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MULTİPL SKLEROZLU HASTALARDA YORGUNLUK VE YÜRÜME KAPASİTESİNİN YAŞAM KALİTESİ ÜZERİNE ETKİSİ

THE IMPACT OF FATIGUE AND WALKING CAPACITY ON QUALITY OF LIFE IN PATIENTS WITH MULTIPLE SCLEROSIS

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ÖZET

AMAÇ: Bu çalışmada, multipl skleroz (MS) hastalarında yorgunluk ve yürüme güçlüğünün yaşam kalitesi (YK) üzerindeki bağımsız ve birleşik etkilerinin değerlendirilmesi ve bu ilişkilerde sosyodemografik ve klinik faktörlerin rolünün incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Türkiye'deki dört üçüncü basamak merkezden toplam 181 MS hastasının dâhil edildiği çok merkezli, kesitsel bir çalışma yürütülmüştür. Katılımcılar Yorgunluk Şiddeti Ölçeği (FSS), 12 maddelik MS Yürüme Ölçeği (MSWS-12) ve Multipl Skleroz Etki Ölçeği (MSIS-29) doldurmuştur. Ayrıca sosyodemografik ve klinik veriler toplanmıştır. Yaşam kalitesi belirleyicilerini incelemek için korelasyon analizleri, alt grup karşılaştırmaları ve çok değişkenli doğrusal regresyon analizleri yapılmıştır.

BULGULAR: MSIS-29 skorları, MSWS-12 ile güçlü (r=0,81), FSS ile orta düzeyde (r=0,54) ilişki göstermiştir (her ikisi için p<0,001). Çok değişkenli regresyon analizinde yürüme güçlüğü (β=0,772) ve yorgunluk (β=0,179) yaşam kalitesinin bağımsız belirleyicileri olarak bulunmuş ve birlikte toplam varyansın %70'ini açıklamıştır (R^2=0,703). Fiziksel yaşam kalitesinde en güçlü belirleyici MSWS-12 iken, psikolojik yaşam kalitesinde hem MSWS-12 hem de FSS anlamlı katkıda bulunmuştur. Tek değişkenli analizlerde düşük eğitim düzeyi ve eşlik eden hastalıklar, çok değişkenli modelde ise kadın cinsiyet daha kötü sonuçlarla ilişkili bulunmuştur.

SONUÇ: MS'de yorgunluk ve yürüme güçlüğü, yaşam kalitesini azaltan başlıca faktörlerdir ve özellikle fiziksel işlevsellik üzerinde yürüme güçlüğü daha güçlü etki göstermektedir. Bulgular, hem motor hem de motor dışı semptomları hedefleyen çok boyutlu bakım yaklaşımlarının önemini vurgulamaktadır. Ayrıca bireysel sosyodemografik ve klinik özelliklerin değerlendirmeye dâhil edilmesi, MS yönetiminin kişiselleştirilmesini destekleyebilir.

ANAHTAR KELİMELER: Multipl Skleroz, Yaşam Kalitesi, Yorgunluk, Yürüme.

ABSTRACT

OBJECTIVE: This study aimed to evaluate the independent and combined effects of fatigue and walking impairment on multiple sclerosis (MS)-specific quality of life (QoL) and to explore the influence of sociodemographic and clinical factors on these associations.

MATERIAL AND METHODS: A multicenter, cross-sectional study was conducted including 181 individuals with MS from four tertiary care centers in Turkey. Patients completed the Fatigue Severity Scale (FSS), the 12-item MS Walking Scale (MSWS-12), and the Multiple Sclerosis Impact Scale (MSIS-29). Sociodemographic and clinical data were collected. Correlation analyses, subgroup comparisons, and multivariate linear regressions were performed to identify predictors of QoL.

