



# Impact of Neuromyelitis Optica Spectrum Disorder on Quality of Life from the Patients' Perspective: An Observational Cross-Sectional Study

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## ABSTRACT

**Introduction:** Neuromyelitis optica spectrum disorder (NMOSD) is associated with a reduced health-related quality of life (HRQoL). The purpose of this study was to describe the impact of NMOSD on HRQoL from the patients'

perspective and its relationship with other disease factors.

**Methods:** An observational, cross-sectional study was conducted at 13 neuroimmunology clinics in Spain. Patients with NMOSD diagnosis (2015 Wingerchuk criteria) were included. The 29-item Multiple Sclerosis Impact Scale (MSIS-29) was used to assess the HRQoL. Different questionnaires were used to measure symptom severity, stigma, mood disorders, pain, fatigue, and difficulties in the workplace. Factors that

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impact HRQoL were identified by Spearman's correlation and multivariate linear regression analysis.

**Results:** Seventy-one patients were included (mean age  $47.4 \pm 14.9$  years, 80.3% female, mean time since disease onset  $9.9 \pm 8.1$  years). The median Expanded Disability Status Scale score was 3.0 (1.5–4.5). The mean ( $\pm$  SD) physical and psychological MSIS-29 sub-scores were  $41.9 \pm 16.8$  and  $20.9 \pm 8.3$ , respectively. Fatigue and body pain were the most prevalent symptoms. Depressive symptoms were found in 44.3% ( $n = 31$ ) of patients. The physical MSIS-29 dimension showed the highest correlation with symptom severity ( $\rho = 0.85584$ ,  $p < 0.0001$ ), whereas the highest correlations for psychological MSIS-29 dimension were pain, MSIS-29 physical dimension, and depression ( $\rho = 0.76487$ ,  $0.72779$ ,  $0.71380$ ;  $p < 0.0001$ , respectively). Pain was a predictor of both dimensions of MSIS-29.

**Conclusion:** Fatigue, pain, and depressive symptoms are frequent problems among patients with NMOSD, impacting on their quality of life. Assessment of patient-oriented outcomes may be useful to achieve a holistic approach, allowing early specific interventions.

**Keywords:** Depression; Fatigue; Health-related quality of life; Neuromyelitis optica spectrum disorder; Patient-reported outcomes

### Key Summary Points

In addition to relapses, neuromyelitis optica spectrum disorder (NMOSD) has a variety of symptoms that can accumulate and increase the burden on patients' lives, but few studies have evaluated this issue and its associated factors.

This is the first study in Spain describing NMOSD's impact on health-related quality of life using a comprehensive battery of patient-reported measurements.

Our results show that NMOSD negatively impacts patients' physical and psychological health-related quality of life even in a clinically stable population with low physical disability.

Symptom severity, depression, pain, fatigue, and workplace difficulties are common features affecting patients' quality of life.

Awareness of these patient-reported symptoms is crucial for implementing appropriate early interventions.

## INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory autoimmune disease of the central nervous system targeting the optic nerve, spinal cord, and brain [1, 2]. The estimated prevalence of NMOSD in Europe is between 1 and 5 cases/100,000 inhabitants, with women up to 10 times more likely to be affected than men, and antibodies to the astrocytic water channel aquaporin-4 (AQP4) found in 73% of cases [3–5]. The main characteristics of NMOSD include acute episodes of optic neuritis or transverse myelitis, along with other symptomatology such as pain, fatigue, anxiety, depression, sleep disorders, and cognitive impairment [6–8].

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The number of attacks, their unpredictability, severity, increasing disability, cognitive impairment, psychiatric symptoms, and financial burden have a strong negative impact on health-related quality of life (HRQoL) of patients with NMOSD and result in high costs for the healthcare system [6, 9–15].

As disease symptoms pose a major risk for patients' HRQoL, further research may be essential to improve knowledge of the different dimensions affected by NMOSD and develop a holistic approach for early interventions. Therefore, in this study, we used a comprehensive battery of different patient-reported measurements to describe NMOSD's impact on HRQoL from the patients' perspective.

## METHODS

We conducted an observational, cross-sectional study at 13 hospital-based neuroimmunology clinics in Spain as part of the PERSPECTIVES-NMO study, which aimed to evaluate the stigmatization among patients with NMOSD [16]. The present analysis aimed to assess the impact of NMOSD on HRQoL from the patients' perspective. Eligibility criteria included age at least 18 years old and a diagnosis of NMOSD according to Wingerchuk 2015 criteria [17].

### Outcome Measures and Procedures

Participating neurologists collected sociodemographic and clinical characteristics from individuals with NMOSD and assessed participants' disability, hand function, and gait using the Expanded Disability Status Scale (EDSS) [18], the 9-Hole Peg Test (9-HPT) [19], and the Timed 25-Foot Walk (T25-FW), respectively.

