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Original Article

Correlations of peripheral blood neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio with renal function and prognosis in patients with lupus nephritis

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Abstract: Objective: To explore the correlations of neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR) with renal function and prognosis in patients with lupus nephritis (LN). Methods: A total of 115 patients with LN (research group) admitted to the Second Affiliated Hospital of Shandong First Medical University during January 2018 and January 2021 and 60 healthy controls (control group) who concurrently underwent physical examination were included in this study. Peripheral blood NLR and LMR were recorded in both arms. According to the estimated glomerular filtration rate (eGFR) at admission, patients with LN were assigned to a normal renal function group and a renal insufficiency group to compare their NLR and LMR values. Further, the cases were divided into good and poor prognosis groups based on the follow-up results, and the NLR and LMR were observed. Pearson test was used to analyze the relationship between NLR, LMR, and eGFR. Independent risk factors for poor prognosis of renal function were analyzed by multivariate logistic analysis. Results: The cases showed higher NLR and lower LMR than the controls (P<0.001). The NLR was lower in patients with normal renal function than in those with renal insufficiency (P<0.001). Patients with poor prognosis presented with significantly higher NLR and lower LMR than those with good prognosis (P<0.001). In cases, eGFR decreased with the increase of NLR, presenting an inverse association (r=-0.572, P<0.001). eGFR increased as the LMR increased, showing a positive correlation (r=0.582, P<0.001). Multivariate logistic analysis identified that infection, hypoproteinemia, moderate or above lupus disease activity, high NLR, and low LMR were independent risk factors for poor prognosis in LN. Conclusions: Peripheral blood NLR and LMR are plausible biologic indicators to predict renal function and prognosis in patients with LN.

Keywords: Neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, lupus nephritis, renal function, prognosis

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that usually involves the kidneys. Lupus nephritis (LN), the most common complication of kidney damage in SLE, is found in 60% of patients with SLE [1, 2]. Characterized by rapid progression and adverse prognosis, LN is an important reason for the high overall morbidity and mortality of SLE [3, 4]. Though not completely unveiled, the pathogenesis of LN is considered to involve many factors such as immunity, genetics, infection, environment and sex hormones [5]. Therefore, it is of great significance to find clinical markers that can predict renal function and prognosis in LN patients.

Studies have shown that neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR), associated with a variety of inflammatory factors, can be used clinically to evaluate the disease activity, severity and prognosis of various autoimmune diseases and tumors [6-8]. NLR and LMR have been widely used as disease biomarkers in clinical practice. For example, Göker et al. [9] reported that NLR was closely related to patients with strain rhinitis, and can serve as a biomarker to predict disease severity in such patients. The study of Okba et al. [10] confirmed that NLR and LMR can be non-invasive biomarkers of disease activity and disease severity in patients with ulcerative colitis. NLR is shown to be elevated in SLE patients, especially LN patients, which

indicates that an increase of NLR can reflect renal involvement in SLE patients [11, 12]. However, the involvement of NLR and LMR in LN has rarely been reported, nor have their roles in renal function and prognosis of LN patients been clarified. Accordingly, this study explored the clinical implications of NLR and LMR in LN, to provide reference data for clinical treatment.

Materials and methods

Clinical data collection

In this retrospective study, 115 patients with LN (research group) admitted to the Second Affiliated Hospital of Shandong First Medical University during January 2018 and January 2021 and 60 healthy people (control group; ≥18 years old) who concurrently underwent physical examination were included. Inclusion criteria of LN patients: with an age over 18 years old; meeting the diagnostic criteria for LN revised by the American College of Rheumatology [13]; with confirmed LN by renal biopsy; with complete clinical and pathological data as well as high degree of compliance with the follow-up. Exclusion criteria of LN patients: with acute or chronic inflammation, acute kidney injury, malignant tumor, autoimmune disease, cardiovascular disease or cardiac insufficiency; with a body temperature >38.5°C; with recent (within the last 4 month) blood transfusion, hormone or immunosuppressant treatment, or renal replacement therapy. This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Shandong First Medical University (2021-087). All subjects gave informed consent and signed an informed consent form.

