



Neutrophil-to-lymphocyte ratio: An effective predictor of corticosteroid response in IgA nephropathy

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ABSTRACT

Background: The neutrophil-to-lymphocyte ratio (NLR) has been shown to have a strong predictive ability for the prognosis of various diseases. However, the role of the NLR in IgA nephropathy is currently unknown. In this study, we attempted to evaluate how useful the NLR is for predicting corticosteroid response in IgA nephropathy. **Methods:** For retrospective cohort with IgA nephropathy, the patients who received corticosteroid therapy were recruited. To identify independent factors for corticosteroid response, the NLR and other parameters were analyzed using the multivariate regression model. The predictive usefulness was determined by the area under the receiver operating characteristics curve (AUROC). Survival analysis was conducted to compare the corticosteroid response between different groups according to the cut-off of NLR.

Results: Multivariate analyses showed that NLR, serum creatinine, uric acid, and estimated glomerular filtration rate (eGFR) were independent factors for corticosteroid response. The AUROC of NLR (0.748) was higher than those of other factors. Patients with NLRs < 2.43 had a higher remission rate than those with NLR \geq 2.43 ($P < 0.001$).

Conclusion: NLR is an effective predictor of corticosteroid response in IgA nephropathy.

1. Introduction

Immunoglobulin A (IgA) nephropathy is defined as prominent IgA deposition in the glomerular mesangium. IgA nephropathy is a typical type of glomerulonephritis globally [1]. The clinical manifestations of IgA nephropathy are broad, and include asymptomatic microscopic hematuria and even rapidly progressive glomerulonephritis [1]. Approximately 15–20% of patients with IgA nephropathy develop end-stage renal disease (ESRD) within 10 years of onset. Moreover, this rate will reach 25–30% within 20 years if uncontrolled. As a result, these patients usually require replacement therapies [2,3]. Currently, the most common treatment for IgA nephropathy is angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [4,5]. Corticosteroid would be beneficial for patients with proteinuria that is persistently above 1 g/24 h [6]. However, the efficacy of the corticosteroid is distinct, and there are few parameters to predict the response to corticosteroid therapy.

The neutrophil-to-lymphocyte ratio (NLR) reveals an unbalanced status between two different immune systems [7]. The neutrophil count (NC) reflects persistent inflammation, while the lymphocyte count (LC) reveals the regulatory immune pathway and malnutrition. Many lines of evidence prove that elevated NLR correlates with poor outcomes in

malignant tumors, acute systemic inflammation, and cardiac disease [8]. However, to the best of our knowledge, no research has investigated the usefulness of NLR in patients with IgA nephropathy. Corticosteroid is commonly used to treat IgA nephropathy because of its anti-inflammatory properties. Thus, in this article, we attempted to explore the correlation between NLR and corticosteroid response in patients with IgA nephropathy.

2. Materials and methods

2.1. Patients

Patients with IgA nephropathy who were admitted at the Department of Nephrology, Tianjin Medical University No. 2 Hospital (Tianjin, China) between 2000 and 2018 were recruited. The inclusion criteria for patients were as follows: (1) over 18 years old; (2) diagnosed as having IgA nephropathy according to pathological results from a kidney biopsy; (3) having persistent proteinuria of > 1 g/24 h after ACEI/ARB treatment for 6 months. Exclusion criteria were as follows: (1) secondary IgA nephropathy; (2) presence of ESRD; (3) malignant tumors with or without metastasis; (4) active infection; (5) uncontrolled diabetes; (6) coronary artery diseases, heart failure; (8) other diseases

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that could impact the NLR value.

The corticosteroid regimen was as follows: intravenous methylprednisolone, 1 g/d for three consecutive days at 1, 3, and 5 months and oral prednisone at 0.5 mg/kg/d on alternate days for 6 months [9]. The patients were followed up each month as outpatients, and remission was defined as proteinuria of < 1 g/24 h during follow-up.

2.2. Clinical and laboratory data collection

The clinical data and laboratory results were collected from all patients recruited. Clinical data included sex, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and response to corticosteroid. Laboratory data included albumin (ALB), uric acid (UA), serum creatinine (Scr), proteinuria, NC and LC.

