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ORIGINAL ARTICLE

Pattern of sleep dysfunction in systemic lupus erythematosus: a cluster analysis

Domenico Paolo Emanuele Margiotta[1] · Alice Laudisio[2] · Luca Navarini[1] · Fabio Basta[1] · Carmen Mazzuca[1] · Silvia Angeletti[3] · Massimo Ciccozzi[3] · Raffaele Antonelli Incalzi[2] · Antonella Afeltra[1]

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Abstract

Objectives To investigate how the different components of sleep dysfunction described in SLE patients combine together in sleep clusters.

Methods We conducted a cross-sectional study on a perspective cohort of 79 SLE patients (mean age 8.2 ± 14.3 years). Sleep was evaluated using Pittsburgh Sleep Quality Index (PSQI). Clusters were defined using the single components of PSQI in a hierarchical clustering model. We used Beck Depression Inventory, Hamilton Anxiety Rating Scale, and Medical Outcomes Study Short Form 36 (SF36) to measure depressive symptoms, anxiety, and quality of life, respectively.

Results Three sleep clusters were identified. The cluster 1 ($N = 47$) is characterized by the lowest values of PSQI total score. The cluster 2 ($N = 21$) presents higher values of sleep latency, but sleep duration similar to cluster 1. In cluster 3 ($N = 11$), we found sleep latency increased as in cluster 2, but the highest values of PSQI total score and reduced sleep duration. Scores of anxiety and sedentary time were higher in clusters 2 and 3 than in cluster 1. Cluster 3 presented the highest scores of depression and reduced mental and physical components of SF36.

Conclusions The combination of different sleep components in SLE patients allowed us to identify three patterns of dysfunction: a first cluster with better sleep latency and duration, a second with increased sleep latency but conserved duration, and a third with impairment of both latency and duration. The stratification of sleep disorders in clusters might be useful for the personalization of therapy in relation to sleep cluster membership.

Keywords Anxiety (MeSH) · Lupus erythematosus · Quality of life (MeSH) · Sedentary behavior · Sleep (MeSH) · Systemic (MeSH)

Introduction

Over the past decades, attention has gradually grown towards the health-related quality of life (QoL) of patients suffering from chronic diseases. Currently, the guarantee of an adequate QoL is one of the fundamental objectives of the recommendations on the management of many rheumatic diseases [1, 2]. Despite advances in biological knowledge and in pharmacological and non-pharmacological therapies [3–8], the QoL of patients with systemic lupus erythematosus (SLE) is often below what is observed for the general population [9, 10]. The available evidence suggests that QoL impairment in SLE is multifactorial in origin, and factors associated with the autoimmune and inflammatory phenomena characteristic of SLE only partially explain it. Alongside the neuropsychological and neuro-psychiatric aspects [11], such as the symptoms of mood disorders, other typical features of SLE,

Domenico Paolo Emanuele Margiotta and Alice Laudisio contributed equally to this work.

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✉ Luca Navarini
l.navarini@unicampus.it

[1] Unit of Allergy, Clinical Immunology and Rheumatology, Department of Medicine, Campus Bio-Medico University of Rome, via Alvaro del Portillo 21, 00128 Rome, Italy

[2] Unit of Geriatrics, Department of Medicine, Campus Bio-Medico of Rome University, Rome, Italy

[3] Unit of Clinical Laboratory Science, Department of Medicine, Campus Bio-Medico of Rome University, Rome, Italy

such as fatigue and pain, seem to affect QoL [12]. Also, physical activity insufficient to meet the WHO recommendations for health and sedentary behavior is associated with a reduction in physical and mental QoL [13].

Several evidences suggest a possible impact of sleep disturbances on QoL in SLE [14–16]. A relevant proportion of SLE patients, ranging between 55 and 85%, present sleep disorders in cross-sectional studies [15–17]. Sleep quality, with pain, fatigue, anxiety, and depression, but not disease activity and damage, influences illness perception in SLE patients [18]. In a model of mediation analysis, Lillis et al. demonstrated that sleep disturbances and depression mediated the relation between pain and cognitive dysfunction in SLE patients, although these relationships need validation in longitudinal studies [19].

