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# Multidimensional Impairment in Multiple Sclerosis—Physical Disability, Cognitive Dysfunction, Sleep Disturbance, Fatigue, Depression, and Their Impact on Quality of Life: Evidence of a Common Pathological Pathway

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Article

# Multidimensional Impairment in Multiple Sclerosis—Physical Disability, Cognitive Dysfunction, Sleep Disturbance, Fatigue, Depression, and Their Impact on Quality of Life: Evidence of a Common Pathological Pathway

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## Abstract

**Background:** Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, that can lead to physical and cognitive disability, fatigue, depression, and sleep disturbance, all of which may impair quality of life (QoL). While physical disability is well known influencing the QoL, the relative contributions of cognitive impairment, fatigue, and sleep quality remain incompletely defined. **Objectives:** To evaluate the relationship between QoL, physical and cognitive disability, sleep quality, fatigue, and depression in people with MS (PwMS), and to explore phenotype-specific differences between relapsing and progressive forms. **Methods:** In this monocentric cross-sectional study, 112 PwMS (77 women, mean age 38.1 years) underwent physical assessment (EDSS, MSFC), cognitive testing (SDMT, PASAT, MoCA, MMSE), and QoL evaluation (MSIS-29, EQ-5D, EQ-VAS, MSNQ). A subgroup of 29 patients also completed the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Modified Fatigue Impact Scale (MFIS), and Beck Depression Inventory (BDI). Correlation, group analyses were performed. **Results:** Progressive MS patients showed greater physical disability (mean EDSS 5.8 vs. 2.6,  $p < 0.001$ ), poorer cognitive performance, and lower QoL. Across the cohort, QoL strongly correlated with physical disability (EDSS) and cognitive performance (SDMT), physical measures showing stronger associations. In relapsing MS, physical and cognitive impairment were linked to reduced QoL, whereas in progressive MS, physical disability predominated. In the sleep subgroup, poorer PSQI scores, longer sleep latency, and greater daytime sleepiness correlated with higher fatigue (MFIS), depressive symptoms (BDI), and reduced QoL (MSIS-29, EQ-5D). **Conclusions:** QoL in MS reflects the combined burden of physical disability, cognitive impairment, fatigue, depression, and poor sleep quality, with phenotype-specific patterns. While physical disability is the main QoL determinant in progressive MS, cognitive deficits with slowed processing speed play an important role in relapsing MS. Comprehensive, multidimensional assessment, including sleep and mood screening, may support individualized management strategies in MS.

**Keywords:** multiple sclerosis; quality of life; cognitive impairment; physical disability; fatigue; sleep quality; depression; patient-reported outcomes

## 1. Introduction

The concept of quality of life reflects the significance and evaluation of life by an individual. It can result from a personal and holistic assessment of one's own life, and depends on the harmonious

fulfillment of human needs, including health. In medicine, quality of life refers to an individual's physical, psychological, and social well-being, as well as their ability to carry out daily activities [1].

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system and is the most common neurological disease in the young adults, with onset most frequently occurring between the second and fourth decades of life [2]. MS leads to both physical and cognitive disability in this population [3], with a significant impact on individual life and society [4]. Axonal loss is an important component of disease progression, a phenomenon underlying disability in this condition. Therefore, evaluating the quality of life of this population is important, as it reflects the extent of the disease's impact on an individual level [5].

The incidence and prevalence of MS have increased in recent years, even in regions previously considered low risk. This trend is associated with improvements in paraclinical evaluation techniques essential to the diagnostic process [6], as well as improved recognition capabilities and revision of diagnostic criteria [7].

To quantify neurological damage, clinical scales are used to measure the degree of clinical impairment and to assess therapeutic response (especially in clinical studies) [8]. The most widely used clinical scale is the EDSS (Expanded Disability Status Scale), developed by J. Kurtzke in 1983, after the clinical experience with the veterans of World War II, measuring disability across different functional scales [9].

However, the EDSS inadequately captures cognitive impairment, present in over 40% of MS patients, prompting the development of a more multidimensional scale in 1999: the MSFC (Multiple sclerosis Functional Composite) [10].

The MSFC consists of three subscales assessing lower limb function (Timed 25 Foot Walk, T25FW), upper limb function (Nine Hole Peg Test, 9HPT), and cognitive performance regarding attention, working memory and mathematical calculation domains (Passed Auditory Serial Addition Test, PASAT) [11].

Early clinical observations of frequent cognitive dysfunction in MS [12], led to the development of more specific tools to assess various cognitive domains. One such tool is the BICAMS (Brief International Cognitive Assessment for MS), composed of Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test – II (CVLT-II), and the Brief Visuospatial Memory Test – Revised (BVM-T-R) [13].

