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ORIGINAL ARTICLE

CORRELATION BETWEEN PROTEINURIA DEGREE AND NEUTROPHIL-TO-LYMPHOCYTE RATIO FOR THE EARLY DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS IN CHILDREN

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ABSTRACT

Background: Lupus nephritis (LN) increases mortality and morbidity in systemic lupus erythematosus (SLE) patients. Clinical and laboratory presentations for LN differ and patients most commonly present in a state of acute kidney failure. One of the indicators of kidney involvement in SLE patients is proteinuria. Neutrophils and lymphocytes play an important role in the pathogenesis of LN. Neutrophil-to-lymphocyte ratio (NLR) is one of the known biomarkers for measuring the degree of LN disease activity, as measured by a simple blood test and easily obtained in a cost-effective manner.

Objective: The aim of this study was to investigate the correlation between the degree of proteinuria and NLR in paediatric SLE patients.

Method: This study was conducted retrospectively, using a cross-sectional research method. Data were extracted from the medical records of 62 patients with paediatric SLE at the time of diagnosis. Patients were divided into two groups according to infection status. All patients had urine dipstick measurements for proteinuria. NLR was calculated by comparing the absolute neutrophil count with absolute lymphocyte number obtained from a patient's peripheral blood sample.

Result: There was an increase in NLR according to the positivity rate of proteinuria, but this was not statistically significant (P >0.05). There was no correlation between NLR and the degree of proteinuria in patients who were diagnosed with early SLE (P >0.05).

Conclusion: There was no significant correlation between NLR and the degree of proteinuria in paediatric patients with an early diagnosis of SLE.

ARTICLE HISTORY

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KEYWORDS

Lupus Nephritis, Systemic Lupus Erythematosus, NLR, Proteinuria.

ABBREVIATIONS:

LN - Lupus Nephritis,
SLE - Systemic Lupus Erythematosus,
EULAR - European League Against Rheumatism,
SLICC - Systemic Lupus International Collaborating Clinic, NLR - Neutrophil-to-Lymphocyte Ratio, CKD - Chronic Kidney Disease,
SD - Standard Deviation.

Introduction

Around five million people in the world suffer from systemic lupus erythematosus (SLE) and every year there are more than 100,000 new cases. However, only 20% of these cases are diagnosed in the paediatric population.[1] Based on hospital health system data, there were around 1.25 million cases of SLE in Indonesia in 2016. Among the 2,166 in patients diagnosed with SLE, 550 died. Based on the Indonesian Systemic Lupus Erythematosus Association (PESLI), the average incidence of new SLE cases in 2016 was 10.5%. However, because the clinical manifestations of SLE are very diverse, it often causes a delay in SLE diagnosis.[2]

Involvement of the kidneys is more common in youngsters than in adults. Renal involvement is reported to occur in 50-75% of paediatric SLE patients, with more than 90% developing lupus nephritis (LN) within two years after diagnosis.[3] SLE scores were considerably greater in the presence of LN than in the absence of LN. LN can manifest in a variety of ways, from "silent" LN (with normal urine analysis results, normal renal function and no proteinuria) to LN with severe proteinuria and nephrotic syndrome (>3.5 g protein in urine per day) or acute nephritic syndrome, which can lead to acute renal failure. Patients with LN are frequently diagnosed after they have developed acute kidney failure, which is characterized by moderate proteinuria with or without haematuria and can be accompanied by leukocyturia. In some cases, patients may also be diagnosed with chronic kidney failure and hypertension as early manifestations of LN.[4]

Several biomarkers can be used to assess the severity of LN risk. Changes in circulating cells, inflammatory mediator concentrations, specific urine proteins and molecular markers that can be measured in renal tissue are all examples of biomarkers.[5] Neutrophils, lymphocytes, monocytes and platelets play important roles in the development of LN, their levels changing with exacerbation or remission of the systemic inflammatory response.[6] The amount of circulating cells

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may be determined by a complete blood count, which can be performed at a variety of health facilities. The neutrophil-to-lymphocyte ratio (NLR) is a biomarker that uses the number of lymphocytes and neutrophils identified on a full blood count to determine the degree of activity of SLE and LN. NLR has a positive correlation with blood urea nitrogen (BUN), serum urea, serum creatine and 24-hour urine protein in one investigation.[7]

The purpose of this study was to examine the correlation between the degree of proteinuria with NLR ratio in paediatric SLE patients. Moreover, data collected at the beginning of the diagnosis of paediatric SLE, is useful for the identification of predictive biomarkers to assess the LN risk in paediatric SLE patients.

