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Original Article NEPHROLOGY

Evaluation of the relationship between the mean platelet volume and the neutrophil/lymphocyte ratio with progression of chronic kidney disease in patients with autosomal dominant polycystic kidney disease

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ABSTRACT

OBJECTIVE: Increased inflammation is known to cause higher mortality and morbidity in autosomal dominant polycystic kidney disease (ADPKD). At the same time, inflammation has been shown to contribute in chronic kidney disease (CKD) progression pathogenesis. Neutrophil-lymphocyte ratio (NLR) and mean platelet volume (MPV) have been lately found to be related with systemic inflammation. Therefore, in this study, it was intended to evaluate any correlation between the NLR and MPV degree and poor prognosis in ADPKD patients.

METHODS: The study sample comprised 86 adult patients (male: 80.2%, mean age: 35.35 years) screened in the Nephrology Outpatient Clinic with the diagnosis of ADPKD. Data were obtained from the electronic database of the hospital. Two groups were made from the patients: Group I included ADPKD patients with CKD Stages I–II and Group II included ADPKD patients with CKD Stages III–V. The relationships between CKD stage and laboratory parameters were analyzed.

RESULTS: Significantly higher NLR (2.64±1.43 vs. 2.02±0.89, p=0.024), MPV (9.84±1.65 vs. 9.08±1.17, p=0.045), and hs-CRP (10.7±2.2 vs. 22.4±8.3, p=0.001) values were determined in Group II than in those with Group I. Positive correlations were statistically significative observed between hs-CRP and MPV and NLR in the patients with ADPKD.

CONCLUSION: The study results demonstrated that significantly NLR and MPV are increased in ADPKD patients with progression of CKD. Therefore, lowering the NLR and MPV level could be new, therapeutic, and preventive alternatives for patients with ADPKD.

Keywords: C-reactive protein; inflammation; mean platelet volume; polycystic kidney disease.

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Autosomal dominant polycystic kidney disease (ADPKD) has a reported prevalence of 1/400–1/1000 and is the most common of human monogenic diseases. ADPKD accounts for 8–10% of the etiology of end-stage renal disease (ESRD) [1].

The increase in proliferation and apoptosis as a result of gene mutations leads to abnormal fluid secretion and the formation of a different extracellular matrix and as a result, cysts occur. As a consequence of these changes, interstitial inflammation develops leading to interstitial fibrosis and kidney failure [2, 3]. In ADPKD, hypertension, which is one of the most critical factors affecting renal disease progression and leads to an increase in cardiovascular mortality and morbidity, occurs before development of kidney failure in 60% of adults. Of patients with kidney disease, more than 80% have hypertension [4].

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Other factors thought to contribute to the development of hypertension in ADPKD include hyperactivation in the endothelial system, a decrease in nitric oxide synthesis and increased the activity of renin-aldosterone-angiotensin system. The presence of hypertension also contributes to disease progression to chronic renal failure [5].

High sensitivity C-reactive protein (hs-CRP) is the most frequently used marker to evaluate inflammation. As the close relationship between CRP levels and morbidity and mortality in chronic kidney disease (CKD) has been shown in numerous studies, it is accepted as an important cardiovascular risk factor [6, 7].

Higher levels of inflammatory markers in patients have been reported to be related to the more rapid progression of CKD. Neutrophil-lymphocyte ratio (NLR) is a recently introduced, inexpensive and readily available indicator, which has been shown to reflect the seriousness and extent of systemic inflammation and atherosclerosis. It has also been used to predict survival and unfavorable clinical outcomes in non-cardiac and cardiac disorders, including ESRD [8–10].

Physiologically, the main function of platelets is to promote hemostasis and contribute to atherogenesis. As platelet size increases, platelet activity increases. The indicator and possibly determinant of platelet function are platelet volume [11]. Patients with renal artery stenosis, ischemic stroke, and acute myocardial infarction are seen to have increased mean platelet volume (MPV) [12–14]. MPV and NLR are valuable indicators of inflammation as they can be evaluated by a simple hemogram test.

The purpose of this study was to examine any correlations between inflammation markers (hs-CRP and NLR) and MPV and the association of these with the progression of CKD in ADPKD patients.

