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CLINICAL STUDY

Neutrophil to Lymphocyte Ratio in Evaluation of Inflammation in Patients with Chronic Kidney Disease

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Abstract

Aim: The current data have proven the pivotal role of inflammation in the development of atherosclerosis and cardiovascular diseases in patients with chronic kidney disease (CKD). Neutrophil to lymphocyte (N/L) ratio has increasingly been reported as a measure of systemic inflammation. This study assessed N/L ratio and investigated its associations with standard inflammatory biomarkers in different stages of CKD patients. *Material and methods*: This cross-sectional study included 30 predialysis, 40 hemodialysis, 35 peritoneal dialysis patients, and 30 healthy subjects. N/L ratio and important clinical and laboratory parameters were registered. Multivariate regression analyses were carried out to investigate the relations of N/L ratio. *Results*: N/L ratio was significantly higher in each patient group compared to the healthy subjects (for all, $p < 0.001$). It was positively correlated with interleukin-6 (IL-6) ($r = 0.393$, $p < 0.001$) and high-sensitivity C-reactive protein (hs-CRP) ($r = 0.264$, $p = 0.002$) levels and negatively correlated with hemoglobin ($r = -0.271$, $p = 0.001$), serum albumin ($r = -0.400$, $p < 0.001$), and high-density lipoprotein (HDL) cholesterol levels ($r = -0.302$, $p < 0.001$). In CKD patients with hypertension (HT), higher N/L ratio was detected when compared to those without HT ($p = 0.006$). Having CKD, the presence of HT, serum albumin, HDL-cholesterol, IL-6, and hs-CRP levels were found to be independent predictors of the ratio after adjusting for significant covariates ($p < 0.001$). *Conclusion*: An easy and inexpensive laboratory measure of N/L ratio might provide significant information regarding inflammation in CKD including predialysis and dialysis patients.

Keywords: chronic kidney disease, inflammation, neutrophil to lymphocyte ratio

INTRODUCTION

The annual mortality rate associated with cardiovascular diseases (CVD) in chronic kidney disease (CKD) patients is approximately 9%, which is almost 10–20 times higher than in the general population.[1] Traditional cardiovascular risk factors such as diabetes, hypertension (HT), and hyperlipidemia remain insufficient to explain this high rate of mortality. In the last decades, many trials have proven a sustained low-grade inflammatory status in CKD patients and inflammation has been accepted as one of the main contributors of CVD development.[2,3] It seems that the future researches will focus on improving therapies in order to alleviate inflammation and eventually CVD burden in this specific population.

Although a variety of markers have been introduced to measure systemic inflammation, complementary markers are still required. Recently, the ratio of neutrophil count to lymphocyte count N/L has been examined as a novel measure of inflammation in distinct populations and has been showed to have prognostic and predictive values especially in those with systemic inflammation.[4–9] In various cancer patients, N/L ratio has been found to be a cost-effective biomarker to stratify the risk of recurrence and mortality.[4–6] In cardiovascular studies, it was also found to be a predictor of mortality in different groups of patients such as myocardial infarction[8] and heart failure.[9]

There are a few studies about N/L ratio and its relationship with other inflammatory markers in patients with CKD.[10,11] Since N/L ratio is a readily available result from the complete blood count test, studies

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about its value in CKD patients are encouraging. Hence, the aim of this study was to investigate the value of N/L ratio as a measure of systemic inflammation in CKD population including predialysis, hemodialysis (HD), and peritoneal dialysis (PD) patients compared to the healthy subjects and to evaluate its potential relations with standard inflammatory biomarkers.

