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ORIGINAL RESEARCH

The Associations of Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Systemic Immune-Inflammatory Index with the Severity and Prognosis of Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy

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Purpose: The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) are biological indicators that reflect the inflammatory state in some immune diseases. This study investigated the associations of the NLR, MLR, PLR, and SII with the severity and prognosis of autoimmune glial fibrillary acidic protein astrocytopathy (GFAP-A).

Patients and Methods: This retrospective study analyzed the data of 62 patients with GFAP-A at the First Affiliated Hospital of Zhengzhou University from January 2020 to August 2024. The Clinical Assessment Scale for Autoimmune Encephalitis (CASE) was used to assess the disease severity at admission and patients were categorized into mild (CASE ≤4) or severe (CASE ≥5) groups. The modified Rankin Scale (mRS) was used to assess the patients' conditions at discharge and follow-up. Patients were categorized into the good (mRS ≤2) or poor (mRS ≥3) prognosis groups at 1-year follow-up. Risk factors affecting the severity and prognosis of GFAP-A were analyzed using binary logistic regression analysis.

Results: The NLR, MLR, PLR, and SII were significantly higher in the severe group than in the mild group. The NLR (OR=1.238, 95% CI: 1.003–1.473, P=0.01) was an independent risk factor for the severity of GFAP-A and was positively correlated with the CASE score (r=0.365, P=0.003). The best cut-off NLR for predicting the severity of GFAP-A was 3.05, with a sensitivity of 80%, specificity of 57.1%, and AUC of 0.729 (95% CI: 0.600–0.858, P=0.004). The mRS score at discharge (OR=7.966, 95% CI: 1.120–56.658; P=0.038) was an independent risk factor for poor prognosis one year after discharge. In addition, the NLR, MLR, PLR, and SII at admission and reduction of the PLR after immunotherapy were not associated with patient prognosis (P > 0.05).

Conclusion: The NLR, an objective, inexpensive, and clinically accessible biomarker, is positively associated with the CASE score, that is, with the severity of GFAP-A. Therefore, the NLR can be used to identify patients with potentially severe GFAP-A at an early stage, thus optimizing the clinical treatment decisions.

Keywords: autoimmune glial fibrillary acidic protein astrocytopathy, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammatory index

Introduction

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein in astrocytes and an important component of the astrocyte cytoskeleton, which plays an important role in astrocyte regeneration, synaptic plasticity, and reactive gliosis.[1,2] Abnormal regulation and expression of GFAP is related to various neurological disorders, including infectious diseases of

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the central nervous system (CNS), neurodegenerative diseases, cerebral edema, traumatic brain injury, and psychiatric disorders.[3] In 2016, the United States' Mayo Clinic Lennon team identified anti-GFAP antibodies in the cerebrospinal fluid and serum of patients with meningoencephalomyelitis and named it autoimmune GFAP astrocytopathy (GFAP-A).[4] GFAP-A affects the brain, meninges, spinal cord, and/or optic nerve. Its clinical manifestations are complex and varied, including fever, headache, ataxia, seizures, mental and behavioral abnormalities, movement disorders, tremors, and autonomic and cognitive dysfunction.[5,6] In addition, due to the heterogeneity of the disease, GFAP-A may become life-threatening within weeks or even days in some patients due to central hypoventilation or severe autonomic dysfunction.[6–9] Currently, there are no unified standards or guidelines for the treatment of GFAP-A. Most patients with GFAP-A respond well to steroid therapy and achieve complete or partial remission upon discharge, and a favorable prognosis. However, some patients are prone to recurrence, leaving varying degrees of functional disability and even death.[5,6,8,10] Therefore, it is vital to establish biomarkers to assess appropriate steroid therapy and clinical treatment decisions for GFAP-A.

Monitoring disease progression and detecting potentially severe disease at an early stage are crucial for managing individual patients with GFAP-A, as this affects clinical treatment decisions. Studies focused on biomarkers related to disease severity and prognosis of GFAP-A are in the beginning stages. Segal et al[11] found that higher neurofilament light chain (NfL) concentrations were associated with magnetic resonance imaging abnormalities and a poor prognosis in patients with GFAP-A, suggesting that NfL may be a biomarker of disease severity and prognosis in GFAP-A. Fu et al[12] found that MIP-3α was positively correlated with disease severity by detecting the expression levels of 200 serum cytokines in patients with GFAP-A. Kimura et al[13] observed elevated levels of TNF-α, IL-27, IL-6, CCL20, GFAP, S100 calcium-binding protein B, and NfL in GFAP-A cerebrospinal fluid samples, suggesting that these may be potential biomarkers of GFAP-A. However, these potential biomarkers of GFAP-A have some limitations in clinical practice. First, due to economic considerations, not all patients will undergo testing for the above biological indicators. Second, due to the requirements of the detection methods, not all hospitals are capable of conducting the detection of the above biological indicators. Finally, cytokines and chemokines in cerebrospinal fluid may be degraded during storage, resulting in inaccurate test results. Therefore, there is an urgent need for objective, inexpensive, and clinically accessible biomarkers to guide the clinical management of patients with GFAP-A.

