IS THERE A RELATIONSHIP BETWEEN PARATHYROID HORMONE AND NEUTROPHIL LYMPHOCYTE RATIO OR PLATELET LYMPHOCYTE RATIO?

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Abstract

Context. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are recent prognostic markers associated with inflammation in many diseases such as chronic kidney disease (CKD), malignancies, myocardial infarction.

Objective. In this study, we investigated the relationship between NLR-PLR and parathyroid hormone (PTH) and vitamin D in patients with high PTH levels.

Design. The patients with high PTH levels in Nephrology and Endocrinology Outpatient clinics were evaluated retrospectively.

Subjects and methods. The medical records of the patients were examined and clinical data, including demographic details, clinical and laboratory findings, treatment and follow-up data were obtained. NLR and PLR were calculated. Serum creatinine, calcium, phosphorus, magnesium, lipid levels, calcium phosphorus product, PTH and vitamin D values were investigated. The relationship between NLR-PLR and laboratory parameters, GFR (MDRD-GFR), PTH and vitamin D were investigated.

Results. 48 male and 253 female patients were enrolled in this study. The mean age was 57.57 ± 13.28 . NLR correlated negatively with albumin, hemoglobin, vitamin D, calcium and cholesterol and it positively correlated with creatinine and PTH. Multiple regression analysis showed that main determinants of NLR were PTH, albumin, LDL-cholesterol, hemoglobin and gender.

Conclusions. In this study NLR and PLR correlated negatively with hemoglobin and cholesterol. Positive correlation between NLR and creatinine could be explained by increased degrees of inflammation associated with more pronounced degrees of renal dysfunction. The impact of PTH on NLR was independent of GFR. In multiple regression model this suggests that PTH could be a pro-inflammatory parameter independent of the degree of renal dysfunction.

Key words: Hyperparathyroidism, neutrophil lymphocyte ratio, platelet lymphocyte ratio, inflammation, chronic kidney disease.

INTRODUCTION

Parathyroid hormone (PTH) plays an important role in the maintenance of calcium phosphorus balance. It mediates renal tubular calcium reabsorption, calcium release from bone and synthesis of 1-25 dihydroxyvitamin D from 25-hydroxy vitamin D in the kidney. High parathyroid hormone level is associated with increased risk of mortality in chronic kidney disease (CKD), the elderly population and diabetic women (1, 2).

Additionally PTH stimulates the release of IL-6 from osteoblasts and liver. IL-6 increases life span and activation of neutrophils, leads marginal neutrophils into circulation. When IL-6 is administered to healthy adults, it decreases the level of total cholesterol, apolipoprotein-B and triglycerides in 24 hours. The mechanism of this action is not known precisely but it has been shown that IL-6 increases hepatic fatty acid synthesis and lypolysis in adipose tissue and decreases cholesterol secretion despite its increasing effect on cholesterol synthesis (3). There is conflicting data regarding the relationship between PTH and inflammatory markers in literature. Some studies showed increased levels of inflammatory markers in hyperparathyroidism while others reported that CRP, IL-6 and leucocyte levels were similar both in hyperparathyroidism and control group (4, 5).

Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are two parameters that can be easily calculated from the hemogram and can more precisely show the level of inflammation than the total leukocyte count. Recent studies indicated that NLR could be a marker of poor prognosis in CKD, malignancies and myocardial infarction. NLR increases proportionately with the degree of renal disease (6). PLR has been recently shown to be a better marker than NLR indicating mortality and inflammation in end stage renal disease (ESRD) (7). The purpose of the

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present study is to estimate the relation of PTH with NLR and PLR independent of the kidney disease.

MATERIALS AND METHODS

Study patients

The patients admitted to Nephrology and Endocrinology Outpatient clinics with increased PTH levels and symptoms between January 2014 and May 2017 were retrospectively analyzed. Parathyroid radionuclide scans of the patients were also assessed. Patients with acute kidney injury, malignancy, infectious symptoms, chronic hemodialysis patients, pregnant women and hemodynamically unstable conditions were not included in the study.

