

# The relationship between neutrophil lymphocyte ratio, platelet lymphocyte ratio, and depression in dialysis patients

Duygu Tutan, MD<sup>a,\*</sup>, Ayşe Erdoğan Kaya, MD<sup>b</sup>, Barış Eser, MD<sup>c</sup>

### Abstract

Chronic kidney disease is a worldwide public health issue with rising incidence, morbidity/mortality, and cost. Depression and chronic renal disease often coexist, and psychological illnesses are associated with poor results. Early identification of depression reduces morbidity and death. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are reported as practical biomarkers of inflammation and immune system activation. In this study, we aimed to determine the association of NLR and PLR with depression in dialysis patients. This study included 71 adults over 18 without known hematologic or oncologic disease, drug use, or chronic inflammatory diseases. Comorbid chronic diseases, laboratory data, and Beck depression inventory scores were prospectively recorded. A comparison of 2 groups according to the existence of depression was made, and a binomial logistic regression test was used to determine the association between the variables and the presence of depression after adjusting for confounding factors. A receiver operating curve analysis was used to differentiate groups with and without severe depression. Seventy-one patients met the study criteria, with 46 hemodialysis and 25 peritoneal dialysis patients. The majority had hypertension and diabetes mellitus, with 47.89% having minimal-minor depression and 52.11% having moderate-major depression. The 2 groups were similar regarding chronic diseases, with no significant differences in serum creatinine levels, glucose, lipid profiles, or electrolytes. However, when the NLR of the 2 groups was compared, the median was higher in patients with moderate or major depression. Multivariate analysis showed no significant differences between the groups in PLR, triglyceride to glucose ratio, and C-reactive peptide to albumin ratio. The best NLR cutoff value was 3.26, with 48.6% sensitivity, 88.2% specificity, 81.8% positive predictive value, 61.2% negative predictive value, and 67.6% test accuracy. Depression is one of the most common psychiatric conditions in dialysis patients and is linked to increased morbidity, mortality, treatment failure, expense, and hospitalization. NLR helped predict moderate-to-major depression in dialysis patients, even after controlling for confounding factors in multivariate analysis. This study indicated that an NLR successfully identified depressive groups, and patients with an NLR value >3.26 were 6.1 times more likely to have moderate or major depression.

**Abbreviations:** CAR = C-reactive peptide to albumin ratio, CI = confidence interval, CKD = chronic kidney disease, <math>CRP = C-reactive peptide, NLR = neutrophil to lymphocyte ratio, PDW = platelet distribution width, PLR = platelet to lymphocyte ratio, ROC = receiver operating curve, TSH = thyroid stimulant hormone, TyG = triglyceride to glucose ratio, WBC = white blood cell count.

Keywords: chronic kidney disease, depression, dialysis, neutrophil-lymphocyte ratio

# 1. Introduction

Chronic kidney disease (CKD) is a global public health problem with increasing incidence, high morbidity/mortality rates, and financial burden on countries, affecting approximately 10% of the worldwide population.<sup>[1-3]</sup> CKD has emerged as one of the leading causes of death worldwide and is one of the few non-communicable medical causes that has seen an increase in disease-related deaths in the last 20 years. Still, the presence of other comorbidities makes the condition even

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more dangerous.<sup>[1]</sup> Psychiatric disorders in this patient population increase morbidity and mortality, leading to increased health expenditures and increased incidence of hospitalization.<sup>[4]</sup> Depression is one of the most common psychiatric disorders in individuals with CKD, with a prevalence of 23% to 29%, and rates as high as 47% have been reported.<sup>[5–8]</sup> The emergence of psychiatric symptoms in many individuals with CKD who need dialysis treatment worsens the quality of life of patients and their caregivers.<sup>[9]</sup> Studies on end-stage renal

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<sup>&</sup>lt;sup>a</sup> Erol Olçok Training and Research Hospital, Department of Internal Medicine, Çorum, Turkey, <sup>b</sup> Erol Olçok Training and Research Hospital, Department of Psychiatry, Çorum, Turkey, <sup>c</sup> Hitit University Faculty of Medicine, Department of Nephrology, Çorum, Turkey.

<sup>\*</sup>Correspondence: Duygu Tutan, Erol Olçok Training and Research Hospital, Department of Internal Medicine, Çorum 19040, Turkey (e-mail: duygus\_781@ hotmail.com).

disease patients have shown the association of depressive symptoms with adverse health outcomes. A meta-analysis by Fabrazzo et al<sup>[10]</sup> showed that patients with depressive symptoms had a higher risk of death.

Early recognition of depression in CKD patients is essential to reduce morbidity and mortality and improve quality of life. There are many studies suggesting that depression and CKD are associated with underlying inflammatory triggers,<sup>[11-14]</sup> and inflammation is known to be effective both in the occurrence and progression of CKD<sup>[15]</sup> and in the severity of depression.<sup>[16]</sup>

The neutrophil to lymphocyte ratio (NLR) is the ratio of the absolute neutrophil count to the total lymphocyte count in the blood. The NLR has been found to be a valuable marker of inflammation and immune system activation, with higher ratios indicating a greater degree of inflammation and immune system activation. In the literature, there are studies related to the use of the Neutrophil/Lymphocyte ratio, an inflammatory marker, as an indicator of inflammation levels in depressive patients.<sup>[17,18]</sup> NLR, an easily accessible and low-cost marker of inflammation, has been shown to have predictive value in several different medical conditions, including cardiovascular disease, malignancies, and infectious diseases.<sup>[19]</sup> For example, a higher NLR has been associated with poorer outcomes in patients with heart disease or cancer and increased mortality in patients with sepsis.<sup>[19]</sup>

