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High Neutrophil-lymphocyte Ratio Predicts Serious Renal Insufficiency in Patients with Lupus Nephritis

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ABSTRACT

Background: Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematosus (SLE).The neutrophil to lymphocyte ratio (NLR) is a promising predictor and prognostic factor. An increased NLR is associated with a poor prognosis of several inflammatory diseases.

Objective: To evaluate the value of NLR in the diagnosis and pre-assessment of the disease severity of LN.

Methods: This retrospective study included 88 patients with LN, 51 SLE patients without kidney involvement, 79 patients with primary chronic nephritis (CN), and 52 healthy controls (HC). The differences among these four groups and diagnostic value of NLR for patients with LN were evaluated.

Results: The NLR of patients with LN before treatment was significantly higher than that of the other three groups. NLR positively correlated with C-reactive protein (CRP), complement 3(C3), C4, and serum creatinine (SCr) (CRP: r=0.337, p=0.007; C3: r=0.222, p=0.042; C4: r=0.230, p=0.035; SCr: r=0.408, p<0.0001) but negatively correlated with total serum IgG (r=-0.226, p=0.041). The level of NLR increased with the severity of renal dysfunction NLR (area under the curve: 0.785, 95% CI: 0.708-0.862) was useful for the diagnosis of LN, and its optimal cut-off value was 5.44 (sensitivity: 65.9%, specificity: 86.3%).

Conclusions: NLR would be useful for the diagnosis of LN and reflects the severity of renal dysfunction Therefore, evaluating NLR before treatment could help clinicians to identify potential renal involvement in patients with SLE and distinguish LN from CN.

Keywords: Lupus nephritis, Neutrophil-lymphocyte ratio, Renal insufficiency, Systemic lupus erythematosus

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INTRODUCTION

Lupus nephritis (LN) is a type of glomerulonephritis that occurs in more than half of patients with systemic lupus erythematosus (SLE) and is one of the most severe target organ complications of SLE. Importantly, LN may also be the initial presentation of SLE. Therefore, it is important to distinguish LN from primary chronic nephritis and general SLE. Multiple pathogenic pathways are involved in LN including the production of autoantibodies, complement activation, immune complex deposition, and abnormal cell apoptosis. Inflammation plays a key role in the pathophysiology of LN. Neutrophil-lymphocyte ratio (NLR) is a biomarker that can reflect inflammation and immunity. Previous research suggests that it is narrowly related to overall survival in patients with malignant tumors (1-3), cardiovascular diseases (4), autoimmune diseases (5-7), and even the overall survival of the general population (8). Although NLR has been identified to be closely associated with the disease activity of SLE and that it significantly increased in the uninfected LN group compared with the healthy control (HC) (6), there is still a lack of comprehension about the relationship between pre-treatment NLR and renal dysfunction in LN. In addition, the role of NLR in differentiating LN from SLE without renal impairment and primary chronic nephritis (CN) is uncertain.

PATIENTS AND METHODS

Patients

This study included patients with LN admitted to the First Affiliated Hospital of Chongqing Medical University from January 2015 to December 2020. The clinical data of all patients was collected by consulting medical records and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The research was carried out in line with the Helsinki Declaration principles.

SLE patients meet the SLE classification criteria revised by the American College of Rheumatology (ACR) in 1982 (9). Simultaneously, patients with SLE may also have one or more of the following illnesses: 1) persistent albuminuria greater than 0.5 g/24 h, or random urine protein+++, or urine protein/creatinine greater than 500 mg/g (50 mg/mmol); 2) cell casts including hemoglobin casts, red blood cell casts, mixed casts, or granular casts; 3) being in line with the Chinese LN diagnosis and treatment guidelines to exclude active urine sediment (except for urinary tract infection, urine white blood cell greater than 5/HPF (high-power field), urine red blood cell greater than 5/HPF)). Entry criteria of LN: The 1982 American College of Rheumatology SLE classification standards updated in 1997, include LN patients with autoantibody positive SLE (anti-nuclear antibody titer ≥1:80, anti-double-stranded DNA antibody, or both) (9). LN was confirmed by biopsy and classified according to the 2003 classification system of the International Society of Nephrology-Society of Nephrology (10, 11). The diagnosis of CN was based on the Mayo clinic/ Nephrology Society consensus report on the pathological classification, diagnosis, and report of glomerulonephritis (10-12). It excluded patients with one of the following conditions: 1) hematological diseases, malignant diseases, or pregnancy; 2) any evidence of accompanying inflammatory diseases; 3) other autoimmune diseases; 4) patients with cerebrovascular and cardiovascular diseases, diabetes, or liver disease. The healthy controls were from the Physical Examination Center of the First Affiliated Hospital of Chongqing Medical University. However, and individuals with tumors or had undergone immunosuppressive treatment were excluded.