Laboratory parameters

The medical records of the patients were examined and clinical data, including demographic details, clinical and laboratory findings, treatment and follow-up data were obtained. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number 20.478.486, date 02.08.2017, Manisa Celal Bayar University Medical Ethics Committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The complete blood count (CBC) and leukocyte differential count were obtained from the medical records. NLR and PLR were calculated. Serum creatinine, calcium (Ca), phosphorus (P), magnesium, lipid levels, calcium phosphorus (CaxP) product, PTH and vitamin D values were investigated. Estimated glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease (MDRD) Study equation. Chronic kidney disease was defined as eGFR <60mL/min/1.73m².

Statistics

“SPSS for Windows version 15 Statistics” was used for data input and statistical analysis. The continuous variables were expressed as means $\pm$ SD, categorical variables were percentages. Statistical significant was determined as $p < 0.05$. Parametric continuous variables were compared by the independent Student T test. Categorical variables were analyzed by Mann Whitney U test. Multivariate regression analysis was made by using linear regression model.

RESULTS

Three hundred and one patients (48 males (15.9%) and 253 (84.1%) females) were enrolled in the study. The mean age of the patients was 57.57 ± 13.28 years. Hypertension was detected in 17.6% of the patients while hiperlipidemia and diabetes prevalencies were 35.2% and 14.3% respectively. Plasma creatinine levels were found 0.97 ± 0.94 mg/dL, GFR-MDRD was 85.96 ± 34.96 mL/min. CKD was detected in 21.3% of the patients. Mean PTH level was 305.99 ± 320.20 pg/mL while NLR and PLR were calculated as 2.34 ± 1.20 and 131.25 ± 57.80 respectively. Parathyroid adenoma was detected in 101 patients with the assessment of parathyroid radionuclide scans. NLR and PLR did not disclose any difference between adenoma and non-adenoma cases. Laboratory parameters of the patients were shown in Table 1.

There were 65 CKD patients. The duration of CKD was 51.14 ± 37.89 months. Hypertension, nephrolithiasis and diabetes were the main diseases in

Table 1. Demographic characteristics and laboratory parameters of all patients

	Patients Mean $\pm$ SD (n=301)
Age (Year)	57.57 $\pm$ 13.28
Gender (M, %)	15.9%
Hypertension (%)	17.6%
Hyperlipidemia (%)	35.2 %
Diabetes (%)	14.3%
CKD	21.3%
CAD	4.3%
Complete blood cell (10 ³ / μ L)	7394.05 $\pm$ 2057.27
Neutrophil(10 ³ / μ L)	4522.12 $\pm$ 1572.92
Lymphocyte(10 ³ / μ L)	2143.05 $\pm$ 751.57
Platelet count(10 ³ / μ L)	255159.50 $\pm$ 69235.60
Hemoglobin (g/dL)	12.67 $\pm$ 1.62
NLR	2.34 $\pm$ 1.20
PLR	131.25 $\pm$ 57.80
Creatinine (mg/dL)	0.97 $\pm$ 0.85
Uric acid (mg/dL)	5.31 $\pm$ 1.27
Calcium (mg/dL)	10.40 $\pm$ 1.22
Phosphorus (mg/dL)	3.09 $\pm$ 0.74
Magnesium (mg/dL)	2.14 $\pm$ 0.23
CaxP product	31.71 $\pm$ 6.63
Albumin (g/dL)	4.32 $\pm$ 0.33
Total cholesterol (mg/dL)	203.49 $\pm$ 42.16
LDL cholesterol (mg/dL)	120.23 $\pm$ 34.89
eGFR	85.96 $\pm$ 34.96
Parathormone (pg/mL)	305.99 $\pm$ 320.20
D vitamin	18.40 $\pm$ 10.66
Alkaline phosphatase(IU/L)	105.04 $\pm$ 77.59

(CKD:Chronic kidney disease, CAD: Coronary artery disease, NLR: Neutrophil-lymphocyte ratio, PLR:Platelet- lymphocyte ratio, eGFR: estimated Glomerular filtration rate).

