

## Original Article

# Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in evaluation of the development of polycystic kidney disease

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**Abstract:** Background: It is well known that the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are available markers of systemic inflammation, and increased inflammation is along with progress of chronic kidney disease (CKD). The inflammation is risk factors for increased morbidity and mortality in autosomal dominant polycystic kidney disease (ADPKD). Therefore, we evaluate the association between the NLR and PLR level and unfavorable prognosis in ADPKD patients. Methods: A total of 65 ADPKD patients with preserved renal function, 50 ADPKD patients with end-stage renal disease (ESRD) need dialysis and 32 healthy volunteers were included. The level of NLR and PLR were recorded in different stages of ADPKD patients, and investigated if NLR and PLR could predict development of ADPKD. We also examined the expression of inflammation marker in renal interstitium of ADPKD patients. Results: The level of NLR ( $5.22 \pm 2.91$  vs  $3.38 \pm 2.03$ ,  $P < 0.001$ ) and PLR ( $203.8 \pm 121$  vs  $152.2 \pm 70.9$ ,  $P < 0.001$ ) were significantly higher in ADPKD patients with dialysis than ADPKD patients without dialysis, and the level of NLR ( $3.38 \pm 2.03$  vs  $1.42 \pm 0.58$ ,  $P < 0.0001$ ) and PLR ( $152.2 \pm 70.9$  vs  $92.7 \pm 26.9$ ,  $P < 0.0001$ ) were significantly higher in ADPKD patients without dialysis than in controls. Increased NLR over 4.3 and PLR over 174 were related to increase the events of dialysis. A cutoff value for NLR  $> 2.65$  and PLR  $> 130.2$  could predict development of renal function deficit (RFD) with the sensitivity 74.7%, 66.7% and specificity 96.9%, 96.9%, respectively. In addition, the CD45 staining significantly increased in ADPKD groups. Conclusions: We conclude that NLR and PLR are significantly higher in ADPKD patients with RFD and increase across worsening CKD stages. Our data suggest that lower NLR and PLR level may be potential and novel preventive and therapeutic options for ADPKD patients.

**Keywords:** Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, polycystic kidney disease, chronic kidney disease, prognosis

## Introduction

The leading cause of mortality in autosomal dominant polycystic kidney disease (ADPKD) is cardiovascular disease [1, 2]. Menon *et al.* demonstrated ADPKD patients with higher plasma level of CRP and interleukin (IL)-6, and the levels of inflammation markers were pronounced with worse kidney disease [3]. Although the CRP and IL-6 are recognized inflammation markers, however, detecting of CRP is still not as a routine examination in nephrology clinics worldwide [4]. Higher levels of inflammatory markers were reported to be associated with faster progression of chronic kidney disease (CKD) in patients, while total

WBC count has been reported to predict deterioration of the kidney function [5]. Neutrophil to lymphocyte ratio (NLR) can easily be calculated by the ratio of neutrophils to lymphocytes in peripheral blood. NLR was introduced as a novel inexpensive and readily available indicator that reflected the severity and extension of systemic inflammation and atherosclerosis, and predicted adverse clinical outcomes, and estimated survival in cardiac and noncardiac disorders including ESRD [6-8]. In recent years, neutrophilia and relative lymphopenia were shown to be an independent predictor of mortality in patients with post-myocardial infarction heart failure [9]. Moreover, several of studies showed NLR was introduced as a potential

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marker to determine inflammation in cardiac and end-stage renal disease (ESRD) [10, 11].

Although Turkmen reported that the ADPKD patients had higher levels of NLR compared with normal group [12], and platelet to lymphocyte ratio (PLR) was reported to be a simple and valuable prognostic marker for acute coronary syndrome in a few studies [13], limited data are available regarding assessment of NLR and PLR in relation to renal diseases, namely in ADPKD patients. The cause-and-effect relationship between ADPKD and NLR, PLR is still no clear. Therefore, the present study was designed to evaluate the NLR and PLR in relation to the progress of ADPKD patients.

### Materials and methods

#### Study population

A total of 115 ADPKD patients [mean (SD) age 50 (10.4) years, 55.7% were females], including 43.5% with end-stage renal disease (ESRD) and 56.5% with preserved renal function, and 32 healthy volunteers [mean (SD) age 47 (9.5) years, 56.3% were females] were included in this cross-sectional study. Exclusion criteria also included acute infections, cancer, steroid use,  $WBC > 10^3/mm^3$ , Platelet count  $< 1000$  mL. The study protocol was approved by the Medical Ethics Committee of Huazhong Science and Technology University. Written informed consent was obtained from all subjects included in the study. The diagnosis of ADPKD was defined by the ultrasonographic criteria described by Ravine *et al.* [14].

