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# The effect of reduced L-glutathione supplementation on TNF-α, hs-CRP, and neutrophil-lymphocyte ratio in maintenance hemodialysis patients

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**Abstract. – OBJECTIVE: Cardiovascular disease is the main cause of mortality in patients with chronic kidney disease stage 5 on dialysis (CKD-5D). High sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), and neutrophil-lymphocyte ratio (NLR) are several inflammatory parameters associated with high cardiovascular events in CKD-5D. The main aim of this study was to evaluate the effect of reduced L-glutathione supplementation on serum hs-CRP, TNF-α, and NLR in patients with CKD-5D.**

***PATIENTS AND METHODS:* This study is a quasi-experimental research with one group pretest-posttest design. Subjects included were patients with CKD-5D who routinely underwent hemodialysis therapy two times a week in Hasan Sadikin General Hospital. Serum hs-CRP, TNF-α, and NLR levels were obtained before and after the intervention of reduced L-glutathione supplementation dosing of one thousand milligrams a day for four weeks. Statistical analysis was then conducted using the Wilcoxon test.**

***RESULTS:* There were 26 hemodialysis patients included in the study, with a median age of 43 years and a male predominance. There was a significant decrease in serum TNF-α level after reduced L-glutathione supplementation for 4 weeks, 5.40 (-10.80-0.00) pg/mL, $p = 0.002$. However, there was no statistically significant decrease in either serum hs-CRP level, 0.40 (-0.70-0.80) mg/L ($p = 0.656$), or NLR with a difference of 0.55 (0.30-1.00) $p = 0.055$.**

***CONCLUSIONS:* Exogenous oral reduced glutathione supplementation for four weeks significantly reduced TNF-α level, but no significant decrease in hs-CRP level and NLR in patients with CKD-5D.**

*Key Words:*
Reduced L-glutathione, TNF-α, High sensitivity C-reactive protein, Neutrophil-lymphocyte ratio, Hemodialysis.

## Introduction

Chronic kidney disease is one of the main global health problems with increasing prevalence. Chronic kidney disease can progress to end-stage renal disease requiring renal replacement therapy such as hemodialysis or renal transplantation[1]. The mortality of chronic kidney disease has also increased in the last three decades. In 2016, chronic kidney disease was ranked 13th in the list of causes of death, and in 2040, it is predicted will be the 5th cause of death[2].

Cardiovascular disease is the main cause of death in chronic kidney disease stage 5 on dialysis (CKD-5D) patients[3]. Inflammation and oxidative stress have essential roles in chronic kidney disease complications, including cardiovascular diseases. Oxidative stress, acidosis, recurrent infection, and intestinal dysbiosis contribute to a chronic inflammatory state in chronic kidney disease. Oxidative stress induces pro-inflammatory cytokines in chronic diseases. Tumor necrosis factor-α is associated with markers of inflammation and malnutrition and also predicts mortality in chronic kidney disease patients[1,4]. C-reactive protein (CRP), an acute phase reactant produced in

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response to inflammation, is considered a powerful predictor of cardiovascular disease in chronic kidney disease patients[5,6]. Neutrophil-lymphocyte ratio (NLR) is a cheaper and widely available marker, especially in low-income countries, and is associated with cardiac death and mortality in chronic kidney disease patients[4,7-9].

In chronic kidney disease patients, there is higher production and reduced clearance of free radicals, causing high oxidative stress, which causes an imbalance between oxidants and antioxidants[10]. Dietary restrictions, loss of vitamins during hemodialysis, and malnutrition reduce antioxidants, causing higher oxidative stress in CKD-5D patients[11]. Therefore, antioxidant supplementation, especially strong and endogenous antioxidants, can be a promising therapy for chronic kidney disease patients to overcome oxidative stress and inflammation[12]. Several studies[13,14] have shown the efficacy of glutathione supplementation in reducing inflammatory parameters in patients without chronic renal disease. However, no studies have been conducted to analyze the effect of reduced glutathione supplementation in chronic renal disease patients.

Reduced glutathione (GSH) is a major endogenous intracellular antioxidant[15]. This study analyzes the effect of supplementation of reduced L-glutathione on inflammatory parameters in CKD-5D patients.