Table 2. Demographic characteristics and laboratory parameters of CKD patient group

	CKD Patients Mean $\pm$ SD or % (n) (N:65)
Age (year)	66.68 $\pm$ 11.79
Gender (M, %)	23.1%
Hypertension (%)	58.5%
Hyperlipidemia (%)	46.2%
Diabetes (%)	21.5%
CAD	12.3%
Etiology	Diabetes 18.5% Hypertension 43.8% Nephrolithiasis 16.9% Post-renal diseases 3.1% Glomerulonephritis 1.5% Unknown 16.2%
Duration of CKD (month)	51.14 $\pm$ 37.89
Complete blood cell ($10^3/\mu\text{L}$)	7372.77 $\pm$ 1955.61
Neutrophil($10^3/\mu\text{L}$)	4717.53 $\pm$ 1634.20
Lymphocyte($10^3/\mu\text{L}$)	1918.92 $\pm$ 677.02
Platelet count($10^3/\mu\text{L}$)	252153.80 $\pm$ 75878.86
Hemoglobin (g/dL)	12.33 $\pm$ 1.87
NLR	2.78 $\pm$ 1.49
PLR	145.73 $\pm$ 65.63
Creatinine (mg/dL)	1.92 $\pm$ 1.18
Uric acid (mg/dL)	6.26 $\pm$ 1.88
Calcium (mg/dL)	10.04 $\pm$ 1.54
Phosphorus (mg/dL)	3.41 $\pm$ 0.92
Magnesium (mg/dL)	2.15 $\pm$ 0.28
CaxP product	33.53 $\pm$ 7.61
Albumin (g/dL)	4.19 $\pm$ 0.42
Total cholesterol (mg/dL)	201.28 $\pm$ 46.22
LDL cholesterol (mg/dL)	117.37 $\pm$ 34.54
eGFR	37.10 $\pm$ 17.14
Parathyroid hormone (pg/mL)	617.46 $\pm$ 501.93
D vitamin	15.45 $\pm$ 10.77
Alkaline phosphatase (IU/L)	128.46 $\pm$ 110.03

(CAD: Coronary artery disease, NLR: Neutrophil-lymphocyte ratio, PLR:Platelet- lymphocyte ratio, eGFR: estimated Glomerular filtration rate).

Table 3. Correlations between NLR- PLR and laboratory parameters

	NLR	PLR
Hemoglobin	r*= -0.212 p<0.001	r= -0.273 p<0.001
Creatinine	r= 0.130 p=0.024	r= 0.045 p=0.440
Calcium	r= -0.146 p=0.011	r= -0.130 p=0.024
Phosphorus	r= 0.054 p=0.347	r= 0.122 p=0.024
CaxP product	r= -0.020 p=0.732	r= 0.061 p=0.291
Albumin	r= -0.184 p=0.001	r= -0.079 p=0.170
Total cholesterol	r= -0.279 p<0.001	r= -0.092 p=0.007
LDL cholesterol	r= -0.266 p<0.001	r= -0.155 p=0.007
eGFR	r= -0.085 p=0.139	r= -0.012 p=0.836
Parathyroid hormone	r= 0.181 p=0.002	r= 0.079 p=0.169
Vitamin D	r= -0.083 p=0.042	r= -0.083 p=0.151
Alkaline phosphatase	r= 0.174 p=0.200	r= 0.041 p=0.418
ALT	r= -0.184 p=0.001	r= -0.127 p=0.028

*Pearson correlation confidence. (CaxP: CalciumxPhosphorus, eGFR: estimated Glomerular filtration rate, ALT: Alanine aminotransferase).

Table 4. Relationship between NLR and gender-comorbid conditions

Group		N	NLR Mean $\pm$ SD	t	df	p*
Gender	Female	253	2.24 $\pm$ 1.03	3.135	299	0.002
	Male	48	2.83 $\pm$ 1.77			
Hypertension	Present	53	3.83 $\pm$ 1.45	-3.357	299	0.001
	Absent	248	2.23 $\pm$ 1.11			
Hyperlipidemia	Present	106	2.11 $\pm$ 1.12	2.435	299	0.015
	Absent	195	2.46 $\pm$ 1.23			
Diabetes	Present	43	2.38 $\pm$ 1.55	-0.208	49.708	0.836
	Absent	258	2.33 $\pm$ 1.13			
Chronic kidney disease	Present	65	2.78 $\pm$ 1.49	-3.387	299	0.001
	Absent	236	2.21 $\pm$ 1.08			
Coronary artery disease	Present	13	Median (quartile 1 and 3) 2.47 (2.17-3.28)	-	-	0.011**
	Absent	288	2.00(1.63-2.69)			

