10.5152/turkjnephrol.2023.22363

Original Article

Turkish Journal of Nephrology

Examining the Relationship between "Neutrophil-to-Lymphocyte Ratio" and Peripheral Blood Inflammatory Factors in the Patients Undergoing Chronic Dialysis

Fariba Samadian[1,2], Nader Sigari[1], Sadra Ashrafi[3], Zhila Farzinpoor[4], Nooshin Dalili[1,2]

[1]Chronic Kidney Disease Research Center (CKDRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Nephrology, Shahid Labbafinejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Student Research Committee, Chronic Kidney Disease Research Center (CKDRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Tropical and Infectious Disease Center, Medical University of Kordestan, Kordestan, Iran

ABSTRACT

Objective: Neutrophil-to-lymphocyte ratio has been considered an inflammatory prognostic factor in end stage kidney disease patients. Since access to laboratory kits has often been difficult and costly for inflammatory factors, such as tumor necrosis factor-alpha and interleukin 6, neutrophil to lymphocyte ratio, if proven, can be a helpful alternative. Thus, we aimed to determine the relationship between neutrophil-to-lymphocyte ratio and other inflammatory factors and their roles in the prognosis of dialysis patients.

Methods: In this prospective study, 70 adult dialysis patients were enrolled. The checklist contains patient information, including age, sex, duration, and onset of dialysis, the leading cause of ESKD, type of dialysis access, arterial blood pressure, and biochemical factors such as CRP, ESR, interleukin 6, tumor necrosis factor-alpha, and so on. Neutrophil-to-lymphocyte ratio was obtained from neutrophil fractionation to lymphocyte.

Results: The results of this study indicated that interleukin 6 levels had a direct and significant relationship with neutrophil-to-lymphocyte ratio ($P < .001$). Also, linear regression analysis showed a direct and significant relationship between interleukin 6 and neutrophil-to-lymphocyte ratio ($P < .0001$, $t = 2.874$, and beta = 0.278), while controlling the effect of confounding variables. Only interleukin 6 was significantly higher in the neutrophil-to-lymphocyte ratio > 2.5 group ($P < .0001$). However, interleukin 6 and tumor necrosis factor-alpha had no significant correlation with the crude number of lymphocytes and neutrophils.

Conclusion: In this study, we showed that higher levels of neutrophil-to-lymphocyte ratio in dialysis patients are associated with age and elevated levels of calcium, interleukin 6 and CRP, and serum ferritin, suggesting a high level of inflammation in these patients.

Keywords: neutrophil-to-lymphocyte ratio, dialysis, inflammatory factors, end stage kidney disease

Corresponding author: Nooshin Dalili ✉ dr.nooshindalili@gmail.com

Received: May 09, 2022 **Accepted:** September 28, 2022

Cite this article as: Samadian F, Sigari N, Ashrafi S, Farzinpoor Z, Dalili N. Examining the relationship between "neutrophil-to-lymphocyte ratio" and peripheral blood inflammatory factors in the patients undergoing chronic dialysis. *Turk J Nephrol.* 2023;32(4):296-303.

INTRODUCTION

In addition to the well-known risk factors, some unknown inflammatory factors lead to a poor prognosis in End Stage Kidney Disease(ESKD) patients. The presence of these factors is connected with oxidative stress and vascular calcification, in dialysis patients.[1-3] Several studies have indicated that prolonged inflammation in ESKD patients is related to premature death.[4] The high levels of inflammatory factors like tumor necrosis factor-alpha (TNF-α), c-reactive protein (CRP), and interleukin 6 (IL-6), both in dialysis patients and in the normal population, are associated with a higher mortality risk.[4,5] White blood cells and their subsets are among the warning factors in the inflammatory status of patients.[6] Interleukin 6 is one of the most important interleukins in the body, secreted by white blood cells and plays a role in inflammatory and immune responses. Interleukin-6, secreted by macrophage cells, T helper lymphocytes, B-lymphocytes, and astrocytes, has a strong effect on plasma cells and lymphocytes. The primary function of this cytokine is to differentiate plasma cells faster and produce more antibodies. High

levels of IL-6 could lead to the overgrowth of these cells in the lymphatic system, indicating inflammation in the body.[7] Tumor necrosis factor-alpha is one of the most well-known causes of tumor necrosis. Tumor necrosis factors are a group of cytokines that end in cell apoptosis (death). Tumor necrosis factor-alpha is mainly produced and released by monocytes and macrophages. Being also produced by lymphocytes and natural killer cells, this factor is one of the key mediators in developing acute-phase inflammatory symptoms in the human body and has a role in septic shock, cachexia, and tumor regression as well.[8]

