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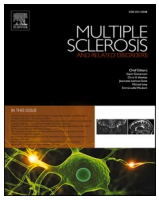

Original article

Patient reported outcomes in NMOSD reflect a high disease burden and do not correlate with the EDSS

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ABSTRACT

Background: The Expanded Disability Status Scale (EDSS) is routinely used to evaluate disability in Neuromyelitis Optica Spectrum Disorder (NMOSD), although it has only been validated in multiple sclerosis (MS) and may not capture important aspects of the patient experience in NMOSD.
Objective: To evaluate the relationship between Patient-Reported Outcomes (PROs), including for pain, fatigue, anxiety, and depression, and EDSS scores in NMOSD.
Methods: This cross-sectional study used baseline visit data from participants with aquaporin-4 antibody positive NMOSD who were enrolled in the multi-centre Canadian NMOSD cohort study CANOPTICS and had consented to the PROs substudy. Participants completed the following PROs: the short-form McGill Pain Questionnaire (sf-MPQ), Modified Fatigue Impact Scale (MFIS), Generalized Anxiety Disorder Assessment 7-item scale (GAD-7), and Beck Depression Inventory II (BDI-II). We evaluated PRO scores overall and stratified by demographic factors including sex, age, and ethnicity. We assessed the correlation among PROs and between each PRO and the EDSS. Multivariable linear regression models were used to identify the association between demographic and clinical characteristics (including EDSS) and two key symptom domains, pain and fatigue, given their high prevalence and impact in NMOSD.
Results: Out of 69 included participants, 57 (82.6%) were female and median (IQR) age was 50 years (40-61). Median (IQR) scores were: sf-MPQ 7 (1-16), MFIS 39 (22-50), GAD-7 5 (2-8), BDI-II 11 (4-19), and EDSS 3.0 (1.5-4.0). Depression and fatigue ($r=0.71$), fatigue and pain ($r=0.62$), and depression and anxiety ($r=0.69$) were correlated, but correlations between EDSS and PROs were weak ($r<0.25$). No significant differences in PROs were observed by sex, age and ethnicity, although female sex was associated with a higher fatigue score in multivariable models (beta = 12.69, 95% CI 0.33-25.04).
Conclusions: There was a substantial burden of fatigue, pain, and mood disorders in this NMOSD cohort; however, these outcomes were weakly correlated with EDSS scores, suggesting that the EDSS may not capture important aspects of the patient experience in NMOSD.

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1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare inflammatory disease of the central nervous system characterized by immune-mediated attacks that primarily target astrocytes, with secondary demyelination. These attacks most frequently present as optic neuritis and transverse myelitis. Fatigue and pain are commonly reported in NMOSD and are often more prominent than in multiple sclerosis (MS) (Masuda et al., 2020). The Expanded Disability Status Scale (EDSS), a disability assessment tool based on the neurologic examination developed and validated for use in MS (Kurtzke et al., 1983), has been routinely used in NMOSD clinical care, clinical trials and research (Wingerchuk et al., 2015; Pittock et al., 2023; Traboulee et al., 2020). However, the EDSS does not adequately capture distinct symptom patterns in NMOSD that significantly affect quality of life (QoL), such as chronic pain, fatigue, and mood disturbances (Seok et al., 2017; Wingerchuk et al., 2015).

Previous work on patient-reported outcomes (PROs) in NMOSD has consistently demonstrated robust correlations between increased symptom severity, particularly of pain, fatigue, and depression, and reduced QoL (Seok et al., 2017; Masuda et al., 2020). In one study, fatigue substantially impaired daily functioning in NMOSD (Seok et al., 2017). Of note, the underlying mechanisms of symptoms such as fatigue and pain may differ in NMOSD compared to MS and thus may require distinct approaches to assessment. In NMOSD, pain has been associated with myelitis, particularly in the upper thoracic segments, while in MS, pain has been linked to both brain and spinal cord lesions, with variability depending on lesion location and type (Li et al., 2022; Seixas et al., 2014). Even when motor recovery occurs following NMOSD myelitis attacks, fatigue and pain can persist and be limiting (Masuda et al., 2020; Racke et al., 2022; Seok et al., 2017).

This study aimed to evaluate the relationship between PROs and EDSS scores in a Canadian multicentre cohort of patients with aquaporin-4 antibody positive (AQP4+) NMOSD. Specifically, we investigated the correlation among four PROs measuring fatigue, pain, anxiety, and depression and then assessed how each of these PROs related to EDSS scores obtained at the same clinical visit. Our goals were to evaluate whether the EDSS could provide an adequate representation of disease burden from the patient's perspective and to help inform future directions for outcome measurement in NMOSD care.

2. Methods

2.1. Participants

This cross-sectional analysis was conducted using data from the initial study visit in the Canadian NMOSD and Other Atypical Demyelinating Diseases Cohort Study (CANOPTICS). CANOPTICS is a national, multi-centre observational study of adults with AQP4+ NMOSD and related conditions (Rotstein et al., 2024). Participants were recruited from academic medical centers across Canada. The seven participating centres at the time of this study were: University of Alberta, University of Manitoba, Western University (London, Ontario), University of Toronto - St. Michael's Hospital, University of Toronto -Sunnybrook Health Centre, University of Ottawa, and Dalhousie University. All eligible participants were required to be at least 18 years old, meet the 2015 International Panel for NMO Diagnosis criteria for AQP4+ NMOSD (Wingerchuk et al. 2015), and provide informed consent for participation in the CANOPTICS PROs substudy. Research ethics board (REB) approval was obtained at each participating site, and written informed consent was obtained from all participants before enrollment. Recruitment rates varied from 31-75% of eligible participants depending on the site. We included only participants who had completed all four PROs at the baseline visit. All data were derived from the initial study visit, which included both neurologist-led clinical assessments and self-administered PRO questionnaires.

Table 1
Clinical thresholds for patient-reported outcome measures.