RESULTS: MSIS-29 scores were strongly associated with MSWS-12 (r=0.81) and moderately associated with FSS (r=0.54) (p<0.001 for both). Multivariate regression demonstrated that walking impairment (β=0.772) and fatigue (β=0.179) were independent predictors of QoL, jointly explaining 70% of the variance in MSIS-29 total scores (R^2=0.703). MSWS-12 was the primary predictor of physical QoL, while both MSWS-12 and FSS contributed to psychological QoL. Lower education and comorbidities were associated with worse outcomes in univariate analyses, and female sex was associated with greater disease impact in the multivariable model.

CONCLUSIONS: Fatigue and walking limitations are major determinants of reduced QoL in MS, with walking impairment exerting a stronger effect on physical functioning. These results highlight the importance of multidimensional care strategies that address both motor and non-motor symptoms, alongside sociodemographic and clinical characteristics, to optimize individualized MS management.

KEYWORDS: Multiple Sclerosis, Quality of Life, Fatigue, Walking.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system characterized by a wide spectrum of symptoms that significantly impair patients' daily functioning and overall quality of life (QoL). Fatigue is among the most common and debilitating symptoms, reported by up to 80% of individuals with MS across all stages of the disease (1). Walking impairment is another frequent and impactful complaint that contributes substantially to physical disability and loss of independence (2). These two symptoms often coexist and interact, amplifying each other's negative effects on functional capacity and psychosocial well-being (3,4). Moreover, their influence on QoL is shaped by various sociodemographic and clinical factors, including sex, education level, comorbidities, and modifiable lifestyle characteristics. Despite the high burden of these symptoms, other important aspects of MS, such as pain, cognitive dysfunction, and bladder disturbances remain under-assessed in routine clinical evaluations. A nuanced understanding of how fatigue and mobility difficulties affect QoL, especially in interaction with individual-level factors, is essential for guiding holistic and personalized MS care.

The Multiple Sclerosis Impact Scale-29 (MSIS-29) is a validated, disease-specific instrument designed to evaluate the physical and psychological impact of MS on daily life (4). Additionally, the Fatigue Severity Scale (FSS) and the 12-item Multiple Sclerosis Walking Scale (MSWS-12) are widely utilized patient-reported outcome measures for assessing fatigue and walking limitations, respectively (5,6). Numerous studies have demonstrated strong associations between these symptoms and QoL in people with MS (PwMS), yet their independent contributions and potential interactions remain subjects of ongoing research (7,8). Fatigue has consistently emerged as a major determinant of both physical and psychological health-related QoL (HRQoL), whereas walking impairment has shown stronger associations with physical disability domains (9,10). However, findings vary across populations and methodologies, underscoring the need for multicenter studies employing standardized tools to better elucidate these relationships (11, 12).

In this context, the present multicenter study conducted across four tertiary care centers in Turkey aimed to investigate the independent and combined effects of fatigue and walking impairment on QoL using the FSS, MSWS-12, and MSIS-29. Beyond symptom measures, we also examined the influence of individual-level factors such as gender, education level, and comorbidities, which may shape the experience of MS but are often underrepresented in routine assessments. By integrating symptom severity with sociodemographic and clinical context, this study offers valuable real-world insight into the multifactorial determinants of QoL in MS and supports a more personalized and comprehensive approach to patient care.

MATERIALS AND METHODS

This multicenter, cross-sectional study included 181 PwMS recruited from four tertiary neurology centers in Turkey: Ankara Etlik City Hospital, Eskişehir City Hospital, Manisa Celal Bayar University, and Kütahya Health Sciences University. All participants had a confirmed diagnosis of MS according to the 2017 McDonald criteria (13) and had been diagnosed for at least one year. Eligible patients were aged between 18 and 65 years and cognitively and physically able to complete the questionnaires independently or with minimal assistance. Patients younger than 18 or older than 65 years, as well as those with severe visual or auditory impairment or cognitive dysfunction that prevented questionnaire completion were excluded.