Pathological studies have revealed the extensive infiltration of lymphocytes, monocytes, and neutrophils around intracranial blood vessels in patients with GFAP-A, which is consistent with the typical imaging feature of GFAP-A with perivascular linear radiolucent enhancement perpendicular to the ventricle of the brain.[6,14–16] These findings suggest that neuroinflammation caused by the interaction of lymphocytes, monocytes, neutrophils, microglia, and antibodies secreted by plasma cells is a possible pathogenesis of GFAP-A. Neutrophils, monocytes, and lymphocytes are inflammatory markers measured using routine blood examinations that are often used to reflect the inflammatory status in patients. The neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) are more representative of the inflammatory state of the body than neutrophil, monocyte, or lymphocyte counts alone. Studies have observed that the NLR and MLR are associated with the severity, activity, and prognosis of some immune diseases of the CNS, including multiple sclerosis (MS), autoimmune encephalitis (AE), neuromyelitis optica spectrum disorder (NMOSD), and myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD).[17–19] Similar to the NLR and MLR, the platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammatory index (SII) are associated with the severity, activity, and prognosis of several immune diseases, including NMOSD, MOGAD, and AE.[19–21] However, the associations of the NLR, MLR, PLR, and SII with the disease severity and prognosis of patients with GFAP-A remain unclear. This study analyzed the associations between these inflammatory indices and the disease severity and prognosis of patients with GFAP-A.

Materials and Methods

Study Patients

Sixty-two patients with GFAP-A who were treated at the First Affiliated Hospital of Zhengzhou University between January 2020 and August 2024 were included in this study (Figure 1). The age range of these patients was 3 to 68 years old. This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the

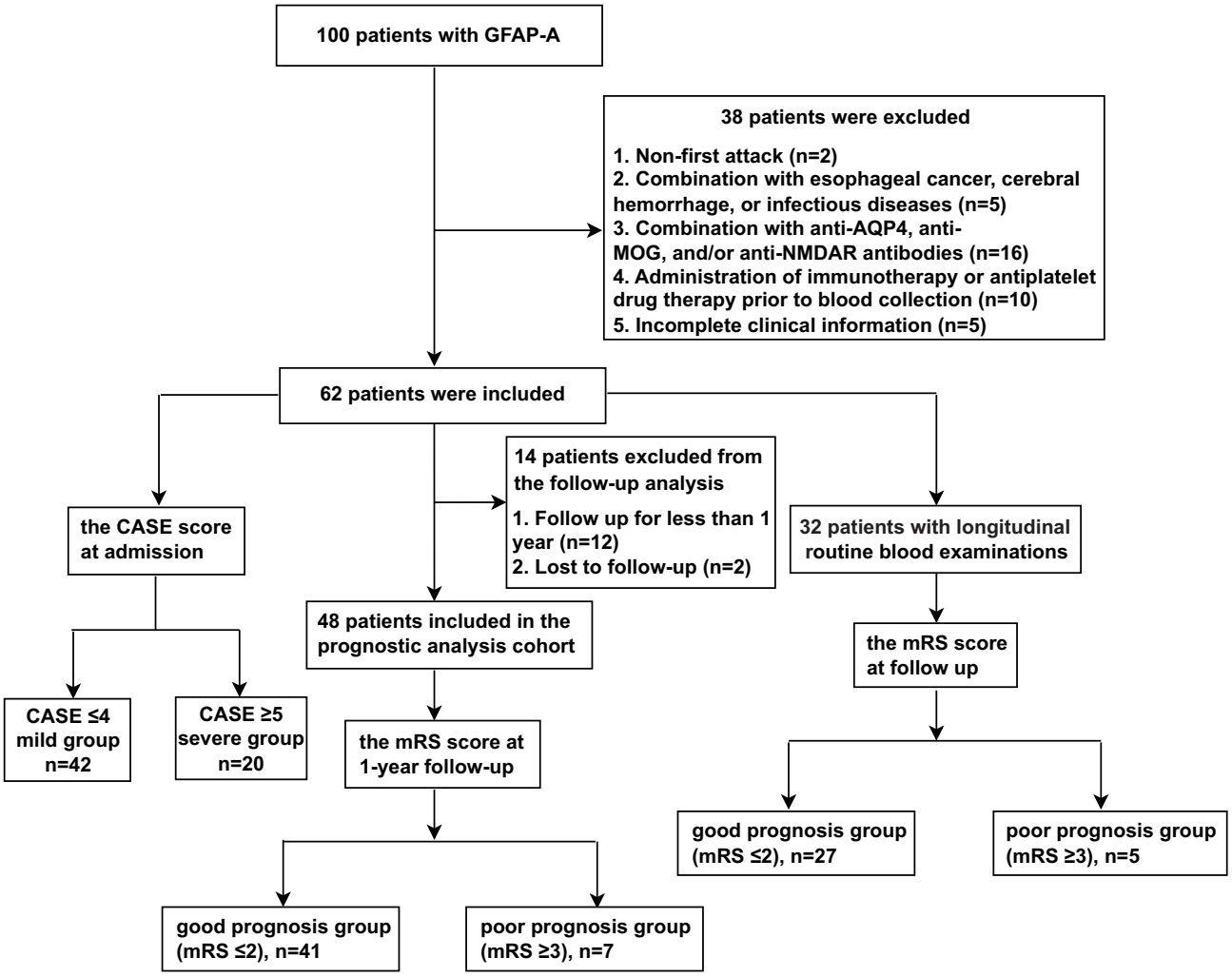

Figure 1 Flowchart of included and excluded patients.

