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RESEARCH / ARAŞTIRMA

Defining the Predictors of Fatigue in People with Multiple Sclerosis

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ABSTRACT

Objective: This study aimed to define the predictors of fatigue in people with multiple sclerosis (MS, pwMS) by evaluating clinical and demographic factors, including disability level, physical performance, sleepiness, and depression.
Material and Methods: A total of 747 pwMS were included in this cross-sectional study. Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS), and multiple linear regression analyses were performed to determine the predictors of fatigue based on total MFIS and its subdomains (physical, cognitive, psychosocial). Independent variables included age, disease duration, number of relapses, number of disease-modifying therapies (DMTs), Expanded Disability Status Scale (EDSS) score, Timed 25-Foot Walk (T25FW), Nine-Hole Peg Test (N-HPT), Epworth Sleepiness Scale (ESS), and Beck Depression Inventory (BDI).
Results: Higher fatigue scores were significantly associated with increased EDSS scores (β=0.191, p<0.001), greater sleepiness (ESS, β=0.188, p<0.001), and higher depression scores (BDI, β=0.556, p<0.001). Slower walking performance (T25FW) was also a significant but weaker predictor (β=-0.09, p=0.02). Similar patterns were observed across MFIS subdomains. Number of DMTs, disease duration, number of relapses, and N-HPT performance were not significant predictors.
Conclusion: Disability level, sleepiness, and depression were the most prominent predictors of fatigue in pwMS. These findings emphasize the importance of integrating physical, psychological, and sleep-related assessments into comprehensive fatigue management strategies for pwMS.
Keywords: Depression, disability, fatigue, multiple sclerosis, sleepiness.

Multipl Sklerozlu Bireylerde Yorgunluk Belirleyicilerinin Tanımlanması

ÖZET

Amaç: Bu çalışma, multipl sklerozlu (MS) bireylerde yorgunluğun belirleyicilerini; engellilik düzeyi, fiziksel performans, uykululuk ve depresyon gibi klinik ve demografik faktörleri değerlendirerek tanımlamayı amaçlamaktadır.
Gereç ve Yöntem: Bu kesitsel çalışmaya toplam 747 pwMS dahil edilmiştir. Yorgunluk, Modifiye Yorgunluk Etki Ölçeği (MYEÖ) kullanılarak değerlendirilmiştir. Yorgunluğun belirleyicilerini tanımlamak amacıyla toplam MYEÖ skoru ve alt boyutları (fiziksel, bilişsel, psiko-sosyal) temel alınarak çoklu doğrusal regresyon analizleri yapılmıştır. Bağımsız değişkenler; yaş, hastalık süresi, atak sayısı, hastalık modifiye edici tedavi (DMT) sayısı, Genişletilmiş Engellilik Durum Ölçeği (EDSS) skoru, Zamanlı 25 Adım Yürüme Testi (Z25AYT), Dokuz Delikli Peg Testi (DDPT), Epworth Uykululuk Ölçeği (EUÖ) ve Beck Depresyon Envanteri (BDE) idi.
Bulgular: Daha yüksek EDSS skoru (β=0,191, p<0,001), daha fazla uykululuk seviyesi (ESS, β=0,188, p<0,001) ve daha yüksek depresyon skorları (BDI, β=0,556, p<0,001) ile yüksek yorgunluk skorlarının anlamlı şekilde ilişkili olduğu bulundu. Daha yavaş yürüme performansı (Z25AYT) da anlamlı ancak daha zayıf bir yordayıcı olarak bulundu (β=-0,09, p=0,02). Benzer sonuçlar MYEÖ alt boyutlarında da gözlemlendi. DMT sayısı, hastalık süresi, atak sayısı ve DDPT performansı anlamlı yordayıcılar değildi.
Sonuç: Engellilik düzeyi, uykululuk ve depresyon, MS'li bireylerde yorgunluğun en belirgin yordayıcıları olarak öne çıkmıştır. Bu bulgular, yorgunluk yönetim stratejilerinde fiziksel, psikolojik ve uyku ile ilişkili değerlendirmelerin bütüncül şekilde ele alınmasının önemini vurgulamaktadır.
Anahtar Kelimeler: Depresyon, engellilik, multipl skleroz, uykululuk, yorgunluk.

1. Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory, and progressive disease characterized by demyelination and axonal degeneration affecting the central nervous system. This damage results in the formation of plaques, known as areas of demyelination (1). It is a significant cause of disability among individuals aged 20-40, with only 3-5% of MS diagnoses reported to occur earlier or later than this age range (2,3). Globally, MS affects more than 2.5 million people. Recent epidemiological studies indicate an increasing trend in the prevalence and incidence of the disease (4).

The complex symptoms of MS vary depending on the location of neural degeneration, affecting different systems. Due to the heterogeneity of pathology, each patient may exhibit unique findings. Common clinical manifestations of MS include fatigue, somatosensory and visual problems, urinary retention/incontinence, balance and gait disturbances, impaired limb skills and coordination, ataxia, spasticity, cognitive dysfunction, and depression (5).

Fatigue, defined as an overwhelming lack of physical and/or mental energy, is one of the most prevalent symptoms associated with MS. It has been reported to affect 75-97% of

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people with MS (pwMS) (6). About 55% of pwMS describe it as one of the worst symptoms they experience, often regardless of their level of disability (7). The presence of fatigue affects quality of life, sleep quality, and overall functionality, while also reducing the likelihood of employment in the community (8–10). This underscores the importance of identifying and treating fatigue-related symptoms in MS management.

Fatigue in MS is a multifactorial symptom with both primary and secondary mechanisms contributing to its onset and persistence. Primary mechanisms include immune-mediated pathways involving elevated proinflammatory cytokines (e.g., TNF-α, interferon-γ), endocrine dysregulation such as alterations in the HPA axis and reduced DHEA levels, and neurodegenerative changes including axonal loss and altered cerebral activation patterns observed in advanced imaging studies. Secondary mechanisms involve comorbid conditions such as sleep disorders, depression, disease subtype and disability level, as well as iatrogenic factors including the side effects of medications commonly used in MS treatment (11).

Fatigue significantly reduces the quality of life in pwMS (9). Furthermore, the literature frequently associates fatigue with sleep quality and depression (12). Although physical performance decline, disability level, polypharmacy, and the number and frequency of relapses are linked to fatigue, more evidence is needed (13–15).

Studies have shown that reducing symptoms associated with fatigue can lead to improvements in fatigue itself (16,17). Identifying symptoms related to fatigue is clinically significant for developing medical treatment and rehabilitation strategies. This study aims to identify the predictors of the fatigue level in pwMS to provide guidance for their medical treatment and rehabilitation.

2. Material and Methods

2.1. Participants

The inclusion criteria were having a diagnosis of MS (18), and willingness to participate in the study. The exclusion criteria were having cognitive impairment severe enough to prevent the application of tests and questionnaires, having an EDSS score higher than 6.5 (reflecting the inability to walk more than 5 meters without aid) and having another chronic disease that could cause fatigue (e.g., cardiovascular disease, chronic pulmonary disease, and autoimmune disorders).

2.2. Outcomes

Information such as age, gender, and clinical data (EDSS score, duration of disease, date of the last relapse, medications used by the participants) was collected from participants and their medical records.

The Expanded Disability Status Scale (EDSS), a globally recognized scale for assessing neurological disability in MS patients, is used to evaluate the level of neurological disability. EDSS scoring is based on the patient's neurological examination and ambulatory status. A score of 0 indicates normal neurological examination, while 10.0 represents death due to the disease. Scores from 1.0–4.5 denote full ambulation, while 5.0–9.5 reflect ambulatory impairment. Scores of 7.0 and above indicate dependence on a wheelchair or bed. Functional systems assessed by EDSS include pyramidal, cerebral, cerebellar, visual, sensory, brainstem, bladder, and bowel functions (19).