Sample collection and testing

Fasting venous blood (5 mL) was collected from each participant the next morning after admission, and the upper serum was collected by centrifugation (3,000 r min^{-1}, 4°C) for 10 min. Neutrophils, lymphocytes, and monocytes were counted by Sysmex XE-2100 automated hematology analyzer (Sysmex Company, Japan), and the NLR and LMR were calculated.

Patient follow-up

Through WeChat, telephone, and outpatient reexamination, the renal function of patients was followed up once a month for 6 months.

Poor renal prognosis was defined as follows: 1) estimated glomerular filtration rate (eGFR) decreased by >30% or serum creatinine level doubled from baseline; 2) progression to end-stage renal disease or a need for renal replacement therapy such as hemodialysis or peritoneal dialysis; 3) renal transplant or death.

Outcome measures

Peripheral blood NLR and LMR were recorded in both the control group and the research group.

Patients were assigned to a normal renal function group (eGFR ≥90 m $L{\cdot}min^{-1}$, n=61) and a renal insufficiency group (eGFR <90 m $L{\cdot}min^{-1}$, n=54) according to the eGFR value at admission, and the NLR and LMR were observed.

After 6 months of follow-up, patients were divided into good (n=66) and poor (n=49) prognosis groups based on the renal prognosis to observe and compare the NLR and LMR values.

The relationship between NLR, LMR, and eGFR was analyzed, and the independent risk factors for poor prognosis of renal function were also investigated.

Statistical analysis

SPSS26.0 (Shanghai Cabit Information Technology Co., Ltd., China) was used for the data analysis, and the visualization of the collected data was achieved by Graphpad Prism 8 (Graph Pad Software Co., Ltd., San Diego, USA). Chi-square test was used to analyze the categorical data expressed as (%). The quantitative data recorded as mean ± standard deviation (Mean ± SD) were compared by independent sample t-test between groups (denoted by t). The correlation of NLR and LMR with eGFR was analyzed by Pearson correlation analysis, and independent risk factors for poor prognosis of renal function were analyzed based on the multivariate binary logistic regression model. A significance level of $P<0.05$ was used in all analyses.

Results

Comparison of baseline data between the research group and the control group

There was no significant difference in gender, age, body mass index (BMI), education level,

Table 1. Comparison of baseline data

Group	Control group (n=60)	Research group (n=115)	χ^2/t	P
Gender				
Male	34 (56.67)	68 (59.13)	0.098	0.754
Female	26 (43.33)	47 (40.87)		
Age (years old)	39.1±6.2	40.3±5.2	1.355	0.177
BMI (kg/m^2)	21.38±2.21	21.78±2.05	1.172	0.243
Education level				
< Junior high school	12 (20.00)	25 (21.74)	0.072	0.789
≥ Junior high school	48 (80.00)	90 (78.26)		
Residence				
Urban	26 (43.33)	58 (50.43)	0.797	0.372
Rural	34 (56.67)	57 (49.57)		
History of smoking				
Yes	23 (38.33)	52 (45.22)	0.763	0.382
No	37 (61.67)	63 (54.78)		
History of drinking				
Yes	31 (51.67)	48 (41.74)	1.569	0.210
No	29 (48.33)	67 (58.26)		

