• Clinical Research •

Visual function in the diagnosis of multiple sclerosis and optic neuritis

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Received: 2024-06-26 Accepted: 2025-03-11

Abstract

• **AIM:** To determine the diagnostic ability of various visual functions in patients with multiple sclerosis (MS) with and without optic neuritis (ON).

• **METHODS:** In this cross-sectional study, we assessed and compared refractive error, visual acuity (VA), and contrast sensitivity (CS) between patients with MS and a matched control group of healthy individuals. The MS patients were further categorized into those with ON and those without.

• **RESULTS:** A total of 133 eyes from 133 participants were assessed, including 66 individuals diagnosed with MS. The mean ages for the MS group and the healthy control group were 37.5±4.27y and 38.45±4.60y, respectively (P=0.346). Among the 66 patients with MS, 18 had ON. The presence of MS was associated with a decrease in best-corrected visual acuity (BCVA) and spherical component of refractive error (P<0.05), whereas ON did not lead to any further decline in these parameters (P>0.05). MS was linked to decreased CS at spatial frequencies of 6 and 18 cycles per degree (CPD; P<0.05), while ON in MS patients resulted in an additional decrease in CS at 3 CPD (P=0.03). The most significant sensitivity for distinguishing MS patients from healthy individuals as well as MS patients with ON from those without ON was found with cylindrical component [associated criterion (AC) >-0.75 D; 71.21%] and CS at spatial frequency of 6 CPD (AC ≤1.56; 72.22%), respectively. Conversely, the highest specificity for these diagnostic measures was associated with BCVA (AC >0 logMAR; 97.01%) and CS at a spatial frequency of 12 CPD (AC ≤0.60; 93.75%), respectively.

• **CONCLUSION:** MS significantly affects refractive error and CS, with ON further reducing CS. Assessing these visual parameters can improve MS monitoring and management.

• **KEYWORDS:** refractive error; contrast sensitivity; multiple sclerosis; optic neuritis; diagnostic ability

DOI:10.18240/ijo.2025.10.15

Citation: Behnia B, Layedh A, Hashemi H, Jamali A, Yekta A, Zamani N, Moravej R, Khabazkhoob M. Visual function in the diagnosis of multiple sclerosis and optic neuritis. *Int J Ophthalmol* 2025;18(10):1922-1928

INTRODUCTION

Multiple sclerosis (MS) represents one of the most prevalent chronic progressive inflammatory diseases affecting the nervous system[1]. The global prevalence of MS has been increasing[2], with several significant risk factors identified. These include genetic mutations, vitamin D deficiency, decreased exposure to ultraviolet B (UVB) radiation, infection with the Epstein-Barr virus, obesity, and smoking[3]. The neurodegenerative changes linked to MS lead to inflammation and persistent injury to the myelin sheaths surrounding axons as well as oligodendrocytes and neuronal cell bodies[4]. These neurological changes caused by MS can disrupt a range of body functions, with visual disturbances being particularly common. Assessments reveal that most

visual defects seen in individuals with MS arise from the involvement of the anterior visual pathways, especially the optic nerve[5].

In patients with MS, visual acuity (VA) is an important indicator for evaluating neuro-performance[4]. Research conducted by Mowry *et al*[6] revealed a strong correlation between high-contrast VA and the results of the Health-Related Quality of Life questionnaire in MS patients. This finding suggests a direct link between VA and the ability to perform daily activities. Assessments conducted by the National Multiple Sclerosis Society Task Force indicated that high-contrast VA lacks the sensitivity required to evaluate visual defects in patients with MS. In contrast, findings from the optic neuritis treatment trial (ONTT) revealed that low-contrast VA is effective in identifying visual dysfunctions in MS patients that high-contrast VA assessments may overlook[7]. The importance of this issue is underscored by the work of Cole *et al*[8] who demonstrated that impaired contrast sensitivity (CS) can result in a diminished vision-related quality of life after an attack of optic neuritis (ON), even among those with normal high-contrast VA. Furthermore, two investigations by Park *et al*[9-10] indicated that low-contrast VA is a valuable tool for the early detection of ON and for recognizing prior occurrences of the condition. Therefore, it is advisable to evaluate low-contrast VA, as this may reveal asymptomatic or subclinical instances of ON[11]. Refractive errors significantly influence VA, and there is growing interest in the potential shared pathogenesis between MS and myopia[12]. Nevertheless, research that concurrently evaluates the components of refractive error alongside both low and high-contrast VA remains limited[13].

