THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2025.33407
Med Bull Sisli Etfal Hosp 2025;59(3):403-409

Original Research

Fatigue, Insomnia, and Disability as Independent Predictors of Depressive Symptoms in Multiple Sclerosis: A Prospective Observational Study

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Abstract

Objectives: This study aimed to identify the clinical factors independently associated with depressive symptoms in patients with multiple sclerosis (MS) and to evaluate the impact of depression on health-related quality of life (QoL).

Methods: In this prospective observational study, 90 patients with MS were evaluated. Age, sex, disease duration, MS subtype, and Expanded Disability Status Scale (EDSS) scores were recorded. The Fatigue Severity Scale (FSS), Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS), Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) scale, and the EuroQol 5-Dimension 3-Level (EQ-5D-3L) questionnaire were administered. The presence of restless legs syndrome (RLS) was also recorded. Depression severity was measured using the Patient Health Questionnaire-9 (PHQ-9). First, univariable associations were examined, and relevant variables were subsequently entered into a multivariable linear regression model using backward elimination.

Results: Higher FSS, ISI, and EDSS scores were independently associated with higher PHQ-9 scores. FSS and ISI scores showed the strongest correlations with depression (ρ=+0.52 and +0.57; $p<0.001$). EDSS showed a modest association (ρ=+0.23, $p=0.031$). Age, sex, and disease duration were not significant predictors. S-LANSS scores, MS subtype, and RLS were significant in univariate analysis but excluded from the final model. Depression scores were significantly associated with higher EQ-5D-3L scores, indicating poorer QoL ($p<0.001$).

Conclusion: Fatigue and insomnia were the strongest independent predictors of depression in MS, surpassing traditional clinical indicators. Routine screening for these symptoms may facilitate earlier detection and treatment of depression and improve QoL in clinical practice.

Keywords: Depression, fatigue, insomnia, mood disorders, multiple sclerosis, quality of life

Please cite this article as "Alis C, Kose N, Sen Kilic S, Genc G, Bulut S. Fatigue, Insomnia, and Disability as Independent Predictors of Depressive Symptoms in Multiple Sclerosis: A Prospective Observational Study. Med Bull Sisli Etfal Hosp 2025;59(3):403-409".

Multiple sclerosis (MS) is a chronic, immune-mediated neurological disorder characterized by demyelination, axonal loss, and neurodegeneration in the central nervous system.[1,2] In addition to physical disability, MS is frequently accompanied by psychiatric comorbidities, particularly depression, which affects up to 50% of patients over the disease course.[3] Despite its high prevalence and clinical significance, depression often goes underrecognized and untreated in MS populations, partly due to overlapping symptoms such as fatigue, cognitive decline, and sleep disturbances.[4,5]

Importantly, depression in MS is not only a consequence of disease burden—it may also worsen disease outcomes. Depression can contribute to increased symptom perception,

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Submitted Date: May 31, 2025 **Accepted Date:** June 26, 2025 **Available Online Date:** October 13, 2025

reduce adherence to disease-modifying therapies (DMTs), and potentially impact immune regulation through stress-related neuroendocrine pathways.[6,7] In patients with MS, depression has also been linked to cognitive impairment, disruptions in occupational functioning, increased risk of suicidal ideation, and poorer quality of life.[3,8]

The pathogenesis of depression in MS is multifactorial, involving neuroinflammatory and neurodegenerative mechanisms as well as psychological and social stressors. Demyelinating lesions affecting mood-related circuits, immune-mediated alterations in neurotransmitter systems, and the psychosocial burden of living with a chronic, unpredictable illness may all contribute to the development of depressive symptoms.[9,10]

Several studies have examined the association between depression and MS-specific clinical features, including disease duration, MS subtype, and neurological disability as assessed by the Expanded Disability Status Scale (EDSS).[5,11] However, recent research has shifted focus to patient-reported outcomes, suggesting that subjective symptoms such as fatigue, insomnia, and neuropathic pain may be stronger correlates of depression than traditional neurological markers.[12,13]

Given its high prevalence and clinical consequences, identifying the key predictors of depression in MS is critical for timely intervention. In this study, we aimed to examine the independent clinical and demographic factors associated with depressive symptoms in a cohort of patients with MS. We also aimed to assess the relationship between depression and health-related quality of life.