The eGFR and NLR were calculated as follows:

$$\text{NLR} = \text{NC} (10^9/\text{L})/\text{LC} (10^9/\text{L})$$

$$\text{eGFR} (\text{mL}/\text{min}/1.73 \text{ m}^2) = a \times (\text{Scr}/b)^c \times (0.993)^{\text{age}}$$

(Modification of Diet in Renal Disease (MDRD) Study Equation for Chinese with minor modification [10])

(a = 141, b = 79.56, c = -0.411, if male and Scr ≤ 79.56;

a = 141, b = 79.56, c = -1.209, if male and Scr > 79.56;

a = 144, b = 61.88, c = -0.329, if female and Scr ≤ 61.88;

a = 144, b = 61.88, c = -1.209, if female and Scr > 61.88).

2.3. Statistical analysis

Continuous data were presented as mean ± SD and categorical data were recorded as rate. Continuous data were compared by *t*-test and categorical data were compared by chi-square test. The Cox proportional hazards model was used to determine independent factors affecting the prognosis. The prognostic usefulness of the independent parameters was identified according to the area under the receiver operating characteristics curve (AUROC). AUROC was determined with 95% CI. The optimal cut-off for each parameter was determined according to the Youden Index. The Kaplan-Meier method was used to estimate time to remission, and differences were compared using the log-rank test. All *P* values were two-sided, and a *P* value < 0.05 was considered as significant statistically. Statistical analyses were performed by SPSS 22.0, GraphPad Prism V.6.01 and MedCalc 18.2.1.

3. Result

3.1. Patient characteristics

In total, 99 patients were recruited in this study. Their characteristics are presented in Table 1. Sixty-six patients achieved remission

Table 1
Characteristics of patients.

Characteristic	Total (n = 99)
Age (year)	37.29 ± 12.13
Sex (male, %)	53/53.5
SBP (mmHg)	129.41 ± 16.08
DBP (mmHg)	85.09 ± 11.33
ALB (g/L)	36.04 ± 8.62
UA (μmol/L)	386.12 ± 102.74
Scr (μmol/L)	91.61 ± 45.88
eGFR (mL/min/1.73 m ²)	85.93 ± 30.47
BMI (kg/m ²)	24.91 ± 4.42
NLR	2.74 ± 1.21
Proteinuria (g/24 h)	3.55 ± 1.30
Remission rate	66/66.7%
Time of remission	4.20 ± 1.79

Table 2

Univariate analysis of the characteristics of patients with IgA nephropathy.

Characteristic	Remission (n = 66)	Non-remission (n = 33)	<i>P</i>
Age (year)	38.03 ± 12.68	35.83 ± 10.98	0.399
Sex (male/%)	35/53	18/54.5	0.887
SBP (mmHg)	130.65 ± 15.79	126.92 ± 16.61	0.279
DBP (mmHg)	81.27 ± 10.61	87.02 ± 11.27	0.017*
ALB (g/L)	38.12 ± 7.31	35 ± 9.08	0.09
UA (μmol/L)	347.92 ± 93.96	405.21 ± 102.25	0.008**
Scr (μmol/L)	74.47 ± 43.34	100.18 ± 45.00	0.008**
eGFR (mL/min/1.73 m ²)	92.30 ± 28.64	82.75 ± 31.07	0.043*
BMI (kg/m ²)	25.13 ± 4.65	24.47 ± 3.94	0.488
NLR	2.51 ± 1.07	3.19 ± 1.35	0.007**
Proteinuria (g/24 h)	3.54 ± 1.29	3.56 ± 1.35	0.047

* *P* < 0.05.

** *P* < 0.01.

with the corticosteroid therapy. The remission rate was 66.7%, and it took 4.2 months on average to achieve remission.