A substantial body of research has examined variations in high and low-contrast VA[9-10,14] and refractive errors[12-13] among individuals at various stages of ON and MS. However, there is a scarcity of studies that specifically address the diagnostic cutoff values of these parameters for diagnosing MS or ON. This study aims to establish diagnostic cutoff points and assess the sensitivity and specificity of refractive errors and both low and high-contrast VA, to facilitate the initial clinical diagnosis of these conditions.

PARTICIPANTS AND METHODS

Ethical Approval The study protocol received approval from the Ethics Committee of Tehran University of Medical Sciences and was carried out in accordance with the principles outlined in the Helsinki Declaration. Written informed consent was obtained from all participants (Ethical code: IR.TUMS.MEDICINE.REC.1399.315).

Participants This cross-sectional study comprised three groups, including MS patients with a history of ON, MS patients without such a history, and healthy control participants. The diagnosis of MS was established through clinical evaluation and adherence to the Poser criteria, supplemented by magnetic resonance imaging (MRI) findings interpreted by a neurologist[15]. The diagnosis of ON was determined based on clinical signs[16] evaluated by an ophthalmologist. Healthy controls were selected from individuals exhibiting no MS-related symptoms, which was further confirmed by MRI results.

Participants under the age of 30 and over the age of 45y, those with ON who presented normal MRI findings, individuals taking medications that could influence CS or VA (such as amiodarone, isotretinoin, and chlorpromazine), as well as those with any ocular conditions that could potentially impact VA, were excluded from the study.

Examinations Initially, uncorrected VA was assessed at a distance of 6 m utilizing the logarithm of the minimum angle of resolution (logMAR) scale for all participants (chart SC 1600 Pola, Nidek Co., LTD, Gamagori, Japan). Subsequently, objective refraction was conducted using an autorefractometer (ARK-1, Nidek Co., LTD, Aichi, Japan). The next phase involved subjective refraction to determine the best-corrected visual acuity (BCVA). Comprehensive ophthalmological evaluations were performed both prior to and following pupillary dilation. An expert ophthalmologist used a biomicroscope (BQ-900, Haag-Streit AG, Koeniz, Switzerland) to assess ocular health, employing a +90 D Volk lens to examine the retina and optic nerve head, while intraocular pressure was measured *via* Goldmann applanation tonometry (GAT). Additionally, color vision was evaluated using the Ishihara test. In this study, CS was measured prior to pupillary dilation, with the BCVA utilizing the Vector Vision CVS1000 (Vector-Vision, Greenville, OH).

Statistical Analysis In this study, the mean±standard deviation (SD) of BCVA, CS across four spatial frequencies [3, 6, 12, and 18 cycles per degree (CPD)], and components of refractive error were reported across four groups: all MS, MS with ON, MS without ON, and a normal control group. Pairwise comparisons were conducted using the independent samples *t*-test. The optimal cutoff point for achieving the highest sensitivity and specificity was established through the Youden index, which assessed the diagnostic accuracy of the aforementioned parameters in distinguishing between healthy controls, MS patients without ON, and those with ON. The area under the receiver operating characteristic curve (AUC) was reported as an indicator of diagnostic value. Statistical analyses for this study were conducted using Statistical Package for Social Sciences (SPSS) version 22, with *P*-values below 0.05 deemed statistically significant.

RESULTS

In this research, a total of 133 participants were recruited, comprising 66 patients in the MS group and 67 individuals

Table 1 BCVA, refractive errors and contrast sensitivity in healthy individuals and patients with MS mean±SD

Visual indices	Normal	All MS	*P*	All MS		
				Non-ON	ON	*P*
BCVA (logMAR)	-0.02±0.05	0.03±0.09	<0.001	0.03±0.09	0.04±0.09	0.782
Refractive error components						
Sphere (D)	0.16±1.1	-0.23±1.13	0.047	-0.14±0.88	-0.47±1.62	0.292
Cylinder (D)	-0.817±0.543	-0.746±0.612	0.480	-0.797±0.666	-0.611±0.422	0.275
SE (D)	-0.25±1.11	-0.6±1.2	0.080	-0.54±0.93	-0.78±1.74	0.474
Contrast sensitivity						
3 CPD	1.34±0.2	1.31±0.25	0.455	1.36±0.26	1.21±0.2	0.030
6 CPD	1.72±0.26	1.53±0.36	0.001	1.57±0.36	1.44±0.37	0.202
12 CPD	1.35±0.27	1.26±0.39	0.149	1.32±0.37	1.12±0.42	0.075
18 CPD	1±0.28	0.87±0.26	0.007	0.88±0.25	0.85±0.3	0.700

CPD: Cycles per degree; SD: Standard deviation; SE: Spherical equivalent; BCVA: Best-corrected visual acuity; MS: Multiple sclerosis; ON: Optic neuritis.

