RESEARCH ARTICLE

The systemic inflammation markers as possible indices for predicting respiratory failure and outcome in patients with myasthenia gravis

Xiaoyu Huang[1,2,]*, Mingming Xu[1,]*, Yingying Wang[1,]*, Zhouao Zhang[1], Fengzhan Li[1], Xiao Chen[1] & Yong Zhang[1] 📵

[1]Department of Neurology, Affiliated Hospital of Xuzhou Medical University, No. 99 Huaihai West Road, Quanshan District, Xuzhou, Jiangsu, China
[2]Department of Neurology, Tianjin Neurological Institute, Tianjin Medical University General Hospital, Tianjin, China

Correspondence
Yong Zhang, Department of Neurology, Affiliated Hospital of Xuzhou Medical University, No. 99 Huaihai West Road, Quanshan District, Xuzhou, Jiangsu, China.
Tel: +86 51685802193;
Fax: +86 51685802193;
E-mail: zy20037416@163.com

*These authors contributed equally to this work.

Abstract

Objective: This study aimed to explore the relationship between systemic inflammation markers and clinical activity, respiratory failure, and prognosis in patients with myasthenia gravis (MG). **Methods**: One hundred and seventeen MG patients and 120 controls were enrolled in this study. Differences in the four immune-related markers of two groups based on blood cell counts: neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and systemic immune-inflammation index (SII) were measured. The stability of the associations between systemic inflammation markers and respiratory failure in MG patients was confirmed by adjusted logistic regression analysis. Moreover, Kaplan–Meier curve and multivariate COX regression models were applied to assess the factors affecting the outcome of MG. **Results**: NLR, PLR, and SII were higher in MG patients than those in controls and were positively associated with MGFA classification, but not LMR. Adjusted logistic regression analysis showed that PLR was an independent predictor of MG with respiratory failure. The ROC curve demonstrated that PLR showed good sensitivity and specificity for the diagnosis of MG with respiratory failure. Kaplan–Meier curve showed that GMG, positive AchR-Ab, respiratory failure, high NLR, PLR, SII, and IVIg exposure correlated with the risk for poor outcomes in MG patients. The multivariate COX regression models indicated that GMG and high SII was a risk factor for poor outcome of MG. **Interpretation**: The systemic inflammation markers expressed abnormally in MG patients, in which PLR may be an independent predictor of respiratory failure, and high SII and GMG were predictive risk factors for poor outcomes in MG patients.

Introduction

Myasthenia gravis (MG) is an autoimmune disease mediated by antibodies attacking the postsynaptic membrane, which leads to neuromuscular junction transmission dysfunction.[1] The clinical characteristics of this disease are fluctuating skeletal muscle fatigue and weakness that can be aggravated by activity, but these clinical features can vary.[2] Currently, acetylcholine receptor (AChR) antibodies, muscle-specific receptor tyrosine kinase (MuSK) antibodies, and low-density lipoprotein receptor-related protein 4 (LRP4) antibodies are considered the most sensitive and specific pathogenic factors leading to the onset of MG.[3] Although the etiology of MG is unknown, inflammation has been considered a key component of MG pathogenesis.[4,5] Under the microenvironment of MG, inflammatory factors express abnormally, which eventually enhances B cell activation and contributes to autoantibody production.[6] At present, the treatment of MG aims at reducing inflammation and neutralizing antibodies, but the therapeutic response often varies.[7] Therefore, precise monitoring of inflammatory activity is crucial for customizing the therapeutic strategy.

The systemic inflammation markers based on blood cell counts include NLR, PLR, LMR, and SII.[8] These indices have been reported as systemic inflammatory response biomarkers playing important roles in various autoimmune diseases.[9–11] NLR is the ratio of the number of neutrophils to lymphocytes from the circulating blood cells. Previous studies have described the association between NLR and neuroimmunology diseases.[11–13] As a useful inflammatory marker, NLR has been applied to evaluate the severity and prognosis of different diseases.[10,11,14] PLR is the ratio of platelet count to lymphocyte count. LMR is calculated with absolute lymphocyte count to monocyte count. Similar to NLR, PLR and LMR are also considered a marker for predicting the severity and prognosis of inflammatory diseases.[10,15,16] SII as a new diagnostic marker was calculated with (platelet × neutrophil)/lymphocyte. Previous study has shown that SII was associated with disease severity and response to immunotherapy in autoimmune encephalitis (AE).[17] Moreover, a recent study has also shown that the SII serves as a reliable assessment tool for the diagnosis and evaluation of disease activity.[18] Although these systemic inflammation markers are widely used to evaluate the severity and prognosis of autoimmune diseases, there is almost no evidence in the literature to clarify the role of NLR, PLR, LMR, or SII in MG.

In the present study, considering the clinical heterogeneity of MG patients, we first explore the relationship between systemic inflammation markers and different clinical subtypes in a large cohort of MG patients. Meanwhile, we also analyzed the predictive value of these inflammatory indicators for respiratory failure and prognosis in MG patients for the first time.

Patients and Methods

Patients

This retrospective study included 225 patients with MG who were diagnosed at the Department of Neurology, Affiliated Hospital of Xuzhou Medical University. Diagnosis of MG was in accord with international guidelines.[19] All patients' data on sex, age, disease duration, antibody type, Myasthenia Gravis Foundation of America classification (MGFA),[20] and MG subtypes including ocular MG (OMG), generalized MG (GMG), early onset MG (EOMG), late-onset MG (LOMG), and thymoma-associated MG (TAMG) was collected from the MG database. Eventually, 117 MG patients were included in this study according to the exclusion criteria. The patients coexisting the following criteria are excluded: (a) patients with incomplete baseline records (b) severe heart, liver, kidney disease, other autoimmune diseases, tumor except

thymoma, thymectomy, or hematologic disease; (c) receive immunosuppressive therapy 3 months before blood routine test. Meanwhile, 120 controls were also enrolled from the physical examination center in our hospital. This study was approved by the Ethics Committee of Affiliated Hospital of Xuzhou Medical University (XYFY2016-KL009, XYFY2019-KL021). This was a retrospective study, patients were not required to provide informed consent.

Laboratory data and the patient follow-up

Complete blood pictures of all participants at admission were measured in the hospital laboratory by standard methods before treatment. Data on the number of white blood cell (WBC), lymphocyte, neutrophil, monocyte and platelet were recorded. NLR was defined as the number of neutrophil to lymphocyte ratio, PLR was defined as the number of platelet to lymphocyte ratio, LMR was defined as the ratio of lymphocyte to monocyte, while SII was calculated with (platelet × neutrophil)/lymphocyte.

