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Vision-related quality of life in neuromyelitis optica spectrum disorder: Evidence of subclinical visual dysfunction

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Abstract

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory demyelinating disorder of the central nervous system that frequently results in permanent neurological disability, most commonly due to recurrent transverse myelitis. Although physical and psychological health-related quality of life in NMOSD has been widely studied, the impact of optic neuritis (ON) on vision-related quality of life (VRQoL) remains underreported. *Methods*: This multicenter cross-sectional study assessed VRQoL using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in 52 patients: 30 with prior ON (NMOSD+ON) and 22 without (NMOSD−ON). VFQ-25 scores were analyzed alongside clinical parameters including best-corrected visual acuity (BCVA), disease duration, and ON history. *Results*: NMOSD+ON patients were older (median 43 vs. 33 years; $p = 0.02$), had longer disease duration (8.5 vs. 4.5 years), and lower BCVA ($p = 0.002$). NEI VFQ-25 composite scores were significantly lower in the NMOSD+ON group (75.7 vs. 98.3), with consistently reduced scores across all subscales ($p<0.001$). Notably, NMOSD−ON patients demonstrated subtle reductions in general vision, near tasks, and distance activities, suggesting subclinical optic nerve involvement. Multivariate regression analysis identified BCVA of both the better and worse-seeing eyes as independent predictors of VRQoL, irrespective of ON history.
Conclusions: These findings underscore the sensitivity of NEI VFQ-25 as a patient-reported outcome measure for detecting visual compromise in NMOSD, including subtle deficits in patients without clinically overt ON.

Keywords: NMOSD, NEI VFQ-25, optic neuritis, subclinical optic neuritis, vision related quality of life

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic autoimmune inflammatory disorder of the central nervous system (CNS) that predominantly affects the optic nerve and spinal cord.1 NMOSD is now recognized as a distinct entity due to the discovery of aquaporin-4 antibody (AQP4-IgG), a highly specific biomarker for the disease.[1,2] NMOSD affects 1-10 individuals per 100,000 individuals worldwide, with a strong female predominance

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and a typical onset in the fourth decade of life.[3-5] Clinically, it presents with ON, TM, and other characteristic syndromes involving the postrema, diencephalon, brainstem, and cortex.[6]

ON in NMOSD is often bilateral, severe, and recurrent, resulting in profound reductions in visual acuity (VA), visual field (VF) loss, and color vision (CV), often with poorer recovery and prognosis than MS-associated ON.[6–8] Spinal cord involvement typically manifests as longitudinally extensive transverse myelitis (LETM), leading to significant motor and sensory impairments, paraparesis or quadriparesis, bladder dysfunction, and tonic spasms.[6,7] These ON and LETM episodes significantly compromise independence, with pooled cohort data suggesting that up to half of patients with NMOSD may develop severe visual or motor disability within 5 years of onset, manifesting as legal blindness or ambulatory dependence despite immunotherapy.[9-11] This cumulative burden contributes to the progressive deterioration of quality of life (QoL).[9-11]

While QoL in NMOSD has been explored in the context of pain, fatigue, and depression, the specific impact of visual impairment following ON on vision-related Q0L (VRQoL) remains under-investigated.[12-14] VRQoL encompasses how visual deficits affect the functional, emotional, and social domains of everyday life, which often do not correlate directly with the measured visual function.[15,16] This study aimed to evaluate VRQoL and its associated factors in patients with NMOSD attending tertiary referral centers and to emphasize the importance of visual function preservation to improve overall QoL.

METHODS

Study design

A cross-sectional study was conducted between January 2024 and January 2025 at three tertiary centers: Hospital Pakar Universiti Sains Malaysia (HPUSM), Hospital Raja Perempuan Zainab II (HRPZ II), and Hospital Tengku Ampuan Rahimah (HTAR). This study received ethical approval from two institutional review boards [USM/JEPeM/KK/23100752; NMRR ID-23-03057-Q8R (IIR)] and adhered to the principles of the Declaration of Helsinki.