Similar to NLR, platelet-to-lymphocyte ratio (PLR) has been studied in various medical conditions and has been found to be a useful prognostic marker in some cases. For example, a meta-analysis of studies on colorectal cancer patients found that elevated preoperative or pretreatment PLR was associated with poor prognosis.<sup>[20]</sup> PLR has been correlated with poor survival in many malignancies and has been verified as predictive of intraductal papillary mucinous neoplasms.<sup>[20,21]</sup> PLR has also been studied as a predictor of treatment response to neoadjuvant therapy in esophageal cancer.<sup>[22]</sup>

Using a biological parameter associated with depression in dialysis patients can provide clinicians with an objective tool to predict the need for psychiatric evaluation and treatment in the follow-up of these patients. In this study, we aim to investigate the association between the neutrophil/lymphocyte ratio and the platelet/lymphocyte ratio, which are noninvasive, inexpensive, easily accessible tests, and can be determined only from a blood count, with depression in dialysis patients.

### 2. Methods

Between January 15, 2023 and March 1, 2023, patients receiving hemodialysis and peritoneal dialysis treatment at Hitit University Faculty of Medicine Department of Nephrology Hemodialysis Unit were selected as the subjects of the study. Seventy-one patients over 18 years of age without known hematologic or oncologic disease, without drug use that would affect laboratory values, and without chronic inflammatory diseases were included in the study. Patients age, gender, type of dialysis, and the existence of chronic diseases such as diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and peripheric artery disease were recorded. After overnight fasting serum glucose, triglyceride, total cholesterol, low density lipoprotein, high density lipoprotein, sodium, potassium, phosphorus levels, white blood cell count (WBC), neutrophil, lymphocyte, monocyte, platelet counts, hemoglobin, platelet distribution width (PDW), C-reactive peptide (CRP), parathormone, ferritin, vitamin B12, folate, thyroid stimulant hormone (TSH), T4, blood urea nitrogen, creatinine, uric acid, calcium, albumin levels, and kt/V values were also recorded prospectively. NLR, PLR, triglyceride to glucose ratio (TyG), and C-reactive peptide to albumin ratio (CAR) values were calculated using the formulas NLR = neutrophil count/lymphocyte count, PLR = platelet count/ lymphocyte count, TyG = serum triglyceride/serum glucose, and CAR = serum CRP/serum albumin and added to the study. Hemodialysis patients had blood drawn just before the middle of the week dialysis sessions, whereas peritoneal dialysis patients had their blood drawn during their outpatient clinical controls. The chronic kidney disease epidemiology collaboration equation was used to generate glomerular filtration rate estimates. Kt/V<sub>urea</sub> was used to determine peritoneal dialysis and hemodialysis qualification. Beck depression inventory was utilized to determine the severity of depression. No patients were lost to follow-up, and no missing data was found at the end for the patient selection and inclusion stage. This study was approved by the Hitit University Faculty of Medicine Clinical Research Ethics Committee, and consent forms were obtained from all of the participants (Decision No: 2023-02/Date:12/01/2023).

This study is planned prospectively. In the a priori power analysis performed by examining the related studies in the literature, the sample size required to obtain a significant result was calculated as 71 patients (G-Power v3.1.9.7).<sup>[23]</sup> All statistical analysis was performed using IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, NY). Descriptive statistics were reported as counts and percentages for categorical variables, the mean ± standard deviation for normally distributed numeric variables, and the median value followed by the minimum and maximum values in parentheses for non-normally distributed numeric variables. The Shapiro-Wilks test was used to assess data distribution. In accordance with the data distribution, the Pearson or Spearman correlation coefficients were used to analyze the associations between the variables. A comparison of numerical measurements for 2 independent research groups for age, blood urea nitrogen, creatinine, uric acid, calcium, hemoglobin, T4, WBC, and PDW was done with a Student t test, and for serum glucose, triglyceride, total cholesterol, low-density lipoprotein, high-density lipoprotein, sodium, potassium, phosphorus levels, neutrophil, lymphocyte, monocyte, platelet counts, CRP, parathormone, ferritin, vitamin B12, folate, TSH, albumin levels, kt/V, NLR, TyG, CAR values, and Beck depression inventory scores were evaluated by a Mann-Whitney U test in accordance with the distribution of the data. The ratio comparisons of the type of dialysis, gender, diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and peripheric artery disease distributions between research groups were evaluated using a Chi-square test. A binomial logistic regression test was used for the multivariate analysis to determine the association between the variables and the existence of depression after adjusting for confounding factors. A receiver operating curve (ROC) analysis was done to differentiate groups with and without severe depression, and the optimal NLR cutoff values were found using the area under the curve and the Youden index. For these cutoff values, sensitivity, specificity, positive predictive value, negative predictive value, test accuracy, and odds ratio values were calculated. For statistical significance, P < .05 was accepted.

#### 3. Results

Seventy-one patients who met the study criteria were included in the study. There were 46 (64.79%) hemodialysis patients and 25 (35.21%) peritoneal dialysis patients. The mean age was  $54.58 \pm 12.51$  years. 45 (63.38%) of the patients were male, and 26 (36.62%) were female. The majority (74.65%) of the patients had hypertension, and diabetes mellitus (25.35%) was the second most common disease (Table 1). Total 34 (47.89%) patients had minimal or minor depression, and 37 (52.11%) had moderate or major depression.

