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Restless leg syndrome in multiple sclerosis: relationship with restless legs syndrome and fatigue, quality of life, daytime sleepiness, sleep quality and anxiety-depression

Multipl sklerozda huzursuz bacak sendromu: huzursuz bacak sendromu ile yorgunluk, yaşam kalitesi, gündüz uykululuğu, uyku kalitesi ve anksiyete-depresyon arasındaki ilişki

Asiye Tuba Özdoğar[1] Enes Aldemir[1,2] Pervin Yeşiloğlu[1,3] Vedat Çilingir[4]

[1]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Van Yüzüncü Yıl University, Van, Türkiye

[2]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Lokman Hekim University, Ankara, Türkiye

[3]Graduate School of Health Sciences, Dokuz Eylül University, Izmir, Türkiye

[4]Department of Neurology, Faculty of Medicine, Yüzüncü Yıl University, Van, Türkiye

ABSTRACT

Aim: This study aimed to explore the association between Restless Legs Syndrome (RLS) severity and fatigue, quality of life, daytime sleepiness, sleep quality, and levels of anxiety and depression in people with multiple sclerosis (MS, pwMS).

Materials and Methods: A total of 73 pwMS were recruited from the MS clinic at Van Yüzüncü Yıl University. RLS was diagnosed based on the International RLS Study Group. Various scales were used to assess sleep quality, fatigue, daytime sleepiness, quality of life, and depression and anxiety, including the Pittsburgh Sleep Quality Index (PSQI), Modified Fatigue Impact Scale (MFIS), Epworth Sleepiness Scale (ESS), Preference-Based Multiple Sclerosis Index (PBMSI), and the Hospital Anxiety and Depression Scale (HADS).

Results: RLS was identified in 20 participants (27.40%). Significant differences were observed between pwMS with and without RLS in terms of subjective sleep quality, sleep disturbances, daytime dysfunction, sleep latency and habitual sleep efficiency sub-scores of the PSQI, total PSQI score, physical, cognitive, and total fatigue scores ($p<0.05$). RLS severity showed a moderate positive correlation with MFIS-physical ($r=0.535$), MFIS-total ($r=0.494$), and PSQI-total scores ($r=0.492$).

Conclusion: This study sheds light on the relationships between RLS severity and factors such as sleep quality and fatigue in pwMS.

Keywords: Multiple sclerosis, Restless leg syndrome, Sleep disorders, Quality of life

ÖZ

Amaç: *Bu çalışma, multipl sklerozlu (MS) bireylerde huzursuz bacaklar sendromu (HBS) şiddeti ile yorgunluk, yaşam kalitesi, gündüz uykululuk, uyku kalitesi ve anksiyete-depresyon seviyeleri arasındaki ilişkiyi incelemeyi amaçlamaktadır.*

Gereç ve Yöntem: *Van Yüzüncü Yıl Üniversitesi MS kliniğinden toplam 73 MS'li birey çalışmaya dahil edildi. HBS tanısı, Uluslararası HBS Çalışma Grubu tarafından belirlenen kriterler esas alınarak konuldu.*

Corresponding author: Asiye Tuba Özdoğar
Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Van Yüzüncü Yıl University, Van, Türkiye
E-mail: *tubaozdogar@yyu.edu.tr*
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Uyku kalitesi, yorgunluk, gündüz uykululuğu, yaşam kalitesi, depresyon ve anksiyete düzeylerini değerlendirmek için Pittsburgh Uyku Kalitesi İndeksi (PUKİ), Modifiye Yorgunluk Etki Ölçeği (MYEÖ), Epworth Uykululuk Ölçeği (EUÖ), Tercihe Dayalı Multiple Skleroz İndeksi (TDMSİ) ve Hastane Anksiyete ve Depresyon Ölçeği (HADÖ) gibi çeşitli ölçekler kullanıldı.

