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Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH

NEPHROLOGY // INTERNAL MEDICINE // IMMUNOLOGY

Assessment of C-Reactive Protein, Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Patients at Different Stages of Chronic Kidney Disease

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ARTICLE HISTORY

Received: September 1, 2022
Accepted: December 19, 2022

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ABSTRACT

Background: Low-grade chronic inflammation is an important feature of chronic kidney disease (CKD). **Aim:** To determine the values of C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with different stages of CKD and to examine how they change depending on the progression of renal damage. **Materials and methods:** A cross-sectional descriptive comparative study included 157 subjects at different stages of CKD which was assessed based on glomerular filtration rate (GFR) calculated according to the MDRD equation. CRP was analyzed by an immunoturbidimetric method. NLR and PLR were calculated by a mathematical calculation after a blood count was performed. **Results:** The present study showed an increase in serum creatinine, CRP, and NLR values with progression of renal failure. There was a statistically significant difference in the creatinine and CRP concentrations between groups with different stages of CKD ($p < 0.001$ for all comparisons). A significant positive correlation was found between NLR and CRP, while negative, significant correlations were observed between NLR and eGFR as well as between PLR and eGFR. There was a slight increase in PLR value with the progression of renal impairment, but the correlation between PLR and CRP was not significant. **Conclusion:** These results suggest that NLR, together with CRP, may serve as an indicator of systemic low-grade inflammation progression in patients with CKD. Larger prospective studies are required to observe the possibility of using NLR as a surrogate marker for CRP in patients with CKD.

Keywords: C-reactive protein, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, chronic kidney disease

INTRODUCTION

Chronic inflammation has a key role in the development of chronic kidney disease (CKD), which was recognized back in 1990. Previous literature findings show that persistent low-grade inflammation is a major feature of CKD, and that the disease itself is insidious by nature, as it is rarely recognized at an early stage, and once it occurs, it develops progressively and irreversibly.[1–4] Different factors contribute to the inflammatory status in CKD: increased production of inflammatory cytokines and their decreased elimination from the body, oxidative stress, acidosis, chronic and recurrent infections, altered metabolism of adipose tissue, intestinal dysbiosis, and others.[1] It is considered to contribute to cardiovascular (CV) and other causes of mortality in this group of patients, as well as to the development of protein-energy imbalance.[3,5] Low-grade chronic inflammation in CKD is characterized by a 2-3 fold increase in acute phase proteins and inflammatory mediators. Recent research emphasizes the importance of monitoring biomarkers of inflammation in CKD.[1,3]

C-reactive protein (CRP) is a well-known inflammatory biomarker. Published papers report increased levels of CRP in patients with CKD compared with healthy controls.[6–8] New hematological inflammatory markers have emerged in the past few years, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), which increase during chronic inflammation.[9–14] Their predictive and prognostic role has been proven in malignancy, hypertension, heart disease, vascular disease, but also CKD.[15] These biomarkers are gaining importance due to their relatively low price and availability, and they can be obtained by doing a routine blood count with a differential blood count. Research confirms that increased NLR and PLR are independent predictors of hypertension and CV death, but also of all other causes of death in the general population.[15] Neutrophilic granulocytes increase in number in inflammation, while the number of lymphocytes decreases. Both markers have been positively correlated with the degree of proteinuria in CKD.[16]

The aim of this study was to determine the values of CRP, NLR, and PLR in patients with different stages of CKD and to determine how their levels change depending on the progression of renal damage.

MATERIALS AND METHODS

Study population

We conducted a cross-sectional descriptive comparative study, in which we included 157 CKD patients treated through the Nephrology Counseling Center and the Clinic of Nephrology of the Clinical Center of the University of Sarajevo. The average age of the study participants was 56.5 ± 16.3 years, 70 (44.8%) were women and 87 (55.41%) were men. The diagnosis of CKD was defined according to the K/DIGO guidelines from 2012. Glomerular filtration rate (GFR) was calculated according to the MDRD (Modification of Diet in Renal Disease) formula: GFR (mL/min/1.73 m^2) = 175 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 1.212 for African-Americans. The subjects were divided into five groups according to the stage of CKD, which was assessed on the basis of estimated GFR (eGFR) as follows: n = 14 (8.9%) had normal renal function (stage 1), n = 27 (17.2%) had slightly reduced renal function (stage 2), n = 37 (23.6%) had moderately reduced renal function (stage 3), n = 29 (18.5%) had severely reduced renal function (stage 4), while n = 50 (31.8%) had markedly reduced renal function (stage 5).

