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Frequency of Cognitive Impairment in Multiple Sclerosis: Association with Neuro-Imaging Parameters and Disease Duration

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ABSTRACT

Cognitive impairment is a frequent but underrecognized feature of multiple sclerosis and contributes to functional decline. Early identification and association with clinical and neuroimaging markers may guide management. **Objectives:** To determine the frequency of cognitive impairment and its relationship with demographic, clinical, and MRI characteristics in multiple sclerosis. **Methods:** This cross-sectional study was conducted at the Department of Neurology, Punjab Institute of Neurosciences, Lahore, from May to December 2025. Seventy-one adults aged 18–50 years with multiple sclerosis, diagnosed according to the 2017 Revised McDonald Criteria, were enrolled. Brain MRI on a 3-Tesla system was evaluated for lesion characteristics and atrophy by a radiologist. Cognitive function was assessed using the Montreal Cognitive Assessment. **Results:** The mean age of participants was 35.08 ± 7.71 years, and the mean disease duration was 6.53 ± 3.24 years. The mean Montreal Cognitive Assessment (MoCA) score was 22.91 ± 5.87, and the mean total MRI lesion count was 16.07 ± 8.98. Cognitive impairment was found in 40.8%, including 21.,1% mild, 12.7% moderate, and 7.0% severe impairment. Relapsing-remitting multiple sclerosis was most common (69.0%), followed by secondary progressive (19.7%) and primary progressive (11.3%). Patients with impairment had older age (p=0.016) and longer disease duration (p=0.012). Cortical lesions and brain atrophy were significantly related to cognitive impairment. **Conclusions:** Cognitive impairment appeared as a frequent feature of multiple sclerosis and was related to advancing age, longer disease duration, and neuroimaging abnormalities.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating disorder of the central nervous system that typically affects adults in early to mid-adulthood and produces cumulative neurological disability [1, 2]. Asian estimates remain heterogeneous, with a regional analysis reporting an age-standardized prevalence of 10.96 per 100,000 population [3]. In Pakistan, available contemporary sources indicate a low to intermediate but rising burden, with an estimated prevalence of approximately 5 to 10 per 100,000 population and increasing recognition of service needs within neurology practice [4]. In this disease, cognitive impairment signifies a clinically related nonmotor manifestation that disturbs functional independence, work productivity, and health-related quality of life [5, 6]. Cognitive impairment in MS is multifactorial, representing inflammatory injury, axonal loss, and grey matter pathology that interrupt distributed neural tissue [7]. Screening studies using the Montreal Cognitive Assessment (MoCA) have shown that a considerable proportion of patients may have measurable

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impairment even when routine clinical follow-up attention on relapse activity and physical disability [8]. In a study assessing cognitive function, 48% patients met criteria for cognitive impairment with a lower mean MoCA score in patients than in healthy individuals (24.58 ± 4.29 vs 28.14 ± 0.73) [9]. Neuroimaging findings provide added biological support for cognitive impairment, mainly cortical involvement and neurodegeneration. Longitudinal studies have shown that cortical lesions identified at diagnosis are associated with cognitive impairment over long-term follow-up, suggesting the significance of lesion location rather than lesion quantity alone [10]. The present study was designed to generate clinically useful evidence to support earlier recognition of cognitive impairment and targeted monitoring in patients at higher risk.

Despite these observations, limitations remain in routine clinical practice where detailed neuropsychological assessment and advanced volumetric magnetic resonance imaging are not available. In many low and middle-income regions, cognitive screening is not regularly added to multiple sclerosis care, and local data relating practical screening tools to routinely reported magnetic resonance imaging features remain scarce. The present study aims to determine the frequency of cognitive impairment among patients with multiple sclerosis using the Montreal Cognitive Assessment and to assess its connotations with demographic factors, disease duration, and MRI markers recorded in everyday practice, including lesion burden, lesion location, cortical lesion presence, and radiological evidence of brain atrophy.

