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Acute neuromyelitis optica spectrum disorder patients' clinical analysis of disability-related biomarkers

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Abstract

Background The clinical features of neuromyelitis optica spectrum disorder (NMOSD) predominantly include optic neuritis and myelitis, among other symptoms. A greater level of disability during the acute phase typically suggests an unfavorable prognosis. Nevertheless, the clinical biomarkers that impact the severity of disability in NMOSD remain unclear.

Methods We analyzed 41 NMOSD patients and 41 normal controls to identify biomarkers associated with the disease. NMOSD patients were categorized into two groups based on their Expanded Disability Status Scale(EDSS) score: mild to moderate disability (EDSS < 4) and severe disability (EDSS ≥ 4). Correlation and ROC analyses were conducted on various biomarkers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio(MLR), cerebrospinal fluid (CSF)/serum albumin quotient(QAlb), CSF/blood immunoglobulin G quotient (QIgG), CSF/blood immunoglobulin A quotient (QIgA), CSF/blood immunoglobulin M quotient (QIgM), to identify markers linked to disability severity and confirm their independence.

Results Significant differences in blood NLR, PLR, and MLR were found between NMOSD patients and normal controls ($P < 0.01$) in biomarker comparison analysis. Significant variations in QAlb, QIgG, QIgA, QIgM, and PLR were noted between the two groups of NMOSD patients stratified by disability severity. A correlation analysis revealed a positive association between QAlb, QIgG, QIgA, QIgM, PLR, and EDSS scores. Levels of QAlb, QIgG, QIgA, QIgM, and PLR were found to be effective indicators of NMOSD severity in Receiver Operating Characteristic (ROC) analysis ($P < 0.01$). Multifactor regression analysis confirmed the independence of PLR in assessing disease severity ($P < 0.01$).

Conclusion 1. QAlb, QIgG, QIgA, QIgM, and PLR have demonstrated efficacy as biomarkers for assessing the severity of NMOSD; 2. PLR has shown promise as a standalone indicator for evaluating disease severity in patients with NMOSD.

Keywords NMOSD, Biomarker, PLR, QAlb, EDSS score, Disability severity

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Introduction

NMOSD is a rare yet severe chronic neuroinflammatory disorder characterized by inflammation primarily impacting the optic nerves and spinal cord, resulting in significant consequences such as vision loss, as well as motor and sensory impairments [1]. Epidemiological data shows that the annual incidence of NMOSD is approximately 0.278 per 100,000 people, with variations across different age groups, genders, and ethnicities. NMOSD has a high relapse rate and disability rate, with 40-60% of patients relapsing within one year, and about 50% of patients experiencing severe visual or motor dysfunction within 5–10 years [2–4]. IgG antibodies targeting Aquaporin-4 (AQP4) are crucial in the development of NMOSD [5], around 70% of patients with NMOSD test positive for anti-AQP4 antibodies [6]. However, studies have indicated that there isn't necessarily a positive correlation between serum AQP4 antibody levels and the severity of acute disability in patients. This inconsistency may be attributed to variations in the degree of blood-brain barrier (BBB) disruption among different patients.

BBB is a critical component of the neuroimmune axis. BBB disruption impairs the controlled exchange of chemokines, cytokines, and immune cells between the CNS and bloodstream, causing increased leakage of substances like IgG and plasma albumin. This disruption is a key pathological feature of NMOSD, supported by animal studies [7, 8] Clinical research has shown a strong correlation between the degree of BBB disruption and disability severity in NMOSD, with the QAlb ratio serving as an indicator of BBB damage. Higher QAlb levels are associated with greater disability in NMOSD patients [9–11].

Previous studies have shown that neutrophils, platelets, and monocytes are key biomarkers of systemic inflammation. Neutrophils initiate inflammatory responses [12], while platelets form platelet-leukocyte aggregates in inflamed tissues, promoting further inflammation. Yan's study found platelets secrete immune regulatory factors that attract neutrophils and lymphocytes [13]. Specific blood biomarkers linked to lymphocytes, such as PLR, NLR, and MLR, can indicate inflammation associated with CNS demyelination and other autoimmune disorders [14–16]. Miguel Cabanillas-Lazo's meta-analysis suggested NLR could predict NMOSD prognosis [17]. Studies have shown that the neutrophil-to-lymphocyte ratio (NLR) rises during relapse in both APQ4 + NMOSD and MOGAD [18, 19]. However, the relationship between blood inflammatory markers and NMOSD disability severity remains unclear. Further exploration of the correlation between plasma inflammatory biomarker levels, blood-brain barrier disruption, and disability severity in NMOSD is essential. This could offer improved diagnostic and treatment approaches for NMOSD patients.

This study aims to explore biomarkers associated with the severity of disability in NMOSD and investigate the relationship between these biomarkers and the level of disability in NMOSD patients.

Methods

Study population

A retrospective analysis was conducted on cases from November 2020 to March 2024, including patients with NMOSD. Diagnosis of NMOSD followed international consensus standards [1]. Exclusion criteria were: (a) Patients with comorbidities such as hypertension, coronary heart disease, diabetes, cerebrovascular disease, tumors, and other chronic diseases; (b) Patients with other autoimmune diseases such as rheumatoid arthritis, Sjogren's syndrome, inflammatory myositis, systemic vasculitis, systemic lupus erythematosus, and thyroid diseases.

