ORIGINAL ARTICLE

UDC: 616.61-008.6
DOI: https://doi.org/10.2298/VSP240103043P

The significance of determining biomarkers of inflammation in chronic kidney failure

Značaj određivanja biomarkera zapaljenja u hroničnoj bubrežnoj slabosti

[1]Milica Petrović*, [1]Violeta Rabrenović*†, Nemanja Rančić†‡

Military Medical Academy, *Clinic for Nephrology, ‡Center for Clinical Pharmacology, Belgrade, Serbia; †University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia

[1]equal contribution of both authors who share the first authorship

Abstract

Background/Aim. Inflammation is the main cause of the onset, progression, and outcome of chronic kidney disease (CKD). The aim of the study was to examine the predictive value of inflammatory biomarkers in patients with CKD stages I–V and their association with parameters characteristic of CKD. **Methods.** A cross-sectional study analyzed 117 adult patients with CKD who were divided into two groups according to the glomerular filtration rate (GFR): Group 1, with normal to mild impairment of renal function (GFR ≥ 60 mL/min/1.73 m^2), stages I and II, and Group 2 with moderate and severe impairment of renal function (GFR < 60 mL/min/1.73 m^2), stages III, IV, and V, who have not started dialysis treatment. In addition to standard laboratory analyses, we determined derived parameters in patients, neutrophil-lymphocyte ratio (NLR), platelet- lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and system inflammation response index (SIRI), as markers of inflammation. **Results.** A statistically significant difference between Groups 1 and 2 was observed for body mass index ($p < 0.003$), for platelets, hemoglobin, creatinine, urea, acidum uricum, iron, phosphorus, parathyroid hormone, and proteinuria 24 hrs ($p < 0.001$), for calcium ($p < 0.031$) and leukocytes ($p < 0.030$). By analyzing the values of NLR, PLR, SII, and SIRI in patients with CKD, a statistically significant difference ($p < 0.001$) was observed between the groups; the values were elevated in Group 2. NLR, PLR, and SII showed statistical significance for essential parameters in CKD (C-reactive protein, creatinine, GFR, hemoglobin, calcium, phosphorus, parathyroid hormone) and SIRI showed statistical significance for phosphorus in Group 2. The most sensitive was NLR at 87.7%, and PLR had the highest specificity, at 81.7%, with cut-off values for PLR – 151.75, NLR – 2.06, SII – 493.57, and SIRI – 0.739. **Conclusion.** Our results indicate that the detection of biomarkers NLR, PLR, SII, and SIRI could have a significant role in predicting inflammation in patients with CKD and would contribute to the timely recognition of patients at risk of developing complications.

Key words:
biomarkers; glomerular filtration rate; inflammation; renal insufficiency, chronic.

Apstrakt

Uvod/Cilj. Zapaljenje ima ključnu ulogu u razvoju, progresiji i ishodu hronične bolesti bubrega (HBB). Cilj rada bio je da se ispita prediktivna vrednost biomarkera zapaljenja kod bolesnika sa HBB stadijuma I–V i njihova povezanost sa parametrima karakterističnim za HBB. **Metode**. Studijom preseka analizirano je 117 odraslih bolesnika sa HBB koji su na osnovu brzine glomerulske filtracije (*glomerular filtration rate* – GFR) podeljeni u dve grupe: Grupu 1, sa normalnom do slabo redukovanom bubrežnom funkcijom (GFR ≥ 60 mL/min/1,73 m^2) stadijum I i II i Grupu 2, sa umerenim i teškim smanjenjem bubrežne funkcije (GFR < 60 mL/min/1,73 m^2), stadijum III, IV i V koji nisu započeli lečenje dijalizom. Pored standardnih laboratorijskih analiza, kao markeri zapaljenja, određeni su izvedeni parametri: odnos neutrofila prema limfocitima (*neutrophil-lymphocyte ratio* – NLR), odnos trombocita prema limfocitima (*platelet-lymphocyte ratio* – PLR) i indeksi zapaljenja *systemic immune-inflammation index* – SII i *system inflammation response index* – SIRI. **Rezultati**. Utvrđena je statistički značajna razlika između Grupa 1 i 2 za indeks telesne mase ($p < 0,003$), za trombocite, hemoglobin, kreatinin, ureu, mokraćnu kiselinu, gvožđe, fosfor, paratiroidni hormon, kao i za 24-satnu proteinuriju ($p < 0,001$), zatim za kalcijum ($p < 0,031$) i leukocite ($p < 0,030$). Analiziranjem NLR, PLR, SII i SIRI kod bolesnika sa HBB uočena je statistički značajna razlika ($p < 0,001$) između grupa; povišene vrednosti ovih markera pokazane su kod bolesnika u Grupi 2. NLR, PLR

