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Egypt J Neurol Psychiatry Neurosurg (2024) 60:53
https://doi.org/10.1186/s41983-024-00826-8

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

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White matter lesion load and location in relation to cognitive impairment in relapsing–remitting multiple sclerosis

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Abstract

Background In relapsing–remitting multiple sclerosis (RRMS) the connection between cognitive impairment (CI) and white matter lesion load (WM-LL) and location is still unclear. This study aimed to identify the relationship between CI in RRMS patients and WM-LL and locations using a fully automated platform. CI and WM-LL were evaluated in 90 patients with RRMS using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) and Automated MRI volumetric measures of WM-LL and lesion distribution. Regression analysis of BICAMS as a dependent variable with different clinical and radiological parameters was performed.

Results Data were obtained from 90 patients with RRMS who had a mean age of 32.74 ± 8.43 years and a female-to-male ratio of 3:1. The mean (± SD) cognitive rating scores for the BICAMS subtests were 28.07 ± 11.78 for the Symbol Digit Modalities Test (SDMT), 42.32 ± 12.46 for the California Verbal Learning Test-II (CVLT-II), and 16.13 ± 8.17 for the Brief Visuospatial Memory Test-Revised (BVMT-R). According to the BICAMS criteria, 29 cases (32.2%) had CI. BICAMS scores were significantly correlated with age, education level, relapse frequency, disease duration, and time to start disease-modifying therapies. Whole WM-LL and periventricular lesion load were significantly associated with CI. After controlling for age, sex, and education, logistic regression analysis revealed that total WM-LL was the best predictor for CI together with duration of illness and years of education. The cut-off value of 12.85 cc for total WM-LL predicted CI.

Conclusions Whole WM-LL and periventricular lesion load are the best anatomical predictors for CI probably due to the effect on the anterior commissural fibers while years of education and duration of disease are the best demographic predictors for CI.

Keywords Multiple sclerosis, Cognitive impairment, BICAMS, Volumetric assessment, Lesion load, Lesion location

Background

Multiple sclerosis (MS) is the most common cause of non-traumatic disability among highly productive young and middle-aged adults [1]. Even though physical disability is the hallmark of the disease, cognitive impairment (CI) has also been recognized as a central feature, affecting up to 70% of patients [2]. CI in the context of MS is evident even at disease onset and increases in both prevalence and severity as the disease progresses [3].

CI can result in difficulties in employment, treatment non-adherence, personality changes, and other psychosocial dysfunctions in patients and even their careers [4].

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Therefore, it is essential for health professionals to evaluate cognitive function objectively both at baseline and during routine follow-up visits [5].

MS-related cognitive deficits mirror subcortical dementia, with effects on attention, information processing speed, memory, executive function, and visuospatial abilities [6]. The Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-II (CVLT-II), and the Brief Visuospatial Memory Test-Revised (BVMT-R) are subtests of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), a popular assessment battery that has strong associations with numerous MRI measures in MS patients [7]. The widespread use of BICAMS stems from its short administration time (only 15 min), multilingual accessibility, and high sensitivity and specificity in evaluating information processing speed and short-term verbal and visual memory [7].

There is some debate over whether MRI volumetric assessments of white matter (WM) and grey matter (GM) structures can be used as predictors of CI and quantify a patient's response to treatment [8–10]. It is possible that discrepancies in the literature may relate to diverse patient profiles, insufficient numbers, different rating scales for assessment, various definitions of CI, different lesion quantification methods, or failure to take lesion location into account [11]. The present study aimed to evaluate the relationship between CI, as measured by BICAMS and physical disability, as measured by EDSS, with different automated MRI measures of white matter lesion load (WM-LL) (lesion volume, normalized volume, lesion burden), lesion distribution and other volumetric assessments.