Study design

This is a single-center retrospective observational cohort study. We collected demographic and clinical data, including variables such as age, gender, AQP4-IgG status, clinical symptoms, medication usage, history of attacks, EDSS scores, QAlb, QIgG, QIgA, QIgM, and cerebrospinal fluid immunoglobulin G index. MOG antibodies were tested in all patients, but only one patient was positive for serum MOG antibodies, so this was not included in the study. QAlb was utilized as an indicator of blood-brain barrier permeability in the study. The formula used to calculate QAlb is QAlb = CSF albumin/serum albumin$\times 10^{-3}$. Considering that QAlb is affected by age, the upper limit of QAlb was adjusted using the formula 4 + (age/15 years) [20]. If QAlb exceeds the normal range, it is classified as increased blood-brain barrier permeability, whereas if QAlb falls within the normal range, it is classified as normal [20]. Cerebrospinal fluid albumin was analyzed using isoelectric focusing, and serum albumin was determined using the latex-enhanced turbidity method [21]. Cerebrospinal fluid and blood samples were collected at admission and before the commencement of any therapeutic interventions. NLR, PLR, and MLR were calculated using peripheral blood cell counts. The neurological impairment of patients upon admission was evaluated by two researchers utilizing the EDSS score [22]. Previous research has indicated that patients can be categorized into two groups based on their EDSS scores: 0-3.5 representing mild to moderate disability, and 4-9.5 indicating severe disability [23, 24]. To explore the independent association between risk factors and disease severity, patients were divided into two cohorts: the mild to moderate NMOSD group (EDSS < 4, $N = 23$) and the severe NMOSD group (EDSS ≥ 4, $N = 18$). During the follow-up period, ten patients (24.4%) experienced

a recurrence. Consequently, the increased EDSS score reflects the disparity between the EDSS score recorded at the time of disease relapse and that observed at the initial attack. Typically, patients are considered to be in the acute phase of their illness if the disease duration is less than 30 days. ROC curves were used to assess the diagnostic accuracy of the test based on EDSS scores, with the optimal cutoff value determined using the Youden Index. Logistic regression analysis was employed for both univariate and multivariate analyses to evaluate the independent factors influencing NMOSD disability severity.

Statistical analysis

The research data were analyzed using SPSS 22.0 software, where the Kolmogorov-Smirnov test revealed a non-normal distribution. Data visualization was performed using GraphPad Prism. Spearman's nonparametric correlation test was chosen to evaluate the relationship between continuous variables, given the non-normal distribution of the data. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test. Non-normally distributed data were represented by the median and interquartile range (25–75%) and analyzed using the Mann-Whitney U-test. Categorical variables were depicted as percentages (%) and compared between groups using the chi-square test. Receiver Operating Characteristic (ROC) curves were utilized to establish critical values. Both univariate and multivariate logistic regression models were applied, with a significance level set at $P < 0.05$ considered statistically significant.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Results

Inter-group clinical characteristics analysis

Table 1 presents a comparison of clinical measurements between 41 NMOSD patients (16 males and 25 females) and 41 healthy control subjects (14 males and 27 females) included in the study. While no significant disparities were found in age and gender between the two groups, variations were noted in the levels of NLR, PLR, and MLR. Figure 1 illustrates the comparison of blood inflammatory markers between NMOSD patients and the normal control group. The results indicate that NLR ($P = 0.01$), PLR ($P < 0.001$), and MLR ($P < 0.001$) levels in NMOSD patients were significantly higher than those in the healthy control group.

Clinical characteristics analysis based on EDSS score groups

In this study, patients were divided into two cohorts according to their EDSS scores: EDSS ≥ 4 ($n = 20$) and EDSS < 4 ($n = 21$). The male-to-female ratio was similar between the two groups. No statistically significant differences were observed in mean age, AQP4-IgG positivity, specific symptoms, cerebrospinal fluid IgG index, NLR value, and MLR value between the two groups. However, significant differences were observed between the EDSS < 4 group and the EDSS ≥ 4 group in PLR value ($P < 0.001$), QAlb value ($P = 0.005$), QIgG value ($P = 0.002$), QIgA value ($P = 0.016$), and QIgM value ($P = 0.002$) (Table 2; Fig. 2).

Relationship between biomarkers and EDSS score

Correlation analysis in the study examined the relationship between each biomarker and EDSS score, as depicted in Fig. 3. QAlb ($r = 0.4102$; $P = 0.0077$), QIgG ($r = 0.5435$; $P = 0.0002$), QIgA ($r = 0.4428$; $P = 0.0037$), QIgM ($r = 0.5801$; $P = 0.0001$), and PLR ($r = 0.5887$; $P = 0.0001$) were all positively correlated with EDSS

Table 1 The demographics and clinical characteristics of participants between NMOSD group and the healthy control group

Clinical characteristics	Healthy control group		NMOSD group		*P*-values
	N = 41		*N* = 41		
Sex, (N,%)	Male	Female	Male	Female	0.819
	14(34.15%)	27(65.85%)	16(39.02%)	25(50.98%)	
Age, y (mean ± SD)	41.76 ± 8.932		40.88 ± 15.330		0.751
AQP4-IgG + of patients(n,%)	—		15(36.58%)		—
Optic neuritis(n,%)	—		6(14.63%)		—
Acute myelitis(n,%)	—		29(70.74%)		—
Mix attacks(n,%)	—		6(14.63%)		—
EDSS<4(n,%)	—		21(51.21%)		—
EDSS ≥ 4(n,%)	—		20(48.79%)		—
NLR(M, IQR)	1.65 (1.06, 2.05)		1.89 (1.52, 3.60)		0.01
MLR(M, IQR)	0.12 (0.08, 0.19)		0.88 (0.21, 1.57)		<0.001
PLR(M, IQR)	76.96 (65.92, 98.56)		127.22 (100.82, 163.30)		<0.001

NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation; *Mix attacks*, including equal to two or more two damaged sites; *AQP4*,aquaporin-4; *EDSS*, Expanded Disability Status Scale; *NLR*,neutrophil-to-lymphocyte ratio; *MLR*, lymphocyte to monocyte ratio; *PLR*, platelet count to lymphocyte ratio