Despite the significance of neutrophil-to-lymphocyte ratio (NLR) as a predictor of inflammatory status and mortality of ESKD patients undergoing dialysis and the ease of calculation and access to this ratio, there are still few studies carried out regarding the role of this ratio and its relationship with different inflammatory factors in the world and most of the studies just evaluate the relation between NLR and 1 or 2 of the inflammatory factors. Hence, this study was conducted to determine the relationship between NLR and other inflammatory factors and their role and status in the prognosis of dialysis patients. Therefore, it can be used instead of inflammatory factors that are less available if it is positive.

METHODS

Study Setting and Patient Selection

The study was descriptive-analytical with a prospective design to determine the relationship between NLR with inflammatory factors of peripheral blood in patients undergoing dialysis with the code of ethics IR.SBMU.MSP.REC.1396.45. The population was selected from among the patients with ESKD undergoing dialysis admitted to the nephrology clinic and dialysis center of Shahid Labbafinejad Hospital using a simple random sampling method. The sample size was calculated as 70 people based on the study of Turkmen et al.[9] with NLR equal to 0.1 and calculation of the first type error (alpha) 0.05 and power 80% with the formula.

$$n=\frac{\left(z_{1-\frac{\mu}{2}}\sqrt{2P(1-P)}z_{1-t}\sqrt{P0(1-P0)+P1(1-P1)}\right)^2}{(P1-P0)^2}$$

MAIN POINTS

- Neutrophil-to-lymphocyte ratio (NLR) has been considered an inflammatory prognostic factor in ESKD patients.
- The study revealed that NLR and other inflammatory parameters are high in ESKD patients who receive dialysis.
- A significant correlation between NLR and interleukin 6 was found in dialysis patients. Hence, instead of measuring these costly and less available biochemical parameters, it is suggested to use NLR as a less costly and affordable measure.

Finally, considering the loss of samples, 12% was added to the sample size, and it became 80 people.

The inclusion criteria were patient's consent, the absence of nephrotic range proteinuria (>3.5 g in 24 h), the absence of active infection and the absence of autoimmune disease .[9]

The purpose of the study was explained to all patients, and they were ensured that their information would be confidential and used only for the study purposes. If they agreed, the patients filled in the relevant informed consent form and entered the project. Eventually, all stages of the project were performed using the information and consent of the patient or his legal guardian.

Statement of Ethics

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences on August 23, 2017 (Approval ID: IR.SBMU.MSP.REC.1396.45). Before performing the study, informed consent was taken from each participant.

Data Collection

The data collection tool was a checklist containing clinical and demographic information of patients like age, gender, duration of dialysis, type of dialysis access, the main cause of ESKD, mean arterial blood pressure, and biochemical factors such as CRP, erythrocyte sedimentation rate (ESR), IL-6, TNF-α, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), calcium (Ca), phosphorus (P), parathyroid hormone (PTH), Vitamin D, creatinine (Cr), albumin, white blood count (WBC), hemoglobin (Hb), platelet (Plt), serum ferritin, and total iron-binding capacity (TIBC). neutrophil-to-lymphocyte ratio was obtained by dividing neutrophils into lymphocytes. In one of the patient's admission, a blood sample was taken, and laboratory tests were requested for the patients.

The laboratory method of measuring blood parameters was obtained mainly through the oxidase-based technique Roche/Hitachi Modular System (Mannheim, Germany) in the central laboratory of Shahid Labbafinejad Hospital. Serum levels of IL-6 and TNF-α were obtained by ELISA in the same laboratory.

Data Analysis

Checklist information was finally entered into Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, Ill, USA). Descriptive statistics (mean, SD, frequency, and percentage) were used to analyze demographic information like age, gender, and body mass index. To ensure normal distribution of data, Skewness and Kolmogorov–Smirnov test were used ($P > .05$). Pearson correlation was used to determine the relationship between NLR and quantitative factors, and bivariate correlation to examine the relationship with other factors. The patients were divided into 2 groups based on the mean NLR of more than 2.5 and less than 2.5. An independent *t*-test was

used to compare the mean NLR with quantitative parameters and chi-square for qualitative variables. Regression analyses were used to determine the independent factors affecting NLR. In all evaluations performed in the study, the power was 80%, type 1 error was 5%, and the significance level was less than .05.