Bulgular: *HBS, 20 katılımcıda (%27,40) tespit edildi. HBS'li ve HBS'siz MS'li bireyler arasında fiziksel, bilişsel ve toplam yorgunluk skorları ile uyku kalitesi değerlendirmesinin subjektif uyku kalitesi, uyku bozuklukları, gündüz işlev bozukluğu, uykuya dalma süresi, efektif uyku alışkanlığı alt skorları ve total PUKİ skoru açısından anlamlı farklılıklar bulundu (p<0,05). HBS şiddeti, MYEÖ-fiziksel (r=0.535), MYEÖ-toplam (r=0.494) ve PUKİ-toplam skorları ile orta derecede pozitif korelasyon gösterdi (r=0.492).*

Sonuç: *Bu çalışma, HBS şiddeti ile uyku kalitesi, yorgunluk ve genel yaşam kalitesi arasındaki ilişkiler hakkında yeni bilgiler sunmaktadır.*

Anahtar Sözcükler: *Multipl skleroz, Huzursuz bacak sendromu, Uyku bozuklukları, Yaşam kalitesi*

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, progressive disease that affects the nervous system by causing demyelination, impacting over 2.5 million individuals worldwide. It primarily affects young adults between 20 and 40 years old, with a higher incidence in women(1) . Although precise data on the prevalence of MS in Turkey is lacking, estimates place it at roughly 96.4 per 100,000 (2). Recent epidemiological studies have noted a rising trend in both the incidence and prevalence of MS (3).

Restless Legs Syndrome (RLS), a sleep disorder, is characterized by uncontrollable, unpleasant sensations in the legs, typically worsening during rest or inactivity, accompanied by a strong urge to move the affected limbs. Meta-analyses have shown that the prevalence of RLS among people with MS (pwMS) ranges from 13.2% to 65.1% (4), and case-control studies reveal that pwMS have a 5.6-fold higher likelihood of developing RLS than the general population (5). Among pwMS, high disability levels and the presence of cervical cord lesions are notable risk factors for RLS (6).

In the general population, RLS tends to be more prevalent in women, older adults, and individuals with a family history of the condition. However, no conclusive evidence shows that this pattern holds in pwMS (7). While some research has found a link between MS duration and the presence of RLS (8,9), other studies have not confirmed this relationship (10,11). Cederberg et al. explored the association between RLS in pwMS and health-related quality of life (HRQoL), finding that those with RLS had lower physical and psychological HRQoL scores compared to pwMS without RLS (12). Additionally, MS patients with RLS were found to experience more severe fatigue and more frequent anxiety symptoms. A moderate negative correlation was found between RLS severity and HRQoL, though this relationship weakened when factors such as fatigue, depression, and anxiety were considered (12).

The findings suggest that symptoms such as fatigue, depression, and anxiety can mediate the link between HRQoL and RLS severity. The study also highlighted the potential importance of anxiety in understanding the relationship between HRQoL and RLS severity, although the exact pathological connection between RLS and anxiety remains unclear. The possible explanation is that anxiety and RLS share several common features, such as muscle tension, restlessness, irritability, fatigue, sleep disturbances, and difficulty concentrating. Consequently, the uncontrollable and unpredictable nature of RLS symptoms may exacerbate anxiety, further diminishing the quality of life in pwMS (12).

While it is well established that RLS is more common in pwMS than in the general population, the precise relationship between RLS severity and other frequently occurring MS-related issues—such as fatigue, HRQoL, daytime sleepiness, sleep quality, and levels of anxiety and depression—remains unclear. This study aims to identify the factors related to RLS in pwMS, with the goal of informing effective treatment strategies to address this common symptom.

MATERIALS AND METHODS

Study Design

This research which has cross-sectional study design involved pwMS who voluntarily participate while attending their routine check-ups at the Neurology Department's MS Clinic of Van Yüzüncü Yıl University Medical Faculty Hospital. Ethic approval was received from Van Yüzüncü Yıl University Noninvasive Research Ethics Committee dated 24.06.2024 with approval number 2024/07-04.

Participants

In a previous study evaluating sleep quality among MS patients with and without RLS, the effect size between the two groups was calculated to be 0.57. Based on the prevalence of RLS in the MS population, the rate of pwMS with and without RLS was determined to be 1/3. Using the G*Power software (version 3.1), it was determined that a minimum of 72 patients (pwMS with RLS: 18, pwMS without RLS: 54) is needed to achieve a power of 85% and an error probability of 0.05.

