

Correlation between Neutrophil-Lymphocyte Ratio and Urea Serum in Hemodialysis Patients at Dr. Doris Sylvanus Hospital

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ABSTRACT

Chronic Kidney Disease (CKD) is a condition characterized by kidney damage for ≥ 3 months, as well as structural or functional abnormalities with or without a decrease in Glomerular Filtration Rate (GFR) < 60 mL/minute/1.73. This damage leads to increased urea levels in the blood, also known as uremia, which can increase the risk of inflammation in CKD patients undergoing hemodialysis (HD). Previous studies revealed that increased urea and Neutrophil-Lymphocyte Ratio (NLR) can be used as inflammatory biomarkers to replace CRP, IL-6, and other indicators. This study aimed to determine the correlation between NLR and serum urea levels in pre- and post-HD CKD patients at Dr. Doris Sylvanus Hospital. An analytical survey method was used with a retrospective design. The process started by taking medical records of patients currently undergoing HD who were selected as respondents. The sample population consisted of 50 (70.4%) males and 21 (29.6%) females. Based on the age group, 43.7% of patients were aged 51-60. The results showed that the average NLR pre- and post-HD were 5.24 ± 4.88 and 10.41 ± 12.31 , respectively. The average urea pre- and post-HD were 195.97 ± 77.88 and 120.97 ± 47.4 , respectively. The bivariate analysis showed a significant weak correlation between NLR and serum urea level pre-HD ($p=0.004$ with $r=0.338$) and post-HD ($p=0.039$ with $r=0.246$) in patients.

Keywords: Chronic kidney disease, hemodialysis, neutrophil-lymphocyte ratio, urea serum

INTRODUCTION

Chronic Kidney Disease (CKD) is a global public health problem with an increasing prevalence, a poor prognosis, and high management costs.¹ The systemic review and meta-analysis in 2016 revealed that its prevalence was 13.4%.² The Indonesian Renal Registry (IRR) also reported that in 2018, 66,433 new CKD patients were found, and this number increased 13 times from 2007.³ The Basic Health Research Data for 2018 showed that the prevalence increased by 0.38% compared to 2013, namely 0.2%.⁴ In 2018, the disease occurrence rate in Central Kalimantan was 0.31%. IRR also revealed that 88 patients were diagnosed with CKD and undergoing hemodialysis (HD) therapy in the region.³

Chronic kidney disease is characterized by kidney damage for ≥ 3 months and structural or functional abnormalities with or without a decrease in Glomerular Filtration Rate (GFR) < 60 mL/minute/1.73. The decrease occurs gradually and persists until it eventually causes end-stage renal failure. Kidney damage is characterized by protein and/or blood in the urine and increased blood urea

levels. Urea is a waste product of the body's protein metabolism and excreted through the kidneys. Accumulation of high urea levels in the blood, also known as uremia, can cause increased morbidity and mortality.⁵

Nelly *et al.* revealed differences in the Neutrophil Lymphocyte Ratio (NLR) in CKD patients pre- and post-HD and a correlation between NLR values and serum urea level. This correlation can be used as a predictor of inflammation and mortality in patients undergoing the treatment.⁶ Guillaume *et al.* also reported that NLR can predict mortality and cardiovascular events but not severe infections.⁷

This study aims to determine the correlation between NLR and serum urea levels in pre- and post-HD CKD patients at Dr. Doris Sylvanus Hospital. Based on previous findings, only a few studies explored this topic, specifically Palangka Raya.

METHODS

This study used an analytic survey method with a retrospective design by taking medical record data for CKD patients in 2021 in the HD room at Dr. Doris

Sylvanus Hospital, Palangka Raya. The sample population consisted of all patients diagnosed with chronic kidney disease, undergoing HD, and having routine blood tests and urea examinations before and after the fifth HD. Patients who dropped out of HD were excluded from this study.

The parameters used included serum urea and NLR before and after the fifth HD due to patient adherence to HD procedures. The lymphocyte ratio compares absolute neutrophil and lymphocyte values from routine patient blood tests. Subsequently, the patient's data were grouped into CKD before and after the fifth HD.

Analysis was carried out using the IBM SPSS statistic 26 program, where all data obtained were tested for normality to determine the distribution using Kolmogorov Smirnov. The results were then presented in the form of average and standard deviation. Statistical analysis was significant when the p-value < 0.05.