Correspondence to: Milica Petrović, Military Medical Academy, Clinic for Nephrology, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: drmilicapetrovic@gmail.com

i SII su pokazali statističku značajnost za važne parametre u HBB (C-reaktivni protein, kreatinin, GFR, hemoglobin, kalcijum, fosfor, paratiroidni hormon), a SIRI je pokazao statističku značajnost za fosfor u Grupi 2. Najsenzitivniji je bio NLR sa 87,7%, a najveću specifičnost imao je PLR – 81,7%, uz *cut-off* vrednosti za PLR – 151,75, NLR – 2,06, SII – 493,57 i SIRI – 0,739. **Zaključak**. Naši rezultati ukazuju da bi detekcija biomarkera NLR, PLR, SII i SIRI mogla imati značajnu ulogu u predviđanju zapaljenja u obolelih od HBB i doprineti blagovremenom prepoznavanju bolesnika sa rizikom od nastanka komplikacija.

Ključne reči:
biomarkeri; glomerulska filtracija, brzina; zapaljenje; bubreg, hronična insuficijencija.

Introduction

Chronic kidney disease (CKD) occurs in all age groups, with a prevalence of 9.1%, which tends to increase, and data indicate that it will become the fifth leading cause of death by 2040 [1, 2]. CKD represents damage to the structure and/or function of the kidneys that lasts at least three months, with a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, where microalbuminuria, proteinuria, and pathological urine sediment indicate significant kidney damage [3]. According to the GFR, there are five stages of CKD.

In patients with CKD, inflammatory processes, which are significant elements of increased morbidity and mortality, are manifested very early. Inflammatory tissue remodeling precedes and characterizes the progression of CKD, leading to fibrous changes, loss of kidney function, and numerous complications such as atherosclerosis and cardiovascular diseases (CVDs) [2, 4]. Determination of biomarkers of inflammation (BI) in patients with CKD is of great importance, bearing in mind that CVDs take a significant percentage (45%) of the cause of lethal outcomes already in the early stages of CKD [4–9]. In patients with CKD, cardiovascular system complications are the most common cause of morbidity and mortality. Acute myocardial infarction is observed in 30%–40% of patients with CKD [10]. Early detection of inflammatory processes is important in patients with CKD. Recently, four new BI potentially crucial in daily practice have been described: neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and system inflammation response index (SIRI) [5–9, 11–14]. Elevated values of NLR and PLR are associated with the progression of CKD towards the end stage and with a high mortality rate [7–9, 11–13], and SII and SIRI have a higher predictive value than other BI and indices in predicting cardiovascular events [14, 15].

The aim of the study was to examine the potential predictive role of BI in patients with CKD stage I–V and their association with parameters characteristic of CKD.

Methods

The cross-sectional study included 117 adult patients with CKD, stages I–V, who did not start the dialysis procedure. Their average age was 56.97 ± 10.16 years; 63 (53.85%) were male and 54 (46.15%) female. The study was conducted according to the provisions of the Declaration of Helsinki, approved by the Ethics Committee of the Military Medical Academy, Belgrade, Serbia (No. 3000-1, from March 13, 2014). GFR was determined according to the CKD estimate GFR (eGFR) formula based on serum creatinine values [16]. We divided patients into two groups according to GFR. In Group 1, there were 60 patients with normal to mild impairment of renal function (GFR ≥ 60 mL/min/1.73 m^2), stages I and II, with the existence of one or more parameters of kidney damage (microalbuminuria, proteinuria, pathological urine sediment, or disorder of renal structures revealed by the visualization method). In Group 2, there were 57 patients with moderate and severe impairment of renal function (GFR < 60 mL/min/1.73 m^2), stages III, IV, and V, who had not started the dialysis treatment.

Patients excluded from the study were those with the following: acute myocardial infarction, cerebrovascular insult, with a diagnosis of inflammatory disease (pneumonia, bronchitis, rhinitis, angiitis, pancreatitis, cholangitis, cholecystitis, allergic dermatitis, urinary infection), with immunosuppressive therapy of malignant disease, and with data about a primary surgical intervention in the last six months.

Parameters determined for all respondents were body mass index (BMI) (normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, obese ≥ 30 kg/m^2) and smoking status. Blood samples for laboratory analysis were taken in the morning, after 12 hrs of fasting. The following were determined: blood count (BC) and differential BC, C-reactive protein (CRP), glucose, urea, creatinine, uric acid, total proteins, albumins, cholesterol, triglycerides, calcium (Ca), phosphorus (P), hemoglobin (Hb), iron (Fe), vitamin D3, parathyroid hormone (PTH); 24-hr proteinuria and urine culture were determined in the urine. Complete BC was performed on an ADVIA® 120 device using flow cytometry, and biochemical analyses were performed on an ADVIA® 1800 device using spectrophotometry. We determined BI (NLR, PLR, SII, and SIRI) in all patients from the BC. NLR was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes. PLR was calculated from the ratio of platelets to lymphocytes. SII was obtained based on the form SII = platelet count (10^9/L) × neutrophil count (10^9/L) / lymphocyte count (10^9/L), and SIRI = neutrophil count (10^9/L) × monocyte count (10^9/L) / lymphocyte count (10^9/L).