Patients with respiratory failure during hospitalization were also collected. Respiratory failure was defined as receiving noninvasive or invasive ventilation or arterial blood gas analysis suggesting that $pH < 7.35$ and $PaCO_2 > 45$ mmHg, or $PaO_2/FiO_2 < 200$.[21] The follow-up started when patients received immunotherapy, up to 24 months or the time achieving good outcome. We usually follow up patients by phone or WeChat every month, and the patients come to our center every 1–3 months for re-examination and evaluation to manage the whole course of MG patients. The prognosis of MG patients was assessed using the MGFA-PIS scale.[19,20] Complete Stable Remission (CSR), Pharmacologic Remission (PR), and Minimal Manifestations (MM) status were considered a good outcome and status below MM was considered a poor outcome.[22]

Statistical analysis

Data were expressed as mean ± SEM or median and interquartile ranges. Categorical variables were analyzed by chi-squared tests. Independent sample *t* test or or one-way ANOVA normal was used for normal distribution data. Mann–Whitney *U* tests or Kruskal–Wallis test was used for skewness distribution data. Spearman's correlation analysis was used to evaluate the relationship between NLR, PLR, LMR, and SII and MGFA classification. Adjusted logistic regression analysis and ROC curve were used to evaluate the risk factors of respiratory failure in MG. Probability curves for poor outcomes were estimated using the Kaplan–Meier method with a log-rank test. COX regression models were used to assess relative

risk. All statistical data were analyzed with SPSS software (version 19, SPSS, Chicago, IL) and Graphpad Prism 8.0 (Graphpad Software, La Jolla, CA). $P < 0.05$ was considered significant.

Results

Patient characteristics and laboratory data

Two hundred and twenty-five MG patients were screened according to the exclusion criteria, and 117 MG patients were eventually enrolled in this study. After the long-term follow-up, 90 patients completed follow-up information (Fig. 1). The detailed characteristics of MG patients are summarized in Table 1. Among these individuals, the clinical subtypes of MG patients include 31 EOMG and 86 LOMG patients, 58 OMG and 59 GMG patients, 37 TAMG and 80 non-TAMG patients, 112 AchR-Ab positive MG and 5 AchR-Ab negative MG patients, and the distribution of the MG patients in different MGFA classification categories at admission (I:II:III:IV:V) was 58:22:16:13:8. No differences were observed in age, gender, and monocyte counts between the HC and MG patients ($P > 0.05$). However, WBC, neutrophils, platelets, NLR，PLR, and SII were higher in MG than in HC ($P < 0.05$), but lymphocytes and LMR were lower in MG than in HC ($P < 0.05$).

Correlations of NLR, PLR, LMR, and SII with different disease subtypes in MG patients

Our study showed that NLR and SII in OMG and GMG patients were significantly higher than those in HC ($P < 0.001$, Fig. 2A1,D1), but no difference was observed between OMG and GMG ($P > 0.05$, Fig. 2A1,D1). PLR and LMR in OMG and GMG patients had no difference ($P > 0.05$, Fig. 2B1,C1), but PLR in GMG was higher than HC ($P < 0.001$, Fig. 2B1) and LMR in GMG was lower than HC ($P < 0.01$, Fig. 2C1). NLR and SII in EOMG and LOMG patients were higher than those in HC ($P < 0.05$, Fig. 2A2,D2), but NLR and SII showed no significant difference between EOMG and LOMG ($P > 0.05$, Fig. 2A2,D2). PLR and LMR in EOMG and LOMG patients had no difference ($P > 0.05$, Fig. 2B2, D2), but PLR in GMG was higher than HC and LMR in GMG was lower than HC ($P < 0.01$, Fig. 2B2,D2). NLR, PLR, and SII in non-TAMG and TAMG patients were higher than those in HC ($P < 0.05$, Fig. 2A3,B3,D3), but NLR, PLR, and SII showed no significant difference between non-TAMG and TAMG ($P > 0.05$, Fig. 2A3,B3,
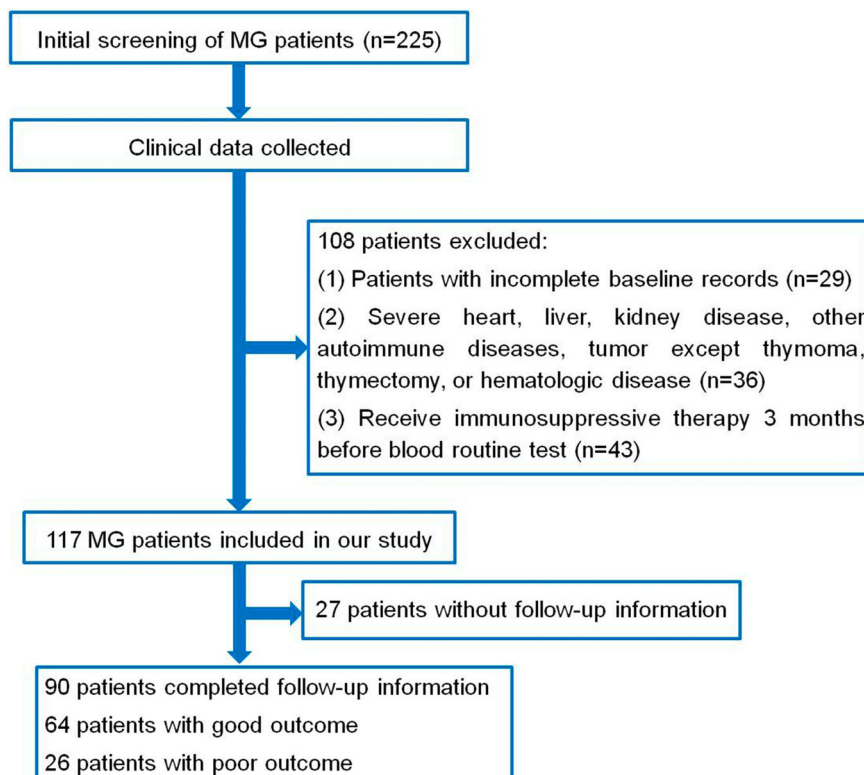


```
Initial screening of MG patients (n=225)
            │
            ▼
Clinical data collected
            │
            │──────▶ 108 patients excluded:
            │        (1) Patients with incomplete baseline records (n=29)
            │        (2) Severe heart, liver, kidney disease, other
            │            autoimmune diseases, tumor except thymoma,
            │            thymectomy, or hematologic disease (n=36)
            │        (3) Receive immunosuppressive therapy 3 months
            │            before blood routine test (n=43)
            ▼
117 MG patients included in our study
            │
            │──────▶ 27 patients without follow-up information
            ▼
90 patients completed follow-up information
64 patients with good outcome
26 patients with poor outcome
```

Figure 1. Flowchart of the study.

