclusion Criteria

All participants were non-smokers and had not received systemic corticosteroids or immunosuppressive therapy prior to enrollment. Patients were excluded if they had:chronic comorbidities or acute infections that could confound fatigue severity or influence inflammatory biomarker levels; ongoing pregnancy; or clinically significant extrapulmonary sarcoidosis.

Clinical Assessment

Pulmonary function was assessed with spirometry to determine forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), along with measurement of the hemoglobin-corrected transfer factor for carbon monoxide (Tlco). Examinations were performed on Lungtest 1000 and Tlco devices (MES, Poland) in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines, and outcomes were reported as percentages of predicted values.

All participants underwent standard chest radiography. For the active-sarcoidosis (A/S) cohort, radiographic staging followed the Scadding classification, while high-resolution computed tomography (HRCT) was obtained when necessary to confirm full radiological remission in patients judged to be in remission.

Symptom and Psychological Assessment

The Polish adaptation of the Sarcoidosis Health Questionnaire (SHQ)[11] was produced using the standard forward-backward translation procedure.[12] Two pulmonologists independently translated the original, reconciled their versions into a single Polish draft, which was then backtranslated and checked against the source questionnaire. The SHQ contains 29 items grouped into three domains—Daily Functioning (DF, 13 items), Physical Functioning (PF, 6 items), and Emotional Functioning (EF, 10 items)—each rated on a 7-point Likert scale. Domain and total scores are calculated as the mean of the item scores, with higher values indicating better health-related quality of life in sarcoidosis.

Self-reported depressive symptoms were measured with the Beck Depression Inventory (BDI).[13] The Polish BDI includes 21 items covering key depressive features (eg, anhedonia, low energy, depressed mood), each offering four response options scored from 0 to 3.[14]

A second depression screen, the nine-item Patient Health Questionnaire (PHQ-9), was employed as a brief measure for mood-disorder detection;[15] a validated Polish version is freely accessible online.[16] Items are rated 0–3 according to

symptom frequency, with higher totals reflecting greater depressive severity—this interpretation applies to both the BDI and PHQ-9.

Fatigue severity was evaluated using the Fatigue Assessment Scale (FAS),[17] for which a Polish translation is also available online.[18] The FAS comprises ten items split into two five-item subscales—Physical Fatigue (FAS-P) and Mental Fatigue (FAS-M); higher scores denote more pronounced fatigue.

Blood Collection and Biochemical Analysis

Fasting venous blood was drawn into additive-free tubes, left to clot for 30 minutes at room temperature, and centrifuged at 1000 × g for 15 minutes at 4 °C. The resulting serum was aliquoted and stored at −70 °C until analysis.

Selected biomarkers were quantified by enzyme-linked immunosorbent assay (ELISA) with the following commercial kits: high-sensitivity C-reactive protein (hsCRP) using the CRP ELISA Kit (Immunodiagnostik AG, Bensheim, Germany); interleukin-6 (IL-6) with the Human IL-6 ELISA Kit (Diaclone SAS, Besançon, France); tumour necrosis factor-α (TNF-α) with the Human TNF-α ELISA Kit (Diaclone SAS, Besançon, France). Absorbance for cytokine assays was read at 450 nm on a Multiskan Ascent microplate photometer (Thermo Labsystems). Plasma 8-isoprostane was measured with the 8-Isoprostane EIA Kit (Cayman Chemical, Ann Arbor, MI, USA), and total antioxidant capacity was assessed using the Antioxidant Assay Kit (Cayman Chemical, Ann Arbor, MI, USA), which quantifies the capacity of sample antioxidants to inhibit oxidation of ABTS (2,2′-azino-bis[3-ethylbenzothiazoline-6-sulfonic acid]) to its radical cation ABTS•+, monitored spectrophotometrically at 405 nm.