Cognitive impairment in MS often begins with deficits in attention and information processing speed, and can progress to difficulties in working memory, planning, and decision-making [14]. These deficits tend to worsen as the disease progresses, correlating with disease duration, increased physical disability, and reduced cognitive reserve [15,16].

Objective tools like the Montreal Cognitive Assessment (MoCA) [17], have demonstrated utility in identifying cognitive dysfunction in MS across several studies [18]. MoCA is widely validated and used in multiple neurological conditions [19,20]. Another frequently used screening tool is the Mini-Mental State Examination (MMSE), which provides a general assessment of cognitive status by evaluating orientation, attention, memory, language, and visuospatial skills. Although MMSE is less sensitive than MoCA in detecting subtle cognitive deficits - particularly in early or mild cases of MS - it remains a commonly used instrument in clinical settings due to its simplicity and familiarity [21].

Subjective changes in cognition, can also be captured by self-report tools like the Multiple Sclerosis Neuropsychological (MSNQ), which evaluates patient-perceived changes in cognitive status over the previous three months [22].

Quality of life in MS is typically assessed using self-reported questionnaires, aiming to capture the multiple deficits associated with the disease. Among the most commonly used are the Multiple Sclerosis Impact Scale (MSIS), and the Modified Fatigue Impact Scale (MFIS). MSIS- 29 evaluates the patient's perceived impact of MS on daily life over the past two weeks, with a total score between 29 and 145 [23]. MFIS assesses fatigue experienced in the past four weeks, covering physical, cognitive, and psychosocial dimensions, with a total score ranging from 0 to 84 [24].

In addition to MS-specific tools, the EuroQol five-dimension index score (EQ-5D), a general health-related quality of life questionnaire developed by the EuroQol group, is also used. It evaluates five health dimensions with different levels of impairment (3-5 levels): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[25]. Along with these questions, the patient gives himself a grade from 0 to 100, the limits being lower as the worst state of health and higher as the best state of health – EuroQol VAS (EQ VAS) scale [26,27].

Sleep, as essential component of daily well-being [28], is frequently disrupted in individuals with MS, particularly in association with fatigue, a commonly reported symptom. Recent studies support the presence of impaired sleep patterns in PwMS [29,30].

Sleep quality is defined by the individual's subjective satisfaction with their sleep experience. It includes parameters such as sleep efficiency, latency, duration, and frequency of awakenings after sleep onset [31]. The Pittsburgh Sleep Quality Index (PSQI), a validated self-report instrument, is widely used to assess these aspects of sleep [32,33]. The daytime consequences of poor sleep are captured using the Epworth Sleepiness Scale (ESS), a self-report questionnaire which measures daytime somnolence. Its score ranges from 0 to 24, with score above 13 indicating moderate, and score above 16 indicating severe daytime sleepiness [34].

Depression is closely related with both sleep disturbance and fatigue in PwMS, each of these symptoms being capable to be influenced and amplified one by another. This triad often creates a complex, that significantly can impact quality of life. Among the available tools, the Beck Depression Inventory (BDI), is one of the most practical and widely self-report instruments for assessing the severity of depressive symptoms in PwMS. It provides a quick, standardized, and sensitive measure of depression, facilitating its recognition and correlation with other symptoms such as fatigue and poor sleep quality [35,36].

Importantly, all these features - physical disability, cognitive dysfunction, fatigue, sleep disturbance, depression, and impaired quality of life - are ultimately linked to the underlying neuropathological hallmark of multiple sclerosis: axonal injury [37]. Axonal damage, resulting from inflammatory demyelination and neurodegenerative processes, represents the key driver of clinical symptoms and long-term neurological disability in MS. Therefore, assessing quality of life and cognitive function in MS not only reflects symptomatic burden but also indirectly captures the extent of axonal injury and disease progression [38,39].

## 2. Materials and Methods

### 2.1. Study Objectives

**The primary objective** of the study was to evaluate the self-reported quality of life in patients with multiple sclerosis (PwMS), specifically in relation to cognitive impairment as assessed by multiple neuropsychological tests. We aimed to determine whether differences in quality of life could be identified between cognitive and physical disability across different clinical phenotypes of the disease.

To this end, we conducted an exhaustive and objective evaluation of a representative cohort of PwMS. Physical disability was quantified using the Expanded Disability Status Scale (EDSS) and the physical subscales of the Multiple Sclerosis Functional Composite (MSFC), while cognitive impairment was assessed using standardized tests such as the Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), Montreal Cognitive Assessment (MoCA), and Mini-Mental State Examination (MMSE).

**A second objective** of the study was to assess the impact of MS on sleep quality using the Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness using the Epworth Sleepiness Scale (ESS). Additionally, we investigated correlations between specific components of sleep disturbance and relevant clinical factors. Fatigue and its subcomponents were assessed using the Modified Fatigue Impact Scale (MFIS), while depressive symptoms were evaluated with the Beck Depression Inventory (BDI).

