

Analysis of Albumin to Globulin Ratio as A Prognostic Predictor in Lupus Nephritis Patients

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ABSTRACT

Lupus Nephritis (LN) is a manifestation of Systemic Lupus Erythematosus (SLE), which targets the kidney. Based on histopathology, the World Health Organization divides the disease into five classes: normal pattern, mesangial, focal, diffuse proliferative, and membranous. Albumin to Globulin Ratio (AGR) compares serum albumin with serum globulin levels. Low AGR value is associated with poor prognosis of diseases such as cancer, liver cirrhosis, and other chronic inflammatory diseases such as LN. This study aimed to analyze the AGR value as a prognostic predictor in LN patients based on disease classes with a retrospective descriptive cross-sectional approach. Total subjects were 109, which consisted of class 1 (n=15), class 2 (n=37), class 3 (n=9), class 4 (n=21), and class 5 LN (n=27). Data of disease classes, serum albumin, and serum globulin/total protein levels were collected. SPSS version 25, Mann-Whitney, Kruskal-Wallis, Chi-Square, and Spearman's correlation test were used for statistical analysis. The ROC curve determined the cut-off. Test results were significant if $p < 0.05$. The lowest mean AGR value (0.79) was found in class 4 LN ($p < 0.05$). The optimal cut-off AGR was 1.10 to categorize mild-moderate and severe degrees. AGR prognostic value: sensitivity=95.8%; specificity=78.8%; Positive Prediction Value (PPV)=78.0%; Negative Prediction Value (NPV)=96.0%, accuracy = 86.2%. There was a negative strong correlation between the AGR value and LN class with a correlation coefficient R of -0.777 ($p < 0.001$). AGR marker has a good sensitivity and specificity as a predictor of LN progression.

Keywords: Albumin to globulin ratio, lupus nephritis, class of lupus nephritis

INTRODUCTION

Lupus Nephritis (LN) is a disease as a manifestation of Systemic Lupus Erythematosus (SLE), which targets the kidneys and is a predictor of poor prognosis for disease progression. The prevalence of SLE varies among countries, from 2.9 cases per 100,000 people to 400 cases per 100,000 people. Approximately 40-45% of the population is estimated to develop lupus nephritis. The presence of kidney damage generally occurs after five years of diagnosis. Based on data from the National Kidney Foundation 2020, it was found that the incidence was higher in children and young people, especially at the age of 10-18 years. Complications of lupus nephritis are more common in males than females, although SLE cases are more common in females, with a ratio of 9:1.¹⁻⁴

The diagnosis of LN is established based on the criteria by the American College of Rheumatology (ACR), such as persistent proteinuria or urine protein greater than 0.5 grams/day (or $> 3+$ on dipstick test) or abnormalities in the urine sediment such as

hematuria and casts in various shapes in the urine.⁵⁻⁷ Renal biopsy remains the gold standard for LN diagnosis. World Health Organization (WHO) classifies LN into five classes such as class 1 (normal pattern), class 2 (mesangial), class 3 (focal), class 4 (diffuse proliferative), and class 5 (membranous) based on the histological pattern and clinical manifestation.⁸

Low serum albumin levels characterize LN a significant consequence of impaired renal filtration. Persistent hypoalbuminemia is a common characteristic of Protein-Energy Wasting (PEW), which is a significant risk factor for morbidity and mortality in LN patients. In contrast to elevated serum globulin levels, this is associated with the production of autoantibodies as the primary pathogenesis of the disease. Gamma globulin is one of the main components of serum globulin. The continuous production of gamma globulin as one of the immunoglobulin and a part of the globulin is considered to be the cause of an increase in serum globulin levels in LN patients.^{9,10}

Late diagnosis of LN is associated with a high-risk factor for renal insufficiency and End-Stage Renal Disease (ESRD), which can increase morbidity and mortality, indicating the urgent need for early identification. Various types of laboratory tests to assess kidney function, such as 24-hour urine protein, urine dipstick, urine protein-creatinine ratio, and creatinine clearance, are often performed; however, these tests have drawbacks in terms of effectiveness. A simple and more clinically reliable alternative laboratory test with lower cost is needed as an indicator to help clinicians early identify patients who are at high risk of impaired renal function and is expected to reduce morbidity and mortality.^{8,9}

