Journal of Pioneering Medical Sciences
Received: February 06, 2025 | Accepted: March 23, 2025 | Published: April 27, 2025
Volume 14, Issue S01, Pages 440-448

DOI https://doi.org/10.47310/jpms202514S0158

Assessment of Quality of Life and Fatigue in Patients with Multiple Sclerosis- A Cross-Sectional Study

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Abstract **Background:** Fatigue and impaired quality of life (QoL) are common and disabling symptoms in patients with multiple sclerosis (MS), which often hamper their physical, emotional and social functioning. It is important to appreciate the interrelation of fatigue and QoL and their individual demographic and clinical determinants, in order to organize management based on patient needs. **Methods:** This cross-sectional descriptive study was conducted over a span of 12 months during the period of January to December 2023. 286 patients with MS, aged between 18 to 65 years, diagnosed for ≥ six months, were enrolled via convenience sampling from the tertiary care and rehabilitation hospital OPDs and inpatient facilities. The Fatigue Severity Scale (FSS) and Multiple Sclerosis Quality of Life-54 (MSQoL-54) questionnaire were used to acquire data. Data analysis was carried out using Pearson's correlation, t-tests, ANOVA and multivariate linear regression with the use of SPSS version 25.0 and considering p-values of<0.05 to be significant. **Results:** The mean age of participants was 38.4±9.6 years with female predominance (60.8%). Most of the participants had relapsing-remitting type of MS (63.6%), with a mean disease duration of 7.2±5.1 years. The mean FSS score was 4.5±1.4 and 48.3% of participants had moderate fatigue. The mean overall QoL score was 61.1±15.1, with mean physical and emotional health composites of 58.4±15.7 and 63.7±14.9, respectively. Fatigue was significantly and inversely correlated with all QoL dimensions (physical health: $r = -0.63$; emotional health: $r = -0.58$; overall QoL: $r = -0.66$; all $p<0.001$). Female gender, older age, lower education, higher EDSS score, progressive type of MS and longer disease duration were significantly correlated with greater fatigue and lower QoL scores (all $p<0.05$). Multivariate regression analysis revealed EDSS score ($\beta = -2.43$), progressive type of MS ($\beta = -8.94$) and severity of fatigue ($\beta = -4.89$) as independent predictors of poor QoL. **Conclusion:** This study validated the general high level of fatigue and moderate level of quality of life impairment in MS patients. Fatigue was significantly correlated with lower physical and emotional well-being and several demographic and clinical variables independently predicted poorer outcomes. These results emphasize the necessity of multi-faceted, patient-focused interventions targeting fatigue as well as disease management to enhance patient quality of life.

Key Words Multiple sclerosis, fatigue, quality of life, MSQoL-54, Fatigue Severity Scale, cross-sectional study, EDSS, predictors, regression analysis

INTRODUCTION

Multiple Sclerosis (MS) is a chronic autoimmune-mediated demyelinating disease of the central nervous system with episodic neurological dysfunction and ongoing neurodegeneration [1,2]. MS is mainly found in young adults but with a relatively high prevalence in women, thus a dynamic of worsening disability with time [3]. Its clinical presentation may include sensory impairment, motor impairment, cognitive impairment, visual impairment and disabling fatigue [4,5].

Fatigue, or an over-whelming feeling of exhaustion, energy loss and decreased ability to work either physically or mentally, is one of the most frequent and disabling manifestations of MS, in about 75-95% of patients [6,7]. MS fatigue is multifactorial and complex and is affected by inflammation, neurodegeneration, depression, sleep disturbances, treatment side effects and physical inactivity [8,9]. Fatigue is very disabling in the daily life, impacts work productivity, social activity and overall quality of life [10].