Each participant completed the following assessment instruments.

The 29-item Multiple Sclerosis Impact Scale (MSIS-29) [20] is a self-reported questionnaire used to determine the impact of multiple sclerosis (MS) on HRQoL. It consists of two composite impact domains/subscales, physical impact (20 items) and psychological impact (9 items). Items are rated using four-point response categories: not at all, a little,

moderately, and extremely. Scores on the physical and the psychological impact subscales can range from 20 to 80 and from 9 to 36, respectively. Lower scores indicate a higher HRQoL.

The SymptomScreen questionnaire (SyMS) [21] is used to rapidly assess symptom severity in 12 neurologic domains commonly affected by MS: mobility, dexterity, spasticity, body pain, sensation, bladder function, fatigue, vision, dizziness, cognition, depression, and anxiety. Each item is assessed on a seven-point Likert scale ranging from 0 (not affected at all) to 6 (total limitation). The total score is calculated as the sum of individual items, ranging from 0 to 72, with higher scores indicating more severe symptom endorsement.

The 8-item Stigma Scale for Chronic Illness (SSCI-8) [22, 23] is an eight-item scale developed to assess internalized and experienced stigma across neurological conditions. It uses a five-point Likert scale ranging from 1 (never) to 5 (always). Total scores range from 8 to 40, with higher scores indicating higher levels of perceived stigma. A cutoff score greater than 8 indicates the presence of stigmatization.

The Beck Depression Inventory-Fast Screen (BDI-FS) [24] is a seven-item questionnaire assessing the level of depressive symptoms. Responses to the items are provided on a four-point scale (no symptoms to severe symptoms). Total scores range from 0 to 21, with higher scores reflecting greater severity of depressive symptoms. Depressive disorders are considered in individuals scoring at least 4. Cutoff scores of at least 4, at least 9, and greater than 12 are used to define the presence of mild, moderate, and severe depression, respectively.

The Fatigue Impact Scale for Daily Use (D-FIS) [25] is an eight-item instrument designed to measure the subjective daily experience of fatigue. Items are rated using a five-point Likert scale from 0 (no problem) to 4 (extreme problem), with total scores ranging from 0 to 32 and higher scores indicating a greater impact of fatigue on daily quality of life.

The MOS Pain Effects Scale (PES) [26] is a six-item questionnaire that assesses how pain and unpleasant sensations interfere with mood, ability to walk or move, sleep, work, recreation,

and enjoyment of life. PES scores can range from 6 to 30, with higher scores indicating greater impact of pain on a patient's mood and behavior.

The Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23) [27, 28] measures difficulties experienced in the workplace across three broad domains, including physical barriers (11 items), psychological/cognitive barriers (8 items), and external barriers (4 items). Participants provide ratings on 23 statements concerning various work difficulties experienced over the past 4 weeks in their current or most recent job using a five-point Likert scale (never, rarely, sometimes, often, and almost always). The three subscales and the total MSWDQ-23 scale are scored as percentages by summing the observed item scores divided by the total possible item scores in each subscale. Each value is then multiplied by 100 to give a maximum score of 100. Higher scores indicate more work difficulties.

### Statistical Analysis

As a result of the lack of previous data about MSIS-29 in patients with NMOSD, the sample size was calculated on the basis of statistical criteria. To estimate MSIS-29 scores with a precision of 0.25 standard deviations and a 95% confidence interval, assuming 10% of non-evaluable patients because of non-available information, a sample of 70 patients was required. For the primary objective, imputation was used to address questionnaires returned with missing data using the following rule: if at least 50% of the items in a scale had been completed, a respondent-specific mean score computed from the completed items was used [29], also known as the half rule.

For the descriptive and univariate analysis, categorical variables were described as the total number of available values and relative percentage per subgroup of interest. Continuous variables were described by the number of available values, mean, standard deviation, and median, Q1, Q3, minimum and maximum. When appropriate, patient characteristics were compared according to AQP4 status using the

chi-square test and Mann–Whitney *U* test. Patients were classified according to employment status as employed vs. other. The other employment status category included all patients not fulfilling the active employment category (temporary sick leave, permanent disability, students, unemployment, retirement, others, unknown). Sociodemographic and clinical characteristics (including the EDSS, the 9-HPT, the T25-FW), and patient-reported measurements scores (SyMS, SSCI-8, BDI-FS, D-FIS, and PES) were described and related to the MSIS-29 scores and the MSWDQ-23 scores using Spearman's correlation. Two multiple linear regression models were constructed using each domain of the MSIS-29 scores as the dependent variable and sociodemographic, clinical, and neuroimaging characteristics as independent variables. The final multivariate model included all variables with a *p* value of less than 0.1. A *p* value lower than 0.05 was considered significant. All analyses were conducted using SAS Enterprise Guide 7.15.