Instrument	Outcome	Mild	Moderate	Severe
BDI-II	Depression	14-19	20-28	≥29
GAD-7	Anxiety	5-9	10-14	≥15
MFIS	Fatigue	<38	38-59	≥60
sf-MPQ	Pain	0-10	11-20	21-45

BDI-II = Beck Depression Inventory II, GAD-7 = Generalized Anxiety Disorder-7, MFIS = Modified Fatigue Impact Scale, sf-MPQ = short form McGill Pain Questionnaire

2.2. Patient-reported outcomes (PROs)

Participants completed four questionnaires to assess symptoms relevant to symptom burden in NMOSD: the short-form McGill Pain Questionnaire (sf-MPQ), the Modified Fatigue Impact Scale (MFIS), Beck Depression Inventory-II (BDI-II), and Generalized Anxiety Disorder 7-item scale (GAD-7). Electronic questionnaires were administered via REDCap, and participants were asked to complete them electronically at their convenience soon after the study visit (Harris et al., 2019). The sf-MPQ assesses pain intensity and quality, including descriptors that capture neuropathic attributes of pain such as burning, shooting, or throbbing sensations (Melzack, 1987). The questionnaire consists of 15 items with scores ranging from 0 to 45. The MFIS evaluates the impact of fatigue on physical, cognitive, and psychological functioning across 21 items, with a total score ranging from 0 to 84 developed specifically for individuals with neurologic disorders (Fisk et al., 1994). The BDI-II includes 21 items assessing depressive symptoms, yielding a total score from 0 to 63 (Beck et al., 1996). The GAD-7 is a brief screening tool for anxiety, consisting of 7 items scored from 0 to 21 (Spitzer et al., 2006). Accepted cut-off scores for clinically significant symptoms are shown in Table 1 (Wang et al., 2013; Johnson et al., 2019; Larson 2013; Lovejoy et al., 2012). The sf-MPQ and MFIS do not allow for scores expressing below-threshold symptoms, in contrast to the BDI-II and GAD-7, although a score of zero indicates the absence of symptoms for each.

2.3. Other variables

Sociodemographic data were collected at the initial visit, including date of birth (used to calculate age at baseline visit), sex at birth (male, female), marital status (single, divorced, separated or widowed; common-law or married; unknown), education level (high school education or less; higher education; unknown) employment status (full time, unemployed due to disability, other/unknown), and living situation (live alone; live with others). Ethnicity was also collected and categorized as Asian, European/White, African or Caribbean, and Other, including people who reported multiple ethnicities.

2.4. Expanded disability status scale (EDSS)

EDSS scores were evaluated by the treating neurologist at the baseline visit following a standardized neurologic examination. The EDSS is an ordinal scale ranging from 0 (normal neurologic exam) to 10 (death due to MS/NMOSD), and is most sensitive to ambulation status (Kurtzke, 1983).

2.5. Analysis

We described baseline demographic and clinical characteristics of the study population, including EDSS scores, and compared participants who completed all four PROs to those who consented to the PROs substudy but did not complete all required questionnaires. Categorical variables (e.g., sex, ethnicity, education) were compared using chi-square or Fisher's exact tests as appropriate. Continuous variables (e.

Table 2
Baseline characteristics of the NMOSD cohort (n=69).

Characteristics		Sample Size n (%)
Age	Under 44	25 (36.2)
	45-59	26 (37.7)
	Over 60	18 (26.1)
Sex at Birth	Male	12 (17.4)
	Female	57 (82.6)
Ethnicity	Asian	23 (33.3)
	European/White	21 (30.4)
	African or Caribbean	17 (24.7)
	Other	8 (11.6)
Level of Education	High School Education or Less	8 (11.6)
	Higher Education	44 (63.8)
	Unknown	17 (24.6)
Employment	Full Time	23 (33.3)
	Unemployed due to disability (long term)	10 (14.5)
	Other/Unknown	36 (52.2)
Living Situation	Live Alone	6 (8.7)
	Live with others	63 (91.3)
Current Marital Status	Single, Divorced, Separated or Widowed	21 (30.4)
	Common Law or Married	43 (62.3)
	Unknown	5 (7.3)
Disease Duration (years)	Mean (SD)	9.3 (7.3)

g., age, PRO scores) were summarized as medians with interquartile ranges and compared using Wilcoxon rank-sum tests.

Among participants with complete PRO data, we assessed associations between demographic characteristics and five outcome measures: the sf-MPQ, MFIS, GAD-7, BDI-II, and the EDSS. Group comparisons were conducted using non-parametric tests, including Wilcoxon rank-sum and Kruskal-Wallis tests, given the non-normal distribution of the outcome variables.

To examine relationships between PROs and the EDSS, we calculated Spearman correlation coefficients. Finally, we used multivariable linear regression models to identify factors associated with pain (sf-MPQ) and fatigue (MFIS). Normality of residuals was checked to ensure model assumptions were met. The first set of models included demographic variables (age, sex, and ethnicity). A second model was created for each outcome which was additionally adjusted for EDSS to assess how the point estimates of associations between sociodemographic factors and the outcome of interest changed after accounting for physical disability (EDSS). These models also allowed us to evaluate the independent association between EDSS and pain and fatigue, adjusting for sociodemographic factors.

All statistical analyses were performed using SAS version 9, with two-tailed p-values < 0.05 considered statistically significant.

3. Results

Of the 108 (73.9%) participants enrolled in CANOPTICS who consented to the PROs substudy, 69 (63.9%) completed all four baseline PROs and were included in the analysis. Most were female (n = 57, 82.6%), and the overall cohort had a median age of 50 years (IQR: 40-61). Of the 69 participants, 21 (30.4%) were northern European/White, 17 (24.7%) were African or Caribbean, 23 were Asian (33.3%), and 8 (11.6%) were of other ethnicities. Most participants had completed at least high school (n = 54, 78.3%), and 10 (14.5%) were unemployed due to disability (Table 2). There were no differences in demographic or clinical characteristics between those who did complete all questionnaires, and those who did not complete all PRO questionnaires and were thus excluded (Table 3).

The PROs scores revealed a substantial symptom burden in this cohort. For example, the median sf-MPQ pain score was 7 (1-16) and 20.3% of participants fell into the severe pain category based on clinical thresholds (Figure 1). Similarly, the median MFIS score was 39 (22-50), with 44.9% experiencing moderate and 7.2% severe fatigue. For depression, 20% had moderate to severe symptoms (BDI-II), and for anxiety, 24.6% had moderate to severe symptoms (GAD-7). These distributions highlight that a significant proportion of individuals with NMOSD experience symptoms that exceed commonly accepted thresholds for clinical concern. The median EDSS score, reflecting neurologist-assessed disability, was 3.0 (1.5-4.0) (Table 4).

We did not observe any statistically significant differences in pain, fatigue, depression and anxiety by age, sex or ethnicity (Figures 2-5). However, females tended to have slightly higher levels of depression, pain, and fatigue. EDSS scores were higher in older individuals, but did not differ meaningfully by sex or ethnicity (Figure 6).