The study was conducted in accordance with the basic principles of the Helsinki Declaration on the rights of patients included in biomedical research and was approved by the Ethics Committee of the Clinical Center of the University of Sarajevo. The study did not include subjects with malignant diseases, acute inflammatory diseases (respiratory, gastrointestinal, and urinary tract) and systemic diseases (systemic lupus erythematosus, rheumatoid arthritis).

Test samples were taken with a standard blood sampling method for biochemical and hematological analysis and processing. Patient samples were collected in Vacutainer serum separator tubes (Becton Dickinson, Rutherford, NJ, USA) in a volume of 3.5 mL. Serum samples were obtained by centrifugation at 4,000 rpm using a SIGMA 3-16P centrifuge (SIGMA Laborzentrifugen GmbH, Osterode am Harz, Germany).

C-reactive protein was determined from a serum sample by immunoturbidimetric method, which was amplified by particles on a Cobas 6000 Roche/Hitachi analyzer. Creatinine was determined by a kinetic colorimetric test based on the Jaffé method on a Cobas 6000 Roche/Hitachi analyzer. The sample for differential blood count was venous blood collected in a vacutainer tube containing EDTA as anticoagulant and was done within two hours of venipuncture on a Cell Dyn Sapphire hematology analyzer (Abbott, USA).

NLR was calculated as the quotient of the absolute number of neutrophilic granulocytes and lymphocytes, obtained as part of the differential blood count. PLR was calculated as the quotient of the absolute number of platelets and lymphocytes, obtained as part of the differential blood count.

Statistical analysis

The data were analyzed using SPSS software for statistical analysis (SPSS-Statistical Package for Social Sciences) version 13.0 (Chicago, IL, USA). The results were expressed as mean ± standard deviation (SD) for normally distributed data or median with interquartile range for skewed variables. Differences between groups were tested by ANOVA test followed by post-hoc analysis through the Scheffe test or by the Kruskal-Wallis test followed by the Mann-Whitney test depending on the normality of the data distribution (normality assessment through the Shapiro-Wilk normality test). Spearman's Rho test was used for correlation analysis. A p value <0.05 was considered statistically significant.

RESULTS

Our results did not show statistically significant differences between groups with different stages of CKD in terms of gender (p = 0.798) and age (p = 0.063). We found an increase in serum creatinine and CRP concentrations with progression of renal failure. There was a statistically significant difference in the values of serum concentration of creatinine and CRP between groups with different stages of CKD (p <0.001 for all comparisons) (Table 1).

NLR in patients with markedly reduced renal function (stage 5) (4.8 [3.0–5.9]) was significantly higher (p <0.001) than in patients with: normal renal function (stage 1) (2.13 [1.55–3.07], p <0.001); slightly reduced renal function (stage 2) (2.34 [2.02–3.59, p <0.001); moderately reduced renal function (stage 3) (2.54 [1.77–3.17], p <0.001); and severely reduced renal function (stage 4) (3.3 [2.5–5.0], p = 0.002). A significant difference in NLR was also found between patients with severely reduced renal function and patients with: normal renal function (p <0.001), slightly reduced renal function (p <0.001), and moderately reduced renal function (p <0.001). A significant difference in NLR was also found when patients with moderately reduced renal function were compared with patients with normal renal function (p = 0.007) and when patients with slightly reduced renal function were compared with patients with normal renal function (p = 0.023) (Figure 1.)

