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Inflammatory and Nutritional Markers as Indicators for Diagnosing and Assessing Disease Activity in MS and NMOSD

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Background: Inflammation and nutritional markers have recently gained recognition for their roles in the fabrication of cognitive control centers demyelinating illnesses. Inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII), and systemic inflammatory response index (SIRI), along with nutritional markers like albumin (ALB), hemoglobin (HB), and body mass index (BMI), may predict disease occurrence. However, their potential in evaluating diseases such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) remains unexplored.

Methods: We retrospectively evaluated 249 NMOSD patients, 244 MS patients, and 249 healthy controls (HC), calculating MLR, NLR, PLR, SII, and SIRI, and measuring ALB, HB, and BMI levels. Logistic regression and ROC curves were used to develop and validate models for diagnosing and differentiating MS and NMOSD. Further, 35 MS patients, 38 NMOSD patients, and 85 matched HC were recruited for validation, and marker changes were monitored over six months.

Results: Comparing MS and NMOSD groups with HC, MLR, NLR, SII, and SIRI were significantly greater, while ALB levels were lower ($P<0.05$). NMOSD patients exhibited higher MLR, NLR, SII, and SIRI, and lower HB and ALB levels contrasted with MS patients ($P<0.05$). These markers correlated negatively with total T lymphocytes and positively with C-reactive protein, the Expanded Disability Status Scale (EDSS), and MRI T2 lesion count. Following remission, NLR, SII, and SIRI decreased, while ALB increased over six months ($P<0.05$). Diagnostic models based on these markers showed AUCs of 0.840 (95% CI:0.806–0.875) for MS and 0.905 (95% CI:0.877–0.933) for NMOSD. Differential diagnosis between MS and NMOSD showed an AUC of 0.806 (95% CI: 0.750–0.863).

Conclusion: Inflammatory and nutritional markers are promising for assessing disease activity in MS and NMOSD. Diagnostic models based on these markers enhance the accuracy and clinical value of differentiating between the two conditions.

Keywords: inflammation, multiple sclerosis, NMOSD, nutrition

Introduction

The central nervous system (CNS) is prone to inflammation-induced demyelination, the most common of which are multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), are attributed to immune-mediated myelin loss.[1,2] In recent years, it has been suggested that NMOSD is more prevalent than MS in Asian populations, and that the pathogenesis, pathological changes, and clinical management of the two diseases differ. MS is primarily caused by an autoimmune response leading to T cell-mediated damage to neuromyelin sheaths in the CNS,[3] whereas

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NMOSD involves autoimmune responses to specific CNS cells or proteins, typically those associated with hydrophobic channels;

Approximately eighty percent of NMOSD patients have positive AQP4-IgG results.[4] NMOSD is also typically more severe than MS, Complete blood count ratios, including the monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII), and systemic inflammatory response index (SIRI),[5] are novel non-specific markers of inflammation. These markers may also have predictive value for disease activity because of their greater expression in inflammatory demyelinating illnesses like MS when compared to healthy controls (HCs).[6] Nutritional indicators, including body mass index (BMI), serum albumin (ALB), and hemoglobin (HB), can also reflect inflammatory status and overall patient health.[7] Inflammatory markers such as the SII and SIRI have been shown to indicate inflammatory activity in various immune-mediated diseases.[8,9] Relevant nutritional indicators, including ALB, HB, and BMI, hold diagnostic value in demyelinating diseases and are involved in the metabolic mechanisms of these conditions to some extent.[10–12] The pathological processes of demyelinating diseases such as MS and NMOSD involve immune system activation and ongoing neuroinflammation. On one hand, the inflammatory response triggered by demyelinating diseases increases the body's energy metabolism. On the other hand, the repair of myelin sheaths requires adequate nutritional support. Existing studies suggest that various inflammatory markers, including the NLR and SII, may play a role in reflecting disease activity and prognosis.[13,14] It has not yet been investigated how nutritional and inflammatory markers may be used in conjunction with MS and NMOSD patients. Consequently, this study seeks to probe the expression of these markers in patients with MS and NMOSD.

Materials and Methods

Research Object

This retrospective analysis encompassed 244 individuals with MS (after the exclusion of 25 patients due to missing clinical, biochemical, or radiological data) and 249 with NMOSD, Participants received care at Capital Medical University's Beijing Tiantan Hospital between the first month of 2018 and December 2023, along with 249 age- and sex-matched HCs. According to the updated 2017 McDonald criteria, MS classification was performed.[15] The diagnosis of NMOSD adhered to the guidelines established by the International NMOSD Diagnostic Group in 2015.[16,17] Strict inclusion and exclusion criteria were applied for both disease groups; patients with other demyelinating conditions, autoimmune disorders, recent infections (within the last 30 days), or malignant tumors were excluded. The healthy control group comprised individuals without a history of or existing neurological diseases, immune-related disorders, infectious diseases, chronic conditions, recent use of immunosuppressive medications, or psychiatric disorders. Additionally, pregnant and breastfeeding women were also excluded. This study complied with all applicable laws and academic regulations and it was conducted in accordance with the Declaration of Helsinki. It received approval from the Ethics Committee of Tiantan Hospital of Capital Medical University (approval number: KY2023-157-03). Informed consent was obtained from all participants.

Sample Collection and Analysis

After a time of fasting, morning blood specimens were taken, and they were examined without preservation within ninety minutes. These samples were gathered during the acute period of the diseases(within two weeks of the most recent recurrence). Laboratory analysis included white blood cell count, neutrophil count, lymphocyte count, monocyte count, platelet count, total T lymphocyte count, 24-h intrathecal synthesis rate (TOURT), HB level, ALB level, BMI, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. Neutrophil, lymphocyte, and platelet counts and HB levels were measured using an automated blood cell analyzer (BC-6900; Mindray, Shenzhen, China); all samples were subjected to additional smear examination. ALB levels were measured using an automatic biochemical analyzer (LABOSPECT 008; Hitachi, Tokyo, Japan). Immunoglobulin G levels were measured by protein electrophoresis (Hydrasys; Sebia, Lisses, France). The cerebrospinal fluid (CSF) TOURT (in mg/24 h) was calculated using Tourtellotte's revised formula: TOURT = [(IgGCSF – IgGS / K1) - (ALBCSF - ALBS / K2) × (IgGS / ALBS) ×

0.43] × 5. Using a FACSCanto II analyzer (USA), fluid cytometry was utilized for recognizing lymphocyte subsets.[18] AQP4-IgG levels were assessed by a third party(Kingmed Diagnostics) using a cell transfection method.