RESULTS

The study was carried out on 70 adult patients with ESKD, undergoing dialysis. The data revealed that the mean and SD of the patient's age was 52.82 ± 17.23 years, and dialysis duration was 8 ± 8.7 years. The mean and SD of inflammatory factors were IL-6 8.4 ± 11.5, TNF-α 2.3 ± 2.1, NLR 2.5 ± 1.3, CRP 12.5 ± 18, and ESR 40 ± 26.7 (Table 1). Additionally, most participants (63.3%) were males, and 85.7% were undergoing hemodialysis. The fistula was used for dialysis in 68.5% of them. As shown in Table 2, ESKD etiology was diabetes mellitus in most of the cases (34.4%).

Pearson linear correlation analysis indicated that NLR level was directly and significantly related to IL-6 ($P < .001$). Moreover, NLR was significantly correlated with CRP ($P = .02$). An increase in NLR is associated with an increase in CRP, and the intensity of this relationship is $r = 0.262$. Furthermore, the direct relationship between NLR and other inflammatory markers such as ESR ($P = .004$), WBC ($P = .02$), and ferritin ($P = .012$) was significant. Age and Ca also had direct relationship with NLR ($P < .05$) (Table 3). Figure 1 presents the relationship between NLR level and IL-6. Moreover, TNF-α level had a direct and significant relationship ($P < .05$) with only Ca (Table 3).

The results of the independent *t*-test and analysis of variance indicated no statistically significant relationship between qualitative variables of gender, type of dialysis, ESKD etiology, and the type of vascular access for dialysis with IL-6, NLR, and TNF-α levels ($P > .05$) (Table 4).

Linear regression analysis was used to eliminate the effect of confounding variables and to specify the relationship between each of the parameters measured with NLR. The analysis results revealed a direct and significant relationship between NLR and IL-6 ($P < .0001$, $t = 2.874$, and beta = 0.278), independent of the effect of other variables. Meanwhile, there were no significant relationships with other variables in this analysis.

Concerning the relationship of quantitative variables with platelet-to-lymphocyte ratio (PLR), none of the studied variables, including IL-6 and TNF-α, had a statistically significant relationship with PLR and with net numbers of lymphocytes and platelets.

DISCUSSION

The study's results indicated that the mean inflammatory parameters in ESKD patients was higher than normal. Additionally, the results revealed that higher levels of NLR in

Table 1. Mean, SD, Minimum, and Maximum of Quantitative Variables

Variables	Mean	Minimum–Maximum	Variables	Mean	Minimum–Maximum
Age (years)	52.28 ± 17.23	19-86	Height (cm)	165 ± 8.5	150-182
Weight (kg)	70 ± 17.4	36-126	Dialysis duration (years)	8 ± 8.7	1-39
MAP (mmHg)	15 ± 1.4	11-19	IL-6 (μg/mL)	8.4 ± 11.5	0.6-86.4
CRP (mg/L)	12.5 ± 18	1-115	ESR (mm/hr)	40 ± 26.7	2-140
TNF-α (ng/mL)	2.3 ± 2.1	0.1-10.3	Albumin (g/dL)	4 ± 0.5	2.8-6
HDL (mg/dL)	35.7 ± 9.9	4-71	TG (mg/dL)	128 ± 83	41-466
LDL (mg/dL)	68.8 ± 21.6	35-136	Total cholesterol (mg/dL)	135 ± 36	75-257
Ca (mg/dL)	8.5 ± 1.4	7.9-11.3	PTH (ng/L)	383 ± 45	4-3345
Vitamin D (ng/mL)	57.6 ± 61	6-366	Hb (g/dL)	10.8 ± 2.2	8.6-13.5
Cr (mg/dL)	8.1 ± 2.4	3.2-14.3	Neutrophil (×10^3/μL)	13.6 ± 2.8	10-77
Lymphocyte (×10^3/μL)	6.2 ± 1	10-41	NLR	2.5 ± 1.3	0.6-7.4
SGPT (U/L)	15 ± 9	5-61	SGOT (U/L)	14 ± 7	5-35
ALP (IU/L)	344 ± 57	108-493	Direct bilirubin (mg/dL)	0.39 ± 0.81	0.1-6
Phosphorus (mg/dL)	5.6 ± 2	2.5-51	Ferritin (μg/L)	47.6 ± 29	8-136
TIBC (μg/dL)	200 ± 46	22-366	WBC (×10^3/μL)	6 ± 2.1	2.6-13.5
Plt (×10^3/μL)	156 ± 30	88-373	PLR	190 ± 86	3-220

MAP, mean arterial pressure; CRP, c-reactive protein; TNF-α, tumor necrosis factor alpha; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Ca, calcium; Cr, creatinine; SGPT, serum glutamic-pyruvic transaminase; ALP, alkaline phosphatase; TIBC, total iron-binding capacity; Plt, platelet; IL-6, interleukin-6; ESR, erythrocyte sedimentation rate; TG, triglyceride; PTH, parathyroid hormone; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; SGOT, serum glutamic-oxaloacetic transaminase; WBC, white blood count; PLR, platelet-to-lymphocyte ratio.