METHODS

This cross-sectional study was carried out in the Department of Neurology, Punjab Institute of Neurosciences, Lahore, over a duration of six months from May to December 2025. Ethical approval of the study was obtained from the institutional review committee (1991/IRB/PINS/Approval/2024;dated 13th December 2024). Patients were enrolled through a non-probability consecutive sampling technique from both the outpatient and inpatient neurology services, and a brain MRI was arranged through the Department of Radiology as part of routine patient care. All scans were interpreted by a consultant radiologist who remained unaware of the patients' cognitive assessment. A sample size of 71 was calculated on the basis of an expected cognitive impairment frequency of 18.3%, with a 95% confidence level and 9% margin of error [11]. Adults between 18 and 50 years of age with multiple sclerosis diagnosed according to the 2017 Revised McDonald Criteria [12] and disease duration of at least 12 months were eligible for inclusion. Only clinically stable patients were enrolled, defined as no relapse and no high-dose corticosteroid use within the preceding 30 days. Participants had to be able to undergo a brain MRI and complete the Montreal Cognitive Assessment under standardized conditions, with satisfactory hearing, vision, and language comprehension. Patients were excluded if they had any other neurological disorders, such as stroke, traumatic brain injury, or epilepsy, psychiatric illness affecting cognitive assessment, systemic illnesses to influence cognition or imaging findings, or contraindications to MRI, including metallic implants or severe claustrophobia, or recent use of medications recognized to affect cognition. After obtaining written informed consent, baseline demographic information, including age, sex, and education level, was recorded, followed by detailed assessments of clinical, neurological, and cognitive functions, including the type of multiple sclerosis and disease duration in years. Baseline laboratory investigations, including complete blood count, erythrocyte sedimentation rate, liver and renal function tests, thyroid profile, cerebrospinal fluid analysis, and vitamin B12 levels, were performed to exclude secondary causes of cognitive impairment. Brain magnetic resonance imaging was performed on a 3-Tesla scanner using routine clinical T2-weighted and fluid-attenuated inversion recovery sequences. Total lesion count and lesion location were recorded based on radiology review. Cortical lesions were coded as present or absent when identifiable on the MRI. Brain atrophy was recorded as present or absent based on the consultant radiologist's report. Cognitive screening was performed using the Montreal Cognitive Assessment by a trained neurologist in a quiet, distraction-free environment. Scores range from 0 to 30, with cognitive impairment defined a priori as a score below 26 [13]. For descriptive reporting, scores were grouped as normal (26–30), mild impairment (20–25), moderate impairment (10–19), and severe impairment (<10). Data were entered and analyzed using SPSS version 26.0. Quantitative variables were reported as mean and standard deviation, while categorical variables were noted as frequencies and percentages. Between-group comparisons for continuous variables were conducted using independent sample t-tests. Associations between categorical variables and cognitive status were assessed using Pearson's chi-square test. All tests were two-tailed, and a p-value <0.005 was considered statistically significant.

RESULTS

The mean age of the patients was 35.08 ± 7.71 years, and the mean disease duration was 6.53 ± 3.24 years. There were 23 males (32.4 %) and 48 females (67.6 %). Cognitive impairment severity showed 59.2 % were normal, 21.1 % had mild, 12.7 % had moderate, and 7.0 % had severe impairment (Table 1).

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Table 1: Baseline Demographic, Cognitive, and Neuro-Imaging Characteristics of Patients with Multiple Sclerosis (n=71)

Variables	Category	Mean ± SD / n (%)
Age (years)	Years	35.08 ± 7.71
Disease Duration	Years	6.53 ± 3.24
Age Group	18–35 Years	35 (49.3%)
	36–50 Years	36 (50.7%)
Sex	Male	23 (32.4%)
	Female	48 (67.6%)
Education Level	No Formal Education	8 (11.3%)
	Primary	15 (21.1%)
	Secondary	28 (39.4%)
	Higher	20 (28.2%)
Moca Score	Mean ± SD	22.91 ± 5.87
Cognitive Impairment Severity	Normal (≥26)	42 (59.2%)
	Mild (20–25)	15 (21.1%)
	Moderate (10–19)	9 (12.7%)
	Severe (<10)	5 (7.0%)
Type of MS	Relapsing–Remitting MS	49 (69.0%)
	Primary Progressive MS	8 (11.3%)
	Secondary Progressive MS	14 (19.7%)
Disease Duration	<5 Years	27 (38.0%)
	5–10 Years	32 (45.1%)
	>10 Years	12 (16.9%)

MoCA: Montreal Cognitive Assessment; MS: Multiple Sclerosis

Out of 71 patients, 42 (59.2 percent) had no cognitive impairment, while 29 (40.8 percent) were classified as cognitively impaired (Figure 1).

