Original Article
The relationship between neutrophil-lymphocyte ratio and early renal fibrosis and renal prognosis in patients with lupus nephritis

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Abstract: Objective: To explore the relationship between neutrophil-lymphocyte ratio (NLR) and early renal fibrosis and renal prognosis in patients with lupus nephritis. Methods: A total of 186 patients with lupus nephritis admitted to our hospital were enrolled and grouped according to the standard of "NLR=3.175". There were 90 patients in the higher NLR group and 96 patients in the lower NLR group. The correlation and independent relationship between NLR/estimated glomerular filtration rate (eGFR) and pathological indicators were explored by comparing the differences of physiological indicators between the two groups. The correlation between NLR/eGFR and renal insufficiency and renal prognosis were explored. Results: The higher NLR group showed increased levels of hs-CRP, white blood cells, neutrophils, platelets, PLR values, eGFR, D-dimer, crescent compared with the lower NLR group, while lymphocyte count in the higher NLR group was lower than that in the lower NLR group. Platelets, neutrophils, white blood cells, serum anhydride, serum C4 and vascular cellulose had positive correlations with NLR. eGFR, age, systolic blood pressure, diastolic blood pressure, neutrophils, leukocytes, NLR, blood uric acid, triglycerides, crescent ratio, endothelial hyperplasia, spherical sclerosis ratio, intraglomerular leukocyte infiltration, platinum loop, microthrombus, nuclear fragmentation, interstitial inflammatory cell infiltration, renal tubular atrophy, interstitial fibrosis, and mesangial cell showed negative correlation with matrix hyperplasia, arteriolar wall thickening and pathological activity scores, but showed positive correlation with hemoglobin and low-density lipoprotein. Conclusion: NLR affects some important renal functions to a certain extent and is not the only risk factor for renal prognosis in patients with LN.

Keywords: Lupus nephritis, neutrophil-lymphocyte ratio, early renal fibrosis, renal function

Introduction

Lupus nephritis (LN) is a major and common cause that leads to death in patients with systemic lupus erythematosus (SLE) [1]. The presence of immune complexes in the glomeruli will cause the activation of a large number of neutrophils and local infiltration of inflammatory cells such as derivatives of monocytes and T lymphocytes, which will leave the kidney in a status of chronic inflammation and damage. According to the existing medical studies, NLRP3 inflammasome has been shown to play a vital and irreplaceable role in the occurrence of LN. Immune complexes, interference factors I, and neutrophil extracellular traps (NETs) in related tissues [2] can increase the activity of NLRP3. For SLE patients, the overreaction of

macrophages can enhance the activation of inflammasome to increase inflammatory cytokines. The inflammasomes can cause the decrease of patients' autoantibodies, leading to the rapid deterioration of nephritis disease [3, 4].

Neutrophil-lymphocyte ratio (NLR) is usually calculated by complete blood count, which is economical to obtain compared with other inflammatory indicators [5]. NLR has obvious advantages of a vital inflammatory index. First, it concentrates the blood. Under the influence of stress response and other factors, the absolute value of white blood cell system is more easily affected than NLR [6]. Secondly, the ratio of neutrophils to lymphocytes can well reflect the increase of neutrophils and the decrease of

lymphocytes in the human immune system. Neutrophils, adhering to the inner walls of human blood vessels, play a very important role in the secretion of inflammatory mediators such as elastase, oxygen free radicals, *etc*., and can also regulate the activities of cells when presenting antigens, which will lead to partial damage to some non-specific immune vascular tissues, while lymphocytes can respond to the regulation of inflammation [7]. Because some signals in lymphocytes are not normally transmitted, it will cause the diseases of immune system. C-reactive protein (CRP), interferon and interleukin-6 (IL-6) have been used in the assessment of inflammatory state. It has been found that NLR, CRP, tumour necrosis factor-α (TNF-α), IL-6, and ESR are closely related to inflammatory state, suggesting a potential link between NLR and inflammation [8].

