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ORIGINAL RESEARCH

Neutrophil-to-Lymphocyte Ratio on Admission is an Independent Risk Factor for the Severity of Neurological Impairment at Disease Onset in Patients with a First Episode of Neuromyelitis Optica Spectrum Disorder

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Purpose: To investigate the relationship between the neutrophil-to-lymphocyte ratio (NLR) and the severity of neurological impairment at disease onset in patients with a first episode of neuromyelitis optica spectrum disorder (NMOSD).

Patients and Methods: This retrospective study included 259 patients with newly diagnosed NMOSD who were hospitalized at our institution between January 2013 and January 2020 (NMOSD group) and 169 healthy control subjects who underwent a physical examination at our hospital during the same period (control group). The clinical data collected included general information, past medical history, biochemical test results, imaging findings, NLR, AQP-4 antibody status, and initial Expanded Disability Status Scale score. A logistic regression model was used to analyze NLR as an independent risk factor for the severity of neurological impairment at disease onset in the NMOSD group. Receiver-operating characteristic curve analysis was used to evaluate the ability of the NLR to predict the severity of neurological impairment at disease onset in the NMOSD group and to determine its critical value.

Results: The NLR was significantly higher in the NMOSD group than in the control group ($P<0.001$). In the NMOSD group, neurological impairment at disease onset was more severe in those with a high NLR than in those with a low NLR ($P<0.001$). At onset of disease, patients with severe neurological impairment had a more significant increase in NLR than those with mild-to-moderate neurological impairment ($P<0.001$). Both univariate (OR 1.180, 95% CI 1.046–1.331, $P=0.007$) and multivariate (OR 1.146, 95% CI 1.003–1.308, $P=0.044$) logistic regression analyses showed that the NLR was positively correlated with the severity of neurological impairment at onset of disease in the NMOSD group. The area under the receiver-operating characteristic curve was 0.687.

Conclusion: The NLR is an independent risk factor for the severity of neurological impairment at disease onset in patients with a first episode of NMOSD.

Keywords: neuromyelitis optica spectrum disorder, neutrophil-to-lymphocyte ratio, first episode, severity, Expanded Disability Status Scale score

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a primary inflammatory demyelinating disease of the central nervous system (CNS) that mainly involves the optic nerve

and spinal cord and characterized by antiaquaporin-4 (AQP4) antibody-mediated autoimmune astrocytopathy.[1] Recent worldwide epidemiological surveys showed differences in the regional and ethnic prevalence of NMOSD and a higher prevalence in Africans and non-whites.[2,3] Most patients with NMOSD have a relapsing-remitting course, with an increase in the number of relapses, a decrease in the recovery rate, an increase in the degree of disability, and, eventually, severe visual or motor impairment with progression of the disease.[4] Diagnosis of NMOSD is based mainly on clinical manifestations, AQP4 antibody status in serum or cerebrospinal fluid (CSF), and manifestations in the spinal cord or optic nerve seen on magnetic resonance imaging (MRI). In recent years, many researchers have focused on biological indicators of the severity of neurological impairment in patients with NMOSD. However, little progress has been made in terms of identification of cost-effective, easily accessible, and reliable biological indicators that would assist in early detection of patients with NMOSD to improve the prognosis.

The neutrophil-to-lymphocyte ratio (NLR) is a novel inflammatory index that has been used to predict the prognosis of non-small cell lung cancer, squamous cell carcinoma of the lung, colorectal cancer, liver cancer, esophageal and gastric cancer, kidney cancer, bladder cancer, melanoma and other malignant tumors, as well as cerebral hemorrhage, cerebral infarction, and cardiovascular disease.[5–15] The NLR has also been associated with the activity of multiple sclerosis, systemic lupus erythematosus, Sjogren's syndrome, Behçet's disease, and other autoimmune diseases.[16–19] However, there are few studies on the NLR in patients with NMOSD and the relationship between the severity of neurological impairment and the NLR in these patients. This study evaluated the relationship between NLR and the severity of neurological impairment at onset of disease in patients with a first episode of NMOSD.