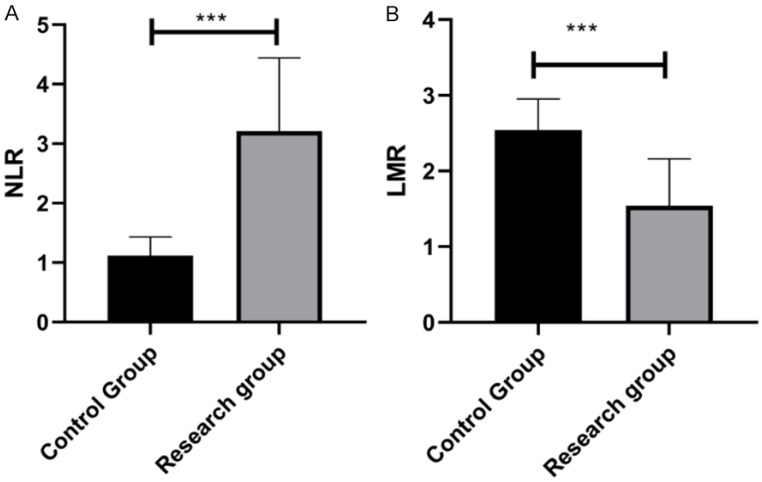

Figure 1. Comparison of NLR and LMR between the research group and control group. The peripheral blood NLR of the research group was significantly higher than that of the control group, while the LMR was significantly lower than that of the control group. ***indicates P<0.001.

residence, smoking history and drinking history between the two groups, indicating comparability. See **Table 1**.

Comparison of NLR and LMR between the research group and the control group

Compared to the control group, the peripheral blood NLR was significantly higher while the LMR was obviously lower in the research group (P<0.001). See **Figure 1**.

Comparison of NLR and LMR between the normal renal function group and the renal insufficiency group

Patients were divided into a normal renal function group (eGFR ≥90 L·min^{-1}, n=61) and renal insufficiency group (eGFR <90 m L·min^{-1}, n=54) based on their eGFR values at admission. It was found that the NLR was significantly lower while the LMR was evidently higher in the normal renal function group compared to the renal insufficiency group (P<0.001). See **Figure 2**.

Comparison of NLR and LMR between the poor prognosis group and the good prognosis group

After 6 months of follow-up, patients were divided into good (n=66) and poor (n=49) prognosis groups according to follow-up outcomes. The results revealed higher NLR and lower LMR in the poor prognosis group as compared to the good prognosis group (P<0.001). See **Figure 3**.

Pearson test to analyze the relationship between NLR, LMR and eGFR

The peripheral blood NLR, LMR, and eGFR of LN patients were collected for Pearson correlation analysis. The results showed that eGFR decreased with the increase of NLR, showing an inverse association (r=-0.572, P<0.001); while eGFR increased with the increase of LMR, presenting a positive correlation (r=0.582, P<0.001). See **Figure 4**.

Multivariate logistic analysis of independent risk factors for poor renal prognosis

Patients were divided into good (n=66) and poor (n=49) prognosis groups based on the renal function results after follow-up. Using the

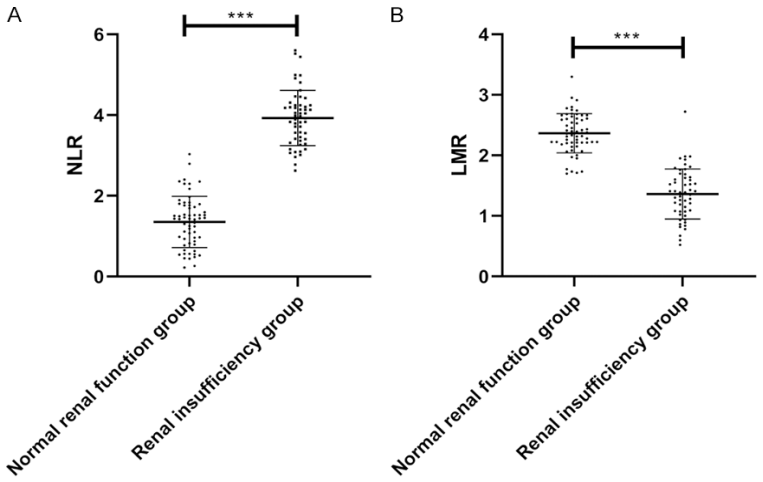

Figure 2. Comparison of NLR and LMR between the normal renal function group and renal insufficiency group. Compared to the renal insufficiency group, the NLR in the normal renal function group was significantly lower, while LMR was significantly higher. ***indicates P<0.001.