Patient selection and data collection

Eligible participants were recruited using a convenience sampling method from the ophthalmology clinic at HPUSM and the neurology clinics at HRPZ II and HTAR due to the rarity of NMOSD. Patients aged 18 years with a confirmed diagnosis of NMOSD, determined by a neurologist based on a constellation of at least one core clinical characteristic of NMOSD and neuroimaging findings typical of the disease, regardless of aquaporin-4 immunoglobulin G (AQP4-IgG) serostatus, were eligible for enrollment. The exclusion criteria included amblyopia, cognitive or psychiatric disabilities, prior ocular trauma or surgery, and any pre-existing ocular pathology resulting in reduced VA before NMOSD diagnosis. All participants provided written informed consent before enrollment.

Patient interviews were conducted to collect demographic data. Clinical data related to comorbidities, presentation, diagnosis, and treatment of NMOSD were retrieved from the patients' medical records. Participants without prior ophthalmic evaluations were referred to the ophthalmology clinic of each hospital for comprehensive assessment, including VA testing, fundus examinations, intraocular pressure measurements, optical coherence tomography (OCT) of the optic nerve head, and Humphrey visual field analysis. VA was assessed using Snellen charts and subsequently converted to logMAR values using a standardized conversion table to facilitate statistical analysis.[17] Ishihara pseudoisochromatic 25 color plates were used to assess CV and as a clinical surrogate for contrast sensitivity testing.[18]

VRQoL assessment using the NEI VFQ-25

The National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) is a brief yet psychometrically robust 25-item version of the original 51-item. It comprises 25 items organized into 12 subscales and three conceptual domains, to evaluate the impact of visual impairment on daily functioning and emotional well-being.[19] The first domain evaluates the general health status (1 item). The second domain assesses visual function and includes general vision (1 item), difficulty with distance-related activities (3 items), difficulty with near tasks such as reading or handling objects (3 items), peripheral vision (1 item), and color vision (1 item). The third domain captures vision-specific QoL, encompassing dependency (3 items), role limitations (2 items), mental health (4 items), social functioning (2 items), driving ability (2 items), and ocular pain (2 items). Each subscale

score is converted to a score between 0 and 100, and higher scores indicate better VRQoL.[19]

A validated Malay version of the NEI VFQ-25 was used in this study[20], as most participants speak *Bahasa Melayu* as the primary language. The questionnaire was administered either by self-completion or with interviewer assistance. Two trained research assistants facilitated the completion of the study and provided support during data collection as needed. Participants with visual or physical limitations were accommodated to ensure accurate and inclusive data entry. The median NEI VFQ-25 scores and corresponding data were entered into a secure database for statistical analysis.

Statistical analysis

All data were systematically recorded and analyzed using IBM SPSS Statistics version 29. Descriptive statistics were used to summarize sociodemographic characteristics, with non-normally distributed numerical data presented as the median (interquartile range) and categorical data as the frequency (percentage). Group comparisons were conducted using the Mann–Whitney U, Pearson's chi-square, and Fisher's exact tests. Associations between clinical variables and NEI VFQ-25 composite scores were initially assessed using simple linear regression, followed with multiple linear regression to identify the independent predictors of VRQoL. All candidate variables were included in the initial model, and non-significant predictors were excluded in the final step. Multicollinearity was assessed using the variance inflation factor, and no significant multicollinearity was detected. Associations between continuous variables were additionally assessed using Spearman's rank correlation. Statistical significance was set at $p \leq 0.05$.

RESULTS

Demographic and clinical profile

A total of 52 patients with NMOSD were recruited, of whom 30 had a history of ON (NMOSD+ON) and 22 did not (NMOSD−ON). Patients in the NMOSD+ON group were significantly older than those in the NMOSD−ON group (median age: 43 vs. 33 years, $p = 0.020$). Most participants were female, and the majority in both groups were of Malay ethnicity (76.7%, NMOSD+ON; 81.8%, NMOSD−ON). The common comorbidities included hypertension, hyperlipidemia, diabetes mellitus, and bronchial asthma. In addition, one patient in the NMOSD+ON group had hyperthyroidism, one patient in the NMOSD−ON group had systemic lupus erythematosus, and another had rheumatoid arthritis. Demographic and clinical characteristics are presented in Table 1.

