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An Underrecognized Comorbidity: Restless Legs Syndrome Drives Fatigue in Pulmonary Sarcoidosis Independent of Mood

Senay Aydın

senay.aydin@sbu.edu.tr

University of Health Sciences

Sinem Nedime Sökücü

University of Health Sciences

Seda Tural

University of Health Sciences

Nevin Pazarcı

University of Health Sciences

Erdoğan Çetinkaya

University of Health Sciences

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Abstract

Purpose

Under strict differential-diagnosis criteria, restless legs syndrome (RLS) prevalence is estimated at 1.9–4.6% among adults (approximately 3.2–3.4% in Turkish population surveys), while broader symptom-based case definitions yield estimates of 5–15%; RLS has also been linked to several cardiovascular, metabolic, and neurological comorbidities. Given the high prevalence of fatigue and sleep disturbances in sarcoidosis, this study aimed to determine RLS prevalence in sarcoidosis patients and its association with fatigue and mood disturbances.

Methods

Sarcoidosis patients diagnosed by radiological and histopathological criteria completed standardized questionnaires; RLS was diagnosed using International Restless Legs Syndrome Study Group (IRLSSG) criteria. Clinical, laboratory, and radiological data were retrospectively collected, and patients were stratified by RLS status. Fatigue, cognition, sleep quality, insomnia, anxiety, and depression were assessed using the Fatigue Severity Scale (FSS), Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS).

Results

RLS was present in 34 patients (35.1%); 72.2% were female, mean age 45.12 ± 11.02 years. No significant intergroup differences emerged in age, sex, anthropometrics, or cognition. RLS patients showed significantly higher fatigue, depression, and anxiety scores ($p = 0.002$, $p < 0.001$, $p < 0.001$), while sarcoidosis stage and Modified Medical Research Council (MMRC) dyspnea scores did not differ ($p = 0.135$). Only IRLSSG severity ($p = 0.040$) and MMRC ($p = 0.001$) remained independent fatigue predictors.

Conclusions

RLS is markedly more prevalent in sarcoidosis, with fatigue independently associated with RLS severity and dyspnea burden rather than mood, suggesting RLS is an underrecognized, modifiable contributor warranting screening.

Introduction

Restless legs syndrome (RLS) is a chronic sensorimotor neurological disorder defined by an urge to move the legs, usually with uncomfortable sensory symptoms that emerge or worsen at rest, are relieved by movement, and follow a nocturnal circadian pattern. The ICSD-3 classifies RLS as a sleep-related

movement disorder, reflecting its close relationship with sleep onset, sleep continuity, and periodic limb movements during sleep [1]. Reported prevalence varies with case-ascertainment strategy: strict differential-diagnosis criteria estimate 1.9–4.6% among adults, versus 5–15% with broader symptom-based definitions [1, 2, 3]; a Turkish door-to-door survey similarly reported approximately 3.2–3.4% [3]. This heterogeneity is relevant when interpreting the higher prevalence observed in sarcoidosis cohorts, discussed below. Its pathophysiology centers on central nervous system iron insufficiency disrupting dopaminergic neurotransmission: pharmacological and postmortem neuropathological studies demonstrate dysfunction of dopaminergic neurons within the hypothalamic A11 nucleus, and reduced brain iron impairs dopaminergic signaling through convergent pathways, including attenuated adenosinergic tone across cortico-striato-thalamo-cortical circuits and altered striatal D2-receptor binding, consistent with diminished dopaminergic tone as a core pathophysiological feature of RLS [1]. Low-grade systemic inflammation is an additional, potentially interacting mechanism: patients with idiopathic RLS show significantly elevated pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), relative to controls, with IL-6 an independent correlate of diagnosis [4]. These findings suggest sustained pro-inflammatory exposure may compromise dopaminergic pathway integrity and precipitate or exacerbate RLS symptoms.