The studies that explored sleep using Pittsburgh Sleep Quality Index (PSQI) demonstrated an impairment of all sleep quality domains in SLE: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleep medications, and daytime dysfunction [14, 15, 20]. According to a recent meta-analysis, subjective sleep quality and habitual sleep efficiency are the most severely affected domains in SLE compared to that in healthy controls [21]. Several factors seem to play a role in sleep dysfunction in SLE, in particular age and symptoms of mood disorders [14–16, 22]. Nevertheless, the impact of disease activity on sleep quality is controversial [15, 23, 24].

In everyday clinical practice, we observe that SLE patients often present complex patterns of sleep dysfunction, with variable combinations of dysfunctional components. Thus, we tried to verify whether clustering of PSQI domains identifies groups of SLE patients with distinctive patterns of sleep impairment and, then, to analyze correlates of group membership.

Methods

Study design and study population

This is a cross-sectional study on a sample of patients from the lupus cohort continuatively followed up at Lupus Clinic of Campus Bio-Medico University of Rome since the inception. Patients affected by SLE according to 2012 SLICC classification criteria were consecutively enrolled in the study [25]. The present study is a part of a project evaluating factors related to QoL in SLE patients. Exclusion criteria for SLE patients were as follows: recent pregnancy (< 2 years before enrolment), active malignancy, end-stage lupus nephritis, treatment with belimumab in the last 2 years, active psychiatric diseases or on-going antipsychotic drugs, recent hospitalization (last 3 months).

Ethical considerations

Ethics committee of Università Campus Bio-Medico di Roma approved the study (protocol number 48/18 OSS ComEt CBM), which complied with the Declaration of Helsinki. All the study participants signed an informed consent prior to enrolment.

Evaluation of sleep quality

We used the Italian version of the Pittsburgh Sleep Quality Index (PSQI) [26]. PSQI is a self-rated questionnaire assessing sleep quality and disturbances over a 1-month period. PSQI is composed by 19 questions, combined to evaluate seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month. Each component score has a range of 0–3 points (0 indicating no sleep disturbances and 3 indicating severe sleep difficulty). The seven components are added to obtain a PSQI total score ranged of 0–21 points [26].

Evaluation of SLE disease

All the patients in study were enrolled from our lupus cohort in which clinical data on lupus disease and therapeutic exposure were prospectively collected since the inception.

Lupus disease activity was evaluated with the Safety of Estrogens in Lupus Erythematosus National Assessment disease activity index (SELENA-SLEDAI) [27, 28]. The SELENA-SLEDAI Flare Index (SFI) was used to assess lupus flares [29]. Damage accrual was evaluated using the SLICC damage index (SDI) [30]. Cumulative exposures to glucocorticoids, antimalarials, and immunosuppressant were retrospectively assessed and expressed as years of exposure. We considered high doses of glucocorticoids a daily dose equal or higher than 7.5 mg of prednisone [31]. We used the International Federation of Diabetes criteria to define metabolic syndrome (MeS), overweight, arterial hypertension, low high-density lipoprotein (HDL) cholesterol, high triglyceride levels, impaired fasting glucose, or diabetes mellitus [32].

Evaluation of QoL, fatigue, mood disorders, and physical activity

QoL was assessed using the Italian version of the Medical Outcomes Study Short Form 36 (SF36), providing two summary components, i.e., the physical component summary (PCS) and the mental component summary (MCS), and eight singular components: physical functioning (PF), role physical (RP), bodily pain (BP), global health (GH),

vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH) [33]. Fatigue was evaluated using the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) [34]. We used the Beck Depression Inventory (BDI) version II to quantify the symptoms of depression and the Hamilton Anxiety Rating Scale (HAM-A) to assess the entity of the anxiety symptoms [35, 36]. All the multivariable models including psychometric variables were adjusted for the evaluation of the alexithymic construct using the Toronto Alexithymia Scale 20 (TAS-20) [37].

Statistical analysis

In the presentation of descriptive statistic, variables were expressed as mean ± standard deviation (SD) or median (interquartile range) as appropriate and the categorical variables as number (percentage).