Statistical Analysis

Statistical analyses were carried out in R version 4.3 (R Foundation for Statistical Computing) on macOS. The sample size was based on the number of consecutive patients fulfilling the inclusion criteria during the recruitment period. Formal power calculation was not performed; therefore, this study should be considered exploratory. Data normality was checked with the Shapiro–Wilk test; because most variables were non-normally distributed, results are reported as medians with interquartile ranges (IQRs). Comparisons between two independent groups used the Mann–Whitney *U*-test, while comparisons across three groups employed the Kruskal–Wallis test, followed—where appropriate—by pairwise Mann–Whitney U post-hoc tests. Associations between continuous variables were examined with Spearman's rank correlation coefficient (r_s). Correlation strength was interpreted as poor ($r < 0.3$), moderate (0.3–0.5), or strong (>0.5). Assumptions for statistical tests were checked, and potential confounders such as age and sex distribution were considered. All tests were two-tailed, with $P < 0.05$ denoting statistical significance.

Results

A total of 71 individuals with sarcoidosis were included in the study and stratified into three groups: 22 patients in clinical and radiological remission with clinically significant fatigue (RS/CFS), 26 patients with active sarcoidosis (A/S), and 23 patients in remission without fatigue (R/S). There were no statistically significant differences in age or sex distribution among the groups ($P = 0.09$ and $P = 0.06$, respectively). Pulmonary function testing revealed significantly lower FEV_1 and FVC values in both the RS/CFS and A/S groups compared to the R/S group, indicating reduced lung function associated with fatigue and disease activity. Demographic data and pulmonary function parameters for the study groups are summarized in Table 2.

Depressive symptoms, assessed by the BDI and quality of life assessed by PHQ-9, as well as both the physical and mental components of the FAS, differed significantly among the groups. The highest scores were observed in patients with sarcoidosis in remission with fatigue (RS/CFS) and those with active sarcoidosis (A/S). Clinically significant fatigue, defined as an FAS score ≥ 22, was present in 41 of 71 participants (57.7%). Detailed results regarding psychological status and fatigue severity are presented in Table 3.

A significant overall difference in hsCRP concentrations was observed across the groups ($P = 0.045$) (Figure 1). Post hoc analysis revealed that hsCRP levels were significantly elevated in both the RS/CFS and A/S groups compared to the

Table 2 Demographic and Pulmonary Function Characteristics

	Total (N = 71)	RS/CFS (N = 22)	A/S (N = 26)	R/S (N = 23)	P-value
Male, n (%)	37 (52.1)	16 (72.7)	12 (46.2)	9 (39.1)	0.06
Age (years)	46.8 (12.3)	45.1 (12.4)	51.0 (10.9)	43.8 (12.9)	0.09
FEV_1 %pred	88.8 (11.5)	87.0 (8.9)†	83.9 (12.6)†	96.2 (8.6)	<0.001
FVC %pred	91.9 (12.6)	91.1 (9.6)	86.8 (12.3)†	98.6 (12.9)	0.003
FEV_1/FVC	0.77 (0.05)	0.77 (0.05)	0.76 (0.06)	0.79 (0.04)	0.08
$T_{l,co}$ %pred	93.6 (12.4)	93.1 (10.0)	91.0 (15.9)	96.9 (9.1)	0.26
Radiological stage I/II/III/IV	30/37/4/0	16/6/0/0	4/18/4/0	10/12/0/0	–

Note: †P < 0.01 vs R/S.

Table 3 Depression, Quality of Life and Fatigue (FAS) Scores

	Total	RS/CFS	A/S	R/S	P-value
BDI	8.8 (6.1)	12.2 (6.9)*	10.3 (5.0)*	3.7 (1.6)	<0.001
PHQ-9	5.4 (4.0)	8.0 (4.8)*	6.3 (2.7)*	1.8 (1.2)	<0.001
FAS-physical	12.2 (4.2)	15.8 (3.5)*,‡	13.0 (2.8)*	7.8 (1.4)	<0.001
FAS-mental	10.0 (3.0)	11.9 (2.8)*,‡	10.9 (2.2)*	7.1 (1.2)	<0.001
FAS-total	22.1 (6.8)	27.7 (5.5)*,‡	23.9 (4.5)*	14.8 (2.0)	<0.001

Notes: *P < 0.001 vs R/S, ‡P < 0.01 vs R/S. Values are presented as median (interquartile range).
Abbreviations: BDI, Beck Depression Inventory; PHQ-9, Patient Health Questionnaire 9; FAS, Fatigue Assessment Scale.