We conducted a quantitative and qualitative assessment of the sleep in PwMS by analyzing sleep parameters over the last month, including sleep and wake times, total sleep duration, sleep latency, and nighttime disturbances (e.g. pain or nocturia). These variables were evaluated alongside physical and cognitive disability, depression severity, daytime sleepiness, and fatigue level, all measured using validated and dedicated scales.

## 2.2. Ethical Considerations and Data Collections

All clinical evaluations were part of the patient annual follow-up and all data were collected from patients records of the National Program for Multiple Sclerosis. Neurological assessments and questionnaire completion were performed outside of any clinical relapse and in the absence of corticosteroid treatment, ensuring that results reflected a stable phase of the disease.

## 2.3. Methods

### Study Population

To address the multiple aspects of quality of life in PwMS, a disease with a highly heterogeneous clinical presentation, we analyzed clinical and demographic data from the database of the Multiple Sclerosis Center of Elias University Emergency Hospital, a monocentric cohort. The evaluations were conducted in two phases.

At the initial assessment, patients underwent thorough a clinical evaluation, including measurement of physical disability, using EDSS score. Motor function was evaluated through physical subtests of MSFC, specifically the T25FW for lower limbs functions and the 9HPT for the upper limbs function (dominant and non-dominant hand).

Cognitive assesment included both general and MS specific tool. General cognitive function was screened using the MoCA and the MMSE scores. To specifically capture the cognitive domains frequently affected in MS, we also administered the PASAT and the SDMT scores.

To evaluate quality of life, we used different self-report questionnaires. General health-related quality of life was assessed using the EQ-5D index score and the EQ VAS scale. The disease specific impact on quality of life was measured with the MSIS-29 scale. To identify self-perceived cognitive difficulties, patients completed the MSNQ questionnaire.

Patients were classified according to clinical phenotype into two main categories: **relapsing forms** including clinically isolated syndrome (CIS) and relapsing-remitting multiple sclerosis (RRMS), and **progressive forms** including secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (PPMS).

In total, 112 patients were included in the study: 77 females and 35 males. Of these, 87 were classified as having relapsing forms and 25 as having progressive forms in MS.

### Sleep Sub-Study

The assess sleep quality, a subgroup of 29 of MS patients was selected. These patients completed the PSQI index and ESS scale. Additional assessments included the MFIS scale and Beck Depression Inventory (BDI), in order to better define the link between sleep quality, fatigue and depression in MS.

## 2.4. Data Analysis

Data acquisition, centralization, and the statistical analysis were performed with Statistical Package for the Social Sciences (version 26.0, SPSS Inc, Chicago), while the manuscript was drafted using Office Microsoft Word 2020.

The following analytical and descriptive statistical methods were applied: **Pearson correlation coefficient** - to evaluate direct or inverse proportional relationship between two sets of quantitative variables,, **Levene two sample t test** – to compare means between two groups, and **ANOVA**

**parametric test** - to analyze the relationship between dependent variable and multiple categories of independent variables.

### 3. Results

#### 3.1. Demographic and Clinical Characteristics

The study included 112 patients diagnosed with MS: 77 women (68.7%) with a mean age of 40.1 years and 35 men (31.3%) with a mean age of 33.6 years. The average age across the cohort was 38.1 years. Most patients (n=87, 77.7%) were diagnosed with relapsing MS forms (CIS or RRMS), while 25 patients (22.3%) had progressive MS forms (SPMS and PPMS).

As shown in Table 1, women were more frequently affected in both relapsing and progressive subgroups. However, men were proportionally more represented in the progressive group (40%) compared to the relapsing group (28.7%).

The mean EDSS score across the cohort was 3.34 (range: 0-7.0), with women showing a slightly higher mean EDSS (3.4) compared to men (3.3). Among clinical subtypes, patients with relapsing forms had a mean EDSS of 2.6, while those with progressive forms had a significantly higher mean EDSS of 5.8.

**Table 1. Demographic and clinical data.**

	N	F (N, p%)	M (N, p%)	EDSS (mean, min-max)
<b>Total</b>	112	77 (68.7%)	35 (31.3%)	3.339 (0-7.0)
<b>Average date (min-max)</b>	38.11 (16-60)	40.16 (18-60)	33.60 (16-55)	
<b>Relapsing forms group</b>	87 (77.7%)	62 (71.3%)	25 (28.7%)	2.609 (0-6.0)
<b>Progressive forms group</b>	25 (22.3%)	15 (60%)	10 (40%)	5.880 (3.0-7.0)

Abbreviations: N – number, p% - percent, EDSS – Expanded Disability Status Scale.