To define the clusters of sleep dysfunction among SLE patients, we used a hierarchical cluster analysis model. Briefly, in the hierarchical clustering, every observation is initially considered an individual cluster. Then, the process combines in a cluster the cases with the lowest distance (or highest similarity). In the iterative process, further observations are added to existing clusters, or new clusters are created combining the existing clusters. We used as distance definition the squared Euclidean distance and as linking method the unweighted pair-group method using averages (UPGMA). The number of clusters was selected using three parameters: the cubic clustering criterion (CCC) and the pseudo F and pseudo t^2 statistics.

We used the following components of PSQI as clustering variables: subjective sleep quality (component 1), sleep latency (component 2), sleep duration (component 3), habitual sleep efficiency (component 4), sleep disturbances (component 5). We did not include the component 6 (use of sleeping medications) and component 7 (daytime dysfunction) in the clustering variables because these components could be directly affected by several factors in SLE patients as fatigue and mood disorders.

Variables were compared among clusters using nonparametric analysis of variance with Kruskal-Wallis test or ANOVA with Bonferroni's correction for multiple comparisons, where appropriate. Categorical variables were compared across clusters using chi-square.

Variables that significantly differ among cluster ($p < 0.05$) were included in logistic regression models predicting the probability of belonging to the different clusters.

Significance level adopted was two-tailed $p < 0.05$. All statistical analyses were performed with SAS University Edition (SAS Institute Inc., SAS Campus Drive, Cary, NC 27513, USA).

Results

Demographic and lupus disease features of enrolled sample

We enrolled 79 SLE patients, 73 females (92%) and 6 males (8%). The mean age mean ± SD was 48.2 ± 14.3 years, and the average disease duration was 10.3 ± 6.7 years. The median (25–75 percentile range) value of the Charlson Comorbidity Index was 2.0 (1.0–3.0). Demographic and SLE disease features are reported in Table 1.

Sleep quality of enrolled sample

The median (range) total PSQI score in SLE sample was 7.0 (4.0–8.0). Considering the value of 5 as PSQI cutoff, 48 (60%) SLE patients were bad sleepers. The median values of the individual component of PSQI were as follows: component 1 (subjective sleep quality) 1.0 (1.0–2.0), component 2 (sleep latency) 1.0 (0.0–2.0), component 3 (sleep duration) 1.0 (0.0–1.0), component 4 (habitual sleep efficacy) 1.0 (0.0–1.0), component 5 (sleep disturbances) 1.0 (1.0–2.0), component 6 (use of sleeping medications) 0.0 (0.0–1.0), component 7 (daytime dysfunction) 0.0 (0.0–1.0). Considering the single questions of the component 5 (sleep disturbances), the average score of the statements was 2.0 (1.0–3.0) for "Have to get up to use the bathroom," 0.0 (0.0–1.0) for "Cannot breathe comfortably," 0.0 (0.0–2.0) for "Cough or snore loudly," 0.0 (0.0–2.0) for "feel too cold," 0.0 (0.0–2.0) for "feel too hot," 0.0 (0.0–1.0) for "have bad dreams," 1.0 (0.0–3.0) for "have pain," and 0.0 (0.0–1.0) for "other reasons."

Clusters of sleep dysfunction

Based on the CCC, the pseudo F, and the pseudo t^2, we identified three clusters of sleep dysfunctions (Supplementary materials).

The cluster 1, the largest one ($n = 47$, 59%), is characterized by significantly lower values of the PSQI total score, PSQI component 2 (sleep latency), and component 5 (sleep disturbances) compared to cluster 2 and cluster 3 (Table 2). We remind that lower values correspond to better quality of sleep.

The cluster 2 consists of 21 (27%) SLE patients and is characterized by significantly higher total PSQI total score, PSQI component 2 (sleep latency), and component 5 (sleep disturbances) compared to cluster 1. The cluster 2 presents significantly lower values of PSQI component 3 (sleep duration) and component 4 (habitual sleep efficacy) than cluster 3 (Table 2).