Table 2. Absolute and Relative Frequency of Qualitative Variables

Variables		Absolute Frequency	Relative Frequency (%)	Variables		Absolute Frequency	Relative Frequency (%)
Gender	Male	45	64.3	Dialysis access	Arteriovenous fistula	48	68.5
					Permanent central venous catheter	9	12.9
	Female	25	35.7		Vascular graft	3	4.3
					Peritoneal catheter	10	14.3
Dialysis	Hemodialysis	60	85.7	ESKD etiology	Genetic	3	4.3
					Diabetes	22	31.4
					Hypertension	16	22.9
					Infection	3	4.3
	Peritoneal dialysis	10	14.3		CKD	2	2.9
					Urinary reflux	2	2.9
					Lupus erythematous	1	1.4
					Proteinuria	2	2.9
					Polycystic kidney disease	1	1.4
					Unknown	18	25.7

dialysis patients were connected with higher levels of serum ferritin, age, calcium, IL-6, and CRP. This suggests the presence of high underlying inflammation in these patients. However, dialysis type had no relationship with inflammatory factors.

Neutrophil-to-lymphocyte ratio has been the focus of many studies recently as one of these factors. This ratio is easily calculated and measured and can be a strong predictor of mortality in patients undergoing coronary artery intervention recently.[10] Furthermore, recent studies have shown that this laboratory ratio can be used as an inflammatory prognostic factor in ESKD patients.[11] As the access to laboratory kits is usually difficult and costly for inflammatory factors like TNF-α and IL-6, the NLR ratio can be used in clinical trials as a low-cost and more affordable alternative when the role of NLR as an inflammatory factor like TNFα, CRP, IL-6, and other inflammatory factors is identified and proven. Okyay et al. revealed that serum inflammatory factors like CRP, IL-6, albumin, HDL, hemoglobin levels, and hypertension are independent factors that affect and determine the NLR levels of patients.[12] Moreover, many studies have shown the role of NLR as a prognostic factor of inflammation in ESKD patients.[12-14] Despite the confirmed role of NLR in the prognosis of the patients undergoing dialysis in some studies, there is still no complete agreement on the NLR value that may show an inflammatory condition in these patients. For instance, in a study by Turkmen et al., NLR levels greater than 3 were considered a sign of inflammation in ESKD patients.[9] However, Malhotra et al. indicated that NLR > 5 is associated with CRP > 10 and is a marker of inflammation in these patients.[14] Platelet to lymphocyte ratio is another variable that its association with inflammatory factors in serum has been studied previously. Ahbap et al[13] showed the relationship between NLR and PLR with high levels of inflammatory factors, especially CRP, in hemodialysis patients. Hence, PLR is another variable that could specify the prognosis of dialysis patients.

Inflammatory processes in ESKD patients are a part of the chronic inflammatory process known as malnutrition inflammation atherosclerosis syndrome.[5] The presence of higher levels of inflammatory factors has been reported in both hemodialysis patients,[15-17] and peritoneal dialysis patients.[18,19] Over the past 2 decades, it has been shown that the increase in inflammatory reactions in this group of patients has been associated with the progression of atherosclerosis in them.[20] Inflammatory cytokines have a key role in developing chronic inflammatory syndrome in these patients. In this respect, NLR is a new index recently introduced as a key inflammatory marker in cardiac and noncardiac diseases.[11,21]

Several studies have indicated that prolonged inflammation in ESKD patients is linked to premature death.[4] The presence of high levels of inflammatory factors such as TNF-α, CRP, and IL-6 is connected with a higher mortality risk both in dialysis patients and in the general population.[4,5] White blood cells and their subsets are considered the warning factors in the inflammatory status of the patients. As one of these factors, NLR has received much attention in recent studies.