The Spearman correlation analysis revealed moderate to strong correlations among the PROs evaluated (Table 5). Fatigue was correlated with depression (r=0.71), pain (r=0.62), and anxiety (r=0.66), while depression and anxiety were also strongly correlated (r=0.69). However, the EDSS was poorly correlated with all PROs evaluated

Table 3
Comparison of missing and non-missing data (n=108).

Characteristics		Non missing (n=69) N (%)	Missing (n=39) n(%)	Chi-square	p-value
Age	Under 44	25 (36.2)	9 (23.1)	3.8555	0.1455
	45-59	26 (37.7)	13 (33.3)		
	Over 60	18 (26.1)	17 (43.6)		
Sex at Birth	Male	12 (17.4)	7 (18.0)	0.0053	0.9417
	Female	57 (82.6)	32 (82.0)		
Ethnicity	Asian	23 (33.3)	13 (33.3)	1.5073	0.6806
	European origin (White)	21 (30.4)	14 (35.9)		
	African or Caribbean	17 (24.7)	6 (15.4)		
	Other	8 (11.6)	6 (15.4)		
Level of Education	High School Education or Less	8 (11.6)	7 (18.0)	1.1356	0.5668
	Higher Education	44 (63.8)	21 (53.8)		
	Unknown	17 (24.6)	11 (28.2)		
Employment	Full Time	23 (33.3)	11 (28.2)	1.2543	0.5341
	Unemployed due to disability (long term)	10 (14.5)	9 (23.0)		
	Other/Unknown	36 (52.2)	19 (48.8)		
Living Situation	Live Alone	6 (8.7)	4 (10.3)		1.0000 [a]
	Live with others	63 (91.3)	35 (89.7)		
Current Marital Status	Single, Divorced, Separated or Widowed	21 (30.4)	9 (23.1)		0.6701[a]
	Common Law or Married	43 (62.3)	28 (71.8)		
	Unknown	5 (7.3)	2 (5.1)		
Disease Duration (years)	Mean (SD)	9.3 (7.3)	11.1 (7.2)		0.2475

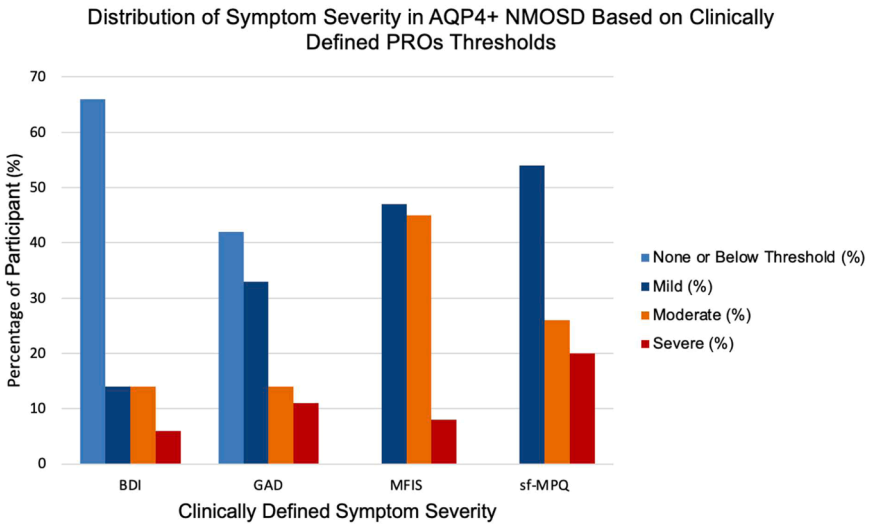

Fig. 1. Distribution of symptom severity in AQP4+ NMOSD based on clinically defined PRO Thresholds.
Bar graph showing proportion of participants (n=69) with none/zero or below-threshold, mild, moderate and severe symptoms across four patient-reported outcome (PRO) domains: depression (BDI-II), anxiety (GAD-7), fatigue (MFIS), and pain (sf-MPQ). Clinical severity was categorized according to clinical cut-offs (Table 1).
BDI-II = Beck Depression Inventory-II, GAD-7 = Generalized Anxiety Disorder-7,
MFIS = Modified Fatigue Impact Scale, sf-MPQ = short-form McGill Pain Questionnaire,
AQP4+ NMOSD = aquaporin-4 antibody positive neuromyelitis Optica spectrum disorder, PRO = patient-reported outcome.

Table 4
Univariate analysis with demographics and outcome variable for non-missing data (n= 69) (Kruskal-Wallis Test).

Characteristics		sf-MPQ Median (Q1, Q3)	p-value	EDSS Median (Q1, Q3)	p-value	MFIS Median (Q1, Q3)	p-value	GAD-7 Median (Q1, Q3)	p-value	BDI-II Median (Q1, Q3)	p-value
Age	**Under 44 (n=25)**	5 (0,15)	0.207	2.0 (1.5,3.0)	0.069	34 (22,47)	0.184	5 (3,10)	0.053	12 (3,15)	0.314
	45-59 (n=26)	11 (5,16)		3.0 (1.5, 3.5)		48 (29,51)		6 (4,10)		13.5 (8,23)	
	Over 60 (n=18)	9 (3,16)		3.0 (2.0, 4.0)		32.5 (10,45)		4 (0,6)		10.5 (4,19)	
Sex at Birth[a]	**Male (n=12)**	2.5 (0,12)	0.134	3.25 (2.5, 4.0)	0.455	23.5 (6, 46)	0.171	4.5 (1.5,5.5)	0.164	4.5 (0.5,17)	0.070
	Female (n=57)	9 (4,16)		3.0 (1.5,4.0)		41 (24,51)		5 (3,10)		12 (6,21)	
Ethnicity	**Asian (n=23)**	5 (4,16)	0.507	2.0 (1.5, 3.5)	0.192	39 (22,50)	0.941	5 (2,7)	0.922	12 (4,22)	0.529
	European/White (n=21)	7 (0,13)		3.0 (1.5, 3.5)		36 (20,49)		5 (2,7)		12 (8,18)	
	African or Caribbean (n=17)	7 (0,13)		3.0 (2.0,4.0)		43 (24,51)		6 (3,11)		14 (9,25)	
	Other (n=8)	5.5 (0,18)		3.5 (3.0,6.0)		42.5 (0, 51)		4 (3.5,7)		7 (3,16)	

sf-MPQ = short form McGill Pain Questionnaire, EDSS = Expanded Disability Status Scale, MFIS = Modified Fatigue Impact Scale, GAD-7 = Generalized Anxiety Disorder-7, BDI-II = Beck Depression Inventory-II
*is $p<0.05$
[a] Wilcoxon two sample test,

($r<0.25$).