Statistical Analysis

Nonparametric continuous data was expressed as median (interquartile range), whereas parametric continuous data were represented as mean ± standard deviation. Categorical variables were described by frequencies or percentages. Student's *t*-test and one-way ANOVA were utilized for contrasting continuous variables, while Mann–Whitney U and Kruskal–Wallis tests were used to evaluate skewed distributions. Fisher's exact test or chi-squared test was used for calculating categorical variables. Dunn's test was utilized to contrast groups many times. To ascertain the factors linked to MS and NMOSD, variables that showed a P-value of less than 0.05 after a one-way analysis of variance were added to the binary logistic regression model. The AUC (area under the receiver operating characteristic curve) was contrasted using the DeLong test. In the binary logistic regression analysis, a forward selection method was employed, progressively incorporating variables from the univariate screening until significant variables were identified in the final model. Indicators not included in the final model were considered removed. The model fit was validated using the Hosmer-Lemeshow test, with larger p-values indicating better fit. The diagnostic value of inflammatory and nutritional indicators was evaluated using ROC curves, with $p < 0.05$ indicating statistical significance. Correlation analyses of ESR, CRP, total T lymphocytes, the Expanded Disability Status Scale (EDSS),[19] average relapse frequency, and MRI T2 lesion count with inflammatory and nutritional indicators were conducted based on the normality of the data. For non-normally distributed variables, Spearman correlation analysis was utilized; for normally distributed variables, Pearson correlation analysis was applied. GraphPad Prism 9.4, R version 4.4.0, and IBM SPSS 26.0 were used for the aforementioned analyses.

Results

Laboratory and Clinical Data

Table 1 and Figure 1 describe baseline participant characteristics. There were no appreciable differences in age or sex across the groups(P>0.05). In contrast to the NMOSD cohort, the MS cohort's EDSS score, Mean attack frequency and MRI T2 lesion count (ranging from 0 to 8) were significantly lower(P<0.05). By contrast to the HC cohort, the MLR, NLR, SII, SIRI, neutrophils, monocytes, and white blood cell counts were all substantially greater in the MS and NMOSD cohorts(P<0.05). The ALB, platelets, and PLR in the MS cohort were substantially lower than those in the HC cohort(P<0.05), whilst the HB, ALB, and platelet counts in the NMOSD cohort were considerably reduced than those in the HC cohort(P<0.05). Furthermore, compared to the MS panel, the NMOSD cohort had considerably lower TOURT, HB, and ALB values and notably greater EDSS scores, ESR, CRP, BMI, MLR, NLR, SII, and SIRI(P<0.05).

Inflammatory and Nutritional Markers in Disease Classification

Of the 244 individuals having MS,12 had clinically isolated syndrome, 204 had relapsing-remitting MS, 17 had secondary progressive MS, and 11 had primary progressive MS. No considerable differences in inflammatory indicators were ascertained among the different MS types (P>0.05). Individuals with secondary progressive MS exhibited significantly lower HB and ALB levels matched to those with relapsing-remitting MS (P<0.05) (Supplementary Table 1). Among the 249 NMOSD individuals, 175 tested positive for anti-AQP4-IgG, while 74 tested negative. Inflammatory indicators did not show considerable deviations between these two groups (P>0.05), but the AQP4-IgG+ subgroup had substantially lower HB levels than the AQP4-IgG- subgroup (P<0.05) (Supplementary Table 2).

Relationship of Inflammatory and Nutritional Indicators with ESR, CRP, and Total T lymphocytes in MS and NMOSD

CRP and the ESR are classical inflammatory markers and total T-lymphocyte numbers reflect adaptive immune responses. In the MS cohort, the ESR and CRP showed a strong positive connection towards the MLR, NLR, PLR, SII, and SIRI, while demonstrating a strong inverse relationship with the amount of total T lymphocytes (P<0.05). Additionally, HB levels were

Table 1 Baseline Clinical Data and Laboratory Indicators

Characteristic	MS (n=244)	NMOSD (n=249)	HC (n=249)	P-value
Age (years)	35.45±12.25	36.76±12.87	37.07±9.90	0.157
Female	171(70.08%)	180(72.29%)	164(65.86%)	0.287
EDSS score	2.66 ±1.99$^{\#\#}$	4.00±2.30	-	<0.001
Disease duration(year) median (min-max)	4.41(0.08–22)	4.58(0.08–40)	-	0.668
Mean attack frequency	1.23 attack/year$^{\#\#}$	1.85 attack/year	-	<0.001
MRI T2 lesion	123(49.80%)$^{\#\#}$	220(88.35%)	-	<0.001
0 to 8 lesions, n(%)				
Smoking	34(13.93%)*	34(13.65%)*	13(5.22%)	0.002
Drinking	13(5.33%)*	26(10.44%)**	3(1.20%)	<0.001
Dyslipidemia	22(9.02%)	27(10.84%)	-	0.412
Systolic pressure (mmHg)	119.79±14.04*	122.37±15.28**	115.88±13.16	<0.001
Diastolic pressure (mmHg)	78.35±10.58**	79.19±11.03**	71.29±9.81	<0.001
History of diabetes	10(4.10%)	15(6.02%)	-	0.330
Heart disease	2(0.82%)	8(3.21%)	-	0.059
Total T lymphocytes	76.80(70.71–81.39)	77.66(72.01–82.91)	-	0.179
TOURT (mg/24 h)	7.20(3.03–13.6)$^{\#\#}$	2.47(0.61–5.30)	-	<0.001
ESR (mm/h)	5(2–13)$^{\#\#}$	8(4–16)	-	0.001
CRP (mg/L)	0.34(0.17–0.87)$^{\#}$	0.61(0.17–1.87)	-	0.004
Hemoglobin (g/L)	136(124–147)$^{\#\#}$	128(119–142)**	137(128–150)	<0.001
Albumin (g/L)	41.8(39.4–43.7)$^{\#\#**}$	40.2(38–42.8)**	44.9(43.5–46.1)	<0.001
BMI (kg/m^2)	22.52±3.7787$^{\#}$	23.88±6.06	22.88±3.00	0.015
White blood cell (109/L)	6.72(5.31–8.46)**	6.82(5.26–9.05)**	5.40(4.65–6.25)	<0.001
Neutrophil (109/L)	3.98(3.00–5.56)**	4.22(3.03–6.06)**	3.39(2.67–4.12)	<0.001
Lymphocyte (109/L)	1.92(1.51–2.31)	1.78(1.30–2.27)	1.79(1.46–2.18)	0.254
Monocyte (109/L)	0.37(0.29–0.47)**	0.39(0.30–0.53)**	0.31(0.25–0.37)	<0.001
Platelet (109/L)	238.5(202.5–275)**	236.5(194.5–276)**	254(218–297)	<0.001
MLR	0.20(0.157–0.27)$^{**\#}$	0.23(0.17–0.31)**	0.17(0.14–0.21)	<0.001
NLR	2.08(1.56–3.17)$^{**\#}$	2.48(1.69–3.81)**	1.87(1.45–2.32)	<0.001
PLR	132.23(101.99–163.95)*	131.04(100–181.38)	141.71(115.41–178.74)	0.014
SII	514.5(346.26–810.52)$^{*\#}$	622.84(361.91–972.13)**	476.95(365.16–605.85)	<0.001
SIRI	0.806(0.54–1.31)$^{**\#}$	0.995(0.59–1.75)**	0.562(0.39–0.77)	<0.001