Sarcoidosis is an idiopathic multisystem inflammatory disorder pathologically defined by non-caseating granuloma formation [5]. Its immunopathogenesis is driven by CD4 + T-cell Th1-polarized cytokine secretion, notably interferon-γ and interleukin-2, with relative suppression of Th2 cytokines such as interleukin-4 and interleukin-5; TNF-α further amplifies this cascade, promoting immune cell activation and tissue infiltration and sustaining the granulomatous inflammation that defines the disease [6]. Given this persistent immune activation, sarcoidosis patients likely sustain a systemic inflammatory burden capable of disrupting dopaminergic homeostasis, making it biologically plausible that the chronic inflammatory state and immune dysregulation of sarcoidosis promote dopaminergic dysfunction through mechanisms analogous to the iron-dopamine pathway of idiopathic RLS. Consistent with this hypothesis, reported RLS prevalence in sarcoidosis cohorts ranges from 16% to 52% [7], well above general-population estimates. The fatigue, depressive symptoms, and anxiety frequently reported by sarcoidosis patients may not be fully attributable to the granulomatous disease process itself; unrecognized comorbid RLS could be an independent contributor. RLS impairs quality of life to a degree comparable with other highly prevalent chronic diseases, with insomnia, anxiety, and depression among its most impairing sequelae [8], and carries a two- to four-fold increased risk of depressive disorders, alongside elevated anxiety, chronic pain, and cognitive impairment [9]. RLS frequently co-occurs with periodic limb movements during sleep, objectively quantifiable by polysomnography; nonetheless, RLS itself remains a clinical diagnosis established through validated symptom-based criteria, without requiring polysomnographic confirmation [10]. Collectively, this suggests that a portion of the fatigue and mood disturbance in sarcoidosis may be attributable to unrecognized, untreated comorbid RLS, whose timely identification could yield meaningful improvement. A recent study characterized RLS within a small-fiber-neuropathy symptom cluster in sarcoidosis patients selected for suspected small fiber neuropathy [7]; to our knowledge, no study has systematically examined RLS prevalence and its fatigue,

depression, and anxiety associations in an unselected pulmonary sarcoidosis cohort using validated instruments and multivariable modelling. This study therefore aimed to determine RLS prevalence in pulmonary sarcoidosis, characterize its association with fatigue, depression, and anxiety, and evaluate whether RLS is an independent, quantifiable contributor to overall symptom burden.

Methods

Study population

The study protocol was approved by the Ethics Committee of Yedikule Chest Diseases and Chest Surgery Training and Research Hospital (approval number: 2014/6, date: 12 June 2014). Eligible adults had an established diagnosis of pulmonary sarcoidosis per American Thoracic Society (ATS) criteria, requiring compatible clinical/radiological findings, histopathological demonstration of non-caseating granulomatous inflammation, and exclusion of alternative diagnoses [11]. Sarcoidosis staging and severity assessment was performed by a pulmonologist blind to other assessments. All participants underwent systematic RLS evaluation by a neurologist with formal sleep medicine training, applying IRLSSG diagnostic criteria: an urge to move the legs with uncomfortable sensory symptoms, onset or worsening at rest, relief with movement, a circadian pattern with evening/nighttime predominance, and exclusion of symptoms attributable to another condition [10]. Differentiation from positional discomfort and peripheral neuropathy relied on the characteristic clinical pattern (rest-induced onset, movement-related relief, evening/nighttime predominance) specified by IRLSSG criteria, which designate RLS a clinical diagnosis not requiring polysomnographic confirmation of periodic limb movements [10]; patients with clinically evident peripheral neuropathy were separately excluded (see below). Patients were stratified into RLS-positive and RLS-negative subgroups for statistical comparison. Reporting followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for cross-sectional studies.

Exclusion criteria comprised hypertension, diabetes mellitus, thyroid or other metabolic disorders, ischemic heart disease, chronic pulmonary disease other than sarcoidosis, hepatic impairment, chronic kidney disease, neuromuscular disorders, peripheral neuropathy, psychiatric illness, and vitamin B12 or folate deficiency. Written informed consent was obtained from all participants before completion of the validated self-report questionnaires, which were administered during a single outpatient encounter.