In multivariable linear regression analyses, female sex was significantly associated with greater fatigue (MFIS score) after adjusting for EDSS (β=12.69; 95% CI: 0.33–25.04) (Table 6). Age and ethnicity were not significantly associated with fatigue scores in either adjusted model. None of the demographic variables (age, sex, or ethnicity) was significantly associated with McGill Pain scores in either model. Finally, EDSS was not associated with pain (β = 2.14, -0.95 to 5.24) or fatigue (β =1.56, -0.06 to 3.19).

4. Discussion

In this multicentre Canadian cohort investigating people with AQP4+ NMOSD, we found that PROs revealed a high burden of pain, fatigue, depression and anxiety and that the EDSS poorly represented this symptomatic burden. Female sex was associated with higher fatigue, but no other demographic factor was associated with PROs. These findings underscore the relevance of PROs in NMOSD in capturing symptoms that are not easily predicted by the neurological exam or the patient's demographic profile. PROs may assist both clinicians and

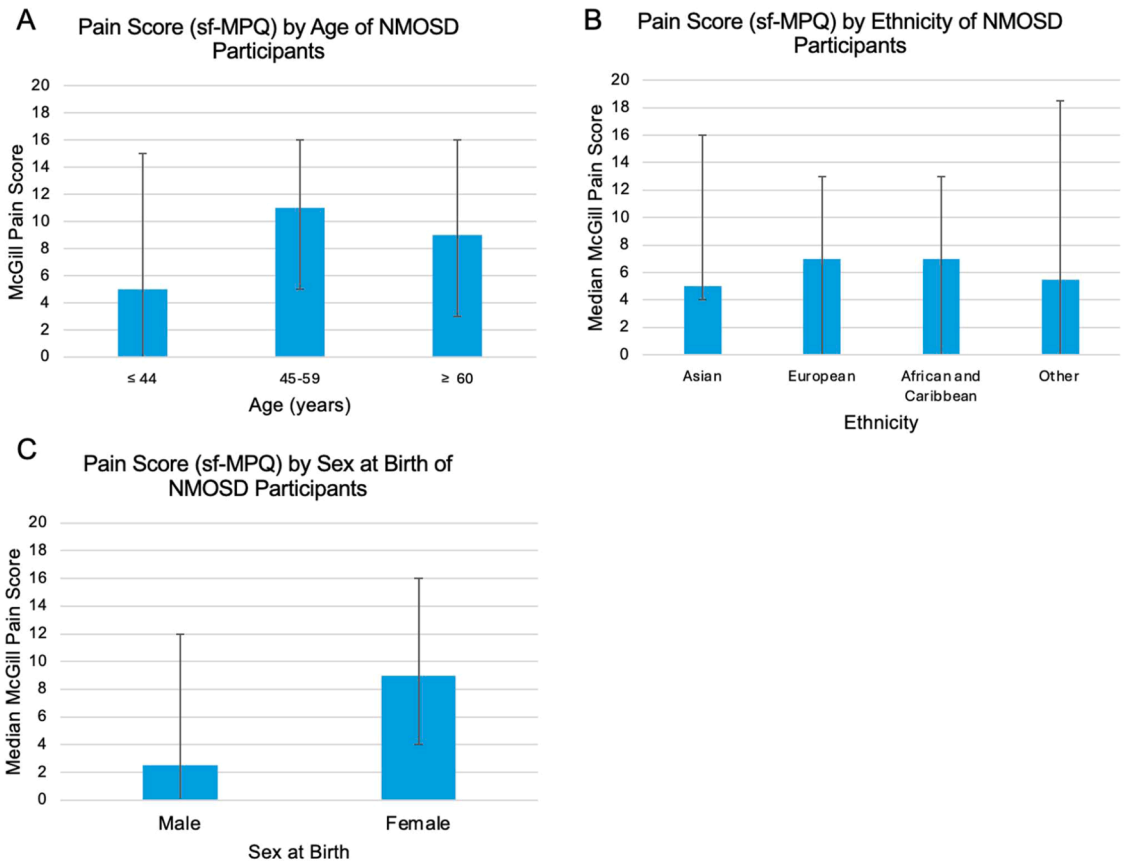

Fig. 2. Pain scores (sf-MPQ) by demographic subgroups.
(A) Distribution of pain scores stratified by age groups (<44, 45–59, >60 years). (B) Distribution of pain scores by ethnicity (Asian, European, African or Caribbean, Other). (C) Distribution of pain scores by sex at birth. Higher sf-MPQ scores indicate greater overall pain severity. Data are presented as median with interquartile range based on a sample of n = 69 NMOSD patients. Group comparisons were performed using the Kruskal-Wallis test, with significance set at $p < 0.05$. Ranges were as follows: age <44 years: 0-34; 45-59 years: 0-32, >60 years: 0-28; Asian: 0-32; European: 0-28, African or Caribbean: 0-23; Other 0-34; male: 0-28; female 0-34. sf-MPQ = short form McGill Pain Questionnaire, NMOSD = neuromyelitis optica spectrum disorder.

researchers in evaluating the full spectrum of disability related to NMOSD.

Female sex was associated with a higher fatigue burden in our multivariable models. Direct sex-comparative analyses of fatigue severity in NMOSD remain limited, although sex-related differences in disease mechanisms and symptom expression have been increasingly recognized (Brasanac et al., 2025). Fatigue is one of the most common symptoms in NMOSD and has been consistently associated with poorer QoL, as well as with depression, pain, sleep disturbance, and disability (Seok et al., 2017; Barzegar et al., 2019; Liu et al., 2023; Liang et al., 2025). The higher fatigue scores observed in females in our cohort may reflect sex-related biological and/or psychosocial differences, Interestingly, fatigue in MS is also reported to be more frequent and severe in women compared to men, with some evidence that these differences are related to both socioeconomic factors such as levels of education and income and biological differences such as patterns of cognitive deficits (Broch et al. 2022, Freedman et al., 2026). In this study, our modest sample size and the underrepresentation of males should lead to caution in interpretation of the higher fatigue burden in women,and the relationship between female sex and fatigue in NMOSD should be confirmed in larger studies.