Methods

Participants

RRMS patients were recruited consecutively from three MS units located in the South of Egypt (Assiut, Sout Valley and Luxor) during the period from the 1st of January to the end of September 2023. Patients were diagnosed with RRMS according to the 2017 McDonald diagnostic criteria [12]. Inclusion criteria: RRMS patients of all ages and either sex, both de novo and old cases attending the MS units during the study period. Exclusion criteria: (a) any patient with evidence of a relapse or steroid administration in the past 30 days; (b) any associated medical conditions that may affect cognition, and those on psychoactive pharmacotherapy; (c) patients who were unable to complete the test as due to visual impairment, upper limb weakness or tremors were also excluded; (d) patients with incomplete clinical data or could not complete all cognitive assessments; and (e) patients without MRI image DICOM files (see flowchart Fig. 1).

Study procedures

This was a cross-sectional, each patient was submitted to the following.

Clinical evaluation

Demographic data (age, sex, educational level represented by the number of educational years) were provided, followed by clinical history and neurological examination including the Expanded Disability Status Scale (EDSS).

Cognitive assessment

Cognition was assessed using the validated Arabic version of BICAMS battery [13]. The BICAMS battery includes SDMT for evaluating the speed of information processing, CVLT-II for assessing verbal learning and memory, and BVMT for evaluating visual learning and memory. The tests were applied in quiet rooms in the MS outpatient clinics on the morning of the scheduled visit just before acquisition of the MRI. The tests were applied by 3 neurologists (one neurologist in each center) who attended a training session on the application of BICAMS before the start of the study to decrease any potential inter-rater variability. Scoring of different subtests was done by the same neurologist. Application and scoring of the three subtests were done according to the international recommendations [14]. A group of age, sex and education-matched control group was used to determine the cut-off values for SDMT, CVLT-II, and BVMTR (22, 38, and 10, respectively). These values were calculated as 1.5 SD below the mean of the healthy age, sex, and education-matched group [15]. Patients were classified as having CI if at least two tests were abnormal [14].

Radiological evaluation

Conventional MRI: A 1.5 T Philips Achieva MRI machine was used with a Uniform MRI acquisition method. This included the acquisition of a T1-weighted spin-echo axial image (TR/TE = 600/15 ms, flip angle = 90°, FOV (frequency/phase) = 220/75, acquisition matrix size = 256 × 256, voxel size = 1 × 1 × 3 mm) and a T2-weighted FLAIR (fluid-attenuated inversion recovery) image (TR/TE = 9000/110 ms, inversion time = 2500 ms, flip angle = 130°, FOV (frequency/phase) = 220/75, acquisition matrix size = 320 × 168, voxel size = 1 × 1 × 3 mm), both covering the entire brain. These images were essential for brain volume and lesion assessments.

Lesion load and volumetric assessment

The volumetric data were acquired from MRI data that included T1 and FLAIR sequences. These sequences