## Patients and Methods

This study is a quasi-experimental research with one group pretest-posttest design. This study was carried out in the Dialysis unit at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Thirty subjects who met the inclusion and exclusion criteria were enrolled in this study. The inclusion criteria were being over 18 years old and having undergone hemodialysis twice a week for at least 3 months. The exclusion criteria were hospitalization, malignancy, unstable conditions such as acute heart failure, acute coronary syndrome, etc., acute bleeding, acute and chronic infection, use of medications with anti-inflammatory capacity in 2 weeks prior, use of exogenous antioxidant supplement in prior 2 weeks, intolerant to reduced L-glutathione, pregnancy, and acute and chronic liver disease. During the intervention, subjects who did not consume glutathione for three days in a row, could not tolerate reduced L-glutathione supplementation, were hospitalized for acute conditions, or withdrew from the research were excluded. The study protocol was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, and written informed consent was obtained from all patients.

The study period was set at 4 weeks. During the intervention, subjects received one thousand milligrams of oral reduced L-glutathione (divided into twice daily under medical supervision). Patients who agreed to participate in the study were administered reduced L-glutathione. High sensitivity C- reactive protein (hs-CRP) as one of the inflammatory parameters was analyzed with an immunoturbidimetry method using Architect c-4000 dan reagent from Abbot Diagnostic- CRP Vario (Milan, Italy). The measurement of soluble tumor necrosis factor-α (TNF-α) was performed on a Bio-Rad model 680 Microplate Reader (Bio-Rad Laboratories, Inc., Hercules, CA, USA) with analysis conducted using Microplate Manager software version 5.2.1 (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Neutrophil-lymphocyte ratio (NLR) was calculated using the formula: absolute neutrophil count/ absolute lymphocyte count, obtained from hematology parameters.

Hemodialysis adequacy was analyzed using the Kt/V formula, in which K is dialyzer clearance of urea, multiplied by t, which is is time/ hemodialysis duration in minutes, divided by V, which is urea distribution volume in mL[16]. Hematological parameters, laboratory values, hs-CRP, and TNF-α levels were obtained before intervention. Blood samples were taken before the dialysis session.

### Statistical Analysis

The characteristics of patients for categorical data were presented as frequencies and proportions, while for numerical data, a normality test was carried out using the Kolmogorov-Smirnov test. If the data distribution was normal, the data analysis was presented as means and standard deviations; however, if the data distribution was not normal, the data analysis was presented as medians. A comparative analysis was conducted to analyze the mean difference of each variable using the Wilcoxon test, as the data distribution was not normal. Data were analyzed using the SPSS software for Windows version 27.0 (IBM, Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

## Results

Thirty subjects were initially enrolled in this study, but two were excluded due to community-acquired pneumonia and acute coronary syndrome. Additionally, one subject was excluded for missing their glutathione intake for three consecutive days and another due to developing an acute upper respiratory tract infection.

Therefore, twenty-six subjects were included. The flow diagram of this study is presented in Figure 1.

The median age of subjects in this study is 43 (34-57) years, with a range of 22 to 68 years old. The majority of subjects in this study are male (18 subjects, 69.2%). The median hemodialysis duration of subjects in this study is 35 months, ranging from 9 months to 128 months. The primary etiology for chronic kidney disease of subjects in this study is hypertension (34.6%) followed by diabetes mellitus (26.9%) and glomerulopathy (26.9%). Hemodialysis adequacy in this study is calculated in Kt/V, with a mean value of 1.6 ± 0.3. The median malnutrition inflammation score (MIS) of subjects in this study is 4, ranging from 2 to 8. A malnutrition inflammation score > 4 indicates malnutrition.

Baseline hematological parameters of subjects in this study are presented in Table I. Hemoglobin has a mean value of 10.0 ± 1.8 g/dL, which is still within the hemoglobin target in CKD-5D patients according to the Indonesian Society of Nephrology (PERNEFRI) 2011, 10-12 g/dL[17]. Leukocyte number is still within the normal limit, 7,162 ± 1,784 cells/mm$^3$, so is the total neutrophil count of 4,729 ± 1,522 cells/mm$^3$, and the total lymphocyte count of 1,411 ± 508 cells/mm$^3$. Thrombocyte count has a median value of 227,500 cells/mm$^3$ ranging from 207,550-260,000 cells/mm$^3$, within normal limits. The mean albumin level in this study is 3.7 ± 0.5 g/dL, total iron binding capacity (TIBC) 216 ± 46 mcg/dL, serum glutamic oxaloacetic transaminase (SGOT) 13.8 ± 4.1, IU/liter serum glutamic pyruvic transaminase (SGPT) 11.4 ± 5.5 IU/liter, all values are within normal limits.