Methods

Study Population

This prospective study was conducted with patients diagnosed with MS who were evaluated at the MS Outpatient Clinic of the Neurology Department at Sisli Etfal Training Research Hospital over a one-month period. Patients were diagnosed according to the McDonald criteria.[14] Written informed consent was obtained from all participants, who were evaluated by a neurologist specialized in demyelinating disorders. Individuals were eligible for inclusion if they had a confirmed diagnosis of MS. Exclusion criteria included the presence of other neurological conditions, age under 18, current use of medications for depression and/or anxiety, and refusal to participate in the study. The study protocol received approval from the Ethics Committee of Sisli Etfal Training and Research (approval date and number: 20.5.2025-4865). All procedures were carried out in accordance with the principles of the Declaration of Helsinki.

Clinical and Psychological Assessments

Demographic characteristics, age at disease onset, duration of illness, disease severity, fatigue level, use of DMTs, number of relapses, types of relapses experienced, MS subtype (relapsing-remitting MS [RRMS], and secondary progressive MS [SPMS]), and the presence of restless legs syndrome (RLS) were recorded. Additionally, data on neuropathic pain and other comorbid medical conditions were collected.

The Expanded Disability Status Scale (EDSS) and the Fatigue Severity Scale (FSS)[15] were used to assess disease severity and fatigue levels, respectively. An average FSS score of 4 or above was considered indicative of clinically relevant fatigue. The self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) was used to determine the presence of neuropathic pain, with a cut-off score of ≥12.[16] Depression was evaluated using the Patient Health Questionnaire-9 (PHQ-9) and categorized as: mild (5-9), moderate (10-14), moderately severe (15-19), or severe (≥20).[17]

Health-related quality of life was assessed using the EQ-5D-3L, a three-level instrument developed by the EuroQol Group.[18] Additionally, insomnia and excessive daytime sleepiness were questioned using Insomnia Severity Index (ISI) and Epworth Sleepiness Scale (ESS), respectively.[19,20] Patients scoring ≥15 on the ISI were classified as having moderate to severe insomnia, while those scoring >10 on the ESS were classified as having excessive daytime sleepiness.[19,20] Associations between these parameters and PHQ-9 scores were investigated.

Statistical Analysis

All analyses were performed using Python version 3.11 (open source), with the following packages: pandas 2.2 for data manipulation, SciPy 1.12 for statistical testing, statsmodels 0.15 for regression analysis, and scikit-posthocs 0.7 for post hoc comparisons. Data visualizations were generated using matplotlib 3.8. All statistical tests were two-sided, and a p value of <0.05 was considered statistically significant. Normally distributed continuous variables were summarized as mean±standard deviation (SD), and non-normally distributed variables as median with interquartile range (IQR). Categorical variables were described as counts and percentages (n, %).

The primary outcome was the PHQ-9 total score (range: 0–27), treated as a continuous measure of depressive symptom burden. Associations between continuous predictors and PHQ-9 were evaluated using Spearman rank correlation (ρ) with corresponding 95% confidence intervals (CIs). Binary predictors were assessed using Welch's t-test, with effect sizes reported as Cohen's d. Categorical variables

with more than two unordered groups were tested via the Kruskal–Wallis H test, with effect size estimated using epsilon squared (ε^2). Significant findings were further explored through Dunn's post hoc tests with Bonferroni correction.

Variables with a p-value <0.20 in univariate testing or deemed clinically relevant (e.g., age, sex, EDSS) were considered for inclusion in multivariable modelling.