Patients and Methods
Study Population
Clinical data were collected retrospectively for the 336 patients with newly diagnosed NMOSD who were admitted as inpatients to the First Affiliated Hospital of Zhengzhou University from January 2013 to January 2020 (NMOSD group). All patients met the diagnostic criteria for NMOSD established by the International Panel for NMO Diagnosis in 2015 and were diagnosed by an experienced neurologist. The following exclusion criteria were applied: 1) not a first episode of NMOSD; 2) other diseases affecting the Expanded

Disability Status Scale (EDSS) score; 3) hematological disease, the active period of other chronic infectious diseases or other conditions that could affect the blood count; 4) hormone therapy, immunosuppressive treatment, or other agents that can affect the blood count within the previous 6 months; and 5) incomplete data. A total of 259 patients were finally included in the study. One hundred and sixty-nine healthy individuals who underwent a physical examination at our institution during the same period and were matched to the NMOSD group for age, sex, smoking history, and history of alcohol consumption were selected as a control group.

The study was reviewed and approved by the Ethics Committee of Zhengzhou University (review number: 2021-KY-0038-002). The requirement for informed consent was waived in view of the retrospective design of the study, the risk of this study is not greater than the minimum risk, and the exemption of informed consent does not have an adverse effect on the rights or welfare of patients. We strictly complied with the Declaration of Helsinki and have anonymized all patient data.

Research Methods
Clinical Data
The medical records of all patients were reviewed. Information on patient age and sex, smoking history, history of alcohol consumption, past medical history (hypertension, diabetes, autoimmune disease, mental disease), and EDSS scores was collected. The initial EDSS score were obtained by either of two experienced neurologists and used to assess the severity of neurological impairment at disease onset in the NMOSD group.

Auxiliary Examinations
All patients in the NMOSD group were fasted for at least 12 hours after admission to hospital and before the start of treatment, blood samples were taken from the cubital vein for a complete blood count. The enrolled patients underwent CSF cytology and MRI (cranial, spinal cord, and optic nerves). The normal reference ranges for relevant indicators established by our hospital laboratory are as follows: white blood cells ($3.5–9.5 \times 10^9$/L), red blood cells ($3.8–5.1 \times 10^{12}$/L), platelets ($125–350 \times 10^9$/L), neutrophils ($1.8–6.3 \times 10^9$/L), lymphocytes ($1.1–3.2 \times 10^9$/L), monocytes ($0.1–0.6 \times 10^9$/L), eosinophils ($0.02–0.52 \times 10^9$/L), and basophils ($0–0.06 \times 10^9$/L); white blood cells in CSF ($0–5 \times 10^6$/L), and CSF lymphocyte ratio (60–70%). The NLR was calculated as the absolute number of neutrophils to the absolute number of lymphocytes. MRI scans showing characteristic manifestations of optic

nerve, spinal cord, and brain were defined as abnormal and scans showing unspecific lesions, normal brain, and brain demyelinating lesions were defined as normal. Spinal cord MRI scans showing the number of affected spinal cord segments was called spinal cord MRI. The Neurology Laboratory of the First Affiliated Hospital of Zhengzhou University uses live cells transfected with AQP4 to detect AQP-4 antibody status in blood or CSF.

All laboratory tests were performed using samples collected for the first time on admission, and the examiner was blinded to all clinical information.

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 software (IBM Corp, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to test the normality of the continuous data. Continuous data conforming to a normal distribution were expressed as the mean ± standard deviation (SD); otherwise, they were expressed as the median (IQR). Categorical data were expressed as the percentage. When continuous data were normally distributed, between-group

differences were examined using the *t*-test, and when not normally distributed, they were analyzed using the Mann–Whitney *U*-test. The chi-square test or Fisher's exact test was used for between-group comparisons of categorical variables. Single-factor logistic regression analysis was used to identify potential factors affecting the severity of neurological impairment at disease onset in the NMOSD group. Multivariate logistic regression analysis was used to determine the independent effect of the NLR on the severity of neurological impairment at disease onset in the NMOSD group. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the diagnostic value of the NLR in predicting the severity of neurological impairment at disease onset in the NMOSD group and to determine its critical value. A *P*-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

Table 1 shows the demographic and clinical characteristics of the two study groups. There was no significant difference in sex, age, smoking history, or history of alcohol

Table 1 Demographic and Clinical Characteristics of Patients in the NMOSD Group and Healthy Subjects in the Control Group