Methods & Materials

This cross-sectional study encompassed 62 paediatric SLE patients (≤18 years). The data was obtained retrospectively from November 2018 to August 2021, via a link to the laboratory database (HCLAB) of Dr. Hasan Sadikin General Hospital Bandung, West Java, Indonesia. The variables assessed were age, gender, date of diagnosis, NLR, degree of proteinuria and other laboratory variables related to SLE, including disease activity and indicators of infection at the time the patient was diagnosed with LES. The NLR was calculated by comparing the number of absolute neutrophils and absolute lymphocytes obtained from peripheral blood samples, while the degree of proteinuria is seen from the urine dipstick results, which consist of negative to positive 4. Patients in this study had been diagnosed with SLE based on the ACR-1997/SLICC-2017/EULAR-2018 LES criteria at the age of under 18 years. Children with an early diagnosis of SLE and kidney problems other than those caused by SLE, as well as those who were already receiving treatment, were excluded from this study. Patients were divided into groups with (n=17) and without acute infection (n=45). The infection referred to in this study was an acute infection that affected the organ system systemically, caused by bacteria, viruses, parasites, or fungi, detected at the initial diagnosis of SLE.

Continuous variables are presented using the mean, standard deviation, median and range and categorical variables are presented using sums and percentages. For group and data comparisons, the Kolmogorov–Smirnov or Shapiro-Wilk tests were used to check the conformity of the data to a normal distribution. The comparison of NLR in the acute infection group with no infection and NLR with the degree of proteinuria was analysed using the parametric One-Way ANOVA or non-parametric Kruskal Wallis comparison test and in the comparison of NLR with proteinuria using the parametric t-test or non-parametric Man Whitney test for initial diagnosis of the child as a whole, without infection and with acute infection. The correlation of the degree of proteinuria with NLR was analysed by Spearman's rho correlation for early paediatric patients overall, without infection and with acute infection. A P value <0.05 was considered statistically significant for all variables.

This research was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran with ethics number 712/UN6.KEP/EC/202.

Results

Laboratory data evaluated for 77 paediatric SLE patients resulted in study where the number of subjects who met the inclusion and exclusion criteria were 62, consisting of 45 patients with an early diagnosis of SLE without infection and 17 patients with acute infection.

In this study, the characteristics of age and sex of patients with an early diagnosis of childhood SLE can be seen in table 1. The median age of patients with an early diagnosis of childhood SLE was 13.7 years, with an age range of 5.4–16.9 years. The majority of paediatric SLE patients were female, with a percentage of 90.3% of the total 62 patients; among them, 17 patients (27.5%) had acute infection, while 45 patients (72.5%) did not.

Table 1. Characteristics According to Age and Sex.

Variables	All Patient (n=62)	No Infection (n=45)	Acute Infection (n=17)
Sex, n (%)			
Male	6 (9.7)	3 (6.7)	3 (17.6)
Female	56 (90.3)	42 (93.3)	14 (82.4)
Age (Years)			
Median	13.7	13.7	13.6
Range	5.4–16.9	7.9–16.9	5.4–16.8

Table 2. Type of Infection.

Type of Infection	n (%)
Urinary tract infection	12 (70.5%)
Septic arthritis	1 (5.9%)
Gastroenteritis	1 (5.9%)
Bronchopneumonia	1 (5.9%)
Pleuropneumonia	1 (5.9%)
COVID-19	1 (5.9%)

The most common type of infection in early childhood SLE diagnosis was urinary tract infection, with a percentage of 70.5% (Table 2). The median NLR was seen to be highest in patients with acute infection (3.64) compared to patients without infection (2.76), but this was not statistically significant (P >0.05) (Table 3). Table 4 shows that more patients presented with positive proteinuria, 66.1% (41) out of a total of 62 patients, with positive 3 being the highest degree of proteinuria at 24.2% (15).