The main result of this study is presented in Table II. The analysis shows that supplementation of reduced L-glutathione for 4 weeks significantly lowered TNF-α with a difference of 5.40 (-10.80-0.00) pg/mL and a *p*-value of 0.002. However, the analysis shows no significant change in either the hs-CRP level [0.40 (-0.70-0.80)], with a *p*-value of 0.656, or the NLR value [0.55 (0.30-1.00)], with a *p*-value of 0.055. The bar chart of hs-CRP, NLR, and TNF-α differences before and after intervention is presented in Figure 2.

## Discussion

The results of this study indicate that supplementing with reduced L-glutathione for four weeks led to a significant reduction in TNF-α

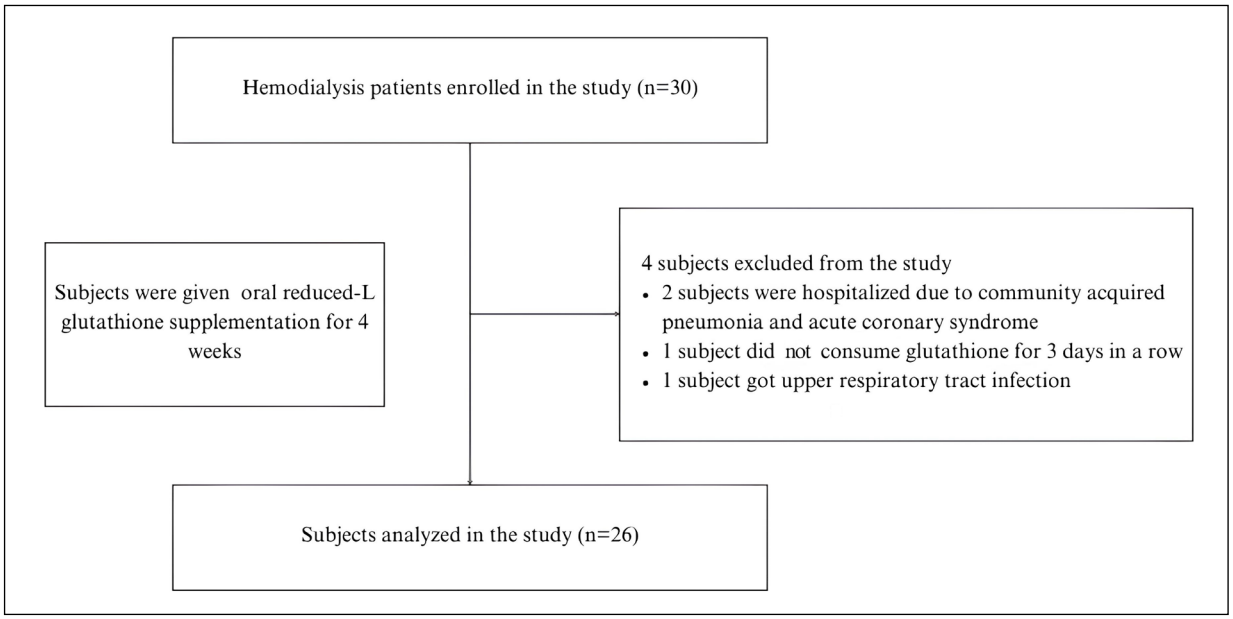


**Figure 1.** Flow diagram for hemodialysis patient recruitment.

**Table I.** Demographics and characteristics of patients.

| Variable | N = 26 |
|---|---|
| **Age, years, median (min-max)** | 43 (34-57) |
| **Sex, n (%)** | |
| Male | 18 (69.2) |
| Female | 8 (30.8) |
| **Hemodialysis duration, months, median (min-max)** | 35 (9-128) |
| **Etiology of CKD, n (%)** | |
| Hypertension | 9 (34.6) |
| Diabetes mellitus | 7 (26.9) |
| Glomerulopathy | 7 (26.9) |
| Chronic pyelonephritis | 3 (11.5) |
| **Kt/V, mean[a]** | 1.6 ± 0.3 |
| **MIS, median (min-max)** | 4 (2-8) |
| **Hematological parameters** | |
| Hemoglobin, mean[a] | 10.0 ± 1.8 |
| Leukocyte, mean[a] | 7,162 ± 1,784 |
| Thrombocyte, median (min-max) | 227,500 (207,550-260,000) |
| Neutrophil, mean[a] | 4,729 ± 1,522 |
| Lymphocyte, mean[a] | 1,411 ± 508 |
| **Laboratory values** | |
| Albumin, mean[a] | 3.7 ± 0.5 |
| TIBC, mean[a] | 216 ± 46 |
| SGOT, mean[a] | 13.8 ± 4.1 |
| SGPT, mean[a] | 11.4 ± 5.5 |

MIS, malnutrition inflammation score; TIBC, total iron binding capacity; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase. [a]Data are presented as the mean ± standard deviation.

levels in CKD-5D patients. Although it did not have a significant impact on hs-CRP levels and NLR, it was linked to lower malnutrition indicators, higher albumin, lower MIS, and better liver function in the subjects of this study.