#### Study parameters

Data on patient demographics, BMI ( $kg/m^2$ ), Systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg in measurements, or being on antihypertensive medications were defined as arterial hypertension, complete blood count, blood biochemistry including uric acid (mg/dL), and lipid parameters including total cholesterol (mg/dL), LDL cholesterol (LDL-c; mg/dL) and triglyceride (mg/dL). ADPKD patients with preserved renal function were classified according to the level of glomerular filtration rate which was estimated according to the Modification of Diet in Renal Disease (MDRD) equation:  $eGFR (ml\cdot min^{-1}\cdot 1.73 m^{-2}) = 186 \times plasma Cr (mg/dl)^{-1.154} \times age$

(years)<sup>-0.203</sup> ( $\times 0.742$ , if female subjects), where the Cr indicates serum creatinine [15]. The renal function deficit (RFD) was defined as a  $eGFR \leq 89 ml\cdot min^{-1}\cdot 1.73 m^{-2}$  and classified as follows:  $eGFR \geq 90 ml\cdot min^{-1}\cdot 1.73 m^{-2}$  with stage 1;  $eGFR = 60-89.9 ml\cdot min^{-1}\cdot 1.73 m^{-2}$  with stage 2;  $eGFR = 30-59.9 ml\cdot min^{-1}\cdot 1.73 m^{-2}$  with stage 3;  $eGFR = 15-29.9 ml\cdot min^{-1}\cdot 1.73 m^{-2}$  with stage 4;  $eGFR < 15 ml\cdot min^{-1}\cdot 1.73 m^{-2}$  with stage 5. Patients in stages 2, 3, and 4 were considered as having RFD. Patients in stage 1 were considered as not having renal function deficit [16].

#### Complete blood count and definition of NLR, PLR

Whole blood cell counts were determined by using automated hematological analyzer Pentra 120 Retic (ABX, Montpellier, France). NLR was calculated as the ratio of the neutrophil and lymphocytes, PLR as the ratio of the platelet and lymphocyte according to the parameters of peripheral blood sample which were obtained at the time of patient's admission and before 24 hours next hemodialysis. ADPKD patients were separated into two groups according to mean value of NLR (group 1:  $PLR < 4.3$ , and group 2:  $NLR \geq 4.3$ ), or the mean value of PLR (group 1:  $PLR < 174$ , and group 2:  $PLR \geq 174$ ).

#### Immunohistochemistry analysis

A total of 6 polycystic kidney tissues from ADPKD patients performed windowing decompression in Tongji Hospital; control tissue was obtained from 6 patients who underwent nephrectomy for renal neoplasms. Paraffin-embedded formalin-fixed tissue was used to perform immunohistochemistry for CD45, which was one of the most abundant molecules expressed on the white blood cell surface. The primary antibody is the Rabbit polyclonal to CD45 (1:100 dilution, Abcam, ab10558). After washing in phosphate-buffered saline, the slides were incubated with goat anti-rabbit IgG antibody conjugated to horseradish peroxidase (DAKO, Tokyo, Japan) for 30 min at room temperature. The signal reaction was visualized with diaminobenzidine, and the slides were then counter-stained with hematoxylin stains.

#### Statistical analyses

Statistical analyses were carried out using the Statistical Package for Social Sciences for Windows version 16.0 (SPSS, Chicago, IL, USA).

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**Table 1.** Demographics, clinical characteristics and laboratory findings in study groups