To identify independent predictors of depressive symptoms (PHQ-9), an ordinary least squares (OLS) regression model was constructed with the following candidate variables: age, sex, EDSS, FSS, ISI, ESS, S-LANSS score, RLS, and alcohol use. Robust standard errors (HC3) were applied to address potential heteroscedasticity. Multicollinearity was assessed using the variance inflation factor (VIF), with variables exceeding VIF >5 marked for potential removal. A backward elimination approach was used, sequentially removing variables with p>0.10 unless clinically essential. Model fit was evaluated using adjusted R^2, and residual diagnostics included assessments for normality, linearity, and influential observations (defined as Cook's distance >4/n).

Associations between depressive symptoms (PHQ-9) and quality of life were examined using the EQ-5D-3L. Two outcomes were analyzed: EQ-5D-3L point score (higher values indicate worse health) and EQ-5D-3L percentage score (higher values indicate better perceived health status). Both were correlated with PHQ-9 using Spearman's rank correlation. Scatter plots were used to visualize the relationships, with fitted linear trend lines for illustration.

Results

Sociodemographic and Clinical Characteristics

A total of 90 patients with a median age of 36.5 years (IQR:27.0–45.0) were included in the study. There were 67 females (74.4%) and 23 (25.6%) males. Detailed baseline characteristics are presented in Table 1.

Among the participants, 81 (90%) had RRMS and 9 (10%) had SPMS. The DMTs used were as follows: dimethyl fumarate (n=34), fingolimod (n=16), natalizumab (n=16), ocrelizumab (n=8), cladribine (n=7), teriflunomide (n=6), and peginterferon beta-1a (n=1). Two patients were not receiving any treatment. A total of 50 patients (55.5%) reported fatigue, and 23 (25.5%) reported neuropathic pain. The median FSS score was 37 (IQR: 27–48), and the median S-LANSS score was 2 (IQR: 0-11.8).

The median PHQ 9 score was 8 (IQR: 5–14). Depression severity was categorized as mild in 33 patients (36.6%), moderate in 17 (18.8%), moderately severe in 19 (21.1%), and severe in 2 (2.2%). The median EQ-5D-3L point score was 7 (IQR:6-9) and the median EQ-5D-3L percentage score was 75% (IQR: 50%–90%). Additionally, the median ISI and ESS scores were 6.5 (IQR: 3-11) and 3.5 (IQR: 2-6), respectively. Nine patients (10%) were classified as having insomnia and 13 (14.4%) as having excessive daytime sleepiness.

Table 1. Baseline characteristics of the study population

Variable	Value
Age, year	36.5 (27.0 – 45.0)
Age at MS diagnosis, year	28.0 (22.0 – 38.5)
MS duration, year	4.0 (2.0 – 8.0)
Number of relapses	2.0 (1.0 – 3.0)
EDSS score	1.0 (1.0 – 2.0)
Sex	
Female	67 (74.4)
Male	23 (25.6)
Other comorbid disease	
No	61 (67.8)
Yes	29 (32.2)
Current smoker	
No	69 (76.7)
Yes	21 (23.3)
Alcohol use	
No	78 (86.7)
Yes	12 (13.3)
Restless Leg Syndrome	
No	68 (75.6)
Yes	22 (24.4)

*Data are presented as median (interquartile range) for continuous variables and as number (%) for categorical variables. EDSS: The Expanded Disability Status Scale; MS: Multiple sclerosis.

Depression and Clinical Correlates

Among all continuous variables, sleep and fatigue-related measures exhibited the strongest positive correlations with depressive symptoms. Specifically, ISI (ρ=+0.57, p<0.001) and FSS (ρ=+0.52, p<0.001) were the most prominent contributors, followed by the S-LANSS score (ρ=+0.42, p<0.001). These variables individually explained approximately 20–30% of the rank variance in PHQ-9 (Table 2).