There have been many reports on the correlation between NLR and such factors as baseline, renal function and urinary protein in patients with LN, while there are few literatures on the correlation between NLR and renal prognosis of patients with LN. Different tissues and organs will have many overlapping damages within a certain period of time [9], which is very complicated in clinical trials and will increase the difficulty of treatment accordingly. The existing intensive immunotherapy has been one of the factors that have reduced the overall mortality of SLE patients in recent years. However, the incidence of ESRD has maintained a very stable state in recent decades [10], which indicates the limitations of the current treatment methods. A concise evaluation index with actual effect is still needed. The relationship between NLR and the factors such as early renal fibrosis and renal prognosis in LN patients became the focus of this study.

Materials and methods

General information

A total of 186 patients with LN who were admitted to our hospital during the whole year of 2019 were enrolled and divided into two groups by the grouping standard of "NLR=3.175". This study was approved by the ethic committee of China-Japan Friendship Hospital. The informed consent was signed by the guardians.

Inclusion criteria were as below: (1) patients who were in accord with the diagnostic criteria for SLE of the American Academy of Rheumatology; (2) those who were confirmed to be LN by renal biopsy; (3) those with complete laboratory, clinical and related pathological data, no fewer than 8 glomeruli in pathological specimen; (4) no limitation of gender, patients aged no less than 14 years.

Exclusion criteria were as below: (1) patients who were in the period of acute or chronic inflammation, with body temperature higher than 38.5°C, combined with acute renal injury; (2) those combined with malignant tumours; (3) those with oral administration of immune preparations or hormones.

Outcome measurement and evaluating standards

It was necessary to investigate some basic information of the patients, such as age and systolic blood pressure (SBP), and record the relevant clinical manifestations of the patients. Special attention was paid to the occurrence of clinical phenomena such as hair loss, photoallergy, edema, and Raynaud's phenomenon [11].

Patients were required to undergo standard laboratory testing of puncture samples before treatment. Testing items included lymphocyte count, neutrophil count, white blood cell count, high sensitive C-reactive protein (hs-CRP), platelet count, PLR, hemoglobin (HGB), plasma albumin (ALB), 24-hour urine protein, serum creatinine (Scr), estimated glomerular filtration rate (eGFR), blood uric acid (UA), low-density lipoprotein (LDL), triglyceride (TG), D-dimer, serum C3/C4, anti-dsDNA antibody, anti-Sm antibody, and the score of lupus activity [12].

The systemic lupus erythematosus disease activity index (SLEDAI) was used to calculate and evaluate the corresponding value of lupus activity [13].

Prior to the corresponding treatment, the patients should be communicated with and informed in order to obtain their consent. After local anesthesia guided by B-ultrasound, percutaneous renal puncture was performed to obtain bilateral renal tissues of experimental subjects. Researchers had to ensure that the

Table 1. Comparison of general clinical indicators between the two groups

Indices	NLR<3.175 (n=96)	NLR≥3.175 (n=90)	t	P
SBP	123.31±19.21	127.65±20.03	1.508	0.00
DBP	81.01±12.35	81.49±12.70	0.261	0.00
Hypertension	32 (33.33)	38 (42.22)	0.896	0.344
Facial erythema	22 (22.92)	24 (26.67)	0.307	0.580
Raynaud's phenomenon	4 (4.44)	2 (2.22)	0.217	0.641
Serosal effusion	10 (10.42)	14 (15.56)	6.049	0.014
Fever	2 (2.08)	7 (7.78)	1.369	0.242
Oral ulcers	6 (6.25)	8 (8.89)	0.346	0.556
Joint pain	17 (17.71)	19 (21.11)	0.748	0.387
Edema	62 (64.58)	66 (73.33)	0.803	0.370
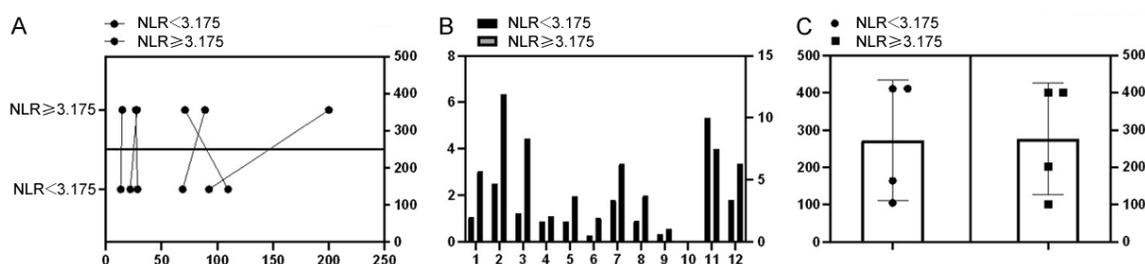
Figure 1. Comparison of laboratory indicators between the two groups. There was no significant difference in 24-hour urinary protein, HGB, ALB, Scr, LDL, the score of lupus activity, serum C3/C4, anti-Sm antibody and anti-dsDNA antibody between the two groups (*P*>0.05).

renal tissues taken met the basic requirement of no fewer than eight glomeruli [14].