Quality of life (QoL) is a true, multidimensional construct encompassing physical, psychological, emotional and social well-being [11]. Multiple sclerosis (MS) decreases QoL due to the unpredictable disease course, physical impairment, cognitive deficits, emotional distress, social isolation and reduced participation in valued activities [12,13]. Previous studies have repeatedly found that MS patients perform poorly on QoL relative to the general population and those with other chronic illnesses [14,15]. Furthermore, it has been established that severity of fatigue is inversely related to QoL, suggesting the significance of fatigue as a powerful predictor of patient-reported outcomes [16,17].

Although literature is said to present evidence of compromised QoL and high burden of fatigue in MS patients, variability remains to be established in the context of demographic and clinical predictors of the two parameters. Notably, the large majority of previously published studies were carried out on Western populations with minimal inclusion from other geographical areas and healthcare systems [18]. Hence, this study sought to measure QoL and fatigue in depth in MS patients, investigating the relationship between the two parameters as well as their demographic and clinical predictors within a cross-sectional study.

METHODS

Research Methodology

This was a 12-month descriptive cross-sectional study between January and December 2023. The participants were enrolled from OPDs and neurology specialist tertiary care and rehabilitation hospitals' inpatient wards. Ethical approval was first taken from the Institutional Ethics Committee. All the procedures followed the principles of the Declaration of Helsinki exactly and informed consent was taken from all the participants before they were enrolled into the study.

Study Population and Inclusion Criteria

MS patients were grouped based on revised McDonald diagnostic criteria 2017 and were recruited. Inclusion criteria included adult volunteers (18-65 years) and MS that had been diagnosed at least six months before entering the study. The subjects must have good cognitive ability to reply and complete self-report questionnaires. The exclusion criteria included hospitalization or acute relapse during the past month, significant cognitive impairment, other concurrent neurological disease and serious comorbidities likely to affect fatigue or QoL.

Sampling Method and Determination of Sample Size

Convenience sampling technique was employed, sampling sequentially available eligible patients to the point where the target sample size was achieved. Sample size was determined using the cross-sectional prevalence formula:

$$N = \frac{Z^2 P(1-P)}{d^2}$$

Where:

- n: Required sample size
- Z: 1.96 (standard normal distribution value at 95% confidence interval)
- P: Anticipated prevalence (fatigue in MS ~75% from previous literature)
- d: Absolute precision (5% margin of error)

Calculating, we obtained:

$$N = \frac{1.96^2 \times 0.75 \times (1-0.75)}{0.05^2 \approx 286}$$

Hence, a total of 286 MS patients participated.

Data Collection Tools

Data collection involved a standardized demographic questionnaire (age, gender, education, marital status, disease duration, MS type, Expanded Disability Status Scale scores, medications). Fatigue was measured with the validated Fatigue Severity Scale (FSS), a nine-item self-report measure of the severity and impact of fatigue on daily functioning. QoL was measured with the Multiple Sclerosis Quality of Life-54 (MSQoL-54) questionnaire, which measures QoL in physical health, emotional health and several MS-specific subdomains. Both questionnaires have demonstrated validity and reliability in MS populations and were translated into the participants' native language.

Data Collection Procedure

Participants were approached individually during regular clinical appointments. Following a detailed explanation and obtaining informed consent, demographic and clinical data were collected using standardized interviews and verification of medical records. Participants thereafter filled out the FSS and MSQoL-54 questionnaires independently, or with assistance if necessary, in order to reduce interference from investigators.

Quantitative Analysis

Data analysis was performed with SPSS software (version 25.0). Descriptive statistics, such as means, standard deviations, frequencies and percentages, provided an overview of demographic and clinical factors. Pearson's correlation coefficient determined the correlation between fatigue and quality of life (QoL) dimensions. Independent-sample t-tests, one-way ANOVA and chi-square tests were applied to compare differences in QoL and fatigue across demographic and clinical groups. Multivariate linear regression analysis was performed to determine predictors of poor QoL and fatigue, with $p<0.05$ set for statistical significance.