Table 2 Results of ROC analysis in distinguishing between normal individuals and those with MS

Visual indices	AUC	*P*	Associated criterion	Sensitivity (%)	Specificity (%)
BCVA (logMAR)	0.349	0.003	>0	27.27	97.01
Refractive error components					
Sphere (D)	0.610	0.029	≤-0.25	43.94	74.63
Cylinder (D)	0.438	0.217	>-0.75	71.21	40.30
SE (D)	0.589	0.075	≤-0.88	36.36	82.09
Contrast sensitivity					
3 CPD	0.545	0.367	≤1	22.73	89.55
6 CPD	0.640	0.005	≤1.69	72.73	47.76
12 CPD	0.560	0.231	≤0.90	27.27	92.54
18 CPD	0.651	0.003	≤0.65	25.76	97.01

ROC: Receiver operating characteristic; AUC: Area under the curve; CPD: Cycles per degree; SE: Spherical equivalent; BCVA: Best-corrected visual acuity; MS: Multiple sclerosis.

in the control group. Within the MS group, 18 cases were diagnosed with ON. The average age of participants in the MS group was 37.5±4.27y, while the control group had a mean age of 38.45±4.60y, with no statistically significant difference observed (P=0.346). Additionally, 53.5% of the MS group and 46.5% of the control group were male.

Table 1 presents the mean and SD for BCVA and CS across spatial frequencies of 3, 6, 12, and 18 CPD. The data indicate that the BCVA is significantly better in the control group than in patients with MS (P<0.001). However, no statistically significant difference in BCVA is observed between MS patients with ON and those without ON (P=0.782). Furthermore, MS patients exhibit reduced CS at spatial frequencies of 6 and 18 CPD when compared to healthy controls, while those with ON demonstrate diminished CS at a spatial frequency of 3 CPD (P<0.05).

Regarding refractive errors, the study found that the spherical component of refractive error was significantly more myopic in the MS group (P=0.047); However, no significant difference was found between MS patients with and without ON (P=0.292). The cylindrical component of refractive error also showed no significant differences between any of the evaluated groups (P>0.05).

Table 2 presents the sensitivity, specificity, associated criterion, and AUC for visual parameters aimed at differentiating between patients with MS and healthy controls. Notably, BCVA exhibited a sensitivity of 27.27% and a specificity of 97.01%. The CS at a spatial frequency of 6 CPD demonstrated the highest sensitivity, while CS at a spatial frequency of 18 CPD achieved the greatest AUC in distinguishing between MS patients and healthy individuals.

Table 3 presents the sensitivity, specificity, associated criterion, and AUC for BCVA and CS across various spatial frequencies for diagnosing ON in patients with MS. The analysis revealed that the AUC for spatial frequency at 3 CPD exhibited the highest value of 0.672, with a diagnostic cutoff point set below 1.18. This resulted in a sensitivity of 55.56% and a specificity of 68.75%.

Figure 1 illustrates the ROC curve and the corresponding AUC for CS across different spatial frequencies, designed to differentiate between MS patients with ON and those without ON.