Patients were divided into 2 groups according to the severity of their depression. Patients who had minimal or minor depression were designated as Group 1, and those who had moderate or major depression were designated as Group 2.

## Table 1

Baseline characteristics, univariate and multivariate analysis between depression groups.

Variables   (n = 71)   depression (n = 32)   depression (n = 37)   significance   Val   Exp (8) (C1995)   significance     Dalaysis type Pertoneal dialysis   46 (64,79%)   22 (64,71%)   22 (64,71%)   24 (64,85%)   0.089   0.03   1.158 (0.218-6-165)   0.05     Age   54,558 ± 12.51   52 (15 5,21%)   12 (55,29%)   22 (98,46%)   0.117   2.651   1.052 (0.993-1.116)   0.0     Gender   Male   43 (63,26%)   12 (23,55%)   15 (40,45%)   -   0.252 (0.144-1.941)   0.0     DM   18 (25,55%)   6 (20,55%)   12 (70,59%)   16 (70,59%)   0.471 (0.50%)   0.474 (0.128-34)   0.017 (0.128-34)   0.0129 (0.128-34,79)   0.0     CAH   11 (15,49%)   4 (17,7%)   7 (18,92%)   0.816 (0.243   0.090 (0.128-34,59)   0.047   1.080 (0.128-34,59)   0.047     CAH   11 (15,49%)   4 (17,7%)   7 (18,92%)   0.816 (0.243   1.080 (1.17-19.105)   0.05     CAH   10 (69,0450)   99 (67-360)   93 (60-200)   0.533   0.467   0.494   0.				U	nivariate analysis		Multivariate logistic regression analysis			
Particular   20 (21-30)   21 (32-29)   24 (22-30)     Age   54-58 ± 12.51   52.15 ± 13.18   56.81 ± 11.59   0.117   2.951   1.052 (0.993-1.116)   0.1     Gender   Male   46 (5.324%)   22 (56.65%)   0.474   0.925   0.526 (0.144-1.941)   0.3     Off   11 (15.45%)   82 (56.62%)   11 (12.35%)   10 (27.03%)   0.735   0.026   1.158 (0.192-6.977)   0.6     CAD   11 (15.49%)   42 (70.59%)   29 (78.38%)   0.618   0.226   0.757 (0.124-3.69)   0.66     CAD   11 (15.49%)   5 (14.71%)   6 (16.22%)   0.861   0.243   1.809 (0.171-19.105)   0.6     CAD   2 (28.2%)   0.098   0.243   1.809 (0.171-19.105)   0.6     CAD   11 (15.49%)   5 (14.71%)   6 (16.22%)   0.861   0.243   1.809 (0.171-19.105)   0.6     CAD   2 (28.45%)   0.980   2 (5.41%)   0.417   0.509   2.648 (0.207-29.494)   0.434     BUN   58.03 ± 18.21   56.82 ± 14.6 <t< th=""><th>Variables</th><th></th><th>•</th><th></th><th></th><th></th><th>Wald</th><th>Exp (B) (Cl %95)</th><th>Statistical significance</th></t<>	Variables		•				Wald	Exp (B) (Cl %95)	Statistical significance	
Age   54.58±12.51   52.15±13.16   56.81±11.59   0.117   2.951   1.052 (0.993-1.116)   0.01     Gender   Male   45 (0.53.28%)   23 (67.65%)   15 (40.54%)   0.747   0.925   0.528 (0.144-1.941)   0.33     DM   18 (25.38%)   8 (23.55%)   10 (27.03%)   0.735   0.026   1.158 (0.192-6.977)   0.026     HT   53 (74.65%)   24 (70.59%)   29 (73.38%)   0.451   0.020   0.835 (0.192-4.173)   0.56     CAD   11 (15.49%)   4 (11.76%)   2 (5.41%)   0.461   0.23   1.809 (0.171-19.105)   0.56     COPD   6 (8.45%)   4 (11.76%)   2 (5.41%)   0.441   0.243   1.809 (0.171-19.105)   0.56     COPD   6 (8.45%)   4 (11.76%)   2 (5.41%)   0.441   0.248   0.202   2.468 (0.207-29.494)   0.441     BND   26 (34%)   0.081   2.25 (3.4%)   0.417   0.509   2.468 (0.207-29.494)   0.451     Catabastrol   1.8 (27-26.33)   1.6 (0.25.13)   1.41 (12-24.033)   0.516 <td>Dialysis type</td> <td>,</td> <td>( )</td> <td>· /</td> <td>( )</td> <td>0.989</td> <td>0.03</td> <td>1.158 (0.218–6.165)</td> <td>0.863</td>	Dialysis type	,	( )	· /	( )	0.989	0.03	1.158 (0.218–6.165)	0.863	
Gender Female   Male 26 (36 62%)   23 (67,65%)   22 (93,46%)   0.474   0.925   0.528 (0.14-1.941)   0.52 (0.158)     DM   18 (25,35%)   11 (15,235%)   10 (27,03%)   0.735   0.026   1.158 (0.192-6.977)   0.62 (0.20   0.835 (0.192-4.173)   0.62 (0.20   0.835 (0.192-4.173)   0.62 (0.20   0.835 (0.192-4.173)   0.62 (0.20   0.835 (0.192-4.173)   0.62 (0.20   0.835 (0.124-3.58)   0.026   1.158 (0.192-6.977)   0.62 (0.20   0.835 (0.124-3.58)   0.045   0.205   0.575 (0.124-3.58)   0.05 (0.20   0.835 (0.127-1.91,05)   0.62 (0.202   0.835 (0.124-3.58)   0.045   0.205   0.246 (0.207-29.494)   0.42 (0.202   0.438 (0.207-29.494)   0.42 (0.202   0.434   0.205   0.435 (0.207-29.494)   0.42 (0.202   0.434   0.205   0.26 (0.202   0.438 (0.207-29.494)   0.42 (0.202   0.434   0.444   0.44 (0.202-00   0.438   0.448 (0.207-29.494)   0.44 (0.202   0.438 (0.207-29.494)   0.44 (0.202   0.448 (0.207-29.494)   0.44 (0.202   0.448 (0.207-29.494)   0.44 (0.202   0.448 (0.202   0.44 (0.202   0.448 (0.202   0.44 (0.202	٨aə	i entonear ularysis	( )	· /	( )	0 117	2 051	1 052 (0 003_1 116)	0.086	