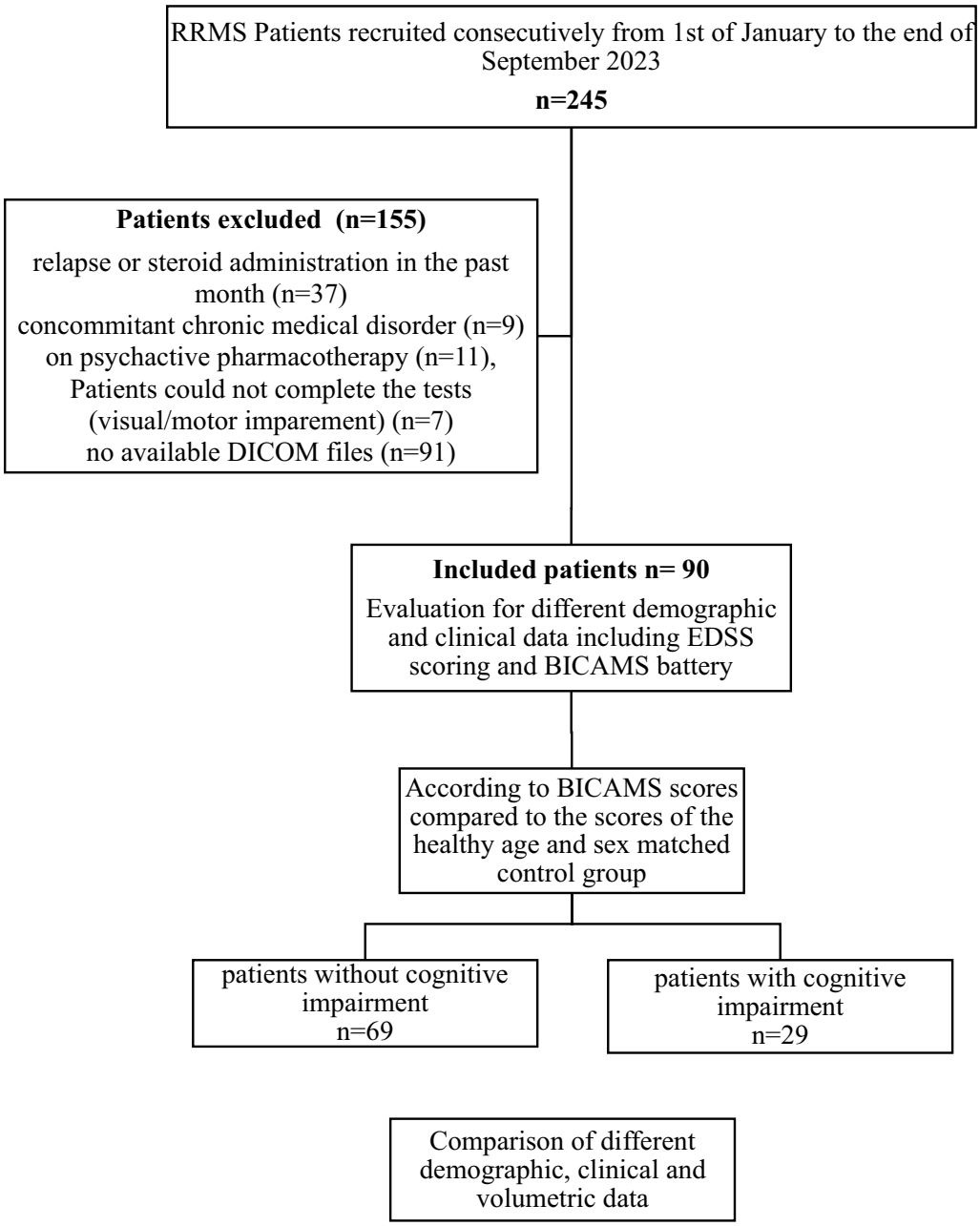

Fig. 1 Flowchart shows the inclusion and exclusion of the study participants

were originally converted from DICOM files to two compressed, anonymized Neuroimaging Informatics Technology Initiative (NIfTI) files: one for T1 and one for FLAIR. These NIfTI files formed the foundation for further analysis.

LesionBrain 1.0 is a web-based program for segmenting white matter lesions [16] that was successfully incorporated into the platform "volBrain" (https://volbrain.upv.es/) [17], offering a complete tool for precise and efficient lesion detection. Image normalization and registration, structural segmentation to identify particular brain areas such as the intracranial cavity, brainstem, cerebellum, and lateral ventricles, and candidate mapping to locate probable lesion sites are all part of the processing pipeline. Following that, lesions are segmented voxel-wise using a three-step technique that includes patch-based multimodal segmentation, patch-based regularization of the resultant lesion probability map, and an ensemble

of shallow neural networks to correct any erroneous patches, decreasing false positives. This pipeline has been rigorously tested using the MSSEG MICCAI Challenge 2016 dataset, displaying good performance with a mean Dice coefficient of 0.66 [18]. This thorough technique enabled the absolute volume of all lesions, whether total or localized, to be measured (in cubic centimeters).