#### 3.2. Cognitive Performance and Quality of Life Assessments

The results from cognitive assessment (SDMT, PASAT, MoCA, MMSE) and quality of life questionnaires (MSIS-29, MSNQ, EQ-5D index, EQ VAS) for the whole cohort and sub-groups, are summarized in Table 2. Patients with progressive MS had consistently lower scores on all cognitive measures and reported greater impairment in quality of life compared to those with relapsing forms ( $p < 0.001$  – Levene t test).

**Table 2. The results obtained from the cognitive evaluations and the reporting scales of the quality of life (Levene test  $p < 0.01$ ).**

	Group 1 Relapsing forms	Group 2 Progressive forms	p value (95% confidence interval)
<b>Total N</b>	112	87	25

<b>SDMT (mean)</b>	38.25 (2-65)	41.61	25.52	<0.001
<b>PASAT (mean)</b>	43.32 (8-60)	46.05	33.84	<0.001
<b>MoCA (mean)</b>	23.62 (5-30)	24.67	19.96	<0.001
<b>MMSE (mean)</b>	27.96 (16-30)	28.44	26.28	0.004
<b>MSIS 29 (mean)</b>	59.67	51.91	86.24	<0.001
<b>MSNQ (mean)</b>	15.89	13.92	22.68	0.009
<b>EQ-5D index (mean)</b>	2.32	1.69	4.48	<0.001
<b>EQ VAS (mean)</b>	71.04	76.21	53.24	<0.001

Abbreviations: SDMT - Symbol Digit Modalities Test, PASAT - Passed Auditory Serial Addition Test, MoCA – Montreal Cognitive Assessment, MMSE – Mini Mental State Examination, MSIS 29 - Multiple Sclerosis Impact Scale 29, MSNQ- Multiple Sclerosis Neuropsychological, EQ-5D- EuroQol five-dimension index score, EQ-VAS- EuroQol Visual Analogue Scale.

### 3.3. Correlations Between Physical Disability and Cognitive Function Measures

We made correlations after the clinical evaluation. Significant negative correlations were found between EDSS and cognitive test scores across the entire cohort ( $p=0.0001$ ) indicating that increased physical disability is associated with poorer cognitive performance. The strongest correlation was observed between EDSS and SDMT ( $r= -0,587$ ), followed by PASAT ( $r= -0.466$ ), MMSE ( $r= -0.400$ ), and MoCA ( $r= -0.390$ ) (Table 3). Patients showed changes in the information processing speed and impairment of the working memory in particular.

**Table 3. EDSS correlation with cognitive tests (Pearson correlation  $p<0.001$ ).**

		<b>SDMT</b>	<b>PASAT</b>	<b>MoCA</b>	<b>MMSE</b>
			<b>(60)</b>	<b>(30)</b>	<b>(30)</b>
<b>EDSS</b>	p	0.0001	0.0001	0.0001	0.0001
	r	-0,587	-0.466	-0.390	-0.400

Abbreviations: SDMT - Symbol Digit Modalities Test, PASAT - Passed Auditory Serial Addition Test, MoCA – Montreal Cognitive Assessment, MMSE – Mini Mental State Examination.

### 3.4. Correlations Between MSIS-29 and Quality of Life Measures

MSIS-29 scores showed statistically significant positive correlations with MSNQ score ( $r=0.622$ ,  $p=0.0001$ ) and EQ-5D index score ( $r= 0.825$ ,  $p=0.0001$ ). In contrast, a strong negative correlation was found between MSIS-29 and EQ VAS scale ( $r= -0.774$ ,  $p= 0.0001$ ), indicating that a higher self-perceived disease burden is associated with a lower subjective health (Table 4).

**Table 4. Correlation between MSIS and self-report scales (Pearson correlation  $p<0.001$ ).**

		<b>MSNQ (60)</b>	<b>EQ-5D index (score)</b>	<b>EQ (VAS score)</b>
<b>MSIS – 29 (145)</b>	p	0.0001	0.0001	0.0001
	r	0.622	0.825	-0.774

Abbreviations: MSIS 29 - Multiple Sclerosis Impact Scale 29, MSNQ- Multiple Sclerosis Neuropsychological, EQ-5D- EuroQol five-dimension index score, EQ-VAS- EuroQol Visual Analogue Scale.

### 3.5. Correlations Between Quality of Life scores, Cognitive Function and Physical Disability Measures

Across the whole cohort, MSIS-29, EQ-5D index score and EQ VAS scores were significantly correlated with both cognitive and physical disability measures (Table 5). Physical disability score (EDSS, T25FW, 9HPT) showed stronger correlations with quality of life measures than cognitive tests. Cognitive performance (particularly SMDT and PASAT) also showed significant correlations with quality of life outcomes, but with slightly lower coefficients. We noted that for the entire cohort, that while both physical and cognitive impairments affect quality of life, physical disability may exert a stronger influence overall ( $r$  coefficient values are higher for the physical disability scales). The correlations were negative between the EQ VAS scores and physical disability measures, and positive between the EQ VAS scores and cognitive functions measures.