The NLR value was higher in patients with proteinuria than in those without proteinuria and tended to increase according to the proteinuria positivity rate (P >0.05) (Tables 5 and 6). The Spearman-Rho correlation test was performed to assess the correlation between NLR and the degree of proteinuria. Table 7 shows that there was no correlation between NLR and the degree of proteinuria in patients with an early diagnosis of SLE.

Table 3. Comparison of NLR Values Between Patients with and without Infection.

	NLR				
Groups	**x̄**	**SD**	**Median**	**Range**	**P-Value**
No Infection	3.49	2.39	2.76	0.79-10.22	0.2
Acute Infection	5.05	4.16	3.64	0.11-16.96	

Mann Whitney

Table 4. Proteinuria Degree.

Variables	All Patient (n=62)	No Infection (n=45)	Acute Infection (n=17)
Proteinuria Degree, n (%)			
Negative	21 (33.9)	13 (28.9)	8 (47.1)
Positive 1	5 (8.1)	5 (11.1)	0 (0)
Positive 2	11 (17.7)	8 (17.8)	3 (17.6)
Positive 3	15 (24.2)	13 (28.9)	2 (11.8)
Positive 4	10 (16.1)	6 (13.3)	4 (23.5)

Table 5. Comparison of NLR with Proteinuria Degree.

	NLR				
Proteinuria Degree	**x̄**	**SD**	**Median**	**Range**	**P-Value**
Negative	3.63	2.64	2.53	1.15-9.55	0.92
Positive 1	2.62	0.75	2.25	1.98-3.53	
Positive 2	4.16	2.85	3.27	0.79-10.23	
Positive 3	3.89	2.85	3.39	0.82-8.4	
Positive 4	4.93	4.95	3.53	0.11-16.96	

Kruskal-Walis

Table 6. Comparison of NLR with Proteinuria.

	NLR				
Proteinuria	**x̄**	**SD**	**Median**	**Range**	**P-Value**
Negative	3.63	2.64	2.53	1.15-9.55	0.59
Positive	4.06	3.22	3.27	0.11-16.96	

Mann-Whitney

Discussion

In this study, the median age of the children with SLE was 13.7 years, ranging from 5.4 to 16.9 years. The results of this study are in accordance with previous case-control study from medical record of children diagnosed with SLE based on the ACR 1997, which showed that the median age of SLE patients was 14 years old, with an age range of 4-18 years.[8]

The majority of paediatric SLE patients in this study were women. This is in accordance with previous retrospective descriptive study from the medical record of children diagnosed to have paediatric SLE based on the SLICC 2012, which showed that the vast majority of paediatric SLE patients were female, with a percentage reaching 87.9% and a female: male ratio of 7.3:1[9], whereas a cohort analytic study of children diagnosed with SLE based on ACR 1997, showed that women comprised 89.9% of paediatric SLE patients, with a female to male ratio of 8.9:1.[10] These results are in accordance with the theory that women are at greater risk of developing SLE compared to men. This indicates that there is a relationship between the incidence of SLE and genes on the X chromosome. Hormonal factors are also involved in the incidence of SLE. Oestrogen and prolactin are known to increase auto-immunity, activation and auto-reactivity of B cells, as well as modulate the activation of lymphocytes and plasmacytoid dendritic cells (pDCs).[11,12]

Infection is a leading cause of death and morbidity in SLE patients. Infection is frequent in SLE and responsible for 25% to 50% of all fatalities. This is because SLE causes excessive immunological reactivation, which disrupts numerous defensive systems against germs, viruses and fungi.[13,14] In the present study, 27.5% of patients arrived with infections and urinary tract infections were the most frequent kind of illness. This is consistent with the findings of previous study, who discovered that 27.5% of paediatric SLE patients were infected at the time of diagnosis, while 72.5% were not, with urinary tract infections dominating at 41%.[10]

Previous case-control study of LN patients whose meet criteria of ACR 1982, discovered that NLR was higher in LN patients with infection than in LN patients without infection. This is consistent with our findings, which reveal that median NLR levels are higher in patients with infection.[6] In this study, more patients presented to clinic with positive proteinuria. This is in accordance with previous studies showing that LN patients generally have moderate proteinuria and/or haematuria. In some cases, leukocyturia was also found, since the current LN diagnosis was confirmed when there were already clinical changes in the patient, while the clinical presentation and laboratory findings of LN were very diverse.[4]

Table 7. Correlation of NLR with Proteinuria Degree.