This retrospective study included a total of 88 patients with LN, 51 SLE patients without renal impairment, 79 patients with CN, and 52 HC.

Clinical and Laboratory Parameter

The clinical laboratory information of each subject was obtained from the clinical record. We recorded the complete blood count (CBC) and serum index of each patient before treatment. The whole blood sample was anticoagulated by EDTA-K2 and analyzed for CBC parameters with XN1000 Hematology Analyzer (Sysmex, Japan). The ratio of the absolute neutrophil count to the lymphocyte count of the whole blood is the NLR. The Beckman Coulter Immage-800 immunochemical system was applied to detect the serum levels of C-reactive protein (CRP), complement 3 (C3), C4, and immunoglobulin G (IgG). A biochemical analyzer (Roche cobas701, Switzerland) was employed to detect the levels of blood urea nitrogen (BUN) and the serum creatinine (SCr). The Erythrocyte Sedimentation Rate (ESR) test was performed by TEST1 (ALIFAX, Italy). Serum anti-dsDNA antibody levels and their quantitative determination were detected by fluorescence enzyme immunoassay (Euroummun, Lubeck, Germany) and enzyme-linked immunosorbent assay (ELISA) (YHLO Union, YHLO, China), respectively. All operations were carried out in strict accordance with requirements of both laboratory and manufacturer.

Statistical Analysis

The results of the continuous variables with normal distribution and the variables in the skewed distribution (Kolmogorov-Smirnov Test) were expressed in the form of Mean±standard deviation (M±SD) and the median (interquartile range) (median (IQR)), respectively. Categorical data were expressed in absolute counts and percentages. Spearman correlation analysis was employed to analyze the association between NLR and other variables (ESR, CRP, C3, C4, Anti-dsDNA, IgG, and SCr) in the LN group. The Mann-Whitney U test was used to analyze the differences among these four groups (LN, SLE, CN, and HC). In addition, the Kruskal-Wallis test was used to calculate the P-value of the three groups with different degrees of renal injury. Finally, the receiver operating curve (ROC) was adopted to evaluate the clinical performance of NLR in distinguishing LN complications in SLE patients. All statistical analysis was performed by SPSS 21.0. A P-value<0.05 is considered statistically significant.

Ethical Considerations

The data of this research was acquired with the endorsement and guidelines of the Institutional Review Board and Biomedical Ethics Committee of Chongqing Medical University. The ethics committee waived the requirement to obtain written informed consent from participants due to the study's retrospective nature. No additional written permission was considered necessary because all patients' analysis was conducted anonymously.

RESULTS

Demographic and Clinical Characteristics of the Research Subjects

All subjects were divided into four groups, namely, LN, SLE, CN, and HC. The basic clinical characteristics of these four groups were shown in Table 1, including age, gender, pathological classification, CRP, C3, C4, antinuclear antibodies (ANA), SCr, etc. The age differences between these four groups were not statistically significant, and there was no significant difference in ANA titer and anti-dsDNA level between LN and SLE. The levels of BUN, SCr, and estimated glomerular filtration rate (eGFR) of LN were significantly higher than those of SLE and HC (P<0.05), but there was no statistical difference between LN and CN (P>0.05).

LN possessed remarkably higher levels of CRP ((median (IQR), 9.5 (5.0-27.2) g/L vs 4.48 (1.9-12.9) g/L, P<0.05) (Figure 1 (a)) but had significantly lower levels of C3 ((median (IQR), 0.45 (0.30-0.56) g/L vs 0.79 (0.55-1.00) g/L, P<0.05) (Figure 1 (b)) and C4 ((median (IQR), 0.12 (0.06-0.17) g/L vs 0.16 (0.11-0.19) g/L, P<0.05) (Figure 1 (c)) than SLE.