MATERIAL AND METHODS

Study Population

The study included predialysis CKD patients and the ones receiving HD or PD therapies for more than 3 months in our university hospital. Patients with active infection or inflammation, type I and II diabetes mellitus, atherosclerotic vascular disease, hepatitis B and C virus infection, impaired hepatic function, autoimmune diseases, current malignancy or history of malignancy, and with immunosuppressive therapy were excluded. Predialysis CKD patients had creatinine clearance rates of <60 mL/min [by the Modification of Diet in Renal Diseases (MDRD) formula] equating to CKD stage 3 or 4. Consecutively, 30 predialysis CKD patients, 40 HD patients, and 35 PD patients fulfilled the inclusion criteria. Thirty age and gender-matched healthy subjects were recruited into the study, leading to a total of 135 subjects. This trial was conducted in the Hospital of Gazi University Medical School in accordance with the principles of Helsinki Declaration and the protocol was approved by local Medical Ethics Committee.

Clinical Data

Data on baseline characteristics and medical history were obtained from patient interviews and hospital charts. For each subject; age, gender, body weight, height, and blood pressure measurements were recorded. Additionally, the following were noted: for CKD patients, etiology of CKD, comorbid conditions, and drug usage; for predialysis patients, glomerular filtration rates; for HD patients, time on dialysis, single-pool K_t/V, urea reduction rates (URRs); and for PD patients, time on dialysis, weekly peritoneal K_t/V, PD clearances, and daily ultrafiltration volumes. The ratio of weight (kg) to the square of height (m) was used for calculation of body mass index (BMI). Arterial blood pressure measurements were performed two times with an appropriate cuff after 10 min resting in upright sitting position and the average value was taken into account. Mean arterial blood pressure (MAP) was calculated with the formula of [diastolic blood pressure (DBP) + (systolic blood pressure (SBP) − DBP)/3]. Use of erythrocyte-stimulating agents (ESAs), vitamin D, phosphate binders (calcium-based ones and sevelamer), iron, lipid-modifying drugs (statins and fibrates), and the types of antihypertensive medications at study baseline were recorded. The estimated glomerular filtration rate was calculated from the MDRD formula[12] for predialysis patients. URRs were calculated from the formula of [(predialysis blood urea nitrogen − postdialysis blood urea nitrogen)/predialysis blood urea nitrogen].

HD patients were receiving three times weekly dialysis for 4 h period with standard bicarbonate dialysate and biocompatible synthetic membranes. All PD patients were treated with continuous ambulatory or automated PD modalities with conventional PD solutions.

We registered HT and dyslipidemia as comorbid conditions. HT was defined as SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg using office blood pressure measurements, or being on a current treatment with an antihypertensive drug. Dyslipidemia was defined as total cholesterol $\geq$200 mg/dL, low-density lipoprotein (LDL) cholesterol $\geq$130 mg/dL, or currently receiving lipid-modifying agents.

Laboratory Measurements

Venous blood samples were drawn from all subjects after an overnight fasting period. Sampling was particularly performed in a morning of midweek dialysis session prior to heparinization in HD patients and before the first exchange of day in PD patients. Complete blood count and biochemistry analyses [creatinine, serum albumin, total cholesterol, triglyceride, LDL cholesterol, high-density lipoprotein (HDL) cholesterol] were detected by automated procedures carried out at the Department of Clinical Biochemistry. The white blood cell differential was determined as part of complete blood count testing. Volume conductivity scatter method was used in Coulter LH 780 analyzer machine (Beckman Coulter Inc., Miami, FL, USA) for measurement of complete blood count. Three milliliters of blood was drawn into a tube containing ethylene diamine tetraacetic acid and the tube was rotated for 5 min, then the blood sample was put in machine and results were drawn. N/L ratio was constructed by dividing neutrophil count to lymphocyte count. Serum IL-6 concentrations were measured using the commercially available human IL-6 enzyme-linked immunosorbent assay (ELISA) kit (Cusabio Biotech, Wuhan, China) according to the manufacturer's instructions. C-reactive protein (CRP) was measured by a high-sensitivity turbidimetry assay (Dako, Glostrup, Denmark).