Inclusion criteria have a definitive diagnosis of MS, aged between 18-65 years, no recent relapse within the last 3 months, willing to participate in the study. Also, pwMS having severe musculoskeletal, cardiovascular, pulmonary, metabolic, or any other conditions that would prevent participation, conditions known to be associated with RLS, such as anemia, rheumatoid arthritis, pregnancy, neuropathies, uremia, or neurological disorders other than MS, severe cognitive impairment as determined by a physician that would prevent the completion of tests, pregnancy are excluded from the study.

Outcomes

Demographic Data

Information such as age, gender, and clinical data (type of MS, EDSS score, year of MS diagnosis, duration, date of the last relapse, medications used by the participants) have been collected.

Expanded Disability Status Scale (EDSS) is a widely accepted tool for evaluating and tracking the level of neurological impairment in MS patients, based on clinical neurological assessments and ambulation abilities. The scale ranges from 0, indicating a normal neurological examination, to 10.0, which signifies death caused by MS. Scores between 1.0 and 4.5 represent full ambulation, while scores from 5.0 to 9.5 indicate various degrees of mobility limitations. Scores of 7.0 or higher reflect dependency on a wheelchair or bed. The EDSS evaluates several functional systems, including the pyramidal, cerebellar, cerebral, sensory, brainstem, visual, bladder, and bowel functions (13).

Criteria for Restless Legs Syndrome (RLS) Diagnosis was initially established by the RLS Study Group in 1995 and have since been revised in 2003 and 2014 (14). Diagnosis is based on the presence of an urge to move the legs due to uncomfortable sensations, symptoms beginning or worsening during rest, relief with movement, and a pattern of symptoms that worsens in the evening or night. Patients meeting all these criteria are diagnosed with RLS by a neurologist.

The International Restless Legs Syndrome Study Group Rating Scale (IRLS): Symptom severity among RLS patients can vary widely, with some experiencing mild symptoms that are alleviated by movement, while others suffer from more severe issues that affect sleep and daily life. To measure the severity of RLS symptoms, the International RLS Study Group developed a scale in 2002. The Turkish version, validated by Ay et al. in 2019 (15). This scale consists of 10 questions, each rated from 0 to 4 (16).

The Epworth Sleepiness Scale (ESS) is used to evaluate daytime sleepiness. It comprises eight questions that ask the patient to rate the likelihood of dozing off in different situations during a typical day. Responses are scored from 0 to 3, and a total score of 10 or higher indicates excessive daytime sleepiness (17). The Turkish version of the scale has been validated as reliable (18).

The Modified Fatigue Impact Scale (MFIS) is commonly used to assess the impact of fatigue. It contains 21 questions that measure the physical, cognitive, and social side of fatigue. Lower scores reflect less fatigue [18]. The Turkish version has been validated, confirming that it is suitable for Turkish MS patients (19).

Buysse et al. developed *the Pittsburgh Sleep Quality Index (PSQI)*. In 1996, Ağargün et al. adapted it into Turkish and made it a self-report tool for assessing sleep quality and disturbances.

The 19-item questionnaire is divided into seven components, each scoring between 0 and 3, providing a total score between 0 and 21 (20,21).

The Hospital Anxiety and Depression Scale (HADS) is used to assess levels of anxiety and depression in participants. It consists of 14 items each scored on a 4-point Likert scale from 0 to 3. The higher scores indicate more severe symptoms (22). The Turkish version, validated by Aydemir et al. in 1997, has been proven to be a reliable scale for assessing anxiety and depression in MS patients (23).

Preference-Based Multiple Sclerosis Index (PBMSI) focuses on five domains: walking, concentration, fatigue, roles/responsibilities, and mood. Each domain offers three response options, with values ranging from 0, meaning the worst health state, to 1, meaning the best (24). The Turkish version of the PBMSI has been validated for reliability by Kahraman et al. (25).

Data Analysis

The data have been analyzed using IBM SPSS Statistics (Version 25.0, Armonk, NY: IBM Corp.). The normality of the data distribution has been checked using the Kolmogorov-Smirnov test and histograms. The median and interquartile ranges were used to present continuous variables. For categorical variables, frequency and percentage values were provided. The Mann-Whitney U test compared clinical and demographic factors and patient-reported outcomes between the groups (RLS positive and RLS negative participants). Effect sizes (ES) were calculated as Cohen's d for between-group comparisons. These effect sizes were interpreted as small (0.2), medium (0.5), and large (0.8) (26). The relationship between RLS severity and other variables in RLS-positive groups has been evaluated using Spearman correlation coefficients. Correlation has been considered small if ≤0.30, moderate if between 0.31 and 0.59, and strong if ≥0.60 (27). Statistical significance has been set at $p<0.05$.