Table 1. Characteristics of MG patients and controls.

Characteristics	Controls (n = 120)	MG (n = 117)	t/z/χ2	P
Age, years	54 (49.00, 62.00)	58 (49.50, 69.00)	−1.918	0.055
Sex, n (%)			0.007	0.931
Female	66 (55.00)	65 (55.56)		
Male	54 (45.00)	52 (44.44)		
Age of onset, n (%)				
EOMG (age<50 years)		31 (26.50)		
LOMG (age ≥ 50 years)		86 (73.50)		
Type, n (%)				
OMG		58 (49.57)		
GMG		59 (50.43)		
MGFA at admission, n				
I:II:III:IV:V		58:22:16:13:8		
Worst MGFA during hospitalization, n				
I:II:III:IV:V		58:20:15:3:21		
Thymoma, n (%)				
Without		80 (68.38)		
With		37 (31.62)		
AchR-Ab, n (%)				
Positive, n (%)		112 (95.73)		
Negative, n (%)		5 (4.27)		
WBC ($\times 10^9$/L)	5.65 (4.90, 6.80)	6.70 (5.40, 8.90)	−4.701	0.000
Neutrophils ($\times 10^9$/L)	3.25 (2.56, 4.01)	4.19 (3.36, 5.75)	−5.903	0.000
Lymphocytes ($\times 10^9$/L)	1.85 (1.60, 2.30)	1.80 (1.40, 2.20)	−2.078	0.038
Plateles ($\times 10^9$/L)	218.15 ± 44.93	234.62 ± 53.21	−2.578	0.011
Monocyte ($\times 10^9$/L)	0.34 (0.30, 0.43)	0.38 (0.28, 0.53)	−1.739	0.082
NLR	1.70 (1.37, 2.04)	2.22 (1.73, 3.78)	−5.829	0.000
PLR	110.91 (91.51, 137.84)	133.13 (97.63, 179.67)	−3.516	0.000
LMR	5.31 (4.63, 6.97)	4.85 (3.62, 5.94)	−3.093	0.002
SII	378.25 (285.35, 452.72)	501.60 (347.74, 917.13)	−6.108	0.000

EOMG, early onset myasthenia gravis; LOMG, late-onset myasthenia gravis; OMG, ocular myasthenia gravis; GMG, generalized myasthenia gravis; MGFA, Foundation of America Clinical Classification; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index.

D3). LMR in non-TAMG and TAMG patients had no difference ($P > 0.05$, Fig. 2C3), but LMR in non-TAMG was lower than in HC ($P < 0.01$, Fig. 2C3). NLR, PLR, SII, and LMR in male and female MG patients had no difference ($P > 0.05$, Fig. 2A4–D4), while NLR and SII in male and female MG patients were higher than those in HC ($P < 0.01$, Fig. 2A4,D4), PLR in female MG patients were higher than in HC ($P < 0.001$, Fig. 2B4), and LMR in male MG patients were lower than in HC ($P < 0.01$, Fig. 2C4). NLR, PLR, SII, and LMR in AchR-Ab-positive and AchR-Ab-negative MG patients had no difference ($P > 0.05$, Fig. 2A5–D5), while NLR, PLR, and SII in AchR-Ab-positive MG patients were higher than in HC

($P < 0.01$, Fig. 2A5–C5), and LMR in AchR-Ab-positive MG patients were lower than in HC ($P < 0.01$, Fig. 2C5).

Correlations of NLR, PLR, LMR, and SII with MGFA classification at admission in MG patients

Spearman's correlation analysis showed that NLR, PLR, and SII were positively correlated with MGFA classification at admission ($r_s = 0.280$, $P = 0.002$; $r_s = 0.287$, $P = 0.002$; $r_s = 0.311$, $P = 0.001$, Fig. 3A,B,D) and LMR was negatively correlated with MGFA classification at admission ($r_s = -0.185$, $P = 0.047$, Fig. 3C).

