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The Relationship Between *Platelet Lymphocyte Ratio* (PLR) with Depressed Level in Patients with Chronic Kidney Disease (CKD) Undergoing Regular Hemodialysis at Haji Adam Malik General Hospital Medan

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ABSTRACT

Background: Inflammation and stress levels associated with *Chronic Kidney Disease* (CKD) can lead to poor quality of life and adverse medical outcomes. Currently, the commonly used inflammatory tests in CKD patients are *C-reactive protein* (CRP), procalcitonin (PCT), and ferritin. Nonetheless, these tests have some drawbacks, such as being less specific, expensive, and difficult to access. Therefore, the *platelet-lymphocyte ratio* (PLR) can be considered as a promising alternative as a prognostic indicator in CKD patients with major depression.

Methods: This research is an analytical study with a cross-sectional design carried out in February 2023 until the number of samples is fulfilled, at the Hemodialysis Installation of RSUP. H. Adam Malik to analyze the relationship of PLR in depressed patients with CKD undergoing regular hemodialysis. The data analysis used is the Pearson correlation test if the data is normally distributed. If the data is not normally distributed, Spearman's correlation test is performed. Statistical analysis used a 95% confidence level ($p<0.05$).

Results: In this study, the demographic characteristics of 86 patients were obtained with a mean age of 49.08 years with a standard deviation of 14.11. Based on the Spearman rho test, it was found that there was no significant correlation between the PLR score and the BDI II score with a p value of 0.975. The r value is 0.003. This shows that there is a very weak correlation between the PLR score and the BD II score.

Conclusion: There is no correlation between Depression level and Platelet Lymphocyte Ratio (PLR) in CKD patients undergoing regular hemodialysis.

Keywords: Depression, *Platelet Lymphocyte Ratio* (PLR), *chronic kidney disease* (CKD), Inflammation

INTRODUCTION

Based on data from the Centers for Disease Control (CDC) in 2007-2010 the highest prevalence of depression was in the age group 40-59 years, namely 9.45%. Data on the incidence of depression in Indonesia vary widely and differ between research areas.[1] Depression is very common and is associated with poor quality of life and increased mortality among adults with chronic kidney disease (CKD). Recent studies have shown that patients with CKD who are not on dialysis have rates of depression up to 3 times higher than those on dialysis in the general population. Depression has been associated with poor quality of life and adverse medical outcomes in patients with CKD or ESRD.[2]

Depression is a predictor that will increase the morbidity and mortality of chronic

kidney failure patients undergoing hemodialysis which has an impact on the level of adherence to treatment or hemodialysis and the patient's immunity. The prevalence of depression varies from 7% to 50%. From these data, countries with CKD suffer the most from depression in Europe.[3,4]

Chronic Kidney Disease disorders are associated with inflammation and stress levels that activate the Hypothalamic-Pituitary-Adrenal Axis (HPA) and autonomic nerves which will increase pro-inflammatory production. The release of pro-inflammatory cytokine cells will activate corticotropin releasing hormone (CRH) in the hypothalamus which will result in the secretion of adrenocorticotropic hormone (ACTH) and finally the HPA axis system will release cortisol glucocorticoids into the blood circulation.[5,6] Various biomarkers have been studied to assess the inflammatory process that occurs in patients with depression and chronic kidney disease (CKD). Recent studies have found that the Platelet Lymphocyte Ratio (PLR) value can be an alternative as a good indicator of inflammation.[7,8]

Several recent studies have shown that platelets are important effectors of innate and adaptive immunity. In the setting of Toll-like receptor agonists and viral infections, platelets interact with neutrophils mediated by the selectin/platelet selectin axis platelet selectin glycoprotein 1 ligand to form heterotypic aggregates and initiate the innate immune response. In addition, the interaction of platelets with neutrophils contributes to the formation of NETs which are called netosis. In addition to acting as immune effectors, platelets share several characteristics with neurons. They all have secretory vesicles that are similar with respect to content, storing molecules such as serotonin or 5-hydroxytryptamine (5-HT), dopamine, glutamate, gamma-aminobutyric acid, and so on. In addition, they also share several proteins, including the serotonin transporter (SRET) and receptors (for example, serotonin 2A and 3A receptors), as well as a number of neuron-associated markers, such as brain-derived neurotrophic factor. These co-binding and proteins have an important role in the pathophysiology of psychotic disorders and are targets of antipsychotic treatment.[9,10]

MATERIALS & METHODS

This research is an analytical study with a cross-sectional design conducted from January to February 2023, at the Hemodialysis Installation of RSUP. H. Adam Malik with the approval of the Research Ethics Commission of the Faculty of Medicine, University of North Sumatra. Consecutive sampling was used in this study.