The cluster 3 comprises 11 (14%) SLE patients and shows the higher values of total PSQI score, PSQI component 3 (sleep duration), component 4 (habitual sleep efficacy), and component 5 (sleep disturbances) compared to the other

Table 1 Demographic and SLE disease features

Demographic features	Number, *N*	79
	Sex, M/F, *N* (%)	6/73 (8%/92%)
	Age, years, mean ± SD	48.2 ± 14.3
	Disease duration, years, mean ± SD	10.3 ± 6.7
	Education: secondary school or upper, *N* (%)	41 (52)
	Education: primary school or lower, *N* (%)	38 (48)
Disease component (BILAG A-C)	Neuro-psychiatric disease, *N* (%)	21 (26)
	Active renal disease, *N* (%)	8 (10)
Previous involvement	Previous renal disease, *N* (%)	18 (23)
Antiphospholipid syndrome		16 (20)
SLE therapy	Mean monthly actual glucocorticoid dosage, milligrams of prednisone or equivalents, median (range)	150.0 (0–250)
	Cumulative exposure to glucocorticoids, years, median (range)	5.0 (3–12)
	Cumulative exposure to high-dose glucocorticoids (daily dose ≥ 7.5 mg), years, median (range)	2.0 (0–6.5)
	Antimalarial, ongoing, *N* (%)	63 (67)
	Antimalarial, cumulative exposure, years, median (range)	4.0 (2–7)
	Azathioprine, *N* (%)	30 (38)
	Methotrexate, *N* (%)	14 (17)
	Mycophenolate mofetil, *N* (%)	13 (16)
	Oral cyclophosphamide, *N* (%)	3 (4)
	IV cyclophosphamide (in the last 1 year), *N* (%)	3 (4)
	Other immunosuppressant, *N* (%)	8 (1)
	Rituximab in the last 2 years, *N* (%)	5 (5)
	Belimumab in the last 2 years, *N* (%)	0 (0)
Disease activity and damage	Actual SELENA-SLEDAI, median (range)	2.0 (0–6)
	Mean SELENA-SLEDAI last year, median (range)	4.0 (0–8)
	Mean number of flares, last 12 months, median (range)	0 (0–1)
	SDI, median (range)	0 (0–1)
Traditional cardiovascular and metabolic risk factors (according to IFD criteria)	Metabolic syndrome, *N* (%)	29 (36)
	Obesity (waist circumference ≥ 80 cm for women and ≥ 94 com for men), *N* (%)	38 (48)
	Raised triglyceride level ≥ 150 mg/dL or specific treatment for this lipid abnormality, *N* (%)	18 (23)
	Reduced HDL cholesterol < 50 mg/dL in females or specific treatment for this lipid abnormality, *N* (%)	21 (27)
	Raised blood pressure systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension, *N* (%)	37 (47)
	Raised fasting plasma glucose (FPG) ≥ 100 mg/dL or previously diagnosed type 2 diabetes, *N* (%)	8 (10)
	Current smokers, *N* (%)	12 (16)
	CVD personal history, *N* (%)	9 (11)
Comorbidity	Diagnosis of fibromyalgia according to 2012 ACR criteria, *N* (%)	23 (29)
	Charlson Comorbidity Index, median (range)	2.0 (1–3)
Drugs with possible impact on sleep	Antidepressants, *N* (%)	8 (10)
	Antiepileptic, *N* (%)	2 (2)
	Gabapentinoids, *N* (%)	4 (5)
	Opioids, *N* (%)	2 (2)
	Benzodiazepines, N (%)	3 (4)
	Drug for sleep disorders, *N* (%)	0

Range, 25 percentile–75 percentile; *ACR*, American College of Rheumatology

Table 2 PSQI components, quality-of-life–related factors, and scores of mood disorders according to cluster membership