Figure 2. Correlations of NLR, PLR, SII, and LMR with different disease subtypes in MG patients. (A1–D1) NLR, PLR, SII, and LMR among the HC, OMG, and GMG. (A2–D2) NLR, PLR, SII, and LMR among the HC, EOMG, and LOMG. (A3–D3) NLR, PLR, SII, and LMR among the HC, non-TAMG, and TAMG. (A4–D4) NLR, PLR, SII, and LMR among the HC, male MG, and female MG. (A5–D5) NLR, PLR, SII, and LMR among the HC, AchR-Ab+MG, and AchR-Ab-MG.
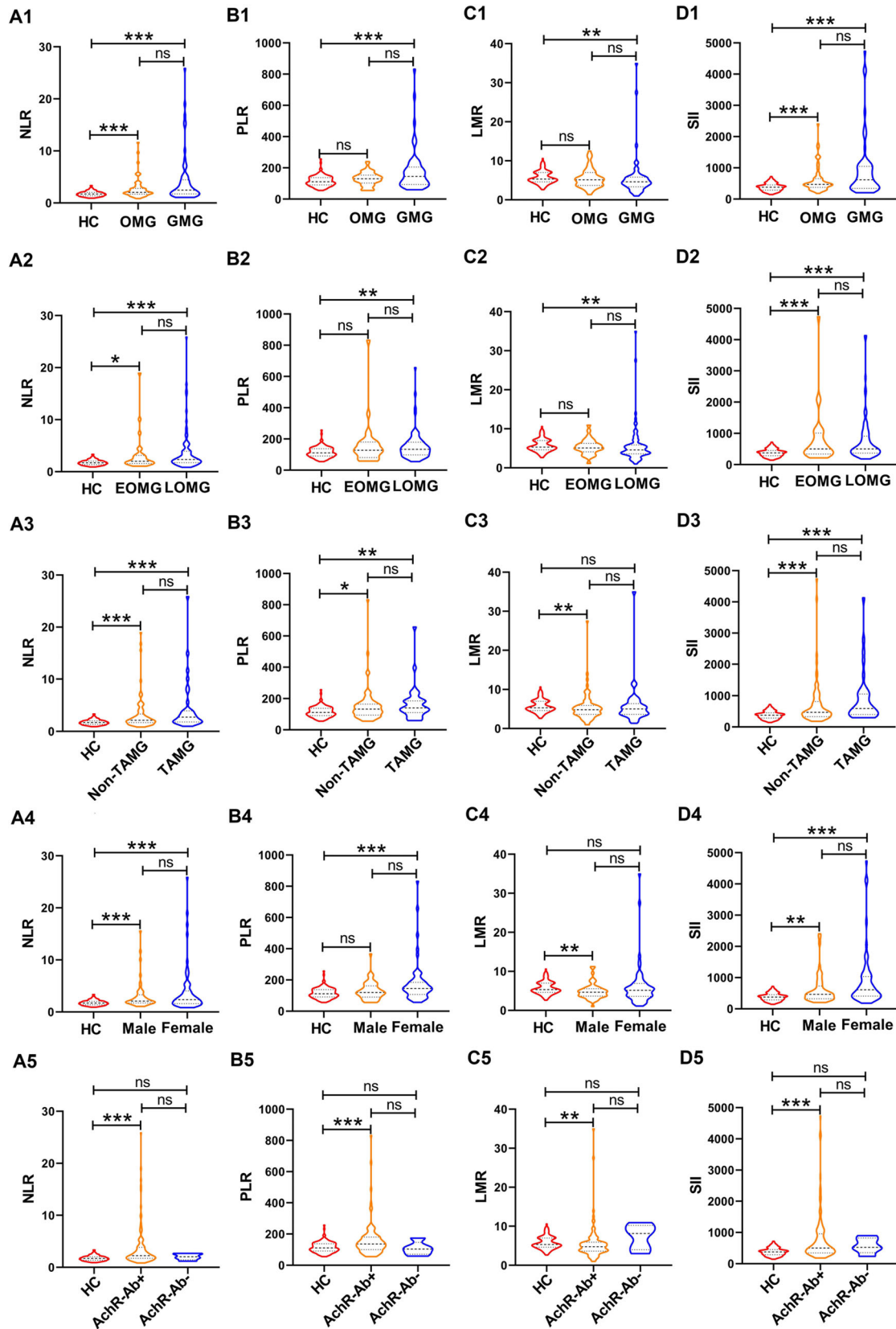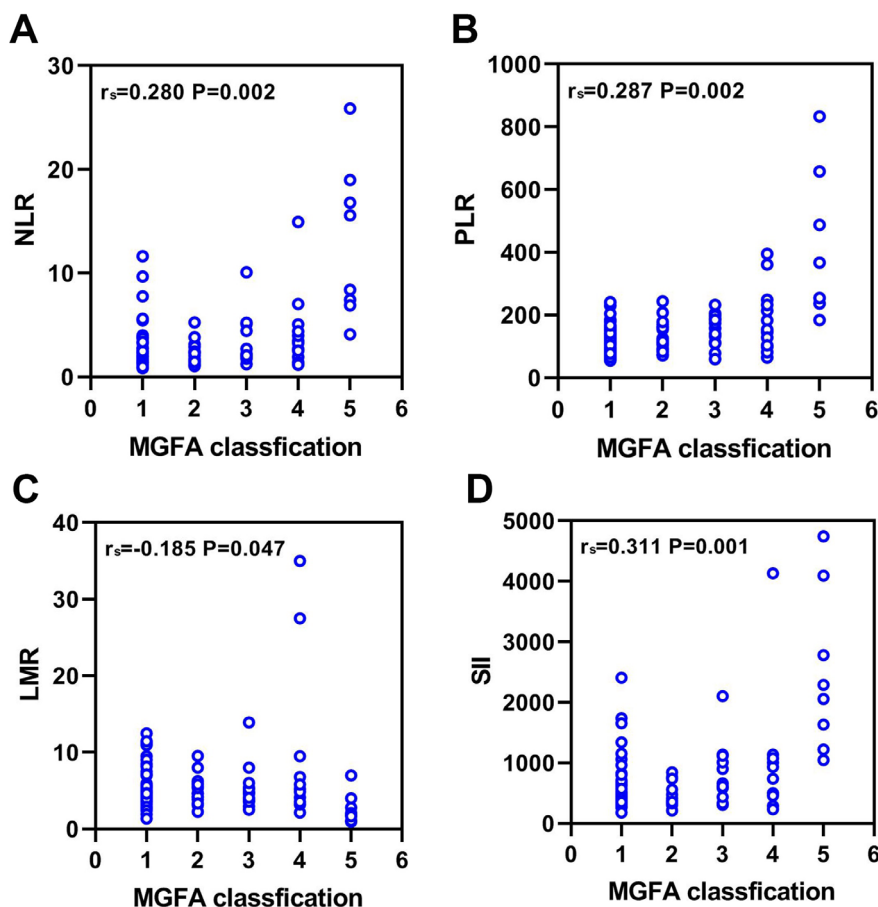
Figure 3. Correlations of NLR, PLR, LMR, and SII with MGFA classification in MG patients. (A–D) Spearman's correlation analysis between NLR, PLR, LMR, and SII and MGFA classification in MG patients.

Predictive factors for respiratory failure in MG patients

Among 117 patients with MG, 8 patients with MGFA Class V have emerged respiratory failure at the beginning of hospitalization, and 13 patients (2 with MGFA Class III and 11 with MGFA Class IV) were in disease progression, the severity of respiratory failure was not reached at admission, but the condition became worse and respiratory failure occurred during hospitalization. Eventually, 21 patients (17.9%) experienced respiratory failure during hospitalization. NLR, PLR, and SII in MG patients with respiratory failure were significantly higher than those in nonrespiratory failure ($P < 0.001$, Table 2). LMR in MG patients with respiratory failure and nonrespiratory failure had no difference ($P > 0.05$, Table 2). To further assess the association of NLR, PLR, and SII with respiratory failure, we employed a model of logistic regression. The unadjusted model demonstrated that PLR and SII were associated with respiratory failure ($P < 0.01$, Table 3). We then adjusted multiple confounders (age, sex, EOMG/LOMG, thymoma, antibody category, and respiratory infection), adjusted model showed that PLR was an independent predictor for predicting respiratory failure after MG ($P < 0.05$, Table 3). According to the ROC curve, PLR with a cut-off value of 181.91 and an area under the curve (AUC) of 0.838 indicated sensitivity (71.4%), specificity (88.5%), positive predictive value (57.7%), and negative predictive value (93.4%) for the diagnosis of MG with respiratory failure (Fig. 4, Table 4).