Clinical Characteristics	Overall People	NMOSD	HCs	*P*-value
Patients (n)	428	259	169	
Age, years, median(IQR)	47(32–56)	45(30–56)	47(36–56)	0.107
Sex, n(%) Male Female	 81(18.9) 347(81.1)	 45(17.4) 214(82.6)	 36(21.3) 133(78.7)	0.311
Smoking, n(%)	15(3.5)	7(2.7)	8(4.7)	0.264
Drinking, n(%)	10(2.3)	5(1.9)	5(3.0)	0.491
WBC, median(IQR), (10^9/L)	6.30(4.98–7.90)	6.80(5.31–8.70)	5.59(4.70–6.60)	<0.001*
RBC, median(IQR), (10^{12}/L)	4.20(3.95–4.54)	4.17(3.93–4.50)	4.27(4.00–4.56)	0.065
PLT, median(IQR), (10^9/L)	227(187–273)	226(186–273)	230(189–275)	0.599
Neutrophil, median(IQR), (10^9/L)	3.70(2.76–5.18)	4.39(3.18–6.29)	3.06(2.51–3.93)	<0.001*
Lymphocyte, median(IQR), (10^9/L)	1.78(1.30–2.14)	1.60 (1.20–2.12)	1.83(1.49–2.17)	0.005*
Monocyte, median(IQR), (10^9/L)	0.44(0.33–0.57)	0.47(0.34–0.63)	0.41(0.32–0.49)	<0.001*
Eosinophil, median(IQR), (10^9/L)	0.07(0.03–0.12)	0.06(0.02–0.10)	0.09(0.06–0.17)	<0.001*
Basophil, median(IQR), (10^9/L)	0.02(0.02–0.04)	0.02(0.02–0.04)	0.03(0.02–0.04)	0.530
NLR	2.06(1.49–3.15)	2.54(1.72–4.27)	1.73(1.36–2.24)	<0.001*

Note: *P<0.05.
Abbreviations: NMOSD, neuromyelitis optica spectrum disorder; HC, healthy control; WBC, white blood cell; RBC, red blood cell; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio.

consumption between the two groups (all $P>0.05$). White blood cell, neutrophil, and monocyte counts and the NLR were significantly higher (all $P<0.001$) and the lymphocyte ($P=0.005$) and eosinophil ($P<0.001$) counts were significantly lower in the NMOSD group than in the control group. There was no significant between-group difference in the red blood cell, platelet, or basophil count (all $P>0.05$).

The median NLR was 2.54 in the 259 patients in the NMOSD group. To evaluate the impact of the NLR on the severity of neurological impairment at disease onset in this group, the patients were divided into a low NLR group (NLR <2.54, n=128) and a high NLR group (NLR ≥2.54, n=131). Table 2 shows the demographic and clinical characteristics of patients in the NMOSD group according to the NLR. There was no significant between-group difference in sex, age, smoking history, history of alcohol consumption, or past medical history of hypertension, diabetes, autoimmune disease, or mental disease (all $P>0.05$). The initial EDSS score was significantly higher in the high NLR group than in the low NLR group ($P<0.001$). As well as differences in the neutrophil and lymphocyte counts, we found significantly higher white blood cell ($P<0.001$) and platelet ($P=0.001$) counts and significantly lower eosinophil ($P<0.001$), and basophil ($P=0.011$) counts in the high NLR group; there was no significant between-group difference in the red blood cell or monocyte count (all $P>0.05$). We also evaluated the AQP4 antibody status in serum and CSF, white blood cells in CSF, CSF lymphocyte ratio, and abnormalities on MRI, brain lesions, spinal cord MRI between the two groups. Compared with the low NLR group, there was a significant increase in the number of white blood cells in the CSF ($P=0.030$) and the number of spinal cord segments affected ($P=0.042$) in the high NLR group. There was no significant difference in the CSF lymphocyte ratio, abnormalities on MRI or brain lesions between these groups (all $P>0.05$). Only 224 patients in the study were tested for AQP4 antibody status, and there was no significant difference between the high NLR and low NLR groups ($P>0.05$).

Patients in the NMOSD group were divided into mild-to-moderate and severe groups according to whether their initial EDSS score was ≤3 or >3 to identify factors that may affect the severity of neurological impairment at disease onset in patients with a first episode of NMOSD. Table 3 compares the demographic and clinical features of these patients according to their initial EDSS score. Compared with patients in the mild-to-moderate group,

those in the severe group were significantly older ($P=0.041$), were significantly more likely to have hypertension ($P=0.011$) and had significantly higher neutrophil counts ($P=0.001$), NLR values ($P<0.001$), and number of spinal cord segments affected ($P<0.001$), as well as significantly more abnormalities on MRI ($P=0.018$); they also had significantly lower lymphocyte ($P<0.001$) and eosinophil ($P=0.027$) counts. There was no significant between-group difference in sex, past medical history (diabetes, autoimmune disease, or mental disease), blood cell count (white blood cells, red blood cells, platelets, monocytes, basophils), AQP4 antibody status, white blood cells in CSF, CSF lymphocyte ratio, brain lesions (all $P>0.05$).