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences IBM-SPSS, version 26.0. Categorical variables were presented as frequency and were analyzed using the Chi-square test. All continuous variables are presented as mean ± standard deviation. The Kolmogo-

rov-Smirnov test was used to test the normality of data distribution. For intergroup comparisons, the Independent samples *t*-test for parametric variables was used. For testing the relationship between variables, Pearson's correlation was used.

Optimal thresholds (cut-off values) of biomarker values (NLR, PLR, SII, SIRI) were determined using the receiver operating characteristic (ROC) curve analysis. The sensitivity, specificity, and cut-off values for NLR, PLR, SII, and SIRI in patients with CKD were obtained. The ROC curve comparisons were performed to verify variations in sensitivity and false positive fractions (1 – specificity) of BI using overall cut-offs. Statistical significance was defined as $p < 0.05$ for all comparisons.

Results

In our patients, the underlying kidney diseases were arterial hypertension – 44 (37.6%), chronic glomerulonephritis – 27 (23.0%), diabetes mellitus – 16 (13.7%), polycystic kidney disease – 14 (12.0%), renal calculus – 12 (10.3%), and tubulointerstitial nephritis (TIN) – 4 (3.4%).

Demographic and laboratory data of patients with CKD are shown in Table 1, which shows individual parameters concerning GFR (Group 1: GFR > 60 mL/min/1.73 m^2; Group 2: GFR ≤ 60 mL/min/1.73 m^2) and summary parameters of patients.

Comparing age, gender, BMI, and smoking status, a statistically significant difference was observed only for BMI ($p < 0.003$). Observing the laboratory analyses, statistical significance ($p < 0.001$) was observed between the groups for platelets, Hb, creatinine, urea, acidum uricum, Fe, P, PTH, and proteinuria 24 hr, $p < 0.031$ for Ca and $p < 0.030$ for white blood cells (Table 1).

An analysis of BI values – NLR, PLR, SII, and SIRI – in patients with CKD showed a statistically significant difference ($p < 0.001$) between the groups. Elevated values of these markers were found in patients in Group 2 with a more severe degree of renal function impairment (Table 2).

Correlation of NLR, PLR, SII, and SIRI and significant parameters in Group 2 are presented in Table 3. A statistically significant correlation was obtained for NLR, PLR, and SII according to CRP, renal function parameters (creatinine and GFR), as well as according to Hb, Ca, and P. NLR and PLR statistically significantly correlated with PTH, and NLR and SII significantly correlated with Fe. SIRI correlated statistically significantly only with P, while the other parameters had no statistical significance.

Table 1

Demographic and laboratory parameters of patients with chronic kidney disease

Parameters	Reference range	All patients (n = 117)	Group 1 (n = 60)	Group 2 (n = 57)	*p*-value
Age (years)		56.97 ± 10.16	56.22 ± 12.08	57 ± 12	0.770
Men/women		63 (53.84)/54 (46.15)	32 (53.33)/28 (46.66)	31 (54.38)/26 (45.61)	1.000
BMI (kg/m^2)		26.26 ± 3.29	25.33 ± 3.16	27.19 ± 3.43	**0.003**
Smokers		44 (37.6)	18 (30)	26 (45.61)	0.081
CRP (g/L)	0.00–4.00	2.78 ± 2.01	2.50 ± 1.54	3.07 ± 2.39	0.172
RBC (×10^{12} /L)	4.50–6.50	4.88 ± 3.64	4.85 ± 0.38	4.91 ± 5.23	0.934
Hb (g/L)	1.30–1.80	130.09 ± 18.82	139 ± 10.15	120.44 ± 20.97	**< 0.001**
WBC (×10^9/L)	4–11	6.62 ± 1.95	6.24 ± 1.64	7.01 ± 2.17	**0.030**
PLT (×10^3/μL)	160–370	240.44 ± 79.44	215.98 ± 51.21	266.18 ± 94.84	**< 0.001**
Urea (mmol/L)	2.50–7.50	14.80 ± 13.64	5.63 ± 1.42	16.08 ± 8.00	**< 0.001**
Creatinine (μmol/L)	62–115	184.15 ± 164.00	76.73 ± 13.58	296.95 ± 171.27	**< 0.001**
Acidum uricum (mmol/L)	220–547	397.04 ± 104.08	357.93 ± 96.95	438 ± 96	**< 0.001**
Cholesterol (mmol/L)					
preferably	< 5.2				
borderline risk	5.2–6.2	5.14 ± 1.11	5.31 ± 1.09	4.91 ± 1.14	0.084
risk	> 6.2				
Triglycerides (mmol/L)					
preferably	< 1.7				
borderline risk	1.7–2.3	1.82 ± 0.98	1.86 ± 1.14	1.76 ± 0.77	0.971
risk	> 2.3				
Iron (μmol/L)	11–31	14.33 ± 6.18	16.27 ± 6.10	12.30 ± 5.63	**< 0.001**
Calcium (mmol/L)	2.15–2.60	2.37 ± 0.15	2.40 ± 0.10	2.34 ± 0.18	**< 0.031**
Phosphorus (mmol/L)	0.78–1.65	1.16 ± 0.29	1.02 ± 0.148	1.29 ± 0.32	**< 0.001**
PTH (pmol/L)	1.30–9.30	16.03 ± 21.54	5.66 ± 2.33	26.15 ± 26.40	**< 0.001**
Vitamin D (nmol/L)					
severe deficiency	< 25				
mild deficiency	25–50	65.99 ± 27.64	69.00 ± 25.15	62.49 ± 29.64	0.202
insufficiency	50–75				
recommended	> 75				
Proteinuria (g/24 hr)	0.00–0.150	0.73 ± 0.97	0.32 ± 0.47	1.15 ± 1.13	**< 0.001**