**Table 5. MSIS, EQ5D correlations with cognitive functions and physical disability measures (Pearson correlation  $p < 0.001$ ).**

		SDMT	PASAT (60)	MoCA (30)	MMSE (30)	EDSS	9HPT DH	9HPT NDH	T25FW
<b>MSIS – 29 (145)</b>	p	0.0001	0.0001	0.001	0.0001	0.0001	0.0001	0.0001	0.0001
	r	-0.544	-0.520	-0.314	-0.491	0.686	0.579	0.610	0.547
<b>EQ-5D index (score)</b>	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
	r	-0.574	-0.524	-0.375	-0.511	0.683	0.593	0.589	0.526
<b>EQ (VAS score)</b>	p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
	r	0.524	0.471	0.336	0.402	-0.683	-0.518	-0.542	-0.515

Abbreviations: SDMT - Symbol Digit Modalities Test, PASAT - Passed Auditory Serial Addition Test, MoCA – Montreal Cognitive Assessment, MMSE – Mini Mental State Examination, MSIS 29 - Multiple Sclerosis Impact Scale 29, EQ-5D- EuroQol five-dimension index score, EQ-VAS- EuroQol Visual Analogue Scale, EDSS – Expanded Disability Status Scale, 9HPT – 9 Hole Peg Test, DH - Dominant Hand, NDH- Non-Dominant Hand, T25FW -25 Foot Walk Test.

### 3.6. Subgroup Analysis: Relapsing vs Progressive Forms – Quality of Life, Physical Disability and Cognitive Function

After dividing the cohort into two sub-groups, regarding the clinical form, relapsing and progressive forms, we performed correlations for every sub-group. In the **relapsing MS group (1)**, there were significant negative correlations between EDSS and cognitive test scores particularly SDMT ( $r = -0.488$ ,  $p = 0.0001$ ), PASAT ( $r = -0.361$ ,  $p = 0.001$ ), MMSE ( $r = -0.294$ ,  $p = 0.006$ ), and with MoCA showed a trend ( $p = 0.053$ ), not reaching a statistical significance (Table 6).

In the **progressive MS group (2)**, although negative correlations were also noted between EDSS and cognitive test scores, they did not reach statistical significance – possible due to the smaller sample size.

**Table 6. Correlations between EDSS and cognitive functions tests (Pearson correlation).**

		SDMT	PASAT	MMSE	MoCA	
			(60)	(30)	(30)	
<b>1</b>	EDSS	p	0.0001	0.001	0.006	0.053
		r	-0.488	-0.361	-0.294	-0.208
<b>2</b>	EDSS	p	0.491	0.012	0.035	0.061
		r	-0.151	-0.492	-0.422	-0.380

Abbreviations: SDMT - Symbol Digit Modalities Test, PASAT - Passed Auditory Serial Addition Test, MoCA – Montreal Cognitive Assessment, MMSE – Mini Mental State Examination, EDSS – Expanded Disability Status Scale.

We continued the analysis of the quality of life for the two subgroups, making correlations between the quality of life score (MSIS-29, EQ-5D index and EQ VAS), cognitive tests scores (SDMT, PASAT, MoCA, MMSE) and physical disability measures (EDSS, T25FW, 9HPT). Quality of life scores (MSIS-29, EQ-5D, EQ VAS) in the **relapsing MS group** correlated significantly with both cognitive and physical disability measures. In the **progressive MS group**, only MSIS-29 and EQ-5D index scores were significantly correlated with EDSS ( $p = 0.003$  and  $p = 0.02$ ), with no significant correlations observed for cognitive scores (Table 7).

**Table 7. Correlations between quality of life questionnaires and cognitive tests, physical disability scores for group 1 - relapsing forms and group 2 - progressive forms (Pearson correlation).**