Statistical Analysis

Statistical analysis was performed using the SPSS (version 18.0, SPSS Inc., Chicago, IL, USA) software package. Distribution of numeric variables was tested by using Kolmogorov–Smirnov test. For nonnormally distributed data, logarithmically transformed values were used if normality was achieved. Data were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Categorical variables were presented as numbers and percentages and compared using chi-square test. Parametric data of four groups were compared with one-way analysis of variance (ANOVA). Tukey test (in

case of homogeneity of variances) and Dunnett's T3 test (in case of heterogeneity of variances) were performed for post-hoc comparisons. Homogeneity of variances was evaluated with Levene's test. Comparisons of nonnormally distributed data even after logarithmic transformation were performed by Kruskal–Wallis test with post-hoc Bonferroni correction test, in which statistical significance was accepted when p-values were <0.008. Comparisons between the two groups were performed with Student t-test for parametric data and Mann–Whitney U-test for nonparametric data. Pearson or Spearman rank correlation test was performed to determine the relationships between continuous variables. Univariate analysis of correlations for N/L ratio was performed prior to multivariate analysis. Independent relationships of N/L ratio were examined with multivariate linear regression analysis with stepwise backward elimination method. All probability values were calculated by assuming a two-sided p-value of ≤ 0.05 with confidence intervals (CIs) at the 95% level.

RESULTS

Baseline clinical characteristics and laboratory results of the subjects included in the study are shown in Tables 1 and 2. There were no differences between the CKD groups and healthy controls with respect to age and gender. Regarding time on dialysis and the causes of kidney diseases, HD and PD patients were similar (for both, $p > 0.05$). SBP, DBP, and MAP measurements were higher in predialysis and PD patients compared to HD patients and healthy subjects ($p < 0.001$). In terms of comorbid conditions; the frequency of HT was significantly higher in predialysis and PD patients compared to HD patients ($p = 0.01$), and the frequency of dyslipidemia was similar among the groups ($p = 0.56$). Data regarding patients' medications and dialysis adequacy are detailed in Table 2.

N/L ratio as well as IL-6 and high-sensitivity C-reactive protein (hs-CRP) concentrations were significantly higher in all CKD groups compared to the healthy subjects (Table 1; for all, $p < 0.001$). Although N/L ratio was higher in PD patients compared to other CKD groups, the difference fell out of statistical significance. Similarly, there was no difference regarding IL-6 and hs-CRP levels among CKD groups (Table 1) (for all, $p > 0.05$). N/L ratio had positive correlations with IL-6 ($r = 0.393$, $p < 0.001$), hs-CRP ($r = 0.264$, $p = 0.002$), SBP ($r = 0.273$, $p = 0.001$), DBP ($r = 0.218$, $p = 0.01$), and MAP ($r = 0.272$, $p = 0.001$) measurements, and inverse correlations with hemoglobin ($r = -0.271$, $p = 0.001$), serum albumin ($r = -0.400$, $p < 0.001$), and HDL-cholesterol levels ($r = -0.302$, $p < 0.001$) (Figure 1). No associations were detected between N/L ratio and BMI, total cholesterol, LDL-cholesterol levels, and dialysis duration (for all, $p > 0.05$). When the study population was divided into two categories according to the mean age (45.8 years), older subjects had significantly elevated N/L ratio compared to the younger ones (1.03 vs. 0.85, $p = 0.02$). In the whole sample, N/L ratio was higher in male patients compared to the females (1.02 vs. 0.86, $p = 0.04$).

When CKD population was divided into two categories based on the presence of HT as comorbidity, it was found that CKD patients with HT had higher N/L ratio compared to those without HT ($p = 0.006$) (Table 3). Compared to healthy subjects, CKD patients without HT had higher neutrophil counts (4420 ± 1558 vs. 3730 ± 1129, $p = 0.04$), N/L ratio [2.30 (1.82–3.28) vs. 1.75 (1.44–2.31), $p = 0.001$], hs-CRP [0.30 (0.14–1.30) vs. 0.12 (0.07–0.21), $p < 0.001$], and IL-6 levels [15.55 (12.80–20.30) vs. 9.30 (8.30–11.68), $p < 0.001$]. There was no difference regarding N/L ratio between patients with or without dyslipidemia in CKD population [3.03 (2.17–3.94) vs. 2.81 (2.15–3.82), $p = 0.44$].