Additional variables such as ESS (ρ=+0.31, p=0.003) and EDSS (ρ=+0.23, p=0.031) also demonstrated significant but comparatively weaker associations. In contrast, demographic and disease-specific variables such as age (ρ=–0.09, p=0.386), MS duration (ρ=–0.08, p=0.479), and age at diagnosis (ρ=–0.06, p=0.597) were not significantly correlated with PHQ-9 scores.

Binary predictors revealed a notable effect of RLS on PHQ-9 scores. Patients with RLS had significantly higher depressive symptoms compared to those without (mean difference: +3.7 points; t=2.89, p=0.007). A trend toward lower

Table 2. The associations between continuous predictors and PHQ-9 scores using Spearman's rank correlation.

Variable	ρ	p
Insomnia severity index	**+0.57**	**< 0.001**
Fatigue severity scale	**+0.52**	**< 0.001**
S LANSS pain score	+0.42	< 0.001
Epworth sleepiness scale	+0.31	0.003
EDSS	+0.23	0.031
Relapse count	+0.18	0.094
Age	−0.09	0.386
MS duration	−0.08	0.479
Age at MS diagnosis	−0.06	0.597

Bold entries remain significant after Benjamini–Hochberg control for a 10 % false discovery rate. EDSS: The Expanded Disability Status Scale; MS: Multiple sclerosis; S-LANSS: The self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale.

PHQ-9 scores was observed in participants reporting alcohol use, though this did not reach statistical significance (p≈0.06). No meaningful differences were found for smoking status or other comorbid conditions (p>0.20 for both).

Overall, subjective symptoms—particularly insomnia and fatigue—emerged as stronger correlates of depression than MS-specific clinical metrics such as EDSS, relapse count, or disease duration (ρ values ranging from approximately 0.15 to 0.25).

Depressive symptom severity was also compared across DMTs and MS clinical subtypes using nonparametric tests due to unequal group sizes and non-normal distributions. No statistically significant difference in PHQ-9 scores was found among the different DMT categories (Kruskal–Wallis H=6.12, df=7, p=0.527; ε^2=0.07). When analyzed by MS subtype, patients with SPMS disease phenotypes had notably higher PHQ-9 scores compared to those with RRMS, with median scores of 14 (IQR: 9–18) vs. 7 (IQR: 5–13), respectively. This difference reached statistical significance (H=4.73, p=0.030; ε^2=0.05). However, due to the small size of the SPMS group and its collinearity with EDSS, MS subtype was excluded from the multivariable model to avoid overfitting.

Multivariable Modelling of Depressive Symptoms

Selection of Candidate Predictors

To identify independent predictors of depressive symptoms, all potential variables were first screened using univariate analysis. Five continuous variables met the prespecified inclusion threshold (p<0.20): FSS, ISI, ESS, and S-LANSS scores. Among binary variables, RLS (p=0.007) and alcohol use (p=0.06) were also eligible. Although not statistically significant, sex was included in all models due to its known clinical relevance.

Categorical variables with multiple levels, including DMT type and MS subtype, were excluded from multivariable analysis due to limited group sizes and lack of robust associations.

Age, sex, and EDSS were included in all models regardless of univariate significance.

Initial Model and Collinearity Diagnostics

An initial linear regression model (ordinary least squares) was constructed with 11 predictors. To ensure valid estimates, robust standard errors (HC3) were applied to adjust for heteroscedasticity. Multicollinearity was assessed using variance inflation factors (VIF), which revealed high overlap between the three sleep-related measures (VIF: 6.3–8.1).

Backward stepwise elimination was applied to remove variables with high collinearity or limited contribution (p>0.10). This resulted in the exclusion of the ESS, S-LANSS, alcohol use, and RLS from the final model.

Final Model Composition

The final model retained five predictors, explaining 57% of the variance in PHQ-9 scores (adjusted R^2=0.57). Residuals were normally distributed, with no influential outliers (Cook's distance <0.15 for all cases). All VIF values were <2.4.