First Affiliated Hospital of Zhengzhou University (No. 2022-KY-0053). All patients included in this study were newly diagnosed with GFAP-A. Currently, there is no unified standard for the diagnosis of GFAP-A. Some patients are often misdiagnosed as viral encephalitis, tuberculous meningitis, or acute disseminated encephalomyelitis, leading to delayed and incorrect treatment.[22,23] We have summarized the following diagnostic points based on relevant literature: (1) acute or subacute onset; (2) clinical manifestations of meningeal, cerebral, spinal cord, or optic nerve involvement or a combination of symptoms; (3) paraventricular linear radial enhancement and/or spinal cord long-segment involvement on MRI; (4) serum and/or cerebrospinal fluid anti-GFAP antibody positivity; (5) responsive to steroid hormone therapy; (6) the exclusion of other diagnoses.[4–6,14] In addition, all blood samples used in this study were obtained prior to the administration of steroid hormones or immunosuppressants, and all relevant clinical data were available for all patients in this study. Patients were excluded from this study if it was not their first GFAP-A attack or they had comorbidities of a tumor, rheumatism, infectious diseases, hematological diseases, other autoimmune diseases, or psychiatric disorders. Patients with severe liver, kidney, or other organic diseases, or other autoimmune antibodies, such as anti-AQP4 antibodies or anti-MOG antibodies, were also excluded from this study. Pregnant patients, those who had been administered steroid hormones or immunosuppressants prior to blood collection, and those with antiplatelet drug therapy use (including aspirin and/or clopidogrel) within 4 months of the study were excluded. Finally, patients with incomplete clinical information were also excluded from this study.

Data Collection

Basic clinical data, laboratory findings, and imaging data were collected from all of the patients. Basic clinical data included sex, age, prodromal events, time from first symptom to consultation, time from first symptom to diagnosis, need for mechanical ventilation, need for intensive care unit (ICU) treatment for at least 48h, clinical manifestations, immunotherapy, and length of hospitalization. Laboratory findings included routine blood examination results, liver function, kidney function, rheumatological and immune indices, tumor markers, cerebrospinal fluid results, and serum and/or cerebrospinal fluid antibody test results. Routine blood examinations were conducted within 24 hours of admission and before immunotherapy in all patients during acute attacks (episodes of neurological deterioration lasting more than 24 hours). Routine blood examination results included white blood cell, platelet, neutrophil, monocyte, lymphocyte, eosinophil, basophil counts. The NLR, MLR, PLR, and SII were calculated based on the routine blood examination results (NLR=neutrophils/lymphocytes; MLR=monocytes/lymphocytes; PLR=platelets/lymphocytes; SII=neutrophils*platelets/lymphocytes). Long-term follow-up was conducted after immunotherapy.

Assessment Scale

The primary endpoints of this study were disease severity at admission and prognosis. The Clinical Assessment Scale for Autoimmune Encephalitis (CASE) consists of nine items, including seizure, memory dysfunction, psychiatric symptoms, consciousness, language problem, dyskinesia/dystonia, gait instability and ataxia, brainstem dysfunction, and weakness, which compensates for the shortcomings of the modified Rankin Scale (mRS) in assessing non-motor symptoms of autoimmune encephalitis.[24] GFAP-A mainly manifests as a combination of the above symptoms; therefore, CASE was used to assess the disease severity of GFAP-A at admission, and patients were categorized based on the CASE score into mild (CASE $\leq$4) or severe (CASE $\geq$5) groups. The mRS was used to assess the patients' conditions at discharge and follow-up, and patients were categorized based on the mRS score at 1-year follow-up (one year after discharge) into the good (mRS $\leq$2) or poor (mRS $\geq$3) prognosis groups.

Statistical Analysis

All statistical analyses were conducted using SPSS statistical software (version 25.0; IBM, Chicago, IL, USA). Continuous data with normal distribution were presented as mean ± standard deviation, and an independent samples *t*-test was used to compare the continuous data. Continuous data that did not conform to a normal distribution were presented as median and interquartile range, and the Mann–Whitney *U*-test was used to compare the continuous data. Categorical data were compared using the chi-square test or Fisher's exact probability method. Spearman correlation analysis was used to test the correlations between the NLR, MLR, PLR, and SII and the severity of GFAP-A. Receiver operating characteristic (ROC) curves were used to evaluate the ability of the NLR, MLR, PLR, and SII to predict the severity of GFAP-A, and the area under the curve (AUC) was calculated. Binary logistic regression was used to analyze the risk factors affecting the disease severity and prognosis of patients with GFAP-A. This study only included patients with GFAP-A and did not compare the GFAP-A groups with healthy controls or other patient groups. All statistical analyses were two-sided, and the level of statistical significance was set at $P < 0.05$.

Results

Patient Characteristics

Sixty-two patients with GFAP-A were included in this study. The clinical features and laboratory findings are shown in Table 1. The clinical manifestations of the patients in this study were diverse and included fever (n=43, 69.35%), headache (n=32, 53.33%), ataxia (n=22, 35.48%), movement disorders (n=15, 24.19%), cognitive dysfunction (n=11, 17.74%), mental and behavioral abnormalities (n=6, 9.68%), seizures (n=5, 8.06%), consciousness disorders (n=17, 27.42%), autonomic dysfunction (n=34, 54.84%), tremors (n=9, 14.52%), and visual abnormalities (n=10, 16.13%). All patients were administered first-line immunotherapy, and no patient received second-line immunotherapy. Fifty-five patients were administered oral steroid hormones and/or mycophenolate mofetil after discharge.