	PSQI clusters			Comparisons among cluster, *p* values			
	Cluster 1	Cluster 2	Cluster 3	1 vs 3[b]	2 vs 3[b]	1 vs 2[b]	Overall[a]
Number, *N* (%)	47 (59)	21 (27)	11 (14)				
Comp 1 (sub sleep qual), median (range)	1.0 (1–2)	2.0 (1–2)	1.0 (1–2)				0.31
Comp 2 (sleep latency), median (range)	0.0 (0–1)	2.0 (2–3)	3.0 (2–3)	< 0.0001	1.0	< 0.0001	< 0.0001
Comp 3 (sleep duration), median (range)	1.0 (0–1)	1.0 (0–1)	3.0 (2–3)	< 0.0001	< 0.0001	1.0	< 0.0001
Comp 4 (hab sleep efficacy), median (range)	1.0 (0–1)	1.0 (0–1)	3.0 (2–3)	< 0.0001	< 0.0001	1.0	< 0.0001
Comp 5 (sleep disturbances), median (range)	1.0 (1–1)	2.0 (1–2)	2.0 (2–3)	< 0.0001	0.017	0.079	< 0.0001
Comp 6 (sleeping medications), median (range)	0.0 (0–0)	0.0 (0–1)	0.0 (0–1)				0.29
Comp 7 (daytime dysfunction), median (range)	0.0 (0–1)	1.0 (0–1)	1.0 (0–2)	0.005	0.49	0.13	0.003
PSQI total score, median (range)	5.0 (4–6)	8.0 (7–8)	12.0 (11–14)	< 0.0001	0.047	< 0.0001	< 0.0001
Comorbidities							
Fibromyalgia, *N* (%)	10 (21)	6 (29)	7 (64)				0.02
Quality-of-life–related factors and symptoms of mood disorders							
PCS, median (range)	46.7 (36.5–67.0)	38.2 (31.5–55.7)	29.4 (16.7–38.8)	0.027	0.24	1.0	0.032
BDI, median (range)	8.0 (3.0–13.0)	12.0 (4.0–21.0)	20.5 (12.0–27.0)	0.006	0.15	0.61	0.007
HAM-A, median (range)	8.0 (5.0–16.0)	17.0 (7.5–23.5)	24.5 (17.0–37.0)	0.001	0.20	0.032	0.001
TAS-20, median (range)	42.5 (36.0–59.0)	51.0 (45.0–61.0)	66.0 (52.0–73.0)	0.022	0.49	0.52	0.021
FACIT-Fatigue, median (range)	40.0 (30.0–43.0)	32.0 (25.0–37.0)	24.0 (18.0–30.0)	0.04	1.0	0.10	0.014
Sedentary behavior, h/day, median (range)	3.0 (1.2–4.5)	4.2 (3.0–6.7)	5.0 (2.5–7.5)	0.15	1.0	0.04	0.021

Range, 25 percentile–75 percentile; *vs*, versus; *Comp*, PSQI component; *sub sleep qual*, subjective sleep quality; *hab sleep efficacy*, habitual sleep efficacy; *PCS*, physical component summary; *BDI*, Beck Depression Inventory version II; *HAM-A*, Hamilton Anxiety Rating Scale; *TAS-20*, Toronto Alexithymia Scale 20

[a] Overall: continuous variables were compared among clusters using non-parametric analysis of variance with Kruskal-Wallis test. Categorical variables were compared across clusters using chi-square

[b] *p* values of binary comparisons among clusters using non-parametric test or ANOVA, with Bonferroni's correction for multiple comparisons

clusters. The cluster 3 presents higher scores of PSQI component 2 (sleep latency) and component 7 (daytime dysfunction) compared to cluster 1 but not to cluster 2 (Table 2).

We did not find significant differences among clusters in PSQI component 1 (subjective sleep quality) and component 6 (use of sleeping medications) (Table 2).

Overall, the cluster 1 is characterized by lower sleep latency and lesser sleep disturbances compared to the others; the cluster 2 is characterized by increased sleep latency and more sleep disturbances than cluster 1, but it presents sleep duration and habitual sleep efficacy similar to cluster 1; the cluster 3 is characterized by sleep latency similar to cluster 2, but it presents lower sleep duration, worsen habitual sleep efficacy, and greater sleep disturbances compared to the other clusters.

Factors associated to clusters of sleep dysfunction

A greater proportion of patients with diagnosis of fibromyalgia were in cluster 3 (64%) than in cluster 1 (21%) and cluster 2 (29%), *p* 0.02 (Table 2).