Table 1. Basic clinical data of four groups (LN, SLE, CN, and HC).

Features	LN (n=88)	SLE (n=51)	CN (n=79)	HC (n=52)
Age, year	45 (30-53)	46 (30-55)	50 (39-61)	43 (29-49)
Gender, M/F	14/74[2,3]	6/45[4,5]	22/57	7/45
ANA, titer	320 (100-1000)	320 (100-1000)		
Anti-dsDNA, IU/ml	50.2 (7.8-492)	48.6 (6.8-563)	/	/
ESR, mm/h	36 (20-61)	34.5 (20-54)	50.0 (38-61)	/
CRP, mg/L	9.5 (5.0-27.2)[1]	4.48 (1.9-12.9)[4]	13.21 (5-36.22)	/
C3, g/L	0.45 (0.30-0.56)[1,2]	0.79 (0.55-1.00)	0.81 (0.66-0.93)	/
C4, g/L	0.12 (0.06-0.17)[1,2]	0.16 (0.11-0.19)4	0.23 (0.18-0.27)	/
BUN, mmol/L	12.85 (6.50-20.25)[1,3]	4.6 (3.7-5.3)[4]	8.95 (5.325-18.73)[5]	4.8 (3.925-5.65)
SCr, umol/L	174.5 (74.25-320.8)[1,3]	58 (51-65)[4]	210 (65.25-653.0)[5]	61.5 (55.00-66.00)
eGFR, mL/(min*1.73m^2)	36.50 (15.10-80.40)[1]	112.9 (99.90-124.0)[4]	13.3 (5.85-50.48)	/

Variables were expressed as medians (interquartile range); LN: lupus nephritis; SLE: systemic lupus erythematosus (SLE) patients without LN; CN: chronic nephritis patients; HC: healthy controls; M/F: male/female; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; C3: complement C3; C4: complement C4; BUN: blood urea nitrogen; SCr: serum creatinine; GFR: glomerular filtration rate. 1: P<0.05 LN vs SLE; 2: P<0.05 LN vs CN; 3: P<0.05 LN vs HC; 4: P<0.05 SLE vs CN; 5: P<0.05 CN vs HC.

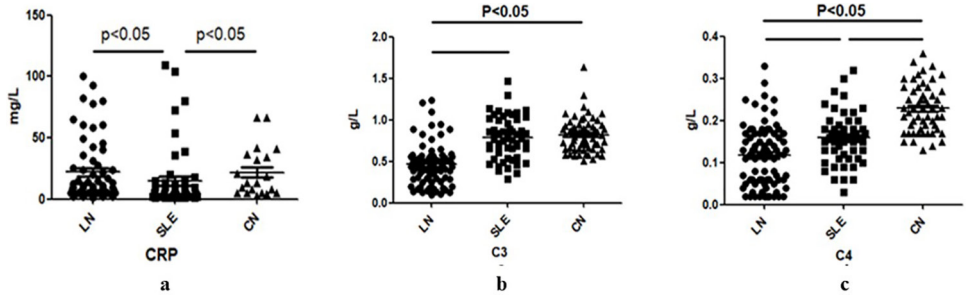

Figure 1. Comparison of CRP (C-reactive protein) (a), C3 (complement 3) (b) and C4 (c) among groups of LN (lupus nephritis), SLE (systemic lupus erythematosus), and CN (chronic nephritis). The differences among these groups were determined by the Mann-Whitney U test. Groups with a P-value<0.05 are highlighted by a horizontal line above.

NLR Level Increased in LN Patients

Table 2 showed the analysis results of CBC indicators of these 4 groups. The WBC counts of LN and CN were significantly higher than those of SLE and HC, but there was no statistical difference between LN and CN. At the same time, the absolute value of neutrophils (Neu#) of LN patients (5.25 (3.63-7.36) $\times10^9$/L) was higher than that of SLE (3.75 (2.33-5.47) $\times10^9$/L) and HC group (3.19 (2.47-4.03) $\times10^9$/L), but no statistical difference between LN and CN was identified. Among the four groups, LN had the lowest lymphocyte count (Lym#), hemoglobin (Hb), and platelet (PLT) levels, but the highest level of NLR (6.48 (3.95-11.76)) and erythrocyte distribution width (RDW) (14.85 (13.7-16.00)%) (Table 2, Figure 2).