This study showed that IL-6 and CRP levels are directly and significantly associated with NLR values. Both of these parameters are higher compared to normal in ESKD patients; however, no correlation was found in the case of TNF-α. Both CRP and IL-6

Table 3. The Correlation Between Quantitative Variables, NLR, TNF-α, and IL-6

	Inflammation Factors					
	NLR		TNF-α		IL-6	
Variables	*r*	*P**	*r*	*P**	*r*	*P**
Age	**0.276**	**.02**	**0.355**	**.35**	**0.240**	**.045**
Duration of dialysis (years)	0.148	.22	0.17	.23	0.148	.22
Ca (mg/dL)	0.31	.009	−0.244	.042	0.301	.01
NLR	–	–	0.145	.523	0.606	.0001
IL-6 (μg/mL)	0.606	.0001	−0.133	.781	–	–
TNF-α (ng/mL)	−0.112	.512	–	–	−0.063	.605
WBC (×10³/μL)	0.312	.02	0.137	.36	0.296	.01
Ferritin (μg/L)	0.30	.012	0.276	.492	0.3	.012
ESR (mm/hr)	0.61	.004	0.169	.32	0.309	.009
CRP (mg/L)	0.262	.02	0.291	.487	0.497	.0001
MAP (mmHg)	0.215	.37	0.109	.298	0.117	.33
Albumin (g/dL)	−0.028	.71	−0.015	.876	−0.009	.92
HDL (mg/dL)	0.235	.42	0.267	.32	0.150	.214
TG (mg/dL)	−0.119	.65	−0.056	.509	−0.044	.720
LDL (mg/dL)	0.219	.47	0.231	.16	0.123	.310
TC (mg/dL)	0.229	.341	0.228	.28	0.128	.289
Phosphorus (mg/dL)	−0.107	.798	−0.076	.798	−0.025	.843
PTH (ng/L)	−0.037	.712	−0.113	.331	−0.018	.886
Vitamin D (ng/mL)	−0.038	.89	−0.052	.652	−0.066	.585
Hb (g/dL)	−0.014	.986	−0.068	.891	−0.004	.971
Cr (mg/dL)	−0.256	.368−	−0.245	.344	−0.134	.268
Neutrophil (×10³/μL)	0.132	.334	0.185	.452	0.085	.486
Lymphocyte (×10³/μL)	0.084	.892	0.214	.693	0.014	.905
SGOT (U/L)	−0.078	.752	−0.153	.547	−0.053	.662
SGPT (U/L)	−0.121	.657	−0.321	.793	−0.020	.868
ALP (IU/L)	−0.147	.682	-0.112	.432	−0.087	.472
Direct bilirubin	−0.105	.498	0.465	.079	−0.065	.593
TIBC (μg/dL)	−0.035	.812	−0.217	.283	−0.017	.831
Plt (×10³/μL)	−0.221	.185	−0.589	.093	−0.089	.485
PLR	−0.077	.801	0.784	.065	−0.084	.671

MAP, mean arterial pressure; CRP, c-reactive protein; TNF-α, tumor necrosis factor alpha; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Ca, calcium; Cr, creatinine; SGPT, serum glutamic-pyruvic transaminase; ALP, alkaline phosphatase; TIBC, total iron-binding capacity; Plt, platelet; IL-6, interleukin-6; ESR, erythrocyte sedimentation rate; TG, triglyceride; PTH, parathyroid hormone; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; SGOT, serum glutamic-oxaloacetic transaminase; WBC, white blood count; PLR, platelet-to-lymphocyte ratio.
*Pearson correlation test.

are considered inflammatory markers in many different diseases. In several studies, higher levels of these 2 markers are associated with higher mortality in patients undergoing dialysis.[22,23] Therefore, the correlation between them and NLR can help us predict the mortality in these patients by just neutrophil and lymphocyte counts without the need to know more laboratory markers. High levels of inflammatory parameters in ESKD patients have a long history. Descamps-Latscha et al indicated that the levels of inflammatory factors in ESKD patients are higher than normal. They showed that it happens in all uremic patients, regardless of the disease stage, that is, those who have not yet reached dialysis or are being treated with peritoneal dialysis or hemodialysis.[24] In previous studies, it has usually been reported that the level of inflammatory factors was different in the 2 groups of patients undergoing peritoneal dialysis and patients undergoing hemodialysis and was mainly higher in hemodialysis patients.[25,26] Some studies have reported higher inflammatory factors in patients undergoing peritoneal dialysis.[9] However, there were no differences between the 2 groups of patients in our study. A probable reason for this difference might be using biocompatible dialyzer membranes in the studies stated.