3.2. Independent prognostic factors for corticosteroid response

A univariate analysis was conducted to compare the baseline levels of age, sex, SBP, DBP, BMI, ALB, UA, Scr, eGFR, proteinuria, and NLR between the remission and non-remission groups. The results are shown in Table 2. The DBP, UA, Scr, eGFR, and NLR of these two groups were significantly different (*P* < 0.05) [Fig. 1]. Subsequently, the Cox proportional hazards model analysis was conducted, and the result showed that NLR, Scr, eGFR, and UA were significant independent prognostic factors for non-remission; the results are shown in Table 3. The NLR values of all the patients from the remission and non-remission groups are shown in Fig. 2.

3.3. The predictive value of the independent factors for the corticosteroid response

We applied the ROC method to analyze the predictive ability of all the independent prognostic factors, including NLR, Scr, UA and eGFR, for the corticosteroid response. As shown in Fig. 3 and Table 4, the AUROC of NLR was 0.748 (*P* < 0.001) and those of Scr, UA, eGFR were 0.710, 0.655 and 0.638 (*P* < 0.01), respectively. Moreover, ROC analysis indicated that the optimal cut-off value of NLR to predict the corticosteroid response was 2.43, with a sensitivity and specificity of 77.63% and 75.76%, respectively.

3.4. Corticosteroid effectiveness analysis according to the NLR value

According to the cut-off value of the ROC analysis result, we categorized all patients into two different groups. One was the high NLR group (NLR ≥ 2.43), and the other was the low NLR group (NLR < 2.43). In the high NLR group, 16 of 41 patients had remission under the corticosteroid therapy (39.02%), while in the low NLR group, 50 of 58 (86.2%) patients had remission. The results of the Kaplan-Meier survival analysis are shown in Fig. 4. The log-rank test analysis results show that patients whose baseline NLRs were < 2.43 had a significantly higher remission rate than those with a NLR of 2.43 and above (*P* < 0.001).

4. Discussion

In this study, we explored the correlation between the NLR and corticosteroid response in patients with IgA nephropathy. The research indicated that in addition to Scr, UA and eGFR, NLR was an independent predictive factor for corticosteroid response. Compared with other parameters, NLR had a higher predictive efficacy. Moreover,