Parameters	All Patient		No Infection		Acute Infection	
	NLR		NLR		NLR	
	r	P-Value	r	P-Value	r	P-Value
Proteinuria degree	0.093	0.236	0.195	0.100	-0.071	0.394

Spearman Rho

There was no significant difference between NLR and proteinuria in this study, although there was a rise in NLR after the increase in degree of proteinuria. This is in contrast to previous two case-control studies in LN patients, found that the mean NLR in LN patients was considerably greater than in SLE patients without nephritis.[15,16] However, this study is in accordance with previous research using retrospective study of SLE patient whose diagnosed based on ACR 1997, who showed that the NLR value trend higher in patients with positive proteinuria compared to those with negative proteinuria.[17] This is consistent with the progression of LN illness. Glomerular damage, which is initially mediated by immune complexes, differs depending on where the immune complexes are deposited. Immune complexes deposited in kidney tissue activate the conventional complement system, as well as macrophages and neutrophils. When the classical complement system is activated, a complement protein chemoattractant is formed, which stimulates neutrophil recruitment and activation. This causes the release of oxygen free radicals, the creation of proinflammatory cytokines and the amplification of immunological and inflammatory responses in renal tissue, leading to glomerular filtration barrier (GFB) breakdown and causing proteinuria.[3,5]

Previous cross-sectional study of SLE patients were newly diagnosed based on the ACR 1997, found a significant correlation between NLR and proteinuria. In addition, two other studies in CKD patients revealed a link between proteinuria and NLR.[7,18,19] However, this study showed that there was no correlation between NLR and the degree of proteinuria. Our study was supported by previous three other studies, which showed that there was no correlation between NLR and proteinuria in SLE patients.[20,21,22]

The NLR is a biomarker used to monitor the inflammatory process and immune response, it has been shown to predict the activity of auto-immune and inflammatory illnesses and can be easily utilized in clinical practice. However, several variables, such as dehydration, overhydration and changes in the management of blood collections, can readily impact the patient's blood cell characteristics. Patients with SLE frequently have haematologic abnormalities, decreased total numbers of red blood cells, white blood cells and platelets can occur as a result of immunological suppression of the bone marrow or excessive destruction of peripheral cells.[21,23] Protein in the urine of SLE patients reveals glomerulus damage, although protein that is recognized as positive might be owing to a very alkaline urine pH (pH >8), such that the protein urine examination with a dipstick can read up to +2 (positive 2). Furthermore, the concentration of the patient's urine might impact the degree of proteinuria; diluted urine can result in lower positive dipstick readings, whereas concentrated urine can result in greater positive dipstick values.[5,17] Furthermore, hypertension and the use of renin-angiotensin-converting enzyme inhibitors may impact the degree of proteinuria in these individuals. As a result, there is no association between NLR and the degree of proteinuria owing to these causes.[20]

The small number of research subjects in this study was a limitation, as were the excluded cases, which reduced statistical power. Furthermore, this study employed a retrospective approach, including secondary data sourced from HCLAB Dr. Hasan Sadikin General Hospital. As a result, the data gathered had the potential to be erroneously reported.

Conclusion

According to the findings of this study, the NLR tended to be higher in the group with acute infection than in the group without infection, as well as in the positive proteinuria compared to the negative proteinuria patient group (also increasing according to the positivity rate), but this trend was not statistically significant. NLR and the degree of proteinuria in children with an early diagnosis of SLE were not related. However, more research is needed to corroborate our findings in terms of parameters (peripheral blood profile, hydration status, blood pressure, anti-hypertensive medication usage and urine profile) that may alter NLR and the degree of proteinuria.

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Compliance with Ethical Standards

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Conflict of Interest: None

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