Notes: Data are expressed as mean ± standard deviation, median (interquartile range), or number (percentage). *P<0.05, **P<0.001 vs HC group. $^{\#}$P<0.05, $^{\#\#}$P<0.001 vs NMOSD group.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; EDSS, Expanded Disability Status Scale; ESR, erythrocyte sedimentation rate; HC, healthy control; MLR, monocyte-to-lymphocyte ratio; MS, multiple sclerosis; NLR, neutrophil-to-lymphocyte ratio; NMOSD, neuromyelitis optica spectrum disorder; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; TOURT, 24-h intrathecal synthesis rate.

significantly negatively correlated with the ESR (P<0.05) (Figure 2A; Supplementary Table 3). In the NMOSD cohort, there was a substantial negative association with total T-lymphocyte counts and an elevated correlation with CRP for the MLR, NLR, PLR, SII, and SIRI (P<0.05). Furthermore, there was a substantial negative correspondence seen between ALB concentrations and either the ESR as well as CRP (P<0.05). (Figure 2B; Supplementary Table 4).

Correlation of Inflammatory and Nutritional Indicators with Disease Severity in MS and NMOSD

In MS and NMOSD, indicators reflecting disease severity include the EDSS, relapse frequency, and the number of T2 lesions in the brain and spinal cord observed via MRI.[20–23] The MLR, NLR, PLR, SII, and SIRI demonstrated significant positive correlations (P<0.05), whereas ALB levels exhibited a significant negative correlation (P<0.05) with EDSS scores in both MS and NMOSD cohorts. Furthermore, in both MS and NMOSD, NLR, SII, and SIRI were positively correlated with MRI T2 lesion counts (P<0.05), while ALB showed a negative correlation with MRI T2 lesion counts only in NMOSD (P<0.05). Although relapse frequency did not reveal statistically significant differences (P>0.05) between MS and NMOSD regarding

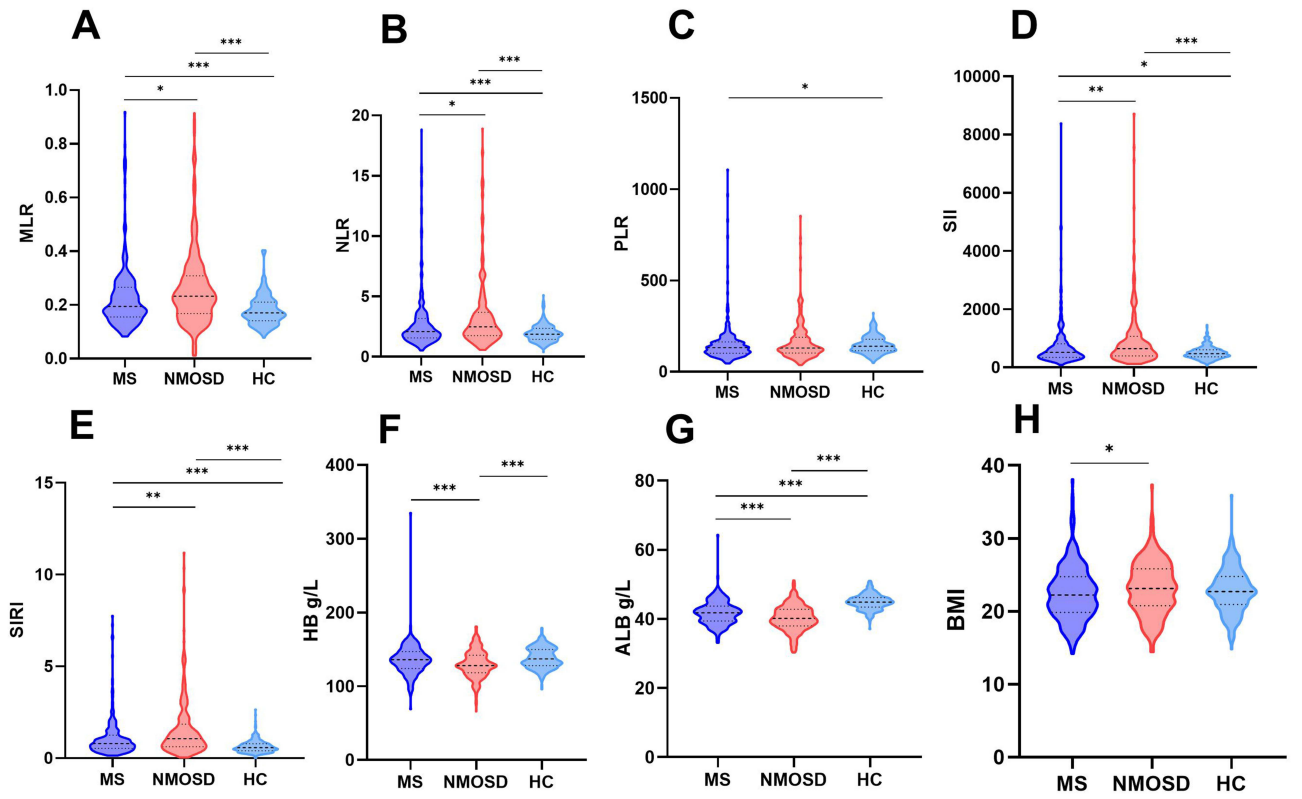

Figure 1 Comparisons of Inflammatory and Nutritional Indicators between Patients with MS and NMOSD and HC. (**A**) MLR, (**B**) NLR, (**C**) PLR, (**D**) SII, (**E**) SIRI, (**F**) HB, (**G**) ALB, and (**H**) BMI. *P<0.05, **P<0.01, ***P<0.001.