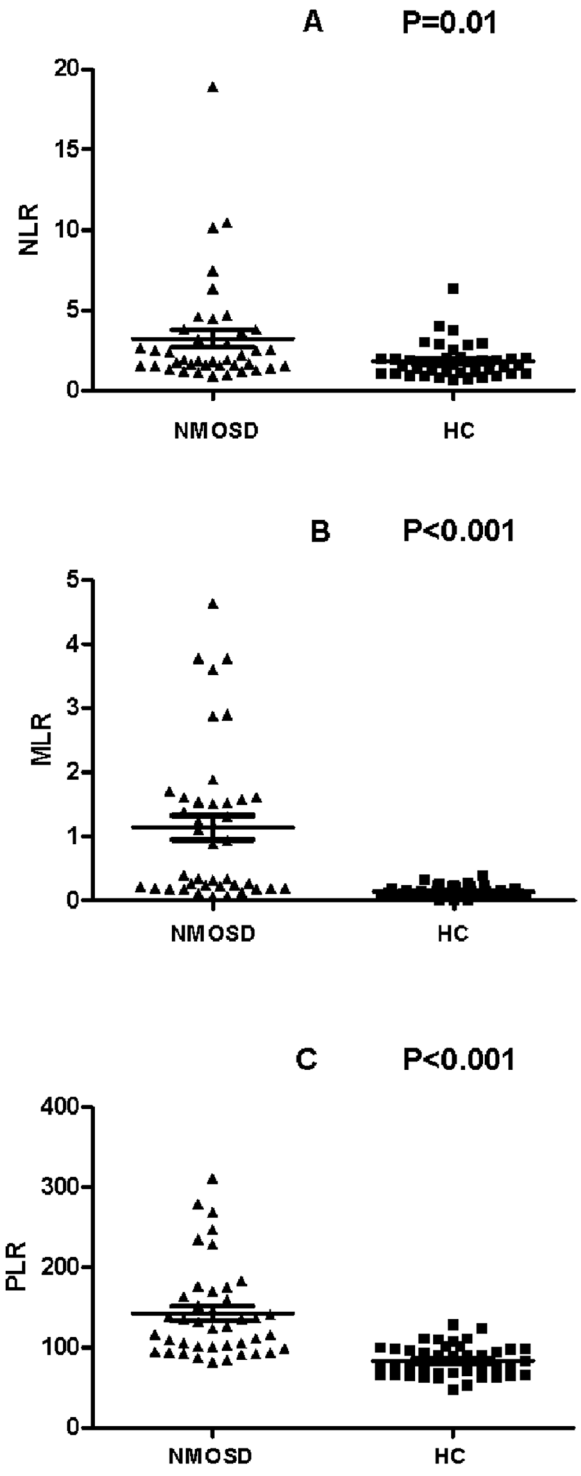

Fig. 1 Comparison of serum inflammatory markers levels between NMOSD patients and HC patients. **A**: Comparison of NLR levels between NMOSD patients and HC patients. NLR: Neutrophil-to-lymphocyte ratio. **B**: Comparison of MLR levels between NMOSD patients and HC patients. MLR: Monocyte-to-lymphocyte ratio. **C**: Comparison of PLR levels between NMOSD patients and HC patients. PLR: Platelet-to-lymphocyte ratio

score. NLR (r=-0.1132; $P=0.4809$) and MLR ($r=0.0057$; $P=0.9717$) showed no significant correlation with the EDSS score.

Additionally, the links between the increased EDSS score and the analyzed indicators were evaluated: the increase of Qalb was positively correlated with the increased EDSS score ($r=0.8801$; $P=0.0008$), as well as the increase of QIgG ($r=0.8186$; $P=0.0038$)、the increase of QIgA ($r=0.8124$; $P=0.0043$) and the increase of NLR ($r=0.8432$, $P=0.0022$). However, no significant correlation was observed between the increased EDSS score and QIgM ($r=0.3693$, $P=0.2936$), MLR ($r=-0.3262$, $P=0.3577$), or PLR ($r=0.3766$, $P=0.2835$).

EDSS, Expanded Disability Status Scale; NLR, neutrophil-to-lymphocyte ratio; MLR, lymphocyte to monocyte ratio; PLR, platelet count to lymphocyte ratio; QAlb, albumin quotient; QIgG, CSF/serum total IgG ratio; QIgM, CSF/serum total IgM ratio; QIgA, CSF/serum total IgA ratio.

Predictive value of biomarkers for the severity of EDSS scores in NMOSD patients

Receiver Operating Characteristic (ROC) analysis was conducted to assess the predictive value of each biomarker for the severity of EDSS scores in NMOSD patients. ROC analysis was conducted to determine the optimal cut-off values, sensitivity, and specificity of QAlb, QIgG, QIgA, QIgM, NLR, PLR, and MLR in differentiating between NMOSD patients with EDSS scores ≥ 4 and < 4, to categorize disease severity. As shown in Fig. 4: QAlb (cut-off value: 6.3; AUC: 0.8213; sensitivity: 65%; specificity: 90.48%; 95% confidence interval: 0.6726–0.9699; $P<0.001$), QIgG (cut-off value: 2.685; AUC: 0.8116; sensitivity: 83.33%; specificity: 73.91%; 95% confidence interval: 0.66631–0.9601; $P<0.001$), QIgA (cut-off value: 2.045; AUC: 0.7585; sensitivity: 55.56%; specificity: 100%; 95% confidence interval: 0.5897–0.9272; $P<0.01$), and PLR (cut-off value: 120.2; AUC: 0.8116; sensitivity: 65%; specificity: 90.48%; 95% confidence interval: 0.6786–0.9446; $P<0.001$) all demonstrated good specificity and sensitivity, allowing prediction of the severity of EDSS scores in patients. They possess clinical predictive significance. NLR (AUC: 0.5821; $P=0.3718$) and MLR (AUC: 0.5676; $P=0.4620$) showed no significant correlation with the severity of EDSS scores and had no clinical predictive value.