Highlight key points

- ADPKD is one of the important causes of ESRD. If we have some parameters to predict ESRD progression in ADPKD, comorbidities (proteinuria, hypertension, etc.) that will accelerate this progression can be followed more closely.
- Correlation between increased inflammation and CKD stages is known. In this study, it was also found that hs-CRP was high in Stages 3–5 CKD patients. It was thought that the positive correlation of MPV and NLR with this parameter could be valuable in terms of showing ESRD progression.
- These parameters can be obtained in a simple blood count makes it even more valuable. It will also be able to make a significant contribution to the cost of follow-up and treatment in this group of patients.

MATERIALS AND METHODS

Sample Collection

The patients comprised in the study were selected from patients who presented at the Nephrology Outpatients Clinic of Sultan Abdulhamid Han Training and Research Hospital between February 1, 2013, and February 1, 2018. All of 86 patients with ADPKD, over the age of 18, were comprised in the study. The study exclusion criteria were defined as active infection, chronic inflammatory disease, diabetes mellitus, hematological disease, or malignancy. Approval for the study was granted by the Gulhane Faculty of Medicine Ethics Committee (decision no: 1491-106-12/1648.4-4957, dated: October 9, 2012). Data were obtained from the electronic database of the hospital. ADPKD was diagnosed according to the ultrasonographic criteria described by Ravine et al. [15].

CKD stages were classified according to estimated glomerular filtration rate (eGFR) calculated by the CKD Epidemiology Collaboration (CKD-EPI) equations [16]. CKD is classified according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines for CKD [17]. In this study, the ADPKD patients were separated into two groups as Stages I–II CKD and Stages III–V CKD. Patient age, body mass index, hemogram, hs-CRP, NLR, MPV, glucose, creatinine, GFR, potassium, lipid profile, uric acid, liver function tests, and albumin values were recorded from the medical files of patients and the two groups were compared.

Statistical Analysis

In the study, data were analyzed by statistical tests which were performed using the IBM Statistical Package for the Social Sciences version 22.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were reported as mean±standard deviation values, number (n) and percentage (%). The Kolmogorov–Smirnov test showed the analysis of the data distribution. Continuous variables showing normal distribution were analyzed with the Student's t-test, and for those not showing normal distribution, the non-parametric Mann–Whitney U-test was applied. According to the normality distribution of discrete data, the Chi-square test or Fisher's exact test was applied. The relationship between hs-CRP, NLR, and MPV was examined with the Pearson correlation coefficient. To determine the associations between

Table 1. The demographic characteristics of the CKD Stage I–II and Stage III–V groups, comorbid disease distribution, and laboratory data

Variables	CKD stages I–II, n= 64	CKD stages III–V, n=22	p
Gender (F/M)	8/56	9/13	**0.004**
Age (year)	30.94±15.15	48.18±18.12	**0.001**
Hypertension (%)	54.7	81.8	**0.024**
Proteinuria (mg/24 h)	274.55±146.13	547.41±233.87	**0.01**
NLR	2.02±0.89	2.64±1.43	**0.024**
MPV (fL)	9.08±1.17	9.84±1.65	**0.045**
GFR (ml/min/1.73m²)	92.97±18.92	41.04±12.87	**0.0001**
BMI (kg/m²)	26.63±4.68	23.75±3.23	**0.006**
White blood cell (per 10^3/μL)	6420.47±1388.94	7239.09±2269.15	0.247
Neutrophil (per 10^3/μL)	140.07±2.40	140.30±2.59	0.611
Lymphocyte (per 10^3/μL)	2012.81±560.60	1912.27±792.40	0.281
Hemoglobin (g/dL)	14.85±1.39	13.53±1.54	**0.001**
Hematocrit (%)	43.77±3.97	40.88±4.56	**0.008**
MCV (fL)	87.74±4.17	87.61±5.42	0.937
Platelets (per 10^3/μL)	236.94±64.37	214.95±45.31	0.237
Glucose (mg/dL)	83.68±12.54	100.59±40.19	0.054
Urea (mg/dL)	30.14±6.76	57.45±29.14	0.882
Creatinine (mg/dL)	0.99±0.15	1.97±1.10	**0.0001**
Potassium (mmol/L)	4.25±0.51	4.50±0.48	**0.020**
HDL cholesterol (mg/dL)	43.28±9.51	41.86±8.40	0.533
LDL cholesterol (mg/dL)	109.02±26.56	103.05±39.78	0.376
ALT (U/L)	25.23±25.45	22.82±13.80	0.913
AST (U/L)	20.45±11.14	18.27±6.23	0.562
Uric acid (mg/dL)	274.55±446.13	547.41±533.87	**0.005**
Albumin (g/dL)	4.40±0.45	4.26±0.39	0.305
hs-CRP (mg/L)	10.7±2.2	22.4±8.3	**0.001**

P<0.05 was accepted as statistically significant; F: Female; M: Male; NLR: Neutrophil/lymphocyte ratio; MPV: Mean platelet volume; CKD: Chronic kidney disease; GFR: Glomerular filtration rate; BMI: Body mass index; hs-CRP: High-sensitive C-reactive protein; MCV: Mean corpuscular volume; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

the dependent (CKD stage) and independent variables (hs-CRP, NLR, and MPV), binary logistic regression analysis was applied. P<.05 was statistically significant.