Predictive factors for outcome in MG patients

Among the 90 MG patients who completed the follow-up, 64 had a good outcome and 26 had a poor outcome, and the mean follow-up time was 13.89 ± 7.76 months. NLR, PLR, and SII in MG patients with poor outcomes were significantly higher than those in the good outcome group ($P < 0.001$, Table 5). LMR in MG patients with poor outcome was lower than those in the good outcome group ($P < 0.01$, Table 5). Given that no unified laboratory reference value, NLR, PLR, LMR, and SII used to identify MG patients with the good or poor outcome

Table 2. Characteristics of respiratory failure and non-respiratory failure groups in MG patients.

Characteristics	Respirator failure (*n* = 21)	Non-respiratory failure (*n* = 96)	$z/t/\chi^2$	*P*
Age, years	52.19 ± 16.01	58.85 ± 14.81	1.840	0.068
Sex, *n* (%)			6.686	0.010
Male	4 (19.00)	48 (50.00)		
Female	17 (81.00)	48 (50.00)		
Age of onset, *n* (%)			5.864	0.015
EOMG (age<50 years)	10 (47.62)	21 (21.88)		
LOMG (age ≥ 50 years)	11 (52.38)	75 (78.12)		
Type, *n* (%)			25.160	0.000
OMG	0 (0.00)	58 (60.42)		
GMG	21 (100.00)	38 (39.58)		
Worst MGFA during hospitalization, *n* (%)				
I	0 (0.00)	58 (60.42)		
II	0 (0.00)	20 (22.92)		
III	0 (0.00)	15 (14.58)		
IV	0 (0.00)	3 (2.08)		
V	21 (100.00)	0 (0.00)		
Thymoma, *n* (%)			0.035	0.852
Without	14 (66.70)	66 (68.80)		
With	7 (33.30)	30 (31.20)		
AchR-Ab, *n* (%)			1.725	0.189
Positive, *n* (%)	19 (90.50)	93 (96.90)		
Negative, *n* (%)	2 (9.50)	3 (3.10)		
Respiratory infection, *n* (%)	9 (42.86)	19 (19.79)	5.165	0.023
NLR	5.06 (3.38, 12.50)	2.04 (1.67, 2.76)	−4.965	0.000
PLR	232.22 (149.63, 364.31)	123.61 (90.44, 159.11)	−4.840	0.000
LMR	4.94 (2.07, 6.40)	4.00 (3.76, 5.93)	−1.634	0.102
SII	1137.01 (1008.07, 2196.73)	466.57 (333.33, 6 59.26)	−5.355	0.000

EOMG, early onset myasthenia gravis; LOMG, late-onset myasthenia gravis; OMG, ocular myasthenia gravis; GMG, generalized myasthenia gravis; MGFA, Foundation of America Clinical Classification; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index.

Table 3. Adjusted logistic regression models for the association of NLR, PLR, and SII with respiratory failure in MG patients.

	Unadjusted model		Adjusted model*	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
NLR	0.772 (0.535–1.116)	0.169	0.744 (0.352–1.572)	0.744
PLR	1.017 (1.005–1.030)	0.007	1.026 (1.003–1.049)	0.026
SII	1.003 (1.001–1.005)	0.005	1.004 (1.000–1.007)	0.066

*Adjusted for age, sex, EOMG/LOMG, thymoma, antibody category, and respiratory infection.
OR, odds ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

were limited. Hence, we determined the cutoff values of NLR, PLR, LMR, and SII by the ROC analysis (Fig. 5A). In Table S1, the AUC of NLR, PLR, LMR, and SII were 0.762, 0.753, 0.298, and 0.785. Due to the AUC of LMR

was less than 0.50, we did not include LMR in the following analysis. The optimal cutoff values were 3.10, 140.28, and 948.01 for NLR, PLR, and SII respectively. The highest sensitivity and specificity were 0.730 and 0.828, 0.846 and 0.656, 0.692 and 0.891, and the positive and negative predictive values were 0.633 and 0.883, 0.500 and 0.913, 0.720 and 0.877 for NLR, PLR, and SII respectively (see Table S1).

To identify independent clinical factors associated with outcome, age of onset, sex, OMG/GMG, antibody type, thymoma, respiratory failure, NLR, PLR, SII, glucocorticoid, immunosuppressant, rituximab, and IVIg exposure were analyzed by the Kaplan–Meier curve (Fig. 5B–N). The results showed that GMG, positive AchR-Ab, respiratory failure, high NLR, PLR and SII, and IVIg exposure correlated with the risk for poor outcome in MG patients (Fig. 5D,E,G,H,I,J,N). The multivariate COX regression models indicated that GMG (HR 2.176, 95% CI 1.188–3.985) and high SII (HR 3.834, 95% CI 1.047–14.035) were risk factors for poor outcome of MG (Table 6).

Figure 4. ROC curve was used to evaluate the accuracy of PLR to predict respiratory failure in MG patients.
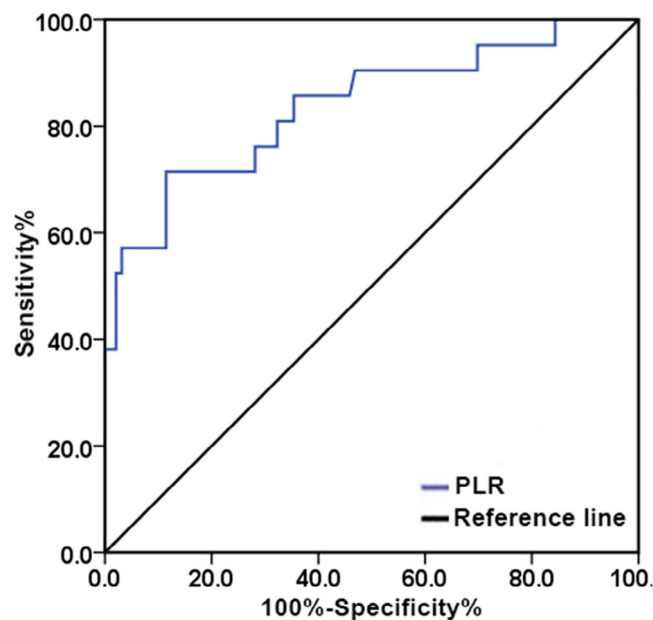

Table 4. Diagnostic value of PLR in MG patients with respiratory failure.

Characteristics	AUC	95% CI	Cut-off value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	P
PLR	0.838	0.731–0.945	181.91	0.714	0.885	0.577	0.934	0.000

AUC, area under the curve; CI, confidence interval; PLR, platelet-to-lymphocyte ratio.