ROC curve analysis was used to distinguish between acute NMOSD patients with EDSS score ≥ 4 and those with EDSS score < 4 using QAlb, QIgG, QIgA, QIgM, NLR, MLR, and PLR. Optimal cut-off values for QAlb, QIgG, QIgA, QIgM, and PLR levels were determined based on the ROC curve area to predict acute NMOSD with EDSS ≥ 4 accurately. The optimal cut-off values for QAlb, QIgG, QIgA, and PLR show good specificity and

Table 2 Demographic and clinical differences between EDSS < 4 and EDSS ≥ 4 in patients with acute NMOSD

Clinical characteristics	EDSS<4		EDSS ≥ 4		*P*-value
	N = 21		*N* = 20		
Sex, (N,%)	Male	Female	Male	Female	> 0.999
	13(61.90%)	8(38.10%)	12(60.00%)	8(40.00%)	
Age, y (mean ± SD)	33.33 ± 672		37.44 ± 15.545		0.453
AQP4-IgG + of patients(n,%)	7(33.33%)		8(40%)		0.906
Focus:					0.172
Optic neuritis(n,%)	4(19.04%)		2(10.00%)		
Acute myelitis(n,%)	16(76.19%)		13(65.00%)		
Mix attacks(n,%)	1(4.77%)		5(25.00%)		
QAlb (M, IQR)	4.74 (4.04, 5.24)		7.17 (5.20, 9.68)		0.005
QIgG (M, IQR)	2.43 (1.95, 2.74)		3.97 (2.68, 5.50)		0.002
QIgA (M, IQR)	1.41 (1.07, 1.60)		1.99 (1.29, 3.23)		0.016
QIgM (M, IQR)	0.28 (0.18, 0.50)		0.78 (0.49, 1.12)		0.002
CSFIgG index (M, IQR)	0.49 (0.41, 0.54)		0.55 (0.50, 0.60)		0.072
NLR(M, IQR)	1.71 (1.23, 2.86)		2.25 (1.59, 3.84)		0.190
MLR(M, IQR)	1.19 (0.26, 1.54)		0.29 (0.21, 1.41)		0.306
PLR(M, IQR)	101.02 (94.21, 116.45)		157.93 (133.70, 230.28)		< 0.001

sensitivity in predicting disability severity in patients based on EDSS scores, making them clinically valuable for prediction. NLR and MLR do not have a significant correlation with EDSS scores, showing no clinical predictive value.

EDSS, Expanded Disability Status Scale; NLR, neutrophil-to-lymphocyte ratio; MLR, lymphocyte to monocyte ratio; PLR, platelet count to lymphocyte ratio; QAlb, albumin quotient; QIgG, CSF/serum total IgG ratio; QIgM, CSF/serum total IgM ratio; QIgA, CSF/serum total IgA ratio.

Univariate and multivariate regression analysis of biomarkers to validate independent factors influencing disability severity

Logistic regression analysis was utilized to perform both univariate and multivariate retrospective analyses on biomarkers potentially influencing NMOSD severity. The results presented in Table 3 indicate that PLR ($P = 0.01$) can function as an independent indicator of NMOSD severity. Conversely, QAlb, QIgG, QIgA, QIgM, NLR, disease location, and AQP4 positivity did not demonstrate statistically significant associations.

Discussion

In the acute phase of NMOSD, disability scores play a crucial role in predicting patient outcomes. Exploring factors and biomarkers associated with acute-phase disability severity is vital for identifying treatment targets for patients. This study found that QAlb, QIgG, QIgA, QIgM, and PLR are effective in assessing the degree of disability in NMOSD. It is noteworthy that this study revealed the potential of PLR as an independent indicator for evaluating the severity of NMOSD in patients.

QAlb, as a biomarker of blood-brain barrier disruption, has attracted significant attention. QAlb has been considered the gold standard for assessment of the BBB function [25]. Additionally, studies by Chen and Yuan revealed a positive correlation between serum albumin levels and the severity of NMOSD, further validating the association of QAlb with blood-brain barrier damage [26, 27]. In our study, a subgroup analysis of EDSS scores was conducted, and the results showed no significant differences among groups in demographic and basic clinical characteristics. However, compared to patients with EDSS scores < 4, those with EDSS scores ≥ 4 exhibited significantly elevated levels of QAlb, QIgG, QIgA, and QIgM. Correlation analysis revealed a positive relationship between the elevated levels of QAlb, QIgG, QIgA, and QIgM and the severity of NMOSD. Our study findings also confirm that during NMOSD, disruption of the blood-brain barrier (BBB) leads to the entry of proteins from the bloodstream into the cerebrospinal fluid, resulting in increased concentrations of albumin and immunoglobulins in the cerebrospinal fluid, thereby elevating QAlb, QIgG, QIgA, and QIgM values. Therefore, higher values of QAlb, QIgG, QIgA, and QIgM reflect greater BBB disruption and more severe disability in patients. This discovery further underscores a direct association between the severity of the disease's disability and the extent of blood-brain barrier damage.