Abbreviations: ALB, albumin; BMI, body mass index; HB, hemoglobin; HC, healthy control; MLR, monocyte-to-lymphocyte ratio; MS, multiple sclerosis; NLR, neutrophil-to-lymphocyte ratio; NMOSD, neuromyelitis optica spectrum disorder; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

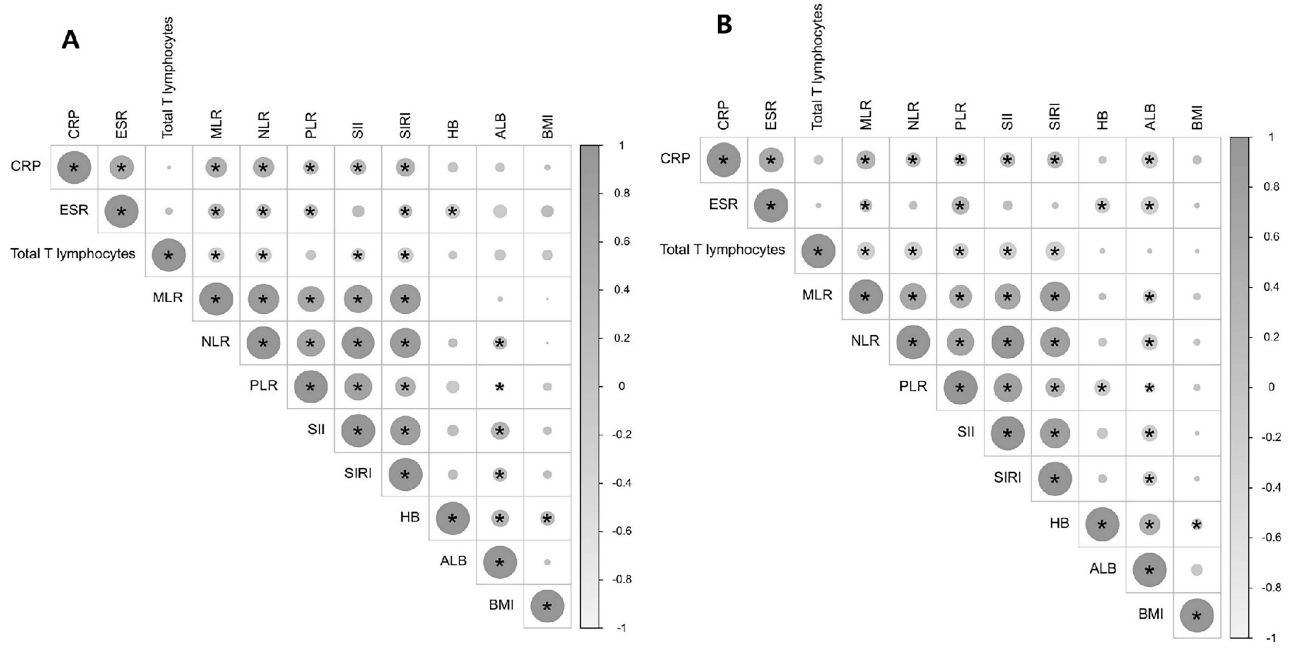

Figure 2 Correlation of Inflammatory and Nutritional Indicators with ESR, CRP, and Total T lymphocytes. Patients with (**A**) multiple sclerosis and (**B**) neuromyelitis optica spectrum disorder. The circle size represents the magnitude of the value. *P<0.05.

Abbreviations: ALB, albumin; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HB, hemoglobin; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

inflammatory and nutritional markers, a positive correlation was observed between inflammatory markers and relapse rates, while nutritional markers displayed a negative correlation. (Tables 2, 3 and Supplementary Table 5).

Utilizing Inflammatory and Nutritional Markers for Logistic Regression Examination

With the presence of MS serving as the response variable Outcome variable and the following explanatory variables: EDSS, TOURT, ESR, CRP, HB, ALB, BMI, MLR, NLR, PLR, SII, and SIRI, multivariable logistic regression analysis was performed after excluding collinearity among the variables. The analysis demonstrated that there had been substantial variations between MS and NMOSD in NLR, EDSS, TOURT, and ESR (P<0.05) (Table 4).

Evaluation of Inflammatory and Nutritional Indicators

Figure 3 displays receiver operating characteristic curves that were established to ascertain the inflammatory and nutritional indicators' diagnostic reliability (with data presented in Supplementary Table 6). For MS, the AUC of the

Table 2 Correlation of Inflammatory and Nutritional Indicators with EDSS

Indicator	MS		NMOSD	
	r	P-value	r	P-value
MLR	0.180	0.017	0.196	0.034
NLR	0.172	0.021	0.201	0.030
PLR	0.151	0.046	0.202	0.031
SII	0.192	0.010	0.201	0.031
SIRI	0.201	0.007	0.192	0.038
HB	0.005	0.951	0.027	0.774
ALB	−0.150	0.048	−0.218	0.019
BMI	0.000	0.996	−0.030	0.758

Abbreviations: ALB, albumin; BMI, body mass index; EDSS, Expanded Disability Status Scale; HB, hemoglobin; MLR, monocyte-to-lymphocyte ratio; MS, multiple sclerosis; NLR, neutrophil-to-lymphocyte ratio; NMOSD, neuromyelitis optica spectrum disorder; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

Table 3 Correlation of Inflammatory and Nutritional Indicators with MRI T2 Lesions

Indicator	MS		NMOSD	
	r	P-value	r	P-value
MLR	0.095	0.142	0.153	0.017
NLR	0.165	0.010	0.177	0.006
PLR	0.043	0.512	0.120	0.061
SII	0.154	0.017	0.149	0.020
SIRI	0.127	0.049	0.151	0.019
HB	−0.001	0.991	0.067	0.298
ALB	−0.103	0.113	−0.129	0.046
BMI	−0.068	0.305	−0.029	0.660

Abbreviations: ALB, albumin; BMI, body mass index; HB, hemoglobin; MLR, monocyte-to-lymphocyte ratio; MS, multiple sclerosis; NLR, neutrophil-to-lymphocyte ratio; NMOSD, neuromyelitis optica spectrum disorder; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

Table 4 Multivariate Logistic Regression Analysis

Variable	B	Wald	P-value	Exp (B)	95% CI
NLR	0.145	5.988	0.014	1.156	1.029–1.299
EDSS	0.307	13.932	0.000	1.36	1.157–1.598
TOURT	−0.107	18.071	0.000	0.898	0.855–0.944
ESR	0.035	5.655	0.017	1.035	1.006–1.065
Normal	−1.543	15.666	0.000	0.214	-

Abbreviations: CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; EDSS, Expanded Disability Status Scale; TOURT, 24-h intrathecal synthesis rate; ESR, erythrocyte sedimentation rate;

combined inflammatory markers was superior to that of each individual indicator, at 0.73 (95% CI: 0.687–0.774). The AUC of the nutritional indicator ALB was greater than that of the combined inflammatory markers, at 0.787 (95% CI: 0.746–0.828), and the AUC of the combined inflammatory markers and ALB was 0.836 (95% CI: 0.801–0.871), significantly higher than that of the other indicators as shown by the DeLong test (P<0.05). For NMOSD, the AUC of the combined inflammatory markers was superior to each individual indicator, at 0.779 (95% CI: 0.738–0.820). The AUC of combined HB and ALB was superior to that of the combined inflammatory markers, at 0.863 (95% CI: 0.83–0.896), and the AUC of the combined inflammatory markers and HB and ALB was 0.91 (95% CI: 0.884–0.936), significantly higher than that of the other indicators as shown by the DeLong test (P<0.05).