Parameter	Control (n = 32)	ADPKD without dialysis (n = 65)	ADPKD with dialysis (n = 50)	P value
Age (years)	47 (22-60)	49.5 (22-72)	51 (23-69)	0.84
Gender (M/F)	18/14	35/30	26/24	0.68
BMI (kg/m <sup>2</sup> )	24.2 ± 2.5	23.7 ± 2.3	22.5 ± 2.7	0.54
Hypertension (n)	0	28	27	P < 0.0001
Uric acid (mg/dL)	3.8 (2.9-4.5)	4.0 (3.0-4.8)	4.0 (2.8-4.5)	0.75
Total cholesterol (mg/dL)	203 (160-250)	207 (169-255)	208 (160-248)	0.35
LDL cholesterol (mg/dL)	122.0 (95-140)	118.0 (85-142)	115 (84-139)	0.62
HDL cholesterol (mg/dL)	44.5 (32-58)	44.0 (30-56)	42.7 (29-55)	0.37
WBC count (10 <sup>3</sup> /mm <sup>3</sup> )	5.94 ± 1.26	5.16 ± 1.73	5.08 ± 1.56	0.016
Neutrophil count (10 <sup>3</sup> /mm <sup>3</sup> )	2.97 ± 0.86	3.43 ± 1.37	3.71 ± 1.40	0.069
Lymphocyte count (10 <sup>3</sup> /mm <sup>3</sup> )	2.25 ± 0.60	1.22 ± 0.58	0.87 ± 0.30	P < 0.001
Platelet count (10 <sup>3</sup> /mm <sup>3</sup> )	198.3 ± 47.9	167.6 ± 78.1	155.2 ± 81.6	0.039
NLR	1.42 ± 0.58	3.38 ± 2.03	5.22 ± 2.91	P < 0.0001
PLR	92.7 ± 26.9	152.2 ± 70.9	203.8 ± 121	P < 0.0001

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. Differences assessed by Chi-square test for categorical variables, and by Kruskal-Wallis test. Statistically significant if P < 0.05.

Abnormally distributed variables were expressed as median (range) and normally distributed variables were as mean ± SD. Differences were considered significant when P values were less than 0.05. The normality of distribution of all variables was tested using the Kolmogorov-Smirnov test. Dichotomous variables were compared using the Chi-square test. Statistical differences between parametric data of two groups were analyzed using the Student's t-test. The Mann Whitney U-test was used to compare nonparametric data. Linear associations between continuous parametric variables were assessed using the Pearson correlation test, while the Spearman correlation test was used to assess the correlation between non-parametric continuous and categorical variables. A receiver operator characteristics curve (ROC curve) analysis was performed to identify the sensitivity and specificity of NLR, PLR cut of value in prediction of RFD.

### Results

#### *Demographics, clinical characteristics and laboratory findings in study groups*

Demographic and clinical characteristics of patient and control groups were summarized in **Table 1**. 65 ADPKD patients with preserved renal function without dialysis and 50 ADPKD

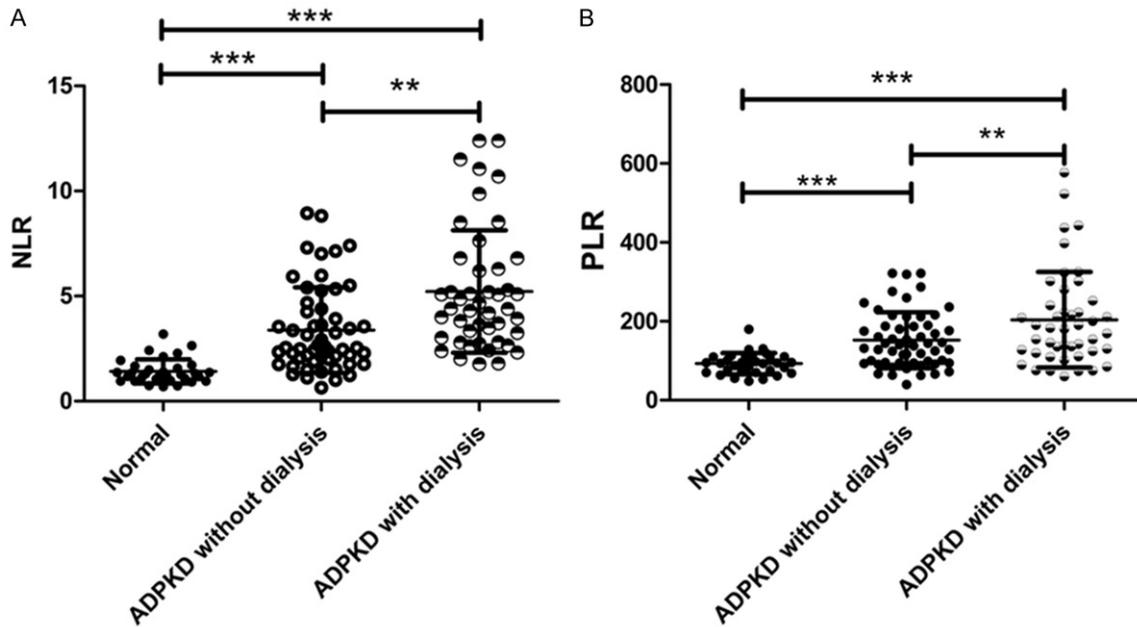
patients need conventional dialysis. Age, sex, body mass index, uric acid, total cholesterol, HDL cholesterol, and LDL cholesterol were similar between ADPKD patients and healthy subjects.