Both albumin and globulin are types of plasma proteins found in the blood; albumin levels are the most widely circulated type of protein. The albumin-to-globulin ratio (AGR) test aims to compare albumin levels with serum globulin levels, which the following equation can calculate: $AGR = \frac{\text{albumin}}{\text{total protein} - \text{albumin}}$. Calculation of AGR value is an economical and simple method to do. Several studies have stated that low AGR values are associated with poor prognosis in patients with various types of diseases, such as cancer (malignancy), liver cirrhosis, and various chronic inflammatory diseases. Based on this background, the authors were interested in analyzing the AGR value in lupus nephritis with various severities.^{7,9,10}

METHODS

This research was a descriptive retrospective study with a cross-sectional approach. It collected secondary data from the medical records of outpatients and inpatients at Dr. Wahidin Sudirohusodo Hospital from January 2019 to December 2021 and was conducted at the Medical Records Installation of Dr. Wahidin Sudirohusodo Hospital from June to October 2022.

The study population was all outpatient and inpatient LN patients at Dr. Wahidin Sudirohusodo Hospital, Makassar, from January 2019 to December 2021. Research subjects were all LN patients diagnosed by clinicians based on clinical symptoms, laboratory test results (urinalysis showed persistent proteinuria or >0.5 gram/day with urine analyzer or $>3+$ on dipstick test, or abnormalities in the urine sediment such as hematuria and casts) and/or histopathological features. Diseases were classified into five classes such as class 1 (normal pattern), class 2 (mesangial), class 3 (focal), class 4 (diffuse proliferative), and class 5 (membranous) based on the

histological pattern and clinical manifestation. Inclusion criteria were patients who had serum albumin, serum globulin and/or serum total protein test results. Patients with impaired liver function, cancer patients, multiple myeloma, and other malignancies were excluded from this study.

Research permission has been approved by the Health Research Ethics Commission, Faculty of Medicine of Hasanuddin University, Hasanuddin University General Hospital, and Dr. Wahidin Sudirohusodo Hospital, Makassar, with number 427/UN4.6.4.5.31/PP36/2022.

Data were analyzed using SPSS version 25. Descriptive calculations and the Kruskal-Wallis test (for non-normally distributed AGR data) were used for statistical analysis. The p -value <0.05 was reported as significant.

RESULTS AND DISCUSSIONS

This study involved a total of 109 patients aged 7-54 years, with a mean age of 21.6 ± 9.9 years. A total of 60 (55.05%) subjects had an age <21 years and 49 (44.95%) subjects had an age >21 years. Research subjects in this study consisted of 12 (11.0%) male patients and 97 (89.0%) female patients. The most common class of lupus nephritis in this study was class 2 (mesangial/mild-moderate stage), which was found in 37 (33.0%) subjects, followed by class 5 (membranous/severe) found in 27 (24.8%) subjects. The characteristics of research subjects can be seen in Table 1.

Table 1. Characteristics of research data

Characteristics of Subjects		Total (n=109)	(%)
Gender	Males	12	11.0
	Females	97	89.0
Age group	<21 years	60	55.0
	>21 years	49	45.0
Class	I (normal)	15	13.8
	II (mesangial)	37	33.9
	III (focal)	9	8.3
	IV (diffuse proliferative)	21	19.3
	V (membranous)	27	24.8

Table 2 shows the descriptive statistics and the mean AGR value in each LN class using the normality test. AGR values in this study varied between 0.45 and 2.11, with a median of 1.04 and a mean of 1.10 ± 0.36 . Based on the normality test, AGR data were not normally distributed.

Table 2. Descriptive statistic results among variables (n=109)

Variable	Min	Max	Median	Mean	SD
Albumin	0.8	4.2	2.60	2.57	0.77
Globulin	1.5	3.7	2.40	2.39	0.44
Total protein	2.5	7.2	5.00	4.95	0.96
AGR	0.45	2.11	1.04	1.10	0.36

Table 3. Comparison of AGR value according to age

Age*	n	Min	Max	Median	Mean	SD	p
≤21 years	60	0.47	2.11	1.04	1.09	0.36	0.708
>21 years	49	0.45	1.80	1.04	1.11	0.36	