BMI – body mass index; CRP – C-reactive protein; RBC – red blood cells; Hb – hemoglobin; WBC – white blood cells; PLT – platelets; PTH – parathyroid hormone. Values are given as mean ± standard deviation or numbers (percentages).

Table 2

Parameters of inflammation in patients with chronic kidney diseases

Parameter	*Group 1 (n = 60)	**Group 2 (n = 57)	*p*-value
Neutrophils (10^9/L)	3.66 ± 1.31	4.57 ± 1.74	**0.002**
Lymphocytes (10^9/L)	1.83 ± 0.55	1.63 ± 0.7	0.063
Monocytes (10^9/L)	0.40 ± 0.12	0.57 ± 0.72	0.078
NLR	2.13 ± 0.98	2.98 ± 1.03	< **0.001**
PLR	125.61 ± 36.30	175.43 ± 66.69	< **0.001**
SII	451.82 ± 204.43	802.50 ± 447.36	< **0.001**
SIRI	0.88 ± 0.65	1.68 ± 1.99	< **0.001**

NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; SII – systemic immune-inflammation index; SIRI – system inflammation response index.
Note: *glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m^2; **GFR < 60 mL/min/1.73 m^2.

Table 3

Correlation of NLR, PLR, SII, and SIRI and significant parameters in patients with GFR < 60 mL/min/1.73 m^2

Parameter		BMI	CRP	CRE	GFR	Hb	Fe	Ca	P	PTH	Proteinuria
NLR	Pearson Correlation	-0.134	0.362	0.368	-0.271	-0.302	-0.269	-0.334	0.328	0.337	0.072
	Sig.	0.321	**0.006**	**0.005**	**0.041**	**0.022**	**0.043**	**0.011**	**0.013**	**0.010**	0.595
PLR	Pearson Correlation	-0.111	0.375	0.467	-0.346	-0.375	-0.221	-0.446	0.329	0.400	0.131
	Sig.	0.411	**0.004**	**0.000**	**0.008**	**0.004**	0.098	**0.001**	**0.013**	**0.002**	0.331
SII	Pearson Correlation	-0.045	0.493	0.500	-0.333	-0.335	-0.260	-0.262	0.447	0.150	-0.070
	Sig.	0.740	**0.000**	**0.000**	**0.011**	**0.011**	**0.050**	**0.049**	**0.000**	0.265	0.604
SIRI	Pearson Correlation	0.014	0.011	0.234	-0.219	-0.074	-0.016	-0.085	0.274	0.074	0.224
	Sig.	0.917	0.935	0.080	0.101	0.583	0.907	0.530	**0.039**	0.582	0.094

CRE – creatinine; Fe – iron; Ca – calcium; P – phosphorus; PTH – parathyroid hormone. For other abbreviations, see Tables 1 and 2.

Table 4

Receiver operating characteristic curve analysis of NLR, PLR, SII, and SIRI

Variable	AUC	Asymptotic sig.	Asymptotic 95% CI		Sensitivity	Specificity	Cut-off value
			lower bound	upper bound			
NLR	0.766	0.000	0.680	0.853	87.7	58.3	**2.06**
PLR	0.758	0.000	0.671	0.845	66.7	81.7	**151.75**
SII	0.818	0.000	0.741	0.895	86.0	68.3	**493.57**
SIRI	0.725	0.000	0.634	0.816	86.0	51.7	**0.739**

AUC – area under the receiver operating characteristic curve; CI – confidence interval; sig. – significance. For other abbreviations, see Table 2.