Samples were chronic kidney disease patients undergoing routine hemodialysis and meeting the inclusion criteria, namely men or women aged > 18 years, CKD patients undergoing routine hemodialysis, received information and gave consent to participate voluntarily and in writing (informed consent) and did not fulfill exclusion. The criteria are patients with impaired consciousness, previously used antidepressants, BDI-II score = 0-13, active infectious disease, autoimmune disease, malignancy and patients not willing to give informed consent.

Data on the basic characteristics of the study population are presented in graphs/tables of frequency distribution and analyzed descriptively. The Kolmogorov-Smirnov test is used to test the normality of the data. To analyze the PLR relationship in depressed patients with CKD, the Pearson correlation test was used if the data were normally distributed. If the data is not normally distributed, Spearman's correlation test is performed. Statistical analysis used a 95% confidence level ($p<0.05$).

RESULT

This study described the demographic characteristics of the 86 patients analyzed where 48 patients (55.8%) were male and 38

patients (44.2%) were female. The mean age of the patients was 49.08 ± 14.11 years. The mean duration of hemodialysis in all patients was 18.09 months with a standard deviation of 26.0.

Table 1. Demographic Characteristics of the Research Sample

Parameter	Total (n)
Gender (n, %)	
Male	48 (55,8%)
Female	38 (44,2%)
Age (years)	
Mean ± standard deviation	49,08 ± 14,11
Median (min-maks)	52 (8-78)
Hemodialysis duration (Months)	
Mean ± standard deviation	18,09 ± 26.0
Median (min-maks)	7 (1-132)

DISCUSSION

Patients were examined for PLR values as a haematological parameter included in this study. The average PLR in all patient samples was 144.01 with a standard deviation of 133.04. The median PLR value is 109.45 with a minimum value of 26.5 and a maximum value of 881.8. This is consistent with the study of Mustafa et al who found that the median (min-max) PLR of patients with Chronic Kidney Disease was 130.4 (50.00-282.09).[8] Mustafa's study also suggested that chronic inflammation is an important factor in the pathogenesis of atherosclerosis in populations with CKD, where there is an increase in inflammatory markers in this population compared to the general population. PLR is an easy, inexpensive, and routinely reported parameter of inflammation as part of a complete blood count. Another study also reported that increased PLR was associated with poor prognosis in patients with cardiovascular disease (i.e. heart failure, myocardial infarction, and other coronary artery disease) in patients on routine hemodialysis.[11]

Table 2. Results of BDI II and PLR Study Samples

Parameter	Total (n)
Skor BDI II	
Mean ± Standard Deviation	28,78 ± 12,48
Median (min-maks)	26.50 (14-55)
PLR	
Mean ± Standard Deviation	144.01 ± 133.04
Median (min-maks)	109.45 (26.5-881.8)

The depression level of the study sample was measured in this study. Depression assessment using BDI II. Scores range from 0 to 63. Score interpretation; 14-19 indicates mild depression, 20-28 indicates moderate depression, 29-63 indicates severe depression. In the descriptive analysis based on the patient's depression category, there were 31 patients with mild depression (36.0%), 18 patients with moderate depression (20.9%) and 37 patients with severe depression (43.0%). This shows that patients with chronic kidney disease who undergo chronic hemodialysis tend to experience major depression. This is in accordance with the study of Fisher et al, where there was a 27.4% incidence of depressive symptoms in patients with mild to moderate CKD.[4,5] Another study by Palmer also found something similar where the incidence of depression was 26.5% in CKD and 39.3% in patients with End Stage Renal Disease (ESRD), where the number of patients showing depressive symptoms increases with the progression of the disease they are suffering from.[12]