*Student's T test, **Mann Whitney U test

Table 5. Relationship between PLR and gender-comorbid conditions

Grup		N	PLR Mean± SD	t	df	p*
Gender	Female	253	128.61±53.71	1.458	56.499	0.069
	Male	48	145.14±74.98			
Hypertension	Present	53	149.66±63.17	-2.383	70.481	0.020
	Absent	248	127.32±55.95			
Hyperlipidemia	Present	106	123.71±52.37	1.743	242.612	0.083
	Absent	195	135.34±60.28			
Diabetes	Present	43	131.57±94.13	-0.039	299	0.969
	Absent	258	131.20±49.52			
Chronic kidney disease	Present	65	145.73±65.63	-2.298	299	0.022
	Absent	236	127.26±54.94			
Coronary artery disease	Present	17	Median (quartile 1 and 3)			0.184**
	Absent	306	130.00(106.38-197.70)			
			116.34(95.19-145.88)			

*Student'sT test, **Mann Whitney U test

Table 6. Linear regression analysis for NLR *(Dependent variable NLR)

	Beta (std)	p
Albumin	-0.575	0.004
LDL cholesterol	-0.006	0.001
Parathyroid hormone	0.001	0.007
Hemoglobin	-0.118	0.004
Gender	-0.584	0.001

*Independent variables (Parathyroid hormone, Calcium, vitamin D, eGFR, hemoglobin, LDL cholesterol, albumin, ALT, gender, hypertension, coronary artery disease) R2=0.203.

the etiology. 52 patients (80%) had vitamin D deficiency and received replacement therapy. Demographic characteristics and laboratory parameters of CKD patient group are shown in Table 2.

NLR correlated positively with creatinine and PTH and negative correlations were detected for hemoglobin, albumin, vitamin D, total cholesterol and LDL cholesterol. Correlations between NLR- PLR and laboratory parameters were shown in Table 3.

NLR levels were significantly different between male and female patients and found 2.83 ± 1.77 and 2.24 ± 1.03 , respectively ($t=3.135$, $p=0.002$). There was not statistically significant difference between males and females' ages, 56.69 ± 16.14 and 57.74 ± 12.84 years respectively. NLR values of the hypertensive patients were higher in comparison to normotensive patients. Diabetes did not have any impact on NLR. NLR values were higher in patients with coronary artery disease and chronic kidney disease. Relationship between NLR and gender-comorbid conditions was shown in Table 4.

Patients with chronic kidney disease had higher PLR values. While hypertensive patients exhibited higher PLR, gender, coronary artery disease and diabetes did not have any effect on PLR. Relationship between PLR and gender-comorbid conditions was shown in Table 5.

Table 7. Linear regression analysis for PLR *(Dependent variable PLR)

	Beta (std)	p
Hypertension	0.117	0.032
LDL cholesterol	-0.154	0.005
Hemoglobin	0.280	<0.001

*Independent variables (LDL cholesterol, Ca,P, hypertension, chronic renal disease, ALT) R2=0.126.

Parathyroid hormone, albumin, LDL-cholesterol and then hemoglobin and gender were significant in multivariate regression analysis for NLR (Table 6). LDL cholesterol, hypertension and hemoglobin were significant in linear regression analysis for PLR (Table 7).

DISCUSSION

In this study we showed that NLR and PLR negatively correlated with the indicators of inflammation such as albumin, hemoglobin and cholesterol. There was a positive correlation between NLR and creatinine, this could be explained by increased degrees of inflammation associated with renal dysfunction. The effect of PTH on NLR was independent from eGFR in multivariate regression model and this suggests that PTH could be a pro-inflammatory parameter independent from the degree of renal dysfunction.