Discussion

The systemic inflammation markers as easily available biomarkers have been reported as highly sensitive measures of inflammation in several autoimmune diseases.[10,23] However, the role of NLR, PLR, LMR, and SII in MG was seldom investigated. In our study, we first reported that NLR, PLR, and SII were significantly higher in MG patients. Moreover, the rise in NLR, PLR, and SII was positively associated with increasing MGFA classification grade. Another important finding was that PLR can indicate risk of respiratory failure in MG patients. Besides, GMG and high SII were independent risk factors for poor outcomes in MG patients.

Under systemic inflammation, WBC and subtype counts will undergo relative changes, which has a vital role in inflammatory diseases.[24] It is common knowledge that neutrophils, as the most abundant type of WBC, represent the part of the innate system.[25] When responding to a microbial invasion, activated neutrophils can release oxygen-free adicals, lytic enzymes, and cytokines, all of which promote the inflammatory response.[26] More importantly, it is known that neutrophil-derived cytokines are closely related to the pathogenesis of MG.[26,27] Besides,

neutrophils participate in the activation, regulation, and effector functions of immune cells, which has caused a renewed interest in their role in autoimmune disease.[28] Lymphocytes usually represent the status of the adaptive system. When inflammation occurs, the number of peripheral lymphocytes usually shows a low level.[29] Moreover, evidence has shown that lymphocyte subset derangment is the trigger factor of MG development, which can be used as an "alarm signal" to reflect the inflammatory state of MG patients.[30] Platelets and monocytes also have regulatory effects on the immune system, which considered as a pro-inflammatory duplex releasing many different cytokines at sites of inflammation.[31] The stability of NLR, PLR, LMR, and SII was rarely affected by physiological, pathological, and physical factors, so they are generally considered to be superior to the single parameters of neutrophil, lymphocyte, monocyte, or platelet.[9,32,33] Thus, increasing attention has been directed to these inflammation markers to reflect the degree of inflammation.

Consistent with prior work,[34] NLR was also increased in MG patients in our study and correlated with disease severity, as defined by MGFA classification grade. Besides, we newly discovered that the PLR and SII were increased,

Table 5. Characteristics of good and poor outcome in MG patients.

Characteristics	Good outcome (n = 64)	Poor outcome (n = 26)	z/χ²	P
Age, years	58 (48.75, 68.75)	57 (47.50, 66.75)	−0.481	0.631
Sex, n (%)			0.106	0.745
Male	27 (42.19)	10 (38.46)		
Female	37 (57.81)	16 (61.54)		
Age of onset, n (%)			1.631	0.202
EOMG (age<50 years)	16 (25.00)	10 (38.46)		
LOMG (age ≥ 50 years)	48 (75.00)	16 (61.54)		
Type, n (%)			13.846	0.000
OMG	40 (62.50)	5 (19.23)		
GMG	24 (37.50)	21 (80.77)		
Thymoma, n (%)			0.652	0.419
Without	45 (70.31)	16 (61.54)		
With	19 (29.69)	10 (38.46)		
AchR-Ab, n (%)			1.261	0.262
Positive, n (%)	61 (95.31)	26 (100.00)		
Negative, n (%)	3 (4.69)	0 (0.00)		
NLR	2.03 (1.60, 2.76)	4.06 (2.40, 9.77)	−3.886	0.000
PLR	120.32 (86.45, 164.25)	180.84 (145.01, 180.84)	−3.748	0.000
LMR	5.38 (4.12, 6.80)	4.00 (2.76, 4.97)	−2.987	0.003
SII	466.57 (324.44, 637.77)	1099.01 (639.02, 1819.75)	−4.229	0.000
Respiratory failure, n (%)	5 (7.81)	14 (53.85)	23.53	0.000
Treatment, n (%)				
Glucocorticoid	61 (95.31)	25 (96.15)	0.031	0.861
Immunosuppressant	39 (60.94)	18 (69.23)	0.548	0.459
Rituximab	7 (10.94)	4 (15.38)	0.341	0.559
IVIg	8 (12.50)	16 (61.54)	22.736	0.000
Thymectomy	19 (29.69)	10 (38.46)	0.652	0.419

EOMG, early onset myasthenia gravis; LOMG, late-onset myasthenia gravis; OMG, ocular myasthenia gravis; GMG, generalized myasthenia gravis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index.

but LMR decreased in MG patients. Recently, the NLR, PLR, LMR, and SII have drawn wide attention as novel nonspecific inflammatory markers. Jiang et al. showed that it was more economical to use NLR to reflect disease severity and the short-time curative effect of MG in children.[35] Besides, a large number of studies also have demonstrated the value of changes in NLR, PLR, LMR, and SII in assessing the severity and co-infections in autoimmune diseases.[9,16,36] Based on our findings and

above opinions, we have reason to infer that an interaction exists between MG pathogenesis and NLR, PLR, LMR, and SII. Considering the clinical heterogeneity of MG patients and driving personalized medicine, we then analyzed the correlation between NLR, PLR, LMR, and SII and the clinical characteristics of MG for the first time. Our study indicated that disease classification, age of onset, thymoma, sex, and antibody type had no effect on the NLR, PLR, LMR, and SII in MG patients. Interestingly, we found that NLR, PLR, and SII showed an increasing trend with the increase of MGFA classification grade, but not obvious in LRM.

Respiratory failure leading to myasthenia gravis crisis (MC) is still one of the important threats to the public health of MG patients.[37] At present, the first-line therapy for MC includes IVIg and plasma exchange.[38] However, the expensive price and unavailability of plasma exchange and IVIg place a heavy burden on the health system.[39] Therefore, exploring a standard biomarker that can be calculated easily and less costly to predict the occurrence of respiratory failure will contribute to medical resource allocation and clinical decision-making. The previous study has shown that NLR and PLR may be independent predictors of respiratory failure in Guillain-Barré syndrome (GBS).[40] Besides, A recent publication demonstrated that SII may be a novel independent indicator to predict the occurrence of respiratory failure in GBS patients.[41] Then, we also compared the NLR, PLR, and SII in MG patients with respiratory failure and explored the risk factors of respiratory failure in MG patients. Our study indicated that PLR showed good predictive value for the diagnosis of MG with respiratory failure. What is more important, we also observed the factors affecting the prognosis of MG patients. It seems that the disease classification and SII may be a helpful prognostic biomarkers of patients with MG according to our study. As mentioned above, SII reflected the complex interplay and potential synergy among platelets, neutrophils, and lymphocytes systemically.[41] Thereby, compared with NLR and PLR, SII might reflect the interaction between the inflammatory response and immune response more objectively.