Statistical analysis

SPSS20.0 statistical software was used to process the data. The measurement data were expressed as ($\bar{x}$ ± s). The difference between groups was compared by the student's t test. The count data were expressed as n (%). The rationality of the data was verified by using statistical methods. The Student's t test was used to detect continuous variables at different time points, and the F test was used to obtain the comparative difference between groups. *P*< 0.05 was considered statistically significant.

Results

Comparison of general clinical indicators between the two groups

There was no significant difference in clinical manifestations such as SBP, diastolic blood pressure (DBP), the proportion of patients with hypertension, facial erythema, Raynaud's phe-

nomenon, serosal effusion, fever, joint pain, oral ulcers, mental disorder or edema, *etc*. between the two groups (*P*>0.05) (**Table 1**).

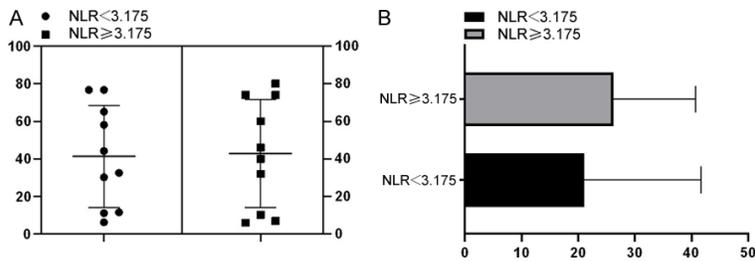*Comparison of laboratory indicators between the two groups*

There was no significant difference in 24-hour urinary protein, HGB, ALB, Scr, LDL, serum C3/C4, UA and anti-dsDNA antibody between the two groups (*P*>0.05) (**Figure 1**).

Comparison of renal pathological indicators between the two groups

The median ratio of crescents of patients in the higher NLR group was higher than that in the lower NLR group. There was no statistical significance in the proportion of glomerulosclerosis, microthrombosis, focal segmental glomerular sclerosis, karyorrhexis, platinum loop, endothelial hyperplasia, the degree of interstitial inflammatory cell infiltration, glomerular leukocyte infiltration, the thickening of arteriolar wall, balloon adhesion, the hyperplasia of mesangial cell and stroma, the score of patho-