Influence of Clinical Parameters on Severity of Neurological Impairment at Disease Onset in Patients Admitted with a First Episode of NMOSD

As shown in Table 4, single factor logistic regression analysis showed that age (OR 1.017, 95% CI 1.001–1.034, $P=0.040$), hypertension (OR 4.373, 95% CI 1.278–14.963, $P=0.019$), abnormalities on MRI (OR 2.328, 95% CI 1.-141–4.751, $P=0.020$), spinal cord MRI (OR 1.016, 95% CI 1.044–1.173, $P=0.001$), the neutrophil count (OR 1.145, 95% CI 1.027–1.277, $P=0.015$), and the NLR (OR 1.180, 95% CI 1.046–1.331, $P=0.007$) were positively correlated with the initial EDSS score in the NMOSD group. Patient sex, smoking history, history of alcohol consumption, past medical history (diabetes, autoimmune disease, or psychiatric illness), AQP4 antibody status, white blood cells in CSF, CSF lymphocyte ratio, brain lesions, and blood cell count (white blood cells, red blood cells, platelets, lymphocytes, monocytes, eosinophils, and basophils) were not significantly correlated with the initial EDSS score (all $P>0.05$).

NLR at Admission is an Independent Risk Factor for Severity of Neurological Impairment at Disease Onset in Patients with a First Episode of NMOSD

We consider that the neutrophil count has a serious impact on the NLR. All factors (except for neutrophils) that were analyzed in the univariate analysis and found to have a P-value <0.2 or >0.2 but believed to have a clinical impact on the initial EDSS, including age, sex, hypertension, diabetes, white blood cells in CSF, and abnormalities

Table 2 Demographic and Clinical Characteristics of Patients Admitted with a First Episode of NMOSD According to the NLR at the Time of Admission

Clinical Characteristics	Overall Patients	Low NLR (<2.54)	High NLR (≥2.54)	P-value
Patients (n)	259	128	131	
Age, years, median(IQR)	45(30–56)	45(28.25–54)	46(31–58)	0.236
Sex, n (%) Male Female	 45(17.4) 214(82.6)	 20(15.6) 108(84.4)	 25(19.1) 106(80.9)	0.463
Smoking, n(%)	7(2.7)	4(3.1)	3(2.3)	0.679
Drinking, n(%)	5(1.9)	2(1.6)	3(2.3)	0.670
Hypertension, n(%)	27(10.4)	10(7.8)	17(13.0)	0.174
Diabetes, n(%)	11(4.2)	6(4.7)	5(3.8)	0.728
Autoimmune disease, n(%)	50(19.3)	24(18.8)	26(19.8)	0.823
Mental disease, n(%)	1(0.4)	1(0.8)	1(0.8)	0.987
AQP-4Ab, n(%) Positive Negative	 138(61.6) 86(38.4)	 74(64.3) 41(35.7)	 64(58.7) 45(41.3)	0.386
CSF WBC, n(%) Normal High	 124(47.9) 135(52.1)	 70(54.7) 58(45.3)	 54(41.2) 77(58.8)	0.030*
CSF lymphocyte ratio, n(%) Normal High Low	 60 (23.2) 173 (66.8) 26 (10.0)	 34(26.6) 82(64.1) 12(9.4)	 26(19.8) 91(69.5) 14(10.7)	0.437
MRI, n(%) Normal Abnormal	 36(13.9) 223(86.1)	 20(15.6) 108(84.4)	 16(12.2) 115(87.8)	0.428
Brain lesion, n(%)	53(20.5)	25(19.5)	28(21.4)	0.713
Spinal cord MRI, median(IQR)	5(1–9)	5(0.25–8)	6(2–11)	0.042*
WBC, median(IQR), (10^9/L)	6.80(5.31–8.70)	6.00(4.90–7.40)	8.30(6.40–10.40)	<0.001*
RBC, median(IQR), (10^{12}/L)	4.17(3.93–4.50)	4.16(3.92–4.49)	4.19(3.94–4.52)	0.378
PLT, median(IQR), (10^9/L)	226(186–273)	211(174.25–255)	234(194–277)	0.001*
Neutrophil, median(IQR), (10^9/L)	4.39(3.18–6.29)	3.31(2.61–4.28)	6.18(4.49–8.19)	<0.001*
Lymphocyte, median(IQR), (10^9/L)	1.60(1.20–2.12)	2.05(1.70–2.59)	1.23(0.96–1.60)	<0.001*
Monocyte, median(IQR), (10^9/L)	0.47(0.34–0.63)	0.46(0.37–0.57)	0.49(0.27–0.69)	0.875
Eosinophil, median(IQR), (10^9/L)	0.06(0.02–0.10)	0.07(0.04–0.13)	0.03(0.01–0.07)	<0.001*
Basophil, median(IQR), (10^9/L)	0.02(0.02–0.04)	0.03(0.02–0.04)	0.02(0.01–0.03)	0.011*
Initial EDSS, median(IQR)	4.5(3.0–6.5)	4(3–5.38)	5(4–7)	<0.001*