The ability of nutritional markers to discriminate between MS and NMOSD was then assessed, with a resultant AUC of 0.655 (95% CI: 0.604–0.705), superior to that of inflammatory markers, at 0.546 (95% CI: 0.495–0.597). The AUC of combined inflammatory and nutritional markers was 0.673 (95% CI: 0.623–0.722), significantly higher than that of the other indicators as shown by the DeLong test (P<0.05).

Diagnosis and Differentiation of MS and NMOSD Based on Inflammatory and Nutritional Markers

Using significant indicators from the univariate analysis as independent variables, collinearity among these variables was addressed. Subsequently, A forward conditional algorithm was utilized for constructing a binary logistic regression model, involving the gradual addition of variables identified in the univariate analysis into the model. Ultimately, a predictive diagnostic model based on inflammatory and nutritional markers was developed (Figure 3 and Supplementary Table 6). The modelY= −18.115- 7.549MLR + 0.014PLR - 0.002SII + 0.434ALB was suggested by binary logistic regression analysis for

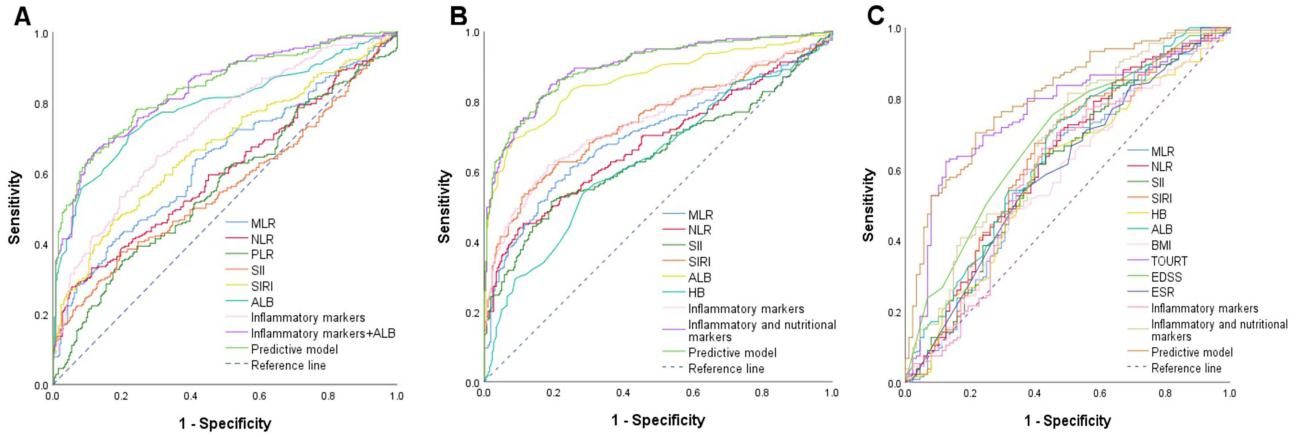

Figure 3 Evaluation of the Diagnostic Efficacy of Inflammatory and Nutritional Markers. Receiver operating characteristic curves show the ability of inflammatory and nutritional markers to (**A**) diagnose MS, (**B**) diagnose NMOSD, and (**C**) differentiate between MS and NMOSD.
Abbreviations: ALB, albumin; HB, hemoglobin; MLR, monocyte-to-lymphocyte ratio; MS, multiple sclerosis; NLR, neutrophil-to-lymphocyte ratio; NMOSD, neuromyelitis optica spectrum disorder; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

the diagnosis of MS (model P-value=0.000<0.05). The MS assessment forecasting model's AUC was 0.840 (95% CI: 0.806–0.875). The model was well-calibrated, according to the Hosmer-Lemeshow goodness-of-fit assessment ($\chi2$=7.237, P>0.05). The modelY = −21.671- 1.764SIRI + 0.541ALB was suggested for the diagnosis of NMOSD (model P-value=0.000<0.05). An AUC of 0.905 (95% CI: 0.877–0.933) was obtained for the model that forecasts for identifying NMOSD; the Hosmer-Lemeshow goodness-of-fit analysis demonstrated that the model was accurately calibrated ($\chi2$=17.387, P>0.05). The model for discriminating between MS and NMOSD is represented as follows:Y= −1.628 + 0.137NLR + 0.341EDSS - 0.103TOURT + 0.032ESR(model P-value=0.000<0.05). AUC of 0.806 (95% CI: 0.750–0.863) was achieved by the forecasting model for differentiating MS with NMOSD; the Hosmer-Lemeshow goodness-of-fit test demonstrated that the model exhibits satisfactory calibration ($\chi2$=3.188, P>0.05). Temporal validation tested the generalizability of the predicted results over time in patients similar to the development cohort (35 patients with MS, 38 with NMOSD, and 85 hC from Beijing Tiantan Hospital of Capital Medical University, recruited from January to April 2024, sex- and age-matched, and with the same inclusion and exclusion criteria). The validated MS model achieved sensitivity and specificity of 88.9% and 73.5% respectively, via an AUC of 0.840 (95% CI: 0.752–0.928). The validated NMOSD model possesses an AUC of 0.961(95% CI: 0.924–0.997) in addition to having sensitivity and specificity of 95.4% as well as 88.9%, respectively. The AUC of the algorithm used for discerning both MS and NMOSD was discovered to be 0.743 (95% CI: 0.581–0.905). The relevant sensitivity as well as specificity with the model were determined to be 47.4% and 100%, respectively. (Figure 4 and Supplementary Table 6).

Changes in Inflammatory and Nutritional Indicators Over the Disease Course

Individuals with MS and NMOSD were assessed for differences in their levels of inflammatory and nutritional markers in periods of disease exacerbation and remission. When contrasted with the onset of the disease, the NLR, SII, and SIRI had been substantially reduced in MS after remission (P<0.05), along with the same indicators plus the PLR were substantially lesser in NMOSD (P<0.05), with the trend being more pronounced in NMOSD. There were not any substantial variations in HB levels (P>0.05), while ALB levels in MS and NMOSD were considerably greater after remission than at the onset of the disease (P<0.05) (Table 5; Figure 5).