Figure 2. Comparison of pathological indicators between the two groups. The median ratio of crescents of patients in the higher NLR group was higher than that in the lower NLR group. There was no statistical significance in the proportion of glomerulosclerosis, microthrombosis, endothelial hyperplasia, platinum loop, focal segmental glomerular sclerosis, glomerular atrophy, interstitial fibrosis, karyorrhexis, the degree of interstitial inflammatory cell infiltration, glomerular leukocyte infiltration, balloon adhesion, the necrosis of glomerular capillary loop, the thickening of arteriolar wall, vascular fibrinoid necrosis, the hyperplasia of mesangial cell and stroma, pathological type, and the score of lupus activity between the two groups (*P*>0.05).
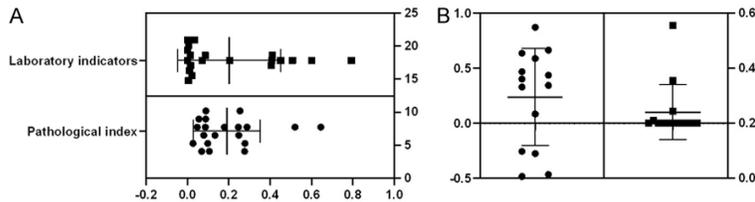
Figure 3. Correlation between eGFR and laboratory indicators in patients with LN. The eGFR was negatively correlated with age, SBP, DBP, neutrophil count, white blood cell count, NLR, UA, and TG, and positively correlated with HGB and LDL. There was no significant correlation between eGFR and routine indicators, such as gender, 24-hour urine protein, lymphocyte count, platelet count, hs-CRP, ALB, D-dimer, serum C3/C4, anti-dsDNA antibody, anti-Sm antibody, PLR, and the score of lupus activity (*P*>0.05).
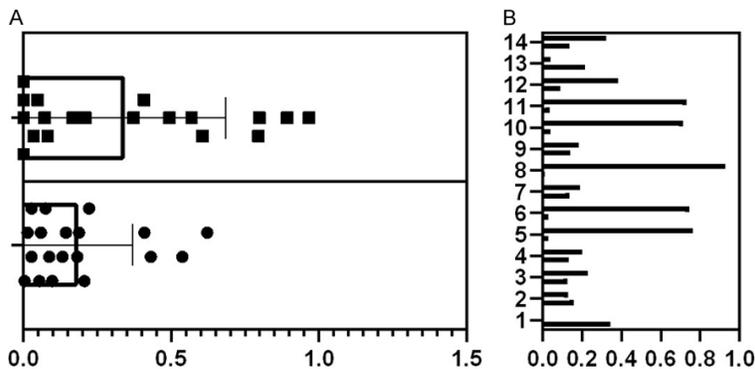
Figure 4. Correlation between eGFR and pathological indicators in LN patients. The eGFR was negatively correlated with the ratio of crescents, endothelial hyperplasia, the proportion of glomerulosclerosis, glomerular leukocyte infiltration, platinum loop, microthrombosis, karyorrhexis, the degree of interstitial inflammatory cell infiltration, glomerular atrophy, interstitial fibrosis, the hyperplasia of mesangial cell and stroma, the thickening of arteriolar wall, and the score of pathological activity. There was no significant correlation between eGFR and necrosis of glomerular capillary loop, segmental sclerosis, vascular fibrinoid necrosis, and pathological chronic index (*P*>0.05).

logical activity, and pathological type between the two groups (*P*>0.05) (**Figure 2**).

Correlation between eGFR and laboratory indicators in patients with LN

The eGFR was negatively correlated with age, SBP, DBP, white blood cell count, UA, neutrophil count, NLR, and TG, and positively correlated with HGB and LDL. There was no significant correlation between eGFR and routine indicators, such as gender, 24-hour urine protein, lymphocyte count, platelet count, ALB, serum C3/C4, and the score of lupus activity (*P*> 0.05) (**Figure 3**).

*Correlation between eGFR and pathological indicators in patients with LN*

The eGFR was negatively correlated with the ratio of crescents, endothelial hyperplasia, the proportion of glomerulosclerosis, platinum loop, microthrombosis, karyorrhexis, glomerular leukocyte infiltration, the degree of interstitial inflammatory cell infiltration, glomerular atrophy, interstitial fibrosis, the hyperplasia of mesangial cell and stroma, and the score of pathological activity. There was no significant correlation between eGFR and segmental sclerosis, pathological chronic index, and vascular fibrinoid necrosis (*P*>0.05) (**Figure 4**).

Correlation between NLR and other indicators in patients with LN

NLR was positively correlated with white blood cell count, platelet count, neutrophil count, Scr, PLR, and serum C4,
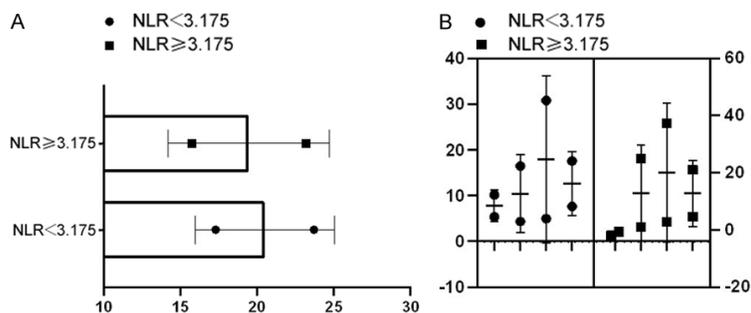
Figure 5. Correlation between NLR and other indicators in patients with LN. NLR was positively correlated with white blood cell count, platelet count, neutrophil count, Scr, PLR, and serum C4, and negatively correlated with lymphocyte count and eGFR. There was no significant correlation between NLR and age, gender, SBP, DBP, HGB, 24-hour urine protein, ALB, hs-CRP, UA, TG, LDL, serum C3, anti-dsDNA antibody, anti-Sm antibody, D-dimer, and the score of lupus activity ($P>0.05$).