RESULTS

The demographic data (Table 1 and Figure 1, respectively) revealed that the participants' mean age was 38.4±9.6 years, with a range of 20 to 64 years. Females were more in number at 60.8% and males were 39.2%. Educationally, the majority of participants had graduate education (36.7%), followed by secondary (31.1%), postgraduate (21.0%) and primary education (11.2%). When marital status was considered, 66.1% were married, 28.7% single and a small number of 5.2% divorced or widowed.

Clinical features (Table 2 and Figure 2, respectively) showed a mean duration of disease of 7.2±5.1 years (range, 0.5-25 years). The Expanded Disability Status Scale (EDSS) score was 3.5±1.8, with most of the patients being classified as having mild disability (51.7%), followed by moderate (36.7%) and severe disability (11.6%). Relapsing-remitting MS was the most frequent form of MS observed (63.6%), followed by secondary progressive (23.4%) and primary progressive (12.9%) forms. For medication use, 54.6% had taken immunomodulators, 23.4% had taken immunosuppressants and 22.0% had symptomatic treatment.

Table 1: Demographic characteristics of study participants

Characteristic	Category	n (%) or Mean±SD
Age (years)	Mean	38.4±9.6
	Range	20-64
Gender	Male	112 (39.2%)
	Female	174 (60.8%)
Education Level	Primary	32 (11.2%)
	Secondary	89 (31.1%)
	Graduate	105 (36.7%)
	Postgraduate	60 (21.0%)
Marital Status	Married	189 (66.1%)
	Single	82 (28.7%)
	Divorced/Widowed	15 (5.2%)

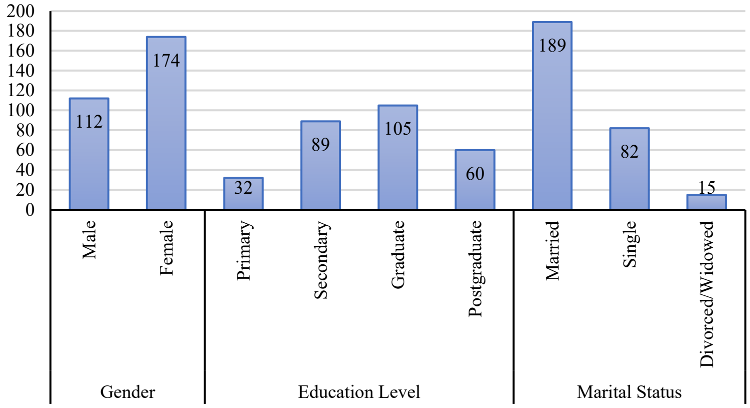

Figure 1: Graphical representation of demographic characteristics of study participants