Discussion

The SII, pioneered by Hu et al in 2014, initially utilized neutrophil, lymphocyte, and platelet counts to evaluate the prognosis of patients undergoing radical hepatectomy. Since its inception, The distinctive and forecasting capabilities of the SII was extensively investigated across a spectrum of cardiovascular and inflammatory conditions.[24] Subsequently, in 2016, Qi et al introduced the SIRI, which integrates monocyte counts alongside neutrophil and lymphocyte counts, aiming to predict survival outcomes for pancreatic cancer patients post-chemotherapy.[25] The inclusion of monocytes

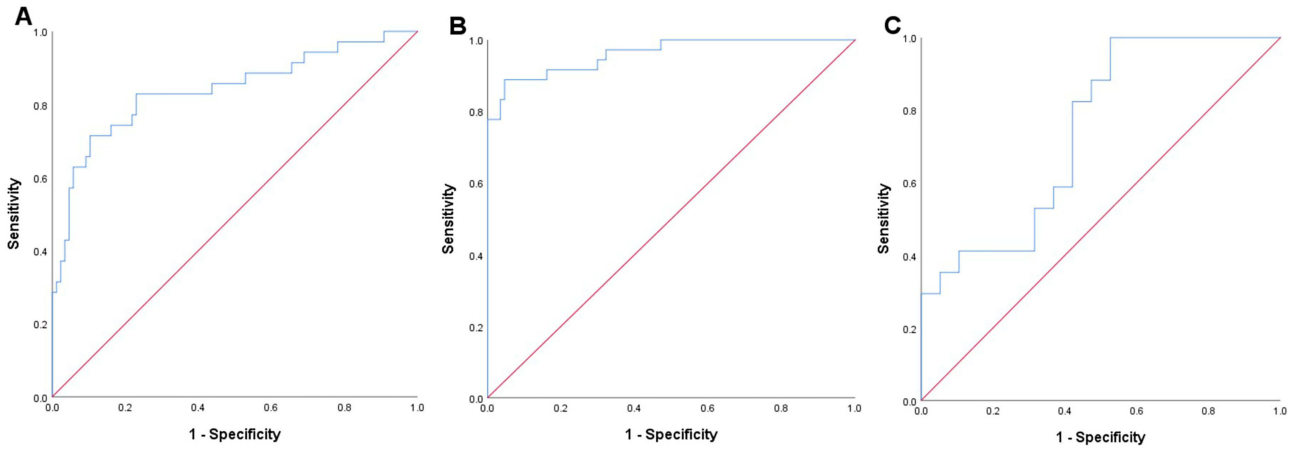

Figure 4 Validation of Diagnostic Models. The models developed for (**A**) multiple sclerosis and (**B**) neuromyelitis optica spectrum disorder were assessed in a separate cohort of patients and healthy controls. (**C**)Validation of Discrimination Models for Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder.

Table 5 Changes in Inflammatory and Nutritional Indicators Over the Disease Course

Indicator	Group	Onset	Remission	P-value
MLR	MS	0.218(0.169–0.303)	0.216(0.173–0.286)	0.490
	NMOSD	0.253(0.176–0.308)	0.217(0.169–0.286)	0.455
NLR	MS	2.243(1.631–3.526)	1.836(1.454–2.628)	<0.05
	NMOSD	2.677(1.817–4.540)	2.288(1.603–3.116)	<0.01
PLR	MS	139.57(107.18–164.91)	152.59(102.85–223.65)	0.412
	NMOSD	143.11(104.69–209.86)	116.03(89.012–161.8)	<0.01
SII	MS	600.4(391.52–909.14)	423.62(322.79–672.09)	<0.01
	NMOSD	708.17(416.34–1145.4)	526.52(335.82–800.57)	<0.01
SIRI	MS	0.889(0.541–1.547)	0.697(0.493–1.039)	<0.01
	NMOSD	1.126(0.658–2.106)	1.013(0.567–1.710)	<0.01
HB	MS	135(124–145)	131(123–143)	0.198
	NMOSD	129(118–142)	129(118–140)	0.925
ALB	MS	40.9(38.5–42.4)	43.3(41.3–45.6)	<0.01
	NMOSD	39.1(37.0–41.8)	41.0(38.8–43.3)	<0.01

Note: Data are expressed as median (interquartile range).
Abbreviations: ALB, albumin; HB, hemoglobin; MLR, monocyte-to-lymphocyte ratio; MS, multiple sclerosis; NLR, neutrophil-to-lymphocyte ratio; NMOSD, neuromyelitis optica spectrum disorder; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

renders the SIRI a more comprehensive reflection of inflammatory status compared to traditional markers like NLR, PLR, and MLR. Indeed, recent comparative studies evaluating the anticipatory efficacy of NLR, PLR, MLR/SII, and SIRI within various inflammatory conditions have consistently demonstrated the superior predictive power of SIRI.[26,27] Theoretically, an ideal inflammatory marker should encompass all pertinent cell types, offering a holistic assessment of