		SDMT	PASAT	MoCA	MMSE	EDSS	9HPT	9HPT	T25FW
			(60)	(30)	(30)		DH	NDH	
<b>1</b>	MSIS-29 (145)	p	0.0001	0.0001	0.173	0.0001	0.0001	0.0001	0.0001
		r	-0.496	-0.464	-0.148	-0.485	-0.583	0.423	0.500
	EQ-5D index (score)	p	0.0001	0.0001	0.056	0.0001	0.0001	0.0001	0.0001
		r	-0.476	-0.427	-0.207	-0.455	0.528	0.443	0.431
	EQ VAS (score)	p	0.0001	0.0001	0.086	0.003	0.0001	0.0001	0.0001

	r	0.488	0.380	0.186	0.312	-0.602	-0.408	-0.419	-0.499
2	<b>MSIS – P 29 (145)</b>	0.587	0.194	0.449	0.258	0.003	0.202	0.087	0.108
	r	-0.122	-0.269	-0.159	-0.235	0.576	0.264	0.349	0.391
	<b>ED-5D (score)</b>	0.186	0.086	0.087	0.050	0.002	0.089	0.029	0.519
	r	-0.286	-0.350	-0.349	-0.397	0.595	0.347	0.438	0.163
	<b>EQ VAS (score)</b>	0.951	0.221	0.307	0.209	0.092	0.969	0.317	0.763
	r	-0.014	0.254	0.213	0.260	-0.344	0.008	-0.208	-0.076

Abbreviations: SDMT - Symbol Digit Modalities Test, PASAT - Passed Auditory Serial Addition Test, MoCA – Montreal Cognitive Assessment, MMSE – Mini Mental State Examination, MSIS 29 - Multiple Sclerosis Impact Scale 29, EQ-5D- EuroQol five-dimension index score, EQ-VAS- EuroQol Visual Analogue Scale, EDSS – Expanded Disability Status Scale, 9HPT – 9 Hole Peg Test, DH - Dominant Hand, NDH- Non-Dominant Hand, T25FW -25 Foot Walk Test.

### 3.7. Subgroup Analysis: Sleep Quality

A subgroup of 29 patients (representing 32.48% of the group, 21F/8 B, mean EDSS=2.4), with relapsing MS forms, completed additional questionnaires to evaluate sleep quality (PSQI), daytime sleepiness (ESS), fatigue (MFIS), as well as depression (BDI).

There were statistically significant correlations between the quality-of-life assessment tests (MSIS-29, EQ5D score and EQ VAS score), and physical disability (EDSS, 9HPT, T25FWT) and cognitive function tests (SMDT, PASAT, MoCA, MMSE), as well as with those that assess fatigue, depression, daytime sleepiness, and sleep quality (MFIS, BDI, ESS and PSQI).

MSIS-29 scores in this subgroup correlated significantly with EQ-5D index and EQ VAS scores ( $p < 0.00001$ ), MFIS total score ( $p = 0.0002$ ), physical ( $p = 0.001$ ), and cognitive subscales ( $p = 0.0003$ ), BDI ( $p < 0.001$ ), ESS ( $p < 0.001$ ), sleep latency ( $p = 0.0009$ ), PSQI total score ( $p = 0.005$ ).

These results show the ability of the MSIS-29 to highlight multiple aspects of the quality-of-life in PwMS.

EQ VAS scores showed negative correlations with fatigue MFIS scores, physical MFIS ( $p = 0.002$ ,  $r = -0.556$ ), cognitive MFIS ( $p < 0.001$ ,  $r = -0.690$ ), indicating the importance of declared fatigue, both physical and cognitive, in the quality of life perceived by patients. (Table 8)

Depressive symptoms were associated with, longer sleep latency ( $p = 0.002$ ), earlier bedtimes ( $p < 0.0001$ ), increased daytime sleepiness ( $p = 0.003$ ), and increased fatigue ( $p < 0.0001$ ).

Daytime sleepiness (ESS) correlated positively with PSQI ( $p = 0.0001$ ,  $r = 0.55$ ), MFIS total ( $p = 0.0001$ ,  $r = 0.65$ ), and MFIS physical and cognitive subscales ( $p < 0.0001$ ,  $r = 0.70$  and  $p = 0.009$ ,  $r = 0.58$ , respectively). The declared fatigue, both physical and cognitive, correlates positively, statistically significant with the quality of sleep, PSQI score ( $p < 0.0001$ ).

Sleep latency also correlated with the PSQI score ( $p = 0.0006$ ), highlighting its impact on perceived sleep quality.

**Table 8. Correlations between quality of life questionnaires, cognitive tests, physical disability, fatigue, depression, daytime sleepiness, and sleep quality scores (Pearson correlation).**