Sociodemographic and clinical data, including age, sex, education, marital and employment status, smoking and alcohol use, family history, dominant hand, disease duration, and comorbidities, were recorded. Patient-reported outcomes were assessed using validated Turkish versions of the FSS, MSWS-12, and MSIS-29 (including physical and psychological subdomains) (14-16). Although the Expanded Disability Status Scale (EDSS) was not formally assessed, only ambulatory patients functionally corresponding to an estimated EDSS score of ≤6.0 were included, as the MSWS-12 is validated for ambulatory PwMS and cannot be applied to non-ambulatory individuals.

Ethical Committee

The study protocol was approved by the Clinical Research Ethics Committee of Ankara Etlik City Hospital (Approval No: AEŞH-EK1-2023-104, Date: July 12, 2023). Written informed consent was obtained from all participants.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), whereas categorical variables were presented as frequencies and percentages. Group comparisons were conducted using Student's t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. Correlations among FSS, MSWS-12, and MSIS-29 scores were assessed using Pearson's or Spearman's coefficients, depending on data distribution. To identify independent predictors of MS-specific quality of life, multivariable linear regression analyses were performed for the MSIS-29 total score as well as its physical and psychological subdomains, with fatigue (FSS), walking impairment (MSWS-12), and relevant demographic and clinical variables (sex, age, education, comorbidities) entered as independent factors. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

A total of 181 PwMS were included in the study. The mean age was 42.3±10.6 years, with a predominance of female participants (75%). Most patients were right-handed (86%), married (67%), and employed (53%). Educational attainment varied, with 42% having completed a university degree (level 3) and 9% holding a postgraduate degree (level 4). A family history of MS was reported by 14% of the participants, while 28% had at least one comorbid chronic condition. Mean scores on patient-reported outcome measures indicated moderate to high symptom burden across the cohort. As shown in Table 1, both physical and psychological subdomains of the MSIS-29 were affected, with additional limitations reported in fatigue (FSS) and walking ability (MSWS-12) **(Table 1)**.

Table 1: Demographic and clinical characteristics of the study sample (n = 181).

Variable	Mean ± SD or n (%)
Age (years)	42.3 ± 10.6
Female sex (%)	136 (75%)
Family history of MS (%)	25 (14%)
Right-handed (%)	156 (86%)
Education (high, level 3–4) (%)	93 (51%)
Married (%)	121 (67%)
Smoking (%)	81 (45%)
Alcohol use (%)	42 (23%)
Employment (%)	96 (53%)
Comorbidity (%)	51 (28%)
MSIS-29 total	64.4 ± 26.1
MSIS-29 physical	48.5 ± 20.3
MSIS-29 psychological	15.9 ± 8.4
FSS total	39.9 ± 12.7
MSWS-12 total	24.0 ± 11.1

Correlation analyses demonstrated strong and consistent associations among fatigue severity (FSS), walking impairment (MSWS-12), and disease-specific quality of life (MSIS-29). The MSIS-29 total score showed a strong positive correlation with MSWS-12 (r=0.81, p<0.001) and a moderate correlation with FSS (r=0.54, p<0.001). When the subscales of MSIS-29 were considered separately, the physical subscore was strongly correlated with MSWS-12 (r=0.83) and moderately with FSS (r=0.47), while the psychological subscore was strongly correlated with MSWS-12 (r=0.76) and moderately with FSS (r=0.54). In addition, MSWS-12 and FSS scores were moderately correlated with each other (r=0.46) **(Figure 1)**.