NLR and Laboratory Indicators in Patients with LN

In order to explore the correlation between NLR in LN patients and various laboratory indicators, we analyzed the relationship between NLR and inflammatory and immune markers in LN patients. We investigated correlations of NLR with anti-dsDNA, IgG, C3, C4, CRP and SCr in LN group (Figure 3). The data showed that NLR positively correlated with C3 (r=0.222, P=0.042), C4 (r=0.230, P=0.035), CRP (r=0.337, P=0.007) and SCr (r=0.408, P<0.0001), but negatively correlated with IgG (r=-0.226, P=0.041) in LN group. However, there was no statistical significance between NLR and anti-dsDNA. Thus, NLR was closely related with inflammatory biomarkers including C3, C4, CRP, IgG, and SCr in patients with LN.

Table 2. Comparison of CBC data among groups (LN, SLE, CN and HC)

Variables	LN	SLE	CN	HC
WBC, $\times10^9$/L	6.24 (5.18-8.64)[1]	5.52 (4.02-6.99)[4]	6.47 (5.24-8.76)	5.79 (5.02-6.68)
Hb, g/L	91.5 (76.3-111.8)[1,,2,3]	125.0 (118.0-131.0)[4,5]	106.0 (85.0-130.0)[6]	140.0 (133.3-148.8)
PLT, $\times10^9$/L	162.0 (121.0-224.8)[2,3]	180 (128.0-235.0)	209.0 (154.0-262.0)	211.5 (178.0-240.0)
Neu#, $\times10^9$/L	5.25 (3.63-7.36)[1,3]	3.75 (2.33-5.47)	4.67 (3.42-6.38)[6]	3.19 (2.47-4.03)
Lym#, $\times10^9$/L	0.82 (0.63-1.15)[1,2,3]	1.32 (0.80-1.98)[5]	1.24 (0.99-1.69)[6]	2.03 (1.65-2.28)
Mon#, $\times10^9$/L	0.41 (0.29-0.58)	0.45 (0.31-0.60)	0.42 (0.32-0.55)	0.37 (0.29-0.43)
RDW,%	14.85 (13.7-16.00)[1,2,3]	13.5 (12.70-14.20)[5]	13.50 (12.70-15.30)[6]	12.80 (12.23-13.35)[,]
NLR	6.48 (3.95-11.76)[1,2,3]	3.03 (2.02-4.42)[5]	3.57 (2.65-5.41)[6]	1.53 (1.24-2.22)

Variables were expressed as medians (interquartile range). CBC: complete blood cell count;LN: lupus nephritis; SLE: systemic lupus erythematosus (SLE) patients without LN; CN: chronic nephritis patients; HC: healthy controls; Hb: hemoglobin; PLT: platelet; WBC: white blood cell count; Neu#: Neutrophil absolute value; Lym#: Lymphocyte absolute value; Mon#: Monocyte absolute value; RDW: Erythrocyte distribution width; NLR: Neutrophils/lymphocytes; 1: P<0.05 LN vs SLE; 2: P<0.05 LN vs CN; 3: P<0.05 LN vs HC; 4: P<0.05 SLE vs CN; 5: P<0.05 SLE vs HC; 6: P<0.05 CN vs HC.

