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The association between platelet to lymphocyte ratio and neutrophil to lymphocyte ratio with inflammatory factors in hemodialysis patients

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ABSTRACT

Introduction: Chronic inflammation is a major factor in the pathogenesis of atherosclerosis in hemodialysis patients compared to healthy individuals. Chronic inflammation is part of the malnutrition, atherosclerosis, and inflammation syndrome in advanced renal failure.
Objectives: In this study, the relationships of platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) with the inflammatory factors were investigated.
Patients and Methods: This cross-sectional study was conducted on 108 hemodialysis patients who were on dialysis for more than three months. For patients, serum levels of urea, creatinine (Cr), sodium, potassium, calcium, phosphate, parathyroid hormone, total cholesterol, triglyceride, ferritin, 25-hydroxy vitamin D, albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and complete blood cell count were assessed before dialysis since serum urea was examined again after dialysis too.
Results: The mean age of the patients (58 male and 50 female) was 63.43 ± 14.65 years. The median values for NLR and PLR were 2.25 and 114.7, respectively. ESR was significantly higher in hemodialysis patients with NLR >2.25 (46.7 ± 29.7 versus 36 ± 22.7) and in those with PLR >114.7 (47.09 ± 27.8 versus 35.6 ± 24.8). Plasma hemoglobin and serum 25-hydroxy vitamin D levels were observed to be lower (10.37 ± 1.6 versus 11.7 ± 1.8 and 33.1 ± 2.5 versus 37.9±15.2) in patients with PLR >114.7. Bivariate correlation showed that PLR and NLR had positive significant correlation with ESR while PLR had a significant negative correlation with values of blood 25-hydroxy vitamin D hemoglobin and Cr.
Conclusion: Due to availability and affordability of PLR and NLR, they could be used for early assessment of inflammation in end-stage renal disease (ESRD) patients. PLR may be better predictor than NLR (to detect inflammation.

Original

Implication for health policy/practice/research/medical education:
In this cross-sectional study, we investigated the relationship of platelet to lymphocyte ratio (PLR) with neutrophil to lymphocyte ratio (NLR) and inflammatory factors. Our study showed erythrocyte sedimentation rate (ESR) was significantly higher in hemodialysis patients with NLR>2.25 and in those with PLR>114.7. Additionally, hemoglobin and 25(OH) vitamin D levels were observed to be lower in patients with PLR>114.7. In bivariate correlation, PLR had also significant negative correlation with 25(OH) vitamin D levels.

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Introduction

Mortality in end-stage renal disease (ESRD) patients is higher than non-kidney disease population (1). Recently, some studies have suggested new risk factors such as chronic inflammation, hyper hemocysteinemia and oxidative stress, which are more common in dialysis patients than the non-kidney disease population. Chronic inflammation in ESRD patients is caused by malnutrition, chronic inflammation and atherosclerosis (MIA syndrome). The MIA syndrome plays an important role in advanced atherosclerosis and consequent cardiovascular events in hemodialysis patients (1).

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Complete blood cell count is a simple, affordable and available test that is routinely performed to assess anemia in hemodialysis patients. In recent years, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) have been proposed as novel inflammatory factors in various diseases such as systemic inflammatory disease, infections, cancers, autoimmune diseases and peripheral vascular disease (2).

Objectives

The purpose of present study was to investigate the relationship between PLR with inflammation and compare that with NLR in hemodialysis patients.

Patients and Methods

Study design

This study was conducted on hemodialysis patients over 18 years of age who underwent dialysis due to ESRD in Tehran Ziaeian hospital for more than three months (2019). Patients with fever, recent infection, active malignancy and connective tissue disorder were excluded from this study. Laboratory tests, including urea, creatinine (Cr), sodium (Na), potassium (K), calcium (Ca), phosphate (Ph), intact parathyroid hormone (iPTH), complete blood cell count (CBC), total cholesterol (TC), triglyceride (TG), ferritin, albumin (Alb), 25-OH vitamin D, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were measured before dialysis since serum urea was assessed again after dialysis. NLR and PLR were calculated too.