In this study we showed a significant positive correlation between NLR and creatinine values. In the literature we could not find any study showing such a relation in patients with hyperparathyroidism. When these data are combined, it can be said that NLR and PLR increased as the kidney function decreased in the context of hyperparathyroidism. This can be explained

by inflammation. Actually there were studies reporting the relationship between NLR-PLR and inflammation in hemodialysis and peritoneal dialysis patients (8-9). This relationship was also shown in patients with stage 3 and 4 chronic kidney disease (10). The relationship between PTH and NLR has been detected in a study involving 32 patients with primary parathyroid adenoma (11). This relation confirmed in our study also and could be ascribed to the prominent proinflammatory effects of PTH rather than adenoma formation.

There were studies investigating the relationship between NLR and anemia in the literature. In a study by Cata *et al.*, anemia and increased NLR were associated significantly with high recurrence rates in patients with non-small cell cancer of the lung (12). In hemodialysis patients higher PLR values were related with erythropoietin resistant anemia (13). Also in our study group there was a negative correlation between both NLR and PLR values and anemia.

Our study has shown a negative correlation between NLR-PLR and plasma calcium concentration. Plasma calcium concentration reflects the sum of bonded and unbonded calcium. Plasma calcium concentration is expected to decrease alongside with increasing degrees of inflammation causing decreased albumin levels. Supporting this hypothesis, negative correlation was observed between albumin level and NLR. In the literature a negative correlation has been shown between albumin and NLR in geriatric patients (14). But we could not find any study investigating the relation between albumin and NLR in hyperparathyroidism.

Vitamin D deficiency is frequent in primary hyperparathyroidism and patients with CKD. Capusa *et al.* showed that hypovitaminosis D was very common irrespective of CKD presence and severity (15). In present study we found the frequency of vitamin D deficiency as 80% in patients with CKD and also high ratios in all group. There are many studies investigating the negative relation between vitamin D levels and NLR-PLR. Tabatabaeizadeh *et al.* showed that high levels of sensitive C-reactive protein (Hs-CRP) and NLR were decreased significantly after vitamin D replacement therapy in 580 adolescent girls (16). A similar relation has been observed between vitamin D deficiency and inflammatory indicators such as Hs-CRP and NLR in hemodialysis and peritoneal dialysis patients (8). A general population study involving 4120 cases also confirmed the strong negative relationship between vitamin D levels and NLR-PLR (17). In our study NLR was negatively related with vitamin D values. All these results suggested that vitamin D

deficiency is a inflammatory condition.

We detected a negative correlation between NLR and total cholesterol-LDL cholesterol. Although such a relation has been observed in patients with chronic renal disease and especially in dialysis patients (18) and has been termed as reverse epidemiology, we could not find any study investigating such a relationship in the context of hyperparathyroidism independent from renal dysfunction. This relationship could be explained by inflammation and/or malnutrition. Another hypothesis is the suppressive effect of PTH on cholesterol secretion although it has increasing effects on fatty acid synthesis and lypolysis in adipose tissue by increasing IL-6 levels (3).

In our study we found NLR significantly higher in males than in females. In recent studies NLR-PLR have been found to be higher in males in healthy controls (19), morbid obese patients (20) and cancer patients (21).

Similar to our study, hypertensive patients exhibited increased levels of NLR-PLR in different studies. Cimen *et al.* found a significant relation between NLR and 24 hour ambulatory blood pressure monitoring (ABPM) values in 300 newly diagnosed essential hypertensive patients (22).

The main limitation of this study is the absence of C reactive protein and/or fibrinogen levels as inflammation markers. Due to the retrospective design, there is no data regarding proteinuria and/or repetition of GFR of patients.

As a result it can be concluded that in multivariate regression analyses, PTH has been a more powerful indicator for NLR in comparison to kidney disease. This fact tempts us to think that PTH is related to inflammation independently from renal disease and NLR can be regarded as an indicator of inflammation in patients with hyperparathyroidism. We plan to perform other studies involving the inflammation markers to support the results of this research.

Conflict of interest

The authors have declared that they have no conflict of interest.

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