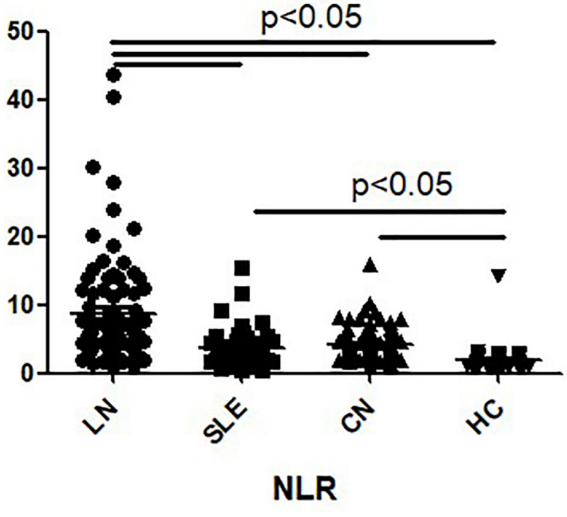

Figure 2. Comparison of NLR (neutrophil-lymphocyte ratio) levels among groups of LN (lupus nephritis), SLE (systemic lupus erythematosus), CN (chronic nephritis), and HC (healthy controls). The ordinate represents the level of NLR ratio. The differences among these groups were determined by the Mann-Whitney U test. Groups with a P-value<0.05 are highlighted by a horizontal line above.

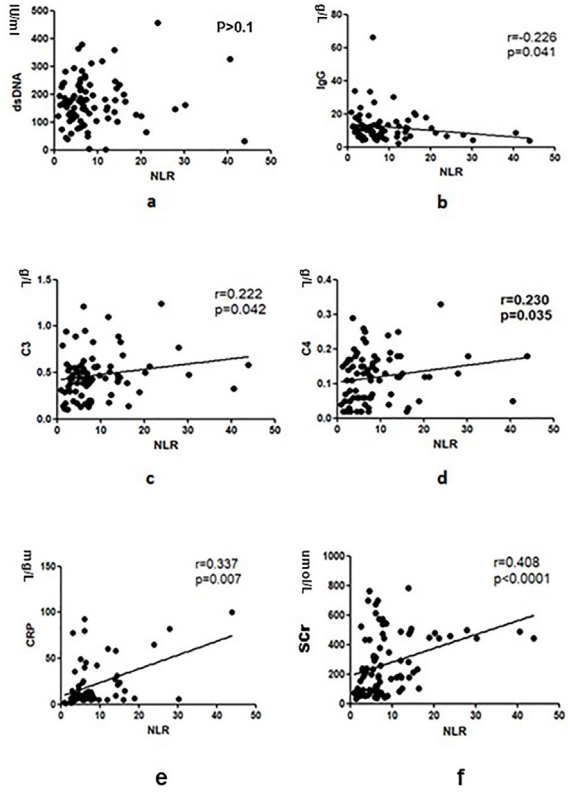

Figure 3. Correlations of NLR (neutrophil-lymphocyte ratio) with anti-dsDNA (a), IgG (b), C3 (complement 3) (c), C4 (d), CRP (C-reactive protein) (e) and SCr (serum creatinine) (f) in LN (lupus nephritis) patients. Spearman correlation analysis was employed to assess these correlations. P-values<0.05 were demonstrated.

Relationship between NLR Level and Renal Function in Patients with LN

To further study the relationship between NLR and renal function in patients with LN, LN patients were divided into three groups according to SCr level (the Chinese chronic renal failure staging): mildly impaired group (SCr<177umol/L), moderately impaired group (177umol/L≤SCr<442umol/L), and severely impaired group (SCr≥442umol/L),

Correlation analysis showed that NLR level increased with the severity of renal impairment in patients with LN. (Table 3 and Figure 4).

Table 3. Relationship between different grades of renal function and NLR in patients with LN

Variables	SCr<177 (n=35)	177≤SCr <442 (n=27)	SCr≥442 (n=26)	P
Age, year	45 (28-52)	51 (40-55)	43 (27-48)	0.055
Gender: M/F	5/30	2/25	7/19	0.143
CRP, mg/L	11.85 (5.00-44.08)	9.410 (5.90-25.30)	9.200 (6.29-20.85)	0.999
ESR, mm/h	30 (18.5-57.0)	41 (23.5-66)	36 (11-50.50)	0.356
eGFR, mL/(min*1.73m^2)	81.40 (58.15-109.0)	24.10 (16.80-33.20)	9.50 (9.00-15.10)	<0.0001
NLR	5.463 (2.344-7.200)	5.926 (3.882-11.79)	10.31 (6.816-20.36)	<0.0001

Variables were expressed as medians (interquartile range). SCr: Serum creatinine; NLR: Neutrophils/lymphocytes; LN: lupus nephritis; M/F: male/female; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; eGFR: Glomerular filtration rate.