R/S group (P = 0.04). No statistically significant differences were found between groups for TNF-α, IL-6, TAS, or 8-isoprostane. Group-wise IL-6 distributions are shown in Figure 2. Detailed inflammatory and oxidative stress biomarker profiles stratified by clinical group are presented in Table 4.

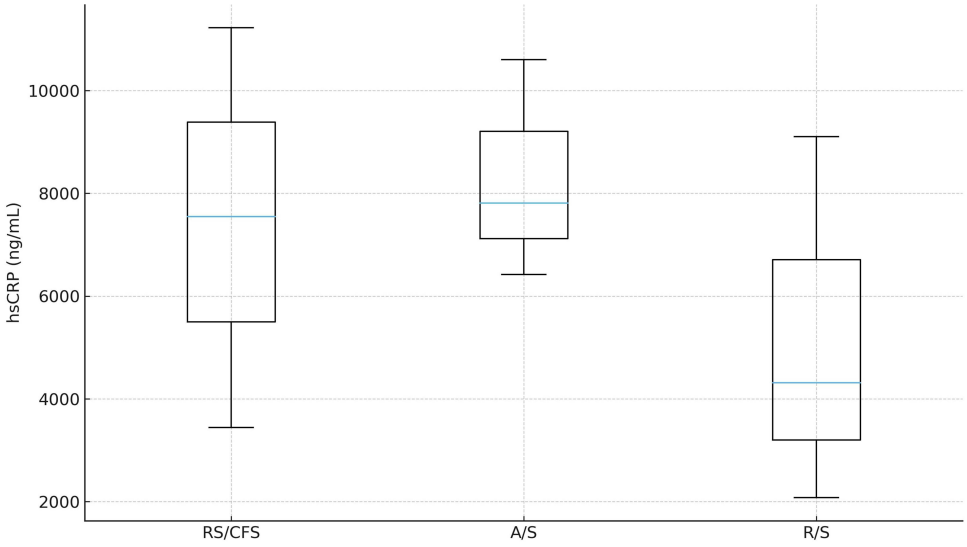

Figure 1 Serum hsCRP concentrations by clinical group. Boxplots represent median and interquartile ranges of serum hsCRP concentrations in patients with remission and fatigue (RS/CFS), active sarcoidosis (A/S), and remission without fatigue (R/S).

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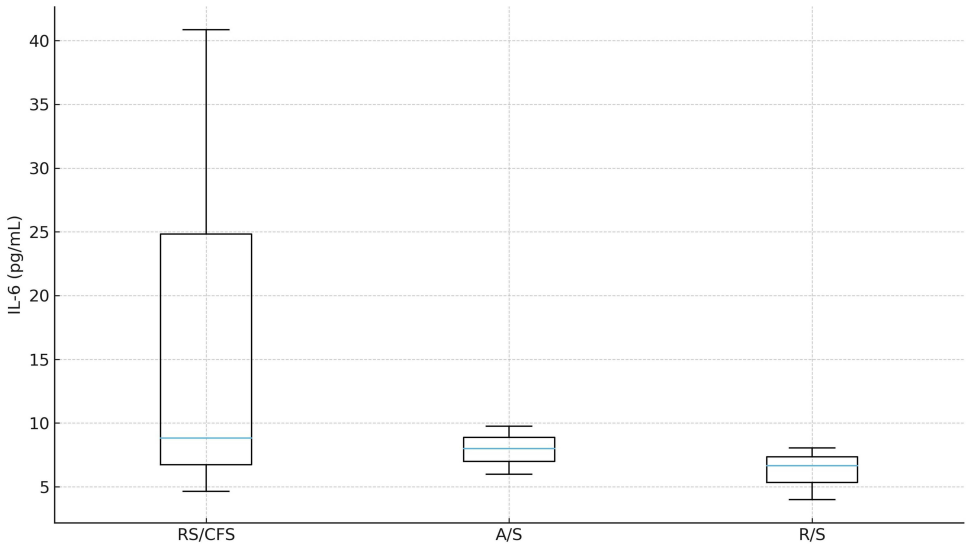