Our study has some limitations. First, this was a single-center study and the number of patients included was relatively low. Second, the elimination of patients based on coexistent diseases limits the value of these systemic inflammation markers. Third, if the coexisting immunosuppression is also not considered, the value of these systemic inflammation markers is compromised for the many patients presenting for exacerbations. Fourth, this study was designed from a retrospective view and it would be better to take the prospective plan to find more evidence. Fifth, this study found that predictive values of these systemic inflammation markers were low, which may be due to the small sample size. Later, the large sample size by the multi-
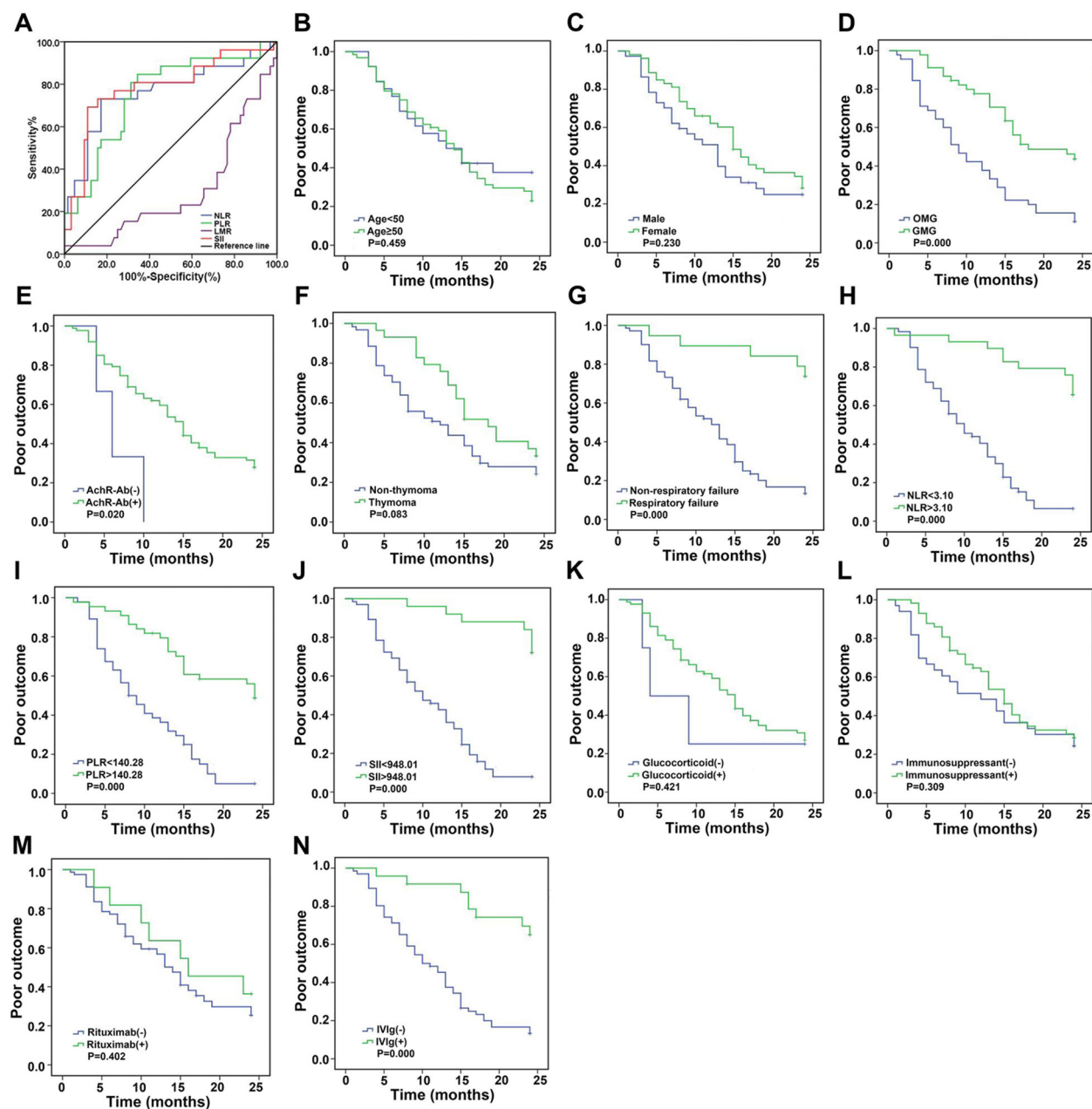
Figure 5. (A) ROC curve was used to evaluate the accuracy of NLR, PLR, LMR, and SII to predict functional outcome in MG patients. (B–N) Kaplan–Meier curves for the age of onset, sex, disease classification, antibody type, thymoma, respiratory failure, NLR, PLR, SII, glucocorticoid, immunosuppressant, rituximab, and IVIg exposure involved in exploring cohort.

center cooperation needs to be carried out to further verify whether these systemic inflammatory markers possess clinical recommendation value.

Conclusions

In conclusion, our study demonstrated that these systemic inflammation markers as easily measurable, available, and cost-effective parameters expressed abnormally in MG patients. PLR may be an independent predictor of respiratory failure, and high SII and GMG were predictive risk factors for poor outcomes in MG patients.

Author Contributions

All authors have made a substantial contribution to the design, data collection, and analysis of the research and the drafting of the manuscript and reviewed and accepted

Table 6. Univariate and multivariate cox regression analysis of clinical factors for predicting the outcome.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age of onset <50 vs. ≥50	0.812	0.461–1.431	0.472			
Sex Male vs. Female	1.344	0.817–2.210	0.245			
Type OMG vs. GMG	2.787	1.672–4.646	0.000	2.176	1.188–3.985	0.012
AchR-Ab (+) vs. (−)	3.635	1.106–11.943	0.033	1.650	0.489–5.564	0.419
Thymoma (+) vs. (−)	1.581	0.924–2.708	0.095			
Respiratory failure (+) vs. (−)	6.550	2.596–16.524	0.000	0.642	0.121–3.416	0.604
NLR <3.10 vs. >3.10	0.764	0.662–0.882	0.000	1.801	0.560–5.791	0.323
PLR <140.28 vs. >140.28	0.991	0.987–0.996	0.000	1.605	0.847–3.042	0.147
SII <948.01 vs. >948.01	0.999	0.998–0.999	0.000	3.834	1.047–14.035	0.042
Glucocorticoid (+) vs. (−)	1.583	0.496–5.056	0.438			
Immunosuppressant (+) vs. (−)	1.289	0.779–2.131	0.323			
Rituximab (+) vs. (−)	1.384	0.631–3.037	0.417			
IVIg (+) vs. (−)	4.932	2.330–10.441	0.000	1.371	0.395–4.756	0.619

HR, hazard ratio; CI, confidence interval; OMG, ocular myasthenia gravis; GMG, generalized myasthenia gravis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Gilhus NE. Myasthenia gravis. N Engl J Med. 2016;375:2570-2581.
2. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016;12:259-268.
3. Mantegazza R, Bernasconi P, Cavalcante P. Myasthenia gravis: from autoantibodies to therapy. Curr Opin Neurol. 2018;31:517-525.