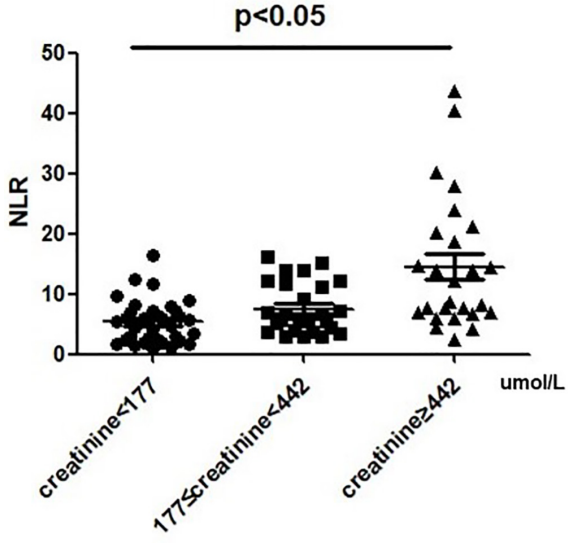

Figure 4. Comparison of NLR (neutrophil-lymphocyte ratio) among different levels of serum creatinine in patients with LN (lupus nephritis). The differences among these groups were determined by the Mann-Whitney U test. Groups with a P-value<0.05 are highlighted by the horizontal line above.

ROC Curves of NLR in LN Patients

ROC curve analysis was performed to establish cut-off points for NLR, and LN patients were defined as "state variables". The area under the curve (AUC) of NLR was 0.785 (0.708-0.862) (Figure 5). NLR could be used for the diagnosis of LN with a specificity of 86.30% and a sensitivity of 65.90%. ROC curve data of NLR showed that it could assist in the differential diagnosis of LN. Besides, the optimal cut-off value for NLR differential diagnosis of LN patients was 5.44, the combination of NLR and urea creatinine is more effective in diagnosing LN (AUC=0.785, 95%CI= (0.708-0.862)). (Figure 5).

DISCUSSION

LN is common in patients with lupus and

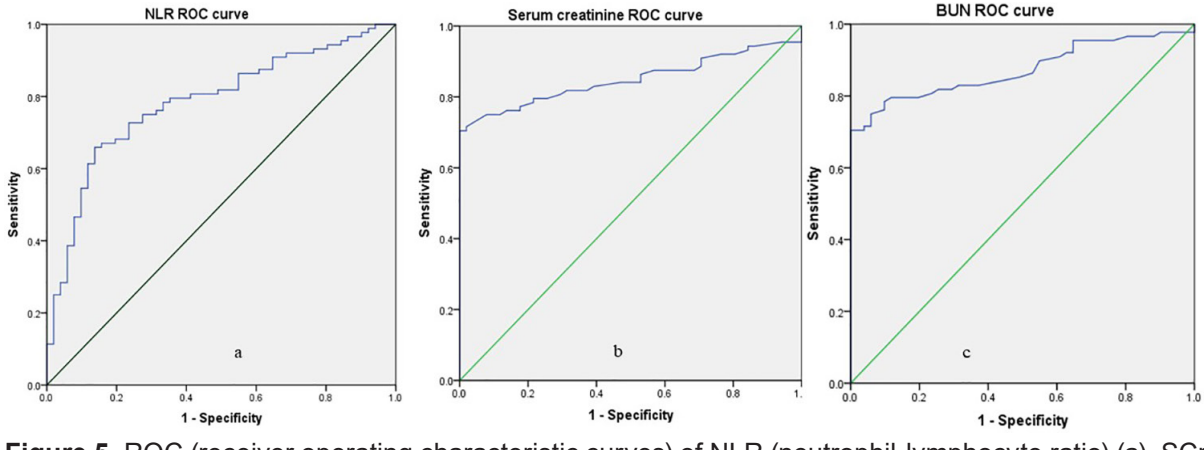

Figure 5. ROC (receiver operating characteristic curves) of NLR (neutrophil-lymphocyte ratio) (a), SCr (serum creatinine) (b), and BUN (blood urea nitrogen) (c) for patients with LN (lupus nephritis) and SLE (systemic lupus erythematosus). Area under curve (AUC) for NLR, SCr and BUN are 0.785 (0.708-0.862), 0.849 (0.784-0.914) and 0.873 (0.815-0.931), respectively.