phils and a prolonged chronic inflammatory response. The statistical significance of neutrophils and lymphocytes reflected by NLR indicated that the increase in neutrophils and physiological stress response were not affected by physical or biochemical factors, and the value was higher than that of the separate counting method. The correlations between NLR and a wide range of crucial indicators made us investigate the value of NLR in the evaluation of inflammation state [17, 18].

and negatively correlated with lymphocyte count and eGFR. There was no significant correlation between NLR and age, gender, SBP, DBP, HGB, 24-hour urine protein, ALB, hs-CRP, UA, TG, LDL, serum C3, anti-dsDNA antibody, anti-Sm antibody, D-dimer, and the score of lupus activity ($P>0.05$) (**Figure 5**).

Correlation between NLR and pathological indicators in patients with LN

NLR was positively correlated with the ratio of crescents and vascular fibrinoid necrosis. There was no significant correlation between NLR and glomerulosclerosis, platinum loop, karyorrhexis, glomerular atrophy, interstitial inflammatory cell infiltration, interstitial fibrosis, the thickening of arteriolar wall, segmental glomerular sclerosis, endothelial hyperplasia, microthrombosis, the necrosis of glomerular capillary loop, the hyperplasia of mesangial cell and stroma, the degree of glomerular leukocyte infiltration, and pathological chronic index ($P>0.05$).

Discussion

There are many systemic oxidative stress responses in body. In the immune tissue, T lymphocytes infiltrate the interstitial area of the renal tubules and further release angiotensin. These conditions may cause chronic inflammation of the renal tissue, and the damage and necrosis of renal tissue are directly related to the increase of neutrophils in the internal circulation [15, 16]. The decrease in the level of lymphocytes could lead to an increase in neutro-

In this study, it was found that CRP was a risk factor that hindered the expansion of renal function. The increase of CRP would reduce the demand for renal function, which was related to kidney damage [19] and the increase of mortality. Malhotra et al. proved the correlation between NLR and CRP in their study which selected 100 HD patients and found that patients with higher NLR levels also had higher CRP levels, confirming a good correlation between NLR and CRP ($r=0.45$, $P<0.001$) [20]. The same results were also obtained in SLE patients. Yang et al. found that CRP level in SLE patients was positively correlated with NLR level [7]. The above studies showed that NLR and CRP had a good correlation. In this study, the median value of NLR was used for grouping experiments, and a good correlation between NLR and CRP was found, which was consistent with the results of previous studies. Therefore, it was speculated whether NLR was associated with renal damage and renal function progression in a variety of renal diseases, including LN patients.

For SLE patients, a higher level of NLR indicated more serious pathological damage. The results of evaluation of the NLR related indicators were useful to understand the condition and prognosis of patients. The NLR related indicators could be obtained by routine blood examination [21]. The pathological change of kidney requires renal biopsy. By contrast, routine tests are relatively economical and easy to perform, and are easily accepted by the family members of patients. This method requires the search for one or more clinical indicators to

conduct a controlled trial during the test [17]. In this test process, it has very important clinical significance. As far as our current research concept is concerned, the relationship between NLR and T2DM remains to be further studied, while the pathological relationship between NLR and LN is relatively few. In this study, it was found that the ratio of NLR and LN was positively related to the vascular fibrinoid necrosis, and for pathological indicators, the correlation was not obvious. Many studies have clarified and summarized the relationship between NLR and DN or CKD [1, 22]. In the process of clinical trials, this relationship is a great risk factor. However, relevant studies also showed that there was no significant correlation between NLR and renal prognosis. The results of Kurtul et al. showed that NLR was not an independent risk factor for renal endpoint event in patients with CKD (HR=1.02, P=0.764) [23]. Whether NLR is associated with renal prognosis is still controversial. There was a significant difference in renal survival rate between the study group and the control group during the research. The results had a greater impact on the renal prognosis, with corrected value of the risk factor greater than 0.05. Due to the small sample size involved in this study, contingency may occur, but overall HR value is still greater than 1. An in-depth research with larger sample size should be performed in the future.

Disclosure of conflict of interest

None.

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