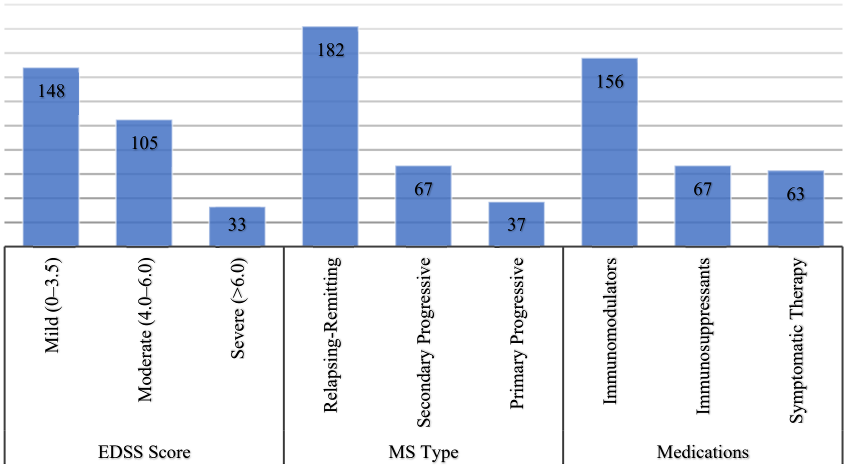

Figure 2: Graphical representation of clinical characteristics

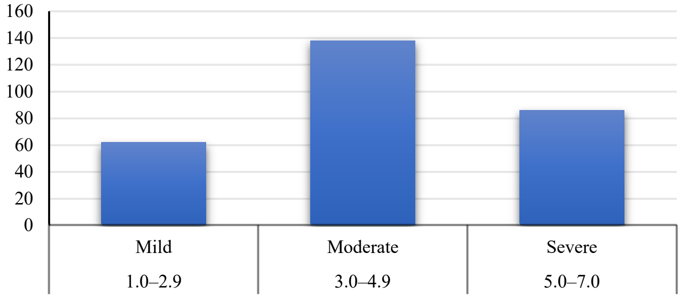

Figure 3: Graphical representation of distribution of FSS scores

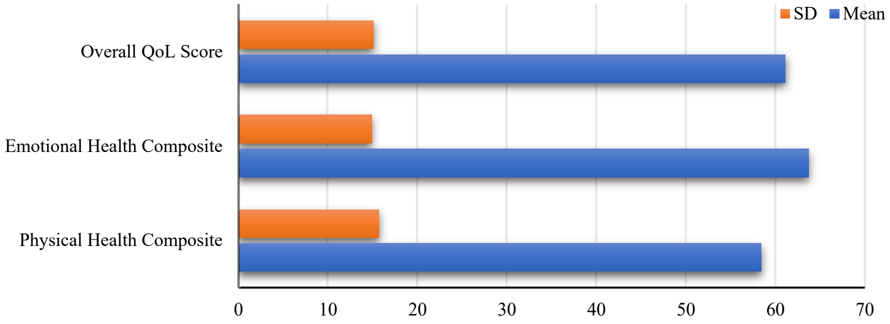

Figure 4: Graphical representation of distribution of MSQoL-54 scores

Table 2: Clinical characteristics

Characteristic	Category	n (%) or Mean±SD
Disease Duration (years)	Mean	7.2±5.1
	Range	0.5-25
EDSS Score	Mean	3.5±1.8
	Mild (0-3.5)	148 (51.7%)
	Moderate (4.0-6.0)	105 (36.7%)
	Severe (>6.0)	33 (11.6%)
MS Type	Relapsing-Remitting	182 (63.6%)
	Secondary Progressive	67 (23.4%)
	Primary Progressive	37 (12.9%)
Medications	Immunomodulators	156 (54.6%)
	Immunosuppressants	67 (23.4%)
	Symptomatic Therapy	63 (22.0%)

Table 3: Distribution of fatigue severity scale (FSS) scores

FSS Score Range	Severity	n (%)
1.0-2.9	Mild	62 (21.7%)
3.0-4.9	Moderate	138 (48.3%)
5.0-7.0	Severe	86 (30.1%)
Mean±SD	4.5±1.4	

Fatigue Severity Scale (FSS) ratings (Table 3 and Figure 3, respectively) exhibited a mean severity of 4.5±1.4. Predominant was moderate severity of fatigue (3.0-4.9 scores) in 48.3%, then severe fatigue (5.0-7.0 scores) in 30.1% and mild fatigue (1.0-2.9 scores) in 21.7%.

The MSQoL-54 scores (Table 4 and Figure 4, respectively) showed the overall impairment of global quality of life, with the total mean QoL score of 61.1±15.1. The physical health composite was 58.4±15.7 and the emotional health composite was 63.7±14.9, showing moderate impairment in both physical and emotional domains.

Correlational analysis (Table 5) indicated a significant inverse correlation between fatigue severity (FSS scores) and all the dimensions of MSQoL-54, i.e., physical health ($r = -0.63$, $p<0.001$), emotional health ($r = -0.58$, $p<0.001$) and total QoL scores ($r = -0.66$, $p<0.001$), reflecting fatigue's enormous negative impact on quality of life.