The Epworth Sleepiness Scale (ESS) is used to measure daytime sleepiness. It consists of 8 questions, each scored from 0–3 by the patient. The scale evaluates the likelihood of falling asleep in specific situations during a typical day when the patient is not excessively fatigued. A total score of 10 or higher indicates excessive daytime sleepiness (20). The Turkish version of the scale has been validated (21).

The Modified Fatigue Impact Scale (MFIS) is a commonly used fatigue scale in clinical and experimental studies. It assesses the physical, cognitive, and social effects of fatigue through 21 items, each scored from 0–4. Lower scores indicate lower fatigue levels. The Turkish validity and reliability of the MFIS have been confirmed (22).

Developed by Beck et al. in 1961, the Beck Depression Inventory (BDI) assesses the characteristics and symptoms of depression. It is a self-report scale consisting of 21 items and takes approximately 10 minutes to complete. Each item includes options scored from 0–3, and the individual selects the option that best describes them. The total score ranges from 0–63, with scores of 0–16 indicating mild, 17–29 moderate, and 30–63 severe depression (23). The Turkish validity, reliability and factor analysis study has been performed by Hisli Sahin et al. (24).

The Timed 25-Foot Walk (T25FW) assesses walking speed in MS patients. Participants are asked to walk a 25-foot (7.62 m) distance as quickly as possible. The test measures walking speed and performance. The average time in seconds from two consecutive trials is calculated as the T25FW score. It is a reliable test widely used to assess changes in walking performance in MS patients (25).

The Nine-Hole Peg Test (N-HPT) is a simple and quick manual dexterity test proven to be valid and reliable in pwMS (26). It involves placing and removing nine pegs from holes on a board as quickly as possible. The dominant hand is tested first, and the time is measured with a stopwatch.

2.3. Data Analysis

IBM SPSS Statistics software (Version 25.0, Armonk, NY: IBM Corp.) was used for data analysis. The normality of continuous variables was checked using the Kolmogorov-Smirnov test and histograms. Continuous variables are reported as mean ± standard deviation. Categorical variables are presented as frequencies and percentages. To examine the predictors of fatigue, a series of multiple linear regression analyses were conducted. Separate models were built for the total MFIS score and each of its subscales (physical, cognitive, and psychosocial domains). The independent variables included demographic (e.g., age) and clinical parameters (e.g., EDSS, number of relapses, number of DMTs, disease duration, performance on T25FW and N-HPT, ESS, and BDI scores). For each predictor, unstandardized coefficients (B), 95% confidence intervals (CI), standardized coefficients (β), t-values, and p-values were reported. Statistical significance set at $p<0.05$.

2.4. Ethical Aspects of the Research

This retrospective cross-sectional study included people who routinely visit the MS Clinic of the Department of Neurology at Dokuz Eylül University Medical Faculty Hospital for their check-ups and have previously volunteered for the ethically approved study titled "Monitoring Physical, Psychosocial, and Cognitive Impacts in People with Multiple Sclerosis: A Prospective Cohort Study.". Also, ethical approval was taken for secondary analysis from Van Yüzüncü Yıl University Non-invasive Ethic Committee (Date: 18.10.2024, Approval Number: 2024/11-27). The written consent form was taken from every participant.

3. Results

A total of 747 pwMS were evaluated, yielding an MFIS total score of 31.54±22.18. The subscores of the scale were as follows: the physical component scored 14.84±10.41, the cognitive component scored 13.40±11.05, and the psychosocial