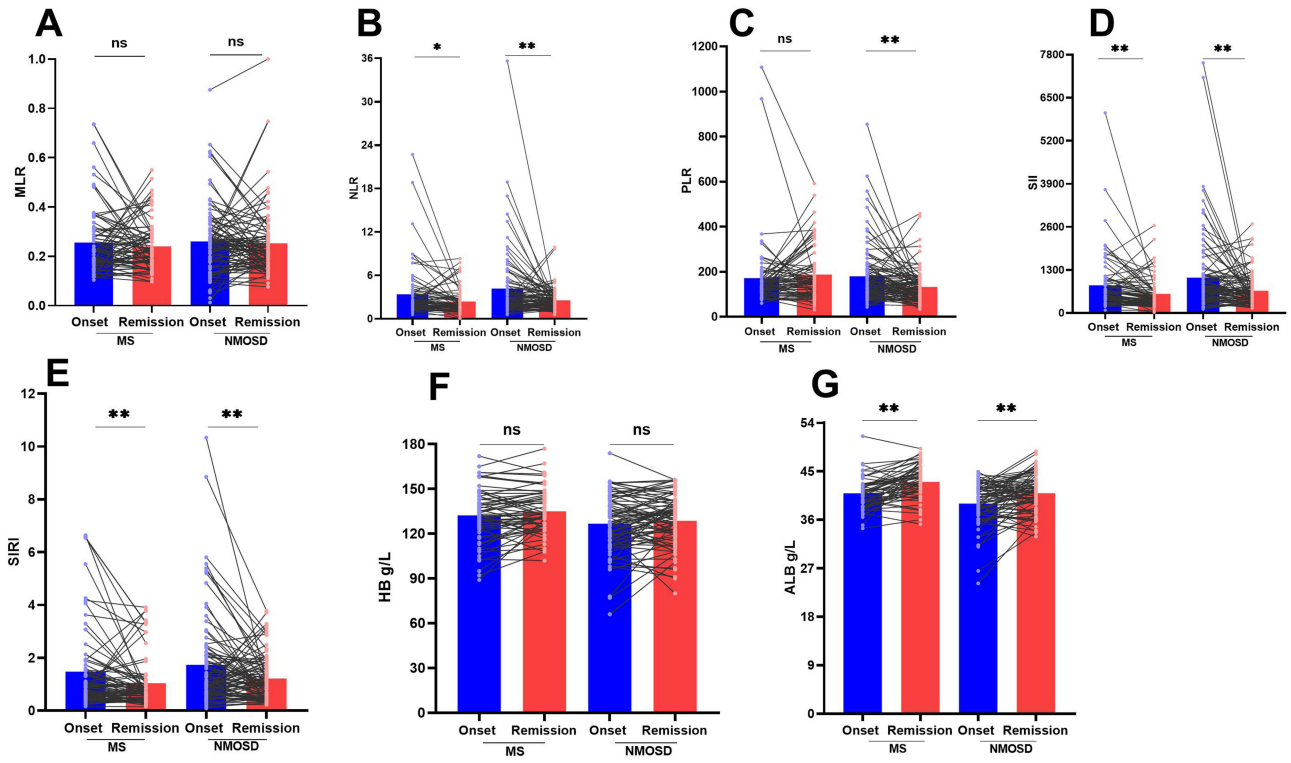

Figure 5 Changes in Inflammatory and Nutritional Indicators over the Disease Course. (**A**) MLR, (**B**) NLR, (**C**) PLR, (**D**) SII, (**E**) SIRI, (**F**) HB, (**G**) ALB. *P<0.05, **P<0.01.
Abbreviations: ALB, albumin; HB, hemoglobin; MLR, monocyte-to-lymphocyte ratio; MS, multiple sclerosis; NLR, neutrophil-to-lymphocyte ratio; NMOSD, neuromyelitis optica spectrum disorder; ns, not significant; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

the immune-inflammatory milieu. Cell count ratios, such as those utilized in SII and SIRI calculations, present a pragmatic approach due to their ease of computation and relatively low cost. Furthermore, the potential for expanding these ratios to incorporate additional cell types allows for more nuanced assessments with minimal resource burden.

Neutrophils are key players in inflammation, as they release reactive oxygen species and various lytic enzymes. These substances not only cause tissue damage but also stimulate the activation of immune-related cells, such as monocytes, thereby perpetuating the inflammatory cascade. Elevated monocyte counts often signify underlying vascular endothelial dysfunction, reflecting the extent of inflammation. Meanwhile, lymphocytes play crucial roles in immunoregulatory pathways, with high levels of inflammation often resulting in lymphocyte apoptosis.[28] MS and NMOSD are autoimmune diseases, in which infiltration of inflammatory cells (monocytes, lymphocytes, and plasma cells) occurs around the small veins, accompanied by reactive glial (glial cell) proliferation, and the synergistic action of various inflammatory cells and cytokines. The detection of various indicators of inflammation, and the determination of the degree of inflammatory response, should therefore provide important information on disease occurrence and progression. Inflammatory processes often manifest in alterations to leukocyte counts, these changes render leukocyte ratios invaluable for the indirect assessment of inflammation.[29] Circulating blood cell counts and their proportions are useful indicators to assess the forecast, status, and trajectory of inflammatory diseases, as several studies have demonstrated.[30] For instance, Investigations have demonstrated correlations regarding the NLR, MPV and the seriousness of Behçet's syndrome.[31] An further investigation examined the application of the SII in forecasting the outlook for individuals with squamous cell cancer.[32] NLR, MLR, and PLR are trustworthy markers of illness progression in disorders that demyelinate the CNS, according to prior research. Individual blood cell counts did not differ within MS and NMOSD in our investigation. MLR, NLR, SII, and SIRI, however, differed substantially between the illness groups (MS or NMOSD) and the HCs. In comparison to individuals with MS, NMOSD individuals had greater levels of MLR, NLR, SII, and SIRI. Hence, relying solely on individual cell counts may not adequately capture the intricate and severe nature of the inflammatory state. Instead, utilizing indices and ratios derived from combining cell counts can offer more robust and comprehensive insights.

Nutritional markers, including BMI, ALB, and HB, have been shown to have prognostic value in a variety of cancers, including gastric, colon, and rectal, In addition, it has been shown that patients with chronic malnutrition and micronutrient deficiencies have an impaired cytokine response and subsequent activation of the immune system.[33–35] Research[36] indicates a close association between systemic inflammatory response and nutritional status. Furthermore, severe inflammation can affect appetite, gastrointestinal motility, and hemodynamic stability, which impacts nutritional status.[37,38] Furthermore, the above three indicators are easily obtainable in clinical practice. Therefore, we included nutritional indicators in our analysis. HB and ALB levels and BMI differed significantly between patients with MS and those with NMOSD, with BMI being lower in MS compared to NMOSD with HB and ALB levels being greater in MS. Therefore, Those with MS had superior nutritional status compared to individuals with NMOSD. This may be because NMOSD is considered more severe than MS.[39] AQP4-IgG$^+$ individuals had comparatively fewer amounts of HB than AQP4-IgG$^-$ patients, according to a correlation between AQP4 antibodies and HB values, Given that AQP4 antibodies may affect the integrity of the blood-brain barrier,[40] thereby altering the delivery of blood components, future studies should aim to increase sample sizes and explore the relationship between AQP4 antibodies and HB in conjunction with physiological mechanisms. This could lead to improved clinical management. The nutritional indicators HB and ALB individually and in combination had greater sensitivity and specificity than inflammatory markers for diagnosing MS and NMOSD.

The discharge of cytokines through immune cells can cause inflammation and damage to the brain. This can then cause anti-inflammatory indications to be produced and the presentation of cytokines to be suppressed, thereby preventing the course of the illness.[41] However, sustained inflammatory reactions have the potential to exhaust the immune system, leading to a reduction in systemic immune activity, inhibition of immunological responses inside cells, and a sharp reduction in peripheral blood lymphocytes, thereby exacerbating disease deterioration. Our research indicates that inflammatory and nutritional markers in the blood are associated with indicators of disease severity, such as the EDSS, MRI T2 lesion count, and relapse frequency. When EDSS scores, lesion counts, and relapse frequencies increase, the inflammatory markers (eg, MLR, NLR, PLR, SII, and SIRI) show a positive correlation, while the nutritional markers (eg, ALB and BMI) exhibit a negative correlation. Furthermore, based on subsequent research findings, the same patient experiences a decreasing trend in inflammatory markers and an increasing trend in nutritional markers during episodes of disease exacerbation and remission over a six-month period. Previous studies[8–14,42–44] have demonstrated that in demyelinating diseases, the immune system erroneously targets the nerve myelin. Upon disease onset,