The study was approved by the investigational review board of Galicia (CEIm-G), Santiago de Compostela, Spain [Registration Number 2019/406, Sponsor Number ROC-NEU-2019-01 (ML41397)], and performed in accordance with the 1964 Helsinki Declaration and its later amendments. According to Spanish legislation (Orden SAS/3470/2009), observational studies require approval by a single ethics committee and this approval applies to all participating centers. Participants were recruited consecutively between November 2019 and July 2020. Written informed consent was obtained from all subjects.

## RESULTS

### Demographic and Clinical Characteristics

A total of 71 patients were included in the study. The mean ( $\pm$  SD) age was  $47.4 \pm 14.9$  years (range 18–81 years), and 80.3% were female. The mean time since disease onset was  $9.9 \pm 8.1$  years, with a mean time since diagnosis of  $6.2 \pm 3.9$  years, and the median EDSS score was 3.0 (interquartile range

**Table 1** Demographic and clinical characteristics according to AQP4 antibody status

	<b>Total<sup>a</sup> n = 71</b>	<b>AQP4 positive n = 54</b>	<b>AQP4 negative n = 16</b>	<b>p value</b>
Age, mean ± SD, years	47.4 ± 14.9	49.3 ± 14.6	41.4 ± 15.1	0.0570
Sex (female), n (%)	57 (80.3)	47 (87.0)	9 (56.3)	0.0068
Education <sup>b</sup> , n (%)				0.4624
Primary	17 (24.6)	14 (26.4)	3 (20.0)	
Secondary	21 (30.4)	18 (34.0)	3 (20.0)	
Tertiary	30 (43.5)	30 (37.7)	9 (60.0)	
Living with family members or a partner, n (%)	63 (90.0)	49 (90.7)	13 (86.7)	0.6438
Employment status <sup>c</sup> , n (%)				0.9262
Employed (part or full-time)	21 (30.0)	15 (27.8)	6 (40.0)	
Temporary sick leave due to NMOSD	2 (2.9)	1 (1.9)	0	
Permanent disability due to NMOSD	17 (24.3)	14 (25.9)	3 (20.0)	
Permanent disability due to other reasons	3 (4.3)	3 (5.6)	0	
Student	3 (4.3)	2 (3.7)	1 (6.7)	
Unemployed	9 (12.9)	7 (13.0)	2 (13.3)	
Retired	12 (17.1)	10 (18.5)	2 (13.3)	
Housework	3 (4.3)	2 (3.7)	1 (6.7)	
Other	0			
Age at onset, mean ± SD, years	41.1 ± 14.8	42.4 ± 14.9	37.1 ± 14.5	0.2750
Time since diagnosis, mean ± SD	6.2 ± 3.9	6.7 ± 3.8	4.2 ± 3.8	0.0171
Time since disease onset, mean ± SD	9.9 ± 8.1	10.7 ± 8.7	6.6 ± 4.8	0.1062
Onset attack type, n (%)				0.1762
Myelitis	34 (47.8)	29 (53.7)	5 (31.3)	
Optic neuritis	27 (38.0)	19 (35.2)	8 (50.0)	
Myelitis + optic neuritis	3 (4.2)	1 (1.9)	2 (12.5)	
Relapsing form, n (%)	59 (83.1)	44 (81.5)	14 (87.5)	0.5748
Number of relapses since diagnosis <sup>d</sup> , mean ± SD	3.0 ± 2.3	3.2 ± 2.5	2.3 ± 1.4	0.3648
Number of relapses in the last year <sup>e</sup> , mean ± SD	0.5 ± 0.9	0.4 ± 1.0	0.8 ± 1.0	0.2311
Coexisting autoimmune disease, n (%)	21 (29.6)	19 (35.2)	2 (12.5)	0.0820
EDSS score <sup>e</sup> , median (IQR)	3.0 (1.5–4.5)	3.0 (2.0–4.5)	2.3 (1.5–3.5)	0.2497
9-HPT, mean ± SD, s				