PLR in patients with markedly reduced renal function (134.2 [110.5–193.6]) was significantly higher (p <0.001) than in patients with: normal renal function (stage 1) (104.2 [77.3–132.2], p <0.001); slightly reduced renal function (stage 2) (120.9 [86.8–167.2], p <0.001); moderately reduced renal function (stage 3) (114.9 [96.1–156.6], p <0.001). A significant difference in PLR was also found between patients with severely reduced renal function (133.1 [112.6–191.1]) and patients with: normal renal function (p <0.001), slightly reduced renal function (p = 0.011), and moderately reduced renal function (p <0.001).

A significant difference in PLR was also found when patients with moderately reduced renal function were compared with patients with normal renal function (p <0.001) and when patients with slightly reduced renal function were compared with patients with normal renal function (p = 0.028) (Figure 2.)

There was a statistically significant positive correlation between NLR and serum CRP concentration (Rho = 0.344; p <0.001) and a statistically significant negative correlation between NLR and eGFR (Rho = –0.328; p <0.001).

A positive, although not significant, correlation was observed between PLR and CRP concentration (Rho = 0.251; p = 0.067), while a negative, significant correlation was observed between PLR and eGFR (Rho = –0.243; p = 0.002) (Table 2).

DISCUSSION

Values of inflammatory markers are elevated in patients with CKD compared with those with normal renal func-

TABLE 1. Basic characteristics of patients at different stages of chronic kidney disease

Variables	Normal renal function (n = 14)	Slightly reduced renal function (n = 27)	Moderately reduced renal function (n = 37)	Severely reduced renal function (n = 29)	Markedly reduced renal function (n = 50)
Age (years)	50.4 ± 16.7	55.3 ± 16.0	53.3 ± 16.0	60.9 ± 15.8	62.6 ± 17.3
Male gender n (%)	9 (64.3%)	14 (51.9%)	23 (62.2%)	15 (51.7%)	26 (52.0%)
Creatinine (μmol /L)	63.0 (56.3–78.0)	80.0$^{\#}$ (72.0–95.0)	144.0$^{\#+}$ (116.5–162.5)	250.0$^{\#+*}$ (218.5–310.0)	502.0$^{\#+*\&}$ (423.0–697.3)
CRP (mg/L)	2.3 (1.9–3.0)	5.8$^{\#}$ (4.8–6.5)	9.4$^{\#+}$ (8.5–10.1)	12.6$^{\#+*}$ (11.2–13.4)	17.2$^{\#+*\&}$ (15.8–18.9)

Data are presented as mean ± standard deviation (SD) or as numerical and percentage values (%) or as median and interquartile ranges; n - number of subjects; CRP - C reactive protein; p - probability

\# p <0.001 – compared to the normal renal function
\+ p <0.001 – compared to the slightly reduced renal function
* p <0.01 – compared to the moderately reduced renal function
& p <0.05 – compared to the severely reduced renal function

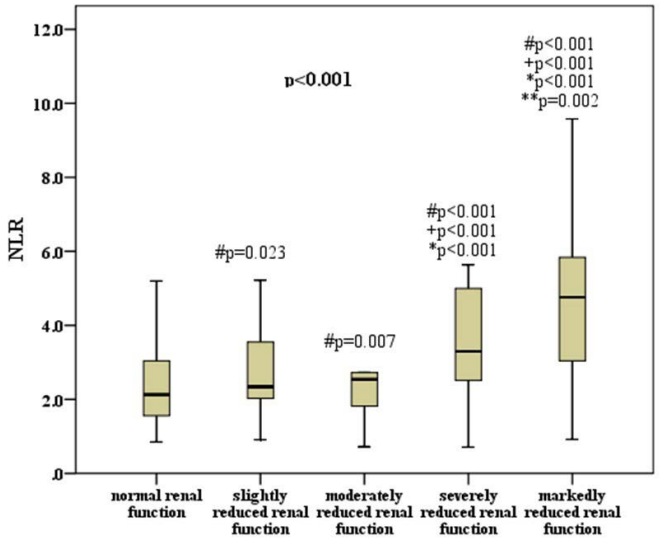

FIGURE 1. The difference in the neutrophil-to-lymphocyte ratio (NLR) values between the patients at different stages of chronic kidney disease

Data are presented as median and interquartile ranges; p - probability

#p – compared to the normal renal function
+p – compared to the slightly reduced renal function
*p – compared to the moderately reduced renal function
**p – compared to the severely reduced renal function