Table 1 Clinical Features and Laboratory Findings of Patients with GFAP-A

	GFAP-A (n=62)
Female, n (%)	23 (37.10)
Age, years	32 (14–48)
Prodromal events, n (%)	19 (30.65)
Time from first symptom to consultation, days	3 (0.75–9.25)
Time from first symptom to diagnosis, days	21.50 (14.00–34.25)
Length of hospitalization, days	18.50 (14.00–26.50)
ICU treatment, n (%)	21 (33.87)
Mechanical ventilation, n (%)	6 (9.68)
CASE at admission	2 (0–5.25)
CASE at the worst condition	5 (1.00–7.25)
mRS at discharge	1 (0–2)
White blood cells, 10^9/L	7.69 (5.20–9.23)
Platelets, 10^9/L	260.21±10.77
Neutrophils, 10^9/L	4.91 (3.64–6.91)
Monocytes, 10^9/L	0.51 (0.36–0.65)
Lymphocytes, 10^9/L	1.60 (0.98–2.10)
Eosinophils, 10^9/L	0.08 (0.02–0.13)
Basophils, 10^9/L	0.02 (0.01–0.03)
NLR	3.40 (2.04–5.77)
MLR	0.31 (0.22–0.54)
PLR	156.99 (118.88–254.45)
SII	786.23 (454.80–1481.18)

Notes: Continuous data were presented as mean ± standard deviation or as median (interquartile range), and categorical data were presented as frequency (%).

Abbreviations: GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; CASE, the Clinical Assessment Scale for Autoimmune Encephalitis; mRS, the modified Rankin Scale; ICU, intensive care unit.

The NLR Was Associated with the Severity of GFAP-A

Clinical Data of Patients in the Mild and Severe Groups

The mild group included 42 patients (67.74%), and the severe group included 20 patients (32.26%). The neutrophil count, NLR, MLR, PLR, and SII were significantly higher in patients in the severe group than in those in the mild group ($P < 0.05$). The basophil count was significantly lower in patients in the severe group than in those in the mild group ($P < 0.05$). No significant differences were observed between the two groups in terms of sex, age, prodromal events, time from first symptom to consultation, and white blood cell, platelet, monocyte, lymphocyte, or eosinophil counts (Table 2).

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Table 2 Clinical Data of Patients in the Mild and Severe Groups

	Mild Group (CASE ≤4)	Severe Group (CASE ≥5)	P
Female, n (%)	19 (45.24)	4 (20)	0.090
Age, years	32 (12.75–47.25)	34 (16.50–50.50)	0.657
Prodromal events, n (%)	16 (38.10)	3 (15)	0.082
Time from first symptom to consultation, days	4 (1–10)	2 (0–5.75)	0.112
White blood cells, 10^9/L	7.16 (5.14–9.25)	8.49 (6.39–9.26)	0.285
Platelets, 10^9/L	262.98±13.51	254.40±18.04	0.713
Neutrophils, 10^9/L	4.31 (2.89–6.54)	5.89 (4.03–7.60)	**0.027**
Monocytes, 10^9/L	0.49 (0.36–0.65)	0.51 (0.34–0.65)	0.982
Lymphocytes, 10^9/L	1.66 (1.06–2.17)	1.15 (0.72–1.86)	0.058
Eosinophils, 10^9/L	0.09 (0.04–0.12)	0.07 (0.01–0.17)	0.502
Basophils, 10^9/L	0.02 (0.01–0.04)	0.01 (0–0.03)	**0.029**
NLR	2.78 (1.50–4.67)	5 (3.23–9.34)	**0.004**
MLR	0.27 (0.20–0.45)	0.43 (0.26–0.74)	**0.044**
PLR	143.29 (111.55–211.04)	193.18 (125.53–377.45)	**0.049**
SII	646.02 (390.94–1077.23)	1228.03 (683.67–2729.92)	**0.010**

Notes: Continuous data were presented as mean ± standard deviation or as median (interquartile range), and categorical data were presented as frequency (%). Bold values were that the differences were significant (P<0.05).
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; CASE, the Clinical Assessment Scale for Autoimmune Encephalitis.

Correlations of the NLR, MLR, PLR, and SII with the Severity of GFAP-A

As shown in Figure 2, the NLR, MLR, and SII were positively correlated with the CASE score of patients with GFAP-A (r=0.365, P=0.003; r=0.283, P=0.026; r=0.313, P=0.013), while no significant correlation was observed between the PLR and the CASE score (r=0.236, P=0.064).

The Predictive Value of the NLR, MLR, PLR, and SII for the Severity of GFAP-A

Figure 3 showed ROC curves of the NLR, MLR, PLR, and SII to predict the severity of GFAP-A. The optimal cut-off value of the NLR for predicting the severity of GFAP-A was 3.05, with a sensitivity of 80%, specificity of 57.1%, and AUC of 0.729 (95% Confidence Interval/CI: 0.600–0.858, P=0.004). The optimal cut-off value of the MLR for predicting the severity of GFAP-A was 0.35, with a sensitivity of 65%, specificity of 66.7%, and AUC of 0.66 (95% CI: 0.512–0.807, P=0.044). The optimal cut-off value of the PLR for predicting the severity of GFAP-A was 176.34, with a sensitivity of 65%, specificity of 73.8%, and AUC of 0.656 (95% CI: 0.504–0.808, P=0.049). The optimal cut-off value of the SII for predicting the severity of GFAP-A was 1055.43, with a sensitivity of 60%, specificity of 76.2%, and AUC of 0.702 (95% CI: 0.563–0.841, P=0.01). Details of the AUC, optimal cut-off, sensitivity, and specificity were shown in Table 3.