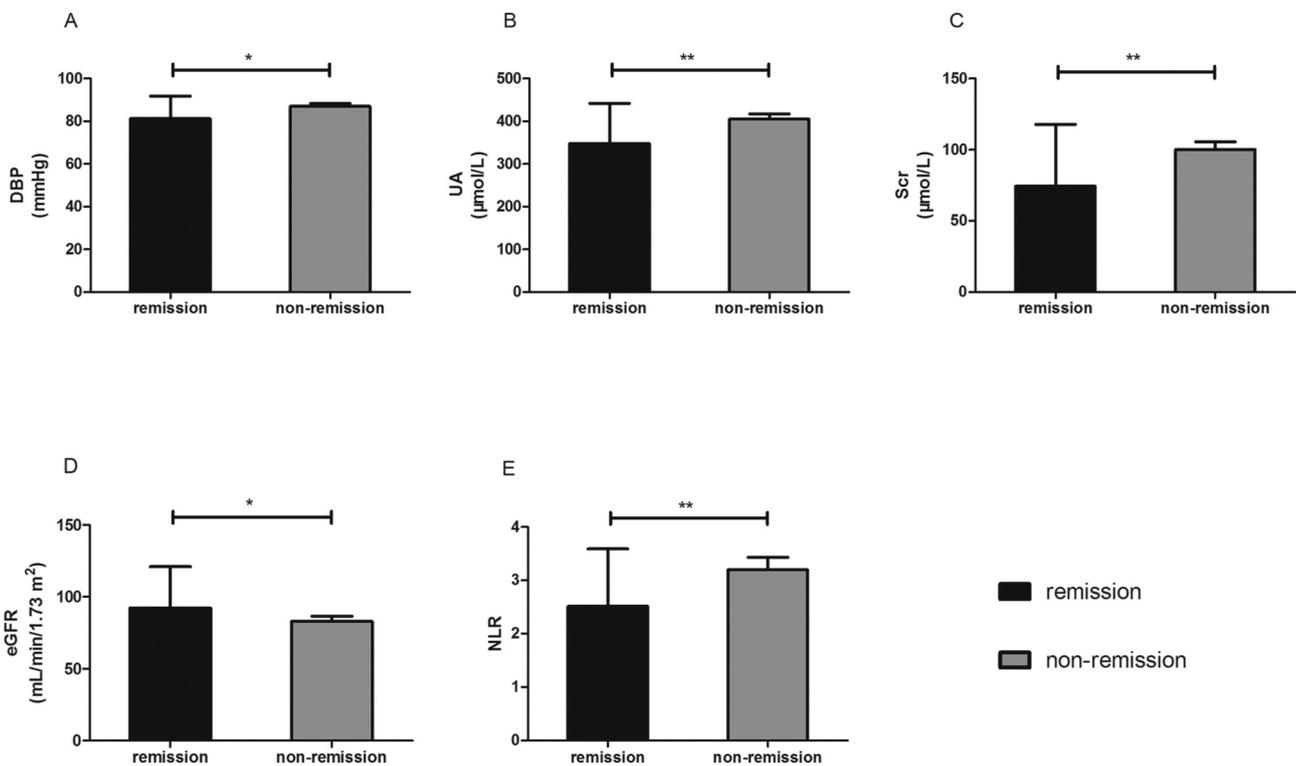


Fig. 1. Univariate analysis results of patients with IgA nephropathy between the remission and non-remission groups (* $P < 0.05$, ** $P < 0.01$).

Table 3
Independent prognostic factors for non-remission in patients with IgA nephropathy.

Parameters	HR	95% CI	P
NLR	1.252	1.097–1.407	0.001
Scr (μmol/L)	1.027	1.013–1.041	0.009
UA (μmol/L)	1.013	1.006–1.020	0.017
eGFR (mL/min/1.73 m ²)	0.796	0.691–0.901	0.034

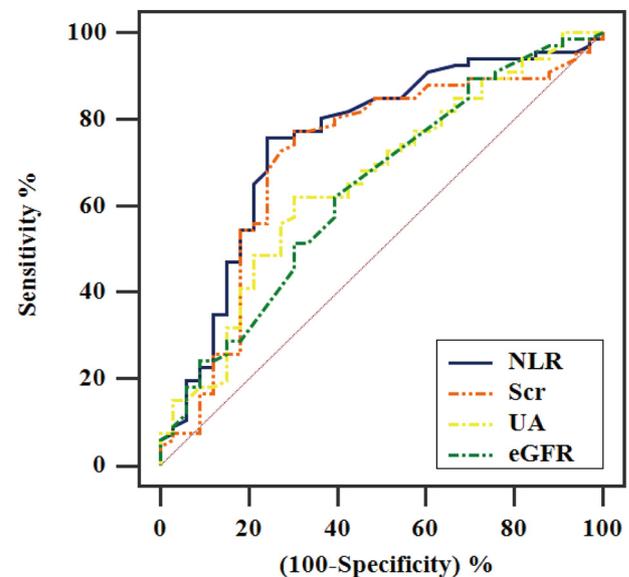


Fig. 3. The ROC and its accuracy of all the independent prognostic factors including NLR, Scr, UA and eGFR for the corticosteroid response in patients with IgA nephropathy.

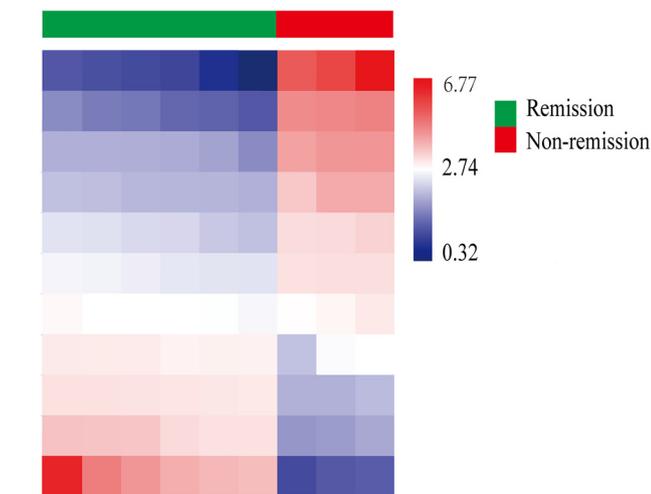


Fig. 2. Data visualization of NLR of all patients with IgA nephropathy from the remission and non-remission groups.

patients with IgA nephropathy who had increased basal NLR showed a poor response to the corticosteroid treatment. These findings indicated that the NLR could be an ideal parameter to predict the response to corticosteroid in patients with IgA nephropathy.