RESULTS

The CKD Stages I–II group comprised eight women and 56 men. The mean age of Group I is 30.94±15.15 years. The CKD Stages III–V group comprised nine women and 13 men. The mean age of Group II is 48.18±18.12 years. Statistically significant distinctions were determined between the two groups in conditions of age, gender, and body mass index (BMI). Advanced age and low BMI were determined to be related to reduce GFR. Hypertension was determined in 18 patients (81.8%) in Group II (p=0.024). The demographic characteristics of the CKD Stage I–II and Stage III–V groups, comorbid disease distribution, and laboratory results are presented (Table 1).

The NLR (P: 0.024) and MPV (P: 0.045) values were found to be significantly high in Group II.

All variables that were statistically related to progression of CKD, at a level of p<0.05, were embodied in a binary logistic regression analysis model. The model with CKD progression for the various predictors, hs-CRP level (p=0.001; Exp(B)=1.52, C.I. 95% 1.29–1.80), MPV (p=0.027; Exp(B)=1.51, C.I. 95% 1.04–2.17), and NLR (p=0.036; Exp(B)=1.66, C.I. 95% 1.03–2.65) independently influenced CKD progression.

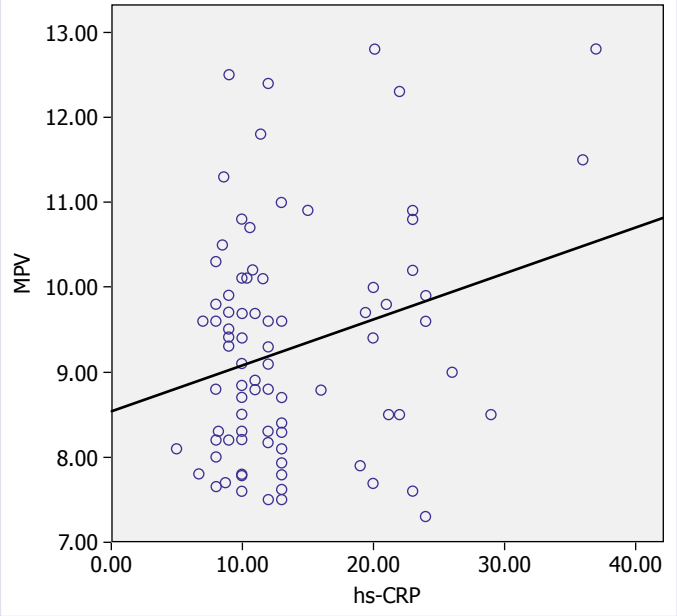

Figure 1. hs-CRP correlation with plasma MPV levels.

hs-CRP: High-sensitivity C-reactive protein; MPV: Mean platelet volume.

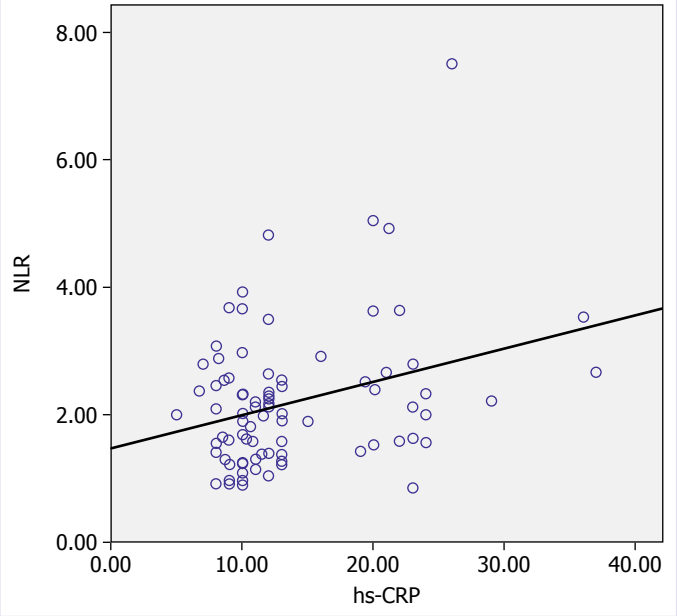

Figure 2. Correlation between NLR and hs-CRP levels.

hs-CRP: High-sensitivity C-reactive protein; NLR: Neutrophil/lymphocyte ratio.