The NLR as an Independent Risk Factor for the Severity of GFAP-A

The neutrophil, lymphocyte, and basophil counts, and the NLR, MLR, and SII were correlated with the GFAP-A severity (P <0.05) (Table 4). The NLR (Odds Ratio/OR=1.238, 95% CI: 1.003–1.473, P=0.01) was identified as an independent risk factor for the severity of GFAP-A (Table 4).

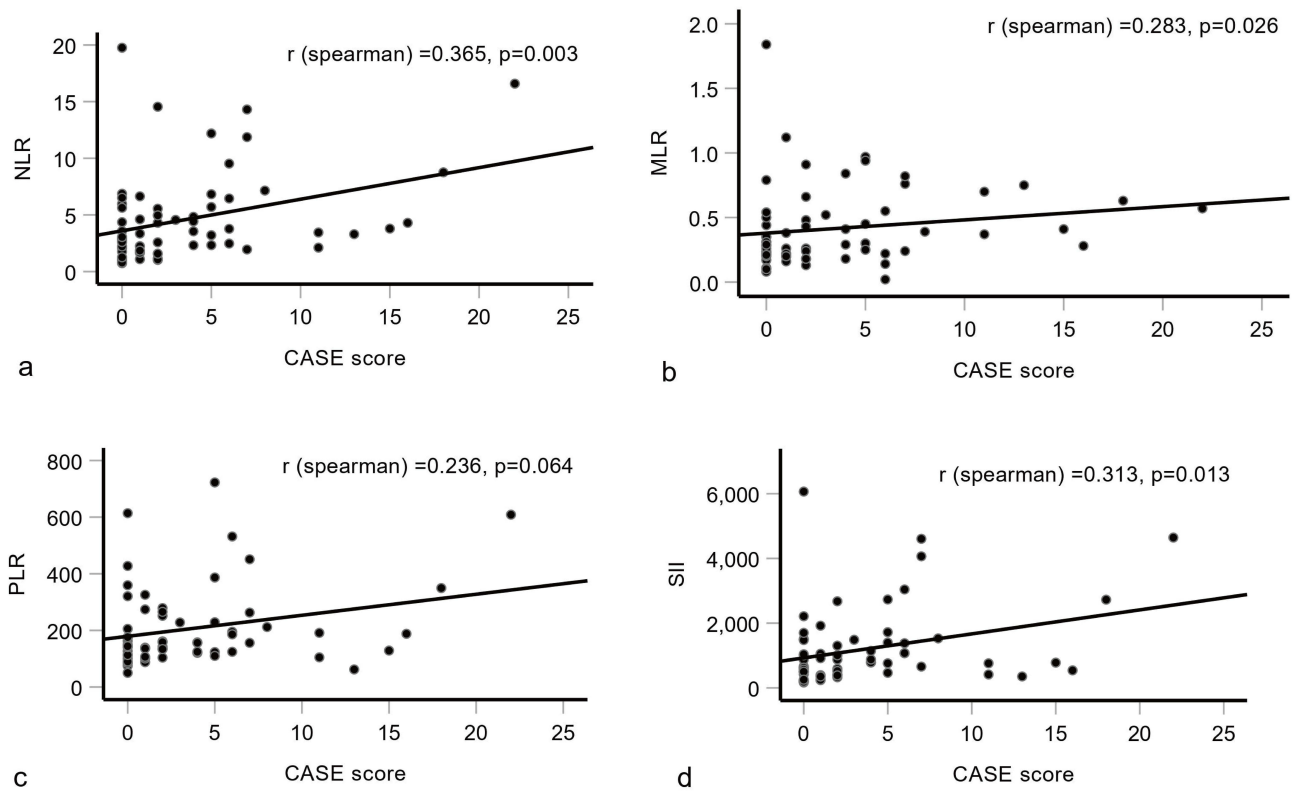

Figure 2 Correlations of the NLR, MLR, PLR, and SII with the CASE score (**a**–**d**).
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; CASE, the Clinical Assessment Scale for Autoimmune Encephalitis.

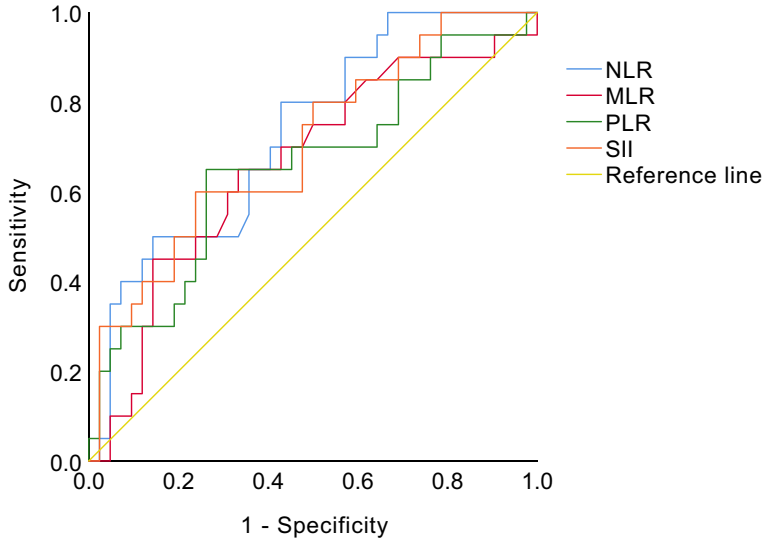

Figure 3 ROC curves of the NLR, MLR, PLR, and SII for predicting the severity of GFAP-A.
Abbreviations: ROC, receiver operating characteristic; GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index.