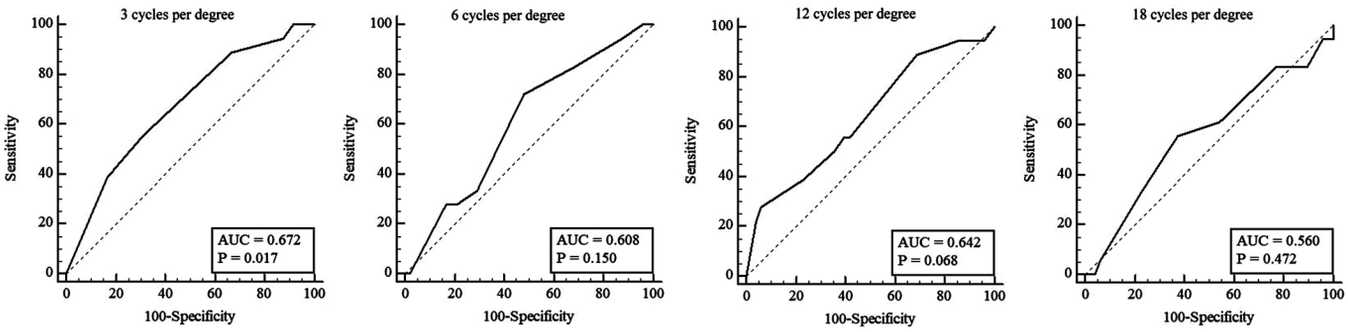

Figure 1 A comparison of the contrast sensitivity in different spatial frequencies with a good AUC for differentiating optic neuritis in multiple sclerosis patients AUC: Area under the receiver operating characteristic curve.

Table 3 Results of ROC analysis, in distinguishing between MS patients with/without ON

Visual indices	AUC	*P*	Associated criterion	Sensitivity (%)	Specificity (%)
BCVA (logMAR)	0.463	0.645	>0	33.33	75.00
Refractive error components					
Sphere (D)	0.487	0.868	>0.25	44.44	75.00
Cylinder (D)	0.432	0.400	>-0.5	38.89	75.00
SE (D)	0.450	0.536	>0	44.44	77.08
Contrast sensitivity					
3 CPD	0.672	0.033	≤1.18	55.56	68.75
6 CPD	0.608	0.181	≤1.56	72.22	52.08
12 CPD	0.642	0.078	≤0.60	27.78	93.75
18 CPD	0.560	0.458	≤0.65	55.56	62.50

ROC: Receiver operating characteristic; MS: Multiple sclerosis; AUC: Area under the receiver operating characteristic curve; CPD: Cycles per degree; SE: Spherical equivalent; BCVA: Best-corrected visual acuity; ON: Optic neuritis.

DISCUSSION

Idiopathic acute demyelination of the optic nerve is frequently observed as one of the initial clinical manifestations in patients with MS[17]. This condition typically results in a reduction of vision lasting between 7 to 10d. In cases of typical ON, it is common for vision to recover to baseline levels within 30d following the onset of symptoms[18]. There are, however, documented instances of significant disturbances in high-contrast VA persisting for as long as 5 to 8y following the initial episode of ON[8]. Consequently, it is crucial to take into account patients' reports of diminished visual quality in conjunction with other manifestations of MS when determining the appropriate investigative measures for these individuals.

This study indicated a significant difference in BCVA when comparing healthy individuals to patients with MS, with mean values of -0.02 and 0.03 logMAR, respectively. Furthermore, the findings revealed that there was no statistically significant difference in BCVA between MS patients who have experienced ON and those who have not, with measurements of 0.04 and 0.03 logMAR, respectively. Sanchez-Dalmau *et al*[19] identified BCVA and color vision as critical metrics for evaluating high-definition visual function in patients with MS. Their findings indicated that MS patients who experienced ON had an average BCVA of 0.00 logMAR, which was significantly lower than the mean -0.02 logMAR observed in those without ON. Additionally, the ONTT cohort study revealed that following the initial episode of ON and the subsequent decline in VA during the first ten days[18], high-contrast VA tends to return to baseline levels, remaining stable for up to 15y in the majority of patients[7]. High-dose intravenous steroid therapy administered during the initial attack has been shown to have no long-term impact on high-contrast VA[20]. The inflammatory mediators produced within the optic nerve[21], along with a reduction in sensory input to higher neural centers[22] in individuals with MS, are likely to contribute to a series of alterations that result in diminished VA. Conversely, it appears that certain changes in the visual function of MS patients are associated with the occurrence of ON, suggesting that the absence of ON should not influence these visual function changes. Nonetheless, it is plausible that individuals without a history of ON may have experienced mild, subclinical episodes of ON[23].