The subjects in this study had a median age of 43 (34-57), which is different from the Indonesian Renal Registry (IRR) 2020 report, in which the majority of patients reported were in the range of 55-64 years old. The etiology of chronic kidney disease in this study aligns with the etiology reported in IRR 2020. The mean of hemodialysis adequacy in this study is 1.6 ± 0.3, still under 1.8, the value recommended by the Indonesian Society of Nephrology (PERNEFRI)[18]. Only 7.69% of the subjects in this study achieved minimal hemodialysis adequacy, which is consistent with the findings of IRR 2020, which reported that only 14% of patients achieved minimal hemodialysis adequacy.

The mean albumin level in this study is 3.7 g/dL, with only 7 subjects (26.92%) having albumin under 3.5 g/dL. This finding is different from that of IRR 2020, which reported that 72% of patients have albumin levels under 3.5 g/dL. The mean TIBC level in this study is 216 mcg/dL, with 21 subjects (80.77%) having a TIBC level under 250 mcg/dL. This albumin and TIBC level will influence the MIS score. The median of MIS in subjects in this study is 4, ranging from 2 to 8, with only 9 subjects (34.62%) having MIS above 4. Therefore, the majority of subjects in this study

**Table II.** Effect of reduced L-glutathione on TNF-α, hs-CRP, and NLR in hemodialysis patients.

| Variable | Pre (n = 26) | Post (n = 26) | Difference (post-pre) | |
|---|---|---|---|---|
| | Median (IQR) | Median (IQR) | Median (IQR) | *p** |
| Tumor necrosis factor-α (TNF-α) (pg/ml) | 11.60 (6.75-18.62) | 5.66 (3.50-11.06) | -5.40 (-10.80-0.00) | 0.002* |
| High-sensitivity C-reactive protein (hs-CRP) | 3.35 (1.50-5.10) | 2.10 (2.00-5.10) | -0.40 (-0.70-0.80) | 0.656 |
| Neutrophil-lymphocyte ratio (NLR) | 3.30 (2.30-4.30) | 3.95 (2.90-4.60) | 0.55 (0.30-1.00) | 0.055 |

CI = confidence interval; IQR = interquartile range. *Wilcoxon test, significant if $p < 0.05$.