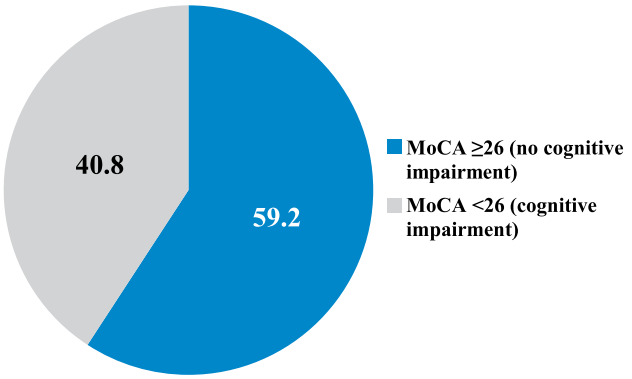

Figure 1: Frequency of Cognitive Impairment Based on MoCA Score

Cortical lesions (72.4% vs. 38.1%, p=0.004) and brain atrophy (48.3% vs. 16.7%, p=0.004) were significantly associated with cognitive impairment (Figure 2).

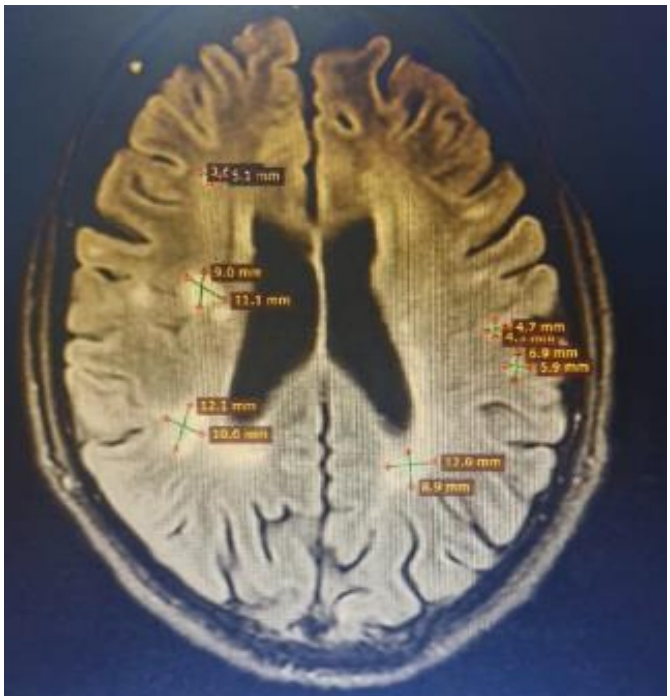

Figure 1: Representative Axial Fluid-Attenuated Inversion Recovery Brain Magnetic Resonance Image Demonstrating Periventricular and Juxtacortical Demyelinating Lesions in Multiple Sclerosis

Patients with cognitive impairment had a higher mean age (37.72 ± 7.39 vs. 33.26 ± 7.47), longer disease duration (7.70 ± 3.25 vs. 5.73 ± 3.02), lower MoCA score (20.15 ± 6.25 vs. 24.81 ± 4.81), and greater total MRI lesions (19.45 ± 10.74 vs. 13.74 ± 6.72), with significant t-values (all p<0.005). Cognitive impairment was more frequent in the older age group (36–50 years: 65.5% vs. 40.5%, p=0.038) and with longer disease duration (>10 years: 27.6% vs. 9.5%, p=0.022) (Table 2).

Table 1: Association of Cognitive Impairment with Demographic, Clinical, and Neuroimaging Parameters

Variables	Category	MoCA ≥26 (No Impairment), n (%)	MoCA <26 (Impairment), n (%)	Test statistic (χ^2 / t-value)	p-value
Age in years	Mean ± SD	33.26 ± 7.47	37.72 ± 7.39	t = -2.49	0.016
Age Group	18–35 Years	25 (59.5%)	10 (34.5%)	χ^2 = 4.304	0.038
	36–50 Years	17 (40.5%)	19 (65.5%)		
Disease Duration in Years	Mean ± SD	5.73 ± 3.02	7.70 ± 3.25	t = -2.58	0.012
Sex	Male	14 (33.3%)	9 (31.0%)	χ^2 = 0.041	0.839
	Female	28 (66.7%)	20 (69.0%)		
Education Level	No Formal Education	5 (11.9%)	3 (10.3%)	χ^2 = 6.095	0.107