Laboratory and clinical assessments

Consecutive eligible patients were enrolled between September 2014 and September 2017, combining prospectively collected RLS/psychometric data (structured interview, single visit) with clinical/laboratory data retrospectively reviewed from records by a pulmonologist. Radiographic staging at diagnosis and at the most recent follow-up was determined using the Scadding classification system [12], with extrapulmonary organ involvement documented. Disease activity indices included serum angiotensin-

converting enzyme (ACE) concentration and exertional dyspnea, graded with the modified Medical Research Council (MMRC) dyspnea scale [13]. Additional variables comprised demographic characteristics; complete blood count parameters; biochemical indices, including serum iron, ferritin, vitamin B12, folate, calcium, and renal function; pulmonary function testing, including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity for carbon monoxide (DLCO); comorbid conditions; and current pharmacotherapy, including immunosuppressive agents and systemic corticosteroids. All parameters were compared between RLS-positive and RLS-negative subgroups.

Cognitive, psychological, and sleep assessments

During the same encounter, all participants underwent standardized cognitive, psychological, and sleep evaluation by a neurologist with subspecialty training. Fatigue-related functional impairment was quantified with the FSS, a nine-item self-report instrument on which higher scores indicate greater fatigue-related disability [14]; the Turkish version has good validity and reliability [15]. Global cognitive function was screened with the MMSE (orientation, memory, attention, language, and visuospatial function; lower scores indicate greater impairment), using the validated Turkish adaptation [16]. Depressive and anxiety symptom severity were assessed with the BDI [17] and BAI [18], respectively, both 21-item, Turkish-validated instruments on which higher scores denote greater symptomatology. Insomnia severity was evaluated with the seven-item ISI [19], using its validated Turkish version [20]. Overall sleep quality was assessed with the 19-item PSQI, with higher scores indicating poorer sleep quality [21]. Excessive daytime sleepiness was assessed with the eight-item ESS, with higher scores reflecting greater somnolence [22]. All instruments used have been validated for the Turkish-speaking population.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics, version 22.0. Continuous variables are expressed as mean ± SD; categorical variables as frequencies and percentages. Normality was assessed before intergroup comparison; RLS-positive and RLS-negative groups were compared using the independent-samples t-test or Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables. Bivariate correlation examined associations between total FSS score and clinical, psychometric, and sleep-related parameters; variables reaching significance on univariate analysis were entered into a multivariable linear regression model to identify independent fatigue predictors. Significance was defined as two-tailed $p < 0.05$. No formal a priori sample size calculation was performed; the achieved sample size (n = 97, 34 RLS-positive) was comparable to or larger than prior sarcoidosis-RLS cohorts (prevalence 16–52%) [7]. Post-hoc power for the primary FSS comparison was calculated with G*Power 3 [23]; given the observed effect size (d = 0.68) and sample sizes (n = 63, n = 34), achieved power exceeded 0.88 ($\alpha = 0.05$, two-tailed). To account for multiple comparisons among the 20 laboratory parameters (Table 3), Benjamini-Hochberg false discovery rate correction was applied.

Results

Among the 97 patients with primary pulmonary sarcoidosis enrolled, RLS was diagnosed in 34 (35.1%); the remaining 63 (64.9%) did not meet diagnostic criteria. The cohort was predominantly female (72.2%), with a mean age of 45.12 ± 11.02 years. RLS-positive and RLS-negative subgroups showed no significant differences in age, sex, anthropometrics, or global cognitive function (Table 1). Radiographic disease stage (at diagnosis and follow-up), extrapulmonary involvement, and MMRC dyspnea scores also did not differ significantly (all $p > 0.05$; Table 1).