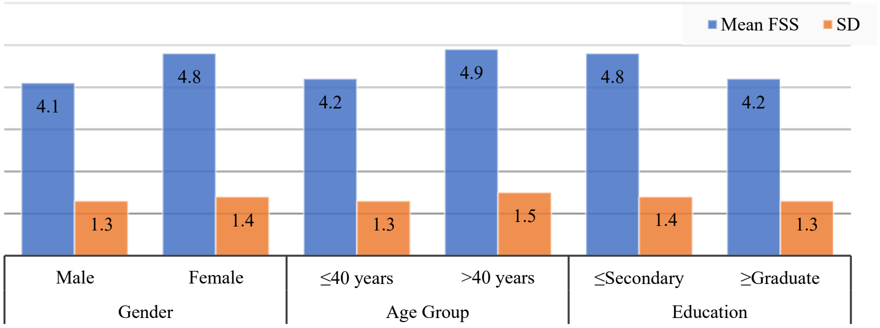

Figure 5: Graphical representation of comparison of fatigue scores across demographic groups

Table 4: Distribution of MSQoL-54 scores

QoL dimension	Mean±SD	Range
Physical health composite	58.4±15.7	18-92
Emotional health composite	63.7±14.9	22-95
Overall QoL score	61.1±15.1	20-93

Table 5: Correlation between FSS scores and MSQoL-54 dimensions

MSQoL-54 dimension	Pearson's r	p-value
Physical health composite	-0.63	<0.001
Emotional health composite	-0.58	<0.001
Overall QoL	-0.66	<0.001

Table 6: Comparison of fatigue scores across demographic groups

Demographic variable	Category	Mean FSS±SD	p-value
Gender	Male	4.1±1.3	0.002
	Female	4.8±1.4	
Age group	≤40 years	4.2±1.3	0.001
	>40 years	4.9±1.5	
Education	≤Secondary	4.8±1.4	0.013
	≥Graduate	4.2±1.3	

Table 7: Comparison of QoL scores across clinical parameters

Clinical variable	Category	Physical QoL (Mean±SD)	Emotional QoL (Mean±SD)	Overall QoL (Mean±SD)	p-value
Disease duration	≤5 years	64.7±14.2	68.1±13.9	66.4±13.5	<0.001
	>5 years	52.8±15.8	57.3±15.2	55.0±15.5	
EDSS scores	Mild (≤3.5)	67.9±13.4	70.5±12.7	69.2±12.9	<0.001
	Moderate (4.0-6.0)	54.6±13.2	59.0±14.1	56.8±13.7	
	Severe (>6.0)	43.1±11.9	49.5±12.2	46.3±12.1	
MS type	Relapsing-remitting	64.5±14.1	68.9±13.2	66.7±13.7	<0.001
	Secondary progressive	49.8±13.8	55.1±14.4	52.4±14.1	
	Primary progressive	46.5±12.1	50.2±12.8	48.4±12.5	

Comparison of fatigue scores between demographic groups (Table 6 and Figure 5, respectively) revealed significantly higher fatigue in females (mean FSS score: 4.8±1.4) compared to males (4.1±1.3, p = 0.002). Older subjects (>40 years) also reported significantly higher fatigue (4.9±1.5) compared to younger subjects (≤40 years; 4.2±1.3, p = 0.001). Lower education level (≤secondary education) was also associated with higher fatigue scores (4.8±1.4, p = 0.013).

Compared with clinical assessments (Table 7 and Figure 6, respectively), lower QoL scores on physical, emotional and total scales were strongly correlated with increased disease duration (>5 years, p<0.001), higher EDSS scores (p<0.001) and progressive MS subtypes versus relapsing-remitting MS (p<0.001). Patients with severe disability and with progressive disease subtypes had the lowest QoL scores.

Multivariable linear regression (Table 8) determined independent predictors of poor QoL and severity of fatigue. Increased EDSS scores (β = -2.43, p<0.001), increased duration of disease (β = -1.17, p<0.001), progressive form of MS (β = -8.94, p<0.001), increased scores of fatigue severity (β = -4.89, p<0.001), female gender (β = -3.75, p = 0.010), increased age (β = -2.91, p = 0.011) and lower education level (β = -2.24, p = 0.041) significantly predicted poor QoL outcomes.