The optimum therapy for IgA nephropathy has remained debatable. The recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis suggested long-term ACEI/ARB therapy, if proteinuria is > 1 g/day, with up-titration of the drug depending on blood pressure [11]. For patients with eGFR > 50 ml/min/1.73 m² and persistent proteinuria higher than 1 g/day, despite 3 to 6 months of optimized supportive treatment (including ACEIs or ARBs and blood pressure control), a 6-month course of corticosteroid therapy is strongly suggested. The randomized studies showed that the patients who were treated with corticosteroid had a significantly better prognosis than controls. After 10 years, 97% of patients did not have a

Table 4
The diagnostic accuracy of the independent prognostic factors in patients with IgA nephropathy under corticosteroid therapy.

Parameters	AUROC	95% CI	Sensitivity (%)	Specificity (%)	P	Cut-off
NLR	0.748	0.651–0.830	75.76	75.76	< 0.001	2.43
Scr ($\mu\text{mol/L}$)	0.710	0.610–0.796	77.27	69.70	0.004	69
UA ($\mu\text{mol/L}$)	0.655	0.553–0.748	62.12	69.70	0.008	383.8
eGFR (mL/min/1.73 m^2)	0.638	0.535–0.732	62.12	60.61	0.020	80

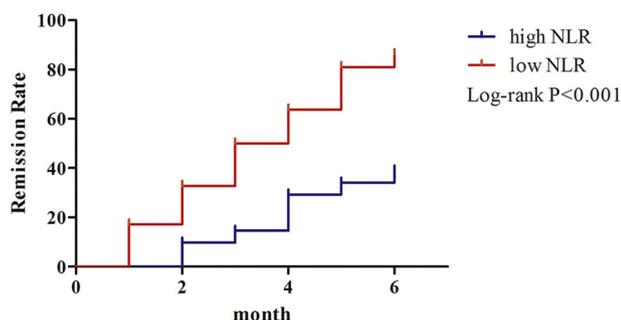


Fig. 4. Corticosteroid response in patients with IgA nephropathy as determined by the Kaplan-Meier survival curve according to NLR. (High NLR: $\text{NLR} \geq 2.43$, low NLR: $\text{NLR} < 2.43$).

doubling of plasma creatinine in the corticosteroid therapy group; the rate in the control group was only 53%. Additionally, the median amount of proteinuria was $< 1 \text{ g/day}$ during follow-up [9,12]. Previous studies have also demonstrated that applying corticosteroids along with ACEIs produced a more valid antiproteinuric effect and a better renal outcome than ACEIs alone [13,14]. On the basis of KDIGO guideline, we recruited patients with IgA nephropathy whose proteinuria was still higher than 1 g/d after ACEIs/ARBs therapy for 6 months in our clinical center and administered corticosteroid therapy to these patients.

Recent research has revealed the existence of many parameters that could indicate the prognosis of IgA nephropathy. Conventionally, serum creatinine, proteinuria, and Oxford classification were regarded as related risk factors for high-risk IgA nephropathy early diagnosis [15]. In addition, there were some new indicators that showed an excellent prognosis predictive ability in patients with IgA nephropathy. In the study by Liu et al., patients with an elevated serum IgG had a relatively higher cumulative renal survival rate [16]. This finding indicated that a decreased serum IgG when renal biopsy was performed was independently correlated with a poor renal outcome in patients with IgA nephropathy [16]. Pathologically, human kidney myeloid leukocytes that express specific intercellular adhesion molecule-3 grabbing non-integrin (SIGN) are the majority of dendritic cells (DCs). DC-SIGN+ cells usually act as proinflammatory mediators and contribute to exacerbate local inflammatory response. Consequently, the density of DC-SIGN+ cells could be a predictor for kidney injuries. To be specific, high renal DC-SIGN+ cell density could serve as a predictive factor for a poor prognosis in patients with IgA nephropathy [17]. Acylcarnitines participate in lipid metabolism and alter mitochondrial function. In addition, a novel finding indicated that plasma acylcarnitines were associated with responses to traditional Chinese medicine in patients with IgA nephropathy. Thus, acylcarnitines could be a potential biomarker for IgA nephropathy [18]. However, no research has suggested indicators that can predict corticosteroid response in patients with IgA nephropathy.