Statistical analysis

Statistical investigation was carried out using the SPSS (Statistical Package for Social Sciences). Data were examined using the Student's *t* test. Linear associations between continuous variables were evaluated using the Spearman's correlation test. The sample correlation coefficient between two variables *x* and *y* is denoted *r* or *rxy*, and can be computed as:

$$r_{xy} = \frac{\mathrm{cov}(x, y)}{\sqrt{\mathrm{var}(x)} \cdot \sqrt{\mathrm{var}(y)}}$$

Cov(x, y) is the covariance of x and y; var(x) is the variance of variable x; and var(y) is the variance of variable y. Negative and positive one, indicated perfectly negative and positive linear relationship, respectively. Coefficient between 0.1-0.3 show small correlation, between 0.3-0.5 indicate medium correlation and more than 0.5 imply strong correlation (3).

Results

Demographic and laboratory findings of the study population are reported in Table 1. More than half of

Table 1. Demographic and laboratory findings of the study population

Parameters	Categories	Mean ± SD	No. (%)
Age (years)	-	63.43±14.65	-
Female/male	-	-	50(46%)/58(54%)
Etiology of ESRD	Diabetic	-	75 (69.4 %)
	Non-diabetic		33 (30.6%)
Access	Fistula	-	47 (43.5%)
	Permanent catheter		61 (56.5%)
Hemoglobin (g/dL)	-	10.86 ±1.7	-
Albumin (g/dL)	-	3.75±0.4	-
Total cholesterol (mg/dL)	-	138 ±39.9	-
Triglyceride (mg/dL)	-	148.7 ±86.04	-
FBS (mg/dL)	-	140.5 ±93.6	-
Cr (mg/dL)	-	6.82 ±2.3	-
Ca (mg/dL)	-	8.15 ±0.99	-
Ph (mg/dL)	-	4.99 ±1.07	-
iPTH (pg/ml)	-	544.5 ±435	-
25(OH) VitD (ng/dL)	-	35.56 ±14.1	-
Alk-P(U/L)	-	355 ±205.6	-
CRP(mg/L)	-	20 ±18	-
Ferritin (ng/dL)	-	500 ±282.6	-
HBS Ab (IU/ml)	-	96 ±28.6	-
ESR (mm/h)	-	41.35 ±26.8	-
NLR	NLR>2.25	3.38±1.04	54 (50%)
	NLR<2.25	1.67±0.42	54 (50%)
PLR	PLR>114.7	172.4±8.06	54 (50%)
	PLR<114.7	81.24±22.7	54 (50%)
UF(L)- Ultrafiltration		2.01 ±0.8	
URR		71.7 ±11.5	
Kt/v		1.61±0.56	

the patients were male and the mean age of patients was 63.43 ± 14.65 years. ESRD patients were classified as diabetic and non-diabetic groups which the most common underlying disease was diabetic. Arteriovenous fistula and permanent catheter were used in 47 and 61 patients, respectively.

In most studies median NLR and PLR were used as a cut off (4,5). We also used median based on the previous studies (4,5). We categorized NLR into two groups according to the median value (Tables 2 and 3). The median values for NLR and PLR were 2.25 and 114.7, respectively. ESR was significantly higher in hemodialysis patients with NLR >2.25 (46.7 ± 29.7 versus 36 ± 22.7) and in those with PLR >114.7 (47.09 ± 27.8 versus 35.6 ± 24.8). Plasma hemoglobin and serum 25-hydroxy vitamin D levels were observed to be lower (10.37 ± 1.6 versus 11.7 ± 1.8 and 33.1 ± 2.5 versus 37.9 ± 15.2) in patients with PLR>114.7.