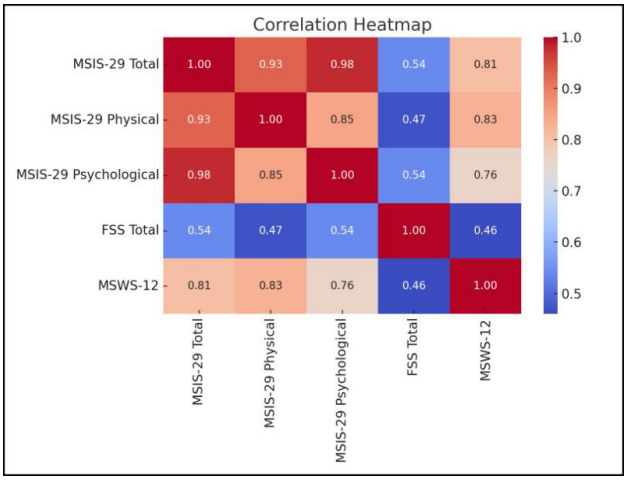

Figure 1: Correlation heatmap between fatigue (FSS), walking impairment (MSWS-12), and quality of life (MSIS-29 total and subscales). The heatmap illustrates Pearson correlation coefficients (r values) among the total and subscale scores of the MSIS-29, FSS, and MSWS-12. Warmer colors indicate stronger positive correlations. All shown associations are statistically significant at p<0.001.

Subgroup comparisons revealed that several demographic and clinical factors were associated with significant differences in symptom severity and QoL scores. Patients with lower education levels (levels 0–2) reported significantly higher MSIS-29 (p = 0.025) and MSWS-12

scores (p=0.007) compared to those with higher education. Marital status was also associated with differences in walking impairment: single patients reported lower MSWS-12 scores than their married or widowed counterparts (p=0.002). The presence of comorbid conditions was associated with significantly higher scores on all three scales, including MSIS-29, FSS, and MSWS-12 (p<0.05 for all). No significant differences in symptom scores were found based on sex **(Table 2)**, smoking, or alcohol use.

Table 2: Comparison of patient-reported outcomes across demographic and clinical subgroups.

Variable	Group	FSS Mean (SD)	FSS p-value	MSWS-12 Mean (SD)	MSWS-12 p-value	MSIS-29 Mean (SD)	MSIS-29 p-value
Sex	Female	40.4 (12.0)	0.77	23.2 (11.0)	0.20	64.6 (26.4)	0.75
	Male	39.0 (13.5)		26.7 (10.8)		63.7 (25.3)	
Education	Low (0–2)	40.9 (11.9)	0.58	27.9 (12.3)	**0.007**	70.6 (23.8)	**0.025**
	High (3–4)	38.3 (13.5)		21.2 (7.9)		58.3 (26.1)	
Marital Status	Single	39.8 (12.7)	0.91	18.2 (8.8)	**0.002**	58.5 (27.6)	0.072
	Married/Other	40.0 (12.4)		25.8 (11.2)		66.9 (25.4)	
Comorbidity	Yes	41.7 (11.9)	**0.041**	26.3 (10.9)	**0.021**	68.8 (25.1)	**0.034**
	No	38.3 (13.0)		22.1 (11.1)		60.2 (26.3)	

Scores are presented as mean (standard deviation, SD). *p*-values reflect statistical significance based on independent-sample t-tests comparing each binary category. FSS, Fatigue Severity Scale; MSWS-12, 12-Item Multiple Sclerosis Walking Scale; MSIS-29, Multiple Sclerosis Impact Scale-29.

Multivariate linear regression analysis identified both fatigue and walking impairment as independent predictors of MS-specific quality of life, as measured by the MSIS-29 total score. MSWS-12 had the strongest impact (β=0.772, p<0.001), followed by FSS (β=0.179, p<0.001). Additionally, female sex was associated with greater perceived disease impact (β=0.088, p=0.040), while younger age showed a borderline effect (β=–0.091, p=0.062). This model accounted for approximately 70% of the variance in MSIS-29 scores ($R^2 = 0.703$) **(Table 3)**.

Table 3: Multivariate Linear Regression for Predicting MSIS-29 Total Score.