Based on previous research on blood inflammatory markers, the PLR and NLR have been evaluated as potential biomarkers for inflammation, disease activity, and prognosis in autoimmune diseases [28, 29]. Our study found significant differences in inflammatory markers (PLR, NLR, MLR) between patients with NMOSD and healthy individuals, indicating that inflammatory

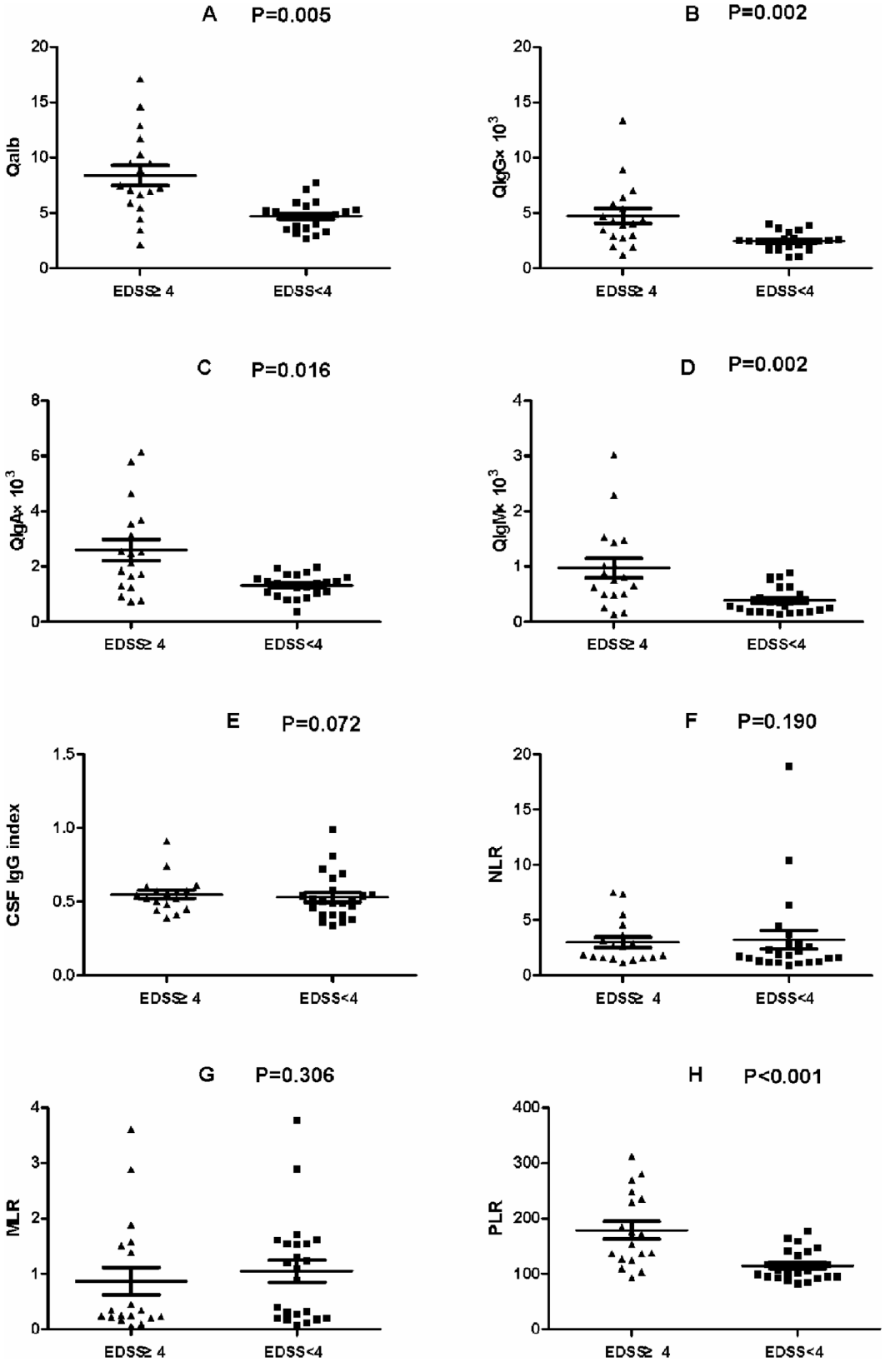

Fig. 2 (See legend on next page.)

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Fig. 2 Comparison of various indicators between the EDSS < 4 group and the EDSS ≥ 4 group. **A**: QAlb levels are higher in the EDSS ≥ 4 groups compared to the EDSS < 4 group. **B**: QIgG levels are higher in the EDSS ≥ 4 groups compared to the EDSS < 4 group. **C**: QIgA levels are higher in the EDSS ≥ 4 groups compared to the EDSS < 4 group. **D**: QIgM levels are higher in the EDSS ≥ 4 groups compared to the EDSS < 4 group. **E**: Comparison of cerebrospinal fluid IgG index between the EDSS < 4 group and the EDSS ≥ 4 group. **F**: Comparison of NLR between the EDSS < 4 group and the EDSS ≥ 4 group. **G**: Comparison of MLR between the EDSS < 4 group and the EDSS ≥ 4 group. **H**: Comparison of PLR between the EDSS < 4 group and the EDSS ≥ 4 group

response and immune dysregulation are key factors in the development of NMOSD.

Carnero Contentti E et al. found that the interaction between the endocrine system and the immune system may significantly promote the onset of NMOSD, indicating that elevated levels of PLR in the blood are often closely associated with the severity and prognosis of NMOSD [30]. Our study results are consistent with those of Carnero Contentti E's study. In subgroup analysis, patients with EDSS scores ≥ 4 showed significantly elevated levels of the inflammatory marker PLR compared to those with EDSS scores < 4 ($P < 0.001$). Correlation analysis demonstrates a positive relationship between PLR and disease severity, indicating a close association between platelet al.terations and the severity of NMOSD within the context of inflammatory responses. The underlying mechanism may involve platelets forming platelet-leukocyte aggregates in inflamed tissues through the secretion of adhesive factors, further promoting and triggering inflammation. Studies by Yan et al. and Chang et al. have identified high expression of intercellular adhesion molecule 2 (ICAM2) on platelets, which plays a role in chemotaxis for neutrophils and lymphocytes, facilitating neutrophil crawling and intercellular extravasation [13, 31]. The binding of neutrophils to endothelial cell ICAM2 increases vascular permeability. This indicates that the mutual influence between platelets and inflammatory cells also plays an important role in the disability level of NMOSD. Additionally, the elevation of platelets may be closely associated with changes in the expression levels of matrix metalloproteinase-9 (MMP-9) and claudin-5. Increased platelets may promote the release and activation of MMP-9 by inducing inflammation and damaging endothelial cells, leading to increased degradation of structural proteins in the vascular basement membrane and increased BBB permeability [32]. Moreover, platelet-induced inflammatory responses may also lead to a decrease in the expression levels of claudin-5, affecting the integrity of tight junctions between brain microvascular endothelial cells and increasing BBB permeability [33, 34]. These combined factors collectively lead to increased blood-brain barrier permeability, exacerbating the sensitivity of NMOSD lesion sites to external factors. This makes harmful substances, inflammatory mediators, and immune cells more likely to enter neural tissues, resulting in neuroinflammation and nerve damage. Both Carnero Contentti E and our study confirm the close correlation between PLR levels and the severity of disability in NMOSD patients [30]. During the follow-up process, The rise in Qalb was positively linked to higher EDSS scores, QIgG, and QIgA, NLR, consistent with past studies. However, relying on a single factor to assess severity or prognosis is inaccurate.