Table 1
Comparison of demographic and anthropometric characteristics between the groups

Variable	RLS- (n = 63)	RLS+ (n = 34)	p
Age, years	43.43 ± 10.97	47.91 ± 11.13	0.069
Female sex, n (%)	43 (68.3%)	27 (79.4%)	0.242
BMI, kg/m²	28.75 ± 5.01	28.33 ± 4.63	0.684
Neck circumference, cm	36.21 ± 3.66	36.85 ± 9.44	0.631
Waist circumference, cm	94.70 ± 12.41	92.53 ± 11.68	0.404
Hip circumference, cm	108.41 ± 9.41	105.97 ± 9.67	0.230
Waist-to-hip ratio	0.87 ± 0.08	0.87 ± 0.08	0.984
Current smoking, n (%)	14 (22.2%)	7 (20.6%)	0.852
Alcohol use, n (%)	5 (7.9%)	2 (5.9%)	0.709
Sarcoidosis stage at diagnosis – 1/2/3, n (%)	39 (61.9%) / 22 (34.9%) / 2 (3.2%)	15 (44.1%) / 17 (50.0%) / 2 (5.9%)	0.235
Sarcoidosis stage at last visit – 0/1/2/3, n (%)	2 (3.2%) / 14 (22.2%) / 27 (42.9%) / 20 (31.7%)	1 (2.9%) / 2 (5.9%) / 22 (64.7%) / 9 (26.5%)	0.118
Extrapulmonary involvement, n (%)	14 (22.2%)	9 (26.5%)	0.639
MMRC dyspnea score	1.11 ± 0.74	1.38 ± 0.85	0.107

BMI: body mass index; MMRC: Modified Medical Research Council dyspnea scale; RLS: restless legs syndrome. Values are mean ± SD or n (%). Independent-samples t-test or Mann-Whitney U test for continuous variables; chi-squared or Fisher's exact test for categorical variables. $p < 0.05$ considered significant.

Despite this baseline comparability, RLS-positive patients showed markedly worse outcomes across sleep- and mood-related domains, with significantly higher PSQI, ISI, FSS, BAI, and BDI scores than RLS-

negative patients (all p ≤ 0.031; Table 2). No significant differences emerged for global cognition (MMSE, p = 0.062) or daytime sleepiness (ESS, p = 0.068).

Table 2
Comparison of cognitive, sleep, and mood-related scores between the groups

Variable (mean ± SD)	RLS- (n = 63)	RLS+ (n = 34)	p
MMSE	28.13 ± 1.69	27.41 ± 1.81	0.055
ESS	3.30 ± 4.11	5.06 ± 4.62	0.057
PSQI	3.05 ± 3.36	10.29 ± 4.09	< 0.001*
ISI	3.19 ± 5.16	15.62 ± 6.45	< 0.001*
MMRC	1.11 ± 0.74	1.38 ± 0.85	0.107
FSS	23.13 ± 17.21	34.35 ± 15.46	0.002*
BAI	8.03 ± 9.64	18.85 ± 13.80	< 0.001*
BDI	8.94 ± 8.14	18.50 ± 11.52	< 0.001*

*MMSE: Mini-Mental State Examination; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; MMRC: Modified Medical Research Council dyspnea scale; FSS: Fatigue Severity Scale; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory. Values are mean ± SD. Mann-Whitney U test used for continuous variables. *p < 0.05.*