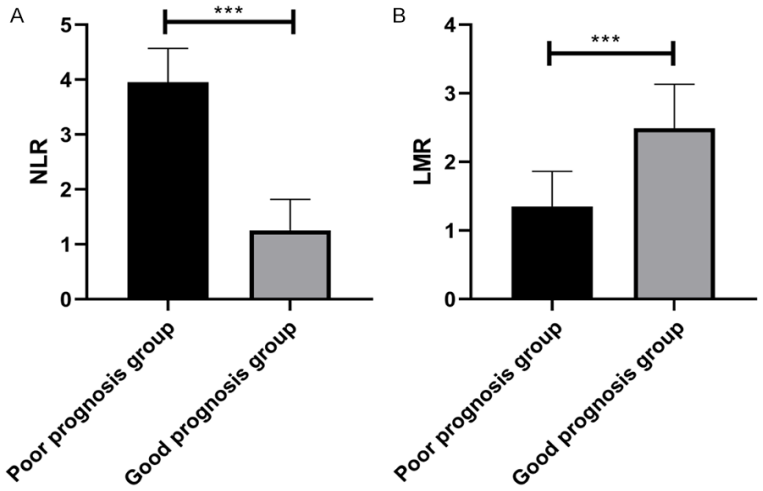

Figure 3. Comparison of NLR and LMR between the poor prognosis group and the good prognosis group. Compared to the good prognosis group, patients in the poor prognosis group had significantly higher NLR and significantly lower LMR. ***indicates P<0.001.

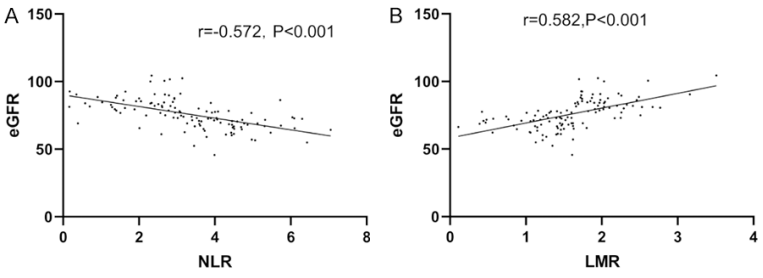

Figure 4. Scatter diagram of correlation between NLR, LMR and eGF. The eGFR of patients decreased with the increase in NLR, showing a negative correlation (r=-0.572, P<0.001), while eGFR increased with the increase in LMR, showing a positive correlation (r=0.582, P<0.001).

clinical and laboratory data of the two groups of patients as independent variables and the occurrence of poor prognosis as the dependent variable, multivariate logistic analysis found that infection, hypoproteinemia, moderate or above lupus disease activity, high NLR, and low LMR remained independent risk factors for poor renal function. See **Table 2**.

Discussion

Lupus nephritis (LN) is a form of glomerulonephritis and also one of the most serious organ-involved complications of systemic lupus erythematosus (SLE). Despite significant advances in understanding the genetics and pathogenesis of LN, LN remains an important cause of death in SLE patients [14]. Reportedly, 10%-30% of patients with proliferative LN will progress to end-stage renal disease [15]. Therefore, it is of importance to seek effective biological indicators to predict the renal function and prognosis of LN patients for disease monitoring and treatment.

Currently, the gold standard for judging LN disease activity and kidney damage is renal tissue biopsy. However, kidney tissue biopsy is an invasive test and is not suitable for frequent examinations to assess disease activity [16]. The pathogenesis of LN is characterized by abnormal activation of innate and adaptive immune response, dysregulation of inflammatory signaling pathway and increased production of cytokines [17]. NLR and LMR, as indicators of systemic inflammation, have been extensively used in research of tumors, cardiovas-

Table 2. Multivariate analysis

Variable	B	Wald	P	OR	95.0% CI for Exp (B)	
					Upper	Lower
Infection	0.835	9.356	0.002	2.281	1.339	3.915
Moderate or above lupus disease activity	0.714	5.520	0.018	1.988	1.124	3.575
High NLR	0.623	5.312	0.021	1.862	1.114	3.208
Low LMR	0.618	5.529	0.023	1.884	1.119	3.314

cular diseases, and diabetes [18-20]. However, the involvement of the two in LN has rarely been reported, nor have their effects on renal function and prognosis of LN patients been elucidated.