4. Wang Z, Yan Y. Immunopathogenesis in myasthenia gravis and Neuromyelitis Optica. Front Immunol. 2017;8:1785.

5. Uzawa A, Kuwabara S, Suzuki S, et al. Roles of cytokines and T cells in the pathogenesis of myasthenia gravis. Clin Exp Immunol. 2021;203:366-374.

6. Hu Y, Wang J, Rao J, et al. Comparison of peripheral blood B cell subset ratios and B cell-related cytokine levels between ocular and generalized myasthenia gravis. Int Immunopharmacol. 2020;80:106130.

7. Dalakas MC. Immunotherapy in myasthenia gravis in the era of biologics. Nat Rev Neurol. 2019;15:113-124.

8. Nøst TH, Alcala K, Urbarova I, et al. Systemic inflammation markers and cancer incidence in the UK biobank. Eur J Epidemiol. 2021;36:841-848.

9. Qin B, Ma N, Tang Q, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol. 2016;26:372-376.

10. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD. The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med. 2019;39:345-357.

11. Xie H, Zhao Y, Pan C, et al. Association of neutrophil-to-lymphocyte ratio (NLR) with the prognosis of first attack neuromyelitis optica spectrum disorder (NMOSD): a retrospective cohort study. BMC Neurol. 2021;21:389.

12. Akil E, Alp R, Aluclu MU, Acar A, Kaplan I. Serum endocan levels in multiple sclerosis relapse and remission. Eur Rev Med Pharmacol Sci. 2021;25:4091-4098.

13. Huang Y, Ying Z, Quan W, et al. The clinical significance of neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio in Guillain-Barré syndrome. Int J Neurosci. 2018;128:729-735.

14. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504.

15. Zhang MH, Wang H, Wang HG, Wen X, Yang XZ. Effective immune-inflammation index for ulcerative colitis and activity assessments. World J Clin Cases. 2021;9:334-343.

16. Li M, Xie L. Correlation between NLR, PLR, and LMR and disease activity, efficacy assessment in rheumatoid arthritis. Evid Based Complement Alternat Med. 2021;2021:4433141.

17. Mei Y, Yang J, Yuan Y, et al. Systemic inflammation index values are associated with worsened disease severity and poor response to autoimmune encephalitis treatment. Front Neurol. 2021;12:709553.

18. Kim JW, Jung JY, Suh CH, Kim HA. Systemic immune-inflammation index combined with ferritin can serve as a reliable assessment score for adult-onset Still's disease. Clin Rheumatol. 2021;40:661-668.

19. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87:419-425.

20. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. 2000;55:16-23.

21. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374:250-259.

22. Yoshimoto Y, Ishida S, Hosokawa T, Arawaka S. Assessment of clinical factors affecting outcome of myasthenia gravis. Muscle Nerve. 2021;64:90-94.

23. Hammad M, Shehata OZ, Abdel-Latif SM, El-Din AMM. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in Behçet's disease: which and when to use? Clin Rheumatol. 2018;37:2811-2817.

24. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102:5-14.

25. Castanheira FVS, Kubes P. Neutrophils and NETs in modulating acute and chronic inflammation. Blood. 2019;133:2178-2185.

26. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13:159-175.

27. Tüzün E, Huda R, Christadoss P. Complement and cytokine based therapeutic strategies in myasthenia gravis. J Autoimmun. 2011;37:136-143.

28. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol. 2011;11:519-531.

29. Núñez J, Miñana G, Bodí V, et al. Low lymphocyte count and cardiovascular diseases. Curr Med Chem. 2011;18:3226-3233.

30. Aarli JA, Heimann P, Matre R, Thunold S, Tönder O. Lymphocyte subpopulations in thymus and blood from patients with myasthenia gravis. J Neurol Neurosurg Psychiatry. 1979;42:29-34.

31. Menezes GB, McAvoy EF, Kubes P. Hyaluronan, platelets, and monocytes: a novel pro-inflammatory triad. Am J Pathol. 2009;174:1993-1995.

32. Schiefer S, Wirsik NM, Kalkum E, et al. Systematic review of prognostic role of blood cell ratios in patients with gastric cancer undergoing surgery. Diagnostics (Basel). 2022;12:593.

33. Almăşan O, Leucuţa DC, Hedeşiu M. Blood cell count inflammatory markers as prognostic indicators of periodontitis: a systematic review and meta-analysis. J Pers Med. 2022;12:992.

34. Yang DH, Qian MZ, Wei MM, et al. The correlation of neutrophil-to-lymphocyte ratio with the presence and activity of myasthenia gravis. Oncotarget. 2017;8:76099-76107.

35. Jiang Z, Ning Z, Yang L, et al. The correlation of neutrophil-to-lymphocyte ratio with the presence and short-time curative effect of myasthenia gravis in children: a retrospectively study. Int J Neurosci. 2021;131:894-901.

36. Yıldız F, Gökmen O. Haematologic indices and disease activity index in primary Sjogren's syndrome. Int J Clin Pract. 2021;75:e13992.

37. Huang Y, Tan Y, Shi J, Li K, Yan J, Guan Y. Patients with myasthenia gravis with acute onset of dyspnea: predictors of progression to Myasthenic crisis and prognosis. Front Neurol. 2021;12:767961.

38. Roper J, Fleming ME, Long B, Koyfman A. Myasthenia gravis and crisis: evaluation and Management in the Emergency Department. J Emerg Med. 2017;53:843-853.

39. Nelke C, Stascheit F, Eckert C, et al. Independent risk factors for myasthenic crisis and disease exacerbation in a retrospective cohort of myasthenia gravis patients. J Neuroinflammation. 2022;19:89.

40. Ning P, Yang B, Yang X, et al. Lymphocyte-based ratios for predicting respiratory failure in Guillain-Barré syndrome. J Neuroimmunol. 2021;353:577504.

41. Wu X, Wang H, Xie G, Lin S, Ji C. Increased systemic immune-inflammation index can predict respiratory failure in patients with Guillain-Barré syndrome. Neurol Sci. 2022;43:1223-1231.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Diagnostic value of NLR, PLR, LMR, and SII in MG patients with poor outcome.