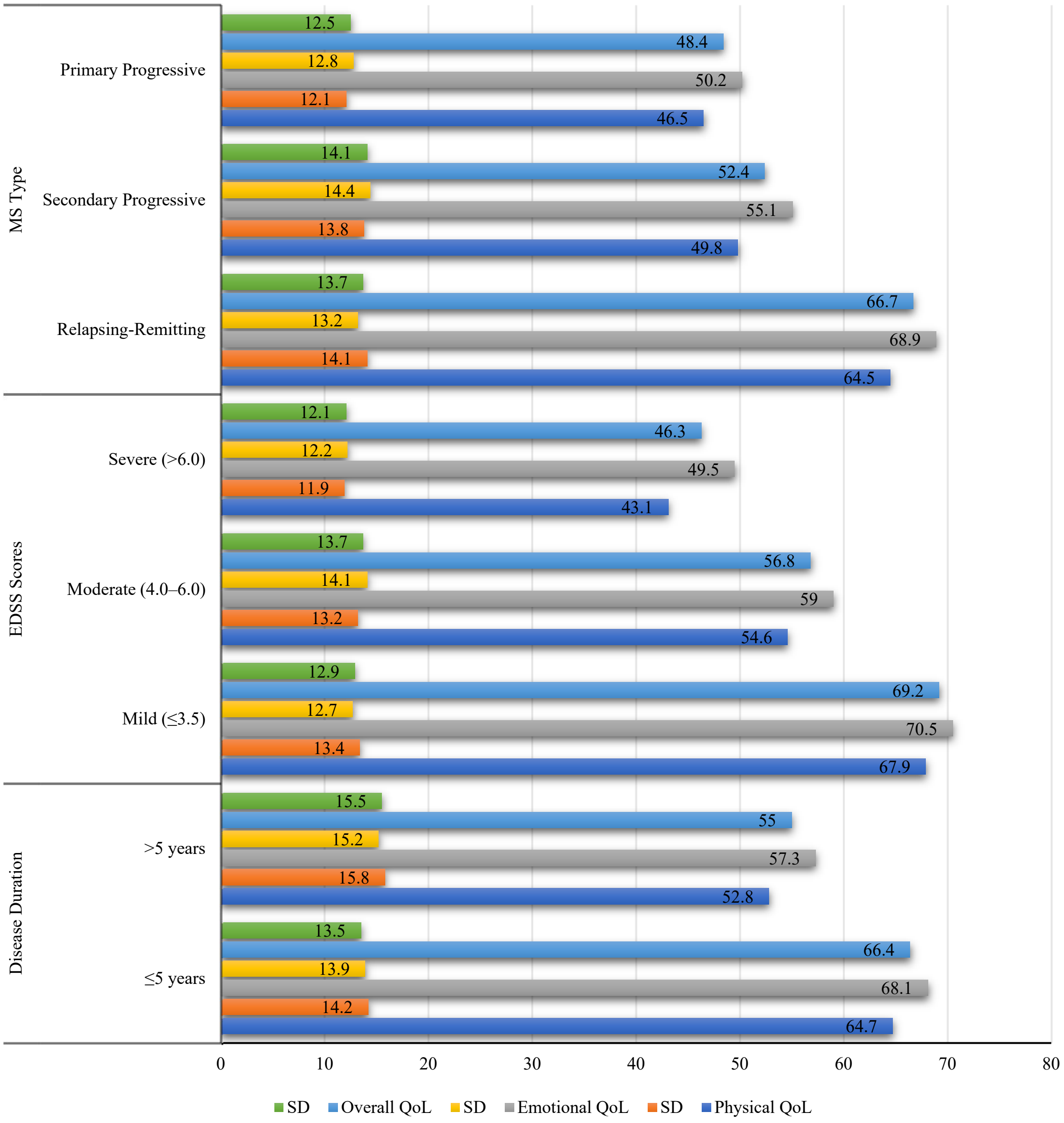

Figure 6: Graphical representation of comparison of QoL scores across clinical parameters