**Table 1** continued

	Total <sup>a</sup> <i>n</i> = 71	AQP4 positive <i>n</i> = 54	AQP4 negative <i>n</i> = 16	<i>p</i> value
Dominant hand <sup>f</sup>	23.9 ± 10.7	24.7 ± 12.0	21.7 ± 5.3	0.3791
Non-dominant hand <sup>g</sup>	25.1 ± 10.4	24.3 ± 7.1	28.1 ± 17.2	0.5268
T25FW <sup>h</sup> , mean ± SD, s	7.6 ± 6.3	8.2 ± 7.0	6.0 ± 2.6	0.1866
Visual acuity (< 20/100), <i>n</i> (%)	18 (27.7)	12 (25.0)	5 (31.3)	0.6240
MSIS-29, mean ± SD				
Physical impact score (20–80)	41.9 ± 16.8	42.6 ± 16.8	40.9 ± 16.8	0.6745
Psychological impact score (9–36)	20.9 ± 8.3	20.3 ± 8.0	23.4 ± 9.2	0.1677
PES score, mean ± SD (6–30)	14.0 ± 6.3	13.8 ± 6.4	14.9 ± 6.0	0.4740
D-FIS score <sup>c</sup> , mean ± SD (0–32)	9.0 ± 8.3	8.9 ± 8.6	10.1 ± 7.4	0.3532
BDI-FS score <sup>c</sup> , mean ± SD (0–21)	3.6 ± 3.4	3.5 ± 3.4	4.3 ± 3.3	0.2534
SyMS score <sup>b</sup> , mean ± SD (0–72)	22.0 ± 14.5	22.7 ± 14.1	20.5 ± 16.0	0.5105
SSCI-8 score <sup>c</sup> , mean ± SD (8–40)	11.9 ± 5.1	11.7 ± 4.8	13.0 ± 5.9	0.5447
MSWDQ-23 total score <sup>i</sup> , mean ± SD (0–100)	23.3 ± 20.3	21.0 ± 17.8	29.4 ± 25.7	0.4081

*AQP4* aquaporin-4, *EDSS* Expanded Disability Status Scale, *9-HPT* 9-Hole Peg Test, *T25-FW* Timed 25-Foot Walk, *MSIS-29* 29-item Multiple Sclerosis Impact Scale, *PES* MOS Pain Effects Scale, *D-FIS* Fatigue Impact Scale for Daily Use, *BDI-FS* Beck Depression Inventory-Fast Screen, *SyMS* SymptoMScreen, *SSCI-8* Stigma Scale for Chronic Illness 8-item version, *MSWDQ-23* Multiple Sclerosis Work Difficulties Questionnaire, *IQR* interquartile range, *SD* standard deviation

<sup>a</sup>1 patient with missing data for AQP4 antibodies

<sup>b</sup>*n* = 69

<sup>c</sup>*n* = 70

<sup>d</sup>*n* = 55 (4 missing values)

<sup>e</sup>*n* = 56 (3 missing values)

<sup>f</sup>*n* = 64

<sup>g</sup>*n* = 63

<sup>h</sup>*n* = 62

<sup>i</sup>*n* = 41

1.5, 4.5). At the time of the study visit, 30.0% were employed, and 24.3% had a permanent disability due to NMOSD. Concomitant autoimmune diseases were present in 29.6% of patients, with systemic lupus erythematosus (7.0%) being the most prevalent, followed by Sjögren's syndrome (5.6%). The majority of patients (93.9%) were receiving a disease-modifying treatment at the time of the study visit. AQP4 antibodies were positive in 54 patients

(77.1%). In the subgroup without AQP4 antibodies, five patients had antibodies against the myelin oligodendrocyte glycoprotein (MOG). Patients' characteristics in the AQP4-positive and AQP4-negative groups were similar, except for a shorter time since diagnosis and a lower proportion of women among AQP4-negative patients. In addition, an upwards trend in the presence of concomitant autoimmune diseases in the AQP4-positive subgroup was observed.



Table 1 shows the demographic and clinical characteristics of the sample in further detail.

### Patient-Reported Outcome Results

Results from the MSIS-29, SyMS, SSCI-8, BDI-FS, D-FIS, PES, and MSWDQ-23 are shown in Table 1. No significant differences were observed between AQP4-positive and AQP4-negative patient subgroups.

Symptom severity was low in the studied population. Individual domain SyMS scores were highest for fatigue and body pain, and lowest for dizziness and hand dexterity. In comparison, vision and bladder control stood out as the domains with the highest levels of perceived severity. Only one patient had a composite score of 0, meaning that the vast majority of patients [98.6% ( $n = 69$ )] had at least one of the 12 domains affected, leading to minor adjustments in their lives.

Both dimensions of the MSIS-29 questionnaire were modestly affected by NMOSD, decreasing health perception with a slightly greater impact in the psychological dimension. Overall, 23.9% ( $n = 17$ ) of patients suffered a moderate/extreme physical impact (mean score at least 3), whereas 28.2% ( $n = 20$ ) experienced a moderate/extreme psychological impact from NMOSD. Of note, 28.2% of participants reported having an urgent need to go to the toilet, which extremely impacted their HRQoL.

The majority of patients (81.4%,  $n = 57$ ) reported fatigue impacting their life in at least one of the statements studied in the questionnaire. The presence of pain was reported in 83.1% ( $n = 59$ ) of patients (score greater than 6), as assessed by the PES scale. The PES questionnaire revealed that in 29.6% ( $n = 21$ ) of patients, pain interferes with their sleep quite a bit or to an extreme degree, and the same effect was reported by 23.9% ( $n = 17$ ) of patients regarding recreational activities.