Predictor	B (Coef.)	SE	β (Standardized)	95% CI	p-value
FSS	0.284	0.076	0.179	0.134 – 0.434	**<0.001**
MSWS-12	1.596	0.108	0.772	1.383 – 1.808	**<0.001**
Sex	5.428	2.617	0.088	0.263 – 10.593	**0.040**
Age	-0.234	0.125	-0.091	-0.481 – 0.012	0.062
Education	0.317	1.012	0.014	-1.681 – 2.314	0.755
Comorbidity	0.894	2.630	0.015	-4.296 – 6.084	0.734

Results of multivariable linear regression analysis identifying independent predictors of disease-specific quality of life (QoL), as measured by the MSIS-29 total score. Unstandardized (B) and standardized (β) regression coefficients are presented along with standard errors (SE), 95% confidence intervals (CI), and p-values. The model included fatigue (FSS), walking impairment (MSWS-12), sex (female), age, education level, and comorbidity as predictors. Statistically significant results (p<0.05) are indicated in bold.

In domain-specific multivariate models, both fatigue and walking impairment independently predicted physical and psychological quality of life outcomes. For the MSIS-29 physical subscore, MSWS-12 emerged as the strongest predictor (β=0.623, p<0.001), followed by FSS (β=0.190, p=0.009)Sex, age, and education were not significant contributors in this model. For the psychological subscore, both MSWS-12 (β=0.360, p<0.001) and FSS (β=0.330, p<0.001) remained significant predictors. Additionally, female sex was associated with greater psychological burden (β=0.126, p=0.023), while age showed a borderline effect (p = 0.058). These findings underscore that while walking impairment is a dominant factor in both domains, fatigue and sex have domain-specific contributions **(Table 4)**.

Table 4: Multivariate Linear Regression Predicting MSIS-29 Physical and Psychological Subscores.

A. Physical Component

Variable	B (Coef.)	SE	β (Standardized)	95% CI Lower	95% CI Upper	p-value
FSS	0.093	0.035	0.190	0.024	0.163	0.009
MSWS-12	0.497	0.050	0.623	0.398	0.596	<0.001
Sex	0.777	1.150	0.036	−1.490	3.044	0.498
Age	−0.084	0.055	−0.097	−0.192	0.024	0.124
Education	−0.572	0.438	−0.082	−1.441	0.296	0.198

B. Psychological Component

Variable	B (Coef.)	SE	β (Standardized)	95% CI Lower	95% CI Upper	p-value
FSS	0.103	0.020	0.330	0.064	0.142	<0.001
MSWS-12	0.181	0.030	0.360	0.122	0.241	<0.001
Sex	1.543	0.671	0.126	0.220	2.867	0.023
Age	−0.061	0.032	−0.120	−0.124	0.002	0.058
Education	−0.093	0.254	−0.021	−0.597	0.411	0.708

Separate multivariate linear regression models were conducted to identify predictors of the MSIS-29 physical and psychological subscales. Standardized coefficients (β), confidence intervals (CI), and p-values are provided. p<0.05 was considered statistically significant. Abbreviations: FSS, Fatigue Severity Scale; MSWS-12, 12-Item Multiple Sclerosis Walking Scale; SE, standard error; CI, confidence interval.

DISCUSSION

In this Turkish multicenter cohort of PwMS, we identified a strong correlation between fatigue severity and walking impairment with disease-specific QoL, as assessed by the MSIS-29. The Pearson correlation coefficient between the MSIS-29 total score and the FSS was moderate (r≈0.54), whereas the correlation between the MSIS-29 and the MSWS-12 was notably high (r≈0.81); both correlations were significant (p<0.001). These results are consistent with international research that highlights fatigue as a significant factor contributing to diminished QoL in MS (17,18) and indicates that impaired walking ability negatively impacts the daily functioning (17). For example, Garg et al. reported that patients experiencing higher levels of fatigue not only exhibited poorer mobility and balance but also had significantly lower physical and mental QoL scores (17). Our regression analyses further corroborated these findings: each one-point increase in FSS was associated with an approximate 0.24–0.29 point increase in