Female   26 (66 62%)   11 (23.35%)   15 (40 54%)   U     DM   18 (25.35%)   0 (27.03%)   0.735   0.026   1.158 (0.192-6.377)   0.26     CAD   11 (15.49%)   4 (11.77%)   7 (18.22%)   0.861   0.243   0.675 (0.124-3.69)   0.67     CHF   11 (15.49%)   5 (14.71%)   6 (16.22%)   0.861   0.243   1.809 (0.171-10.15)   0.67     COPD   6 (8.45%)   4 (11.76%)   2 (6.41%)   0.444   1.809 (0.171-10.15)   0.67     PAD   2 (2.82%)   0 (0%)   2 (6.41%)   0.444   1.809 (0.171-10.15)   0.67     Glucose   98 (60-360)   99 (67-360)   93 (60-200)   0.53   1.77   1.76   1.77   1.72   1.76   1.76	0	Malo						· /	0.336	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Genuel					0.474	0.925	0.520 (0.144-1.941)	0.550	
HT 53 (74,65%) 24 (70,59%) 29 (78,38%) 0.451 0.020 0.895 (0.192-4.173) 0.50   CAD 11 (15,49%) 5 (14,71%) 6 (16.22%) 0.861 0.243 1.809 (0.171-19,105) 0.60   CHF 11 (15,49%) 5 (14,71%) 6 (16.22%) 0.861 0.243 1.809 (0.171-19,105) 0.60   COPD 6 (8,45%) 4 (11,77%) 2 (6,41%) 0.444 0.494   BUN 58.03 ± 18.21 56.82 ± 14.6 59.14 ± 2.13 0.591 2.468 (0.207-29.494) 0.44   Creatinine 8.27 ± 2.49 8.04 ± 2.09 8.07 ± 2.82 0.442 0.444   Glucose 98 (60-360) 99 (67-360) 93 (60-200) 0.538 5.35	DM	remale	· /			0 725	0.000	1 150 (0 100 6 077)	0.873	
CAD   11   (15,49%)   4   (11,76%)   7   (18,29%)   0.518   0.205   0.675   0.124-36.00   0.60     CHF   11   (15,49%)   5   (14,71%)   6   (16,22%)   0.611   0.243   1.809   0.171-19.105   0.6     CPD   6   (8,45%)   4   (11,77%)   2.65,41%)   0.447   0.59   2.686   0.207-29.494   0.4     PAD   2.(2,82%)   0   (0%)   2.64,41%)   0.447   0.591   1.0591   1.0591   1.016,52-6981   0.447   1.016   1.016,52-6981   0.447   1.016   1.016,52-6981   0.447   1.01   1.01   4.02,2-801   0.434   1.01   1.01   1.02,63,63,43,43   1.03,63,2-23,83   1.03,63,2-23,83   1.03,63,2-23,83   1.01,62,2-6931   0.447   1.01   1.02,03,63,2-3,33   1.02,03,63,2-3,33   1.01,62,2-6,03   0.434   1.01,14   1.01,14   1.01,14   1.01,14   1.01,14   1.01,14   1.01,14   1.01,14   1.01,14   1.02,13,13,13,13,13,13,13,13,13,13,14,1			( )					( )		
CHF   11 (15.49%)   5 (14.71%)   6 (16.22%)   0.861   0.243   1.809 (0.171-19.105)   0.6     COPD   6 (8.45%)   4 (11.76%)   2 (5.41%)   0.447   0.509   2.468 (0.207-29.494)   0.4     PAD   2 (2.82%)   0 (0%)   2 (5.41%)   0.494   0.494     BUN   58.03±18.21   56.82±14.6   59.14±21.13   0.591   0.422     Guasse   98 (60-360)   99 (67-360)   93 (60-200)   0.538   1.50			· /	( /				( )	0.887	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$			( )		( /				0.651	
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$ \begin{array}{llllllllllllllllllllllllllllllllllll$				( /	( /		0.509	2.468 (0.207–29.494)	0.475	
			( )	( )	( /					
Glucose   98 (60-360)   99 (67-360)   93 (60-200)   0.538     Triglycaride   149 (52-698)   150 (64-550)   140 (52-698)   0.447     LDL   87 (38-253)   89 (38-253)   80 (38-204)   0.53     HDL   40 (21-80)   40.5 (21-80)   40 (28-60)   0.504     Uric Acid   6.15 ± 1.34   6.2 ± 1.46   6.11 ± 1.24   0.769     Sodium   138 (129-142)   138 (130-142)   0.736     Potassium   5.3 (3 4-7)   5.2 (3 4-8)   0.596     Calcium   8.58 ± 0.72   8.66 ± 0.76   8.51 ± 0.68   0.399     Phosphorus   4.6 (2.5-8.3)   4.66 (2.7-6.3)   4.63 (1.68-7.92)   -0.011     Umphocyte   1.5 (0.52-3.19)   1.47 (0.72-3.8)   0.858										
Triglyceride 149 (52–699) 150 (64–550) 140 (52–699) 0.447   Total cholesterol 159 (91–331) 162 (101–331) 157 (91–287) 0.434   LDL 87 (38–253) 89 (38–253) 80 (38–260) 0.504   HDL 40 (21–80) 40.5 (21–80) 40 (28–60) 0.504   Uric Acid 6.15 ± 1.34 6.2 ± 1.46 6.11 ± 1.24 0.769   Sodium 38 (129–142) 138 (129–142) 138 (130–142) 0.736   Potassium 5.3 (3.4–8) 5.35 (3.4–7) 5.2 (3.4–8) 0.596   Calcium 8.58 ± 0.72 8.66 ± 0.76 8.51 ± 0.68 0.399   Phosphorus 4.6 (2.5–8.3) 4.65 (2.7–6.3) 4.63 (168–7.92) <0.001			$8.27 \pm 2.49$							
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$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Triglyceride		149 (52–698)	150 (64–550)	140 (52–698)	0.447				