No significant relationships were found between TNFα and other parameters in the present study. There was only a direct and significant relationship with blood calcium levels. However, TNF-α is associated with hemoglobin or total blood cholesterol in some previous studies.[3,9]

IL-6 levels were significantly connected to plasma calcium levels, serum ferritin and CRP levels, age, neutrophil count, or lymphocyte count alone. Similar findings have been reported in previous studies. Hence, one can conclude that to understand the increase in inflammatory levels in these patients, the number of lymphocytes or neutrophils alone cannot be enough, and the ratio of the 2 is essential.

The results of the regression analysis indicated that only IL-6 had a strong significant association with NLR. The findings revealed that using a simple NLR allows determining the inflammation easily in ESKD patients and the severity of inflammation in these patients such that it is not necessary to measure costly and scarce parameters such as IL-6. This is because the measurement and calculation of NLR itself show the patient's inflammatory status and the approximate levels of IL-6. At the same time, this low-cost ratio can be easily measured and calculated in any medical center. Nonetheless, since the cutoff point of this ratio has not been determined in this study, it is also recommended to determine this number in future studies to evaluate it more accurately at patients' bedside.

The findings revealed that IL-6 was significantly higher in the group with NLR greater than 2.5 ($P < .0001$). None of the variables, IL-6 or TNF-α, were significantly related to the "net number" of lymphocytes or neutrophils.

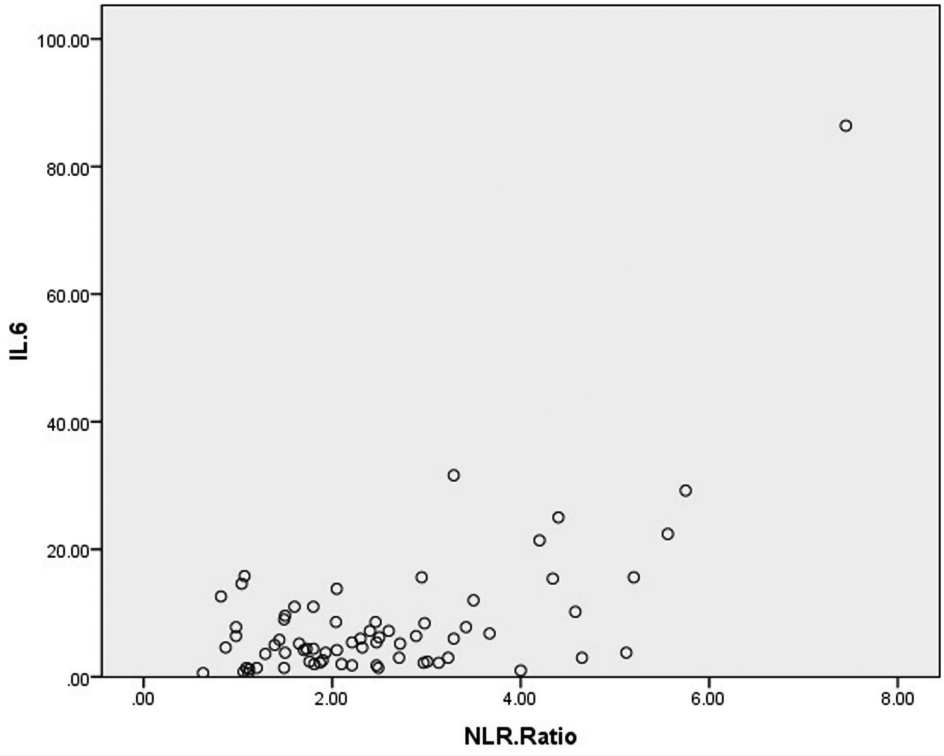

Figure 1. Linear correlation between NLR ratio and IL-6.

Table 4. The Correlation Between Qualitative Variable and IL-6, NLR, and TNF-α.