Statistical analysis of data

SPSS for Windows version 26 was used to perform statistical analysis (Cary, NC, USA). Data were represented as mean and standard deviation for numerical data and frequencies with percentages for categorical data. The Shapiro–Wilk and Kolmogorov–Smirnov tests were employed to determine the normality of the distribution. To assess the differences and correlations between variables, suitable parametric or nonparametric tests were utilized. Pearson or Spearman correlation tests were used to determine the relationship between variables. To evaluate the link between variables, multivariate logistic regression and linear regression analysis were used. For all tests, a P-value of less than 0.05 was considered significant.

Results

Clinical data and brain volumetric measures

Data were obtained from 90 patients with RRMS who had a mean age of 32.74 ± 8.43 years and a female-to-male ratio of 3:1. The mean (± SD) of EDSS was 3.2 ± 1.73, the mean (± SD) of cognitive rating scores were; SDMT, 28.07 ± 11.78; CVLT-II, 42.32 ± 12.46; BVMRT, 16.13 ± 8.17. According to the BICAMS criteria, 29 cases (32.2%) had CI. Regarding the spatial distribution of lesions, the periventricular region had the highest lesion volume. Most of our patients (92.2%) were taking DMTs: Interferon was the commonest (55.6%) followed by Fingolimod (28.9%). Other demographic, clinical, psychometric, and volumetric data are shown in Table 1.

Comparisons between patients with and without CI are illustrated in Table 2. Patients with CI were significantly older, had fewer years of education, and had a longer duration of illness with a higher number of relapses. They also had higher EDSS scores, total WM lesion volumes, and Table 3 illustrates the results of the correlation analyses. Age, years of education, disease duration, number of relapses, EDSS, DMT duration, and time to start DMT were significantly correlated with all subtests of the BICAMS, while no correlation was found with age at onset of illness. Total WM-LL and periventricular lesion volume showed significant negative correlations with all BICAMS subtests.

The results of multivariate stepwise logistic regression analysis, with adjustment for age, sex, and current DMT are illustrated in Table 4. The key variables were years of education (inverse relationship with cognitive impairment, $P=0.008$), disease duration (positive association, $P=0.004$), and WM-LL (positive association, $P=0.042$). These findings highlight the significance of education years, disease duration, and lesion volume as predictors of CI.

Table 1 The demographic and clinical data of 90 RRMS patients

	Mean ± SD (range)
Age (years)	32.74 ± 8.43(16–55)
Sex (male/female) (%)	(24/66) (26.76%/73.3%)
Education years	11.80 ± 4.84 (0–20)
Disease duration (months)	55.44 ± 50.15(3–240)
Number of relapses	3.41 ± 2.36 (2–12)
Age at onset (years)	27.14 ± 7.81(12–45)
EDSS	3.2 ± 1.73(1–5.5)
DMT duration (months)	19.83 ± 21.34(0–96)
Time to start DMT (months)	35.60 ± 44.71(3– 228)
SDMT	28.07 ± 11.78(6–54)
CVLT	42.32 ± 12.46(14–74)
BVM-RT	16.13 ± 8.17(0–32)
Total WM-LL	18.14 ± 15.88(0.07–62.40)
Juxtacortical WM-LL	5.69 ± 10.72 (0.02–58.43)
Periventricular WM-LL	11.66 ± 13.81 (0–48.81)
Infratentorial WM-LL	0.24 ± 0.45 (0–1.68)
Cognitive impairment (yes/no) (%)	(29/61) (32.2%/67.8%)
Current DMT	
No treatment number (%)	7 (7.8%)
Interferon B number (%)	50 (55.6%)
Fingolimod number (%)	26 (28.9%)
Teriflunomide number (%)	3 (3.3%)
Rituximab number (%)	2 (2.2%)
Ocrelizumab number (%)	2 (2.2%)

DMT disease-modifying therapy, *SDMT* Symbol Digit Modalities Test, *CVLT-II* California Verbal Learning Test-II, *BVMT-R* Brief Visuospatial Memory Test-Revised, *EDSS* Expanded Disability Status Scale, *WM-LL* white matter lesion load

Table 5(A) and Fig. 2 show the ROC curve and an area under the curve (AUC) of 0.700 for total white matter lesion load (Total WM-LL) in diagnosing cognitive impairment (CI). The AUC, with a standard error of 0.057, is statistically significant ($P=0.002$), suggesting moderate predictive accuracy.