MSIS-29 (indicating worsening QoL), and each one-point increase in MSWS-12 corresponded to approximately a 0.59–1.57 point increase in MSIS-29, depending on the subscale. Consequently, fatigue and ambulatory disability emerged as the primary determinants of QoL in our cohort. Interventions aimed at addressing fatigue and mobility are likely to result in substantial improvements in QoL, as suggested by Young et al., who found that fatigue was the most significant influence on QoL in a large MS cohort (18). Indeed, that study demonstrated fatigue to be "clearly dominant" even when accounting for disability and psychosocial factors. However, our study revealed a somewhat different pattern than that of many previous cohorts. In our multivariate models, walking impairment (MSWS-12) emerged as the strongest independent predictor of MS-specific QoL, not only for the physical but also for the psychological components of the MSIS-29. The standardized effect of walking impairment exceeded that of fatigue, even for psychological well-being, suggesting that mobility limitations may impose a broader emotional and social burden than is often appreciated. This constitutes an important contribution, as relatively few studies have demonstrated such a pronounced influence of walking impairment on psychological QoL, particularly in ambulatory patients with low-to-moderate disability.

Our analysis revealed that certain sociodemographic factors influenced patient-reported outcomes. Patients with higher educational attainment reported more favorable scores (lower MSIS-29 and MSWS-12 scores), whereas those with comorbid conditions exhibited poorer outcomes across all measures. This finding aligns with that of Yamout et al. (a Middle Eastern MS QoL study), who identified higher education and employment as predictors of better QoL (19). We also observed slightly higher adjusted MSIS-29 scores among women and younger patients, consistent with Casetta et al.'s finding that the impact of disability on QoL can vary by sex, with some domains being more affected in women (20). Notably, in our cohort, univariate tests did not reveal a significant QoL difference between men and women, suggesting that any gender effect was modest. Neither smoking nor alcohol use was significantly associated with the symptom scores in our sample. However, other studies have reported that smokers with MS experience worse fatigue and depression and lower overall QoL than non-smokers (21,22). For instance, a recent study from Turkey found that greater lifetime cigarette exposure (pack-years) correlates with poorer walking ability, heightened fatigue and depression, and reduced health-related quality of life (22). These findings underscore that lifestyle factors, such as smoking, can exacerbate the MS symptom burden, even though our study may have been underpowered to detect such effects. In addition, some reports suggest that day-to-day lifestyle habits may influence patients' overall MS experience (23), which is consistent with the multifactorial nature of QoL, as observed in our cohort. Subgroup analyses in our study indicated that socioeconomic factors may influence the perceived impact of MS-related symptoms.

Patients with lower educational attainment and, notably, those who were employed, reported higher MSIS-29 scores. This counterintuitive result may reflect the additional strain associated with balancing occupational responsibilities and the challenges of the disease. Alternatively, this may be explained by confounding variables such as age and disease duration, as many of the more severely disabled individuals in our cohort were older and retired. These findings suggest that both socioeconomic disadvantage and active employment status may shape the lived experience of MS in different ways.

Another significant observation was the role of comorbidities. Participants with coexisting chronic conditions exhibited significantly higher scores on all patient-reported measures, including fatigue, walking impairment, and overall QoL than those without. This is consistent with prior research indicating that comorbidities, such as cardiovascular disease, metabolic disorders, and depression, can exacerbate MS-related disability and symptom burden. These results underscore the importance of adopting integrated multidisciplinary management strategies for PwMS with comorbidities.

Our comprehensive regression models, which accounted for a range of patient factors, underscore the predominance of fatigue and walking impairment in determining the MS-specific QoL. Notably, the MSIS-29 physical subscale was most strongly influenced by the MSWS-12 walking score, whereas the MSIS-29 psychological subscale was significantly affected by both the FSS and the MSWS-12. These findings highlight the clinical importance of managing fatigue and mobility limitations to enhance patients' physical and mental well-being. They also suggest that bolstering patients' psychological resilience, such as through self-efficacy and coping strategies, could be beneficial, as indicated by Young et al., who identified self-efficacy as a critical factor alongside fatigue and disability (18). The high R^2 values of our models (~0.65–0.71) indicate that fatigue and walking scores together account for a substantial proportion of the variance in QoL, and this level of explained variance appears higher than that reported in many previous studies, where symptom clusters generally account for approximately half of the variability in QoL. Thus, while earlier work has often identified fatigue as the "dominant" factor for MS QoL (18), our findings suggest that, in an ambulatory cohort, walking impairment may assume at least an equally important role, and in some domains, even greater.