Table 3
Comparison of laboratory parameters between the groups

Variable	RLS- (n = 63), mean ± SD	RLS+ (n = 34), mean ± SD	p	FDR p
Fasting blood glucose, mg/dL	93.87 ± 11.81	95.41 ± 10.33	0.525	0.618
Urea, mg/dL	29.85 ± 6.74	29.44 ± 8.40	0.791	0.829
Total cholesterol, mg/dL	191.01 ± 37.69	208.32 ± 47.19	0.053	0.370
Triglycerides, mg/dL	127.32 ± 61.26	149.85 ± 96.29	0.167	0.600
HDL cholesterol, mg/dL	47.57 ± 11.67	50.52 ± 14.98	0.289	0.600
LDL cholesterol, mg/dL	118.18 ± 30.58	127.79 ± 42.93	0.254	0.600
Iron, µg/dL	47.61 ± 25.63	58.33 ± 27.87	0.064	0.370
Ferritin, ng/mL	35.07 ± 33.29	43.93 ± 48.96	0.300	0.600
HbA1c, %	5.89 ± 0.48	6.03 ± 5.35	0.250	0.600
CRP, mg/L	6.29 ± 5.35	5.27 ± 4.73	0.361	0.600
Folate, ng/mL	8.56 ± 10.48	7.05 ± 2.43	0.417	0.600
TSH, µIU/mL	2.38 ± 1.94	2.18 ± 1.01	0.519	0.618
T3, pg/mL	2.55 ± 0.50	2.45 ± 0.50	0.391	0.600
T4, ng/dL	0.24 ± 0.43	0.09 ± 0.29	0.046*	0.370
Vitamin B12, pg/mL	254.06 ± 128.04	245.65 ± 161.95	0.784	0.829
ESR, mm/h	21.67 ± 13.83	22.34 ± 13.23	0.829	0.829
WBC, $\times 10^3/\mu L$	6.65 ± 1.75	7.28 ± 1.47	0.074	0.370
RBC, $\times 10^6/\mu L$	4.81 ± 1.12	4.64 ± 0.42	0.420	0.600
Hemoglobin, g/dL	13.63 ± 3.79	13.15 ± 1.44	0.481	0.618
Serum ACE level, U/L	66.60 ± 37.62	94.22 ± 89.20	0.255	0.600

*HbA1c: glycated hemoglobin; CRP: C-reactive protein; TSH: thyroid-stimulating hormone; ESR: erythrocyte sedimentation rate; WBC: white blood cell count; RBC: red blood cell count; ACE: angiotensin-converting enzyme; FDR: false discovery rate (Benjamini-Hochberg). Values are mean ± SD. Mann-Whitney U test used for continuous variables; raw p < 0.05 marked with *. No comparison remained significant after FDR correction.*

Comprehensive laboratory assessment, including fasting glucose, urea, lipid profile, iron, ferritin, HbA1c, CRP, folate, vitamin B12, ESR, complete blood count, TSH, and serum ACE, revealed no significant

intergroup differences (all p > 0.05; Table 3). Serum free T4 was nominally lower in RLS-positive patients (0.09 ± 0.29 vs. 0.24 ± 0.43; unadjusted p = 0.046), not remaining significant after correction for multiple comparisons (FDR-adjusted p = 0.37; Table 3).

To identify independent fatigue determinants, FSS scores were examined via bivariate correlation with disease- and symptom-related variables, and significant correlates entered a multivariable regression model. On univariate analysis, IRLSSG severity, BDI, BAI, MMRC dyspnea, and PSQI scores were all significantly and positively correlated with FSS (Table 4). After multivariable adjustment, only IRLSSG severity (t = 2.161, p = 0.039) and MMRC dyspnea (t = 2.327, p = 0.027) remained independent predictors; associations with BDI, BAI, and PSQI were no longer significant when considered jointly.

Table 4
Multivariable linear regression analysis of factors associated with fatigue severity (FSS)

Variable	r; p	t	Sig.	95% CI for B	Tolerance; VIF
IRLSSG	0.736; <0.001*	2.161	0.039*	0.035 to 1.297	0.411; 2.433
BDI	0.576; <0.001*	0.935	0.358	−0.338 to 0.907	0.245; 4.082
BAI	0.580; <0.001*	0.121	0.904	−0.450 to 0.507	0.289; 3.460
MMRC	0.681; <0.001*	2.327	0.027*	0.835 to 13.128	0.458; 2.186
PSQI	0.448; 0.004*	−0.423	0.676	−1.412 to 0.929	0.550; 1.818

*IRLSSG: International Restless Legs Syndrome Study Group severity score; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; MMRC: Modified Medical Research Council dyspnea scale; PSQI: Pittsburgh Sleep Quality Index; CI: confidence interval; VIF: variance inflation factor. *p < 0.05.*