In their meta-analysis, Miguel Cabanillas-Lazo et al. proposed that NLR could also serve as a prognostic factor for NMOSD. In our study, although NLR showed significant differences between NMOSD and control populations, further subgroup analysis and single-factor/multi-factor regression analysis did not reveal a significant correlation with EDSS scores. This discrepancy may be attributed to sample size and population distribution variations. The differing clinical outcomes from Miguel Cabanillas-Lazo et al. also underscore the complexity of the underlying pathophysiology of NMOSD disability, indicating the need for further clinical analysis and validation [17].

Fang X et al. found a significant correlation between PLR and the onset of NMOSD [35]. In our ROC analysis, QAlb, QIgG, QIgA, QIgM, PLR, and other biomarkers demonstrated good clinical predictive value in determining the severity of disability, further confirming the clinical relevance between NMOSD disability and biomarkers. Multivariable logistic regression analysis further confirmed that PLR could serve as an independent predictor of NMOSD severity. Yan et al. suggested that QAlb might serve as an independent prognostic indicator for disability in NMOSD patients [36]. However, our study results do not support this conclusion, as the small sample size may have affected the multivariate regression analysis, preventing it from yielding significant conclusions. The inconsistency in results could stem from differences in sample size, population demographics, and the number of influencing factors considered in the analysis, which may have impacted our assessment of the role of independent factors in disability severity.

Sonia D'Souza et al.'s research indicates that platelets are the first blood elements to enter the brain from the peripheral blood after BBB damage in patients with MS. Early-stage prevention of increased platelets in peripheral blood can prevent disease progression [37]. Both NMOSD and MS stem from immune-mediated inflammatory reactions, sharing certain similarities in their pathogenesis. This study demonstrates that PLR can serve as an independent influencing factor affecting the severity of NMOSD, highlighting the significant impact of platelets on the prognosis of NMOSD disability.