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Total cholester	bl	159 (91–331)	162 (101–331)	157 (91–287)	0.434				
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	LDL		87 (38-253)	89 (38-253)	80 (38-204)	0.53				
Sodium   138 (129–142)   138 (129–142)   138 (130–142)   0.736     Potassium   5.3 (3.4–8)   5.35 (3.4–7)   5.2 (3.4–8)   0.596     Calcium   8.58 ± 0.72   8.66 ± 0.76   8.51 ± 0.68   0.399     Phosphorus   4.6 (2.5–8.3)   4.65 (2.7–6.3)   4.6 (2.5–8.3)   0.986     Hemoglobin   10.69 ± 1.36   10.96 ± 1.16   10.45 ± 1.5   0.114     Neutrophil   3.96 (1.68–7.92)   3.28 (1.85–5.64)   4.63 (1.68–7.92)   <0.001	HDL		40 (21-80)	40.5 (21-80)	40 (28-60)	0.504				
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Uric Acid		$6.15 \pm 1.34$	$6.2 \pm 1.46$	$6.11 \pm 1.24$	0.769				
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Sodium		138 (129-142)	138 (129–142)	138 (130-142)	0.736				
$ \begin{array}{cccc} Calcium & 8.59 \pm 0.72' & 8.66 \pm 0.76' & 8.51 \pm 0.68' & 0.399 \\ Phosphorus & 4.6 (2.5-8.3) & 4.66 (2.5-8.3) & 0.986 \\ Hemoglobin & 10.69 \pm 1.36 & 10.96 \pm 1.16 & 10.45 \pm 1.5 & 0.114 \\ Neutrophil & 3.96 (1.68-7.92) & 3.28 (1.85-5.64) & 4.63 (1.68-7.92) & <0.001 \\ Lymphocyte & 1.5 (0.52-3.8) & 1.5 (0.52-3.19) & 1.47 (0.72-3.8) & 0.858 \\ WBC & 7.02 \pm 1.94 & 6.72 \pm 2.02 & 7.31 \pm 1.86 & 0.205 \\ Platelet & 213 (42-520) & 201.5 (42-480) & 215 (126-520) & 0.486 \\ PDW & 11.9 \pm 1.86 & 11.7 \pm 1.74 & 12.08 \pm 1.98 & 0.404 \\ CRP & 8 (0.9-31) & 3.51 (0.9-26) & 8 (3-31) & 0.083 \\ Parathormone & 365 (1-1660) & 395.5 (1-1660) & 365 (1-1494) & 0.95 & 0.732 & 1.001 (0.999-1.003) & 0.35 \\ Ferritin & 463 (57-2000) & 471.5 (57-2000) & 452 (94-2000) & 0.831 & 1.765 & 0.999 (0.998-1) & 0.1 \\ ktV & 1.7 (0.9-4.93) & 1.92 (0.9-3.45) & 1.67 (1.22-4.93) & 0.245 & 0.211 & 1.338 (0.386-4.635) & 0.65 \\ Vitamin B12 & 480 (150-2000) & 404 (150-2000) & 530 (225-1613) & 0.165 & 0.654 & 1.001 (0.999-1.003) & 0.42 \\ Folate & 12.3 (2-20) & 8.1 (2.2-20) & 17.6 (2-20) & 0.211 & 0.484 & 1.038 (0.934-1.154) & 0.4 \\ TSH & 1.6 (0.33-8.7) & 1.42 (0.33-5.7) & 2 (0.4-8.7) & 0.437 & 1.760 & 1.315 (0.877-1.972) & 0.1 \\ Monocyte & 0.56 (0.25-1.3) & 0.55 (0.26-1.3) & 0.58 (0.25-1.29) & 0.904 \\ Albumin & 38 (20-47) & 37 (22-47) & 38 (20-44) & 0.768 \\ NLR & 2.44 (0.84-8.27) & 2.23 (0.84-8.27) & 3.21 (0.84-7.45) & 0.004 & 6.477 & 2.554 (1.241-5.258) & 0.02 \\ PLR & 134.76 (42-553.19) & 140.75 (42-312.06) & 131.79 (55.26-553.19) & 0.489 & 1.299 (0.970-2.056) & 0.26 \\ NLR & 2.44 (0.84-8.27) & 2.23 (0.84-8.27) & 3.21 (0.84-7.45) & 0.004 & 6.477 & 2.554 (1.241-5.258) & 0.02 \\ PLR & 134.76 (42-553.19) & 140.75 (42-312.06) & 131.79 (55.26-553.19) & 0.849 & 1.299 (0.770-2.056) & 0.42 \\ NLR & 2.44 (0.84-8.27) & 2.23 (0.84-8.27) & 3.21 (0.84-9.97) & 0.899 & 0.483 & 1.209 (0.770-2.056) & 0.42 \\ NLR & 2.44 (0.84-8.27) & 2.23 (0.84-8.27) & 3.21 (0.84-9.97) & 0.899 & 0.493 & 1.209 (0.770-2.056) & 0.42 \\ NLR & 2.44 (0.84-8.27) & 2.23 (0.84-8.27) & 3.21 (0.84-9.97) & 0.899$										
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Monocyte   0.56 (0.25–1.3)   0.55 (0.26–1.3)   0.58 (0.25–1.29)   0.904     Albumin   38 (20–47)   37 (22–47)   38 (20–44)   0.768     NLR   2.44 (0.84–8.27)   2.23 (0.84–8.27)   3.21 (0.84–7.45)   0.004   6.477   2.554 (1.241–5.258)   0.0     PLR   134.76 (42–553.19)   140.75 (42–312.06)   131.79 (55.26–553.19)   0.849   1.891   0.992 (0.98–1.004)   0.1     TyG   1.33 (0.32–9.97)   1.35 (0.32–5.25)   1.33 (0.34–9.97)   0.809   0.483   1.209 (0.707–2.068)   0.4     CAR   0.2 (0.02–1.18)   0.11 (0.02–1.18)   0.22 (0.08–0.89)   0.049   0.321   2.151 (0.152–30.423)   0.5			· · · · · ·		· /		1.760	1.315 (0.877-1.972)	0.185	
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			1.33 (0.32–9.97)	1.35 (0.32–5.25)	1.33 (0.34–9.97)	0.809	0.483	1.209 (0.707–2.068)	0.487	
PDI aporo 17 (0. 50) 12 (0. 16) 27 (17, 50) <0.001	CAR		0.2 (0.02-1.18)	0.11 (0.02–1.18)	0.22 (0.08-0.89)	0.049	0.321	2.151 (0.152–30.423)	0.571	
	BDI score		17 (0-52)	12 (0–16)	27 (17–52)	< 0.001				
Depression Minimal and minor 34 (47.89%)	Depression	Minimal and minor	34 (47.89%)							
Moderate and major 37 (52.11%)		Moderate and major	37 (52.11%)							