Importantly, although the EDSS was not formally assessed in this study, only ambulatory patients functionally corresponding to an estimated EDSS ≤6.0 were included due to the use of the MSWS-12. This methodological feature strengthens the internal consistency of our findings and helps explain why even relatively modest gait and balance limitations translated into a disproportionately large impact on both physical and psychological QoL in our study cohort.

Notably, improvements in physical function alone may not result in lasting improvements in fatigue or QoL. Smedal et al. reported that although a short inpatient physiotherapy program led to immediate improvements in fatigue and MSIS-29 scores, these gains were lost by three months post-treatment, despite patients maintaining improved walking performance (4). This finding underscores the necessity of interventions beyond physical rehabilitation to achieve sustained fatigue management, such as incorporating energy conservation strategies, cognitive-behavioral therapy, or other psychosocial approaches. Supporting our overall results, a recent large-scale MS registry study using novel segmentation methods found that symptom burden particularly depression, fatigue, pain, and severe gait impairment predominantly drives low health-related quality of life (HRQoL), whereas traditional demographics (e.g., education and marital status) showed minimal association (24). Collectively, these insights advocate for a multidisciplinary management approach: optimal MS care should encompass not only disease-modifying treatments to limit disability but also targeted therapies for fatigue (e.g., amantadine and mindfulness-based fatigue management), mobility rehabilitation, psychological support, and self-management programs to empower patients.

While fatigue and walking difficulties are prominent symptoms of MS, numerous other symptoms remain under-recognized in routine clinical assessments, yet they can significantly impair the QoL. For instance, pain, cognitive dysfunction, bladder and bowel problems, and social isolation are frequently reported by patients as debilitating, but these factors are not directly captured by the MSIS-29, which primarily focuses on mobility and the general physical and psychological impact. In reality, many of these symptoms tend to co-occur and exacerbate each other's effects. Recent patient-reported outcome studies indicate that day-to-day fluctuations in fatigue often coincide with changes in pain and mood, with symptom clusters collectively worsening patients' well-being and functional status (25). Even patients with MS with minimal overt disability can experience fatigue, depression, or anxiety that significantly erodes their quality of life (26), underscoring the need to address these "invisible" symptoms regardless of a patient's EDSS score. Consistent with this, large cohort analyses have demonstrated that subjective symptoms such as depressed mood and pain can result in QoL decrements comparable to those resulting from physical disability (10). The ubiquitous presence of fatigue, affecting approximately 70% of PwMS, further establishes it as a predominant contributor to

QoL loss at the population level (10). Meanwhile, difficulties with gait and balance rank among the most impactful symptoms on health-related QoL across diverse MS populations (27). Notably, in progressive disease courses, issues such as spasticity and bladder dysfunction may assume greater prominence, whereas in relapsing forms, fatigue and depression often dominate (10,27). These insights highlight that a narrow focus on mobility and fatigue alone may overlook other critical determinants of patients' quality of life.

We advocate for more comprehensive assessments in both research and practice to capture these underexplored dimensions of the phenomenon. Incorporating validated pain scales, neuropsychological tests for cognitive impairment, and measures of mood (depression/anxiety), energy, and social participation would facilitate a more thorough mapping of the "hidden" facets of MS disability. This approach can inform more holistic and individualized management plans. Additionally, addressing modifiable lifestyle factors, such as smoking cessation, exercise and wellness programs, and treatment of comorbid conditions, may provide further quality-of-life benefits for patients. Overall, our findings, in conjunction with the literature, suggest that improving the quality of life in MS will require multidimensional interventions targeting not only the apparent motor symptoms but also the pervasive fatigue and psychosocial challenges that many patients encounter.

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