Research permission was obtained from the Health Research Ethics Commission Faculty of Medicine, Palangka Raya University, with number 39/UN24.9/LL/2022.

RESULTS AND DISCUSSION

Among the 110 patients who underwent HD in 2021, 71 fulfilled the predetermined inclusion criteria. Respondents consisted of 50 (70.4%) males and 21 (29.6%) females, as shown in Table 1. Based on gender, male patients undergoing HD were higher due to several factors, such as lifestyle and hormones.

Table 1. Gender distribution of CKD patients

Gender	Frequency	Percentage
Male	50	70.4%
Female	21	29.6%
Total	71	100%

Habits like smoking were a more significant risk factor for causing CKD by increasing the sympathetic nervous system, leading to increased blood pressure, tachycardia, and accumulation of catecholamines in the circulation. This phase caused several blood vessels to experience vasoconstriction, such as coronary arteries. Therefore, smoking increases renal vascular resistance, which decreases the glomerular filtration rate and filter fraction.⁸ Other habits, such as the consumption of energy drinks, also affect the organ's function.⁹ Factors, including hormones, were one of the causes of high CKD prevalence in males. This fact aligns with the underlying mechanism that males have the testosterone hormone, which plays a

role in accelerating the process of CKD. This hormone-induced apoptosis in podocytes is essential in developing glomerulosclerosis and tissue fibrosis through an androgen receptor-dependent mechanism. It also enhanced the apoptotic process in proximal tubular cells by stimulating the c-Jun amino-terminal kinase pathway. In turn, it activated the Fas ligand-dependent apoptotic pathway associated with increased expression of caspase 8, 9, and 3, which was the cause of continued apoptosis in tissues.¹⁰⁻¹²

Based on age, 31 of the patients undergoing HD were aged 46-55 years old, namely 43.7%. Decreasing kidney function is a normal process along with the aging process, and at the age of 40, there is often a progressive decrease in the GFR and Renal Blood Flow (RBF) of around 10 mL/minute/1.73 m² (Table 2).

Table 2. Age distribution of CKD patients

Age	Frequency	Percentage
26-35 years old	3	4.2%
36-45 years old	10	14.1%
46-55 years old	31	43.7%
56-65 years old	26	36.6%
>65 years old	1	1.4%
Total	71	100%

An increase in age every decade causes triglycerides in the blood to increase by 30-50%, eventually affecting nephrosclerosis. Therefore, it was estimated that there is a decrease in kidney function by 10 mL/minute/1.73. At > 40 years, there is a progressive decline due to the addition of sclerotic tissue, loss of nephrons and tissue from the renal cortex, decreased blood flow to the organ, and reduced glomerular surface.^{13,14}

In this study, the average post-HD was higher than the pre-HD NLR, namely 10.41±12.3 and 5.24±4.88, respectively, as shown in Figure 1.

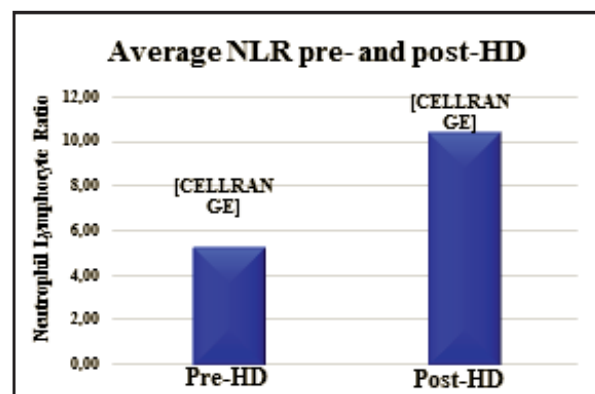


Figure 1. Average NLR pre- and post-HD

Based on the data, the average urea in pre- and post-HD was 195.97 ± 77.88 and 120.97 ± 47.40 , respectively, as shown in Figure 2. This result is inversely proportional to the average NLR, where the urea was found to decrease after HD.