Variables		NLR mean	*P*	IL-6 mean	*P* value	TNF-α mean	*P*
Gender	Male	2.3 ± 1.1	.082*	8.8 ± 11.9	.15*	3.4 ± 2	.09*
	Female	2.7 ± 1.5		8.2 ± 11.3		2.1 ± 2.1	
Dialysis	Hemodialysis	2.4 ± 1.6	.13*	8.8 ± 11.9	.32*	2.3 ± 2.1	.097*
	Peritoneal dialysis	2.6 ± 1.7		8 ± 10.5		2.2 ± 2.1	
Dialysis access	Arteriovenous fistula	1.9 ± 0.9	.092**	9.7 ± 13.1	.37**	2.4 ± 2.3	.16**
	Permanent central venous catheter	2.7 ± 1.2		9.4 ± 12.5		1.9 ± 1.4	
	Vascular graft	2.8 ± 1.6		7.2 ± 10.1		2.7 ± 2.2	
	Peritoneal catheter	2.2 ± 1.3		7.8±10.5		2.2 ± 1.8	
ESRD etiology	Genetic	2.4 ± 1.9	.18**	8.3 ± 1.06	.23**	2.1 ± 1.6	.28**
	Diabetes	2.5 ± 1.3		8.3 ± 11.2		2.5 ± 2.4	
	Hypertension	2.6 ± 1.4		7.8 ± 10.8		2.2 ± 1.3	
	Infection	2.7 ± 1		9.4 ± 12.5		2.7 ± 2	
	CKD	2.9 ± 1.8		8.9 ± 11.9		2.5 ± 2.2	
	Urinary reflux	2.8 ± 1.2		8.4 ± 10		2.4 ± 2.1	
	Lupus erythematous	2.4		8.1		2.5	
	Proteinuria	2.9 ± 1.5		8.6 ± 11.7		2.5 ± 2.3	
	Polycystic kidney disease	2.7		8.5		2.1	
	Unknown	2.4 ± 1.1		8.2 ± 10.8		2.1 ± 1.7	

IL-6, interleukin-6; NLR, neutrophil-to-lymphocyte ratio; TNF-α, tumor necrosis factor-alpha.
*Independent *t*-test.
**Analysis of variance test.

After proving the significant relationship of NLR with the inflammatory status and inflammatory factors of the patients, particularly, IL-6, in the next step, a cutoff is needed to categorize the patients into some stages based on the inflammatory severity. Indeed, the information and results obtained from this study are completed by reaching the correct cutoff point of this ratio in future studies, then can be used practically and clinically. Although some numbers have been proposed in previous studies, none of these numbers is based on the gold standard and ROC analysis. Instead, they are just according to the greater abundance of data in that numerical range and vary in different studies.[3,4,9]

One of the limitation in the persent study was that it was performed only in one educational and medical center. To deal with this shortcoming, it is suggested to study this issue in several medical centers and cities to reduce future study errors. Moreover, in addition to the factors considered in this study, there are several other factors, such as medications in hemodialysis patients, that need to be considered in future articles.

CONCLUSION

The study revealed that NLR and other inflammatory parameters are high in ESKD patients who receive dialysis. Moreover, there is a significant correlation between NLR and IL-6. Hence, instead of measuring these costly and less available biochemical parameters, it is suggested to use NLR as a less costly and affordable measure. Nevertheless, the inflammatory process in ESKD patients is so complicated and determining the exact relationship between NLR and its role in the inflammatory process, particularly the onset of chronic kidney disease, needs more examination.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Shahid Beheshti University of Medical Sciences (Date: 2017/8/23, Number: IR.SBMU.MSP.REC.1396.45).

Informed Consent: Written informed consent was obtained from the patients who participated in this study or their legal guardians.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.S, N.D; Design – F.S, S.A, NS; Supervision – N.D, F.S; Resources – N.D, F.S; Materials – N.S, Z.F; Data Collection and/or Processing – N.S, Z.F; Analysis and/or Interpretation – S.A, N.D; Literature Search – N.S, S.A; Writing Manuscript – S.A, N.D, F.S; Critical Review – N.D, S.A.

Acknowledgments: The authors would like to express our gratitude to all the personnel of dialysis center and Chronic Kidney Disease Research Center(CKDRC) of Shahid Labbafinejad hospital and also all the patients who took part in our study.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