We did not observe an association between age and PROs in this cohort. This may reflect differences in disability accumulation between NMOSD and MS. In MS, disability often worsens with age due to progression independent of relapse activity (PIRA), whereas in AQP4+ NMOSD, disability accumulation is directly related to relapses and the extent of relapse recovery (Wingerchuk et al., 2015; Siriratnam et al., 2024). This has been confirmed in recent observational studies in which PIRA was rare in AQP4+ NMOSD occurring in only 2.2% (Siriratnam et al., 2024). In cohorts treated with effective relapse-preventing therapies, disability and symptom burden may therefore remain relatively stable across age groups. Alternatively, our modest sample size may have limited our ability to detect small associations between age and PROs.

The EDSS was originally developed and validated for use in MS where it has become the most widely accepted outcome measure in both research and clinical practice (Kurtzke et al., 1983). In MS, several studies have reported at least moderate correlations between EDSS scores and PROs related to fatigue, depression, and overall QoL. (Kaya Aygünoğlu et al., 2015; Luostarinen et al., 2023; Aparicio-Castro et al., 2025). For instance, Kaya Aygünoğlu et al. (2015) found significant associations between EDSS and fatigue and mood symptoms, while Luostarinen et al. (2023) reported a strong correlation ($r = 0.75$, $p < 0.01$) between EDSS and fatigue severity for relapsing-remitting MS patients. Similarly, Aparicio-Castro et al. (2025) reported that higher EDSS scores were significantly associated with higher scores on both the BDI and MFIS, with depression and fatigue strongly associated with reduced QoL. These correlations tend to be strongest in people with more advanced MS, while slightly less robust in those with milder disease (Meyer-Hoock et al., 2014).

In contrast, our study found no meaningful correlation between EDSS and any of the PROs in NMOSD, despite the fact that this was a cohort with substantial disability (median EDSS 3.0). This discrepancy with findings in MS may be due to differences in pathophysiology and

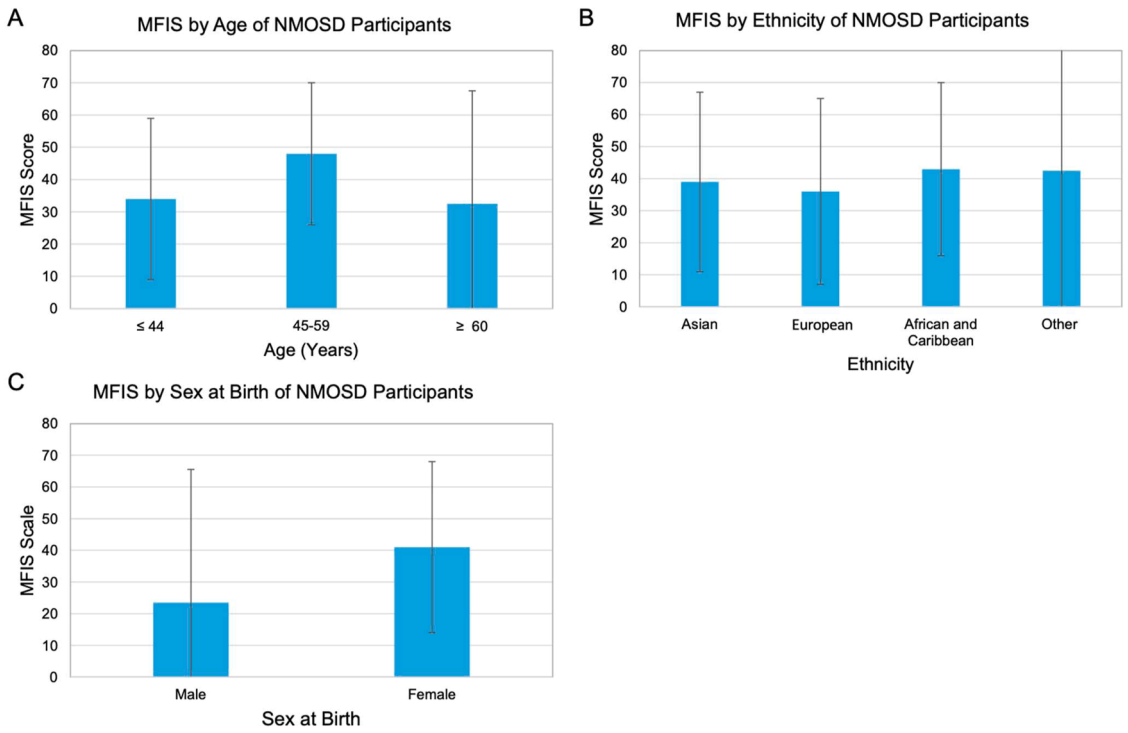

Fig. 3. Fatigue scores (MFIS) by demographic subgroups.
(A) MFIS scores stratified by age groups (<44, 45–59, >60 years). (B) MFIS scores by ethnicity (Asian, European, African or Caribbean, Other). (C) MFIS scores by sex at birth. Higher MFIS scores indicate greater fatigue severity. Data are presented as median with interquartile range based on a sample of n = 69 NMOSD patients. Group comparisons were performed using the Kruskal–Wallis test, with significance set at $p < 0.05$. Ranges were as follows: age <44 years: 0-73; 45-59 years: 2-68, >60 years: 0-62; Asian: 0-68; European: 0-62, African or Caribbean: 27-58; Other 0-73; male: 1-52; female 0-73.
MFIS = modified fatigue impact scale, NMOSD = neuromyelitis optica spectrum disorder.

symptom distribution of the disease, or the scale's emphasis on ambulation. Even in MS, however, longitudinal studies have demonstrated that the EDSS incompletely captures patient-reported disability and disease burden over time (Bevan et al., 2014). In some studies, PROs were more strongly associated with future disability progression than baseline EDSS scores (Vaughn et al., 2023). Furthermore, Foong et al. (2023) demonstrated that the Patient Determined Disease Steps (PDDS), a patient-reported measure of disability, is not interchangeable with EDSS in mild to moderate MS, highlighting that clinician-assessed and patient-reported disability scales capture different dimensions of disability. An additional consideration is the ecological validity of the EDSS in NMOSD. While the EDSS remains a widely used measure of neurologic disability, it is heavily weighted toward ambulation and may not reflect symptoms that substantially affect daily functioning and QoL. Fatigue, pain, mood, and anxiety, may have a greater impact on employment, social participation, interpersonal relationships, and independence. These results suggest that there are limitations to relying on EDSS alone in demyelinating diseases and underscore the need to integrate PROs into clinical care and research.