BDI = Beck depression inventory, BUN = blood urea nitrogen, CAD = coronary artery disease, CAR = C-reactive peptide albumin ratio, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CRP = C-reactive peptide, DM = diabetes mellitus, HDL = high-density lipoprotein, HT = hypertension, LDL = low-density lipoprotein, NLR = neutrophil-lymphocyte ratio, PAD = peripheral artery disease, PDW = platelet distribution width, PLR = platelet-lymphocyte ratio, TSH = thyroid stimulating hormone, TyG = triglyceride-lymphocyte ratio, WBC = white blood cell count.

When the 2 groups were univariately compared, no statistically significant difference was observed between groups in terms of dialysis type, age, or gender (P = .989, P = .117, P = .474, respectively).

The 2 groups were similar in terms of chronic diseases, and there were no significant differences in the prevalence of comorbidities such as hypertension, diabetes, and cardiovascular disease (P = .451, P = .735, P = .518, respectively) (Table 1). The mean serum creatinine level of Group 1 was  $8.48 \pm 2.09$ , and the mean serum creatinine level of Group 2 was  $8.07 \pm 2.82$ , indicating no statistically significant difference between the 2 groups (P = .492). There were no significant differences found in serum glucose levels, blood lipid profiles, or electrolytes between the 2 groups (Table 1). The difference in mean hemoglobin levels between the 2 groups was found to be not statistically significant (P = .23); the mean hemoglobin level of Group 1 was  $10.96 \pm 1.16$  and was  $10.45 \pm 1.5$  for Group 2.

The median neutrophil count was higher in Group 2 compared to Group 1 (P < .001), with a median count of 4,63 (1.68–7.92) for Group 2 and 3.28 (1.85–5.64) for Group 1, respectively. But there was no significant difference in the lymphocyte count between the 2 groups (P = .858), with a median count of 1.5 (0.52–3.19) for Group 2 and 1.47 (0.72–3.8) for Group 1, respectively. There was no difference in terms of WBC, platelet count, PDW, CRP, parathormone, ferritin, vitamin B12, folate, kt/V, TSH, T4, monocyte count, and albumin levels (Table 1).