Note: *P<0.05.
Abbreviations: AQP-4, aquaporin-4; EDSS, Expanded Disability Status Scale; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; WBC, white blood cell; RBC, red blood cell; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio.

Table 3 Demographic and Clinical Characteristics of Patients with a First Episode of NMOSD According to the Initial EDSS Score

Clinical Characteristics	Overall Patients	Low Initial EDSS(≤3)	High Initial EDSS(>3)	P-value
Patients (n)	259	85	174	
Age, years, median(IQR)	45(30–56)	42(27–52)	47(32–58)	0.041*
Sex, n(%) Male Female	 45(17.4) 214 (82.6)	 13(15.3) 72 (84.7)	 32(18.4) 142 (81.6)	0.537
Smoking, n(%)	7(2.7)	1(1.2)	6(3.4)	0.290
Drinking, n(%)	5(1.9)	1(1.2)	4(2.3)	0.538
Hypertension, n (%)	27(10.4)	3(3.5)	24(13.8)	0.011*
Diabetes, n(%)	11 (4.2)	1 (1.2)	10(5.7)	0.087
Autoimmune disease, n(%)	50(19.3)	17 (20)	33(19.0)	0.843
Mental disease, n(%)	2(0.8)	0 (0)	2 (1.1)	0.321
AQP-4Ab, n(%) Positive Negative	 138(61.6) 86(38.4)	 46(60.5) 30 ((39.5)	 92(62.2) 56(37.8)	0.812
CSF WBC, n(%) Normal High	 124(47.9) 135(52.1)	 46(54.1) 39((45.9)	 78(44.8) 96(55.2)	0.160
CSF lymphocyte ratio, n(%) Normal High Low	 60(23.2) 173(66.8) 26(10.0)	 20(23.5) 58(68.2) 7(8.2)	 40(23.0) 115(66.1) 19(10.9)	0.796
MRI, n(%) Normal Abnormal	 36(13.9) 223(86.1)	 18(21.2) 67(78.8)	 18(10.3) 156(89.7)	0.018*
Brain lesion, n(%)	53(20.5)	21(24.7)	32(18.4)	0.237
Spinal cord MRI, median(IQR)	5(1–9)	2(0–7)	6(3–9)	<0.001*
WBC, median(IQR), (10^9/L)	6.80(5.31–8.70)	6.40(5.30–8.35)	7.35(5.48–8.92)	0.099
RBC, median(IQR), (10^{12}/L)	4.17(3.93–4.50)	4.19(3.91–4.44)	4.15(3.93–4.52)	0.782
PLT, median(IQR), (10^9/L)	226(186–273)	213(177.5–266.5)	230 (188–273.25)	0.126
Neutrophil, median(IQR), (10^9/L)	4.39(3.18–6.29)	3.79(2.72–5.06)	4.91(3.39–6.65)	0.001*
Lymphocyte, median(IQR), (10^9/L)	1.60(1.20–2.12)	1.90(1.40–2.36)	1.50(1.10–2.09)	<0.001*
Monocyte, median(IQR), (10^9/L)	0.47(0.34–0.63)	0.47(0.36–0.62)	0.46(0.32–0.65)	0.694
Eosinophil, median(IQR), (10^9/L)	0.06(0.02–0.10)	0.06(0.03–0.10)	0.05(0.02–0.10)	0.027*
Basophil, median(IQR), (10^9/L)	0.02(0.02–0.04)	0.03(0.02–0.04)	0.02(0.02–0.04)	0.522
NLR, median(IQR)	2.54(1.72–4.27)	1.91(1.50–2.71)	3.06(1.90-2-5.29)	<0.001

Note: *$P<0.05$.
Abbreviations: AQP-4, aquaporin-4; EDSS, Expanded Disability Status Scale; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; WBC, white blood cell; RBC, red blood cell; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio.