The NLR has been regarded as an indicator of systemic inflammatory response and stress. It has been validated that the NLR has a predictive ability for survival and outcomes in solid tumors [19], coronary artery diseases [20], acute pancreatitis [21] and primary biliary cholangitis [7,8]. Various studies have investigated the relationship between NLR and kidney disease, and most relate to kidney tumors. Elevated preoperative and postoperative NLR are significantly

correlated with not only increased risk of local recurrence but also distant metastasis in patients with localized clear-cell renal cell carcinoma after radiofrequency ablation [22]. Similarly, the NLR is also an excellent survival predictor in patients with metastatic renal cell carcinoma treated with systemic therapy [23]. In addition, NLR and platelet-to-lymphocyte ratio (PLR) were easily obtainable and reproducible predictors of acute rejection in the kidney allograft. Serial monitoring of these ratios could help identify subclinical inflammation before evidence of allograft dysfunction [24]. Because of the high prevalence of diabetes nephropathy, NLR may act as a potential indicator for evaluating kidney injury in patients with diabetes, due to its negative correlation with eGFR and positive correlation with urinary albumin excretion [25]. In addition, a study from Taiwan showed that in men aged under 60 years, increased NLR was related to higher chronic kidney disease (CKD) morbidity [26]. However, we have not found any articles that attempt to apply NLR as a predictor in IgA nephropathy. IgA vasculitis (IgAV) is a common etiology of secondary IgA nephropathy. A previous study reported that NLR could predict renal involvement in IgAV [27]. Similar to our present study, it was also retrospective research that adopted NLR as an indicator in IgA-involved inflammatory diseases. However, our study has provided more notable discoveries. Compared to the study by Nagy et al. [27], the sample size of the present study is significantly larger. Moreover, we attempted to evaluate the predictive ability of corticosteroid response in IgA nephropathy, instead of regarding the NLR as an inflammatory marker.

In our study, the NLR showed an excellent predictive ability for corticosteroid response in IgA nephropathy patients. The possible reasons for this ideal result are as follows. The NLR is the ratio of neutrophils to lymphocytes. Neutrophils usually participate in inflammation, while lymphocytes could release inflammatory cytokines and mediate a variety of immune reactions. Thus, the higher NLR value might be related with the more severe inflammatory reaction. As it is known, corticosteroid has a strong anti-inflammatory effect, and it is suggested for use in patients with IgA nephropathy who have persistent proteinuria of $> 1 \text{ g/24 h}$ after ACEIs/ARBs therapy. However, not all patients with IgA nephropathy would show the desired response to corticosteroids. We assumed that an increased NLR reflects severe renal inflammation, and as a result, patients with an elevated NLR do not benefit from corticosteroid treatment.

To the best of our knowledge, this study is the first to use NLR to evaluate the corticosteroid response in patients with IgA nephropathy, but it still has some limitations. This is a retrospective study from a single center, and the study population is small. The follow-up period is also short. Thus, a longer follow-up period and more detailed studies into the underlying mechanisms are necessary in future.

In conclusion, the current study shows that NLR is a predictive index for corticosteroid response in patients with IgA nephropathy. Further studies with long-term follow-up will provide more detail about the relationship between NLR and IgA nephropathy.

Author contributions

Conception and design: Hu Yang.
Analysis and interpretation of the data: Weiwei Zhang.
Drafting of the article: Ying Li.
Critical revision of the article for important intellectual content:

Rong Li.

Supportive foundations

None.

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