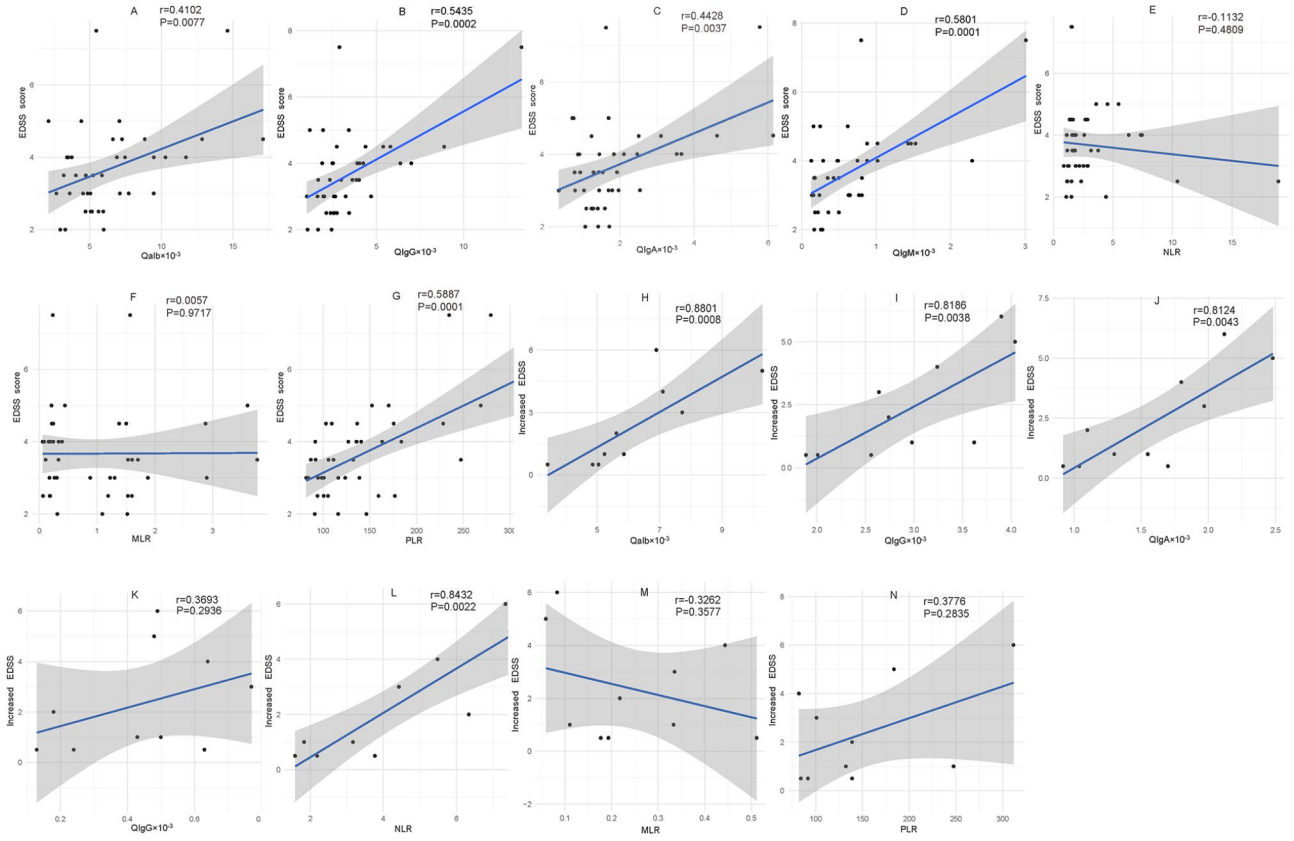

Fig. 3 A-G Spearman rank correlation between EDSS score and indicators. **A**: The increase of QAlb was positively correlated with EDSS score ($r=0.4102$; $P=0.0077$). **B**: The increase of QIgG was positively correlated with the EDSS score($r=0.5435$; $P=0.0002$); **C**: The increase of QIgA was positively correlated with the EDSS score ($r=0.4428$; $P=0.0037$); **D**: The increase of QIgM was positively correlated with the EDSS score ($r=0.5801$; $P=0.0001$); **E**: Correlation between EDSS score and NLR (r=-0.1132; $P=0.4809$); **F**: Correlation between EDSS score and MLR($r=0.0057$; $P=0.9717$); **G**: The increase of PLR was positively correlated with EDSS score $r=0.5887$; $P=0.0001$); H–N Correlation between increased EDSS scores and indicators analyzed via the Spearman rank test; **H**: The increase of QAlb was positively correlated with increased EDSS score ($r=0.8801$; $P=0.0008$). **I**: The increase of QIgG was positively correlated with increased EDSS score ($r=0.8186$; $P=0.0038$); **J**: The increase of QIgA was positively correlated with the EDSS score ($r=0.8124$; $P=0.0043$); **K**: Correlation between increased EDSS score and QIgM ($r=0.3693$, $P=0.2936$); **L**: The increase of NLR was positively correlated with the EDSS score ($r=0.8432$, $P=0.0022$); **M**: Correlation increased between EDSS score and MLR ($r=-0.3262$, $P=0.3577$); **N**: Correlation increased between EDSS score and PLR ($r=0.3766$, $P=0.2835$)

Therefore, further research should delve into the effects of medications on peripheral blood platelet count and PLR values, as well as their impact on the severity of NMOSD in patients. Such studies can contribute to laying the foundation for personalized clinical interventions and individualized treatment strategies for NMOSD.

Conclusion

This study identified QAlb, QIgG, QIgA, QIgM, and PLR as effective biomarkers for assessing the severity of NMOSD. In particular, PLR emerged as a potential independent indicator for evaluating the severity of NMOSD in patients. These findings provide new insights and methods for the clinical assessment of NMOSD disability, aiding in a more precise evaluation of patient conditions and prognosis. Moreover, the discovery of these disability-related biomarkers in NMOSD opens up possibilities for providing more effective interventions to reduce the severity of disability and improve outcomes.

Limitation

Despite our efforts to ensure the representativeness of the samples and the accuracy of the data, the relatively small sample size in this study may affect the stability and reliability of the results. Additionally, being a single-center study, there may be limitations related to regional and population-specific factors, as well as potential selection bias. Another limitation is the lack of blood sample information during the relapse and remission phases, which could have provided more insights into disease activity and its impact on the results. Due to the insufficient data collected from MS patients in the study, which did not reach statistical power, the comparison of biomarkers between NMOSD and MS was not included in this study.