Our results align with previous studies assessing pain, fatigue and mood disorders in NMOSD, which have consistently shown a profound and multifaceted burden. Pain has been reported by over 80% of patients, including those in remission, and in other studies, was associated with reduced QoL and persistent fatigue (Beekman et al., 2019; Fujihara et al., 2021). Distinctive pain forms in NMOSD include paroxysmal tonic spasms, which occur in up to 25% and may limit function after transverse myelitis even where there is good motor recovery (Kim et al., 2012). Neuropathic pain is also one of the most common and clinically important pain phenotypes in NMOSD and is frequently associated with spinal cord lesion burden and myelitis-related injury (Asseyer et al., 2020; Li et al., 2022), as well as poorer QoL and greater psychological burden, including depression (Ayzenberg et al., 2021; Hyun et al., 2020). Regional spinal cord volume loss has been associated with pain severity (Asseyer et al., 2024) but other contributors to pain in NMOSD are poorly characterized. Eye pain, frequently with associated headache, is commonly reported and can be independent of recovery of visual acuity yet can limit daily activities, ability to concentrate, and energy (Asseyer et al., 2020).

Despite this, pain, fatigue, depression, and anxiety disorders in NMOSD remain underrecognized, insufficiently treated in routine practice and poorly understood (Mealy et al., 2020). Sleep architecture is disrupted in NMOSD, characterized by decreased slow-wave sleep, altered REM dynamics, and thalamic atrophy, which contribute to ongoing fatigue (Thomas et al., 2025; Zhang et al., 2022). Depression affects roughly a third of patients and nearly half of caregivers, often emerging or worsening after diagnosis even in those without prior psychiatric history (Tan et al., 2024; Esiason et al., 2024). Anxiety is also common and may co-occur with depression, further complicating coping and QoL (Tan et al., 2024; Esiason et al., 2024). In one recent qualitative study, contributors to psychological challenges in NMOSD included mistrust of medical professionals, lack of support following the diagnosis, changes in relationships, the inability to live in a way aligned with personal values and priorities (i.e., deviation from values-based living), internalization of feelings, and avoidant coping strategies (Esiason et al., 2024). Yalachkov et al. reported that both psychiatric distress and physical disability were significantly associated with QoL in NMOSD, with psychiatric distress showing a particularly strong relationship with mental QoL domains (Yalachkov et al., 2021). Sociodemographic factors, including race and social supports may influence various dimensions of disease impact, including psychological health, symptom burden, and social functioning. Yet the overall severity of NMOSD's impact appears to be independent of these variables based on our findings and others' work (Gholizadeh et al., 2024). Together, these findings underscore the need for tailored interventions addressing the

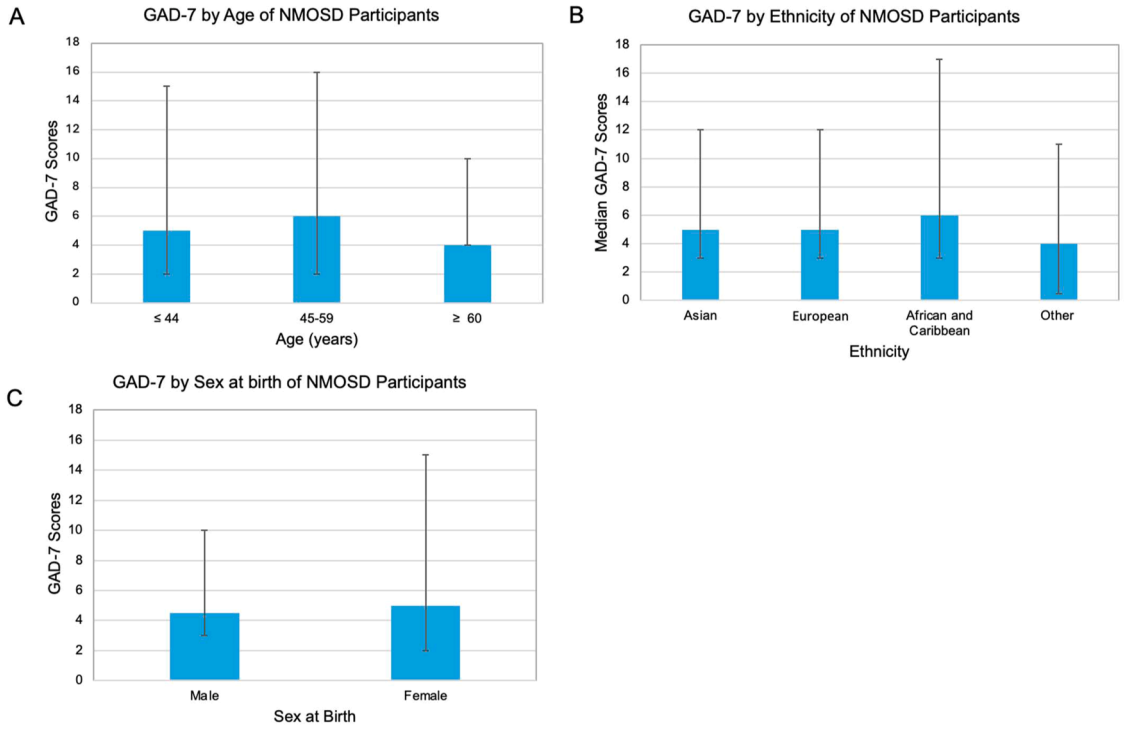

Fig. 4. Anxiety Scores (GAD-7) by Demographic Subgroups.
(A) GAD-7 scores stratified by age groups (<44, 45–59, >60 years). (B) GAD-7 scores by ethnicity (Asian, European, African or Caribbean, Other). (C) GAD-7 scores by sex at birth. Higher GAD-7 scores indicate higher anxiety levels. Data are presented as median with interquartile range based on a sample of n = 69 NMOSD patients. Group comparisons were performed using the Kruskal-Wallis test, with significance set at $p < 0.05$. Ranges were as follows: age <44 years: 0-17; 45-59 years: 0-21, >60 years: 0-15; Asian: 0-19; European: 0-28, African or Caribbean: 0-17; Other 0-21; male: 0-11; female 0-21.
GAD-7 = Generalized Anxiety-Disorder-7, NMOSD = neuromyelitis optica spectrum disorder.