Table 5(B) provides a cut-off value of 12.85 cc for total WM-LL, yielding a sensitivity of 75.9% and specificity of 60.7%.

Discussion

Although MRI parameters of structural brain damage are closely linked to cognitive disabilities, they are not incorporated in routine clinical assessment due to the need to employ sophisticated types of analysis and measurements

Table 2 Comparison between patients with and without cognitive impairment

	RRMS group without cognitive impairment, *n* = 61 (mean ± SD)	RRMS group with cognitive impairment, *n* = 29 (mean ± SD)	*P*
Age (years)	30.84 ± 7.94	36.76 ± 8.1	< 0.001
Education years	13.38 ± 3.61	8.48 ± 5.43	< 0.001
Disease duration (months)	38.33 ± 30.97	91.45 ± 62.89	< 0.001
Number of relapses under the current DMT	2.80 ± 1.82	4.69 ± 2.83	0.002
Age at onset (years)	26.87 ± 8.02	27.72 ± 7.44	0.621
Current EDSS	2.75 ± 1.69	4.172 ± 1.48	< 0.001
Current DMT duration (months)	16.54 ± 18.66	26.76 ± 25.05	0.057
Time to start DMT (months)	21.77 ± 23.82	64.69 ± 62.01	< 0.001
Total WM-LL	14.89 ± 15.213	24.95 ± 15.31	0.005
Juxtacortical WM-LL	5.23 ± 9.87	6.63 ± 12.44	0.599
Periventricular WM-LL	9.41 ± 13.34	16.39 ± 13.81	0.028
Infratentorial WM-LL	0.22 ± 0.44	0.28 ± 0.46	0.603

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *WM-LL* white matter lesion load

Table 3 Correlation of different sub-items of BICAMS to study variables

		SDMT	CVLT	BVM-RT
Age (years)	*r*	− 0.475**	− 0.318**	− 0.365**
	Sig. (2-tailed)	< 0.001	0.002	< 0.001
Sex	*r*	− 0.016	0.137	− 0.024
	Sig. (2-tailed)	0.882	0.197	0.822
Education years	*r*	0.496**	0.294**	0.442**
	Sig. (2-tailed)	< 0.001	.005	< 0.001
Disease duration (months)	*r*	− 0.533**	− 0.506**	− 0.540**
	Sig. (2-tailed)	< 0.001	< 0.001	< 0.001
Number of relapses	*r*	− 0.493**	− 0.458**	− 0.517**
	Sig. (2-tailed)	< 0.001	< 0.001	< 0.001
Age at onset (years)	*r*	− 0.158	− 0.080-	− 0.080
	Sig. (2-tailed)	0.136	0.452	0.456
EDSS	*r*	− 0.525**	− 0.334**	− 0.457**
	Sig. (2-tailed)	< 0.001	0.001	< 0.001
DMT duration	*r*	− 0.345**	− 0.282**	− 0.322**
	Sig. (2-tailed)	0.001	0.007	0.002
Time to start DMT	*r*	− 0.434**	− 0.433**	− 0.452**
	Sig. (2-tailed)	< 0.001	< 0.001	< 0.001
Total WM-LL	*r*	− 0.428**	− 0.231*	− 0.399**
	Sig. (2-tailed)	< 0.001	0.029	< 0.001
Juxtacortical WM-LL	*r*	− 0.136	− 0.044-	− 0.189
	Sig. (2-tailed)	0.202	0.683	0.075
Periventricular WM-LL	*r*	− 0.323**	− 0.204-	− 0.248*
	Sig. (2-tailed)	0.002	0.054	0.018
Infra tentorial WM-LL	*r*	− 0.096-	0.019	− 0.094
	Sig. (2-tailed)	0.371	0.862	0.378