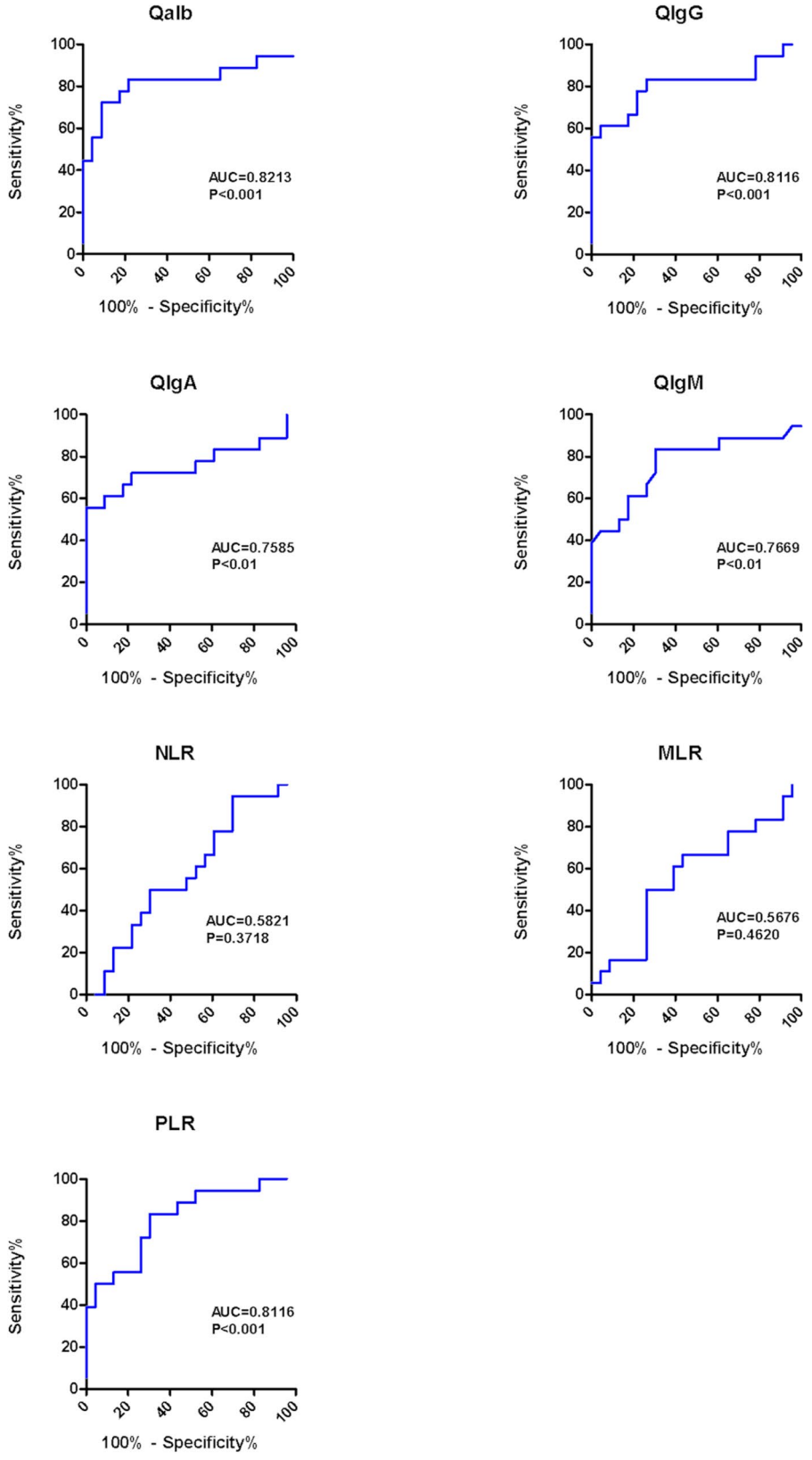

Fig. 4 Blood-brain barrier and PLR biomarkers can predict the severity of acute NMOSD

Table 3 Univariate and multivariate analysis

Variables	Univariate					Multivariate				
	β	S.E	Z	*P*	OR (95%CI)	β	S.E	Z	*P*	OR (95%CI)
QAlb	0.49	0.19	2.58	0.005	1.63 (1.12 ~ 2.36)	0.94	1.65	0.57	0.567	2.57 (0.10 ~ 65.15)
QIgG	0.91	0.35	2.6	0.002	2.48 (1.25 ~ 4.91)	-1.27	3.39	-0.37	0.709	0.28 (0.00 ~ 217.33)
QIgA	1.34	0.58	2.32	0.016	3.80 (1.23 ~ 11.77)	0.16	2.64	0.06	0.952	1.17 (0.01 ~ 205.90)
QIgM	3.43	1.28	2.69	0.002	30.85 (2.53 ~ 376.19)	2.84	3.57	0.8	0.426	17.11 (0.02 ~ 18612.63)
CSF-IgG-index	2.62	2.4	1.09	0.072	13.75 (0.12 ~ 1526.51)	12.19	17.19	0.71	0.479	195867.25 (0.00 ~ 8469069605917589504 0.00)
NLR	-0.01	0.1	-0.07	0.190	0.99 (0.82 ~ 1.20)	-0.18	0.18	-0.99	0.322	0.84 (0.59 ~ 1.19)
PLR	0.04	0.01	2.86	**<0.001**	1.04 (1.01 ~ 1.07)	0.06	0.02	2.58	**0.01**	1.06 (1.01 ~ 1.11)
Lesion location	1.1	0.67	1.65	0.099	3.00 (0.81 ~ 11.09)	-0.95	1.38	-0.69	0.492	0.39 (0.03 ~ 5.81)
AQP4	0.29	0.65	0.44	0.658	1.33 (0.37 ~ 4.77)	0.11	1.27	0.08	0.933	1.11 (0.09 ~ 13.45)

QAlb,albumin quotient; *QIgG*, CSF/serum total IgG ratio; *QIgM*, CSF/serum total IgM ratio; *QIgA*, CSF/serum total IgA ratio; *NLR*, neutrophil-to-lymphocyte ratio; *MLR*, lym-phocyte to monocyte ratio; *PLR*, platelet count to lymphocyte ratio; AQP4,aquaporin-4

OR, Odds Ratio; CI, Confidence Interval

Abbreviations

NMOSD	Neuromyelitis Optica Spectrum Disorder
EDSS	Expanded Disability Status Scale
NLR	Neutrophil-to-Lymphocyte Ratio
PLR	Platelet-to-Lymphocyte Ratio
MLR	Monocyte-to-Lymphocyte Ratio
CSF	Cerebrospinal Fluid
Qalb	CSF/Serum Albumin Quotient
QigG	CSF/Blood Immunoglobulin G Quotient
QigA	CSF/Blood Immunoglobulin A Quotient
QigM	CSF/Blood Immunoglobulin M Quotient
ROC	Receiver Operating Characteristic
CDC	Complement-Dependent Cytotoxicity
CNS	Central Nervous System
IgG	Immunoglobulin G
ROC	Receiver Operating Characteristic
NMO-IgG	Immunoglobulin G Anti-Aquaporin-4 Autoantibodies

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Author contributions
XYZ and HJY conducted Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing-original draft, and Visualization in this study. HY, JS, YYL, HTZ, YZL, HKL, LZ, and ZRY participated in Conceptualization, Writing - review & editing, and Supervision of the manuscript. CBD contributed to Conceptualization, Methodology, Writing - review & editing, and Supervision. All authors reviewed and edited the final manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study received approval from the Medical Ethics Committee of Jining No.1 People's Hospital (KYLL-202307-102), and written informed consent, including neurological consent, was obtained from all participants or their legal guardians. The research adhered to the principles outlined in the Helsinki Declaration and was conducted by approved guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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