RESULTS

A total of 73 pwMS, 20 with RLS and 53 without RLS, were included in the study. The distribution of the pwMS with RLS according to RLS severity assessed with IRLS was as follows: 3 participants had very severe, 4 participants had severe, and 13 participants had moderate RLS symptoms. The mean RLS severity was 19.95±7.0 (min/max: 12/35). There were no significant differences between RLS-positive and RLS-negative pwMS in terms of age, gender, EDSS score, disease duration of MS, number of relapses, and the MS type ($p>0.05$). (Table-1) provides comprehensive details on the participants' demographic and clinical characteristics.

There was a significant difference between RLS-positive and negative pwMS regarding perceived physical, cognitive and total fatigue scores, and sleep latency and habitual sleep efficiency sub-scores of the sleep quality questionnaire with a medium effect size ($p<0.05$). Also, a significant difference was determined in subjective sleep quality, sleep disturbances, daytime dysfunction and total score of PSQI with a large effect size ($p<0.05$). There were no significant differences between groups in quality of life, psychosocial parameters of the fatigue scale, depression and anxiety level, and sleep duration sub-score of the sleep quality assessment ($p>0.05$). The detailed information is presented in (Table-2).

There was a moderately positive correlation between RLS severity, physical and total fatigue scores, and total sleep quality score ($p<0.05$). Conversely, there was no significant correlation between RLS severity and EDSS score, disease duration of MS, number of relapses, cognitive and psychosocial sub-scores of MFIS, quality of life, daytime sleepiness, and depression and anxiety level ($p>0.05$). The correlation coefficients are presented in (Table-3).

Table 1. Demographic and clinical characteristics of the participants

	PwMS with RLS (n=20)	PwMS without RLS (n=53)	*p*
Age (years)	33.0 (25.75; 44.25) Min/max: 22/59	29.0 (24.0; 35.0) Min/max: 18/58	0.109
Gender, n (%)			
Female	16 (80.0%)	38 (71.7%)	0.471
Male	4 (20.0%)	15 (28.3%)	

EDSS score	1.25 (0; 2.0) Min/max: 0/3.5	1.0 (0; 2.0)	0.947
Disease duration of MS (years)	8.0 (5.0; 13.0) Min/max: 1/29	6.0 (2.25; 9.0) Min/max: 0/19	0.052
Number of relapses	3.0 (2.0; 4.0) Min/max: 1/11	2.0 (1.25; 4.0) Min/max: 1/10	0.481
MS type, n (%)			
RRMS	20 (100%)	51 (96.2%)	0.378
PPMS	0 (0%)	2 (3.8%)	

EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis, RRMS: Relapsing Remitting MS, PPMS: Primary Progressive MS
Data are expressed as median and interquartile range (IQR)

Table-2. Comparison of patient-reported outcome measures between RLS-positive and RLS-negative pwMS