* Statistically significant difference (p < 0.05)

**Statistically significant difference (p < 0.01)

DMT disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *WM-LL* white matter lesion load

Table 4 Multivariate stepwise logistic regression analysis for predicting CI using clinical and volumetric results, with adjustment for age, sex and current DMT administered

	B	S.E	Wald	*df*	Sig
Education years	− 0.199	0.075	7.080	1	0.008
Disease duration	0.022	0.007	8.463	1	0.004
Lesion volume	0.036	0.018	4.142	1	0.042

of volumetric MRI measurements which are not routinely available in most centers [19]. The reliability of these measures using largely automated approaches has not been proven, while studies employing other methods yielded conflicting results [20].

In the present study, CI was found in 32.2% of patients which is lower than the frequency of CI reported in several previous studies which ranged from 40 to 70% [21]. Compared with patients who had normal cognition, patients with CI were older, had fewer years of education, a longer duration of illness with higher relapse frequency, a higher EDSS, and higher total WM-LL and periventricular LL. Each of these items was also significantly correlated with the three sub-items of BICAMS. Similar results have been reported by Khedr and colleagues, 2022, and Elshebawy and colleagues 2021 [15, 22]. Many reports have pointed out that increased age is a risk factor for cognitive decline in MS [15, 22–24]. Aging is usually associated with brain atrophy and CI in the general population while in MS, this rate of atrophy is accelerated [25, 26]. Aging increases the probability of secondary progression in MS due to exhaustion of brain reserve [27]. Cognitively impaired patients had higher EDSS scores [28,

Table 5 A. Area under the curve and B. Cut-off value of total WM-LL for diagnosing cognitive impairment

A. Area under the curve, total WM-LL in cc for predicting cognitive impairment				
Area	**Std. error**	**Asymptotic Sig**	**Asymptotic 95% confidence interval**	
			Lower bound	**Upper bound**
0.700	0.057	0.002	0.589	0.810
B. Cut-off value				
Positive if greater than or equal to		**Sensitivity**		**Specificity**
12.85 cc		75.9%		60.7%

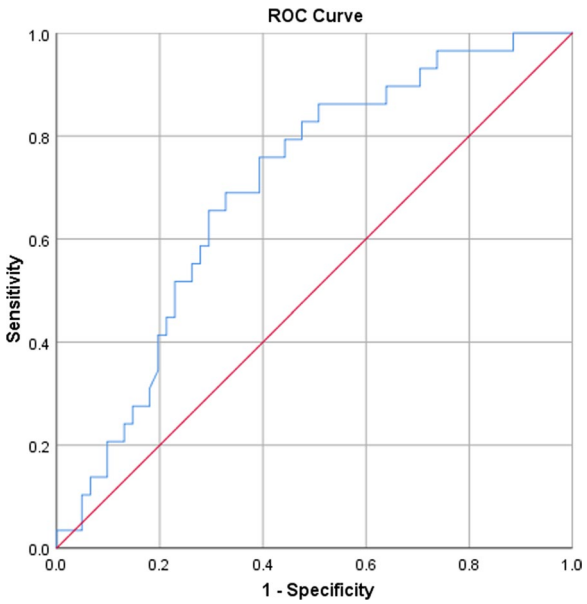

Fig. 2 Shows ROC curve for total white matter lesion load (WM-LL) for diagnosing cognitive impairment. The ROC curve and an area under the curve (AUC) of 0.700 for Total WM-LL in diagnosing cognitive impairment (CI). The AUC, with a standard error of 0.057, is statistically significant ($P = 0.002$), suggesting moderate predictive accuracy

29]. Since physical performance requires higher-order information processing, understanding the relationship between cognition and physical performance is important when considering cognition as an important risk assessment measure [30]. The only protective factor for physical disability was a higher educational level due to increased cognitive reserve and brain plasticity [31].