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	Primary	12 (28.6%)	3 (10.3%)		
	Secondary	12 (28.6%)	16 (55.2%)		
	Higher	13 (31.0%)	7 (24.1%)		
Disease Duration Groups	<5 Years	21 (50.0%)	6 (20.7%)	$\chi^2 = 7.668$	0.022
	5–10 Years	17 (40.5%)	15 (51.7%)		
	>10 Years	4 (9.5%)	8 (27.6%)		
Moca Score	Mean ± SD	24.81 ± 4.81	20.15 ± 6.25	t = 3.54	0.001
Total MRI Lesions	Mean ± SD	13.74 ± 6.72	19.45 ± 10.74	t = -2.76	0.007
Periventricular Lesions	Yes	30 (71.4%)	24 (82.8%)	$\chi^2 = 1.209$	0.271
Juxtacortical Lesions	Yes	25 (59.5%)	23 (79.3%)	$\chi^2 = 3.067$	0.080
Infratentorial Lesions	Yes	12 (28.6%)	12 (41.4%)	$\chi^2 = 1.258$	0.262
Spinal Cord Lesions	Yes	10 (23.8%)	11 (37.9%)	$\chi^2 = 1.642$	0.200
Cortical Lesions	Yes	16 (38.1%)	21 (72.4%)	$\chi^2 = 8.096$	0.004
Brain Atrophy	Yes	7 (16.7%)	14 (48.3%)	$\chi^2 = 8.229$	0.004

MoCA: Montreal Cognitive Assessment. χ^2: Pearson chi-square statistic. t: independent samples t-test. SD: standard deviation. Independent t-test used for continuous variables; Pearson's Chi-square test applied for categorical variables. p-value <0.005 was considered statistically significant

DISCUSSION

The present study demonstrated that cognitive impairment is a frequent complication of multiple sclerosis, with a mean age of 35.08 ± 7.71 years and a mean disease duration of 6.53 ± 3.24 years. The overall mean Montreal Cognitive Assessment (MoCA) score was 22.91 ± 5.87, and 40.8% of patients had cognitive impairment defined as MoCA <26, whereas 59.2 % remained cognitively intact. Total MRI lesion burden averaged 16.07 ± 8.98, and cognitive impairment was significantly associated with higher age, longer disease duration, lower MoCA scores, greater total lesion counts, as well as the presence of cortical lesions and brain atrophy. Given the cross-sectional design, temporal change in cognition could not be evaluated, and the findings should be interpreted as associations at a single assessment rather than evidence of progression. Age and disease duration emerged as important correlates of cognition in the present Study. Patients with cognitive impairment were older (p=0.016) and had longer disease duration (p=0.012). These findings are consistent with the meta-regression from Wu *et al.* who found that the prevalence of impairment increased with older age (p=0.017) and longer disease duration (p=0.005) [14]. The present findings therefore reinforce robust evidence that age and especially disease duration are key determinants of cognitive decline in multiple sclerosis, even when absolute disability levels may still be moderate. The frequency of cognitive impairment in this study (40.8%) falls within the upper range of estimates reported in the international literature and is remarkably close to the 40% of patients with MoCA <26 described by Taub *et al.* whose mean MoCA score was higher at 25.86 ± 2.92 [13]. Al-Falaki *et al.* observed MoCA-defined impairment in 48 % of patients, with a mean total MoCA of 24.58 ± 4.29 compared with 28.14 ± 0.73 in healthy controls [9]. The pooled prevalence of cognitive impairment in relapsing–remitting multiple sclerosis in the meta-analysis by Wu *et al.* was 32.5% (95% CI 29.3–36.0%), somewhat lower than the 40.8 percent observed here, but within the heterogeneity range of 10.2–60.0% across included studies [14]. By contrast, Bouman *et al.* described a much higher burden of impairment, with 73.6% of patients classified as cognitively impaired and only 26.4% preserved, reflecting longer disease duration (11.6 ± 6.9 years) and older age (48 ± 11 years) in that cohort [15]. Taken together, the current prevalence aligns with the notion that approximately one-third to one-half of adults with multiple sclerosis exhibit clinically relevant cognitive deficits, with higher rates in progressive and long-standing disease. The proportional distribution of clinical phenotypes in this study, with relapsing–remitting multiple sclerosis in 69.0%, primary progressive in 11.3%, and secondary progressive in 19.7%, aligns with the typical dominance of relapsing–remitting disease in clinic-based samples. Taub *et al.* reported that MoCA impairment rates were higher in secondary progressive (55%) and primary progressive (56%) than in relapsing remitting disease (33%) [13]. Brochet and Ruet noted that the prevalence in relapsing remitting disease tends to be around 31–45% [16]. A study by Brochet *et al.* confirmed higher impairment rates in secondary progressive disease, with representative figures of 79.4% versus 44.5% in relapsing–remitting [17]. Sabanagic-Hajric *et al.* also reported worse MoCA performance in progressive types, with significant correlations between progressive phenotype and executive and language dysfunction [18]. Thus, although causal inference is limited in the present cross-sectional design, the relatively high overall prevalence of impairment and the strong imaging associations are biologically congruent with a sample that includes a substantial proportion of progressive disease [19]. A key contribution of this study is the demonstration