When the NLR of the 2 groups was compared, the median was found to be higher in patients with moderate or major depression (P = .004), 3.21 (0.84–7.45) for Group 2, and 2.23 (0.84–8.27) for Group 1. Similarly, patients with moderate to major depression have had higher CRP levels than patients with minimal or minor depression (0.11 (0.02–1.18) vs. 0.22 (0.08–0.89), P = .049). The PLR and TyG ratios did not differ between groups (P = .849, P = .809).

A multivariate analysis including age, gender, dialysis type, comorbidities, parathormone, ferritin, kt/V, vitamin B12, folate, and TSH as covariates also showed no significant differences in PLR, TyG, and CRP-albumin ratios between the groups (P = .169, P = .487 and P = .571, respectively). The binomial logistic regression model correctly classified 77.5% of the cases ( $R^2 = 0.343$ , P < .05), and NLR remained an independent predictor even after adjusting for potential confounders in the multivariate analysis (Exp [B] with 95% confidence interval [CI] = 2.554 [1.241–5.258], P = .011).

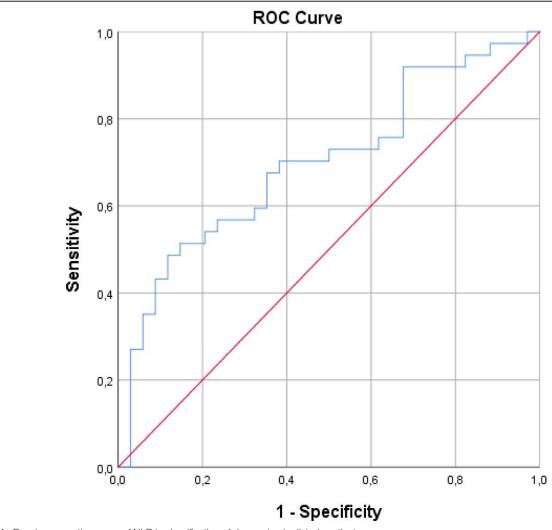
To determine the optimal NLR cutoff value for the distinction of depression groups, a ROC analysis was used (area under curve [standard error] 0.698 [0.063], CI%95 [0.575–0.821], P = .004) (Fig. 1). The best NLR cutoff was found to be 3.26 with 48.6% sensitivity, 88.2% specificity, 81.8% positive predictive value, 61.2% negative predictive value, and 67.6% test accuracy (odds ratio 7.105, 95% CI 2.084–24.221, P = .001) (Table 2). A patient whose NLR is higher than 3.26 is approximately 6.1 times more likely to belong to the moderate or major depression group than those with a lower NLR.

#### 4. Discussion

Depression is the most common psychiatric disorder in dialysis patients, affecting 22% to 39% of patients.<sup>[24]</sup> In our study, the rate of depression was found to be 47.89%, which was higher than in the literature. The presence of comorbid depression in dialysis patients has been associated with increased morbidity, mortality, inadequate response to treatment, and increased treatment cost and duration of hospitalization.<sup>[25-27]</sup> Depression can impair the dialysis process, treatment adherence, immune system function, and nutritional status.<sup>[24,28]</sup> Depressed dialysis patients have elevated levels of proinflammatory cytokines, and depression is associated with poor outcomes.<sup>[29]</sup> Chronic inflammation has been implicated in atherosclerosis, osteoporosis, diabetes, cancer, depression, and CKD.<sup>[30]</sup>

Inflammation, an immune response that safeguards the body against harmful agents, can exert intricate effects on the central nervous system, potentially influencing the development and progression of depression.<sup>[31,32]</sup> A growing body of scientific evidence supports a strong association between inflammation and depression, indicating that chronic or excessive inflammation may significantly impact mood regulation and brain function.<sup>[31-34]</sup>

Prior research has shown that inflammation is associated with higher odds of developing depression.<sup>[33–35]</sup> Depressed patients are associated with elevated markers of inflammation, such as inflammatory cytokines and acute-phase proteins. Additionally, the administration of inflammatory stimuli has been linked to the onset of depressive symptoms.<sup>[35]</sup> Proinflammatory agents



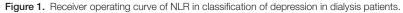


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Diagnostic values of variables and results of receiver operating curve analysis.
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		Diagnostic values					ROC analysis			Odds ratio		
Variables	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy	Area (SE)	%95 CI	Р	Odds ratio	%95 CI	Р
NLR	3.26	48.6%	88.2%	81.8%	61.2%	67.6%	0.698 (0.063)	0.575-0.821	.004	7105	2084-24.221	.001

CI = confidence interval, NPV = negative predictive value, P = statistical significance, PPV = positive predictive value, ROC = receiver operating curve, SE = standard error.

have been found to contribute to the development of depressive symptoms, and patients with depression have increased levels of both central and peripheral proinflammatory cytokines.<sup>[36]</sup> Significantly, the pathophysiology of depression may involve oxidative stress due to the release of reactive oxygen radicals from activated neutrophils.<sup>[37,38]</sup>

One of the suggested mechanisms through which inflammation affects depression involves the activation of the immune system. Following exposure to stressors, the immune system releases pro-inflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor-alpha.<sup>[32]</sup> These cytokines can affect the brain composure through various pathways, such as crossing the blood-brain barrier or activating the vagus nerve, thereby triggering alterations in neurotransmitters activity such as serotonin, dopamine, and norepinephrine, which play pivotal roles in regulating mood.<sup>[31]</sup> Imbalances in these neurotransmitters have been linked to the development of depressive symptoms.<sup>[31]</sup>