*Mann-Whitney test *21 years was used based on the mean age

Table 4. Comparison of AGR value according to gender

Gender	n	Min	Max	Median	Mean	SD	p
Female	97	0.48	2.11	1.09	1.12	0.35	0.051
Male	12	0.45	1.65	0.82	0.90	0.38	

*Mann-Whitney test

Table 5. Comparison of AGR value according to LN class

LN Class	n	Min	Max	Median	Mean	SD	p
1	15	1.22	2.11	1.58	1.56	0.22	<0.001
2	37	0.55	1.87	1.36	1.30	0.29	
3	9	1.00	1.50	1.04	1.12	0.15	
4	21	0.45	1.16	0.78	0.79	0.16	
5	27	0.47	1.12	0.78	0.80	0.16	

*Kruskal-Wallis test

The mean AGR was higher at age >21 years (1.11) than at age ≤21 years (1.09) but not statistically significant (p>0.05). This result indicated no significant relationship between age and AGR value. A higher AGR was found in females (1.112) compared to males (0.90), but not statistically significant (p>0.05). This finding indicated no significant relationship between gender and AGR value. The highest AGR value (median and mean) was found in class 1 (1.58 and 1.56), whereas the lowest AGR was found in class 4 (0.78 and 0.79) (p<0.001). This result indicated a significant relationship between the AGR value and the LN class. A comparison of this AGR value can be seen in Tables 3, 4, and 5.

The following comparison analyzed in this study was the relationship between AGR values among LN classes, which was then analyzed using the multiple comparisons test. The results showed no significant difference in AGR values between class 4 and class 5 LN. However, there was a significant difference in all AGR values among other classes(p<0.05) (Figure 1).

There was a significant negative correlation between the LN class and the AGR value (p <0.001); a higher LN class (indicating a more severe disease) would lead to a lower AGR value. Based on the

correlation coefficient (R) obtained in this study, there was a strong correlation between the LN class and the AGR value (R> 0.750) (Table 6).

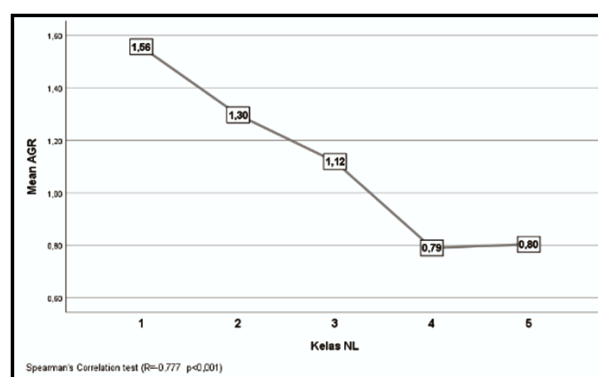


Figure 1. The curve of comparison in AGR value according to LN class

Table 6. Correlation between LN class and AGR value

Type	Variable	Statistic	AGR
Spearman's rho	LN class	R	-0.777
		p	0.000
		n	109

*Spearman's correlation test

To determine the AGR cut-off value, ROC curve analysis was performed to obtain the Area Under the Curve (AUC). To perform ROC curve analysis, the LN class was grouped into 2 categories: the severe class (classes 4 and 5) and the mild/moderate class (classes 1, 2, and 3) (Figure 2).

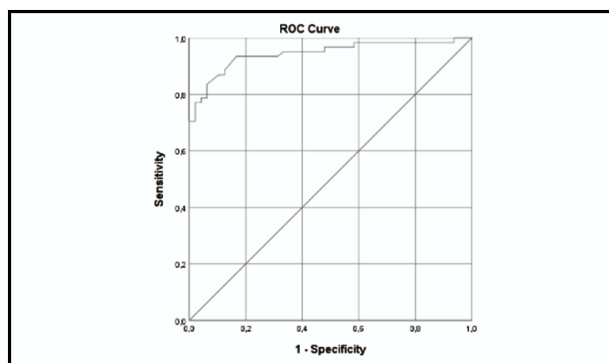


Figure 2. ROC curve

Table 7 shows that a significant AUC value obtained in this study was 0.945 (p <0.001), indicating that the AGR cut-off value can be used as a prognostic instrument for the severity of LN. Based on the coordinate value of the ROC curve, a cut-off value of 1.10 was obtained, which provided optimal sensitivity and specificity.