		SDMT	PASAT	MoCA	MMSE	EDSS	9HPT	9HPT	T25FW	MFIS	MFIS	MFIS	BDI	ESS	PSQI
		(60)	(60)	(30)	(30)		DH	NDH		p	c	t			
MSIS-29 (145)	p	0.715	0.004	0.815	0.077	0.032	0.067	<0.001	0.064	0.001	0.0003	0.0002	<0.001	<0.001	0.005
	r	-0.071	-0.517	-0.045	-0.333	0.400	0.345	0.631	0.348	0.578	0.619	0.625	0.725	0.297	0.505
EQ-5D (score)	p	0.378	0.009	0.301	0.146	0.012	0.093	0.002	0.021	0.045	0.013	0.014	0.005	0.652	0.147
	r	-0.170	-0.474	-0.199	-0.277	0.458	0.318	0.550	0.426	0.376	0.454	0.415	0.504	0.078	0.276
EQ-VAS (score)	p	0.180	0.069	0.010	<0.001	0.008	0.179	0.005	0.104	0.002	<0.001	<0.001	0.029	0.115	0.049
	r	0.256	0.342	0.472	0.629	-0.482	-0.408	-0.504	-0.308	-	-0.690	-0.663	-0.406	-0.22	-0.36

0.556

Abbreviations: SDMT - Symbol Digit Modalities Test, PASAT - Passed Auditory Serial Addition Test, MoCA – Montreal Cognitive Assessment, MMSE – Mini Mental State Examination, MSIS 29 - Multiple Sclerosis Impact Scale 29, EQ-5D- EuroQol five-dimension index score, EQ-VAS- EuroQol Visual Analogue Scale, EDSS – Expanded Disability Status Scale, 9HPT – 9 Hole Peg Test, DH - Dominant Hand, NDH- Non-Dominant Hand, T25FW -25 Foot Walk Test, MFIS – Modified Fatigue Impact Scale, p physical, c – cognitive, t- total, BDI – Beck Depression Inventory, ESS – Epworth Sleepiness Scale, PSQI – Pittsburgh Sleep Quality Index.

### 3.8. ANOVA Analysis of Sleep Disturbance

Further ANOVA analysis was performed on responses from the PSQI related to sleep initiation and maintenance (no event, under 1 event, 1-2 events, 3 or more events per week during the last month). Patients who had difficulty falling asleep  $\geq 3$  times per week reported significantly higher scores on MSIS-29 ( $p=0.0005$ ), BDI ( $p=0.0006$ ), ESS ( $p=0.003$ ), and MFIS (physical  $-p=0.003$  and cognitive  $-p=0.0002$  components) (Table 8a). Thus, patients with sleep disturbances and prolonged sleep latency report greater depression, fatigue, and reduced quality of life in the context of multiple sclerosis.

Nocturnal awakenings also correlated with increased depression (BDI,  $p = 0.0007$ ) and fatigue (MFIS total,  $p = 0.0001$ ) (Table 8b). In most cases, these awakenings were attributed to nighttime disturbances such as pain or nocturia. Sleep maintenance disorders, characterized by nocturnal awakenings, are associated with increased depression and fatigue in PwMS.

**Table 9 PSQI: sleep latency/awakenings during night - ANOVA statistical analysis with quality of life, depression and fatigue measurements**

Table 9. a – Prolonged sleep latency - first 30 min.

Group	Nr	MSIS 29	BDI	ESS	MFIS p	MFIS c
NO	13	39.9	5.3	5.3	16.6	12.6
<1/Week	11	47.5	4.8	5.2	9.8	7.6
1,2/Week	1	106	20	12	39	29
$\geq 3$ /Week	4	77	22	13.25	36.5	30.75

p | 0.000572 0.000604 0.003256 0.000364 0.000212

Abbreviations: MSIS 29 - Multiple Sclerosis Impact Scale 29, MFIS - Modified Fatigue Impact Scale, p physical, c - cognitive, BDI - Beck Depression Inventory, ESS - Epworth Sleepiness Scale, PSQI - Pittsburg Sleep Quality Index.

**Table 9. b – Awakenings during night.**

Group	Nr	BD	MFIS t
NO	4	2.5	14
<1/Week	12	2.3	16.4
1,2/Week	4	16.26	47
>=3/Week	9	14.1	51.3
p		0.000734	0.000146

Abbreviations: MFIS - Modified Fatigue Impact Scale, t - total, BDI - Beck Depression Inventory.

## 4. Discussion

The demographic and clinical characteristics of our study group are consistent with known epidemiological patterns in MS [40]. Women represented the majority of cases, with a female-to-male ratio of 2.2:1 and a mean age of 38.1 years. This aligns with global data showing a higher incidence in women, especially in relapsing forms of the disease [41]. Notably, a higher proportion of men was observed in the progressive MS subgroup (40%) compared to the relapsing group (28.7%), reinforcing prior observations that male sex may be associated with a more aggressive disease course and worse prognosis [42]. The mean EDSS score of 3.3, reflects a population with moderate physical disability. Subgroup analysis revealed a significantly higher disability burden in patients with progressive MS (mean EDSS = 5.8) compared to those with relapsing MS forms (mean EDSS = 2.6), consistent with expected disease trajectories and previously published data [43–46].