Discussion

This cross-sectional study identified an RLS prevalence of 35.1% in pulmonary sarcoidosis, substantially higher than the 5–15% typically reported in general adult populations [1, 2], including the pooled global estimate of 7.12% from a recent 52-study systematic review [2], and close to the midpoint of the 16–52% range previously reported across sarcoidosis-specific cohorts [7]. This range likely reflects heterogeneity in diagnostic methodology, disease duration, and referral patterns. Nonetheless, the several-fold enrichment relative to general-population estimates observed across virtually every published cohort is unlikely to reflect chance alone and suggests a disease-specific predisposition, lending further support to the hypothesis that the chronic, low-grade immunoinflammatory activation intrinsic to sarcoidosis predisposes affected individuals to RLS through pathways converging with the central iron-dopamine axis long established as the core pathophysiological substrate of idiopathic RLS [1]. Under this framework, granuloma-driven cytokine release, particularly interferon-γ, interleukin-2, and TNF-α, may function as a chronic, disease-intrinsic precipitant additive to, or synergistic with, the regional CNS iron insufficiency characteristic of primary RLS [24]. This offers a plausible pathophysiological explanation

for the disproportionately high RLS prevalence reported not only in sarcoidosis but across chronic inflammatory and hypoxemic pulmonary disorders more broadly [25].

Notably, none of the conventional markers of sarcoidosis severity or disease activity, including radiographic stage, extrapulmonary involvement, serum ACE, and MMRC dyspnea, were significantly associated with RLS status. This is consistent with a well-established pattern in the sarcoidosis literature, whereby fatigue and other non-organ-specific manifestations occur largely independently of standard disease-activity indices [26], and comorbid conditions such as RLS remain frequently underrecognized despite contributing to fatigue and cognitive complaints [7]. This parallels other chronic inflammatory diseases, where symptomatic burden correlates poorly with clinician-rated or radiographic activity, suggesting symptom domains including fatigue, mood, and RLS arise partially independent of the peripheral granulomatous process. RLS therefore appears to be a distinct, disease-stage-independent comorbidity, so even patients with mild or quiescent disease should not be presumed low-risk for undiagnosed RLS.

Relative to RLS-negative patients, those with RLS reported worse sleep quality, insomnia, fatigue, and depressive and anxiety burden, consistent with the well-documented adverse impact of RLS on quality of life and psychiatric wellbeing [8, 9], where RLS impairs functioning to a degree comparable with other major chronic diseases and substantially increases the risk of clinically significant depressive and anxiety symptoms. This magnitude suggests RLS may be clinically consequential rather than merely incidental, supporting the premise that unrecognized comorbid RLS may be an additional, modifiable driver of the fatigue-affective symptom cluster in sarcoidosis, rather than an epiphenomenon of pre-existing distress.

A further finding was that only IRLSSG severity and MMRC dyspnea remained independent fatigue predictors on multivariable analysis, despite strong univariate correlations with depression, anxiety, and sleep quality. This suggests fatigue in sarcoidosis patients with comorbid RLS is predominantly associated with RLS severity and respiratory symptom burden, with mood and sleep disturbance as parallel manifestations rather than independent causal contributors. This implies that fatigue outcomes in sarcoidosis trials may be more responsive to RLS-directed therapy than to antidepressant or anxiolytic treatment alone, and argues for RLS severity to be captured as a covariate in future fatigue trials.

Although RLS-positive patients had significantly worse sleep quality, no significant between-group difference emerged in global cognitive performance on the MMSE. This null finding likely reflects the limited sensitivity of the MMSE for subtle deficits, particularly in a relatively young cohort where ceiling effects are common. A meta-analysis of sixteen studies (> 4,600 individuals) found RLS negatively associated with global cognition and attention, though effects on memory and executive function were less consistent [27], indicating impairment is real but domain-specific, a pattern a brief instrument like the MMSE is poorly positioned to capture. Our null finding should therefore not be interpreted as absence of cognitive sequelae; rather, it underscores the need for future studies to employ more detailed

neuropsychological testing targeting processing speed, executive function, sustained attention, and working memory.