- Fatigue Severity (β=+0.15, p<0.001): Each 10-point increase in FSS was associated with a 1.5-point increase in PHQ-9.
- Insomnia Severity (β=+0.24, p<0.001): Each 5-point increase in ISI was linked to a 1.2-point increase in PHQ-9.
- EDSS (β=+0.50, p=0.046): Higher disability scores were modestly associated with higher depression scores.
- Age (β=−0.03, p=0.073): A trend toward lower PHQ-9 scores with increasing age was observed, though not statistically significant.
- Sex (β=+0.52, p=0.55): No independent association was found after adjustment.

Fatigue and insomnia emerged as the strongest independent predictors of depressive symptoms in this MS cohort. Neurological disability contributed to a lesser extent, while age showed a weak inverse trend. Neither sex nor lifestyle factors (e.g., alcohol, smoking, RLS) were independently associated with depression after accounting for other variables.

Patients reporting poorer overall health status also had significantly higher depression scores, supporting the bidirectional relationship between health-related quality of life and mood in MS. Both EQ-5D-3L index and percentage scores were moderately and significantly correlated with PHQ-9 (both p<0.001) (Table 3).

Table 3. The relationship between quality of life and depression

Variable	Spearman ρ with PHQ 9	p	Direction
EQ 5D 3L point (higher = worse health)	+0.47	< 0.001	Worse health → higher PHQ 9
EQ 5D 3L % (higher = better health)	0.45	< 0.001	Better health → lower PHQ 9

EQ-5D-3L: EuroQol-5 Dimensions-3 Levels questionnaire; PHQ-9: Patient Health Questionnaire-9.

Discussion

In this prospective study of patients with MS, we found that fatigue severity, insomnia, and neurological disability were independently associated with depressive symptoms. Among these, fatigue and insomnia emerged as the most robust predictors, each contributing significantly to PHQ-9 variance. Additionally, depressive symptoms were significantly related to poorer perceived health-related quality of life. These findings underscore the central role of patient-reported outcomes in understanding and addressing depression in MS.

Fatigue was the most powerful predictor of depressive symptoms in our multivariable model. This aligns with a substantial body of literature indicating that fatigue is not only highly prevalent in MS but also closely linked to emotional well-being.[5,12,21,22] While fatigue has traditionally been conceptualized as a consequence of neurological damage or systemic inflammation, emerging evidence suggests a deeper mechanistic overlap with depression. Heitmann et al.[23] proposed that neuroinflammation in MS may disrupt reward processing pathways, particularly in the mesolimbic system, leading to anhedonic symptoms that manifest as both fatigue and depression. Similarly, Dobryakova et al.[24] have suggested that dopaminergic imbalance in the cortico-striatal circuitry plays a central role in MS-related fatigue, implicating disrupted motivation and affect regulation as common underlying mechanisms. These neurobiological models help explain why fatigue is not only prevalent in MS but also so tightly linked with depressive affect. Our findings support this interpretation and suggest that fatigue should be addressed not only as a physical complaint but also as a window into broader affective dysregulation.

Insomnia was the second strongest predictor of depression in our cohort. Sleep disturbances are increasingly recognized as core features of psychiatric comorbidity in MS, and our findings echo prior studies that report strong correlations between insomnia symptoms and depressive affect.[25,26] Neuroinflammatory processes affecting sleep-regulating brain regions, along with MS-related pain, nocturnal spasms, or bladder dysfunction, may all contribute to sleep fragmentation in MS patients.[25,26] Our results suggest that clinicians should routinely assess insomnia as part of depression screening in MS, as addressing insomnia could provide dual benefits for mood and functional status.

We also found that higher EDSS scores were modestly associated with more severe depressive symptoms. Although the strength of this relationship was weaker than fatigue or insomnia, it remains consistent with prior studies showing that physical disability, particularly reduced mobility and dependence in activities of daily living, is a psychological stressor in MS.[11,22] Notably, some earlier studies have reported stronger associations between EDSS and depression;[22] however, our data suggest that subjective experiences such as fatigue and sleep quality may play a more prominent role in patients' psychological burden than clinician-rated disability alone.