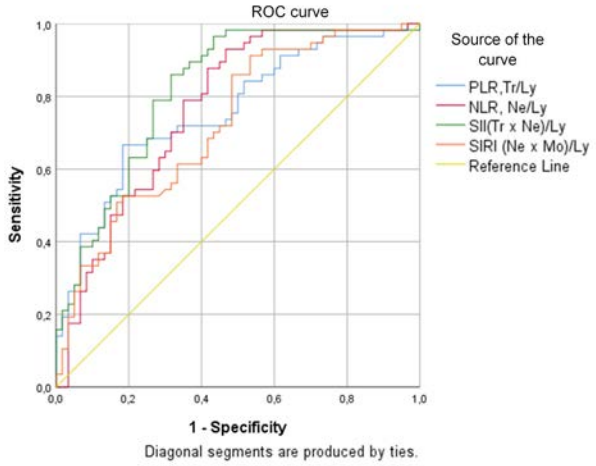

Fig. 1 – Receiver operating characteristic (ROC) curve of NLR, PLR, SIRI, SII for Group 2. For abbreviations, see Table 2.

The ROC analysis of the NLR, PLR, SIRI, and SII are shown in Table 4 and Figure 1. The area under the ROC curve (AUC) value of the NLR was 0.766, and the best cut-off value was 2.06 (p = 0.000). The AUC value of the PLR was 0.758, and the best cut-off value was 151.75 (p = 0.000). The AUC value of the SIRI was 0.725, and the best cut-off value was 0.739 (p = 0.000). The AUC value of the SII was 0.818, and the best cut-off value was 493.57 (p = 0.000).

Discussion

Inflammatory processes underlying the formation and rupture of atherosclerotic plaque, the formation of thrombus, and the subsequent development of cardiovascular complications have a proven influence on the development and progression of CKD [17–21]. Chronic inflammation causes in CKD are numerous (uremia, oxidative stress, infections, dyslipidemia, malnutrition, hypervolemia, dialysis) [22]. Ac-

cording to the results and investigations of previous studies, NLR, PLR, SII, and SIRI can be considered promising BI, progression, and predictors of mortality in patients with CKD [23]. Studies that included patients with different stages of CKD before the start of dialysis focused mainly on NLR and PLR markers. At the same time, the results for SII and SIRI were published somewhat less often and more often in patients on dialysis [23–26]. In our study comparing the group of patients with higher and lower GFR values, a statistically significant difference ($p < 0.001$) was obtained for the biomarkers NLR, PLR, SII, and SIRI, which had elevated values in the group with lower GFR .

Comparing NLR and PLR in patients with CKD, several authors found that PLR is a better BI than NLR and a superior predictor of mortality in patients with CKD [4, 24].

Our results indicated that both NLR and PLR statistically significantly correlated with parameters significant for CKD (CRP, creatinine, GFR, Hb, Ca, P, PTH), where the significance was more pronounced for PLR. However, unlike PLR, NLR statistically significantly correlated with Fe. Looking at SII in correlation with parameters significant in CKD, it is possible to see that it indicates statistical significance to CRP, creatinine, GFR, Hb, Ca, P, and Fe, indicating systemic inflammation in our patients. Similar results indicated that these biomarkers' association with inflammation was observed in studies focusing on patients with heart failure, autoimmune diseases, neurological disorders, etc. [10, 25, 27, 28].

In a study that included 85 patients with different stages of CKD (not on dialysis), Brito et al. [11] found increased values of NLR and PLR in patients with elevated high-sensitivity (hs)-CRP compared to the group of patients with hs-CRP within reference limits. In the same group of patients, a positive correlation between PLR and hs-CRP was observed. Similar results were observed by Li et al. [24], indicating a positive correlation of both NLR and PLR with hs-CRP in a group of 611 patients with CKD in the terminal stage of renal failure. The correlation between CRP and NLR, SII, and SIRI was observed in patients with acute lupus nephritis and heart failure [27, 28].

Analyzing the association of elevated values of BI with creatinine values, Toraman et al. [29] observed a positive correlation between NLR and creatinine in the studied group of 301 patients with CKD, indicating that an increase in inflammation leads to an increase in renal weakness and a negative correlation for NLR and PLR according to Hb and cholesterol.

We obtained similar results in our study. NLR, PLR, and SII correlated positively with creatinine and negatively with Hb. An increase in NLR, PLR, and SII is related to decreased Hb concentration and worsening of anemia in our patients. Moreover, these BI were related to an increase in creatinine and progression of renal failure.

Examining the association between SII and SIRI and mortality from all causes and cardiovascular mortality in 42,875 adult subjects, Xia et al. [30] observed that elevated values of SII and SIRI were significantly associated with lower levels of GFR.

In contrast to this study, in our patients, there was a correlation of NLR, PLR, and SII with elevated serum creatinine values and lower GFR values, but not for the SIRI.

The connection between inflammation and anemic syndrome in CKD has been confirmed in many studies, so the increased value of NLR and PLR in patients with CKD is described as having a negative correlation with the anemia parameters [31].