Our findings demonstrate that quality of life (QoL) in MS patients is influenced by both physical and cognitive disability, regardless of the self-report tools used - whether general measurements like EQ-5D (including the VAS score) or disease-specific tools such as MSIS-29 and MSNQ [47,48]. This is consistent with prior studies, yet our analysis distinguishes itself through the comprehensive and objective evaluation of both physical (EDSS, MSFC) and cognitive (SDMT, PASAT, MoCA, MMSE) function, and their correlation with patient perceived QoL. In contrast to other studies focusing on one dimension, our approach offers a multifaceted perspective, incorporating both clinician and patient-reported outcomes [49–51].

Importantly, we observed that in relapsing MS forms, QoL is significantly impacted by both physical and cognitive deficits [52], particularly by early cognitive changes such as reduced information processing speed and impaired working memory [53]. In progressive forms, however, physical disability remains the dominant determinant of QoL [54]. These findings support the clinical relevance of distinguishing between MS phenotypes in patient management and rehabilitation strategies [55].

The impact of non-motor symptoms, such as sleep disturbances, fatigue, and depression, in QoL is well recognized [56]. In our study, sleep quality (assessed by using the PSQI and ESS in a subgroup) was found to be impaired, consistent with recent evidence [57]. Although the analysis was limited by the small sample size, we identified a multifactorial origin of poor sleep quality, involving pain, nocturia, fatigue, and mood disturbances. As shown in prior research, lesion location and axonal damage in sleep-regulating brain regions (e.g., hypothalamus, brainstem) likely contribute to this clinical picture [58,59].

The MSIS-29 proved especially valuable, as it incorporates dimensions often omitted by traditional disability scales, such as fatigue, sleep impairment, and depressive symptoms [60]. This supports its utility as a comprehensive QoL measure in clinical and research settings [61].

In line with previous literature, depressive symptoms were more prevalent in patients reporting daytime sleepiness and higher levels of physical and cognitive fatigue [62]. Depression not only affects QoL directly but also serves as a significant mediator of poor sleep quality, leading to sleep fragmentation and prolonged sleep latency [51,63]. Our findings emphasize the need for routine assessment and management of mood and sleep disorders in MS care.

The study's strengths include its broad, multidimensional design, integrating objective clinical tests (EDSS, MSFC, cognitive batteries) with validated self-report questionnaires (EQ-5D, MSIS-29, MFIS, PSQI, MSNQ) [64]. This allowed for phenotype-specific analysis, distinguishing the relative contributions of cognitive and physical disability to QoL in relapsing vs. progressive MS forms. Furthermore, the use of multiple cognitive instruments (including MoCA and MMSE) strengthens the reliability of the cognitive assessment. However, several limitations must be acknowledged. First, data on sleep, fatigue, and depression were not available for all patients, limiting the power of subgroup analyses. Second, the sleep-focused analysis was conducted on a small subset of 29 patients, which reduces the statistical power for analyzing sleep-related correlations and may limit the interpretation of those results. Third, the cross-sectional nature of the study without longitudinal follow-up may limit the ability to assess causal relationships or long-term progression of symptoms. Fourth, the single-center design may limit the possibility to generalize to broader or more diverse populations with different care settings, ethnic backgrounds, or health systems.

Additionally, the absence of neuroimaging data is a limitation, as it prevents direct correlation between lesion burden, axonal injury, and clinical symptoms.

Nonetheless, the observed associations between cognitive and physical disability and reduced QoL due to the presence of fatigue or sleep disturbance, are likely mediated by both inflammatory and neurodegenerative mechanisms, particularly axonal injury, which plays a central role in the progression of MS-related disability. Axonal damage underlies both physical disability and cognitive decline, reinforcing the need for neuroprotective strategies in MS management [61].

## 5. Conclusions

This study highlights the complex and interdependent relationships between physical disability, cognitive impairment, depression, fatigue, and sleep quality in multiple sclerosis. Quality of life in MS is not determined by a single factor but rather reflects the cumulative burden of multiple domains of dysfunction. While physical disability remains the primary determinant in progressive MS, cognitive deficits, particularly reduced information processing speed, play a more significant role in relapsing forms.

A contributor to these symptoms is axonal damage, which occurs early in the disease and underlies both motor and cognitive decline. Axonal degeneration, driven by inflammation and demyelination, is a key pathological hallmark of MS and correlates with irreversible neurological disability. It represents the biological basis through which physical and cognitive impairment contribute to poorer quality of life.

Given the multifactorial burden of MS, we recommend the routine use of comprehensive assessment tools such as the MSIS-29 and EQ-5D, supplemented by cognitive screening, sleep, and fatigue evaluation. Recognizing and addressing these interrelated factors can guide more personalized, multidisciplinary care strategies aimed to improve the lives of PwMS.

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