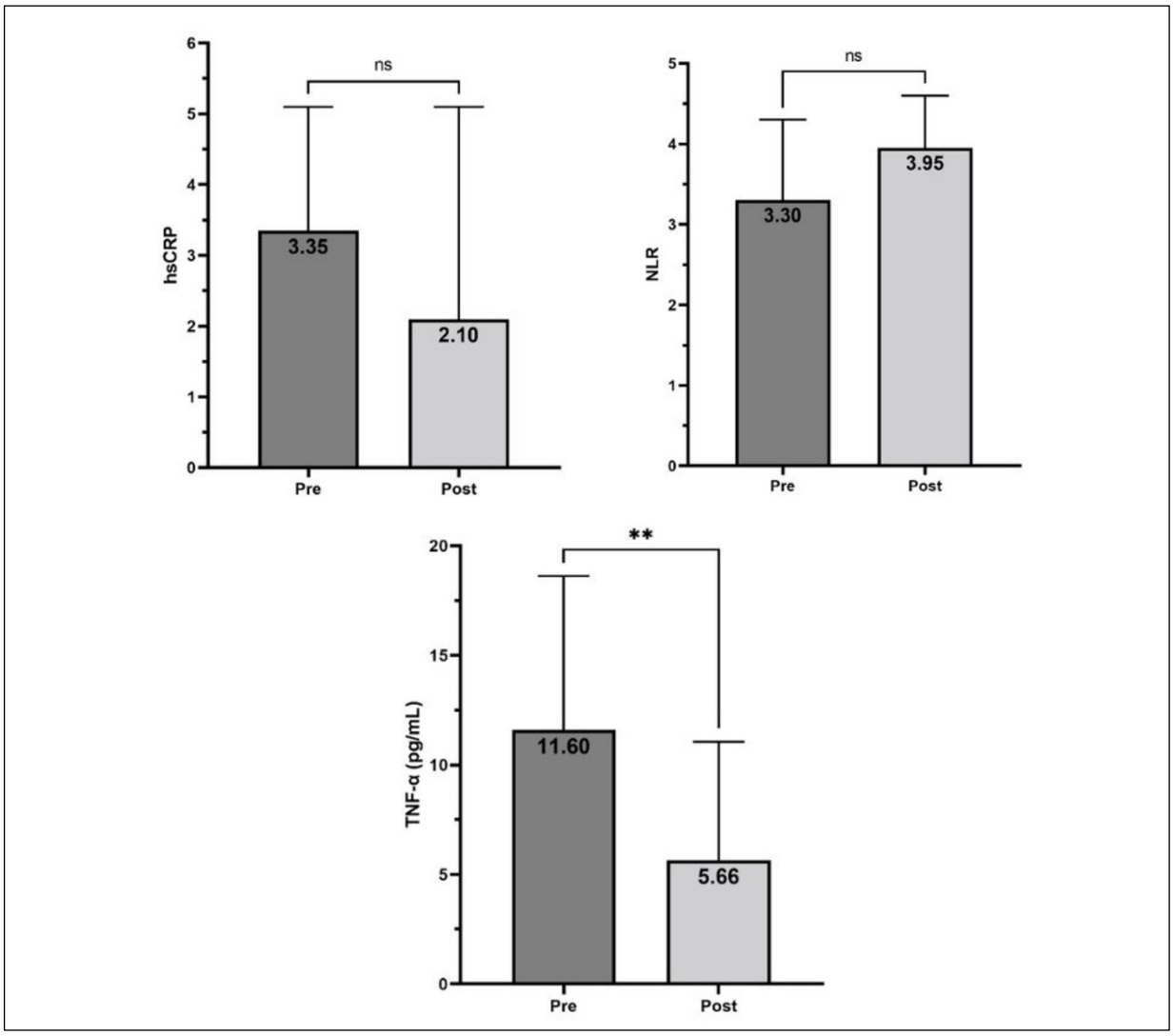


**Figure 2.** Barchart of hs-CRP, NLR, and TNF-α difference before and after supplementation of reduced L-glutathione in CKD-5D patients.

have MIS under 4, indicating low malnutrition and inflammation in subjects in this study. Low albumin level is associated with high hs-CRP and mortality in CKD-5D patients[19]. The majority of subjects in this study have albumin levels above 3.5 g/dL. As albumin and hs-CRP are mainly produced in the liver, this good nutrition status and liver condition could be associated with low baseline hs-CRP levels of subjects in this study, causing no significant decrease in hs-CRP levels in this study.