Table 4 Single-Factor Logistic Regression Analysis of Factors Related to the Severity of Neurological Impairment at Disease Onset in Patients with a First Episode of NMOSD

Factors	OR	Initial EDSS	P-value
		95% CI	
Age	1.017	(1.001–1.034)	0.040*
Sex	0.801	(0.396–1.620)	0.537
Smoking	3.000	(0.355–25.324)	0.313
Drinking	1.976	(0.218–17.960)	0.545
Hypertension	4.373	(1.278–14.963)	0.019*
Diabetes	5.122	(0.645–40.687)	0.122
Autoimmune disease	0.936	(0.487–1.798)	0.843
Mental disease	798,345,125.800	(0.000–0)	0.999
AQP-4Ab	1.071	(0.608–1.890)	0.812
CSF WBC	1.452	(0.862–2.444)	0.161
CSF lymphocyte ratio	1.042	(0.922–1.177)	0.512
MRI abnormality	2.328	(1.141–4.751)	0.020*
Brain lesion	0.687	(0.368–1.282)	0.238
Spinal cord MRI	1.106	(1.044–1.173)	0.001*
WBC	1.066	(0.973–1.169)	0.169
RBC	1.197	(0.707–2.028)	0.504
PLT	1.002	(0.998–1.006)	0.261
Neutrophil	1.145	(1.027–1.277)	0.015*
Lymphocyte	0.976	(0.880–1.082)	0.639
Monocyte	1.196	(0.521–2.748)	0.673
Eosinophil	0.300	(0.036–2.491)	0.265
Basophil	0.003	(0.000–1438.217)	0.376
NLR	1.180	(1.046–1.331)	0.007*

Notes: *P<0.05.
Abbreviations: AQP-4, aquaporin-4; EDSS, Expanded Disability Status Scale; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; WBC, white blood cell; RBC, red blood cell; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

Table 5 Multivariate Logistic Regression Analysis of Factors Related to the Severity of Neurological Impairment at Disease Onset in Patients with a First Episode of NMOSD
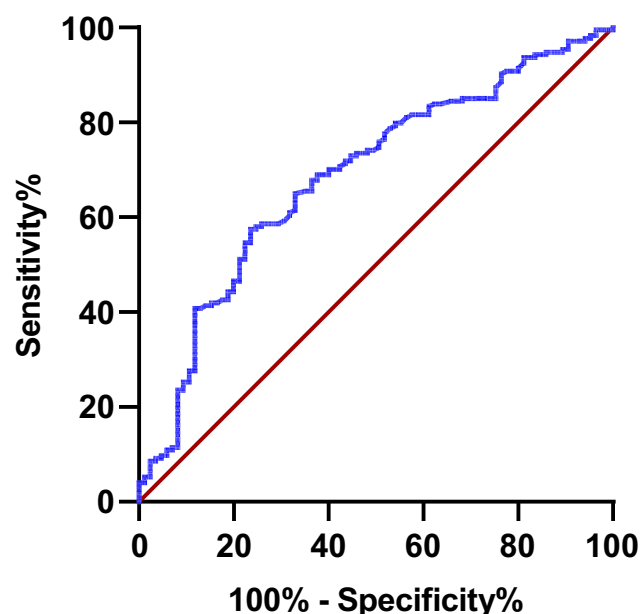
Factors	OR	Initial EDSS	P-value
		95% CI	
Age	1.010	(0.991–1.029)	0.297
Sex	0.526	(0.233–1.191)	0.123
Hypertension	3.259	(0.892–11.901)	0.074
Diabetes	3.662	(0.426–31.452)	0.237
CSF WBC	1.169	(0.657–2.082)	0.595
MRI abnormality	1.519	(0.629–3.667)	0.352
Spinal cord MRI	1.084	(1.012–1.161)	0.022*
WBC	0.973	(0.867–1.091)	0.637
NLR	1.146	(1.003–1.308)	0.044*
Eosinophil	0.281	(0.022–3.618)	0.330

Notes: *P<0.05.
Abbreviations: EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

Discussion

To the best of our knowledge, this is the first study to investigate the relationship between the NLR at the time of admission and the severity of neurological impairment at disease onset in patients with a first episode of NMOSD. We found that the NLR was significantly higher in these patients than in healthy controls. In the NMOSD group, neurological impairment at disease onset was significantly more severe in patients with a high NLR than in those with

on MRI, spinal cord MRI, and white blood cells, NLR, eosinophils were included in the multivariate logistic regression model. As shown in Table 5, the NLR (OR 1.146, 95% CI 1.003–1.308, P=0.044) and spinal cord MRI (OR 1.084, 95% CI 1.012–1.161, P=0.022) were independent risk factors for the severity of neurological impairment at disease onset in the NMOSD group.