Although the median disease duration was longer in the NMOSD+ON group (8.5 vs. 4.5 years), the difference was not statistically significant ($p = 0.320$). Overall, 82.7% of the patients were seropositive for AQP4-IgG. Recurrent ON was observed in 29 (96.7%) of 30 patients within the NMOSD+ON group. BCVA was significantly poorer in these patients ($p = 0.002$), with legal blindness recorded in 33.3% and 13.3% of patients unilaterally and bilaterally, respectively. Transverse myelitis was prevalent in both groups but more common among patients with NMOSD−ON (81.8%) than among patients with NMOSD+ON (46.7%). Brain stem symptoms and diplopia were infrequent, and no significant between-group differences were observed.

NEI VFQ-25 subscale and composite score

Table 2 summarises the NEI VFQ-25 subscale scores among patients with NMOSD. Patients in the NMOSD+ON group reported significantly lower median scores across nearly all subscales, with the most pronounced reductions observed in general vision [60 (IQR: 37.5–82.5)] and mental health [68.8 (IQR: 40.6–96.9)]. Although median subscale scores in the NMOSD−ON group reached the maximum value of 100, the IQR variability was observed across several subscales, including general vision (IQR: 90–100) and driving (IQR: 95.8–100). The median NEI VFQ-25 composite score was also significantly lower in the NMOSD+ON group than in the NMOSD−ON group (75.7 vs. 98.3, $p < 0.001$). Figure 1 provides a visual comparison of median subscale scores between the two groups.

Predictors of VRQoL based on NEI VFQ-25 composite scores

To identify predictors of VRQoL, multivariate regression analyses was performed using the NEI VFQ-25 composite score as the dependent variable (Table 3). In simple linear regression analysis, female sex, history of ON, BCVA of the best and worst eyes, and abnormal color vision were significantly associated with VRQoL. Backward stepwise regression revealed that

Table 1: Demographic and clinical characteristics of NMOSD patients

Variables	Total NMOSD n = 52	NMOSD+ON n = 30	NMOSD−ON n = 22	p-value
Age (years)				
Median (IQR)	38.5 (20–62)	43.0 (22–62)	33.0 (20–55)	0.002[a]
Gender, n (%)				
Male	7 (13.5)	5 (16.7)	2 (9.1)	0.685[b]
Female	45 (86.5)	25 (83.3)	20 (90.9)	
Race, n (%)				
Malay	41 (78.8)	23 (76.7)	18 (81.8)	
Chinese	9 (17.3)	7 (23.3)	2 (9.1)	0.100[b]
Indian	2 (3.9)	0	2 (9.1)	
Education level, n (%)				
Primary	3 (5.8)	1 (3.3)	2 (9.1)	
Secondary	32 (61.5)	18 (60)	14 (63.6)	0.652[b]
Tertiary	17 (32.7)	11 (36.7)	6 (27.3)	
Comorbidity, n (%)				
Yes	17 (32.7)	9 (30.0)	8 (36.4)	0.629[c]
No	35 (67.3)	21 (70.0)	14 (63.6)	
Recurrence of optic neuritis				
Yes	-	29 (96.7)	-	<0.001[c]
No		1 (3.3)		
Transverse myelitis, n (%)				
Yes	32 (61.5)	14 (46.7)	18 (81.8)	0.010[c]
No	20 (38.5)	16 (53.3)	4 (18.2)	
Brain stem symptoms, n (%)				
Yes	7 (13.5))	2 (6.7)	5 (22.7)	0.119[c]
No	45 (86.5)	28 (93.3)	17 (77.3)	
Diplopia, n (%)				
Yes	7 (13.5)	3 (10.0)	4 (18.2)	0.438[c]
No	45 (86.5)	27 (90.0)	18 (81.8)	
Abnormal color vision				
Yes	20 (38.5)	20 (66.7)	0 (0)	<0.001[c]
No	32 (61.5)	10 (33.3)	22 (100)	
Duration of the disease (years)				
Median (IQR)	6.0 (1–25)	8.5 (1–25)	4.5 (1–18)	0.320[a]
BCVA of the better-seeing eye (logMAR) Median (IQR)	0.00 (0.00–3.00)	0.18 (0.00–3.00)	0.00 (0.00–0.22)	0.002[a]
BCVA of the worse-seeing eye (logMAR) Median (IQR)	0.00 (0.00–3.00)	1.09 (0.00–3.00)	0.00 (0.00–0.18)	0.001[a]
AQP4-IgG positivity (%)				
Yes	43 (82.7)	26 (86.7)	17 (77.3)	0.468[c]
No	9 (17.3)	4 (13.3)	5 (22.7)	