Table 8: Multivariate linear regression analysis

Predictor	β-Coefficient	95% CI	p-value
EDSS score	-2.43	-3.15, -1.72	<0.001
Disease duration (years)	-1.17	-1.72, -0.62	<0.001
MS type (Progressive)	-8.94	-13.2, -4.68	<0.001
FSS score	-4.89	-6.01, -3.77	<0.001
Female gender	-3.75	-6.59, -0.91	0.010
Age (>40 years)	-2.91	-5.12, -0.70	0.011
Education (≤Secondary)	-2.24	-4.39, -0.09	0.041

DISCUSSION

The current study extensively investigated fatigue and QoL in MS patients, with marked impairment in both. In line with earlier research, fatigue was also found to be one of the most disabling and common symptoms that had a detrimental effect on the daily life, social life, work responsibilities and general QoL of the patients. The high rate of severe fatigue found is consistent with earlier research studies determining the role of fatigue as a key determinant of the course of MS, rather than clinical measurement of disability.

Fatigue in MS is typically characterized by patients as one of the most common and labile symptoms, typically rated as more disabling than pain or mobility impairment. In contrast to normal fatigue, MS fatigue includes severe physical and mental tiredness that is not necessarily proportional to activity levels and is not relieved by rest to a sufficient degree. Pathological fatigue is multifactorial, resulting from complex interactions between neuroinflammatory processes, demyelination, neuroendocrine changes and psychosocial stressors [19]. The therapeutic difficulty of fatigue in MS is not only due to its subjective nature but also due to the lack of standardized therapeutic protocols that effectively address both physiological and psychosocial determinants.

One of the newer fields of study is the potential role that diet may play in modulating fatigue severity. Ketogenic diets and anti-inflammatory diets, for instance, have been demonstrated to reduce fatigue through metabolic reprogramming and reduced neuroinflammation [19,20]. These diets can improve mitochondrial function and glucose metabolism and deliver neuroprotective benefits in the MS brain. Clinical trials of ketogenic and altered anti-inflammatory diets have produced promising reductions in fatigue, as well as improvements in cognitive clarity and emotional stability in MS patients, so that diet can be utilized as a low-cost, non-pharmacologic adjuvant therapy [19,20].

Exercise and physical activity, although oftentimes feared by fatigued patients, have ironically been two of the most powerful non-pharmacologic treatments for MS fatigue. Individualized exercise regimens, particularly those with resistance and endurance training, have had significant effects on fatigue and quality of life scores [21]. Individualized exercise to the patient's function and fatigue level minimizes worsening and maximizes psychological and physical effect. Astonishingly, studies have also identified the neuroplastic benefits of chronic physical activity, with findings of increased functional connectivity and reduced lesion burden in the brain with longer duration [21].

In addition to physical therapy, behavioral and psychosocial interventions are key elements of management strategies. Interventions like mindfulness-based interventions, Cognitive Behavioral Therapy (CBT) and guided imagery have been found to be beneficial in reducing perceived fatigue and improving the quality of life in multiple sclerosis patients [22,23]. These interventions are beneficial by promoting emotional resilience, reducing the cognitive burden of stress and anxiety and providing a sense of greater autonomy over symptom control. The intervening role of psychological well-being between fatigue and quality of life is increasingly being seen as a key point of emphasis for holistic care. Yet another promising area is integrative and neuromodulation therapies.

Pulsed electromagnetic field therapy and transcranial electrical stimulation were found to show preliminary success in decreasing fatigue severity and mobility in MS patients, though evidence is limited [24]. Similarly, complementary therapies such as Swedish massage, mechanical hippotherapy and traditional Iranian dietary habits are being studied for their possible efficacy in treating fatigue, mood and sleep-each of which is greatly connected with the overall QoL in MS [25,26].