Figure 2 Serum IL-6 concentrations by clinical group. Boxplots represent median and interquartile ranges of serum IL-6 concentrations in patients with remission and fatigue (RS/CFS), active sarcoidosis (A/S), and remission without fatigue (R/S).

When stratified by fatigue severity, patients with clinically significant fatigue (FAS ≥22) exhibited significantly higher serum IL-6 concentrations compared to those without fatigue (8.07 vs 6.64 pg/mL; P = 0.007). No significant differences were observed between groups for hsCRP, TNF-α, TAS, or 8-isoprostane levels. Detailed data on FAS and biomarker concentrations are provided in Table 5.

IL-6 demonstrated a moderate positive correlation with both fatigue severity, as measured by the total FAS, and depressive symptoms assessed by the BDI (r=0.33; P=0.008). No significant correlations were observed between fatigue or depression scores and levels of hsCRP, TNF-α, TAS, or 8-isoprostane. As anticipated, BDI scores correlated strongly with PHQ-9 scores (data not shown). Detailed correlations between questionnaires and biomarkers are summarized in Table 6.

Lung-Function Correlates of Fatigue

A weak inverse correlation was observed between the mental fatigue component of the Fatigue Assessment Scale (FAS-M) and forced expiratory volume in one second (FEV_1) (r = –0.26, P = 0.03). No other significant associations were detected between lung function parameters and fatigue measures.

Table 4 Inflammatory and Oxidative-Stress Biomarker Profiles Stratified by Clinical Groups

Parameter	RS/CFS	A/S	R/S	P
hsCRP (ng/mL)	7549.8 [3442.6–11221.6]	7813.3 [6421.3–10603.0]	4313.3 [2082.1–9101.5]	0.045†
TNF-α (pg/mL)	5.37 [4.79–5.66]	4.94 [4.20–5.43]	5.60 [4.74–5.83]	0.19
IL-6 (pg/mL)	8.81 [4.63–40.85]	7.98 [5.97–9.75]	6.64 [4.00–8.05]	0.14
TAS (mM)	7.70 [5.96–11.08]	9.40 [7.42–13.00]	9.75 [7.09–13.11]	0.24
8-isoprostane (pg/mL)	415.7 [382.4–427.5]	426.7 [400.9–430.9]	412.8 [403.4–422.0]	0.39

Notes: †Post-hoc: R/S < RS/CFS and A/S (P = 0.04). Values are presented as median (interquartile range). Reference ranges: hsCRP < 5 mg/L, IL-6 < 7 pg/mL, TNF-α < 8 pg/mL, TAS 7–14 mM, 8-isoprostane < 400 pg/mL.
Abbreviations: hsCRP, high sensitivity C-reactive protein; TNF, tumor necrosis factor; TAS, total antioxidant status.

Table 5 Comparison of Biomarker Levels in Patients with and Without Clinically Significant Fatigue (FAS ≥22)

Biomarker	FAS < 22 (n = 30)	FAS ≥ 22 (n = 41)	P
hsCRP (ng/mL)	4662.7 (2348.5–9560.4)	7813.3 (5052.2–11101.3)	0.07
TNF-α (pg/mL)	5.49 (4.29–5.75)	5.29 (4.43–5.63)	0.56
IL-6 (pg/mL)	6.64 (4.63–7.98)	**8.07 (5.97–19.45)**	**0.007**
TAS (mM)	11.01 (7.32–13.44)	8.35 (6.27–11.60)	0.17
8-isoprostane (pg/mL)	416.4 (406.0–428.0)	418.3 (393.7–429.3)	0.93

Notes: Median (IQR) biomarker concentrations in patients with and without clinically significant fatigue (FAS ≥22). Comparisons are between groups (Mann–Whitney *U*-test). Bold values indicate statistically significant differences ($P < 0.05$).
Abbreviations: hsCRP, high sensitivity C-reactive protein; TNF, tumor necrosis factor; TAS, total antioxidant status.