In this study, a VA threshold of 0.00 logMAR was determined to serve as the diagnostic cut-off point. This threshold revealed a high specificity of 97.01% for MS and 75.00% for ON. In contrast, the sensitivity was found to be low, with values of 27.27% for MS and 33.33% for ON. These results suggest that a BCVA below 0.00 logMAR can reliably rule out the presence of MS and ON with significant confidence. Nevertheless, when BCVA does not fall below this threshold, one cannot

confidently conclude that MS or ON are absent. Limited studies have addressed this subject, with Talman *et al*[24] noting that a change in BCVA exceeding 5 letters (or more than one line on the ETDRS chart) is regarded as a significant alteration in individuals with MS. They further assert that changes below this threshold do not adequately reflect variations in BCVA among this population. Although the current study reveals a significant difference in BCVA between the groups examined, the clinical implications are limited, and such differences are not deemed clinically significant. One factor that may affect the observed outcomes is the influence of pharmacological treatments administered to these patients. For instance, Perez-Velilla *et al*[25] found that the use of Fingolimod in MS treatment is associated with a reduction in BCVA. Consequently, any observed decline in BCVA cannot be definitively attributed to the presence of MS or ON, highlighting the necessity for further research in this area.

It has been shown that most daily activities do not require a BCVA of 0.00 logMAR, and a reduction to 0.3 logMAR does not impede the performance of daily living tasks or driving[26]. Mowry *et al*[6] demonstrated that a decline of two lines in BCVA is necessary to observe a decrease in the scores of the health-related quality of life (HRQOL) questionnaire among patients with MS. Conversely, low-contrast VA is relevant for daily activities that do not demand performance near the upper thresholds of BCVA[27]. Numerous studies have investigated low-contrast VA in MS patients[9-10,28], revealing consistent findings of defects across various spatial frequencies in the presence of MS and ON. Some studies employed the Sloan chart to evaluate VA at contrast levels of 1.25% and 2.5%[9-10], while others utilized the Mentor B-VAT[29] or Pelli-Robson[30] charts to assess and quantify CS in individuals with MS.

In the present study, the CS was assessed using the CSV-1000 across four spatial frequencies: 3 (0.1 decimal), 6 (0.2 decimal), 12 (0.4 decimal), and 18 (0.6 decimal) CPD[31]. The evaluation of the four mentioned spatial frequencies in the CSV-1000 were chosen for their clinical and functional relevance in evaluating CS across various visual tasks and situations including broader visual impairments, daily activities, and fine detail vision. The findings indicated a reduction in CS at all four spatial frequencies among MS patients when compared to healthy controls. Furthermore, MS patients with ON exhibited lower CS than those without ON. Statistical analysis revealed significant differences in the spatial frequencies of 6 and 18 CPD between MS participants and normal controls, as well as in the spatial frequency of 3 CPD when comparing MS patients with ON to those without. Satue *et al*[32] noted that the reduction in CS measured by the CVS-1000 test across all four spatial frequencies was statistically significant in patients diagnosed with MS. Moreover, the variation in severity of the disease[33] may contribute to the differing degrees of reduction observed at various spatial frequencies. Alterations in contrast CS associated with MS have been documented in various studies[29-30]. Nunes *et al*[29] similarly reported that among the spatial frequencies examined, MS patients exhibited the highest and lowest CS at spatial frequencies of 6 and 20 CPD, respectively. The findings of the current study indicate that the presence of ON leads to a further reduction in CS among MS patients, with the most significant decline observed at 3 CPD. Additionally, González Gómez *et al*[30] found that CS, as measured by the Pelli-Robson chart, was approximately 0.1 lower in MS patients with ON compared to those without. Most research in this area suggests that the most pronounced decrease in CS occurs at lower spatial frequencies[29].

Alterations in the neural pathways of patients with MS indicate that the lateral connections to the monocular columns of the visual cortex exhibit greater damage in specific regions[34-35]. The findings of this study reveal that among the four spatial frequencies evaluated, the CS was lowest at 18 CPD and highest at 6 CPD across all participants. Notably, the current study indicates that a CS threshold of 1.69 at 6 CPD demonstrates the highest sensitivity (72.73%) for diagnosing MS, while a CS greater than 0.65 at 18 CPD yields the highest specificity (97.01%). Furthermore, it was found that a CS below 1.56 at 6 CPD provides the highest sensitivity (72.22%) for diagnosing ON in MS patients, with a CS above 0.65 at 12 CPD showing the highest specificity (93.75%). These results underscore the critical role of assessing CS at spatial frequencies near 6 CPD in cases where MS is suspected. A review of existing literature indicates that the use of CS cut points as a diagnostic criterion for MS has not been previously explored, suggesting that the outcomes of this study may serve as a reference for future research.