Considering that elevated NLR and PLR values were also registered in patients with resistance to erythropoietin, Valga et al. [32] indicate that NLR and PLR can be used as markers for monitoring resistance to erythropoietin. Our study also determined the association of NLR, PLR, SII, and anemia parameters.

Examining the relationship between markers of renal osteodystrophy and BI in patients with CKD, a positive correlation was observed in the relationship of PTH with NLR and PLR, which is independent of GFR and suggests that PTH could be a pro-inflammatory parameter independent of the degree of renal failure [29, 33, 34].

Furthermore, many authors have recently noticed a correlation between reduced vitamin D values and elevated BI values. One of the first studies related to the association between vitamin D concentration and the indices SII and SIRI, by Dziedzic et al. [35, 36] indicates a correlation between the concentration of vitamin D and the SII and SIRI as markers of inflammation significant in atherogenesis [35, 36].

The correlation of BI with parameters of renal osteodystrophy in our subjects with CKD verified the statistical significance of all four biomarkers with P (NLR, PLR, SII, and SIRI), three with Ca (NLR, PLR, and SII), and only two with PTH (NLR and PLR). None of the BI had statistical significance with vitamin D, probably because most subjects were on vitamin D therapy starting from stage III of CKD.

According to previous studies, there is no established standard threshold value of BI for an increased risk of an unfavorable outcome. Our results for NLR and PLR indicate that NLR sensitivity is 87.7% and specificity 58.3% and PLR sensitivity is 66.7% and specificity 81.7%. Our results are similar to those of Brito et al. [11], who, by examining BI in patients with CKD who are not on dialysis, indicated that the cut-off value for NLR (with 76.19% sensitivity and 48.44% specificity) was 1.98 and for PLR (with 85.71% sensitivity and 51.56% specificity) the cut-off value was 116.6. Similar results were also noted by Aneez et al. [13] in a study that included 85 subjects with proteinuria and CKD. The sensitivity of NLR according to the stages was as follows: for stage IIIa, it was 91.4%; for IIIb, it was 92.6%; for stage IV, it was 89.7%. The specificity of NLR was the following: for stage IIIa, 86.7%; for IIIb, 87.11%; for stage IV, 89.3%. The sensitivity of PLR was: for stage IIIa, 81.4%; for IIIb, 94.4%; for stage IV, 89.7%. The specificity of PLR was: for stage IIIa, 89.0%; for IIIb, 90.36%; for stage IV, 85.7%. The AUC for NLR was as follows: for IIIa, 0.976; for IIIb, 0.965; for stage IV, it was 0.962. The AUC for PLR was: for IIIa, 0.938; for IIIb, 0.981; for stage IV, 0.968.

The association of BI (NLR, PLR, SII, SIRI) and CKD is most often described in hemodialysis patients and less so in predialysis patients. 37. Tonyali et al. [37] were the first to publish a study on the predictive value of NLR on GFR in patients after partial or radical nephrectomy. NLR values were higher in patients with GFR < 60 mL/min/1.73 m^2 compared to the control group. The cut-off value for NLR was 3.18, with 39% sensitivity and 81% specificity.

By analyzing the statistical correlation in our group of patients, we observed that all four investigated BI (NLR, PLR, SII, and SIRI) in patients with CKD had statistical significance in Group 2 (p = 0.001); the most sensitive was NLR with 87.7%. The highest specificity was for PLR with 81.7%, with threshold values for PLR – 151.75, NLR – 2.06, SII – 493.57, and SIRI – 0.739. By analyzing SII and SIRI, we found that both markers had the same sensitivity of 86%. SII was more specific, with 68.3% vs. 51.7% for SIRI, with the cut-off values for SII being 493.57 and for SIRI 0.793.

In the available literature, several papers are on determining NLR and PLR BI in patients with CKD, while SII and SIRI are less common. According to recent studies, an essential place next to NLR and PLR is occupied by SII, which was more often examined in cardiac patients [25].

The first study related to the correlation of SII and CKD included 10,787 adult subjects from the United States of America when it was established that elevated SII values positively correlated with CKD and that the male population was more often affected [38]. In the future, the SIRI biomarker may be important in the assessment and prognosis of CKD patients, as it is associated with all-cause mortality and CVD mortality according to Wei et al. [39].

Additional tests and studies on a larger sample are needed to determine the exact role and importance of determining these BI further.

Conclusion

Our study's results are similar to those of other authors who indicated that biomarkers of inflammation (NLR, PLR, SII, and SIRI) were statistically significantly elevated in patients with moderate and severe impairment of renal function. In patients with moderate and severe impairment of renal function stages III, IV, and V who did not start dialysis treatment, statistically significant correlations were observed in relation to the NLR, PLR, and SII, for most of the examined parameters characteristic of chronic kidney disease, while SIRI had no statistical significance.