Chronic inflammation may also negatively impact neuroplasticity, the brain ability to adapt and form new connections.<sup>[39]</sup> Reduced neuroplasticity, particularly in brain regions like the hippocampus and prefrontal cortex, has been associated with depression.<sup>[39]</sup> The activation of the hypothalamic-pituitary-adrenal axis, a critical system involved in the body stress response, is another suggested mechanism by which inflammation affects depression.<sup>[40]</sup> Prolonged activation of the hypothalamic-pituitary-adrenal axis can lead to increased cortisol levels, which may contribute to the development of depression.<sup>[40,41]</sup> Moreover, inflammation can disrupt the gut-brain axis, a bidirectional communication system between the gut microbiota and the brain and can contribute to depressive symptoms.<sup>[42]</sup>

NLR is a measure that combines 2 WBC subsets that reflect 2 inversely linked immune pathways. It is a more consistent measurement than individual WBC counts and is simply determined using differential WBC counts.<sup>[43]</sup> NLR is frequently used in many fields because it is a low-cost, easily-accessible biomarker and is effective at indicating the degree of inflammation. Studies have found a relationship between NLR and the progression of end-stage renal failure.<sup>[23,44]</sup> Another study found that NLR is a biomarker for predicting systemic involvement in adult IgA vasculitis patients.<sup>[45]</sup>

Several studies have suggested that a higher NLR may be associated with an increased risk of developing depression. Wang et al<sup>[46]</sup> found an association between NLR and clinically relevant depressive symptoms in people with diabetes. In a cross-sectional study, Feng et al<sup>[47]</sup> found high NLR is a significant predictor of depressive symptoms in patients. There are also works contradicting the relationship between NLR and depression. Zhu et al<sup>[48]</sup> explored the relationship between inflammation and depression using NLR, MLR, and PLR as inflammatory markers and found NLR to be not correlated with depression.

Several mechanisms could account for the connection between NLR and depressive symptoms, and both neutrophilia and lymphocytopenia are well-known inflammatory reactions to diverse stressors.<sup>[49–52]</sup> NLR predictive ability in dialysis patients is thought to be reliant on the link between inflammation and nutritional state.<sup>[52]</sup> Also, in hemodialysis patients, lymphocytopenia has been identified as a sign of malnutrition.<sup>[51]</sup> Hence, recent evidence linking inflammation, malnourishment, and depression in

dialysis patients might explain NLR predictive capacity to anticipate depressive symptoms in this community.<sup>[49,50]</sup>

This study found that NLR is an important predictor for moderate-to-major depression in patients undergoing dialysis, even after adjusting for potential confounders. This finding is consistent with previous studies that have shown an association between inflammation and depression in the general population.<sup>[46,47]</sup> ROC analysis determined that an NLR cutoff of 3.26 had 88.2% specificity and 48.6% sensitivity in distinguishing between depression groups. Patients with an NLR higher than 3.26 were approximately 6.1 times more likely to belong to the moderate or major depression group than those with a lower NLR.

Notably, the PLR, TyG, and CAR values did not differ between the depression groups, indicating that these biomarkers may not be as useful for identifying depression in this population. The multivariate analysis also failed to show significant differences in PLR, TyG, and CRP-albumin ratios between the groups after adjusting for potential confounders.

Our research has a number of limitations. Due to the nature of an observational study, we can only discuss the association between inflammation, inflammatory markers, and depression; this work cannot establish a causal relationship. The findings may not be representative of the overall population because of the relatively small sample size and reliance on a single hospital. Still, it can guide clinicians about depression in maintenance hemodialysis patients.

#### 5. Conclusion

In conclusion, we found a significant frequency of moderate to major depression among dialysis patients. These findings offer valuable clinical implications, wherein NLR monitoring could aid in early depression detection and intervention, ultimately enhancing patient outcomes and quality of life. Accessible and affordable, NLR might serve as a useful novel indicator for predicting the prevalence of major depressive symptoms in patients undergoing hemodialysis and peritoneal dialysis treatments. However, it is important to note that NLR is not a definitive diagnostic tool and should be used in conjunction with other clinical and laboratory parameters to make treatment decisions.

### **Author contributions**

Conceptualization: Duygu Tutan, Ayşe Erdoğan Kaya. Data curation: Duygu Tutan, Barış Eser. Formal analysis: Duygu Tutan, Ayşe Erdoğan Kaya. Investigation: Duygu Tutan, Ayşe Erdoğan Kaya, Barış Eser. Methodology: Duygu Tutan, Ayşe Erdoğan Kaya. Project administration: Duygu Tutan. Resources: Duygu Tutan, Ayşe Erdoğan Kaya. Software: Duygu Tutan, Ayşe Erdoğan Kaya. Software: Duygu Tutan, Ayşe Erdoğan Kaya, Barış Eser. Supervision: Duygu Tutan, Barış Eser. Validation: Duygu Tutan, Barış Eser. Visualization: Duygu Tutan. Writing – original draft: Duygu Tutan, Ayşe Erdoğan Kaya, Barış Eser.

Writing – review & editing: Duygu Tutan, Ayşe Erdoğan Kaya.

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