Regarding the medications of CKD patients ($n = 105$), N/L ratio was similar between patients who have been or have not been treated with ESA ($p = 0.99$), vitamin D ($p = 0.67$), calcium-based phosphate binders ($p = 0.17$), sevelamer ($p = 0.99$), iron ($p = 0.88$), anti-lipidemic drugs ($p = 0.54$), renin angiotensin system blockers ($p = 0.52$), beta-blockers ($p = 0.12$), calcium channel blockers ($p = 0.07$), and alpha blockers ($p = 0.93$).

In multivariate linear regression model, serum albumin, HDL-cholesterol, IL-6, hs-CRP, presence of HT, and presence of CKD had remained as the independent variables for predicting N/L ratio (Table 4).

DISCUSSION

This study manifested that predialysis and dialysis patients with CKD had higher N/L ratio as well as IL-6 and hs-CRP levels compared to the healthy subjects, and N/L ratio had positive correlations with these inflammatory biomarkers. This study also showed that CKD patients with HT had higher N/L ratio than those without HT. These findings provide that a simple calculation of N/L ratio might be a surrogate marker for evaluation of inflammation in CKD patients.

Activation of the immune system, caused by inflammation, increases white blood cell counts. Increased white blood cells and its neutrophil component were evidenced as significant predictors of overall and CVD-associated mortality in PD patients.[13] In a large cohort including HD patients, increased neutrophil count and decreased lymphocyte count have been reported to be useful parameters of poor outcome.[14] In our study, compared to the healthy subjects, PD patients had higher neutrophil and lower lymphocyte counts and predialysis patients had higher neutrophil counts. Two recent studies have evaluated the use of N/L ratio in CKD patients.[10,11] An et al. have shown significantly increased N/L ratio in PD patients compared to the healthy subjects. They also defined this simple calculation as a

Table 1. Clinical and laboratory characteristics of the study population.

			Dialysis patients		
	Healthy subjects ($n = 30$)	Predialysis patients ($n = 30$)	HD patients ($n = 40$)	PD patients ($n = 35$)	p-Value
Age (years)	44.73 ± 10.49	50.33 ± 11.17	44.1 ± 13.4	44.83 ± 13.96	0.17
Gender (male, n, %)	13 (43.3 %)	16 (53.3 %)	28 (70 %)	18 (51.4 %)	0.14
BMI (kg/m^2)	24.90 ± 2.80	26.69 ± 4.96	23.6 ± 3.5 a	24.49 ± 4.32	0.02
Systolic blood pressure (mm Hg)	105 (95–120)[a,b]	120 (110–135)	115 (100–130)	120 (110–140)	<0.001
Diastolic blood pressure (mm Hg)	67.5 (60–80)[a,b]	80 (70–90)	70 (60–80)[a]	80 (75–90)[c]	<0.001
Mean arterial blood pressure (mm Hg)	81 ± 9.8[a,b]	94 ± 12.3	86 ± 13.7[a]	95 ± 13.4[c]	<0.001
Hemoglobin (g/dL)	14.02 ± 1.60[a,b,c]	11.69 ± 1.56	11.37 ± 1.50	11.18 ± 1.83	<0.001
WBC count (U/L)	6310 ± 1502[a]	7754 ± 2099	6817 ± 1867	6967 ± 1651	0.02
Neutrophil count (U/L)	3730 ± 1129[a,b]	5074 ± 1947	4297 ± 1434	4752 ± 1422	0.004
Lymphocyte count (U/L)	2038 ± 645[b]	1838 ± 479	1643 ± 702	1447 ± 301[a]	<0.001
Creatinine (mg/dL)	0.71 (0.67–0.78)[a,b,c]	2.16 (1.57–3.54)	9.62 (8.33–11.0)[a]	9.37 (6.99–11.51)[a]	<0.001
Albumin (g/dL)	4.43 ± 0.34[a,b,c]	3.89 ± 0.36	3.70 ± 0.34	3.50 ± 0.30[a]	<0.001
Total cholesterol (mg/dL)	189.23 ± 29.29[c]	179.80 ± 43.09	158.13 ± 39.58	187.37 ± 42.29[c]	0.003
Triglyceride (mg/dL)[d]	96.5 (80–139.3)[b,c]	115 (96.8–193)	147 (101.3–254.5)	146 (114–202)	0.004
LDL-cholesterol (mg/dL)	117.17 ± 23.75[c]	108.42 ± 33.76	87.85 ± 24.28[a]	120.09 ± 34.84[c]	<0.001
HDL-cholesterol (mg/dL)	49.63 ± 12.00[b,c]	41.67 ± 12.66	31.9 ± 7.00[a]	35.80 ± 10.67	<0.001
N/L ratio[d]	1.75 (1.44–2.32)[a,b,c]	2.54 (1.75–3.42)	2.42 (1.81–4.08)	3.15 (2.56–3.94)	<0.001
IL-6 (pg/dL)[d]	9.30 (8.30–11.68)[a,b,c]	16.30 (11.39–22.18)	16.05 (13.05–21.55)	18.05 (14.55–31.05)	<0.001
hs-CRP (mg/dL)	0.12 (0.07–0.21)[a,b,c]	0.63 (0.12–2.52)	0.36 (0.17–1.09)	0.24 (0.13–1.26)	<0.001