In patients with ADPKD, incidence of hypertension, neutrophil counts, NLR and PLR were significantly higher, while white blood cell count, lymphocyte count and platelet count were significantly lower compared to that in healthy subjects (**Table 1**).

#### *Evaluation of the relation between NLR, PLR and dialysis*

ADPKD patients without dialysis had a mean NLR of 3.38 ± 2.03, which was significantly lower than the ADPKD patients with dialysis had a mean NLR of 5.22 ± 2.91, both of the NLR significantly higher than normal group (**Figure 1A**). As far as the PLR, ADPKD patients with dialysis had an obvious high level of PLR (203.8 ± 121 vs 152.2 ± 70.9, P < 0.001), and whether the ADPKD patients with dialysis or not, the level of PLR significantly higher than normal group (**Figure 1B**). Furthermore, according to the mean of NLR, the ADPKD patients were separated into two groups (group 1: NLR < 4.3, and group 2: NLR ≥ 4.3), there were no statistically significant difference between two

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**Figure 1.** A. NLR, neutrophil-to-lymphocyte ratio; B. PLR, platelet-to-lymphocyte ratio between groups, ADPKD, auto-somal dominant polycystic kidney disease, \* $P < 0.05$ ; \*\* $P < 0.001$ ; \*\*\* $P < 0.0001$ .

**Table 2.** Demographic, clinic and laboratory features of ADPKD patients according to NLR and PLR groups

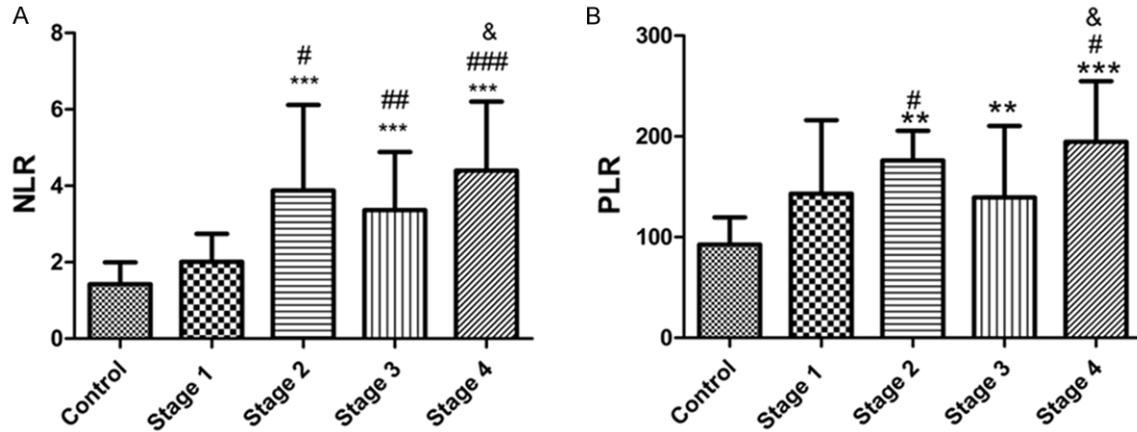
Parameter	All ADPKD (n = 115)	NLR < 4.3 (n = 66)	NLR $\geq$ 4.3 (n = 49)	P value	PLR < 174 (n = 65)	PLR $\geq$ 174 (n = 50)	P value
Age (years)	50 (22-72)	48.5 (22-72)	52 (25-67)	0.43	50.5 (22-72)	50 (25-64)	0.25
Gender (M/F)	64/51	36/30	28/21	0.78	32/33	26/24	0.77
BMI (kg/m <sup>2</sup> )	22.7 $\pm$ 3.5	23.8 $\pm$ 4.3	21.5 $\pm$ 2.0	0.57	22.3 $\pm$ 4.5	20.8 $\pm$ 3.9	0.32
Hypertension (n)	55	30	25	0.55	27	28	0.085
Uric acid (mg/dL)	4.0 (2.8-4.8)	3.9 (2.8-4.6)	4.1 (2.9-4.8)	0.39	3.8 (2.8-4.7)	4.1 (2.8-4.8)	0.26
Total cholesterol (mg/dL)	207.3 (160-255)	207 (169-255)	208 (160-248)	0.35	209 (160-239)	310 (165-255)	0.15
LDL cholesterol (mg/dL)	123 (84-142)	118 (85-142)	115 (84-139)	0.62	120 (87-142)	114 (84-140)	0.33
WBC count (10 <sup>3</sup> /mm <sup>3</sup> )	5.3 $\pm$ 2.0	4.9 $\pm$ 1.57	6.0 $\pm$ 2.4	0.019	5.05 $\pm$ 1.59	5.42 $\pm$ 1.90	0.49
Neutrophil count (10 <sup>3</sup> /mm <sup>3</sup> )	3.6 $\pm$ 1.4	3.1 $\pm$ 1.1	4.7 $\pm$ 2.1	< 0.0001	3.31 $\pm$ 1.20	4.07 $\pm$ 1.70	0.04
Lymphocyte count (10 <sup>3</sup> /mm <sup>3</sup> )	1.1 $\pm$ 0.5	1.3 $\pm$ 0.49	0.68 $\pm$ 0.22	< 0.0001	1.23 $\pm$ 0.52	0.79 $\pm$ 0.33	< 0.0001
Platelet count (10 <sup>3</sup> /mm <sup>3</sup> )	160.3 $\pm$ 78.8	157.9 $\pm$ 76.6	164.2 $\pm$ 83.1	0.85	133.3 $\pm$ 58.1	201.3 $\pm$ 89	< 0.0001
PLR/NLR	179.2 $\pm$ 112.4	130 $\pm$ 54.3	256.1 $\pm$ 135.1	< 0.0001	3.15 $\pm$ 1.76	5.71 $\pm$ 2.79	< 0.0001
ADPKD with dialysis	43.5%	37.9%	59.2%	0.024	44.4%	51.1%	0.49