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Table 3 The Predictive Value of the NLR, MLR, PLR, and SII for the Severity of GFAP-A

	AUC	95% CI	Cut-off	Sensitivity	Specificity	P
NLR	0.729	0.600–0.858	3.050	0.800	0.571	**0.004**
MLR	0.660	0.512–0.807	0.350	0.650	0.667	**0.044**
PLR	0.656	0.504–0.808	176.340	0.650	0.738	**0.049**
SII	0.702	0.563–0.841	1055.430	0.600	0.762	**0.010**

Note: Bold values were that the differences were significant (P<0.05).
Abbreviations: GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; AUC, the area under the curve; CI, confidence interval.

Table 4 Binary Logistic Regression Analysis of Factors Related to the Severity of GFAP-A

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Neutrophils	1.312 (1.025–1.680)	**0.031**	1.658 (0.953–2.882)	0.073
Lymphocytes	0.427 (0.191–0.951)	**0.037**	0.474 (0.130–1.729)	0.258
Basophils	0.001 (0–0.054)	**0.035**	0.001 (0–21.416)	0.395
NLR	1.191 (1.026–1.381)	**0.022**	1.238 (1.003–1.473)	**0.010**
PLR	1.004 (1.000–1.008)	**0.034**	1.006 (0.994–1.019)	0.297
SII	1.001 (1.000–1.001)	**0.028**	0.999 (0.997–1.001)	0.592

Note: Bold values were that the differences were significant (P<0.05).
Abbreviations: GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; OR, odds ratio; CI, confidence interval.

The mRS Score at Discharge as an Independent Risk Factor for the Poor Prognosis One year After Discharge of GFAP-A

Among the 62 patients included in this study, 12 were followed up for less than 1 year, and two were lost to follow-up; therefore, these 14 patients were excluded from the follow-up analysis. The remaining 48 patients were grouped according to the mRS score at 1-year follow-up (one year after discharge). Forty-one patients were included in the good prognosis group (85.42%) and seven patients were included in the poor prognosis group (14.58%). The need for mechanical ventilation, ICU treatment, length of hospitalization, CASE score at admission and at the worst condition, and mRS score at discharge were associated with a poor prognosis one year after discharge (P <0.05) (Table 5). The mRS score at discharge (OR=7.966, 95% CI: 1.120–56.658; P=0.038) was identified as an independent risk factor for the poor prognosis one year after discharge of patients with GFAP-A (Table 6).

Changes in the NLR, MLR, PLR, and SII After Administration of Immunotherapy

Routine blood examination results during follow-up were available for 32 patients, including 27 with a good prognosis and five with a poor prognosis. The NLR, MLR, and SII were not significantly different before and after immunotherapy (P >0.05); however, the PLR was significantly reduced after immunotherapy (153.01 vs 121.16, P=0.039) (Table 7).

Table 5 Univariate Logistic Regression Analysis of Factors Associated with a Poor Prognosis in GFAP-A

	OR (95% CI)	P
Sex	0.900 (0.188–4.304)	0.895
Age	1.005 (0.966–1.046)	0.793
Prodromal events	0.879 (0.154–5.028)	0.885
Time from first symptom to consultation	0.965 (0.865–1.076)	0.524
Time from first symptom to diagnosis	1.000 (0.974–1.027)	0.993
Mechanical ventilation	19 (2.609–138.383)	**0.004**
ICU Treatment	12.923 (1.408–118.612)	**0.024**
Length of hospitalization	1.078 (1.009–1.153)	**0.027**
CASE at admission	1.215 (1.052–1.403)	**0.008**
CASE at the worst condition	1.199 (1.062–1.353)	**0.003**
mRS at discharge	3.540 (1.600–7.836)	**0.002**
White blood cells	0.955 (0.715–1.276)	0.756
Platelets	0.998 (0.989–1.007)	0.641
Neutrophils	1.064 (0.802–1.412)	0.666
Monocytes	0.321 (0.017–5.959)	0.446
Lymphocytes	0.417 (0.128–1.356)	0.146
Eosinophils	0.002 (0–58.088)	0.238
NLR	1.162 (0.995–1.357)	0.057
MLR	2.999 (0.385–23.375)	0.295
PLR	1.004 (1.000–1.009)	0.055
SII	1.000 (1.000–1.001)	0.149

Note: Bold values were that the differences were significant (P<0.05).

Abbreviations: GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; CASE, the Clinical Assessment Scale for Autoimmune Encephalitis; mRS, the modified Rankin Scale; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

Twenty-four patients had a reduced PLR after immunotherapy. However, a decrease in the PLR after immunotherapy was not correlated with the prognosis of patients with GFAP-A (P=0.779).