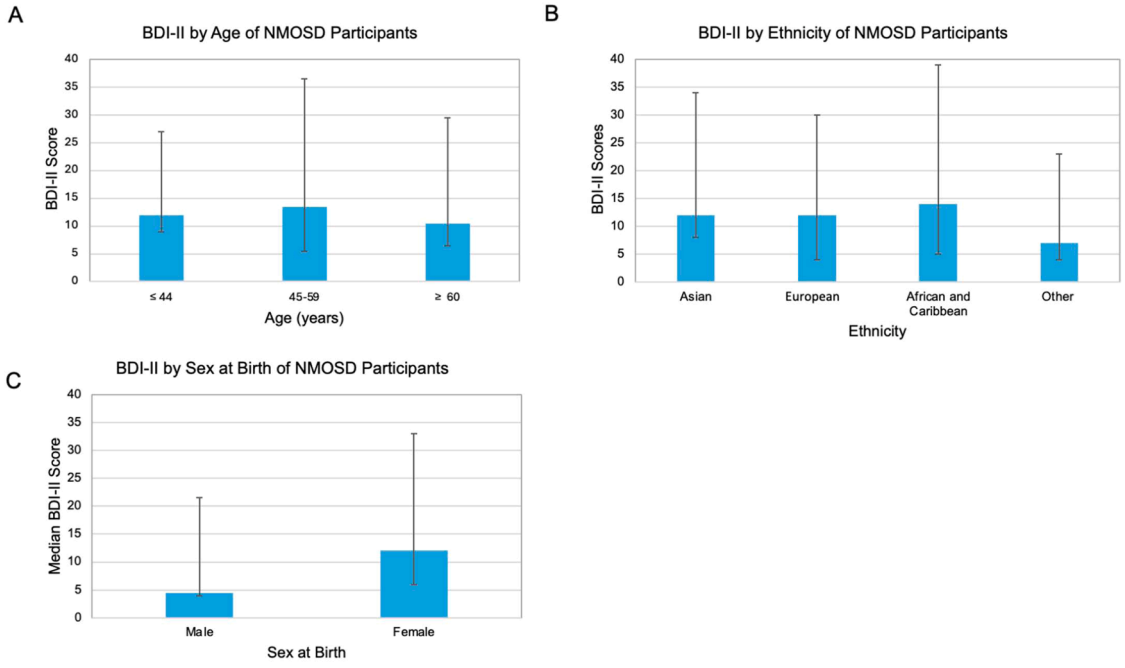

Fig. 5. Depression scores (BDI-II) by demographic subgroups.
(A) BDI-II scores stratified by age groups (<44, 45-59, >60 years). (B) BDI-II scores by ethnicity (Asian, European, African/Caribbean, Other). (C) BDI-II scores by sex at birth. Higher BDI-II scores reflect more severe depressive symptoms. Data are presented as median with interquartile range based on a sample of n = 69 NMOSD patients. Group comparisons were performed using the Kruskal-Wallis test, with significance set at $p < 0.05$. Ranges were as follows: age <44 years: 0-34; 45-59 years: 1-31, >60 years: 0-24; Asian: 0-28; European: 0-26, African or Caribbean: 11-24; Other 0-34; male: 0-29; female 0-34.
BDI-II = Beck Depression Inventory-II, NMOSD = neuromyelitis optica spectrum disorder.

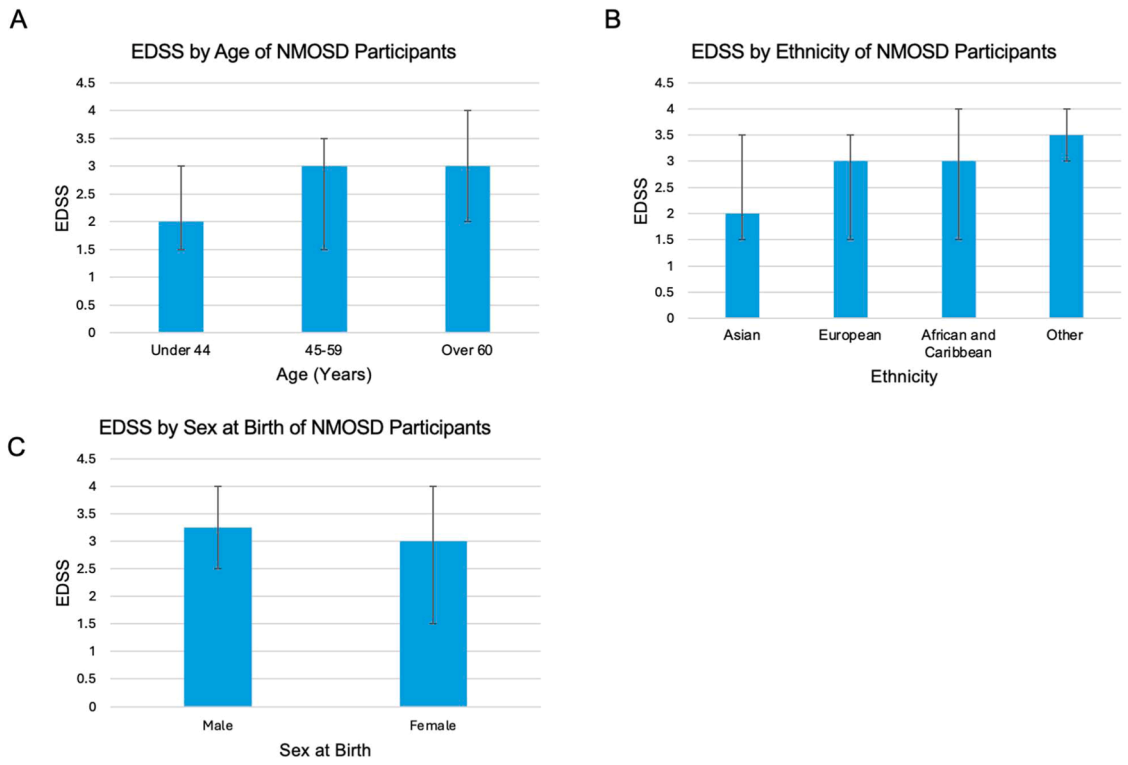

Fig. 6. Expanded disability status scale (EDSS) scores by demographic subgroups.
(A) EDSS scores stratified by age groups (<44, 45-59, >60 years). (B) EDSS scores by ethnicity (Asian, European, African/Caribbean, Other). (C) EDSS scores by sex at birth. EDSS ranges from 0 to 10, with higher scores greater neurologist-assessed disability. Data are presented as median with interquartile range based on a sample of n = 69 NMOSD patients. Group comparisons were performed using the Kruskal-Wallis test, with significance set at $p < 0.05$. Ranges were as follows: age <44 years: 0-6; 45-59 years: 0-7, >60 years: 1-6.5; Asian: 0-6.5; European: 1-6.5, African or Caribbean: 3-6.5; Other 0-7; male: 1-5; female 0-7.
EDSS = Expanded Disability Status Scale, NMOSD = neuromyelitis Optica spectrum disorder.