Plasma hemoglobin for higher and lower than median values of PLR was 10.37 (g/dL) and 11.7(g/dL), respectively which was significant in 95 percent ($P = 0.004$). Vitamin D levels in patients with PLR higher than 114.7(33.1 ± 2.5) were significantly lower than those with PLR lower than (37.9 ± 15.2; $P = 0.07$). Another significant variable was ESR, since in patients with PLR> 114.7 was significantly higher than PLR<114.7 ($P = 0.02$).

Table 4 shows the results of the bivariate correlation between NLR and PLR and other parameters. PLR had negative correlation with plasma hemoglobin, serum Cr and 25-hydroxy vitamin D, while it had positive correlation with ESR. NLR had positive correlation with ESR.

Discussion

Chronic systemic inflammation is observed in 30-50 patients undergoing hemodialysis (6). This inflammation may be due to dialysis-related or non-dialysis related factors (6). Dialysis related factors are membrane bio-incompatibility and back filtration of endotoxin from the dialysate and non-dialysis related factors include non-access related infections, comorbidities (6), pro-inflammatory cytokine, acidosis and oxidative stress (7).

In recent decade, serum CRP, pro-calcitonin, and ferritin are widely used as inflammatory factors in hemodialysis patients, although these traditional biomarkers in dialysis patients have their limitations. Other markers include interleukin 6 and TNF-α (8).

Numerous studies have examined the relationship between PLR and NLR and clinical implications in cardiovascular disease and some malignancies (9-12).

One study compared NLR and PLR in 62 patients with ESRD who were hemodialysis or peritoneal dialysis for more than six months. In this study, patients with PLR more than 140 had higher levels of IL-6, and TNF alpha. They concluded that PLR is a better predictor for inflammation in ESRD patients than NLR (13). In another study, among 611 non-hemodialysis chronic kidney disease (CKD) patients, a positive correlation between NLR and PLR with high-sensitivity C-reactive protein (hs-CRP) was observed (8). The current study investigated the association between NLR and PLR with various inflammatory factors in ESRD patients. ESR in patients with NLR >2.25 and PLR> 114.7 were significantly higher than those with NLR <2.25 and PLR<114.7 respectively.

Table 2. Biochemical data of the study population according to neutrophil-to-lymphocyte ratio

Parameters	NLR<2.25	NLR>2.25	*P* value
Hemoglobin (g/dL)	6.97 ± 2.2	6.66 ± 2.4	0.28
Albumin (g/dL)	3.82 ± 0.4	3.67 ± 0.4	0.56
Total cholesterol (mg/dL)	139 ± 43.9	136.9 ± 35.9	0.73
Triglyceride (mg/dL)	155 ± 88	142 ± 84	0.43
Cr (mg/dL)	6.97 ± 2.19	6.66 ± 2.39	0.48
Ca (mg/dL)	8.22 ± 1.1	8.08 ± 0.93	0.45
Ph (mg/dL)	4.97 ± 1.07	5 ± 1.07	0.91
iPTH (pg/mL)	564 ± 496	525 ± 366	0.64
25(OH)VitD (ng/dL)	37.7 ± 16.03	33.4 ± 11.66	0.11
Alk-P (U/L)	245 ± 33.3	157 ± 21.5	0.95
CRP (mg/L)	17.4 ± 17	21 ± 18	0.32
Ferritin (ng/dL)	515 ± 300	486 ± 266	0.59
HBS Ab (IU/ml)	35 ± 32	26 ± 24	0.1
ESR (mm/hr)	36 ± 22.7	46. 7 ± 29.7	0.03**
UF (L)	2.04 ± 0.85	1.98 ± 0.74	0.6
Urea reduction ratio	72.5 ± 10.8	70.9 ± 12.2	0.5
Kt/v	1.67 ± 0.64	1.55 ± 0.47	0.3

** Significant in 95%.

Table 3. Biochemical data of the study population according to platelet-to-lymphocyte ratio