Discussion

GFAP-A is a novel autoimmune inflammatory disease of the CNS associated with antibodies to GFAP. Meningitis, encephalitis, myelitis, optic neuritis, or a combination of these serve as the main clinical manifestation, and the typical imaging feature is perivascular linear radiolucent enhancement perpendicular to the ventricle of the brain.[5,6] Most patients with GFAP-A respond well to treatment such as steroid hormones, intravenous immunoglobulin, plasma exchange, immunosuppressants, and monoclonal antibodies and have a good prognosis; however, some patients relapse, and the disease may progress to residual dysfunction or death.[6,25] In the current study, the majority of patients with GFAP-A were middle-aged, and the number of male patients was higher than the number of female patients. These

Table 6 Multivariate Logistic Regression Analysis of Factors Associated with a Poor Prognosis in GFAP-A

	OR (95% CI)	P
Mechanical ventilation	452.128 (0.035–5,886,952.793)	0.206
ICU Treatment	22.835 (0.834–625.293)	0.064
Length of hospitalization	1.144 (0.966–1.355)	0.119
CASE at admission	0.888 (0.544–1.451)	0.636
CASE at the worst condition	0.728 (0.356–1.489)	0.384
mRS at discharge	7.966 (1.120–56.658)	**0.038**

Note: Bold value was that the difference was significant (P<0.05).
Abbreviations: GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; CASE, the Clinical Assessment Scale for Autoimmune Encephalitis; mRS, the modified Rankin Scale; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

Table 7 The NLR, MLR, PLR, and SII Before and After Immunotherapy in GFAP-A

	GFAP-A	Good Prognosis (mRS≤2)	Poor Prognosis (mRS≥3)	P_1*	P_2*
NLR before immunotherapy	3.78 (2.25–6.59)	3.57 (1.58–5.97)	8.76 (3.67–15.57)	0.052	
NLR after immunotherapy	3.64 (1.71–5.62)	3.55 (1.87–5.40)	5.69 (1.39–10.31)	0.622	0.702
NLR decreased after immunotherapy, n (%)	17 (53.13)	12 (44.44)	5 (100)	**0.046**	
MLR before immunotherapy	0.31 (0.19–0.62)	0.29 (0.18–0.55)	0.57 (0.30–0.77)	0.253	
MLR after immunotherapy	0.32 (0.18–0.43)	0.31 (0.17–0.37)	0.38 (0.18–1.04)	0.499	0.386
MLR decreased after immunotherapy, n (%)	18 (56.25)	14 (51.85)	4 (80)	0.355	
PLR before immunotherapy	153.01 (121.67–277.63)	144.24 (113.28–228.79)	278.79 (142.53–479.07)	0.139	
PLR after immunotherapy	121.16 (90.21–175.09)	120.93 (89.32–153.71)	284.33 (91.01–326.97)	0.253	**0.039**
PLR decreased after immunotherapy, n (%)	24 (75)	20 (74.07)	4 (80)	0.779	
SII before immunotherapy	958.24 (474.65–1517.20)	871.21 (421.40–1400.19)	2676.36 (961.43–3684.99)	**0.040**	
SII after immunotherapy	1055.59 (420.61–1642)	1032.12 (447.93–1628.26)	1390.48 (360.01–4101.79)	0.551	0.968
SII decreased after immunotherapy, n (%)	16 (50)	12 (44.44)	4 (80)	0.333	

Notes: Continuous data were presented as median (interquartile range), and categorical data were presented as frequency (%). Bold values were that the differences were significant (P<0.05). P_1* was obtained by comparing data from the good prognosis group with those from the poor prognosis group. P_2* was obtained by comparing the NLR, MLR, PLR, and SII before and after immunotherapy.
Abbreviations: GFAP-A, autoimmune glial fibrillary acidic protein astrocytopathy; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index; mRS, the modified Rankin Scale.

findings differ from those of previous studies, in which no difference in sex was reported among patients with GFAP-A.[4,6,22] These differing results may be related to racial and economic differences or a result of the insufficient sample size in the current study. Similar to previous studies, patients with GFAP-A presented with fever, headache, ataxia, movement disorders, and autonomic dysfunction in this study.[4,6] Despite the gradual increase in the number of studies regarding

GFAP-A, few studies regarding biological indicators related to the disease severity and patient prognosis have been reported. Objective and inexpensive biological indicators are urgently needed to guide clinical practice.