ROC Curve for NLR at Admission Predicts Severity of Neurological Impairment at Disease Onset in Patients with a First Episode of NMOSD

As shown in Figure 1, the ROC curve for NLR predicted the severity of neurological impairment at disease onset in the NMOSD group. Table 6 shows that the area under the ROC curve was 0.687 (95% CI 0.618–0.755). The critical value was 2.754, the sensitivity was 57.5%, and the specificity was 76.5%.

Figure 1 The ROC curve of NLR predicts the severity of neurological impairment at disease onset in patients with a first episode of NMOSD.

Table 6 Ability of the ROC Curve for NLR to Predict the Severity of Neurological Impairment at Disease Onset in Patients with a First Episode of NMOSD

AUC	SE	95% CI	Cut-Off Value	Sensitivity	Specificity
0.687	0.035	0.618–0.755	2.754	0.575	0.765

Abbreviations: AUC, area under the curve; SE, standard error; CI, confidence interval.

a low NLR. Moreover, the NLR was significantly higher in the group with severe neurological impairment than in the group with mild-to-moderate neurological impairment at disease onset. Both univariate and multivariate regression analyses revealed a significant positive correlation of the NLR with the severity of neurological impairment at disease onset in the NMOSD group. Therefore, the NLR at the time of admission is an independent risk factor for the severity of neurological impairment at disease onset in patients with a first episode of NMOSD. The results of the ROC curve analysis indicated that the NLR on admission may also be a valuable predictor of the severity of neurological impairment at disease onset in these patients.

It is currently believed that the main pathogenic mechanism of NMOSD involves antibody-mediated complement-dependent cytotoxic pathways that cause damage to astrocytes, leading to infiltration of inflammatory cells and release of inflammatory mediators followed by para-inflammatory mechanisms that damage oligodendrocytes and cause demyelination.[20] The main cytokines and inflammatory cells involved in the pathogenesis of NMOSD are interleukin (IL)-17, IL-8, IL-6, IL-1β, IL-10, IL-3, IL-4, neutrophils, T-cells, macrophages, and eosinophils.[21–25] Neutrophils are recognized as an indicator of acute systemic inflammation. In the acute phase of inflammation, neutrophils proliferate and become activated rapidly, and then migrate to the site of inflammation.[26] Studies have found a higher proportion of TH17 cells and higher concentrations of TH17-related cytokines, such as IL-17, IL-6, IL-21, IL-23, and TGF-β, in the serum of patients with NMOSD and that these cells and cytokines promote recruitment of neutrophils.[27] Research in a mouse model of NMOSD found that neutrophil colony-stimulating factor aggravated the disorder whereas neutrophil protease inhibitors reduced its severity. Therefore, neutrophils are likely to play an important role in the pathogenesis of NMOSD.[28] A variety of agents targeting neutrophils are presently under investigation in clinical trials, and it is anticipated that clinical application of some of these agents will reduce the degree of disability

in patients with NMOSD.[29] Lymphocytes are also an important component of white blood cells and participate in humoral and cellular immunity. B lymphocytes produce pro-inflammatory cytokines and antibodies that are involved in the pathogenesis of inflammatory diseases of the CNS. They also produce anti-inflammatory cytokines that play a role in autoimmune regulation.[30] Treatment that targets B lymphocytes significantly reduces disease activity and improves the prognosis of NMOSD but, for various reasons, including high cost, is not widely used in clinical practice. Autoreactive T-cells also contribute to the pathogenesis of NMOSD by regulating the passage of antibodies across the blood-brain barrier and helping to create a local inflammatory environment.[31]