Notes: Continuous variables are shown as mean ± SD if normally distributed and as median (IQR, interquartile range) if nonnormally distributed. Categorical variables are shown as frequency and percentages. HD, hemodialysis; PD, peritoneal dialysis; BMI, body mass index; WBC, white blood cell; LDL, low-density lipoprotein; HDL, high-density lipoprotein; N/L, neutrophil to lymphocyte; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein. $p < 0.05$.

[a]Group versus predialysis patients

[b]Group versus PD patients.

[c]Group versus HD patients.

[d]Logarithmically transformed values were used for one-way ANOVA testing; data are presented as median values and IQR.

Table 2. Baseline characteristics of patients with CKD.

		Dialysis patients		
	Predialysis patients ($n = 30$)	HD patients ($n = 40$)	PD patients ($n = 35$)	p-Value
Time on dialysis (months)	–	58.90 ± 48.77	45.06 ± 31.63	0.15
Etiology of CKD (n, %)				0.57
HT	15 (50%)	10 (25%)	13 (37.1%)	
Glomerulonephritis	4 (13.3%)	6 (15%)	6 (17.1%)	
Nephrolithiasis	3 (10.1%)	4 (10%)	3 (8.6%)	
Unknown	4 (13.3%)	14 (35%)	6 (17.1%)	
Others	4 (13.3%)	6 (15%)	7 (20.1%)	
Comorbidities (n, %)				
HT	22 (73.3%)	16 (40%)	22 (62.9%)	0.01
Dyslipidemia	11 (36.7%)	10 (25%)	10 (28.6%)	0.56
Medications (n, %)				
ESA	–	25 (62.5%)	17 (48.6%)	<0.001
Vitamin D	12 (40%)	23 (57.5%)	20 (57.1%)	0.28
Ca-based phosphate binders	5 (16.7%)	23 (57.5%)	15 (42.9%)	0.003
Sevalemer	2 (6.7%)	15 (37.5%)	8 (22.9%)	0.01
Iron	3 (10%)	33 (82.5%)	19 (54.3%)	<0.001
Anti-lipidemic agents	8 (26.7%)	8 (20%)	10 (28.6%)	0.66
ACE/ARB	16 (53.3%)	9 (22.5%)	8 (22.9%)	0.009
Beta-blockers	16 (53.3%)	5 (12.5%)	12 (34.3%)	0.001
Ca-channel blockers	15 (50%)	7 (17.5%)	18 (51.4%)	0.003
Alpha-blockers	7 (23.3%)	–	5 (14.3%)	0.008
spK_t/V per week	–	1.51 ± 0.28	–	–
Urea reduction rate (%)	–	71.65 ± 6.14	–	–
Peritoneal K_t/V per week	–	–	2.03 ± 0.62	–
CrCl (L/week/1.73 m^2)	–	–	65.80 ± 29.29	–
Daily UF volume (mL)	–	–	1003 ± 343	–
eGFR (mL/min)	35.90 (16.90–58.20)	–	–	–