The findings of the present study suggest that there may be differences in cognitive performance among MS patients according to the type of disease-modifying therapy (DMT). Patients receiving Interferon B had higher scores on visuospatial memory as measured by the Brief Visuospatial Memory Test-Revised Total Recall (BVM-RT), despite their lower level of education. Although they had similar EDSS scores and duration of illness, they also had a significantly lower relapse rate than patients receiving fingolimod as the latter is usually considered as 2nd line of treatment in such cases.

The main results of the present study are that three factors can be considered as predictors of CI in RRMS: years of education, disease duration, and whole WM-LL.

Education years

The odds of cognitive impairment decrease for each additional year of education. This is consistent with Elshebawy and colleagues, and Khedr and colleagues, who found that a low educational level was a predictor of CI in MS patients [15, 22]. Education is one of the factors responsible for the formation of cognitive reserve. A higher educational level is thought to increase the brain's resilience to disease burden, at least up to a certain limit [32]. Several studies have linked better cognitive performance with higher education levels and cognitive reserve [15, 22, 33, 34]. However, Russo and colleagues [35] and Patti and colleagues [36] found no significant differences between cognitively preserved or impaired patients regarding their educational level.

Disease duration

We found that for each additional year of disease duration, the odds of CI increase. This aligns with the studies above, which identified longer disease duration as a predictor of CI [22].

Lesion volume

We found that for each unit increase in lesion volume, the odds of cognitive impairment increase. The area under the curve of total WM-LL predicting CI was 0.700 (95% confidence interval 0.589–0.810). The optimal cut-off value of the total WM-LL predicting CI was equal to or greater than 12.85 cc with a sensitivity of 75.9% and specificity of 60.7%. Calculation of the cut-off value of WM-LL could be utilized for early detection of CI even

in asymptomatic patients. However, it is important to note that cognitive impairment in MS is a complex issue and can be influenced by many factors such as frequent relapses, progressive form, higher clinical disability, and immunosuppressive treatment [22]. It might be beneficial to consider these additional factors in future analyses.

Although most previous studies agree that there is a relationship between WM-LL and CI, as reflected in the statements of the National MS Society [37]. Fulton and colleagues discovered that out of 12 neurocognitive indicators assessed, only SDMT and Rey Auditory Verbal Learning test were associated substantially with lesion burden [38]. Patti and colleagues (2015) observed that aberrant white matter (AWM) percentage, a marker of lesion burden, predicted poor performance in SDMT Test 9 years in this study [39]. According to Giorgio et al., the connection between CI and lesion burden is modest, suggesting that CI in MS has a complicated and multifaceted etiology that is insufficiently described by pathological markers detected by standard MRI [40]. Nocentini et al. demonstrated that CI was linked with global brain atrophy and T2-lesion volumes as determined by voxel-based morphometry (VBM) [41]. Another research employing 3.0 T MRI with enhanced identification of tiny lesions undetected by conventional MRI found a significant connection between CI and WM-LL [42]. A recent Egyptian study that compared WM-LL in double inversion recovery (DIR) with SDMT cognitive scores discovered that the total WM-LL was adversely connected with SDMT cognitive scores [43].

Overall, the connection between cognitive performance and lesion burden is modest, suggesting that cognitive impairment in MS has a complex and multifaceted etiology that is not fully described by pathological markers detected by standard MRI [40]. While some studies have found a significant correlation between regional lesion load and CI in MS patients, others suggest that this relationship is moderate or complex. More research is needed to fully understand this relationship.