involved the kidneys in 30%-75% of cases, in addition, it is characterized by proteinuria and cellular tubules and can be observed in both onsets during the whole course of the disease (13). About 10%-30% of patients with LN may develop the end-stage renal disease (14). This risk has remained stable throughout the last three decades (15). The extrarenal involvement with concomitant pulmonary, cardiac, or neurological involvement indicates the need for renal replacement therapy (RRT) including renal dialysis and/or kidney transplantation (13). These patients had poorer long-term prognoses and quality of life. Along with this, approximately 27%-66% of remission patients may subsequently develop episodes of LN (16). Therefore, more convenient, secure, and rapid indicators are needed to assist in the diagnosis of renal inflammation, protect renal function, and prevent a recurrence.

Recent studies have revealed that the pathogenesis of LN is due to the influence of immune system disturbance on passive target organs, the damage of terminal organs by non-immune factors through the regulation of target organ resistance and the local inflammatory response (13, 16, 17). Coupled with this, the imbalance of lymphocytes and neutrophils contributes to the development of SLE. It has been reported that NLR elevates in SLE patients and can reflect inflammatory response and disease activity degree of SLE patients (6, 18-21). Neutrophils and lymphocytes have been reported to play an important role in LN and their levels vary with the remission and aggravation of systemic inflammatory response (17, 22-24). Importantly, neutrophil and lymphocyte counts have been routinely used in clinical practice and were easy to detect. NLR levels are calculated automatically and provided regularly in CBC tests. It is a very ideal indicator for rapid judgment of renal function in patients with LN. This retrospective study enrolled four study subjects: LN (patients with lupus nephritis), SLE (systemic lupus erythematosus patients without LN), CN (patients with chronic nephritis), and HC (healthy controls). To clearly illustrate the correlation of NLR with LN, we specifically set up two condition controls (SLE and CN) to exclude other interference factors.

Previous studies have indicated that the NLR could be a useful marker in the assessment of the inflammatory response of SLE and can be used for monitoring the disease activity of SLE (19, 25). Specifically, we also identified that SLE patients with LN had significantly higher NLR than those without lupus nephritis (6, 26, 27). Therefore, these results implied that NLR might be an indicator for reflecting renal involvement in SLE patients. To further study the role of NLR in lupus nephritis, we included patients with non-lupus chronic nephritis (CN) in the case-control group for the first time. Although there was no significant difference in neutrophil count between LN patients and CN patients, the lymphocyte count of LN was lower than that of CN patients. Finally, the NLR level of LN patients was higher than that of CN patients. Meanwhile, in patients with LN, NLR levels increased with the severity of renal impairment. In this study, the optimal prediction threshold of NLR for LN was 5.44 (sensitivity 86.3%, specificity 65.9%, AUC=0.785). The prediction threshold of NLR for LN in this study is higher than that of other studies (6). One theory is that the subjects we included were in worse shape than the ones we left out, and set more stringent case-control groups.

To the best of our knowledge, this is the first systematic evaluation of the association between NLR and renal function in patients with LN, and exploration of the NLR differences between patients with LN and CN. Coupled with this, the correlation between NLR level and clinical indicators in patients with LN was discussed. The present study included systemic immune markers and variables related to the renal function. Our data show that NLR is associated with the renal function (SCr) and inflammatory biomarkers (C3, C4, CRP, and IgG) in LN patients.

Furthermore, we did not have a great understanding of the interplay between NLR level and prognosis caused by irregular clinical follow-up.

CONCLUSION

In conclusion, the NLR of patients with LN was higher than that of patients with CN and SLE without LN and showed an aggressive increase with an increasing degree of renal insufficiency. These results suggest that NLR could be a potential marker for predicting LN and assessing the severity of renal injury in patients with LN.

AUTHOR CONTRIBUTIONS

HXW and DJT designed the study, wrote the article, and consulted literature. QT and LZ performed experiment and statistical data. XJJ revised manuscript. All authors contributed to the article and approved the submitted version.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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