Parameters	PLR<114.7	PLR>114.7	*P* value
Hemoglobin (g/dL)	11.7 ± 1.8	10.37 ± 1.6	0.004**
Albumin (g/dL)	3.8 ± 0.4	3.6 ± 0.36	0.41
Total cholesterol (mg/dL)	138.2 ± 41	138.2 ± 39	0.99
Triglyceride (mg/dL)	159.5 ± 86	138 ± 85	0.19
Cr (mg/dL)	7.3 ± 2.3	6.3 ± 2.1	0.23
Ca (mg/dL)	8.16 ± 1.1	8.14 ± 0.93	0.89
Ph (mg/dL)	4.97 ± 1.08	5 ± 1.07	0.88
iPTH (pg/mL)	530 ± 482	558 ± 384	0.7
25(OH)VitD (ng/dL)	37.9 ± 15.2	33.1 ± 2.5	0.07*
Alk-P (U/L)	342 ± 245	367 ± 158	0.5
CRP (mg/L)	17 ± 17.66	21 ± 18	0.2
Ferritin (ng/dL)	491 ± 287	509 ± 280	0.7
HBS Ab (IU/ml)	33 ± 30.5	28 ± 26.7	0.3
ESR (mm/h)	35.6 ± 24.8	47.09 ± 27.8	0.02**
UF (L)	2.01 ± 0.8	2 ± 0.7	0.9
Urea reduction ratio	73 ± 10	703 ± 12	0.2
Kt/v	1.68 ±0.6	1.53 ±0.23	0.18

* Significant in 90%; ** Significant in 95%.

Table 4. Bivariate correlation between PLR and NLRwith other parameters

Parameters	PLR		NLR	
	r	*P* value	r	*P* value
Cr	-0.28	0.003***	-0.47	0.6
25-hydroxy vitamin D (ng/dL)	-0.23	0.021*	-0.17	0.07
Hemoglobin (g/dL)	-0.318	0.001***	-0.101	0.2
PLT (10^3/uL)	0.47	0.000***	0.09	0.3
ESR (mm/h)	0.3	0.001**	0.22	0.02*

* Significant in 90%; ** Significant in 95%;*** Significant in 99%;

Although several studies have suggested a relationship between vitamin D levels and inflammation (14), some reports have not shown this relationship (14-16). One study reported a significant negative correlation between PLR and NLR and vitamin D (17). In our study, mean vitamin D levels were lower in patients with higher than median PLR (>114.7). We found a negative correlation between PLR and vitamin D, while no association was found between NLR and vitamin D.

One multicenter international study showed a positive correlation between CRP levels and mortality in hemodialysis patients (17). In the current study, the mean CRP levels were higher than normal. However no significant differences between the groups with NLR higher and lower than median (NLR >2.25, NLR <2.25) and PLR lower and higher than median (PLR <114.7, PLR >114.7) was detected. Additionally, CRP level was not related to NLR and PLR in bivariate correlation too.

Inflammation in CKD patients is one of the main predisposing factors for erythropoietin resistance and anemia (18). Moreover, evidence suggests that PLR is associated with erythropoietin resistance (19, 20) and is considered as a marker for predicting anemia in hemodialysis patients (21). In the present study, patients with PLR above 114.7 had lower hemoglobin levels. Moreover, in bivariate correlation, a negative correlation between PLR and plasma hemoglobin was found.

Conclusion

We observed higher ESR levels in ESRD patients with NLR and PLR greater than median. PLR and NLR showed positive significant correlation with ESR. PLR also had a significant negative correlation with vitamin D and hemoglobin. Due to availability and affordability of PLR and NLR, they could be used for early assessment of inflammation in ESRD patients consequently, therapeutic interventions could reduce mortality rate in these patients.

Limitations of the study

Our study was single-center on a limited number of patients. Larger studies on this subject are suggested.

Authors' contribution

MG, MK and MR were the principal investigators of the study. MG, MK and MR were included in preparing the concept and design. MG, MK and MR revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

None declared.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Tehran University of Medical Sciences approved all study protocols (IR.TUMS.VCR.REC.1397. 942). Accordingly, written informed consent was taken from all participants before any intervention. Ethical issues (including plagiarism, data fabrication and double publication) were also completely observed by the authors.

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