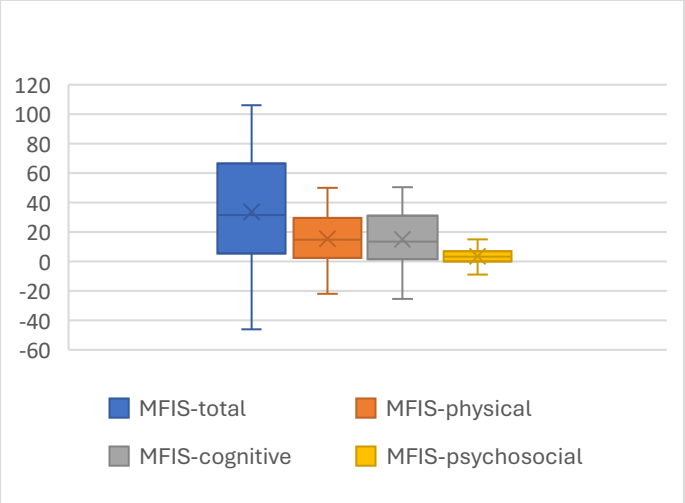

Figure 1. Presentation of MFIS scores of the patients

component scored 3.23±1.70 (Figure 1). The mean age was 39.62 years±12.47, and the sample included mostly female participants. The mean EDSS score was 2.85±2.27, with an average disease duration of 9.90±8.73 years. Participants had experienced an average of 3.90±3.19 and had used approximately 2.41±1.32 different disease-modifying therapies (DMTs) (Table 1).

Table 1. Demographic and clinical characteristics of the participants

	All participants (n=747)
Age (SD) (years)	39.62 (12.47)
Gender, n (%)	
Female	504 (67.5)
Male	243 (32.5)
EDSS score	2.85 (2.27)
Disease duration (years)	9.90 (8.73)
Number of relapses	3.90 (3.19)
Number of DMTs	2.41 (1.32)
Timed 25 Foot Walk Test (seconds)	7.35 (6.21)
Nine-Hole Peg Test (seconds)	28.39 (25.19)
Epworth Sleepiness Scale	5.18 (4.39)
Beck Depression Inventory	12.04 (9.55)

SD: standard deviation, **EDSS:** Expanded Disability Status Scale, **DMT:** Disease-Modifying Therapies

Multiple regression analysis was conducted to identify the variables that significantly predict fatigue among pwMS for both total MFIS score and subscores. For MFIS total score, the overall model was statistically significant, accounting for approximately 52% of the variance in fatigue scores (adjusted R^2=0.516). Among the examined predictors, EDSS score, ESS, and BDI emerged as statistically significant contributors to fatigue. Specifically, higher EDSS scores were associated with increased fatigue (B=2.135, 95% CI=1.103 to 3.166, p<0.001), indicating that greater physical disability is a key determinant. Similarly, both ESS (B = 0.956, 95% CI = 0.618 to 1.293, p<0.001) and BDI (B=1.284, 95% CI=1.128 to 1.440, p<0.001) showed strong positive associations with fatigue, underscoring the influence of excessive daytime sleepiness and depressive symptoms. Additionally, performance on the T25FW was a statistically significant negative predictor (B=-0.321, 95% CI=-0.590 to -0.051, p=0.02), suggesting that slower ambulation is modestly related to increased fatigue levels. In contrast, age, number of relapses, number of DMTs, disease duration, and N-HPT scores were not significantly associated with fatigue (all p>0.05).

In the physical domain, significant predictors included age (β=0.100, p=0.017), EDSS score (β=0.270, p<0.001), ESS (β=0.171, p<0.001), and BDI (β=0.472, p<0.001). For MFIS-cognitive scores, significant predictors were T25FW (β=-0.117, p=0.005), ESS (β=0.185, p<0.001), and BDI (β=0.556, p<0.001). In the psychosocial domain, disease duration (β=0.114, p=0.016), EDSS score (β=0.254, p<0.001), ESS (β=0.099, p=0.006), and BDI (β=0.519, p<0.001) emerged as significant predictors. Across all domains, depression (as measured by BDI) was consistently a strong predictor of fatigue, along with disability level and sleepiness (Table 2).

4. Discussion

This study aimed to identify the clinical and functional predictors of fatigue in pwMS using a comprehensive regression model. The results revealed that neurological disability (EDSS), depression (BDI), and daytime sleepiness (ESS) are the most significant contributors to fatigue, as measured by the MFIS. These findings are in line with the conceptualization of MS-related fatigue as a multifactorial phenomenon involving physical, psychological, and neurophysiological dimensions.