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that total MRI lesion burden, cortical involvement, and brain atrophy are strongly associated with cognitive impairment. Patients with MoCA <26 had significantly higher total lesion counts (p=0.007), and cortical lesions and brain atrophy were represented in the impaired group (72.4% and 48.3%, both p=0.004). Curti *et al.* reported a similar mean lesion count (22.7 ± 16.42 overall) and demonstrated higher lesion burden in patients with cortical lesions (p=0.002) and in progressive versus relapsing-remitting disease (p=0.001) [11]. Bouman *et al.* further linked multi-domain impairment to smaller cortical grey matter, thalamic, and hippocampal volumes [15]. Van Doninck *et al.* observed that impaired patients had lower raw hippocampal, thalamic, cortical, and grey matter volumes, although only normalized cortical volume remained significantly different after correction for intracranial volume [20]. From a clinical perspective, the findings support the routine use of MoCA as a practical screening tool to detect cognitive impairment in multiple sclerosis, mainly in older patients, have longer disease duration or exhibit cortical lesions and radiological atrophy Al-Falaki *et al.* and Taub *et al.* both noted that MoCA is useful to identify cognitive impairment in multiple sclerosis, with abnormalities most frequently involving memory, attention, visuospatial functions, and executive processing [9, 13]. The study has several strengths, including standardized cognitive screening with the Montreal Cognitive Assessment, which was done along with brain MRI within the same clinical setting, allowing individual patient-level relation of cognitive status with lesion burden and atrophy. Recruitment from both inpatient and outpatient neurology services increases clinical relevance, and radiological evaluation was done by qualified specialists, reducing the likelihood of error in identifying lesion types and brain atrophy. The inclusion of disease duration and age stratification further supports the interpretation of associations.

Important limitations exist. Disability scores, fatigue, depression, and medication effects were not assessed, even though these factors are recognized to influence cognitive outcomes. MoCA offers a global screen but does not substitute detailed neuropsychological testing. Since the study was conducted at a single center, the findings may not be fully applicable to other clinical settings. Future studies should implement long follow-up with standardized disability scoring, validated measures of depression and fatigue, and quantitative volumetric imaging to model cognitive trajectories and determine whether imaging markers add prognostic value beyond clinical measures.

CONCLUSIONS

Cognitive impairment was common in patients with multiple sclerosis and associated with many demographic and disease-related factors. Poorer cognition on screening was common in those with old age, longer disease duration, and those showing structural changes on brain imaging. These findings suggest that cognitive decline should be regarded as an important part of the overall disease burden rather than an isolated complication. Integrating cognitive assessment into routine neurological follow-up may improve patient monitoring, allow earlier identification of decline, and may support timely rehabilitation and supportive care aimed at maintaining daily functioning and quality of life.

Authors' Contribution

Conceptualization: AS, MSA
Methodology: AS, IN, FA
Formal analysis: QG, MSA, IN, MZ, FA
Writing and Drafting: QG, MSA, IN, MZ, FA
Review and Editing: AS, QG, MSA, IN, MZ, FA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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