Table 3. Depression Category of Research Samples Based on BDI II

Depression Category	Frequency (n)
Mild	31 (36%)
Moderate	18 (20.9%)
Severe	37 (43.0%)

Based on the Spearman rho test, it was found that there was no significant correlation between the PLR score and the BDI II score with a p value of 0.975 and the r value is 0.003. This shows that there is a very weak correlation between the PLR score and the BD II score. Previous studies that assessed predictors of depression through inflammatory markers in patients with CKD, only used NLR and RDW and studies using PLR as predictors were still very limited. In his study Feng et al suggested that NLR could be an independent predictor of depressive symptoms in patients on routine hemodialysis with a p value of 0.001, where the NLR level of depressed patients was

significantly higher than that of healthy control patients and positively correlated with the severity of depression.[13]

However another study by Turkmen et al showed that PLR and NLR were found to be positively correlated with inflammatory markers including tumor necrosis factor-a (TNF-a) and interleukin (IL)-6 in ESRD patients. Turkmen et al also found that PLR is superior in determining inflammation compared to NLR. This shows that PLR has the potential to be a predictor of depression through inflammatory markers in CKD patients. However, the findings in this study show a very weak correlation between PLR and BDI II scores, which indicates that PLR values do not differ significantly between each level of depression.[14]

In another study conducted by Kayhan et al. 2017 found that patients with major depression with psychotic features had a higher PLR than other patients. Another important finding was the absence of a significant difference in parameters between inpatients and outpatients with major depression without psychotic features. Platelet activation and hemostatic changes have important roles in psychiatric disorders besides inflammation. Although serotonin and epinephrine-stimulated platelet activation has been reported commonly with depression, it may also have a role in anxiety. In addition, this activation also has a stimulant effect on platelet hyperaggregatability. The significance of PLR levels in psychotic patients may be related to platelets acting more efficiently in psychiatric disorders than in inflammatory cases. In particular, recent studies conducted in other areas reported that PLR is better than NLR for determining the severity of inflammation.[4,10,15]

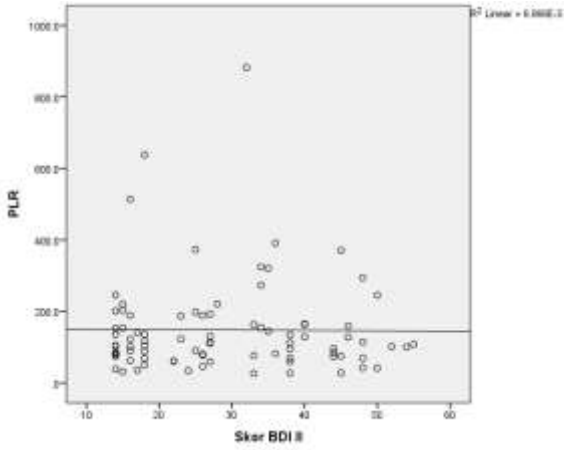

Figure 1. Scatter Plot Graph of RDW to BDI II Scores.

Many studies have reported a positive association between depression and inflammation, with some suggesting the possibility that depression is an inflammatory disease. A higher PLR value in individuals with symptoms of depression and anxiety can be used as a predictor of increased risk of cardiovascular disease in patients. In addition, increasing the PLR value in depressed patients is also important for clinical improvement because a high RDW is associated with an increased risk of stroke, anemia and atherosclerosis. 11 However, another study that compared individuals with depressive symptoms with those without mental illness reported that there was no significant difference in the PLR values of the two groups. This could be due to differences in the number of research samples, thereby reducing statistical significance.[10,16,17]

The strength of this new study is that it links PLR to depression. This research method also uses a correlation test so that the strength of correlation can be assessed in addition to its significance. Hopefully this research can be the basis for other studies in the future.

The limitation of this study is the cross-sectional research design which only allows to determine the correlation between variables and not a causal relationship. One center study could also be a limitation of this study. Several other important aspects for the assessment of depression such as

family history, social background, and other co-morbidities were not evaluated.

CONCLUSION

There is no correlation between Depression level and Platelet Lymphocyte Ratio (PLR) in CKD patients undergoing regular hemodialysis

Declaration by Authors

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