Abbreviations: NMOSD+ON, NMOSD with optic neuritis; NMOSD−ON, NMOSD without optic neuritis, IQR, interquartile range; BCVA, best-corrected visual acuity; AQP4-IgG, aquaporin-4 immunoglobulin G
[a]Mann–Whitney; [b]Fisher exact test; [c]Chi square test; p-value < 0.05, significant

Table 2: Subscale NEI VFQ-25 scores in patients with NMOSD

NEI VFQ-25 Subscale	NMOSD n = 52 Median (IQR)	NMOSD+ON n = 30 Median (IQR)	NMOSD−ON n = 22 Median (IQR)	p-value*
General health	50 (25, 75)	50 (25, 75)	50 (25, 75)	0.444
General vision	80 (60, 100)	60 (37.5, 82.5)	100 (90, 100)	<0.001
Near activities	91.7 (79.2, 100)	83.3 (58.1, 100)	100 (98.9, 100)	<0.001
Distance activities	91.7 (79.2, 100)	75 (51, 98.9)	100 (98.4, 100)	<0.001
Peripheral Vision	100 (87.5, 100)	75 (50,100)	100 (100, 100)	<0.001
Color Vision	100 (90.7, 100)	100 (87.5, 100)	100 (100, 100)	<0.001
Social functioning	100 (87.5, 100)	75 (50, 100)	100 (100, 100)	<0.001
Mental health	87.5 (68.8, 100)	68.8 (40.6, 96.9)	100 (96.9,100)	<0.001
Role difficulties	100 (87.5, 100)	75 (50, 100)	100 (100, 100)	<0.001
Dependency	95.8 (76.0, 100)	75 (45.8, 100)	100 (100, 100)	<0.001
Driving	91.7 (70.8, 100)	83.3 (54.1, 100)	100 (95.8, 100)	0.031
Ocular pain	100 (100, 100)	100 (93.8, 100)	100 (100, 100)	0.003
Composite score	**94.6 (81.8, 100)**	**75.7 (54.9, 96.6)**	**98.3 (96.6, 100)**	**<0.001**

NMOSD+ON, NMOSD with optic neuritis; NMOSD−ON, NMOSD without optic neuritis; IQR, interquartile range *p-values represent comparisons between NMOSD+ON and NMOSD−ON groups only (Mann–Whitney U test); $p < 0.05$ was considered statistically significant.