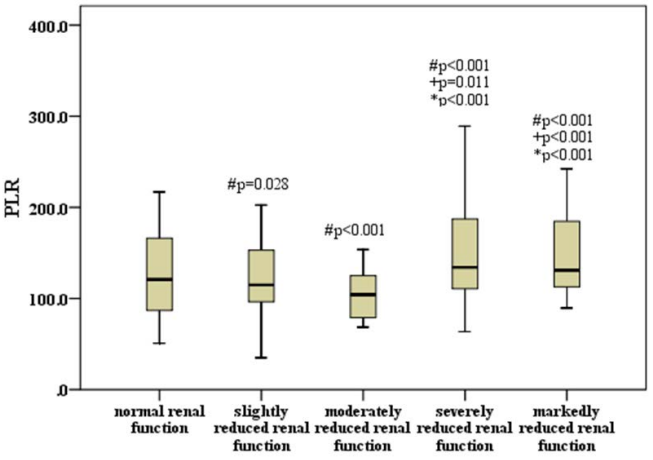

FIGURE 2. The difference in the platelet-to-lymphocyte ratio (PLR) values between the patients at different stages of chronic kidney disease

Data are presented as median and interquartile ranges; p - probability

#p – compared to the normal renal function
+p – compared to the slightly reduced renal function
*p – compared to the moderately reduced renal function

tion and higher levels of these markers are associated with worsening of renal function.[17–20] Uremia of varying degrees affects the general condition of patients with CKD, especially those in the final stages.[21,22] Inflammatory cytokines are produced and released under the influence of uremia, which causes chronic inflammation throughout the body.[21] It is known that inflammation begins in the early stages of CKD.[7,8] Our study showed an increase in CRP values with the progression of renal impairment and found a statistically significant difference in the values of serum concentration of CRP between all groups of subjects with different stages of CKD. Liu *et al.* have investigated the inflammatory status in subjects with CKD, dividing them into three groups: CKD 1-2, CKD 3-4, and CKD-5. They found a statistically significant difference in CRP values between groups, as well as an increase in CRP values with progression of renal impairment.[23] Our results are consistent with the results of Tbahriti *et al.*, who found higher CRP values in subjects who had moderately reduced, severely reduced, and markedly reduced renal function compared with those who had normal and slightly reduced renal function.[24] A previous study compared the CRP values of healthy subjects with the CRP values of subjects in end-stage renal failure (without renal replacement therapy, who were on peritoneal dialysis and hemodialysis) and found higher CRP levels in subjects with end-stage renal failure and increasing CRP values with the progression of renal impairment.[25] In their study, Adejumo *et al.* found higher values of CRP in a group of subjects with impaired renal function compared with the healthy population.[26] Lalramenga *et al.* also showed that inflammation measured by CRP levels increases with declining renal function in patients with CKD.[27] Numerous studies have shown that an increase in CRP levels is associated with the progression of CKD.[28,29] Sharain *et al.* investigated the progressive increase of inflammatory biomarkers in CKD stage 2–4 and final stage and confirmed a statistically significant increase

TABLE 2. Correlation between NLR and PLR with CRP and eGFR in patients with chronic kidney disease

Variables	CRP (mg/L)		eGFR (mL/min/1.73m^2)	
	Rho	p	Rho	p
NLR	0.344	< 0.001	- 0.328	< 0.001
PLR	0.251	0.067	- 0.243	0.002

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; p, probability; Rho, Spearman's correlation coefficient

in CRP among CKD subjects in stage 2–4 and final stage, as well as higher CRP values compared to healthy subjects.[30]

Contrary to these studies, a group of Indonesian authors did not find a statistically significant difference in hsCRP values between groups of subjects with moderately impaired, severely impaired, and markedly impaired renal function. This was explained with the small sample of 72 subjects.[31] The latest research by a group of Chinese authors showed that long-term exposure to high CRP values was associated with an increased risk of developing CKD.[32]