The blood cell count alone is readily affected by many physiological factors, including pressure and stress, and cannot be used alone to predict inflammation. However, the NLR is not easily affected by other factors in the body and reflects the inflammatory state and extent of the associated damage more reliably than the blood cell count. A recent study showed that the NLR was higher during acute episodes of NMOSD than during periods of remission, indicating that there is a relationship between the NLR and activity of NMOSD.[32] Another study in pediatric patients with demyelinating disease found an increase in NLR in children during an acute episode of myelin oligodendrocyte glycoprotein antibody disease and that the NLR was related to disease activity.[33] Previous studies of inflammatory diseases of the CNS have rarely investigated the relationship between the NLR and the severity of disease. In our present study, the NLR at the time of admission was an independent risk factor for severity of neurological impairment at disease onset in patients with a first episode of NMOSD. The area under the ROC curve was 0.687, we can use NLR as a predictor of the severity of neurological impairment at disease onset in patients with first-onset NMOSD. In actual clinical work, the NLR may aid early detection and active treatment of first-onset NMOSD patients with a high degree of disability, which may improve the prognosis in these patients.

A further finding in this study was of more abnormalities on MRI and a greater number of spinal cord segments affected in patients with severe NMOSD than in those with mild-to-moderate NMOSD, and the number of spinal cord segments affected is an independent risk factor for the severity of neurological impairment at disease onset in patients with a first episode of NMOSD. NMOSD is an inflammatory disease of the CNS characterized by optic neuritis and longitudinally extensive transverse myelitis. It manifests on MRI as inflammatory demyelinating lesions of the long spinal cord and inflammation of the optic nerve, which is important for the diagnosis of NMOSD. Studies have shown that abnormalities of the brain on MRI are common in patients with NMOSD. In the absence of optic nerve and spinal cord involvement, the characteristic manifestations of abnormalities on brain MRI are essential for early detection of the disease and improvement of the prognosis.[34,35] At present, there are few studies on MRI manifestations in patients with NMOSD according to severity.

Of note, a recent cohort study by Carnero Contentti et al concluded that NLR is not an independent outcome predictor of LATAM patients with AQP4-IgG-positive NMOSD, which seems to be slightly different from our finding.[36] There are several possible explanations for the discrepant finding. First, their study only included patients with NMOSD who were AQP4 antibody-positive whereas our study included patients with NMOSD who were AQP4 antibody-positive, AQP4 antibody-negative, and untested. A previous study has shown that AQP4 antibody status affects the EDSS, course and prognosis of NMOSD patients.[37] Second, their study participants came from three different countries in Latin America whereas most of our study population came from a central region of China. The influence of regional and ethnic differences on the degree of disability cannot be ignored. Third, the purpose of the study by Carnero Contentti et al was mainly to assess the influence of NLR on the prognosis of patients with first-onset NMOSD whereas we mainly investigated the relationship between the NLR and the severity of neurological impairment at disease onset in patients with a first episode of NMOSD. The difference in research purposes may also be one of the reasons for the slightly different conclusions.

A recent study showed that hypertension is a common comorbidity in patients with NMOSD. The prevalence of hypertension was significantly higher in patients with highly active NMOSD than in controls.[38] Another study found that hypertension was more common and that blood pressure levels were higher in female patients with acute NMOSD than in those with multiple sclerosis.[39] Other researchers have found that hypertension is associated with progression and prognosis of multiple sclerosis.[40] Our present study shows that patients with severe NMOSD have a higher incidence of hypertension than those with mild-to-moderate NMOSD, which is similar to previous studies.

The discovery of the AQP-4 antibody in patients with NMOSD has further deepened our understanding of this clinical entity and provided clinicians with more diagnostic evidence. Previous studies have shown that patients with NMOSD have a longer duration of symptoms, a polyphasic course, and a poorer prognosis if they are AQP-4 antibody-positive than if they are AQP-4 antibody-negative.[37] However, our analysis did not find a correlation between the AQP-4 antibody and the severity of neurological impairment at disease onset in patients with a first episode of NMOSD. This finding may reflect the fact that our hospital cannot detect AQP-4 status in CSF or serum in the early years. However, although AQP4 antibody status is unrelated to disability in these patients, there may be a relationship with the AQP4 titer. Given that detection of the AQP4 antibody at our hospital is mainly qualitative, few patients have been tested for their AQP4 antibody titer, so a more detailed analysis cannot be performed. This is one of the shortcomings of this research. Larger cohort studies are needed to confirm the relationship between AQP4 antibody status and the severity of neurological dysfunction in patients with NMOSD.

Conclusion

In summary, the NLR at the time of admission is an independent risk factor for the severity of neurological impairment at disease onset in patients with a first episode of NMOSD. However, given the single-center retrospective nature of this study, our findings await confirmation in larger multicenter cohort studies.

Disclosure

The authors report no conflicts of interest in this work.

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