Refractive error is a critical factor influencing both high and low CS[36]. The findings of this study indicated that the mean values of spherical and spherical equivalent (SE) components of refractive error exhibited statistically significant differences across various evaluations, with a notable trend towards myopic shifts associated with MS and ON. In the research conducted by Gil-Casas *et al*[13] the mean SE values for the control group, MS patients with unilateral ON, and those with bilateral ON were recorded as -0.30, +0.32, and +0.17 diopters (D), respectively. Although MS patients in this study demonstrated a greater degree of hyperopia compared to healthy controls, the presence of bilateral ON resulted in a slight myopic shift when compared to patients with unilateral ON. Hiyoshi *et al*[12] conducted a cohort study over a period of 48y, involving 1 559 859 participants aged between 20 and 68y, of whom 3134 were diagnosed with MS. That study aimed to explore the potential relationship between variations

in vitamin D levels and myopia in individuals with MS. However, the findings indicated no statistically significant correlation between the occurrence of MS and myopia, even after controlling for confounding variables. In this research, myopia was defined as an SE of less than -1.00 diopters. It appears that the limited changes in the studied parameters, along with their initial values falling within the emmetropic range, suggest that the observed differences lack clinical significance.

Vural *et al*[37] reported that the amplitude of accommodation in patients with MS was significantly reduced, measuring 4.05 D, in contrast to 6.00 D observed in healthy individuals. This finding suggests that while MS and ON do not induce substantial alterations in refractive errors, a slight myopic shift may arise from a reduction in accommodation amplitude coupled with an increase in neuronal impulses, which may also serve to offset the decrease in accommodation. The study indicates that myopia values below the thresholds of -0.25 and +0.25 exhibited good specificity (74.63% and 75%, respectively) for identifying healthy controls; however, myopic shifts beyond these thresholds demonstrated low sensitivity for diagnosing MS (43.94%) and the presence of ON (44.44%).

The study revealed a numerical reduction in astigmatism among MS patients, with values of -0.746 D in the MS group compared to -0.817 D in control subjects. Additionally, astigmatism was measured at -0.611 D in MS patients with ON versus -0.797 D in those without ON. However, these variations did not reach statistical significance. It is important to consider that higher order aberrations remain unchanged in MS[37], suggesting that the limited alterations in astigmatism may be attributed to variations in accommodation[38]. Nonetheless, since accommodation responses below 4.00 D are unlikely to produce significant changes in astigmatism[39], the observed differences in this study's participants were not statistically significant. Furthermore, the findings indicate that astigmatism values lower than -0.75 D exhibit a sensitivity of 71.21% for diagnosing MS, while values better than -0.50 D demonstrate a specificity of 75% for diagnosing ON in MS patients. It is crucial to emphasize that the cut points established in this research are specific to the study's participants and should be considered alongside other parameters for clinical application.

The findings of the present study must be interpreted with caution due to several limitations. First, the sample size, particularly in the subgroup of MS patients with ON (n=18), is relatively small. This limits the statistical power and may have influenced the ability to detect significant differences between groups. Furthermore, the study did not differentiate between different forms of MS (*e.g.*, relapsing-remitting *vs* progressive). Another limitation of this study is its cross-sectional design, which provides only a snapshot of visual function at a single point in time. Additionally, the study was conducted at a single center, which raises concerns about the generalizability of the results to other populations due to variations in risk factors such as vitamin D levels, UVB exposure, and genetic predispositions[40]. Besides, the age restriction (30–45y) applied in this study may limit the applicability of the findings to younger or older populations, who might experience different patterns of visual dysfunction due to MS or ON[41].

In conclusion, MS induces a range of alterations in the visual system's functions, which can manifest with or without the presence of ON. Given the scarcity of research aimed at determining the diagnostic thresholds for various visual function parameters, the findings of this study may serve as a foundational reference for subsequent investigations. Future researches are encouraged to address the mentioned limitations by conducting larger and more diverse studies to establish robust diagnostic thresholds for visual function parameters, exploring differences in visual system alterations across various forms of MS, and performing longitudinal studies to understand the progression of visual impairments in MS patients over time. These findings could guide clinicians in developing more precise diagnostic tools and therapeutic interventions for visual dysfunctions in MS patients.

ACKNOWLEDGEMENTS

Conflicts of Interest: Behnia B, None; **Layedh A,** None; **Hashemi H,** None; **Jamali A,** None; **Yekta A,** None; **Zamani N,** None; **Moravej R,** None; **Khabazkhoob M,** None.

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