Notes: Categorical variables are shown as frequency and percentages. Continuous variables are shown as mean ± SD if normally distributed and as median (IQR, interquartile range) if nonnormally distributed. HD, hemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease; HT, hypertension; ESA, erythrocyte-stimulating agent; Ca, calcium; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CrCl, weekly creatinine clearance; UF, ultrafiltration; GFR, glomerular filtration rate.

predictor of overall and CVD-associated mortality.[10] Similarly, Turkmen et al. have assessed N/L ratio in patients receiving dialysis therapies and found it to be higher in PD patients compared to the HD patients. They have also manifested a positive correlation between N/L ratio and TNF-α levels.[11] The findings in our study were consistent to some extent with these two reports. In our study, N/L ratio was absolutely higher in PD and HD patients compared to the healthy subjects as shown in IL-6 and hs-CRP levels. Unlike the previous two reports, in our study, increased N/L ratio was also manifested in predialysis CKD patients. Multivariate regression analysis defined these well-established markers of inflammation as the independent factors for predicting of N/L ratio. All of these findings offer N/L ratio as an inflammatory biomarker for CKD patients.

Previous data have demonstrated increased levels of inflammatory mediators in hypertensive patients,[15,16] and low-grade inflammation in the vascular wall has been shown to be a contributor to the pathophysiology of HT.[17] Recently, in a population-based large-scale study, a significant association was defined between N/L ratio and HT.[18] However, such an association has not been previously defined in CKD patients. In this study, positive correlations of N/L ratio with blood pressure measurements and the linear association of the ratio with the presence of HT were manifested. We have also shown higher N/L ratio and IL-6 values in the subset of hypertensive CKD patients compared to the normotensive ones. Cellular responses mediated via endothelial dysfunction could have let increased biomarkers in the setting of HT. We did not observe any differences in N/L ratios in terms of anti-hypertensive medications. However, it is plausible that controlling HT in CKD patients might alleviate systemic inflammation, and N/L ratio might provide an additional information in the setting of HT. However, this issue needs to be further analyzed in other studies.

Similar to the study of Turkmen et al.,[11] our study manifested negative correlations of N/L ratio with serum albumin, hemoglobin, and cholesterol levels. We found out these parameters also as the independent predictors of N/L ratio. Increased proinflammatory cytokines inhibit hepatic albumin and pre-albumin syntheses and also lead to erythropoiesis impairment.[19–22] Previous data have suggested close relationships between low serum albumin levels and CRP concentrations,[23] CVD development,[24] and mortality in PD and HD patients.[25,26] Low HDL-cholesterol level is related to atherogenesis, and according to our study, increased N/L ratio was accompanied by decreased HDL-cholesterol levels. All of these findings were supporting the assumption that N/L ratio might be accepted as a marker of