Table 6 Spearman's Rank Correlations Between Biomarkers and Questionnaire Scores

Biomarker	FAS rs (P)	BDI rs (P)
hsCRP	0.14 (0.27)	0.25 (0.14)
TNF-α	–0.10 (0.43)	–0.14 (0.25)
IL-6	**0.33 (0.008)**	**0.33 (0.007)**
TAS	–0.20 (0.11)	–0.02 (0.85)
8-isoprostane	0.05 (0.71)	0.10 (0.42)

Notes: Spearman's rank correlation coefficients (r_s) between biomarkers and questionnaire scores (FAS, BDI, PHQ-9). Bold values indicate statistically significant correlations ($P < 0.05$).
Abbreviations: hsCRP, high sensitivity C-reactive protein; TNF, tumor necrosis factor; TAS, total antioxidant status.

Discussion

In this study, we found that sarcoidosis patients in remission experiencing clinically significant fatigue exhibited elevated levels of hsCRP compared to non-fatigued remission patients, while those with active disease also showed higher hsCRP. IL-6 concentrations correlated positively with both fatigue severity and depressive symptoms and were significantly higher in patients with fatigue. However, other inflammatory cytokines (TNF-α), oxidative stress markers (total antioxidant status and 8-isoprostane) did not differ significantly between groups. These findings suggest that low-grade systemic inflammation, particularly involving hsCRP and IL-6, may contribute to fatigue and mood disturbances in sarcoidosis during remission. It remains unclear why only some patients in remission develop clinically significant fatigue despite comparable inflammatory activity. Genetic or epigenetic predispositions may explain this heterogeneity and warrant further research.

The relationship between inflammation and mental health disturbances in somatic diseases is an active area of investigation. Inflammatory cytokines such as IL-18 and IL-1β have been implicated in the development of depressive symptoms in chronic obstructive pulmonary disease (COPD).[19] Similarly, inflammation-related biomarkers are involved in the pathogenesis and progression of sarcoidosis[20] and CFS,[21] potentially explaining the mechanisms underlying chronic fatigue syndrome in sarcoidosis.

However, population-based evidence linking inflammatory processes to fatigue development in somatic diseases remains limited. To our knowledge, no previous study has investigated inflammatory and oxidative stress biomarkers specifically in sarcoidosis patients during remission with CFS. This study is the first to explore whether inflammatory molecules contribute to fatigue, depressive symptoms, and impaired quality of life in sarcoidosis patients in remission. Our findings provide new insights into inflammation-associated factors involved in fatigue during sarcoidosis remission.

Chronic fatigue syndrome and sarcoidosis share common inflammatory pathways, and immune markers such as hsCRP and IL-6 have been prospectively associated with new-onset fatigue in somatic diseases.[22] Elevated hsCRP levels in CFS patients persist even after adjusting for confounders such as body mass index,[23] reinforcing the hypothesis of low-grade inflammation as a key contributor to fatigue development.[24]

The reduction in lung function observed in RS/CFS despite clinical and radiological remission may reflect residual structural changes or undetected microinflammation.[25] Previous studies found no consistent link between fatigue and lung function, suggesting other contributing mechanisms.[26–28] BMI was not recorded in our study, which represents a limitation given its known association with CRP elevations.[29]

In sarcoidosis, previous studies have found increased CRP levels predominantly in patients with higher adiposity.[10] Additionally, correlations have been reported between hsCRP and markers of low-grade metabolic inflammation and thyroid hormone metabolism, including free and total iodothyronines, which are altered in CFS.[30] Such metabolic-inflammatory interactions may underlie fatigue and mental health symptoms in sarcoidosis and warrant deeper exploration.