Table 5
Spearman Rho correlation test between outcome variables (n= 69).

Variables	sf-MPQ	EDSS	MFIS	GAD-7	BDI-II
sf-MPQ	1	0.234	0.621**	0.452**	0.511**
EDSS	0.234	1	0.133	0.087	0.122
MFIS	0.621**	0.133	1	0.594**	0.713**
GAD-7	0.452**	0.087	0.594**	1	0.690**
BDI-II	0.511**	0.122	0.713**	0.690**	1

BDI-II = Beck Depression Inventory II, EDSS = Expanded Disability Status Scale, GAD-7 = Generalized Anxiety Disorder-7, MFIS = Modified Fatigue Impact Scale, sf-MPQ = short form McGill Pain Questionnaire
** $p< 0.01$

unique dimensions of NMOSD with respect to fatigue, pain, depression, and anxiety.

Several important questions remain unanswered. Longitudinal studies are necessary to elucidate how PRO scores evolve over time and how they respond to therapeutic interventions. It is still unclear whether PROs can predict long-term outcomes, such as disability progression, relapse frequency, or treatment response in NMOSD. As therapeutic options expand, understanding how individual treatments impact specific PROs could be an important consideration in choosing between options in clinical care.

Our study, while providing valuable insights, also has several limitations. Although CANOPTICS is a large multi-centre NMOSD cohort, our analytic sample was modest, and certain subgroups, such as males, were underrepresented. This limitation restricts our ability to assess sex-based differences in PROs and may reduce the generalizability of our findings. Some analyses also showed wide confidence intervals, reflecting limited statistical precision due to the relatively small sample

Table 6
Multivariable linear regression analysis for fatigue (MFIS) and pain (sf-MPQ).

Variables	Fatigue (MFIS)		Pain (sf-MPQ)	
	Model 1 Beta coefficient (CI)	Model 2 Beta coefficient (CI)	Model 1 Beta coefficient (CI)	Model 2 Beta coefficient (CI)
Intercept	34.84 (23.11 to 46.56)*	30.72 (17.65-43.79)*	7.41 (1.18 to 13.65)*	4.41 (-2.43 to 11.27)
Age				
Under 44	ref	ref	ref	ref
45-59	6.36 (-4.51 to 17.23)	3.46 (-8.11 to 15.04)	2.85 (-2.92 to 8.64)	0.74 (-5.32 to 6.81)
Over 60	-1.73 (-14.44 to 10.97)	-4.23 (-17.36 to 8.89)	2.16 (-4.59 to 8.93)	0.34 (-6.54 to 7.23)
Sex				
Male	ref	ref	ref	ref
Female	11.91 (-0.47 to 24.20)	**12.69 (0.33 to 25.04)***	3.66 (-2.92 to 10.25)	4.22 (-2.24 to 10.70)
Ethnicity				
European	ref	ref	ref	ref
Asian	1.73 (-9.81 to 13.28)	2.68 (-8.86 to 14.23)	3.92 (-2.21 to 10.06)	4.61 (-1.4 to 10.67)
African or Caribbean	2.17 (-11.02 to 15.37)	6.63 (-12.55 to 13.99)	2.26 (-4.75 to 9.28)	1.20 (-5.75 to 8.16)
Others	-4.63 (-21.00 to 11.74)	-8.11 (-25.12 to 8.90)	0.98 (-7.72 to 9.69)	-1.54 (-10.47 to 7.37)
EDSS		2.14 (-0.95 to 5.24)		1.56 (-0.06 to 3.19)

Model 1: Unadjusted for EDSS, Model 2: EDSS Adjusted,
MFIS = Modified Fatigue Impact Scale, sf-MPQ = short form McGill Pain Questionnaire, EDSS = Expanded Disability Status Scale
* $p<0.05$, CI = 95% confidence interval

and variability in PROs in this cohort. Additionally, the cross-sectional design precludes causal inference and does not capture changes in symptom burden over time. We were also unable to account for some potentially important clinical variables including disease-modifying therapy use, symptomatic medication use such as analgesics and antidepressants, relapse history or relapse rate, MRI lesion burden, or formal QoL measures, all of which may influence disability, and patient-reported symptom severity. We did not collect patient-reported measures of sphincter dysfunction in CANOPTICS, although bladder and bowel symptoms are common in NMOSD due to spinal cord involvement and may significantly impact daily functioning and QoL. About one-third of consented participants did not complete all questionnaires and were excluded. Clinical and demographic characteristics did not differ across included and excluded participants but we cannot completely rule out the possibility of selection bias. Future studies should incorporate larger, more diverse cohorts and adopt longitudinal designs to provide insights into the dynamic nature of NMOSD symptomatology and its response to treatment.

5. Conclusion

Our findings suggest that fatigue, pain, anxiety, and depression pose a substantial symptomatic burden in people living with AQP4+ NMOSD, yet these symptoms are not captured by the EDSS, which focuses primarily on ambulatory function. While the EDSS was originally developed for grading disability in MS, it has been widely adopted as an outcome measure in NMOSD clinical trials and for routine monitoring of disability in the clinic. Integrating PROs into standard NMOSD assessments could provide a more holistic evaluation of well-being, thereby facilitating individualized management strategies. Future efforts should prioritize longitudinal evaluations of these outcomes and explore strategies to integrate patient-reported measures into research protocols and clinical care.

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CRediT authorship contribution statement

Elisa Saeedzadeh: Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Manav V. Vyas:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Shristi Sharma:** Writing – review & editing, Methodology, Formal analysis. **Nandita Vas:** Writing – review & editing, Project administration, Investigation, Data curation. **Robert Carruthers:** Writing – review & editing, Investigation. **Anibal Chertcoff:** Writing – review & editing, Investigation. **Courtney Casserly:** Writing – review & editing, Investigation. **Mark S. Freedman:** Writing – review & editing, Investigation. **Liesly Lee:** Writing – review & editing, Investigation. **Ruth Ann Marrie:** Writing – review & editing, Investigation, Formal analysis. **Jennifer A. McCombe:** Writing – review & editing, Investigation. **Sarah A. Morrow:** Writing – review & editing, Investigation. **Natalie E. Parks:** Writing – review & editing, Investigation. **Penelope Smyth:** Writing – review & editing, Investigation. **Dalia L. Rotstein:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

Elisa Saeed Zadeh has nothing to declare.

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Shristi Sharma has nothing to declare.

Nandita Vas has nothing to declare.

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