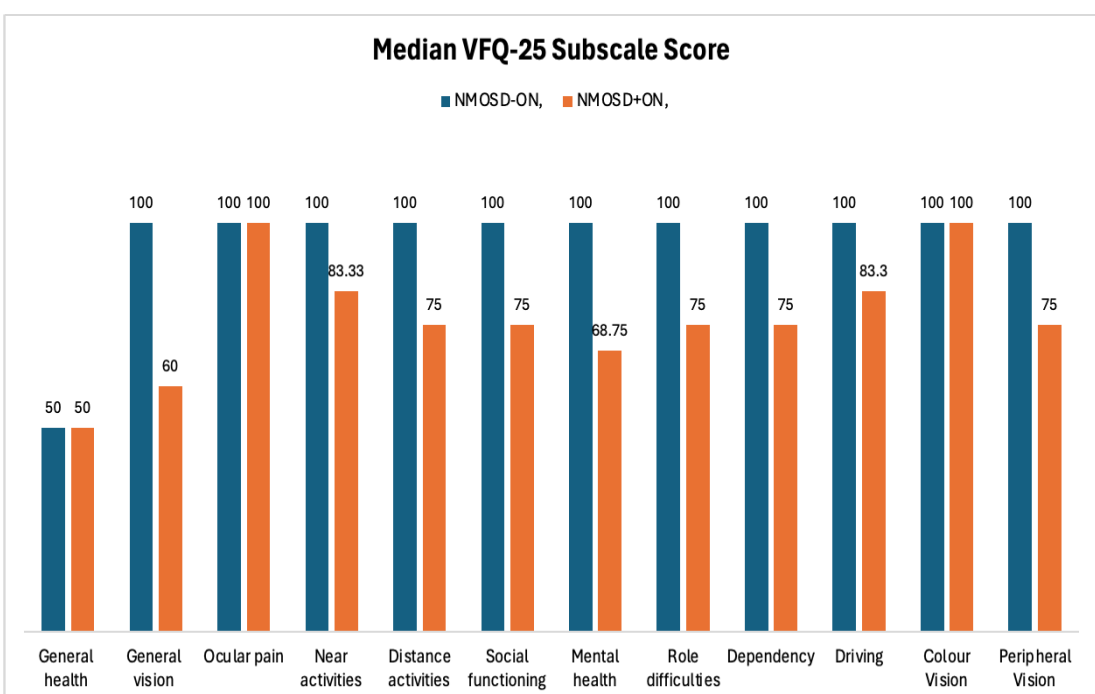

Figure 1. Median NEI VFQ-25 subscale scores in patients with NMOSD compared with those with a history of optic neuritis (NMOSD+ON) and those without (NMOSD−ON).

Table 3: Associated factors of NEI VFQ-25 composite score among patients with NMOSD

Variables	Simple linear regression analysis		Multiple linear regression analysis	
	Crude B (95% CI)	p-value	Adj. B (95% CI)	p-value
Age	−0.65 (−1.35, 0.05)	0.070		
Gender	−11.78 (−34.45, 10.89)	0.032	−1.05 (−11.15, 9.05)	0.835
Race	7.35 (−11.66, 26.39)	0.442		
Education level	3.27 (−13.38, 19.92)	0.695		
Duration of the disease	−9.42 (−25.44, 6.60)	0.243		
History of optic neuritis	−30.35 (−43.63, −17.07)	<0.001	−3.96 (−13.24, 5.32)	0.395
AQP4-IgG seropositivity	−2.19 (−22.86, 18.47)	0.832		
BCVA-best eye (logMAR)	−29.53 (−36.01, −23.06)	<0.001	−17.88 (−23.23,−12.52)	<0.001
BCVA-worst eye (logMAR)	−19.76 (−23.54, −15.99)	<0.001	−8.43 (−13.92, −2.94)	0.003
Abnormal CV	−41.88 (−52.70, −31.07)	<0.001	−10.34 (−23.91, 3.24)	0.132
Transverse myelitis	6.56 (−9.41, 22.53)	0.413		
Brainstem symptoms	18.96 (−3.31, 41.23)	0.093		
Diplopia	8.67 (−14.11, 31.45)	0.448		

The backward multiple linear regression method was applied, and the variables of gender and optic neuritis status were excluded due to their statistical non-significantness. No multicollinearity interactions were observed between the variables. A p-value < 0.05 is considered significant.

BCVA in the best ($p < 0.001$) and worst ($p = 0.003$) eyes was an independent predictor.