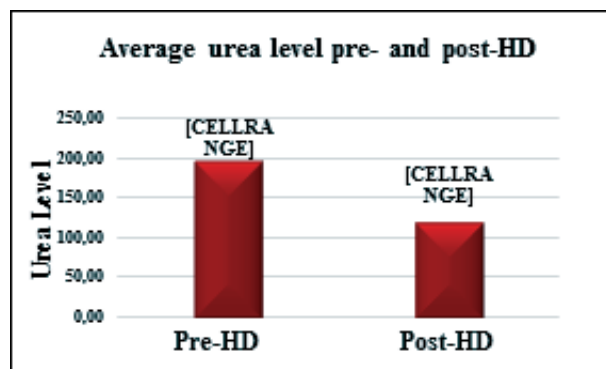


Figure 2. Average Urea Level Pre- and Post-HD

Based on the bivariate analysis of the correlation between NLR and urea level pre-HD, p-value <0.005 (0.004) and $r = 0.338$ was obtained, as shown in Table 3. This result indicated that there was a significant weak correlation between both parameters. The correlation test between NLR and urea level post-HD obtained a p-value <0.005 (0.039) $r = 0.246$. Therefore, both NLR and urea levels had weak significant correlations, as shown in Table 4.

Table 3. Correlation analysis between NLR and urea level pre-HD

Variable	NLR pre-HD	
	R	P
Urea pre-HD	0.338	0.004

Description: r: Correlation; P: Probability

Table 4. Correlation analysis between NLR and urea level post-HD

Variable	NLR post-HD	
	R	P
Urea post-HD	0.246	0.039

Description: r: Correlation; P: Probability

Changes in CKD patients' immune response were caused by uremia, vitamin D deficiency, excessive iron accumulation, and hemodialysis treatment.⁶ In this study, increased high blood urea levels caused NLR pre- and post-HD, also known as uremia. The analysis's results proved that although there was a decrease in serum urea level after hemodialysis, most of the patients still had uremia, as shown in Figure 2.

In uremia, ubiquitin-like peptides inhibit the binding of polymorphonuclear leukocytes (PMNLs)

to c5a molecules, which ultimately causes a decrease in the function of the immune system.^{6,15} PMNLs are a critical element of non-specific cellular immune defense and participate in the primary immune reaction. Impaired PMNLs function increases the risk of bacterial infection, as well as morbidity and mortality in patients.¹⁶

Uremia was also associated with oxidative stress, which triggered inflammation in patients. Oxidative stress occurs when there is an imbalance between free radical production and antioxidant defenses. The Reactive Oxygen Species (ROS) responsible for oxidative stress is superoxide. The primary source of superoxide is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in phagocytes and endothelial cells. It is often converted by superoxide dismutase (SOD) into hydrogen peroxide (H_2O_2).^{17,18} Reactive oxygen species produced from this process affected the increase in oxidative stress, causing inflammation and contributing to atherosclerosis's pathogenesis. This process led to increased cardiovascular disease (CVD) morbidity and mortality in patients.¹⁹

Apart from uremia, HD procedures were considered to contribute to the inflammatory response caused by blood contamination from endotoxin in the dialysis fluid. Soluble pyrogenic bacteria can penetrate through the dialyzer membrane and cause monocyte activation and cytokine production induction in the filtration and back-diffusion of contaminated dialysate. This process led to a complex response associated with a decrease in the immune system due to defects in T lymphocyte cells, thereby causing inflammation.²⁰

Inflammation in patients caused by these factors can be measured using the NLR, an inflammatory marker. The ratio can be assessed easily and affordably because the required data can be obtained from patients' routine blood tests.²¹

This study revealed an increase in NLR, indicating the occurrence of inflammation, a common symptom in patients and associated with morbidity and mortality in CKD. Inflammation assessed by NLR was associated with a state of uremia, which causes oxidative stress with increased reactive oxygen and myeloperoxide.²² Therefore, increased urea can also be used as a biomarker of inflammation and NLR in CKD patients undergoing HD.

CONCLUSIONS AND SUGGESTIONS

Based on this study, the following conclusions can be drawn: The average NLR pre- and post-HD was 5.24 ± 4.88 and 10.41 ± 12.31 ,

respectively. These results indicated an increase in post-HD; The average urea level pre- and post-HD was 195.97 ± 77.88 and 120.97 ± 47.40 , respectively. This data showed a decrease in post-HD; CKD patients had a significantly weak correlation between NLR and urea level pre-HD ($p=0.004$ with $r = 0.338$) and post-HD ($p=0.039$ with $r = 0.246$). Uremia in patients causes various inflammatory mechanisms. Hence, urea and NLR can be used as biomarkers to assess inflammation.

Based on the limitations, further studies using a larger population are suggested, and attention must be paid to HD frequency, which is likely to affect the results obtained. Quantitative analysis is also needed between NLR and urea pre- and post-HD to determine significant differences between these parameters.

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