	PwMS with RLS (n=20)	**PwMS without RLS (n=53)**	**Cohen's d**	**p**
PBMSI	0.50 (0.38; 0.86) Min/max: 0.07/1	0.68 (0.54; 0.89) Min/max: 0.20/1	0.33	0.075
MFIS-Physical	19.0 (10.50; 25.75) Min/max: 1/32	11.0 (5.0; 18.0) Min/max: 0/35	0.67	**0.010**
MFIS-Cognitive	20.0 (13.25; 30.75) Min/max: 4/36	11.0 (4.5; 22.5) Min/max: 0/38	0.71	**0.007**
MFIS-Psychosocial	4.0 (0.25; 6.0) Min/max: 0/8	1.0 (0; 4.0) Min/max: 0/8	0.41	0.124
MFIS-Total	49.0 (24.75; 58.0) Min/max: 11/76	26.0 (10.5; 37.0) Min/max: 0/77	0.72	**0.006**
PSQI- subjective sleep quality	2.0 (1.0; 2.0) Min/max: 0/3	1.0 (1.0; 1.0) Min/max: 0/3	1.03	**<0.001**
PSQI- sleep latency	2.0 (0.25; 3.0) Min/max: 0/3	1.0 (0; 2.0) Min/max: 0/3	0.64	**0.023**
PSQI- sleep duration	0 (0; 2.0) Min/max: 0/3	0 (0; 1.0) Min/max: 0/3	0.33	0.278
PSQI-habitual sleep efficiency	0 (0; 1.75) Min/max: 0/3	0 (0; 0) Min/max: 0/3	0.58	**0.027**
PSQI- sleep disturbances	2.0 (1.0; 2.0) Min/max: 0/3	1.0 (1.0; 1.0) Min/max: 0/2	0.93	**0.001**
PSQI- use of sleeping medication	0 (0; 0) Min/max: 0/3	0 (0; 0) Min/max: 0/0	NA	**0.004**
PSQI- daytime dysfunction	1.0 (0; 2.0) Min/max: 0/3	0 (0; 0.5) Min/max: 0/3	0.81	**0.002**
PSQI-total score	8.5 (3.25; 11.75) Min/max: 1/20	3.0 (2.0; 6.0) Min/max: 0/12	0.98	**0.001**
ESS	3.5 (1.25; 5.75) Min/max: 0/15	3.0 (0.5; 7.5) Min/max: 0/18	0.01	0.717
HADS-D	7.0 (1.5; 12.75) Min/max: 0/14	7.0 (4.0; 9.5) Min/max: 0/18	0.14	0.531
HADS-A	7.0 (4.25; 12.75) Min/max: 0/19	6.0 (3.0; 9.5) Min/max: 0/20	0.24	0.359

PBMSI: Preference-Based Multiple Sclerosis Index, MFIS: Modified Fatigue Impact Scale, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, HADS-D: Hospital Anxiety and Depression Scale-Depression, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, RLS: Restless Legs Syndrome, MS: Multiple Sclerosis.
Data are expressed as median and interquartile range (IQR)

Table-3. Correlation coefficients between the RLS-severity and patient-reported outcomes measurements and characteristics of MS

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13
1. RLS severity	1												
2. Disease duration	-0.040	1											
3. EDSS	0.244	0.552*	1										
4. Number of relapses	0.002	0.266	0.133	1									
5. MFIS-Physical	0.535*	-0.122	0.185	-0.013	1								
6. MFIS-Cognitive	0.384	0.122	0.154	0.091	0.760**	1							
7. MFIS-Psychosocial	0.439	0.158	0.227	-0.095	0.758**	0.612**	1						
8. MFIS-Total	0.494*	-0.015	0.168	0.001	0.926**	0.926**	0.747**	1					
9. PBMSI	-0.307	0.140	-0.109	-0.287	-0.783**	-0.749**	-0.727**	-0.814**	1				
10. ESS	0.254	-0.014	0.134	-.039	0.478*	0.620**	0.664**	0.630**	-0.668**	1			
11. PSQI-total	0.492*	-0.006	0.185	0.064	0.817**	0.734**	0.698**	0.794**	-0.730**	0.281	1		
12. HADS-D	0.182	0.232	0.131	-0.081	0.658**	0.692**	0.771**	0.671**	-0.613**	0.650**	0.547*	1	
13. HADS-A	0.346	0.025	0.112	-0.270	0.675	0.432	0.716**	0.594**	-0.456**	0.604**	0.439	0.748**	1

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).
EDSS: Expanded Disability Status Scale, **PBMSI:** Preference-Based Multiple Sclerosis Index, **MFIS:** Modified Fatigue Impact Scale, **PSQI:** Pittsburgh Sleep Quality Index, **ESS:** Epworth Sleepiness Scale, **RLS:** Restless Legs Syndrome, **MS:** Multiple Sclerosis

DISCUSSION

This study provides important insights. Firstly, RLS-positive pwMS have worse sleep quality and fatigue levels than RLS-negative pwMS. Also, RLS severity is correlated with physical and general fatigue and sleep quality. On the other hand, RLS severity is not related to characteristics of MS such as disability level, disease duration, and number of relapses.