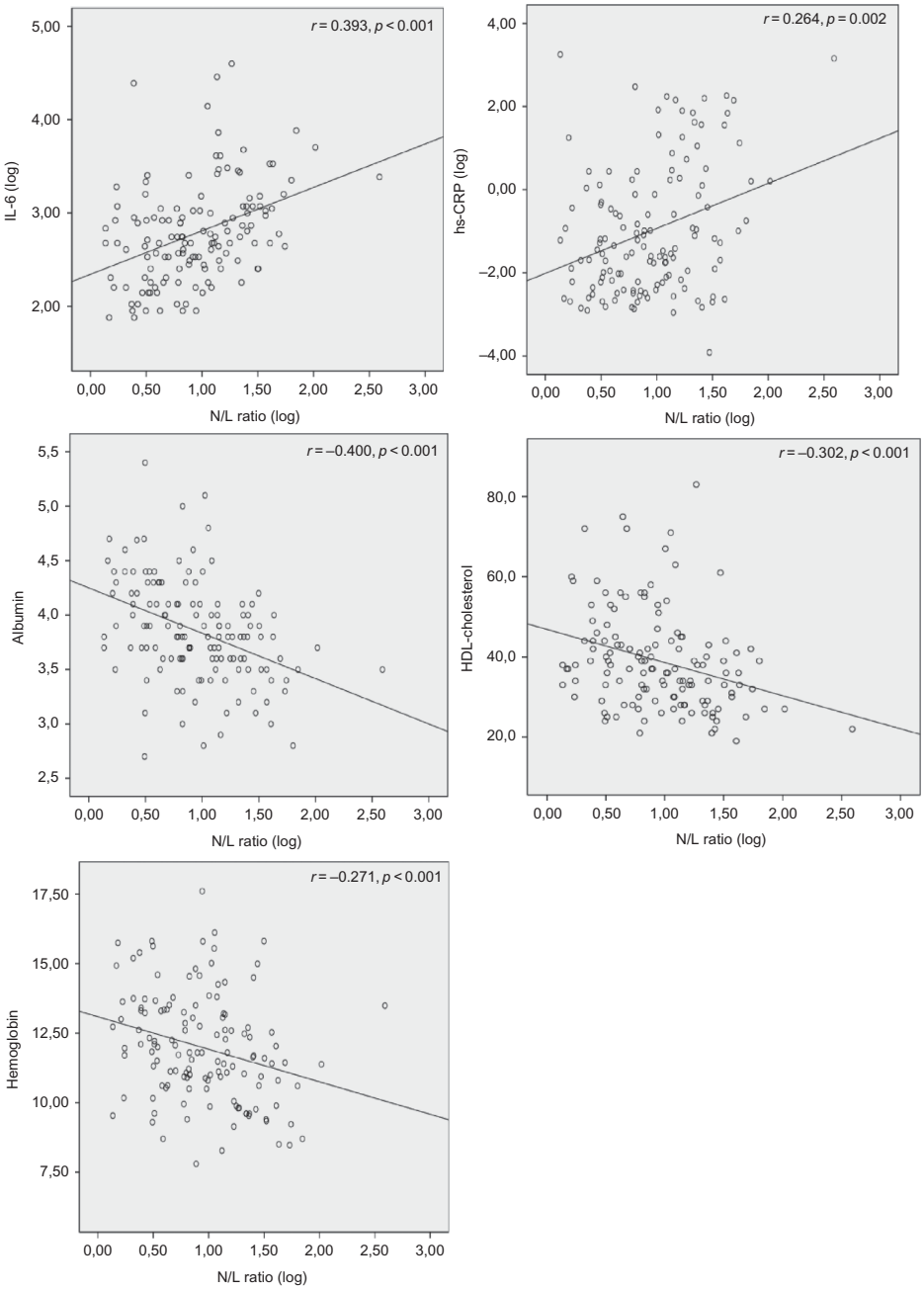

Figure 1. Scatter plot figures for positive and negative correlations of N/L ratio.

Table 3. Blood pressure measurements and inflammatory parameters in CKD patients with and without HT.