Other variables—such as disease duration, sex, age at diagnosis, MS subtype, and number of relapses—did not show significant associations with depressive symptom severity in our study. These findings are consistent with recent work suggesting that static disease variables may be less important for predicting mood outcomes than dynamic or subjective factors.[5,11,22] Although patients with SPMS had higher PHQ-9 scores in univariate analysis, MS subtype was excluded from the multivariable model due to collinearity with EDSS. Thus, we cannot confirm its independent effect. Still, this aligns with the view that disability may be more strongly linked to depression than disease course alone.[11]

We observed a moderate correlation between PHQ-9 scores and S-LANSS, a measure of neuropathic pain. Although this variable did not retain significance in the final model due to collinearity, our univariate findings are in line with prior research showing that chronic pain contributes to depressive symptoms in MS.[3,23,27] Similarly, patients with RLS had significantly higher PHQ-9 scores than those without. While RLS did not remain significant in multivariate analysis, this suggests that sleep-related movement disorders may also contribute to mood disturbances and merit clinical attention.[28]

Quality of life, as measured by the EQ-5D-3L, showed a moderate negative correlation with PHQ-9 scores. This supports existing evidence that depression significantly impairs perceived health and functional well-being in MS.[3,8] The strong link between depressive symptoms and both

EQ-5D-3L point and percentage scores highlights the importance of mood assessment not only for psychiatric care, but also as a determinant of broader health outcomes in this population.

This study has several strengths. First, it employed a comprehensive set of both clinical and patient-reported measures, allowing for a multidimensional assessment of depression in MS. The use of validated scales such as the PHQ-9, FSS, ISI, and EQ-5D-3L enhances the reliability and comparability of our findings. Second, by including a multivariable regression model with robust statistical controls, we were able to identify independent predictors of depressive symptoms beyond basic clinical descriptors. Third, the exclusion of patients receiving psychiatric medications reduced potential confounding effects of pharmacological treatment on mood assessments.

However, some limitations should also be noted. First, the cross-sectional design precludes any inference about the directionality or causality of the observed associations. Longitudinal studies are needed to clarify whether symptoms such as fatigue and insomnia contribute to the development of depression or vice versa. Second, the relatively small sample size, particularly within subgroups such as SPMS, may have limited statistical power to detect more nuanced associations. Third, the reliance on self-reported measures introduces potential reporting bias. Finally, exclusion of patients currently receiving antidepressant or anxiolytic medications may have led to underestimation of depression prevalence and potentially excluded individuals with more severe psychiatric symptoms.

Conclusion

In this study, fatigue, insomnia, and disability emerged as the strongest predictors of depressive symptoms in patients with multiple sclerosis. Among these, patient-reported symptoms—especially fatigue and insomnia—were more strongly associated with depression than traditional clinical measures. These findings highlight the importance of incorporating psychosocial symptom screening into routine MS care to better identify and manage depression. Importantly, our results also demonstrate that depressive symptoms are significantly associated with poorer health-related quality of life in this population, further underscoring the need for timely recognition and intervention.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital (approval date and number: 20.05.2025-4865).

Conflict of Interest: The authors declared no conflict of interest.

Peer-review: Externally peer-reviewed.

Funding: The authors declared that they have no grants or financial disclosure.

Informed Consent: Written informed consents were obtained from all the patients.

Authorship Contributions: Concept – C.A., G.G., S.B.; Design – C.A., G.G., S.B.; Supervision – G.G., S.B.; Materials – C.A., S.Ş.K., N.K., G.G., S.B.; Data collection &/or processing – C.A., S.Ş.K., N.K., G.G., S.B.; Analysis and/ or interpretation – C.A.; Literature search – C.A.; Writing – C.A.; Critical review – C.A., S.Ş.K., N.K., G.G., S.B

Use of AI for Writing Assistance: No artificial intelligence tool was used in the preparation of this manuscript.

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