REFERENCE

1. Muntner P, Fau HJ, Astor BC, Bc Fau AR, Folsom AR, Fau FA, et al. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol*. 2005;16(2):529-538. [CrossRef]
2. Himmelfarb J, Fau SP, Ikizler TA, Fau IT, Hakim RM, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Internatonal*. 2002;62(5):1524-1538. [CrossRef]
3. Turkmen K, Fau GN, Uysal M, et al. Fetuin-A, inflammation, and coronary artery calcification in hemodialysis patients. *Indian J Nephrol*. 2011;21(2):90-94. [CrossRef]
4. Benedetto FA, Fau MF, Tripepi G, Fau TG, Zoccali C, Zoccali C. Prognostic value of ultrasonographic measurement of carotid intima media thickness in dialysis patients. *J Am Soc Nephrol*. 2001;12(11):2458-2464. [CrossRef]
5. Stenvinkel P, Chung SH, Heimbürger O, Lindholm B. Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. *Perit Dial Int*. 2001;21(3):S157-S162. [CrossRef]
6. Wirth MD, Sevoyan M, Hofseth L, Shivappa N, Hurley TG, Hébert JR. The Dietary inflammatory Index is associated with elevated white blood cell counts in the National Health and Nutrition Examination Survey. *Brain Behav Immun*. 2018;69:296-303. [CrossRef]
7. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014;6(10):a016295-a016295. [CrossRef]
8. Zelová H, Hošek J. TNF-α signalling and inflammation: interactions between old acquaintances. *Inflamm Res*. 2013;62(7):641-651. [CrossRef]
9. Turkmen K, Fau GI, Yerlikaya FH, Fau Fh, Tonbul HZ, Tonbul HZ. The relationship between neutrophil-to-lymphocyte ratio and inflammation in end-stage renal disease patients. *Ren Fail*. 2012;34(2):155-159. [CrossRef]
10. Horne BD, Fau AJl, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? *J Am Coll Cardiol*. 2005;45(10):1638-1643. [CrossRef]
11. Tamhane UU, Fau AS, Montgomery D, Fau MD, Rogers E-K, Fau RE, et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol*. 2008;102(6):653-657. [CrossRef]
12. Okyay GU, Fau IS, Oneç K, et al. Neutrophil to lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. *Ren Fail*. 2013. [CrossRef]
13. Ahbap E, Sakaci T, Kara E, et al. Neutrophil-to-lymphocyte ratio and platelet-tolymphocyte ratio in evaluation of inflammation in end-stage renal disease. *Clin Nephrol*. 2016;85(4):199-208. [CrossRef]
14. Malhotra R, Fau MD, von Gersdorff G, et al. Relationship of neutrophil-to-lymphocyte ratio and serum albumin levels with C-reactive protein in hemodialysis patients: results from 2 international cohort studies. *Nephron*. 2015;130(4):263-270. [CrossRef]
15. Zimmermann J, Fau HS, Pruy A, Fau PA, Metzger T, Metzger TF, et al. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int*. 1999;55(2):648-658. [CrossRef]
16. Iseki K, Fau TM, Yoshi S, Fau YS, Fukiyama K, Fukiyama K. Serum C-reactive protein (CRP) and risk of death in chronic dialysis

patients. *Nephrol Dial Transplant*. 1999;14(8):1956-1960. [CrossRef]
17. Yeun JY, Fau LR, Mantadilok V, Fau MV, Kaysen GA, Kaysen GA. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis*. 2000;35(3):469-476. [CrossRef]
18. Noh H, Fau LSw, Kang SW, et al. Serum C-reactive protein: a predictor of mortality in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int*. 1998;18(4):387-394. [CrossRef]
19. Haubitz M, Brunkhorst R. C-reactive protein and chronic Chlamydia pneumoniae infection--long-term predictors for cardiovascular disease and survival in patients on peritoneal dialysis. *Nephrol Dial Tranplantation*. 2001;16(4):809-815. [CrossRef]
20. Stenvinkel P, Fau KM, Johnson RJ. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia--the good, the bad, and the ugly. *Kidney Int.* 2005;67(4):1216-1233. [CrossRef]
21. Walsh SR, Cook EJ, Goulder F. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol*. 2005;91(3):181-184. [CrossRef]
22. Rao M, Guo D, Perianayagam MC, et al. Plasma interleukin-6 predicts cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis*. 2005;45(2):324-333. [CrossRef]
23. Li W, Xiong L, Fan L, et al. Association of baseline, longitudinal serum high-sensitive C-reactive protein and its change with mortality in peritoneal dialysis patients. *BMC Nephrol*. 2017;18(1):211. [CrossRef]
24. Descamps-Latscha B, Fau HA, Nguyen AT. Balance between IL-1 beta, TNF-alpha, and their specific inhibitors in chronic renal failure and maintenance dialysis. Relationships with activation markers of T cells, B cells, and monocytes. *J Immunol*. 1995;154(2):882-892.
25. Canivet E, Fau LS, Wong T, et al. Cuprophane but not synthetic membrane induces increases in serum tumor necrosis factor-alpha levels during hemodialysis. *Am J Kidney Dis*. 1994;23(1):41-46. [CrossRef]
26. Tielemans C, Fau HC, Schurmans T, et al. Effects of UltraPure and non-sterile dialysate on the inflammatory response during in vitro hemodialysis. *Kidney Int*. 1996;49(1):236-243. [CrossRef]