the immune response is activated, triggering a cascade of inflammatory reactions, accompanied by alterations in the infiltration of perivascular and parenchymal lymphocytes. Indicators such as SII and SIRI serve as reflections of the inflammatory state present in the bloodstream. Mechanistically, during the inflammatory progression of demyelinating disorders, the activation of the immune system leads to the mobilization and recruitment of inflammatory cells, including neutrophils and monocytes. These cells release a variety of inflammatory mediators, such as cytokines and chemokines. As the inflammatory response escalates, the counts of neutrophils and monocytes in SII and SIRI are likely to rise. In the initial phases of the disease, the immune system's assault on myelin is relatively constrained, with a limited release of inflammatory mediators; consequently, SII and SIRI may exhibit only a slight increase. When demyelinating diseases become more severe, a substantial number of immune cells engage in the inflammatory process, resulting in extensive damage to the nerve myelin. In this scenario, a large mobilization of inflammatory cells occurs, and platelets may also become involved due to the activation of coagulation mechanisms, culminating in marked elevations in SII and SIRI. Moreover, nutritional indicators should not be overlooked in demyelinating diseases. ALB, an important protein in the blood, plays a crucial role in maintaining the stability of the microenvironment surrounding nerve cells and in the repair of nerve myelin. In demyelinating diseases, ALB levels may fluctuate due to insufficient intake and inflammatory consumption, potentially influencing disease progression and prognosis. BMI reflects an individual's body fat and nutritional metabolic status; a low BMI suggests malnutrition, which can weaken immune function and impair tissue repair, thereby affecting the recovery of nerve myelin. Both inflammatory markers and nutritional indicators are significant in the onset, progression, diagnosis, and prognostic assessment of demyelinating diseases. Different time points of acute phase recurrence may lead to fluctuations in the patient's nutritional and inflammatory markers, reflecting individualized physiological, immune, and metabolic responses. Future research should focus on further exploring the changes in these markers across different recurrence periods, as well as the interrelationships and mechanisms underlying the inflammatory and nutritional indicators. This will be of great clinical value in enhancing our understanding and treatment of these conditions.

In this study, inflammatory indicators were positively correlated with CRP levels and the ESR and negatively correlated with total T lymphocyte numbers in MS and NMOSD, and the nutritional markers ALB and HB levels were inversely linked with CRP levels and the ESR. The inflammatory response triggered by disease activation leads to the stimulation of the complement system, resulting in the production of various cytokines. These inflammatory mediators enhance the synthesis of CRP and accelerate the ESR, while also interfering with normal metabolic processes. MS and NMOSD are both classified as autoimmune diseases. Research on total T lymphocytes provides insight into the overall immune status, with relevant literature[45,46] indicating that T lymphocytes play a central role in immune responses and participate in the regulation of inflammation and autoimmunity. Studies demonstrate that an increase in regulatory T (Treg) cell numbers can suppress the secretion of inflammatory cytokines, thereby reducing blood inflammatory markers. Furthermore, T cells can secrete anti-inflammatory cytokines that inhibit the activity of other inflammatory cells, further decreasing inflammatory marker levels. Microglia, the primary immune cells in the central nervous system, are responsible for capturing and presenting antigens to T cells, thereby promoting their activation and proliferation, which enhances the immune response. However, in certain neurological diseases, such as multiple sclerosis, the persistent activation of microglia may result in chronic inflammation, inhibiting T cell function and causing T cell exhaustion and functional decline. As inflammation persists, T cell activity decreases, impairing their numbers and function, ultimately leading to a relative reduction in T lymphocytes. Combined inflammatory markers and nutritional markers were better at diagnosing MS and NMOSD than individual indicators; But compared to inflammatory indicators, nutritional markers had a higher diagnostic value. A new diagnostic model analysis revealed that the combined diagnostic model of inflammatory response and nutritional indicators achieved an AUC of 0.673 (0.623–0.722), indicating good discriminatory power. Additionally, our study identified ESR, EDSS, TOURT, and NLR as independent influencing factors between MS and NMOSD. Incorporating these clinical indicators further enhanced the model's discriminatory ability. Therefore, this study demonstrates that differences in inflammatory levels, disease severity, and cerebrospinal fluid protein levels between MS and NMOSD can provide important diagnostic information, thereby augmenting traditional clinical laboratory analyses. The establishment of a diagnostic model with higher sensitivity and specificity will help clinicians make more accurate judgments.

In what we discovered of our study, NLR, SII, and SIRI had greatly decreased for individuals with MS during the onset of the illness to the point at which remission; similarly, NLR, PLR, SII, and SIRI were substantially lower for NMOSD individuals.

Furthermore, compared to the onset of the disease, ALB levels were considerably greater in both MS and NMOSD after disease remission. Investigations that are pertinent demonstrate that shortages in certain elements and energy-producing proteins might exacerbate inflammation through malnourishment, suggesting that poor nutritional status during disease onset exacerbates inflammation's progression.[47] According to this study, ALB and NLR/SII/SIRI can be utilized as markers of disease progression for MS and NMOSD. Thus, inflammatory status can be reflected by inflammatory markers including MLR, NLR, PLR, SII, and SIRI.

This study's strength lies in its utilization of standard hematological markers routinely assessed in clinical practice to identify inflammatory and nutritional biomarkers, thereby aiding clinicians in tailoring personalized assessment plans. This study systematically employs inflammatory and nutritional markers for the first time in the diagnosis and differentiation of MS and NMOSD. Building on previous literature, this research further validates the significance of these markers in monitoring the progression of neuroinflammatory diseases. By assessing the coefficients of each variable within the model, we can determine their respective contributions to predictive outcomes. For instance, early intervention can be initiated when a patient exhibits elevated SIRI alongside reduced ALB levels. By inputting clinical data into the model, predictive values can be computed to assess the likelihood of disease manifestation. But because it was a retrospective, single-center research, it had several restrictions, making it difficult to establish causal relationships. The lack of long-term follow-up outcome analysis meant that the findings were insufficient to clearly define the prognostic value of these markers in the disease. Future long-term prospective longitudinal studies should focus on the significance of these markers in the management and treatment decisions of the disease, particularly their potential applications in personalized treatment, and explore the mechanisms underlying the observed associations. Therefore, multicenter prospective studies are required to settle the foretelling significance of these inflammatory and nutritional indicators in individuals with MS and NMOSD. Further studies are also required to identify more valuable inflammatory and nutritional markers than those analyzed here.

Conclusions

Our study provides preliminary evidence supporting the potential applications of inflammatory and nutritional markers in the diagnosis, differentiation, and monitoring of disease severity in MS and NMOSD. Therefore, we recommend that clinicians closely monitor these markers in conjunction with patients' clinical presentations and imaging findings to further assess disease status and determine the need for early intervention. Additionally, our research has developed diagnostic and differential predictive models based on nutritional and inflammatory markers, demonstrating good diagnostic efficacy and significant clinical value.

Ethics Approval and Consent to Participate

Study procedures were performed in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects. This study was performed in compliance with relevant laws and institutional guidelines and approved by the Ethics Committee of Tiantan Hospital of Capital Medical University (approval number: KY2023-157-03), and informed consent was obtained from all patients before data collection.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version.

Author Contributions

All authors made significant contributions to this study, encompassing a range of key responsibilities. These included designing the paper's framework, conducting experimental manipulations and overseeing the research process, collecting and analyzing data, creating graphs and charts, revising the manuscript, generating writing ideas, providing guidance in the composition of the article, and finalizing the paper.

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Disclosure

The authors declare that they have no competing interests.

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