The entity of anxiety symptoms progressively increased between clusters, with HAM-A median (range) values of 8.0 (5.0–16.0) in cluster 1, 17.0 (7.5–23.5) in cluster 2, and 24.5 (17.0–37.0) in cluster 3. However, only the differences in the entity of anxiety among clusters 1 and 3 and among clusters 1 and 2 were statistically significant. The severity of depressive symptoms measured by BDI was higher in cluster 3 (20.5 (12.0–27.0)) than in cluster 1 (8.0 (3.0–13.0)) and in cluster 2 (12.0 (4.0–21.0)), $p = 0.0006$ between clusters 1 and 3, while the differences of BDI score among clusters 2 and 3 were not significant. We found significantly lower values of FACIT-Fatigue score in cluster 3 (24.0 (18.0–30.0)) compared to those in cluster 1 (40.0 (30.0–43.0)), $p = 0.04$ (Table 2),

The amount of daily time spent in sedentary activities was significantly greater in cluster 2 (4.2 (3.0–6.7)) and cluster 3 (5.0 (2.5–7.5)) than in cluster 1 (3.0 (1.2–4.5)), but the differences were significant only between clusters 1 and 2 ($p = 0.014$) (Table 2).

Overall, the average values of mental and physical component summary of SF36 score were significantly decreased in cluster 3 compared to those in cluster 1. The detailed results of SF36 score were reported in supplementary materials.

Clusters did not differ in age, disease duration, and Charlson Comorbidity Index. The distribution of patients with

different education levels did not significantly differ among clusters (Supplementary materials).

Seventy-three percent of patients in cluster 3 were in overweight compared to 40% in cluster 1 and 52% in cluster 2, but the differences were not significant (Supplementary materials).

Clusters did not differ in actual disease activity (SELENA-SLEDAI), damage index (SDI), and cumulative therapeutic exposure to glucocorticoids, to high doses of glucocorticoids, and to antimalarials. Also, the amount of physical activity evaluated using IPAQ did not distinguish clusters (Supplementary materials).

We reported in Table 3 the models of logistic regression analysis with dependent variable the probability of being in the cluster 2 or 3, using as reference level being in cluster 1. The entity of anxiety symptoms (HAM-A score) was the only variable significantly associated to the probability of being in cluster 2 (OR, 95% confidence interval) (1.11, 1.01–1.23, $p = 0.035$) and in cluster 3 (1.23, 1.01–1.52, $p = 0.041$).

Discussion

Sleep dysfunction has been reported in a large proportion of SLE patients [15–17]. However, the impairment of sleep quality may be the effect of different combinations of multiple sleep components. Our study is the first to investigate these combinations and, in this way, to define a real-life picture of sleep troubles in the individual SLE patient.

We identify three clusters of sleep dysfunction in our SLE sample. The cluster 1 includes patients with lowest sleep disturbances, reduced sleep latency, and good sleep duration and efficacy (patients with the best sleep quality). The cluster 2 is characterized by increased sleep latency but conserved sleep duration. In these clusters, we observed, in particular, a greater burden of anxiety symptoms compared to cluster 1. The cluster 3, the smallest one, shows the highest levels of sleep dysfunction, in particular, increased sleep latency as cluster 2, but also reduced sleep duration and efficacy. In this cluster, the most severe anxiety symptoms and increased depressive complaints coexisted with a reduced health-related quality of life both in physical and mental components; the physical and social functioning was particularly compromised (Fig. 1). Taken together, the individual features of each cluster suggest the possibility of differential, cluster-specific management of sleep disorders in SLE.

None of demographic features, as age and education levels, characterizes the different clusters. Likewise, the factors related to SLE disease, such as disease activity, disease duration, damage accrual, type of organ involvement, and therapeutic exposure, do not seem to influence the patterns of sleep. The impact of disease features, in particular disease activity, on sleep quality has been described by several authors [15, 16, 24, 38], but denied by many others [15, 22, 23, 39].

While both the frequency of sleep disturbances and the total PSQI score increased progressively across the three clusters, the entity of dissatisfaction concerning subjective sleep quality did not distinguish the three clusters. Several studies described a discrepancy between objective measures of sleep, like polysomnography or actigraphy, and subjective evaluation by self-reported questionnaires [40]. In fact, self-assessment of sleep quality could be influenced by factors such as sociocultural confounders, cognitive and memory dysfunctions, and mood disorders [41].