Spearman's rank correlation analysis supported the regression findings, revealing significant inverse associations between BCVA and NEI VFQ-25 composite scores. The BCVA of best-eye showed a moderate correlation ($\rho = -0.587$, $p < 0.001$), while the BCVA of worst-eye showed a stronger correlation ($\rho = -0.788$, $p < 0.001$). As illustrated in Figure 2, increasing logMAR values, which indicate poorer VA, were associated with declining NEI VFQ-25 composite scores, underscoring the functional impact of acuity loss on patient reported QoL.

DISCUSSION

This study examined the differences in demographic, clinical, and VRQoL among patients with NMOSD, with and without a history of ON. The strong female predominance and age distribution observed in our cohort are consistent with established epidemiological patterns.[3,21] Although previous Malaysian data have reported similar proportions of NMOSD cases among Malay and Chinese individuals[4], our cohort was predominantly Malay. This distribution likely reflects the population demographics of Kelantan, where most participating centres are located, and may not be representative of national or regional prevalence patterns.

Consistent with previous reports, our NMOSD+ON cohort demonstrated significantly lower NEI VFQ-25 composite and subscale scores reflecting the visual disability associated with ON.[22-24] The greatest declines were observed in the visual function domains, including general vision, near activities, distance activities, and peripheral vision, extending to vision-specific QoL domains, including social functioning, mental health, role difficulties, dependency, and driving. These findings reflect the substantial functional and psychosocial burden associated with ON-related visual impairment in NMOSD.

Importantly, high NEI VFQ-25 scores in NMOSD−ON patients should not be interpreted as the absence of visual disability. Rather, they reflect near-ceiling performance on a questionnaire with limited sensitivity for detecting mild or early visual dysfunction, while subtle visual difficulties may still be present and perceived as mild by patients. In our cohort, although the median subscale scores in the NMOSD−ON group approached ceiling values, the IQR variability was observed across several domains, including general vision, near and distance activities, driving, and mental health (Table 2). This variability indicates that a subset of NMOSD−ON patients reported visual difficulties despite the absence of clinically overt