Furthermore, new digital health platforms and telerehabilitation interventions are transforming the provision of fatigue management. Internet-delivered CBT, home physio and online education on fatigue have been linked with high adherence and large treatment effects on patient-reported fatigue and emotional functioning, especially in situations where face-to-face care is not feasible [27]. These interventions provide patients with direct feedback and skills for behavior, bridging the gap between professional advice and self-management in everyday life.

Our findings were in agreement with Saxby *et al.* [28], who conducted a 12-month lifestyle intervention trial and observed a significant improvement in mental quality of life (MSQoL-54 mental component: $\Delta = 0.24$, 95% CI 0.01-0.47, $p = 0.04$) and fatigue (MFIS: $\Delta = -7.26$, 95% CI -13.3 to -1.18, $p = 0.02$). Their population was restricted to early-stage multiple sclerosis patients who did not choose to receive disease-modifying therapies, while our study was conducted in a more general clinical population.

Our finding that greater fatigue and lower educational level were predictive of worse QoL was also reported by Reece *et al.* [29], who reported that clinically significant fatigue was linked with 10% loss of digital course attendance. They also reported that university-level education raised commencement by 19%, as in our finding that lower educational level ($\beta = -2.24$, $p = 0.041$) was predictive of worse QoL.

Ryerson *et al.* [30] contrasted natalizumab administered every six weeks with every four weeks and had no difference in Neuro-QoL fatigue scores between groups (LSM difference = 0.52, $p = 0.292$). This contrasted with our own study, where fatigue had a statistically significant and independent effect on QoL outcomes in all areas.

Hochsprung *et al.* [31] conducted a review on pulsed electromagnetic field therapy and reported improvement in subjective outcomes such as pain and rest but no statistically significant differences between the treatment and placebo groups. Our study also found that while subjective fatigue was both common and significant, its detection and management needed measures beyond physical intervention alone, hence further reinforcing the necessity of keeping patient-reported outcomes at the top of research as well as practice priorities.

Motl *et al.* [32] further validated our findings by showing that an intervention of physical activity had a significant effect on decreasing FSS scores ($p<0.01$) and MFIS physical scores ($p<0.05$). Our hypothesis that fatigue is not only a common symptom but also one that can be modified, especially by organized behavior interventions, was confirmed by their study.

On the other hand, Khadadah *et al.* [33] conducted a randomized trial investigating the use of CPAP in multiple sclerosis patients with sleep apnea and no statistically significant improvement in FSS scores was found after six months ($p = 0.09$), even though sleepiness scores were improved at three months ($p = 0.03$). These results emphasized that fatigue is not only associated with comorbid sleep disorders, supporting our findings that fatigue in multiple sclerosis is complex and inherently associated with the progression of the disease.

Petrou *et al.* [34] examined the cognitive effect of GranaGard on multiple sclerosis patients and found improved verbal memory (CVLT-II z-score: 0.891 to 1.415, $p = 0.012$); however, no significant differences were observed in fatigue measurement. Their results stressed that cognitive therapy may enhance certain functional items but not fatigue, thereby proving our hypothesis that fatigue is a prominent and independent determinant of quality of life in patients with multiple sclerosis.

Limitations to this research include its cross-sectional design, in that causality or temporal relationship between fatigue and QoL cannot be determined. Convenience sampling also may influence generalizability. Longitudinal designs and sampling of larger size are called for in future research to further confirm these results as well as respond to interventions to aid fatigue management and QoL.

CONCLUSIONS

This cross-sectional study reports widespread impairment of QoL and disabling fatigue in MS patients again showing the central role of fatigue as a main etiology for reduced satisfaction with life and functioning. Demographic and clinical factors influence the results heavily and individualized, multidisciplinary treatment strategies are indicated. Active monitoring of fatigue and assessment of QoL need to be a top priority for health care providers and incorporated into patient-specific care plans to maximize symptom control and patient health. Longitudinal studies to determine causality and assess the quality of interventions to enhance QoL and fatigue control in MS patients are indicated in the future.

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