The pivotal role of mood disorders in sleep dysfunction among SLE patients has been widely reported [14–17, 19, 22–24, 39, 42]. We found that anxiety symptoms progressively increase across clusters: the severity of anxiety in cluster 2 is greater than in cluster 1 and the severity of anxiety in cluster 3 is greater than in cluster 2, and logistic regression analysis

Table 3 Variable associated to cluster 2 or cluster 3 membership

Reference level: being in cluster 1	Dependent variable: being in cluster 2		Dependent variable: being in cluster 3[a]	
Independent variables	OR (95% CI)	*p*	OR (95% CI)	*p*
HAM-A score	1.11 (1.01–1.23)	0.035	1.23 (1.01–1.52)	0.041
BDI score	0.96 (0.85–1.08)	0.46	1.01 (0.83–1.22)	0.93
TAS-20 score	1.01 (0.96–1.06)	0.67	1.06 (0.96–1.16)	0.23
Fibromyalgia (yes vs no)			2.02 (0.25–16.2)	0.51
Age (years)	0.99 (0.95–1.04)	0.96	0.98 (0.91–1.06)	0.62
Sex (female vs male)	0.08 (0.01–1.04)	0.053		
PCS score			1.07 (0.97–1.17)	0.18

Multivariable logistic regression models. The logistic regression models were controlled for the entity of alexithymia construct (measured by TAS-20), for age and sex

PCS, physical component summary; *BDI*, Beck Depression Inventory version II; *HAM-A*, Hamilton Anxiety Rating Scale; *TAS-20*, Toronto Alexithymia Scale 20

[a] The variable sex was not included in the model because cluster 3 includes only one male patient

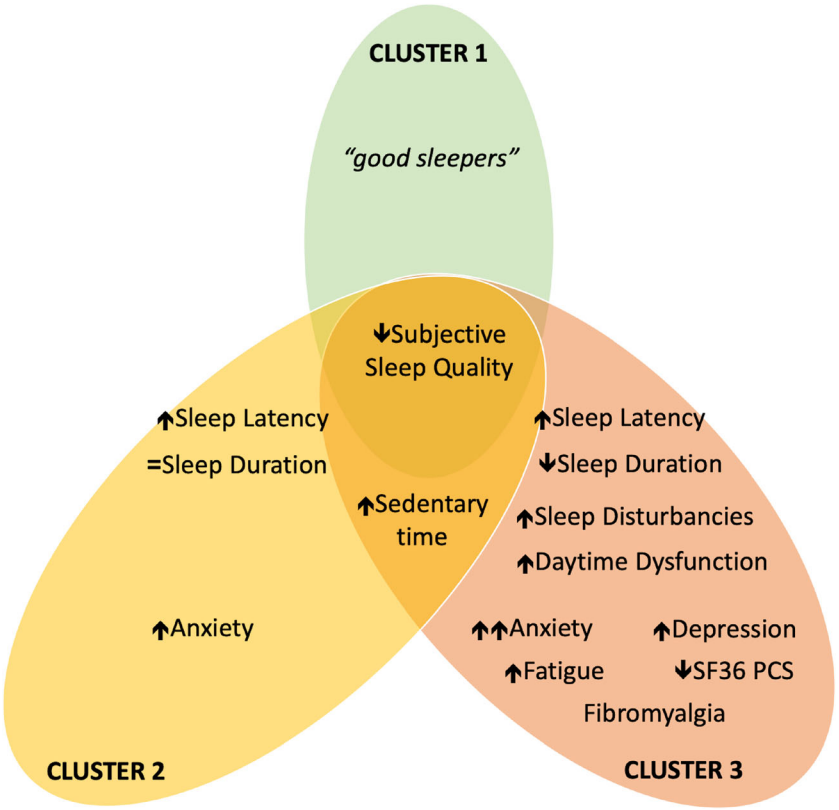

Fig. 1 Main features of the sleep clusters in SLE. SF36-PCS, SF36 physical component summary

confirmed that anxiety symptoms are the main independent correlate of cluster membership. Otherwise, the entity of depressive symptoms was comparable between cluster 1 and cluster 2, but significantly greater in cluster 3. In interpreting these results, the psychometric properties of the PSQI questionnaire deserve consideration: the poor sleep quality expressed by high PSQI score seems to be closely associated to psychological distress [40]. Another innovative aspect of our study is the evaluation of sedentary behavior besides physical activity. Interestingly, we found that sedentary time is increased in clusters 2 and 3.