According to a meta-analysis conducted on RLS in MS, there are controversial results regarding the comparison of pwMS with and without RLS in terms of demographic and clinical characteristics such as EDSS score (17 studies), disease duration (16 studies), MS types (11 studies), age (17 studies), and gender (17 studies). As a result, the rate of studies finding the relationship between RLS and demographic and clinical characteristics of pwMS was as follows: 52.9% for EDSS score, 18.8% for disease duration, 27.3% for MS types, 35.3% for age, and 18.8% for gender (4). Our study showed no significant differences between pwMS with and without RLS regarding EDSS score, disease duration, MS types, age, and gender. Even though there is a pattern for the presentation of RLS in the general population, the results are conflicted in MS. The reason for the conflicted results could be MS, which is a heterogeneous disease whose

presentation is changed from patient to patient. Also, studies use different assessment methods to diagnose RLS and evaluate RLS severity.

Cederberg et al. examined the relationship between RLS severity, and the common symptoms observed in MS. The study included a total of 275 pwMS; 74 (26.9%) were RLS-positive. When comparing RLS-positive MS individuals with RLS-negative ones, the RLS-positive group reported poorer physical and psychological health-related quality of life, higher perceived fatigue levels, and more anxiety symptoms. In the RLS-positive group, the severity of RLS was found to be associated with the physical and psychological sub-parameters of health-related quality of life, sleep quality, perceived fatigue, depression, and anxiety (12). Similarly, we found a significant difference between groups regarding sleep quality and fatigue. Also, there is a positive correlation between RLS severity and sleep quality. However, the groups showed parallel results in quality of life, depression, and anxiety levels in our study. This difference between studies could arise from participants with different disability levels. The average Patient Determined Disease Steps score was 3.5 in the Cederberg study (12), while the mean EDSS score was 1.24 in our study. The quality of life, depression, and anxiety levels could be worsened with disability level, and the presence of RLS is one of the factors affecting the deterioration at this point. Also, Sevim et al. conducted a nationwide, multicenter, cross-sectional study that assessed 1,068 MS patients using the Hamilton Anxiety and Depression Scales. Their results showed that patients with RLS had significantly higher anxiety and depression scores than those without. However, the percentage of secondary progressive MS, which is related to higher levels of anxiety and depression level compared to the other MS types (28), was higher than in our study.

Cederberg et al. investigated the relationship between physical function and RLS symptomology, such as presence, severity and frequency. They evaluated 22 pwMS with RLS and showed that physical function decreased as the severity of RLS increased (29). In another study, they enrolled 275 pwMS and divided them into two groups: pwMS with RLS (n=74) and without RLS (n=201). The authors assessed how cognitive functions are affected by the presence and severity of RLS. The results revealed that pwMS with RLS have worse cognitive functions and increased RLS severity than without RLS, which is corelated to worse sleep quality and cognitive performance (29). In our study, even though we did not assess the physical and cognitive functions of the participants, we determined that pwMS with RLS have worse perceived physical and cognitive fatigue than pwMS without RLS. We hypothesize that the presence and severity of RLS causes worse sleep quality. The worse sleep quality beats a decline in cognitive and physical functions.

This study has both limitations and strengths. One limitation is that the participants' disability level was low, and most participants have relapsing-remitting MS, which may affect the generalizability of the findings. However, this is also a strength, as it reduces the potential confounding effects of other symptoms that may occur in individuals with higher levels of disability associated with MS. We did not assess the use of medication for restless legs syndrome (RLS) symptoms, which may have influenced the outcomes. Besides, we did not use objective sleep measurements. Although objective methods were not used, all selected assessment methods are valid, reliable, and have high psychometric properties in MS.

CONCLUSION

This study offers new insights into the connections between RLS severity, total sleep quality, physical component score, and total fatigue score in pwMS. Also, the total and most sub scores of the sleep quality and the fatigue scores (except psychosocial) showed the difference between pwMS with and without RLS. The findings suggest a potential approach to mitigating sleep quality and fatigue declines by addressing RLS. Understanding the intermediary factors linking RLS with sleep disturbances and fatigue in MS could provide important guidance for interventions.

Ethical Approval: Ethical approval was obtained from the Ethics Committee of Non-Interventional Clinical Trials of Van Yüzüncü Yıl University with the Approval Number: 2024/07-04, and Approval Date: 24.06.2024

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