The immune system is significantly disturbed in hemodialysis patients. Uremic toxins cause this acquired immune disturbance, elevating the production of IL-1, IL-6, IL-12, and TNF-α. Acute inflammation activates macrophages/ monocytes to produce TNF-α, which is an early indicator of inflammation[20]. A study by Pencak et al[21] shows that TNF- α is elevated in hemodialysis patients compared to healthy adults. The findings of this study also align with the findings of Thang et al[22], that TNF-α increased in subjects with normal hs-CRP. Reduced L-glutathione can decrease TNF-α level significantly, 5.40 (-10.80 – 0.00) pg/mL with $p = 0.002$. This finding aligns with a study conducted in China that glutathione intervention reduces significantly TGF-β, TNF-α, IL-6, and IL-8 levels in hepatitis B patients. Reduced L-glutathione inhibits nuclear factor κB (NFκB), a transcription factor that has an important role in

differentiation, cellular necrosis, and production of pro-inflammatory cytokines IL-6, IL-8, and TNF-α[13].

The results of this study show that the use of reduced-L glutathione did not have an impact on hs-CRP and NLR. This finding is consistent with a double-blind, placebo-controlled clinical trial conducted in Washington[23], which found that oral supplementation of reduced glutathione at a dosage of 1,000 mg for four weeks did not lead to any significant changes in oxidative stress markers in healthy adult populations. A randomized controlled clinical trial[24] conducted in Germany also shows that glycine and n-acetylcysteine supplementation for two weeks did not change either GSH level or GSH to GSSG ratio significantly in healthy adults. However, post hoc analyses revealed increased glutathione generation in a subset of subjects with high oxidative stress and low baseline GSH status. Therefore, the low baseline hs-CRP and NLR in this study caused no significant change after glutathione supplementation. C-reactive protein is an acute phase reactant produced in the liver that increases proportionally to inflammation by increasing pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α, so its fluctuations depend on inflammatory cytokines level[19,25].

In this study, oral supplementation of glutathione did not significantly change the NLR.0.55 (0.30-1.00), with a *p*-value of 0.55. Uduagbamen et al[26] showed that serum albumin correlates negatively with NLR. Therefore, low baseline NLR in this study can be associated with high baseline albumin in subjects in this study. A study[27] conducted in China showed that higher NLR significantly correlates with higher hs-CRP (> 3 mg/liter) with a cut-off value of 5.07, sensitivity of 65.67%, and specificity of 66.37%. In the study, it is also shown that NLR correlates with age. In this study, the median NLR is 3.30, lower than the cut-off in the study; this can be caused by the lower median age in this study, which is 43 years, compared to the mean age in the previously mentioned study, 56.91 years. Therefore, the good nutrition status and good liver function of subjects in this study could be related to low baseline hsCRP and NLR in this study. The subjects with acute and chronic infection were also excluded from this study, which could be associated with low inflammation and correlated with low baseline hsCRP and NLR in this study.

### Limitations

There are several limitations in this study, including the small sample size. This study is a quasi-experimental research study with a one-group pretest-posttest design. Further analysis needs to be conducted using a randomized controlled trial to confirm the outcome of this study. Also, further analysis of the correlation between the baseline characteristics of subjects in this study and the outcome of this study is not conducted.

A larger study with longer duration in hemodialysis patients with varied comorbid also needs to be conducted to validate the outcome of this study before implementation in daily practice. Several measurements may provide additional information but were not measured in this study, such as other inflammatory cytokines (interleukin-6, transforming growth factor/ TGF-β, etc.).

## Conclusions

Exogenous reduced L-glutathione supplementation at a dose of one thousand milligrams per day for 4 weeks significantly reduced TNF-α level, but no significant decrease in hs-CRP level and NLR in patients with CKD-5D. Further studies are required to validate the outcome of this study.

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Ethics Approval

The Hasan Sadikin General Hospital's Ethical Research Committee provided ethical approval (number LB.02.01/X.6.5/483/2023, date of approval: 4th December 2023).

### Informed Consent

All subjects provided written informed consent for inclusion before they participated in the study.

### Availability of Data and Materials

The data used to support the findings in this study have been included in this article.

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### Authors' Contributions

Rudi Supriyadi: conceptualization, data curation, investigation, validation, supervision, writing (original draft), reviewing, and editing. Melissa Chandra: conceptualization, data curation, investigation, writing (original draft), reviewing, and editing. Afiatin Makmun: data curation, reviewing, editing. Indra Wijaya: data curation, reviewing, editing. Ria Bandiara: reviewing, editing. Rudi Wisaksana: reviewing, editing.

### AI Disclosure

Artificial intelligence-assisted technology was used solely for grammar and spelling checks.

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