In this study, we first collected the peripheral blood NLR and LMR of cases and controls for comparison. The results showed higher NLR and lower LMR in cases than in controls, which indicated that NLR and LMR were significantly differentially expressed in healthy people and LN patients. It was shown that increased circulating neutrophil levels and decreased lymphocyte levels in patients with chronic kidney disease are associated with chronic inflammatory response [21]. Then we divided the patients into a normal renal function group and a renal insufficiency group according to the eGFR value at admission to compare their NLR and LMR levels. Compared to the renal insufficiency group, NLR was significantly lower while LMR was significantly higher in the normal renal function group, suggesting that both high NLR and low LMR in peripheral blood may indicate renal insufficiency. The patients were followed up for 6 months. Comparing the NLR and LMR levels of patients with good prognosis with those with poor outcome, it was found that the NLR was significantly higher while the LMR was lower in patients with poor prognosis, indicating that NLR and LMR may be biologic indicators for monitoring the prognosis of LN patients.

NLR reflects neutrophil and lymphocyte counts, in which the increase of neutrophils indicates nonspecific inflammation and the decrease of lymphocytes suggests physiological stress. Compared to each single factor, the combination is not easily affected by physical, biochemical or physiologic factors, and is more valuable than counting alone in predicting inflammation [22]. Similarly, LMR is an inflammatory biomarker that monitors the balance between the host immune system and the tumor microenvironment and is a simple prognostic indicator of tumors [23]. This study showed that there were significant differences in NLR and LMR in patients showing differences in renal function and prognosis, suggesting that NLR and LMR were biologic indicators of renal function and prognosis in LN patients. Soliman et al. [24] also showed that the NLR of LN patients was positively correlated with blood urea nitrogen and serum creatinine levels, suggesting that NLR can better evaluate patients' renal function.

eGFR is an important index to evaluate chronic nephropathy [25]. We speculated that there may be a close association between NLR, LMR, and eGFR. By collecting peripheral blood NLR, LMR, and eGFR of LN patients at admission and conducting a Pearson test, we found that eGFR decreased with the increase of NLR, presenting a negative correlation (r=-0.572), while eGFR increased with the increase of LMR, showing a positive correlation (r=0.582). The results indicate that NLR and LMR, strongly correlated with eGFR, and can be biologic indicators to monitor the renal function of LN patients. Lymphocyte apoptosis is common in inflammatory reactions, and neutrophils, as a type of phagocyte, also participate in the complex mechanism of inflammation and immune response regulation in the body [26]. Patients with low renal function and poor prognosis tend to experience more severe renal tissue inflammation, with increased apoptosis of lymphocytes and proliferation of neutrophils and megakaryocytes, resulting in increased NLR [27]. At the end of the study, we used multivariate logistic regression analysis to analyze the independent risk factors of poor renal prognosis. The results showed that infection, hypoproteinemia, moderate or above lupus disease activity, high NLR, and low LMR were independent risk factors of poor renal outcome. The results of Zou et al. [28] suggest that NLR is associated with early renal fibrosis and renal

prognosis. Liu et al. [29] reported that NLR and LMR may be useful biomarkers for predicting LN. The findings of these preceding studies were similar to ours.

This study has confirmed that NLR and LMR are useful biomarkers for predicting renal function and renal prognosis in patients with LN, but there is still some room for improvement. As patients were only followed up for 6 months, it is hoped that the long-term survival of patients will be followed up in future studies to improve our research.

To sum up, this study posits that peripheral blood NLR and LMR may be candidate biologic indicators to predict the renal function and prognosis of patients with LN.

Disclosure of conflict of interest

None.

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