NLR is a cheap, routinely used, and repeatable test, and many studies have found that it can be an indicator of systemic inflammation.[15] This biomarker indicates an imbalance between effector cells (neutrophils) that reflect oxidative stress and regulatory cells (lymphocytes) that reduce the pro-inflammatory state.[33,34] NLR, as a new biomarker of inflammation, reflects both the adaptive immune response (lymphocyte-mediated) and the innate immune response (neutrophil-mediated).[35–37] A high neutrophil count primarily reflects infection, while a low lymphocyte count indicates poor general health and physiological stress.[38] With respect to NLR, our study showed that NLR was significantlly higher in patients with markedly reduced renal function (stage 5) than in patients with normal renal function (stage 1), slightly reduced (stage 2), moderately reduced (stage 3), and severely reduced renal function (stage 4), respectively. A significant difference in NLR was also observed between patients with severely reduced renal function and patients with other stages of CKD, as well as with patients presenting with normal renal function.

In their study, Yilmaz *et al*. found a statistically significant difference in NLR values in subjects who had moderately reduced and severely reduced eGFR compared with healthy volunteers.[7] Another group of authors from Turkey also reported that NLR was significantly higher in patients in the final stage of CKD (without renal replacement therapy, who are on peritoneal dialysis and hemodialysis).[39] NLR was also significantly associated with a rapid decline in the eGFR, defined as a decline of >5 mL/min/1.73 m^2/year in subjects with severely reduced renal function, who had a higher initial NLR.[40]

Liu *et al*. studied NLR values in patients with autosomal dominant polycystic kidney disease who had normal renal function, in patients with mildly, moderately, and severely reduced renal function, and in healthy volunteers. They reported no statistically significant difference in NLR values between subjects who had normal renal function (stage 1) and a control group of healthy volunteers. Simultaneously, they showed that the value of NLR increased statistically significantly with the progression of chronic renal failure (stages 2, 3, and 4).[41] In inflammation, the number of neutrophils increases and the number of lymphocytes decreases, and studies suggest that NLR could be used as a simple marker of inflammation. Some studies have shown that higher initial NLR levels correlate with lower eGFR values, and higher NLR levels are associated with a decrease in eGFR.[37,42]

PLR is also a cheap and readily available laboratory test that reflects an increased systemic inflammatory status.[43] Numerous studies testify to the close connection between PLR and inflammation.[44–46] Prolonged inflammation leads to an increased proliferation of a series of megakaryocytes, which in turn causes an increase in platelet count.[44,47] The bone marrow increases the number of neutrophils and decreases the number of lymphocytes during chronic stress.[48] In addition, in cases of chronic continuous inflammation, there is an increase in the number of neutrophils and a decrease in the number of lymphocytes (due to the simultaneous redistribution of lymphocytes to lymphocyte organs and due to lymphocyte apoptosis).[49] With regards to PLR, our study showed a slight increase in value with the progression of renal impairment, but there was no significant correlation with serum CRP levels. Similar results were obtained by the study of Sevencan *et al*., who in a group of hypertensive patients with normal, slightly reduced and moderately reduced renal function were not able to demonstrate that PLR affects the progression of the disease.[15] Tatar *et al*. did not find a statistically significant association between PLR and eGFR in patients with CKD (stages 3–5).[49] All this suggests that an increase in PLR is not directly correlated with the progression of renal dysfunction. Subjects in the final stage of CKD, who were on hemodialysis and peritoneal dialysis, were found to have higher PLR values than NLR and also had a positive correlation with other inflammatory biomarkers.[50]

The present study has a few limitations. Firstly, its cross-sectional design prevented us from deducing any causal relations between our findings. Secondly, the sample size was relatively small, consisting of patients with CKD from one center and, therefore, the results cannot be representative for the entire population of patients with CKD.

CONCLUSIONS

The present study showed an increase in CRP and NLR values with the advancement of CKD. A significant positive relationship between CRP values and NLR was established in our study. In light of these results, it can be concluded that NLR, together with CRP, may serve as an

indicator of systemic low-grade inflammation and progression in patients with CKD. Larger prospective cohort studies in various ethnic groups are required to assess the possibility of using NLR as a surrogate marker for CRP in patients with CKD.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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