Neuroinflammation caused by interactions between lymphocytes, monocytes, neutrophils, microglia, and antibodies secreted by plasma cells may be a pathogenetic mechanism of GFAP-A.[6,14–16] Long et al[14] retrospectively analyzed 19 patients with GFAP-A, including four who underwent brain tissue biopsy. The neuropathological results suggested that the inflammatory lesions were mainly infiltrated by T lymphocytes, B lymphocytes, plasma cells, scattered neutrophils, and eosinophils with obvious activation of microglia around the cerebral blood vessels.[14] Yamakawa et al[26] reviewed the neuropathological results at autopsy in two patients with GFAP-A, and reported findings consistent with those reported by Long et al. Iorio et al[15] observed inflammatory changes in the local meningeal tissue infiltrated by macrophages and $CD8^+$ T cells in a meningeal biopsy specimen of a patient with GFAP-A. Neutrophils and monocytes play important roles in the innate immune system. Neutrophils can damage the blood-brain barrier and increase its permeability by releasing a variety of proinflammatory factors, thus promoting the development of autoimmune diseases of the CNS.[27–29] Moreover, neutrophils can induce monocytes to accumulate at the site of inflammation by releasing large amounts of cytokines. Subsequently, monocytes differentiate into macrophages, which play an important role in the formation of antigen-presenting cells and activate lymphocytes to initiate acquired immunity.[28,30,31] T and B lymphocytes are vital members of acquired immunity, and cytotoxic $CD8^+$ T cell-mediated immune responses play an important role in the pathogenesis of GFAP-A.[4,32] In addition, it has been reported that platelets can transmit signals for leukocyte differentiation, migration, and infiltration via the secretion of cytokines, chemokines, and their receptors, thus playing an important role in inflammatory diseases of the CNS, such as MS and MOGAD.[33–36] Platelets can increase the permeability of the blood-brain barrier by promoting neutrophil migration, thereby promoting the progression of neuroinflammation.[37,38] Neutrophils, monocytes, lymphocytes, and platelets are biological indicators derived from routine blood examinations that reflect the inflammatory state of the body. Routine blood examinations are easily performed, clinically accessible, and inexpensive, and can provide a detailed snapshot of the peripheral immune cells. Currently, a single leukocyte subtype count is commonly used for the clinical assessment of the degree of inflammation in the body, which is susceptible to physiological and/or pathological factors. In contrast, the NLR, MLR, PLR, and SII have higher stability and can more accurately assess the inflammatory degree in the body and reflect disease severity.[39]

Monitoring disease progression and the early detection of potentially severe disease are critical for the management of individual patients with GFAP-A, as it can help determine the optimal treatment, such as the need for combination first-line immunotherapy, early use of monoclonal antibodies, or addition of immunosuppressants. However, there is currently no ideal biomarker for predicting the severity and progression of GFAP-A. The NLR, MLR, PLR, and SII are related to the severity, activity, and prognosis of several autoimmune diseases of the CNS. A study of 199 patients with AE reported that the NLR and MLR were significantly increased in patients with severe AE, and a high NLR and MLR were independent risk factors for patients with severe AE, though they were not associated with patient prognosis.[17] In contrast to the conclusions of Liu et al, Qiu et al[40] found that a high NLR on admission was correlated with a poor prognosis in patients with AE, which may be due to differences in research methods, sample size, and follow-up times between the studies. Hemond et al[41] found that the NLR and MLR were closely associated with the severity of neurological dysfunction and whole-brain atrophy in patients with MS, and that patients with a high NLR were more likely to relapse.[42] Lin et al[19] reported that a high PLR level was positively correlated with MOGAD activity and relapse and that the PLR can be used to differentiate between MS and NMOSD.[43] Moreover, Mao et al[21] reported that the SII was related to the disease severity and prognosis of patients with AE. No studies regarding the associations of the NLR, MLR, PLR, and SII with GFAP-A have been reported. Therefore, this is the first study to investigate the associations between these inflammatory indices and the severity and prognosis of GFAP-A. In the current study, the NLR (OR=1.238, 95% CI: 1.003–1.473, P=0.01) was identified as an independent risk factor for the severity of GFAP-A and was positively correlated with the CASE score (r=0.365, P=0.003). The optimal cut-off value of the NLR was 3.05, with a sensitivity of 80%, specificity of 57.1%, and AUC of 0.729 (95% CI: 0.600–0.858, P=0.004), which supported the use of the NLR as a predictor of GFAP-A severity. In addition, the NLR, MLR, PLR, and SII measured at admission were not related to the prognosis of GFAP-A (P>0.05). The PLR significantly decreased after immunotherapy (P=0.039), though the reduction in the PLR after immunotherapy was not correlated with the prognosis of GFAP-A (P>0.05). Last,

the mRS score at discharge (OR=7.966, 95% CI: 1.120–56.658; P=0.038) was identified as an independent risk factor for the poor prognosis one year after discharge of patients with GFAP-A. These findings are still in the preliminary stages and require external validation in the future. Our data suggest that an NLR of 3.05 or higher may indicate a severe condition of GFAP-A. For these patients, physicians should optimize clinical treatment decisions as early as possible, such as extending the duration of steroid therapy, combining first-line immunotherapy, or starting second-line immunotherapy early, which may reduce the likelihood of recurrence or residual neurological dysfunction in patients. However, we have not evaluated the correlation between NLR levels and the specific methods and duration of immunotherapy of the patients, and we will further investigate this correlation in the future. Taken together, these results indicate that the NLR is a potential biomarker to predict the severity of GFAP-A and monitor disease progression.

This study is not without limitations. First, it was a small-sample and single-center study, rendering it susceptible to selection bias. Second, this was a retrospective study. The presented data were retrospectively obtained from an electronic medical record system, and the follow-up of most patients was conducted retrospectively, which may lead to information and confounding biases. Therefore, a prospective, multicenter study with a larger sample size is needed to verify the conclusions of the current study. Finally, since tumors, infectious diseases, hematological disorders, and other autoimmune diseases can affect NLR, MLR, PLR, and SII, we excluded patients with these comorbidities. Therefore, the results of this study may not be extrapolated to all patients with GFAP-A.

Conclusion

This is the first study to explore the associations between the NLR and GFAP-A severity. The NLR is a clinically inexpensive, accessible, and widely-available inflammatory marker that is positively associated with the severity of GFAP-A. Therefore, this biomarker can help physicians monitor disease progression and identify patients with severe disease at an early stage, thus allowing for optimal treatment decisions.

Data Sharing Statement

The data that support the results of this study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was performed in line with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2022-KY-0053). Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

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