IL-6 has been repeatedly implicated in CFS pathophysiology. Elevated IL-6 levels were observed in post-COVID-19 patients with fatigue,[31] and higher IL-6 correlates with depressive symptoms commonly co-occurring with CFS.[32] Inflammation and immune markers, including IL-6, are promising candidates for tracking CFS progression and tailoring treatments.[33] Peripheral IL-6 may reflect central nervous system processes because IL-6 crosses the blood-brain barrier,[34] affecting brain regions involved in fatigue and depression.[35] However, data remain mixed; for example, pre-existing IL-6 elevation did not predict chronic fatigue risk in mild COVID-19.[36]

Experimental studies also suggest IL-6 infusion induces fatigue-like symptoms,[37] and increased pro-inflammatory cytokines can promote muscle catabolism leading to fatigue.[38] This mechanism may partially explain fatigue in sarcoidosis.

In sarcoidosis specifically, there is a negative association between Th2 cytokines (IL-4, IL-5, IL-10) and chronic fatigue, suggesting a diminished Th2 counter-regulatory response in fatigued patients.[39] Furthermore, altered levels of IL-8 and monocyte chemoattractant protein (MCP)-1 were observed, indicating complex immune dysregulation contributing to fatigue persistence during remission.

Oxidative stress is another important factor in both CFS and sarcoidosis pathogenesis. Multiomics analyses link fatigue with antioxidant and detoxification pathways.[40] Markers such as 8-isoprostane are elevated in sarcoidosis patients' exhaled breath and broncho-alveolar lavage fluid.[7] This study uniquely evaluated oxidative stress markers in sarcoidosis-associated fatigue, although no significant differences were found, consistent with previous research.[41,42]

In other post-viral fatigue syndromes, including Long COVID, oxidative damage and reduced antioxidant defenses have been implicated.[43] Antioxidant supplementation (CoQ10 and selenium) improves fatigue symptoms and oxidative status in CFS patients.[44] Therefore, oxidative stress biomarkers warrant further study as potential contributors and therapeutic targets in sarcoidosis fatigue.

This study has several limitations that should be acknowledged. The cross-sectional design precludes establishing causal relationships between inflammatory markers and the presence of fatigue or depressive symptoms in sarcoidosis patients. The relatively small sample size, particularly within subgroup analyses, may limit the statistical power and generalizability of our findings. Although the groups were comparable in terms of age and sex, no formal matching or adjustment for potential confounding factors such as body mass index, comorbidities, or medication use was performed, which could influence both inflammatory profiles and symptom severity. Furthermore, the biomarker panel was limited to selected inflammatory and oxidative stress markers, while other relevant pathways implicated in fatigue and depression—such as neuroendocrine dysfunction or mitochondrial impairment—were not evaluated. The absence of neuroimaging or cerebrospinal fluid analyses also restricts insight into central nervous system involvement in these symptoms.

Additionally, important variables including sleep quality, physical activity levels, and psychosocial stressors were not assessed, potentially confounding the observed associations. Future studies should also incorporate sarcoidosis activity markers such as sIL-2R and ACE to refine remission criteria and exclude microactive disease. Finally, as a single-center study, the findings may have limited external validity, underscoring the need for larger, multi-center, longitudinal studies to confirm and expand upon these results. Another limitation of our study is the lack of systematic data on disease duration. We were therefore unable to report the median time since sarcoidosis diagnosis across the study groups. Disease duration may influence both symptom burden and biomarker levels, and future studies should incorporate this parameter.

Conclusions

Our study emphasizes the clinical relevance of IL-6 as a potential stratification biomarker. Low-grade systemic inflammation may underlie fatigue and depression in sarcoidosis remission. Longitudinal, multi-omics studies are needed to validate IL-6 as a therapeutic target and to develop tailored interventions.

Disclosure

The authors report no conflicts of interest in this work.

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