The only comorbidity relevant to sleep clustering seems to be the fibromyalgia, which was significantly more prevalent in cluster 3 compared to the other ones. Thus, it is not surprising that cluster 3 is associated to severe fatigue, which is a pivotal component of fibromyalgia together with sleep dysfunction. These findings are in concert with the work of Moon et al. that underlined the role of poor sleep quality for poor QoL in SLE patients with and without fibromyalgia [43].

Treat to target recommendations underlines the importance of a comprehensive approach to SLE patients. A better management of sleep dysfunctions should be part of this approach. Understanding the combination of the sleep dysfunction component in SLE could be useful to improve patient management in the perspective of personalized medicine.

Pharmacotherapy of sleep dysfunction is complex and involves a wide spectrum of drug classes, with differential impact on sleep onset, sleep maintenance, and early awakening [44]. Considering the sleep cluster membership, drugs with prevalent impact on sleep onset could be useful in cluster 2, while cluster 3 seems to require a more complex pharmacologic approach. Several non-pharmacologic interventions have shown efficacy in insomnia (Fig. 2). These approaches include sleep hygiene and cognitive behavioral therapies

Fig. 2 Tailored approach to sleep dysfunction according to cluster membership

CLUSTER 1	CLUSTER 2	CLUSTER 3
Sleep hygiene		
	Minimize sedentary time. Physical activity promotion.	
	Management of mood disorders	
	Pharmacologic therapies (drugs with effect on sleep onset)	Complex Pharmacologic therapies (control of sleep onset, sleep duration and sleep disturbances)
		Cognitive Behavioural Therapies

(CBT) [45]. In clusters 2 and 3, in which sleep latency seems to be prolonged, sleep hygiene education controlling diet and lifestyle (caffeine, nicotine, alcohol, regular physical exercise), promoting a non-disruptive sleep environment (light, noise, heat), and creating a stable sleep pattern could be suggested. Encouraging patients to reduce sedentary time should be part of the sleep therapies targeting these clusters. In a randomized controlled trial, CBT was the only intervention with significant long-term impact on in sleep efficiency and time awake after sleep onset. CBT could be particularly relevant in cluster 3 in which we found a high prevalence of fibromyalgia, increased fatigue, and severe symptoms of mood disorders (both anxiety and depression) (Fig. 2). The 2016 update of EULAR recommendations for management of fibromyalgia underlines the importance of CBT as additional individualized therapy [46].

Our study presents some limitations. Firstly, the small size of the enrolled SLE sample limited the possibility of stratifying patients according to comorbidities and to therapy. Moreover, only few patients were taking sleep drugs. So, we could not analyze the distribution of drug assumption among sleep clusters. Another limitation was the cross-sectional design of the study which prevented us from drawing conclusion about cause-effect relations between sleep disturbances and related factors. However, this cross-sectional study was conducted on a prospective lupus cohort, in which clinical data on lupus disease and therapeutic exposure were prospectively collected. The historical completeness of clinical and therapeutic data is the main strength of the study. Another noteworthy issue of the study is the comprehensive evaluation of patients, including, besides disease activity and therapy, also pain, fatigue, physical activity, symptoms of mood disorders, and measures of health-related quality of life. All the multivariable analyses were corrected for the entity of the alexithymic construct, taking into account the possibility that this condition, highly prevalent in SLE, could influence the psychometric properties of the selected questionnaires.

In conclusion, the combination of the different components of sleep dysfunction in SLE patients could be used to identify three sleep clusters with specific features. If confirmed in larger samples, the cluster membership could help to improve a tailored management of sleep disorders in SLE patients.

Compliance with ethical standards

Ethics committee of Università Campus Bio-Medico di Roma approved the study (protocol number 48/18 OSS ComEt CBM), which complied with the Declaration of Helsinki.

Disclosures None.

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