A statistically significant positive correlation was determined between hs-CRP and MPV and NLR (r=0.26, r=0.31, respectively; p<0.05) (Fig. 1, 2).

The Hgb (p= 0.001) and Htc (p=0.008) values, related with chronic disease anemia that develops as a result of a decrease in GFR, were determined to be statistically significantly low in the CKD Stages III–V group. The potassium (p=0.02) and uric acid (p=0.005) parameters, which were expected to be higher as the CKD level increased, were also found to be significantly higher in the Stages III–V CKD group. No significant distinction was determined between two groups in lipid parameters and liver function tests.

DISCUSSION

The results obtained in this study demonstrated that NLR and MPV are indicators of inflammation in ADPKD, and as the disease progresses and GFR decreases, NLR and MPV increase. The NLR and MPV level in ADPKD patients were also seen to predict poor prognosis. The main findings of this study confirmed the hypotheses that MPV and NLR were significantly high levels in ADPKD patients with dialysis, MPV and NLR significantly increased with advancing CKD stages, and NLR and MPV were predictive of the occurrence of CKD events, and were seen to have a significant positive correlation with blood urea nitrogen.

Several studies have found an increased NLR in patients with CKD [18–20]. Gul et al. [21] reported that the NLR level did not show any significant differences compared with healthy volunteers. In contrast, Turkmen reported a higher NLR in ADPKD patients than in a control group [22], and the most important detection of a study by Akbas et al. [23] was that NLR ≥4.3 was related to a 1.5-fold increased risk of dialysis. In the present study, the NLR of ADPKD patients with both groups was found to be <3.

Although MPV is a routine parameter in hemogram tests, many clinicians do not take this simple laboratory test into consideration for CKD patients. MPV has been examined as an atherosclerotic/inflammatory biomarker in many conditions but there have been few reported analyses in kidney diseases. The relationship between CKD and platelet activation in patients with hemodialysis and glomerular disease has been evaluated in some studies in literature [24]. In patients with ADPKD, increased platelet activation may contribute to increased vascular injury in the arterial wall and cause arterial stiffness through inflammation mediators. Platelet activation induced by inflammation is thought to cause the cytokines release with consequent arterial intimal thickening. Therefore, it seems that in

ADPKD groups, high MPV levels may be associated with some perspectives on inflammation which is stimulated by underlying ADPKD. CKD is a pro-thrombogenic state, leading to increased rates of cardiovascular adverse outcomes [25]. In CKD, cardiovascular problems are associated with traditional (e.g.: Hypertension, diabetes mellitus, or age) and non-traditional risk factors such as oxidative stress, albuminuria, or inflammation, mostly originating from the CKD itself. At all stages of CKD, there is an elevated risk of thromboembolic and cardiovascular events. In a study by Ucar et al. [26], the relationship between MPV and GFR was evaluated in patients with stable acute coronary syndrome and these patients were reported to have lower GFR but higher MPV levels.

There were some limitations to this study, primarily that it was retrospective and cross-sectional in design with data from a single center. Therefore, the relatively small sample size was due to the limited selection of patients. The second limitation is that the study population only included Turkish patients, and it is, therefore, not known whether these results can be generalized to other ethnic populations. There is a need for larger cohort studies to be able to overcome study bias and to more exactly establish the association between the NLR and renal function decrease in CKD patients.

Conclusion

The results of this study demonstrated that the NLR and MPV level are independent risk factors for the progression of kidney disease in ADPKD patients with CKD Stages III–V. Thus, it can be recommended that NLR and MPV values are evaluated as a simple, easy, and economical method. NLR and MPV are routine tests in a complete blood count and can provide important information on the course and prognosis in many inflammatory conditions. However, to obtain more clinical benefit from NLR and MPV evaluation, there is a need for standardization of clinical laboratories and for more research on this subject.

Ethics Committee Approval: The Gulhane Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 09.10.2012, number: 1491-106-12/1648.4-4957).

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