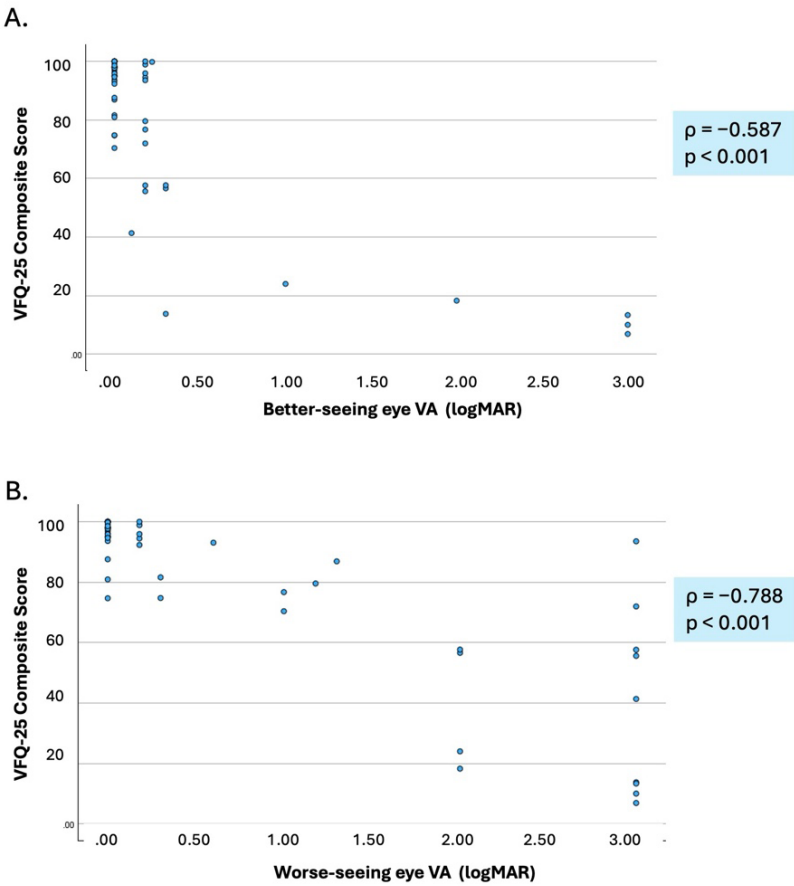

Figure 2. Scatterplots showing the Spearman rank correlation between BCVA (logMAR) and vision-related quality of life as assessed by the NEI VFQ-25 composite score for the better- (A) and worse-seeing (B) eyes in patients with NMOSD. Spearman correlation coefficients (ρ) and p-values are shown. Increasing logMAR values (poorer acuity) were associated with decreased VFQ-25 scores (reduced VRQoL).

ON. These patient-reported findings align with prior structural studies reporting RNFL thinning, macular ganglion cell layer atrophy, and reduced contrast sensitivity in non−ON eyes of patients with NMOSD[25-27], supporting the presence of subclinical optic nerve involvement in clinically silent eyes.

Emerging evidence further supports bilateral anterior visual pathway vulnerability in NMOSD. Structural and functional abnormalities, including reduced VA, VF deficits, and peripapillary RNFL thinning, have been reported in contralateral non-ON eyes shortly after unilateral ON onset.[28] In addition, the pathogenic AQP4-IgG–mediated astrocytopathy targeting retinal Müller cells may precede clinically overt ON, contributing to early retinal vulnerability.[29] These mechanisms may underlie the subtle VRQoL impairments observed in NMOSD−ON patients, particularly in domains sensitive to contrast sensitivity and peripheral vision.

VA alone does not fully explain VRQoL. Consequently, VRQoL is not intended to quantify VA–based disability, but to reflect patient-perceived functional limitations across multiple visual domains, capturing the combined effects of binocular and non-acuity visual factors rather than a single VA threshold. Even in patients with apparently normal VA, visual function may still be impaired by VF defects, dyschromatopsia, diplopia, or other non-acuity disturbances. Importantly, when VA differs between the two eyes, impairment in the fellow eye can disrupt binocular vision, depth perception, contrast sensitivity, and peripheral awareness, leading to functional difficulties in daily activities such as facial recognition, object identification, mobility, and driving, as reflected in NEI VFQ-25 subscale

scores.[30-36]

Although the color vision subscale did not retain significance in our multivariate analyses, its clinical relevance in remains well recognised. Colour vision deficits following ON, including tritan defects in acute phases and red-green impairment in chronic stages, may affect daily visual tasks requiring fine chromatic discrimination.[37-40] Integrating chromatic testing with psychophysical assessments and NEI VFQ-25 scoring may therefore provide a more nuanced understanding of visual disability, supporting earlier intervention and tailored rehabilitation strategies. Screening tools such as Farnsworth D-15 test, with its sensitivity to acquired dyschromatopsia and broader axis coverage than Ishihara plates, may further complement psychophysical testing and patient-reported outcomes in NMOSD surveillance.[41-43]

In contrast to previous studies linking AQP4-IgG seropositivity with poorer VRQoL[44], no significant association was found between this antibody serostatus and NEI VFQ-25 scores in our cohort. This finding suggests that patient-reported outcomes may reflect cumulative structural damage rather than active immunological status. Similar VRQoL impairments have been reported in both AQP4-IgG– and MOG-IgG–associated ON,[45] further supporting the notion that attack severity, recurrence, and bilaterality may be more predictive of visual disability than antibody subtype alone.

Despite the valuable insights gained, this study is limited by its relatively small sample size and cross-sectional design, which limit causal inference and generalisability. Incomplete structural assessments, including OCT and visual field testing reflect real-world constraints related to resource availability and patient disability. Nevertheless, our findings support the NEI VFQ-25 as a valuable multidimensional tool capturing functional and psychosocial aspects of vision loss. The subtle VRQoL reductions observed in NMOSD−ON patients suggest that subclinical visual dysfunction may be missed during routine clinical assessment, highlighting the value of incorporating patient-reported outcomes into comprehensive NMOSD care.

DISCLOSURE

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Conflicts of interests: None

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