A total of 41 patients completed the MSWDQ-23 questionnaire (Table 2). The mean MSWDQ-23 total score was  $23.3 \pm 20.3$ , with external barriers being the dimension most affected among patients. In addition, 75.6% ( $n = 31$ ) of patients experienced some barriers in

**Table 2** Description of MSWDQ-23 scores according to employment status

	Overall $n = 41$	Employed $n = 21$	Other employment status $n = 20$
Psychological/cognitive barriers			
Mean (SD)	19.1 (19.6)	9.5 (11.5)	29.2 (21.5)
Median (IQR)	15.9 (2.3; 29.5)	4.5 (0.0; 15.9)	27.3 (8.0; 46.6)
Physical barriers			
Mean (SD)	25.8 (23.5)	11.9 (12.3)	40.3 (23.9)
Median (IQR)	18.8 (9.4; 40.6)	9.4 (0.0; 18.8)	37.5 (21.9; 57.8)
External barriers			
Mean (SD)	29.9 (28.1)	22.3 (26.5)	37.8 (28.2)
Median (IQR)	25.0 (0.0; 56.3)	12.5 (0.0; 43.8)	34.4 (15.6; 62.5)
MSWDQ-23 total score <sup>a</sup>			
Mean (SD)	23.3 (20.3)	12.6 (12.5)	34.6 (21.1)
Median (IQR)	18.5 (5.4; 33.7)	8.7 (2.2; 20.7)	32.6 (14.1; 48.4)

*MSWDQ-23* Multiple Sclerosis Work Difficulties Questionnaire, *SD* standard deviation, *IQR* interquartile range  
<sup>a</sup>MSWDQ-23 scores range from 0 to 100, with higher values indicating greater workplace problems. Values were missing for 30 patients. 41 patients completed the MSWDQ-23 questionnaire (21 employed, other employment status = 2 temporary sick leave due to study disease, 7 permanent disability due to study disease, 1 student, 4 unemployed, 5 retired, and 1 missing at study visit)

the psychological/cognitive dimension, 85.4% ( $n = 35$ ) in the physical dimension, and 70.7% ( $n = 29$ ) in the external barriers dimension.

Patients employed at the time of the study obtained lower scores (fewer workplace difficulties) than those not actively employed.

### Correlation Between HRQoL and Disability, Symptom Severity, Mood Disorders, Fatigue, and Pain

The physical and psychological dimensions of the MSIS-29 showed significant correlation between them (Table 3). The physical dimension of the MSIS-29 significantly correlated with disability, symptom severity, depressive symptoms, fatigue, and pain, although the strongest correlation was seen with symptom severity ( $\rho = 0.85584$ ,  $p < 0.0001$ ). The psychological dimension showed a significantly strong correlation with symptom severity, depressive symptoms, fatigue, and pain ( $\rho = 0.69589$ ,  $0.71380$ ,  $0.64005$  and  $0.76487$ ,  $p < 0.0001$ , respectively), and a weak correlation with EDSS. Overall, symptom severity exhibited the highest correlation with MSIS-29 for both dimensions.

We found that pain, fatigue, and depressive symptoms displayed a high correlation between them. Symptom severity showed a high correlation with pain and mood disorders and a moderate correlation with EDSS and fatigue. Mood disorders and pain displayed a significant

but low or moderate correlation with EDSS, while fatigue was not significantly correlated with disability.

The stepwise linear regression analysis revealed that some employment status categories were the best predictors of a poor score for the physical dimension of MSIS-29, followed by pain (PES score), stigma (SSCI-8 raw score), overall symptom severity (SyMS composite score), and hand impairment (dominant hand 9-HPT) (adjusted  $r^2 = 0.89$ ,  $p < 0.0001$ ) (Table 4). A higher number of years since the NMO/D diagnosis predicted a better physical health score. The major predictors of lower psychological quality of life were higher levels of pain and stigma.

### Correlation Between Work Difficulties and Disability, Symptom Severity, Stigma, Mood Disorders, Fatigue, and Pain

Employment status and other work-related characteristics were predictors of HRQoL dimensions; we therefore assessed the relationship between work difficulties and disability, symptom severity, stigma, mood disorders, fatigue, and pain (Table 5). The psychological/cognitive barriers dimension of the MSWDQ-23 questionnaire showed the highest correlation

**Table 3** Correlation coefficients across questionnaires and disability,  $n = 70$

	EDSS	D-FIS	PES	BDI-FS	SyMS	MSIS-29 psychological
MSIS-29 physical	0.67539	0.52165	0.62515 <sup>a</sup>	0.51243	0.85584 <sup>b</sup>	0.72779 <sup>a</sup>
MSIS-29 psychological	0.36858 <sup>**</sup>	0.64005	0.76487 <sup>a</sup>	0.71380	0.69589 <sup>b</sup>	
SyMS	0.58643 <sup>c</sup>	0.56130 <sup>b</sup>	0.66387 <sup>b</sup>	0.62122 <sup>b</sup>		
BDI-FS	0.29437 <sup>*b</sup>	0.66302	0.66393			
PES	0.34529 <sup>**</sup>	0.66725				
D-FIS	0.17458 <sup>NS,b</sup>					