The association between disability level and fatigue has been well-established in prior studies. For instance, a meta-analysis by Induruwa et al. noted that higher EDSS scores are moderately associated with increased fatigue severity, likely due to the cumulative burden of physical limitations and energy inefficiency during ambulation and daily activities (27). Our results support this, as higher EDSS scores significantly predicted total MFIS scores and all subdomains, particularly the physical dimension.

Depression emerged as the strongest and most consistent predictor across all fatigue domains, corroborating findings from Chalah and Ayache, who suggested shared biological mechanisms between fatigue and depression in MS, including dysregulation of the hypothalamic-pituitary-adrenal axis, inflammatory cytokine activity, and alterations in brain connectivity, especially in frontal and limbic circuits (28). According to regression models, depression was the most significant contributor to fatigue in every aspect of MFIS. These overlapping pathways not only complicate diagnosis and treatment but also necessitate dual-targeted interventions for both symptoms.

The significant role of daytime sleepiness, as evidenced by ESS scores, echoes prior research indicating that sleep-related disorders are highly prevalent and underdiagnosed in MS. A study by Strober (2015) emphasized that excessive daytime sleepiness and poor sleep hygiene contribute significantly to subjective fatigue reports. Moreover, fatigue and poor sleep share bidirectional links, potentially creating a vicious cycle that perpetuates functional decline and psychological distress (29).

T25FW was a modest but significant predictor of cognitive and total fatigue, suggesting that lower extremity function influences the perception of fatigue. Previous studies, such as Heine et al. (2015), have highlighted how reduced walking capacity correlates with physical fatigue, though not always with cognitive or psychosocial domains (30). Interestingly, N-HPT did not predict fatigue in any model, supporting the notion that fine motor impairment may not substantially contribute to perceived fatigue, or that upper limb function is less demanding in daily life for many pwMS.

Contrary to some earlier findings, neither polypharmacy, disease duration, nor relapse history significantly predicted fatigue in our

Table 2. Determining the predictors for fatigue

	B	*95% CI*	β	t	P value
MFIS-Total					
Age (years)	0.124	-0.017; 0.266	0.070	1.724	0.085
Number of relapses	0.171	-0.419; 0.760	0.024	0.568	0.570
Number of DMTs	0.506	-0.902; 1.913	0.028	0.706	0.481
Disease duration	0.121	-0.107; 0.348	0.046	1.042	0.298
EDSS score	2.135	1.103; 3.166	0.191	4.067	**<0.001**
T25FW (seconds)	-0.321	-0.590; -0.051	-0.090	-2.341	**0.020**
N-HPT (seconds)	-0.071	-0.200; 0.058	-0.036	-1.075	0.283
ESS	0.956	0.618-1.293	0.188	5.569	**<0.001**
BDI	1.284	1.128-1.440	0.556	16.193	**<0.001**
MFIS-Physical					
Age	0.081	0.015; 0.148	0.100	2.391	**0.017**
Number of relapses	0.150	-0.128; 0.428	0.045	1.058	0.290
Number of DMTs	0.472	-0.197; 1.140	0.057	1.387	0.166
Disease duration	0.029	-0.079; 0.136	0.024	0.529	0.597
EDSS score	1.390	0.904; 1.876	0.270	5.616	**<0.001**
T25FW (seconds)	-0.089	-0.216; 0.038	-0.054	-1.377	0.169
N-HPT (seconds)	-0.027	-0.087; 0.034	-0.030	-0.858	0.391
ESS	0.403	0.243; 0.562	0.171	4.965	**<0.001**
BDI	0.503	0.429; 0.576	0.472	13.431	**<0.001**
MFIS-Cognitive					
Age	0.034	-0.043; 0.111	0.038	0.858	0.391
Number of relapses	0.035	-0.286; 0.356	0.010	0.214	0.831
Number of DMTs	-0.146	-0.917; 0.624	-0.016	-0.373	0.709
Disease duration	0.066	-0.058; 0.190	0.050	1.049	0.295
EDSS score	0.410	-0.151; 0.971	0.073	1.435	0.152
T25FW (seconds)	-0.209	-0.355; -0.062	-0.117	-2.799	**0.005**
N-HPT (seconds)	-0.031	-0.102; 0.039	-0.032	-0.880	.380
ESS	0.474	0.290; 0.658	0.185	5.063	**<0.001**
BDI	0.645	0.560; 0.730	0.556	14.936	**<0.001**
MFIS-Psychosocial					
Age	0.006	-0.012; 0.024	0.030	0.483	0.483
Number of relapses	-0.024	-0.099; 0.051	-0.028	0.535	0.535
Number of DMTs	0.083	-0.98; 0.263	0.038	0.367	0.367
Disease duration	0.036	0.007; 0.065	0.114	0.016	**0.016**
EDSS score	0.339	0.207; 0.470	0.254	0.000	**<0.001**
T25FW	-0.021	-0.056; 0.013	-0.050	0.220	0.220
N-HPT	-0.009	-0.025; 0.008	-0.037	0.299	0.299
ESS	0.060	0.017; 0.104	0.099	0.006	**0.006**
BDI	0.143	0.123; 0.163	0.519	0.000	**<0.001**