REFERENCES

1. *Carney EF.* The impact of chronic kidney disease on global health. Nat Rev Nephrol 2020; 16(5): 251.
2. *Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D,* et al. US renal data system 2019 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2020; 75(1 Suppl 1): A6–7.
3. *National Kidney Foundation.* K/DOQI clinical practice guidelines for diabetes and CKD: 2012 update. Am J Kidney Dis 2012; 60(5): 850–86.
4. *Yuan Q, Wang J, Peng Z, Zhou Q, Xia X, Xie Y,* et al. Neutrophil-to-lymphocyte ratio and incident end-stage renal disease in Chinese patients with chronic kidney disease: Results from the Chinese cohort study of chronic kidney disease (C-STRIDE). J Transl Med 2019; 17(1): 86.
5. *Altunoren O, Akkus G, Sezal DT, Ciftcioglu M, Guzel FB, Isiktas S,* et al. Does neutrophyl to lymphocyte ratio really predict chronic kidney disease progression? Int Urol Nephrol 2019; 51(1): 129–37.
6. *Woziwodzka K, Dziewierz A, Pawica M, Panek A, Krzanowski M, Gołasa P,* et al. Neutrophil-to-lymphocyte ratio predicts long-term all-cause mortality in patients with chronic kidney disease stage 5. Folia Med Cracov 2019; 59(4): 55–70.
7. *Zhang J, Lu X, Wang S, Li H.* High neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are associated with poor survival in patients with hemodialysis. BioMed Res Int 2021; 2021: 9958081.
8. *Umeres-Francia GE, Rojas-Fernández MV, Herrera-Añazco P, Benites-Zapata VA.* Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as a risk factor for mortality in Peruvian adults with chronic kidney disease. Ren Replace Ther 2022: 8; 30.
9. *Duan S, Sun L, Zhang C, Wu L, Nie G, Huang Z,* et al. Association of platelet-to-lymphocyte ratio with kidney clinicopathologic features and renal outcomes in patients with diabetic kidney disease. Int Immunopharmacol 2021; 93: 107413.
10. *Jankowski J, Floege J, Fliser D, Böhm M, Marx N.* Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. Circulation 2021; 143(11): 1157–72.
11. *Brito GMC, Fontenele AMM, Carneiro ECRL, Nogueira LAL, Cavalcante TB, Vale AAM,* et al. Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Nondialysis Chronic Kidney Patients. Int J Inflam 2021; 2021: 6678960.
12. *Jin Z, Wu Q, Chen S, Gao J, Li X, Zhang X,* et al. The associations of two novel inflammation indexes, SII and SIRI with the risks for cardiovascular diseases and all-cause mortality: A ten-year follow-up study in 85,154 individuals. J Inflamm Res 2021; 14: 131–40.
13. *Aneez FA, Shariffdeen N, Haleem FA, Thangarajah BR, Rasaratnam K.* Correlation between neutrophil to lymphocyte ratio and platelet to lymphocyte ratio with proteinuria in different stages of chronic kidney disease. Egypt J Intern Med 2024; 36(1): 6.
14. *Zhang Y, Xing Z, Zhou K, Jiang S.* The predictive role of systemic inflammation response index (SIRI) in the prognosis of stroke patients. Clin Interv Aging 2021; 16: 1997–2007.
15. *Xiao S, Wang Z, Zuo R, Zhou Y, Yang Y, Chen T,* et al.. Association of Systemic Immune Inflammation Index with All-Cause, Cardiovascular Disease, and Cancer-Related Mortality in Patients with Cardiovascular Disease: A Cross-Sectional Study. J Inflamm Res 2023; 16: 941–61.
16. *Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI,* et al. A new equation to estimate glomerular filtration rate. An Intern Med 2009; 150(9): 604–12. Erratum in: Ann Intern Med 2011; 155(6): 408.
17. *Amdur RL, Feldman HI, Dominic EA, Anderson AH, Beddhu S, Rahman M,* et al. Use of measures of inflammation and kidney function for prediction of atherosclerotic vascular disease events and death in patients with CKD: findings from the CRIC study. Am J Kidney Dis 2019; 73(3): 344–53.