All values have  $p < 0.0001$  except for NS = non-significant

MSIS-29 29-item Multiple Sclerosis Impact Scale, SyMS SymptoMScreen, BDI-FS Beck Depression Inventory-Fast Screen, PES Pain Effects Scale, D-FIS Fatigue Impact Scale for Daily Use, EDSS Expanded Disability Status Scale

\* $p < 0.05$ ; \*\* $p < 0.01$

<sup>a</sup> $n = 71$

<sup>b</sup> $n = 69$

<sup>c</sup> $n = 68$



**Table 4** Multivariate linear regression analysis of sociodemographic, clinical, and neuroimaging characteristics related to the physical and psychological dimensions of health-related quality of life (MSIS-29)

	Estimate	SE	t value	p value
MSIS-29 physical dimension				
Employment status				
Employed	Ref.	NA	NA	NA
Employed-sick leave due to NMOSD	7.154380	4.019832	1.78	0.0822
Permanent disability due to NMOSD	7.241089	2.637959	2.74	0.0088
Permanent disability not due to NMOSD	4.924847	4.286278	1.15	0.2569
Student	3.149009	3.394496	0.93	0.3588
Unemployed	− 1.824505	3.046121	− 0.60	0.5523
Retired	6.002214	2.487172	2.41	0.0201
Housework	19.450953	3.679419	5.29	< 0.0001
Years since NMO diagnosis	− 0.610604	0.214308	− 2.85	0.0067
Dominant hand 9-HPT (s)	0.251258	0.073172	3.43	0.0013
SyMS composite score	0.377865	0.097077	3.89	0.0003
SSCI-8 raw score	0.642608	0.231835	2.77	0.0082
PES score	0.940046	0.201495	4.67	< 0.0001
MSIS-29 psychological dimension				
SSCI-8 raw score	0.316583	0.144719	2.19	0.0329
PES score	0.698613	0.125454	5.57	< 0.0001

Independent models were used for each dimension. The final regression model was constructed using a stepwise regression analysis for variable selection. All variables with a *p* value of less than 0.1 in univariate analyses were included in the model, and the final model only included those that remained below this threshold when combined. The final model for each dimension includes only shown variables. MSWDQ-23 was not included in the multivariate analysis because of the high level of missing values

*NA* not applicable, *9-HPT* 9-Hole Peg Test, *MSIS-29* 29-item Multiple Sclerosis Impact Scale, *NMO* Neuromyelitis Optica, *PES* MOS Pain Effects Scale, *SyMS* SymptoMScreen, *SSCI-8* Stigma Scale for Chronic Illness 8-item version

with the physical dimension of the questionnaire. Significantly, high correlations were found with fatigue, followed by mood disorders, symptom severity, and pain, and a moderate correlation was found with stigma. Non-significant low correlations were present for disability. The physical barriers dimension displayed the highest correlation with pain ( $\rho = 0.82712$ ,  $p < 0.0001$ ), followed by symptom severity, mood disorders, and fatigue. Moderate to low

significant correlations were present with stigma, EDSS, and hand dexterity.

## DISCUSSION

Understanding HRQoL and well-being in patients suffering from NMOSD is relevant for improving patient care. Evaluations of HRQoL are being used as outcome measures in clinical trials on NMOSD [30–32], and new studies are

**Table 5** Correlation coefficients across MSWDQ-23, patient-reported outcomes (PROs), and disability,  $n = 41$ 

	EDSS	T25FW	Dominant hand 9-HPT	D-FIS	PES	BDI-FS	SSCI-8	SyMS	MSWDQ-23 (Physical barriers)
MSWDQ-23 (Psychological/ cognitive barriers)	0.25477 <sup>NS</sup>	0.29207 <sup>NS,d</sup>	0.28362 <sup>NS,c</sup>	0.71177 <sup>a</sup>	0.62733	0.68408 <sup>a</sup>	0.54532 <sup>***a</sup>	0.68067 <sup>b</sup>	0.81117
MSWDQ-23 (Physical barriers)	0.48870 <sup>**</sup>	0.21524 <sup>NS,d</sup>	0.39924 <sup>*c</sup>	0.65436 <sup>a</sup>	0.82712	0.71901 <sup>a</sup>	0.52392 <sup>***a</sup>	0.79879 <sup>b</sup>	

All values have  $p < 0.0001$  except for NS = non-significant

MSWDQ-23 Multiple Sclerosis Work Difficulties Questionnaire, EDSS Expanded Disability Status Scale, T25FW Timed 25-Foot Walk, 9-HPT 9-Hole Peg Test, D-FIS Fatigue Impact Scale for Daily Use, PES Pain Effects Scale, BDI-FS Beck Depression Inventory-Fast Screen, SyMS SymptomScreen, SSCI-8 Stigma Scale for Chronic Illness 8-item version