	CKD patients with HT ($n = 60$)	CKD patients without HT ($n = 45$)	p-Value
Systolic blood pressure (mm Hg)	120 (120–140)	110 (100–130)	0.003
Diastolic blood pressure (mm Hg)	80 (76.25–85)	70 (60–80)	0.001
Mean arterial blood pressure (mm Hg)	96.67 (86.67–101.67)	83.33 (73.33–96.67)	0.001
Lymphocyte count (U/L)	1527 ± 423	1774 ± 663	0.022
Neutrophil count (U/L)	4859 ± 1635	4420 ± 1558	0.17
Total white blood cell count (U/L)	7209 ± 1799	7036 ± 2030	0.65
N/L ratio[a]	3.13 (2.37–4.25)	2.30 (1.82–3.28)	0.006
IL-6 (pg/dL)[a]	18.30 (14.05–27.68)	15.55 (12.80–20.30)	0.026
hs-CRP (mg/dL)[a]	0.38 (0.12–1.96)	0.30 (0.14–1.30)	0.57

Notes: Continuous variables are shown as mean ± SD if normally distributed and as median (IQR, interquartile range) if nonnormally distributed.

[a]Logarithmically transformed values were used for Student t-test comparison and data were presented as median (IQR). CKD, chronic kidney disease; HT, hypertension; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein.

Table 4. Univariate and multivariate linear regression analysis with N/L ratio as dependent variable in the whole sample.

	Univariate analysis			Multivariate analysis (constant = 1.299, adjusted-R^2 = 0.311, $p < 0.001$)		
Parameter	β	CI 95%	*p*-Value	β	CI 95%	*p*-Value
Age	0.006	(−0.0001, 0.012)	0.055			
Gender	0.163	(0.010, 0.317)	0.037			
BMI	−0.006	(−0.025, 0.013)	0.543			
SBP	0.007	(0.003, 0.011)	0.001			
DBP	0.009	(0.002, 0.015)	0.007			
MAP	0.009	(0.003, 0.014)	0.002			
Hb	−0.060	(−0.101, −0.025)	0.001			
LDL-C	−0.0005	(−0.003, −0.002)	0.686			
HDL-C	−0.011	(−0.017, −0.005)	<0.001	−0.007	(−0.013, −0.001)	0.022
Albumin	−0.384	(−0.535, −0.233)	<0.001	−0.206	(−0.391, −0.021)	0.030
IL-6 (log)	0.331	(0.198, 0.464)	<0.001	0.176	(0.036, 0.317)	0.014
hs-CRP	0.031	(0.011, 0.052)	0.003	0.019	(0.0002, 0.037)	0.048
HT	−0.119	(−0.222, −0.016)	0.024	0.251	(0.098, 0.405)	0.002
Groups	0.441	(0.271, 0.611)	<0.001	0.418	(0.109, 0.726)	0.008

Notes: Parameters used for multivariate regression analysis: age, gender (male vs. female), BMI, MAP, Hb, HDL-C, albumin, IL-6, hs-CRP, HT (with vs. without) and groups (CKD vs. healthy controls). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; Hb, hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IL-6, interleukin-6; hs-CRP, high-sensitivity C-reactive protein; HT, hypertension.

systemic inflammation. On the other hand, further trials are needed to identify the association of N/L ratio with nutritional status.

Previously, male subjects were found to have higher N/L ratio in advanced colorectal cancer[27] and myocardial infarction.[28] In accordance with the literature, in this study, males were also found to have higher N/L ratio. Additionally, N/L ratio was found to be higher in older subjects and univariate regression analysis revealed a linear trend between N/L ratio and age. Most probably, increased inflammation with aging revealed this result.

The relatively small number of the study population and absence of certain cardiovascular end points should be taken into account as limitations of this study. The cross-sectional design prevents us from interpreting the relationships of N/L ratio as causal in nature. We did not investigate the effect of smoking habitats on the association between serum N/L ratio levels and inflammation. Larger scale prospective design studies are needed to provide more definite conclusions.

In conclusion, this study showed elevated N/L ratio in patients receiving dialysis therapies and also in predialysis CKD patients. Significant associations with well-known markers of inflammation encourage the use of N/L ratio as a measure of inflammation in this population. We assume that wide availability of this ratio could place it in clinical practice after validation of these results in further clinical studies with certain cardiovascular end points.

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