Disruption of cortico-cortical and cortico-subcortical connections involved in cognitive processing may be the mechanism through which WM-LL causes deficiencies in specific domains of cognition[39]. According to Reuter and colleagues, CI is present in approximately one-quarter of MS patients in the early stages, and the location of macroscopic lesions altered performance in verbal and spatial learning but had no effect on attention and executive functioning [44]. Despite the comparable anatomical distribution of WM-LL, Rossi and colleagues discovered that lesion volume was larger in cognitively impaired individuals than in cognitively preserved patients [45]. Khedr and colleagues, 2023 found that GM atrophy particularly thalamic atrophy was the best predictor of CI as they measure only the gray matter in their study [15]. Kutzelnigg and colleagues showed that, with disease progression, WM abnormalities become more diffuse with increased demyelination in the GM [46]. Since neither WM nor GM abnormalities alone could fully explain CI in MS, WM lesion location may give a stronger correlation with the severity of cognitive impairment [47]. It has been shown that lesions in WM tracts connecting associative areas are correlated with CI in RRMS patients [48, 49]. The effect of WM-LL in strategic tracts in predicting CI may be far more important than the proposed diffuse abnormalities in the normal-appearing WM [50].

Confirming our result Papadopoulou et al. found that WM lesion volume significantly predicted SDMT and by trend PASAT performance [51]. However, cortical lesion volume did not predict CI. Others [52, 53] found the cortical lesions and atrophy associated with cognitive impairment in RRMS while Akaishi et al., and Naghavi et al., and Khedr et al. found that deep gray matter atrophy is highly correlated with overall cognitive impairment in RRMS. This controversy in results may be related to methodological differenced in measuring MRI [15, 54, 55].

Integration of the relatively simple measures of automated brain volumetry and WM-LL and location in routine monitoring of RRMS patients may be able to detect patients' early patients with CI and consequently could be detecting transiting to secondary progression and allow early intervention. Recently Kania et al. concluded that baseline volumetric measures are stronger predictors of cognitive performance than relapse activity, which yet again highlights the importance of atrophy in MS prognosis [56].

The present study was cross-sectional and did not allow us to shed light on the longitudinal changes in the relationship between the quantitative MRI measures of WM-LL with CI over the course of the disease. Also, the use of a 1.5 T MRI scanner did not allow more advanced MRI measurements (WM tractography). We recommend further studies on larger populations and on other phenotypes like PPMS for a better understanding of the underlying correlates.

Conclusion: In the current study, total WM-LL can be used as a predictor of CI and this finding means that the CI in RRMS is a subcortical type of impairment due to periventricular WM-LL. It may be related to affection of anterior commissural fibers of corpus callosum while years of education and duration of disease are the best demographic predictors for CI.

Abbreviations

RRMS	Relapsing–remitting multiple sclerosis, CI: cognitive impairment
WM	White matter
WM-LL	White matter lesion load

GM	Grey matter
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
SDMT	Symbol Digit Modalities Test
CVLT-II	California Verbal Learning Test-II
BVMT-R	Brief Visuospatial Memory Test-Revised
EDSS	Expanded Disability Status Scale (EDSS)

Acknowledgements
None.

Author contributions
E.M.K. contributed to the study conception, design of the work, statistical analysis, and critical revision of the manuscript. M.Y.E. contributed to the design of the work, data recruitment from MS patients and controls, preparing the volumetric reports, and statistical analysis. D.M.M. contributed to data recruitment from MS patients, collected cognitive and EDSS scores, and drafted the manuscript. A.N. contributed to the drafting of the manuscript. All authors gave final approval of the version to be published.

Funding
None.

Availability of data and materials
All data generated or analyzed during this study are available from corresponded on request.

Declarations

Ethics approval and consent to participate
This research was approved by The Institutional Review Board (IRB) of the Faculty of Medicine, Assiut University (IRB no: 17300884), and it conforms to the provisions of the Declaration of Helsinki. All participants provided informed written consent.

Consent for publication
The participant has consented to publishing their data result.

Competing interests
The authors have no competing interest to declare that are relevant to the content of this article.

Received: 1 March 2024 Accepted: 29 March 2024
Published online: 15 April 2024

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