Based on the ROC curve and AUC table, the AGR cut-off value that provided optimal sensitivity and specificity was 1.10, with a sensitivity of 95.8% and a specificity of 78.8%. Based on these statistical data, it can be concluded that a LN patient whose AGR ≤ 1.10 was most likely to develop a severe degree (grade 4 and 5). Contrastingly, an LN patient whose AGR > 1.10 was most likely to have mild/moderate LN (grade 1-3). The calculation of the AGR prognostic value is shown in Table 8.

This study involved a total of 109 LN patients with ages of 7-54 years, and the most common age was ≤ 21 years (55.0%). This fact was in line with data from the National Kidney Foundation in 2020, stating that a higher incidence of LN was found in children and young people, especially at the age of 10-18 years. Most of the LN patients in this study were females, with a total of 97 (89%) subjects. This data was inconsistent with data from the National Kidney Foundation, which states that complications of LN are more common in males than females. However, there are higher SLE cases in females with a ratio of

Table 8. Calculation of prognostic value

AGR Cut-Off	Severity of LN		Total
	Severe	Moderate/Mild	
≤1.10	46	13	59
>1.10	2	48	50
Total	48	61	109

*Chi-Square (p<0.001)

9:1. The most common LN class in this study was class 2 (mesangial), followed by class 5 (membranous). According to the WHO, grade 4 lupus nephritis has the highest incidence and accounts for 40% of LN, followed by class 2, which accounts for 20% of LN.

The results of the analysis of AGR values based on age using the Mann-Whitney test found that the mean AGR value was lower in the age group ≤21 years compared to the age group >21 years but not statistically significant (p> 0.05). The analysis of AGR values based on gender showed that the mean AGR value was lower in males than in females. This finding follows data from SLEDAI (SLE disease activity index) and several previous studies, which suggested that although SLE cases are more common in females, complications of LN are more common in males than females. This is associated with the role of androgen hormones in the damage of kidney cells by stimulating the process of apoptosis. Although this study shows lower AGR value in males than in females, it was not statistically significant.

The difference in AGR values based on the LN class was analyzed using the Kruskal-Wallis test. The highest average AGR in class 1 LN was 1.56, followed by class 2 with an average AGR of 1.30. This study followed the Recommendation Guidebook of the Indonesian Rheumatology Association, which suggests that there is almost no significant decline in kidney function in class 1 and 2 LN, which indicates a good prognosis. The average AGR value in class 3 LN was 1.12, slightly lower than in class 1 and 2 LN. The lowest average AGR value was found in class 4 LN, also in accordance with the statement by the Recommendation Guidebook of the Indonesian Rheumatology Association that the stage of diffuse proliferative glomerulonephritis (grade 4) has the worst prognosis; 11-48% of patients will experience renal failure within five years. A study by I Gusti Ngurah Agung in Udayana also stated that class 4 LN

Table 7. The area under the curve of AGR

AUC	Std. Error	p	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.945	0.022	0.000	0.902	0.988

with 50% glomerular involvement had the worst prognosis.¹¹ Class 5 LN has a pretty good prognosis, similar to primary membranous nephropathy, but with a low probability of severe nephrotic syndrome. This study obtained the average AGR value of 0.80 in class 5, slightly higher than class 4 LN.

This study's results found a significant negative correlation between AGR scores and LN classes. A lower AGR value will lead to a higher LN class (more severe disease). There was a strong correlation between the AGR values and the LN class ($R > 0.750$).

CONCLUSIONS AND SUGGESTIONS

There was a significant difference between the AGR values in each disease class, with the lowest average AGR in class 4 (diffuse proliferative) and the highest AGR in class 1 (normal histological pattern) with a $p < 0.001$. These data indicated a significant relationship between the AGR value and the LN class. The AGR cut-off value was 1.10 (sensitivity of 95.8 and specificity of 78.8%) to divide the disease stage into two categories such as the severe category (grades 4 and 5) and the mild-moderate category (grades 1, 2, and 3). AGR can be used as a predictor of the progression of LN patients with good sensitivity and specificity.

The results of this study were expected to be useful for clinicians, who should consider AGR markers for assessing the progressivity of lupus nephritis to lower the possibility of disease worsening.

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