18. *Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M,* et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrol 2012; 7(12): 1938–46.
19. *Medina-Leyte DJ, Zepeda-Garcia O, Domínguez-Pérez M, González-Garrido A, Villarreal-Molina T, Jacobo-Albavera L.* Endothelial dysfunction, inflammation and coronary artery disease: potential biomarkers and promising therapeutical approaches. Int J Mol Sci 2021; 22(8): 3850.
20. *Kaufmanova J, Stikarova J, Hlavackova A, Chrastinova L, Maly M, Suttnar J,* et al. Fibrin clot formation under oxidative stress conditions. Antioxidants (Basel) 2021; 10(6): 923.
21. *Fracassi F, Crea F, Sugiyama T, Yamamoto E, Uemura S, Vergallo R,* et al. Healed culprit plaques in patients with acute coronary syndromes. J Am Coll Cardiol 2019; 73(18): 2253–63.
22. *Kadatane SP, Satariano M, Massey M, Mongan K, Raina R.* The role of inflammation in CKD. Cells 2023; 12(12): 1581.
23. *Tang L, Deng Y, Lai J, Guo X, Liu P, Li S,* et al. Predictive Effect of System Inflammation Response Index for Progression of Chronic Kidney Disease in Non-Dialyzing Patient. J Inflamm Res 2023; 16: 5273–85.
24. *Li P, Xia C, Liu P, Peng Z, Huang H, Wu J,* et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in evaluation of inflammation in non-dialysis patients with end-stage renal disease (ESRD). BMC Nephrol 2020; 21(1): 511.
25. *Shi S, Kong S, Ni W, Lu Y, Li J, Huang Y,* et al. Association of the systemic immune-inflammation index with outcomes in acute coronary syndrome patients with chronic kidney disease. J Inflamm Res 2023; 16: 1343–56.
26. *Li L, Chen K, Wen C, Ma X, Huang L.* Association between systemic immune-inflammation index and chronic kidney disease: A population-based study. PLoS One 2024; 19(2): e0292646.
27. *Rabrenović V, Petrović M, Rabrenović M, Pilčević D, Rančić N.* The significance of biomarkers of inflammation in predicting the activity of lupus nephritis. J Med Biochem 2024; 43(1): 116–25.
28. *Ao G, Wang Y, Qi X, Wang F, Wen H.* Association of neutrophil-to-lymphocyte ratio and risk of cardiovascular or all-cause mortality in chronic kidney disease: a meta-analysis. Clin Exp Nephrol 2021; 25(2): 157–65.
29. *Toraman A, Aras F, Hekimsoy Z, Kursat S.* Is there a relationship between parathyroid hormone and neutrophil lymphocyte ratio or platelet lymphocyte ratio? Acta Endocrinol (Buchar) 2019; 5(1): 96–101.
30. *Xia Y, Xia C, Wu L, Li Z, Li H, Zhang J.* Systemic immune inflammation index (SII), system inflammation response index (SIRI) and risk of all-cause mortality and cardiovascular mortality: A 20-year follow-up cohort study of 42,875 US adults. J Clin Med 2023; 12(3): 1128.
31. *Gluba-Brzózka A, Franczyk B, Olszewski R, Rysz J.* The influence of inflammation on anemia in CKD patients. Int J Mol Sci 2020; 21(3): 725.
32. *Valga F, Monzón T, Henriquez F, Santana-del-Pino A, Antón-Pérez G.* Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios as markers of erythropoietin resistance in chronic haemodialysis patients: A multicentre cross-sectional study. Nefrologia 2020; 40(3): 320–7.
33. *Tian-tian L, Shu-man T, De-guang W.* Effect of parathyroidectomy on NLR and PLR in patients with renal secondary hyperparathyroidism. J Clin Nephrol 2021; 21(2): 119–23.
34. *Yilmaz G, Sevinc C, Ustundag S, Yavuz YC, Hacibekiroglu T, Hatipoglu E,* et al. The relationship between mean platelet volume and neutrophil/lymphocyte ratio with inflammation and proteinuria in chronic kidney disease. Saudi J Kidney Dis Transpl 2017; 28(1): 90–4.
35. *Dziedzic EA, Gąsior JS, Tuzimek A, Paleczny J, Junka A, Dąbrowski M,* et al. Investigation of the associations of novel inflammatory biomarkers-systemic inflammatory index (SII) and systemic inflammatory response index (SIRI)-with the severity of coronary artery disease and acute coronary syndrome occurrence. Int J Mol Sci 2022; 23(17): 9553.
36. *Dziedzic EA, Gąsior JS, Saniewski T, Dąbrowski M.* Vitamin D deficiency among Polish patients with angiographically confirmed coronary heart disease. Pol Merkur Lekarski 2021; 49(292): 278–82.
37. *Tonyali S, Ceylan C, Yahsi S, Karakan MS.* Does neutrophil to lymphocyte ratio demonstrate deterioration in renal function? Ren Fail 2018; 40(1): 209–12.
38. *Liu X, Li X, Chen Y, Liu X, Liu Y, Wei H,* et al. Systemic immune-inflammation Index is associated with chronic kidney disease in the U.S. population: insights from NHANES 2007–2018. Front Immunol 2024; 15: 1331610.
39. *Wei L, Mao S, Liu X, Zhu C.* Association of systemic inflammation response index with all-cause mortality as well as cardiovascular mortality in patients with chronic kidney disease. Front Cardiovasc Med 2024; 11: 1363949.

Received on January 3, 2024
Revised on February 18, 2024
Revised on May 19, 2024
Accepted on May 28, 2024
Online First June 2024