\* $p < 0.05$ ; \*\* $p < 0.01$

<sup>a</sup> $n = 40$

<sup>b</sup> $n = 39$

<sup>c</sup> $n = 38$

<sup>d</sup> $n = 37$

emerging worldwide. However, there is still a lack of research that focuses on HRQoL in patients diagnosed with this disorder [6, 9, 11, 14, 33]. Furthermore, patients with NMOSD also suffer from various symptoms like pain, fatigue, and depression, all of which can affect their quality of life and should be addressed. Additionally, most patients present a recurrent relapsing course, and AQP4-positive patients tend to have a higher prevalence of concomitant diseases, making these symptoms accumulate and increase the burden on their quality of life. Thus, the primary goal of this study was to assess the HRQoL of patients with NMOSD using the MSIS-29 and explore how it is impacted by different disease factors.

Overall, this study has shed light on the perspective of patients with NMOSD, who suffer a marked psychological and physical impact that is mainly affected by symptom severity. According to our results based on different PROs, depression, fatigue, pain interference with daily activities, and work-related difficulties are common features even in a clinically stable population with low physical disability.

Similar to results reported by Yalachkov et al. in a population with low physical disability [15], our study showed that NMOSD has a marked psychological impact on patients' life [mean (SD) 20.9 (8.3)], while the physical impact was more modest [mean (SD) 41.9 (16.8)]. However, these results differ from previous reports by Beekman et al. and Huang et al. that evaluated HRQoL in patients with NMOSD in North America and China, which reported that emotional health remained generally unimpaired or less impaired compared to poor physical health results [9, 11]. The discrepancies observed could be due to the different ethnicity, questionnaires used in the studies, and disease activity in the cohorts, as Chinese and North American populations included a higher percentage of patients who had relapsed within the previous year (52.5% and 38.0%, respectively), in comparison to our cohort (28.6%). In addition, the presence of pain—although measured on a different scale—seemed to be higher in these cohorts, and pain severity and walking impairment have been reported as two independent predictors explaining 53.9% of the

physical quality of life composite variability as measured with the Short Form 36 Health Survey (SF-36) [34]. Furthermore, our study included patients with a longer disease duration since diagnosis (6.2 years in our study, compared to 3.7 and 5.0 years in China and North America patients, respectively). Although Beekman et al. found a correlation between seronegative or unknown AQP4 status and a lower impact on quality of life, we could not find differences between positive or negative serostatus and MSIS-29 results [9].

Despite being a population with low disability and symptom burden, symptom severity was one of the predictors of HRQoL and exhibited the highest correlation with MSIS-29 for both dimensions. Bladder control and vision were the domains with the highest levels of perceived severity and having an urgent need to go to the toilet was reported as having an extreme impact on the HRQoL of almost one-third of the patients. Similarly, previous studies have reported bodily pain, bowel and bladder dysfunction, and visual impairment as the predominant physical issues affecting quality of life [9, 11]. Moreover, previous reports have shown a correlation between bladder and bowel dysfunction and a significant physical, psychological, and social impact in 87% of patients with transverse myelitis, thus lowering their HRQoL [35]. These results highlight the need to address bladder and bowel symptoms with nutrition advice and appropriate treatment to improve urinary symptoms in patients with NMOSD and, consequently, improve their quality of life.

More than 44% of patients experienced depression, although most cases were mild, and remarkably no patients scored within the severe category. Our prevalence and severity were lower than in studies measuring depression prevalence among NMOSD in Argentina, the USA, and Germany [34, 36, 37]; however, pain and disability were higher in these cohorts, and ethnicity also differed. It should be noted that our results on depression were similar to those reported by Yalachkov et al., as both populations had similar disease duration, low physical disability, and the same questionnaire was used, although the fast screen BDI questionnaire was

used in our sample [15]. Nonetheless, we should note that our study did not record depression treatment or psychotherapy. Consistent with the findings in these cohorts, depression significantly correlated with fatigue and pain. We also found a high correlation between depression and the psychological and physical dimensions of the MSIS-29, while a more modest correlation was found with disability. These results highlight the need for active screening for psychological disorders in this population group, offering early treatment and rehabilitation and thus improving HRQoL [14].