DMT: Disease-Modifying Therapies, **T25FW:** Timed 25 Foot Walk, **N-HPT:** Nine-Hole Peg Test, **ESS:** Epworth Sleepiness Scale, **BDI:** Beck Depression Inventory.

models. While Thelen et al. suggested a link between polypharmacy and perceived fatigue, it is possible that the type rather than the number of medications may be more critical in fatigue etiology (13). Moreover, our findings suggest that current

symptom burden, especially psychological and sleep-related symptoms, may outweigh the influence of chronicity or treatment complexity.

Taken together, these findings suggest that fatigue in MS should be addressed using a multidisciplinary and biopsychosocial model, targeting not only physical disability but also mood disorders and sleep quality. Interventions such as cognitive behavioral therapy, graded exercise programs, sleep hygiene education, and pharmacological treatment of mood disorders may be beneficial. Future studies should explore longitudinal trajectories of fatigue and utilize objective sleep measures (e.g., polysomnography, actigraphy) to further elucidate the interplay between sleep and fatigue in MS.

5. Conclusion and Recommendations

The findings underscore the need for a multidimensional approach to fatigue management in MS, incorporating interventions that target disability, sleep quality, and mental health. Clinicians should consider routine screening for sleep disturbances and depressive symptoms in pwMS experiencing fatigue, as addressing these factors may alleviate fatigue and improve overall quality of life. Future research should explore longitudinal changes in fatigue and its predictors to establish causality. Additionally, studies incorporating objective sleep assessments, such as polysomnography, may provide deeper insights into the relationship between sleep disturbances and fatigue in MS.

6. Contribution to the Field

This study contributes to the existing literature by providing a comprehensive evaluation of fatigue predictors using a large sample of pwMS. By incorporating both physical and non-physical parameters into regression models, it demonstrates that fatigue is not merely a consequence of physical impairment but is significantly driven by psychological and sleep-related factors. The consistent identification of depression and sleepiness as key predictors supports the need for a multidisciplinary approach in managing fatigue in MS. These insights can inform the development of individualized rehabilitation and treatment strategies that address the full spectrum of factors contributing to fatigue, ultimately aiming to enhance the quality of life for pwMS.

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None.

Conflict of Interest

There is no conflict of interest with any person and/or institution.

Authorship Contribution

Concept: SÖ, ATÖ; Design: SÖ, SA Supervision: SÖ, YŞ, ATÖ; Funding: SÖ, YŞ; Materials: SÖ, SA; Data Collection/Processing: ATÖ, PY, YŞ; Analysis/Interpretation: ATÖ; Literature Review: PY, ATÖ; Manuscript Writing: SÖ, ATÖ, PY; Critical Review: YŞ, SA.

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