None of the peripheral laboratory markers conventionally linked to RLS pathophysiology (iron, ferritin, inflammatory indices) differed significantly between groups, nor did serum ACE. This is consistent with the well-documented dissociation between peripheral and central iron status in RLS: cerebrospinal fluid and neuroimaging studies demonstrate regional brain iron insufficiency, particularly within the substantia nigra and thalamus, despite normal serum iron and ferritin [28]. This is corroborated at the cellular level by neuron-derived extracellular vesicle analyses showing disrupted brain iron handling despite normal peripheral indices [28]. These findings reinforce that routine peripheral testing is insufficient to confirm or exclude RLS in sarcoidosis, and that diagnosis must rely on clinical history and validated criteria, given limited availability of confirmatory investigations such as polysomnography or brain iron imaging [7].

The nominally lower serum free T4 in RLS-positive patients (unadjusted $p = 0.046$) is consistent with prior reports linking impaired thyroid function, including subclinical hypothyroidism, to RLS prevalence and severity [29], and with the requirement of thyroid hormone for normal dopaminergic neurodevelopment and receptor signaling. This difference did not survive correction for multiple comparisons across the 20 laboratory parameters tested (FDR-adjusted $p = 0.37$) and should be regarded as hypothesis-generating rather than confirmed. Whether a genuine thyroid-RLS association exists in sarcoidosis, via subclinical granulomatous thyroid infiltration or nonthyroidal-illness-related T4 suppression, would require dedicated, adequately powered studies incorporating TSH and autoantibodies.

These findings have potential clinical implications: the independence of RLS from conventional severity markers, combined with its strong associations with fatigue, mood disturbance, and impaired sleep, suggests clinicians managing sarcoidosis patients with unexplained fatigue, depression, or anxiety should routinely screen for RLS, irrespective of radiographic stage. As RLS is amenable to both pharmacological and non-pharmacological treatment [1], its recognition offers a concrete, modifiable therapeutic target that may help reduce symptom burden and improve quality of life, complementing rather than substituting for standard sarcoidosis management.

Limitations

Several limitations should be acknowledged. First, the cross-sectional design precludes causal inference; longitudinal studies are needed. Second, RLS diagnosis relied on clinical evaluation rather than polysomnography, so coexisting periodic limb movement disorder could not be formally excluded, though the criteria applied are recommended for RLS research. Third, small-fiber neuropathy was not systematically assessed and may have contributed to RLS symptoms. Fourth, the modest sample size limits power for laboratory sub-analyses, which should be viewed as hypothesis-generating. Fifth, the single-center design may limit generalizability, and immunosuppressive or corticosteroid therapy effects on outcomes were not independently analyzed. Sixth, the extensive exclusion criteria yielded a well-

characterized but selected sample, limiting generalizability to complex populations. Finally, in the absence of a matched control group, RLS prevalence was compared with literature-derived estimates, consistent with prior sarcoidosis-RLS studies, though prospectively matched comparisons would further strengthen these findings.

Conclusions

RLS is common in pulmonary sarcoidosis, affecting more than one in three patients in this cohort, and appears to arise independently of objective disease severity. Its presence is strongly associated with poorer sleep quality, greater fatigue, and elevated depressive and anxiety symptoms. Multivariable analysis identified RLS severity and respiratory symptom burden, rather than mood or sleep disturbance, as the principal independent correlates of fatigue. These findings support systematic RLS screening in sarcoidosis patients with unexplained fatigue or affective symptoms, and highlight RLS as an underrecognized, treatable contributor to disease morbidity warranting greater clinical attention.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Yedikule Chest Diseases and Chest Surgery Training and Research Hospital (approval number: 2014/6, date: 12 June 2014). Written informed consent was obtained from all participants prior to enrolment, in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

S. A. made substantial contributions to the conception and design of the work, and wrote the main manuscript text. S.A. , S.N.S., N.P. and S.T. the acquisition, analysis, and interpretation of data and drafted the work and revised. E.Ç. approved the version to be published and revised it critically for

important intellectual content. All authors reviewed the manuscript, approved the version to be published and agree to be accountable for all aspects of the work in ensuring.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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