Several studies have identified fatigue as a common complaint among patients with NMOSD [6, 38, 39]. Furthermore, this symptom is most commonly rated as moderate/severe [40]. However, fatigue was rated as having a low impact on daily quality of life within our population when assessed by the D-FIS scale, although it affected more than 80% of individuals. These observations are in marked contrast with a retrospective observational study including 522 patients with NMOSD by Eaneff et al. [40], which reported that 53% of patients experienced moderate-severe fatigue symptom severity. These differences are likely explained by the different questionnaires and patient selection methods. While the impact of fatigue was relatively low within our cohort, higher fatigue scores were correlated with a worse psychological and physical quality of life. This is in line with results observed by Shi et al. [6], in which chronic fatigue [measured using the Fatigue Impact Scale (FIS)] showed a significant negative correlation with HRQoL, although the correlation was not as strong as the one found by Barzegar et al. [41]. Barzegar et al. [41] found that fatigue was the most important variable to predict the variance of physical and mental components of HRQoL, and depression was also a predictive factor of mental HRQoL.

Previous studies have reported the presence of pain in 62–86% of patients [7, 8, 34, 42]. In our study, the pain was markedly prevalent as well, impacting mood, walking ability, sleep, work, recreation, and enjoyment of life. However, pain in our population was not as severe as that reported by Ayzenberg et al. in a cohort of 166 patients from 13 tertiary referral centers

[34], with moderate to severe NMOSD-associated chronic pain in 55.2% of patients even when receiving with symptomatic treatment. Similar to our results, they found that pain severity but not physical impairment was associated with depression, and that pain, depression, and walking impairment were three main HRQoL predictors. As in previous studies, the psychological and physical dimensions of quality of life were correlated with pain in our cohort [10, 42]. Furthermore, the pain was a predictor for the physical and psychological dimensions of HRQoL.

Eaneff et al. [40] reported that almost all patients with NMOSD claimed at least some impairment in their ability to fulfill their goals or participate in work or other activities, suggesting that impairment in the ability to work may be a significant concern for these patients. In our study, more than 70% of patients reported work difficulties in at least one dimension (psychological/cognitive, physical, external barriers). Work difficulties were most prevalent in the physical dimension (85.4%), and the dimension of the external barriers was the most affected. More workplace problems were noted among patients not actively employed. In addition, several categories within patients not actively employed and hand impairment were significant predictors of a low score for the physical dimension of HRQoL. Physical and psychological work difficulties exhibited a significantly high correlation with symptom severity, mood, fatigue, and pain. In comparison, only physical difficulties exhibited a significantly moderate to low correlation with stigma, disability, and hand impairment. These findings are likely related to the marked psychological burden of our study population.

Our results underscore that NMOSD manifestations interfere with the ability to work, which in turn negatively impacts HRQoL. These findings are in line with previous reports. Moreover, they stress the need for further research and interventions in this field, with patients experiencing high unemployment rates, which are often related to worsening of symptoms, greater disability, lessened mobility, impaired hand function, fatigue, and cognitive dysfunction [9–11, 40, 43].

Several limitations should be noted regarding our study. First, the cross-sectional design did not allow us to assess changes or causal relationships in HRQoL of patients over time as the study consisted of a single visit. Likewise, causal inferences were not possible. Second, as patients with NMOSD present several symptoms which could act as barriers and prevent them from completing questionnaires (such as motor limitations, fatigue, etc.), this could cause our results to be underestimated. An adjusted analysis based on patients' medication should have been performed [34]. However, we did not collect medication details, which is an important limitation of the study. Furthermore, although recruitment was consecutive, visits were performed during the coronavirus pandemic, and this could potentially have affected patients' willingness to participate in those more severely impaired. Third, although the majority of people in Spain are Caucasian, we did not collect ethnicity data, thereby underestimating its influence on the results. Fourth, a more extended and detailed psychological evaluation instead of a 9-item questionnaire would have been better to achieve a clearer understanding on how NMOSD impact patients' lives. Further longitudinal studies including patients with different age ranges may help to confirm our results and to determine whether the disease duration might have impact on the patients' perspectives. Nevertheless, we describe the perception of HRQoL and the prevalence of different key symptom domains among a sample of patients treated in 13 different hospitals throughout Spain, allowing results to be generalized to community practice. To the best of our knowledge, this is the first study on HRQoL and related factors among patients with NMOSD in Spain.

## CONCLUSION

Evaluating the impact of NMOSD on HRQoL from the patients' perspective is essential to allow early effective interventions that may help improve patients' well-being. Our findings clearly confirm the negative impact and significant burden of NMOSD on the psychological

and physical dimensions of HRQoL, even in a clinically stable population with low physical disability. Symptom severity, stigma, depression, pain, fatigue, and work-related problems are common features affecting patients' quality of life. There is a need for healthcare providers to be aware of these symptoms and to adopt appropriate interventions to improve overall HRQoL in patients with NMOSD. Future studies should investigate HRQoL longitudinally and consider developing specific PROs for NMOSD to improve understanding of this disease.

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consecutively between November 2019 and July 2020. Written informed consent was obtained from all subjects.

**Data Availability.** Qualified researchers may request access to individual patient-level data through the corresponding author. The datasets generated during the analysis of the study are available from the corresponding author on reasonable request.

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