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. Differences assessed by Chi-square test for categorical variables, and by Kruskal-Wallis test. Statistically significant if  $P < 0.05$ .

groups in terms of hypertension, uric acid, triglyceride, total cholesterol and Platelet count. However, ADPKD patients with  $NLR \geq 4.3$  had significantly higher WBC count, neutrophil count, PLR ( $130 \pm 54.3$  vs  $256.1 \pm 135.1$ ,  $P < 0.0001$ ), especially the incidence rate of dialysis (37.9% vs 59.2%,  $P = 0.024$ ) when compared to patients with  $NLR < 4.3$ , while the lymphocyte count was lower (Table 2). As well, the

ADPKD patients were separated into  $PLR < 174$  and  $PLR \geq 174$ , except the same of characteristics, however, patients with  $PLR \geq 174$  had higher neutrophil count, platelet count, NLR ( $3.15 \pm 1.76$  vs  $5.71 \pm 2.79$ ,  $P < 0.0001$ ), but the lymphocyte count was lower compared with patients with  $PLR < 174$ , and the incidence rate of dialysis had no significant difference (44.4% vs 51.1%,  $P = 0.49$ ) (Table 2).

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**Figure 2.** A. \*\*\*Control vs ADPKD-CS, Control vs ADPKD-DS, Control vs ADPKD-RFS, \*\*\* $P < 0.0001$ , respectively. #ADPKD-normal vs ADPKD-CS,  $P < 0.05$ ; ##ADPKD-normal vs ADPKD-DS,  $P < 0.01$ ; ###ADPKD-normal vs ADPKD-RFS,  $P < 0.0001$ . &ADPKD-DS vs ADPKD-RFS,  $P < 0.05$ . B. \*\*Control vs ADPKD-normal, Control vs ADPKD-CS, Control vs ADPKD-DS, \*\* $P < 0.01$ , respectively. \*\*\*Control vs ADPKD-RFS,  $P < 0.0001$ . #ADPKD-normal vs ADPKD-CS, ADPKD-normal vs ADPKD-RFS,  $P < 0.05$ , respectively. &ADPKD-DS vs ADPKD-RFS,  $P < 0.05$ . ADPKD, autosomal dominant polycystic kidney disease; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ADPKD-CS, autosomal dominant polycystic kidney disease-compensated stage; ADPKD-DS, autosomal dominant polycystic kidney disease-decompensated period; ADPKD-RFS, autosomal dominant polycystic kidney disease-renal failure stage.

**Table 3.** Bivariate correlation analysis of NLR and PLR to other parameters

Variable	NLR		PLR	
	r	P	r	P
Age (years)	0.07	0.48	-0.31	0.0026
Albumin (g/L)	-0.36	0.032	-0.41	0.04
Hb (g/L)	-0.2	0.05	-0.04	0.70
BUN ( $\mu\text{mol/L}$ )	0.34	0.0005	0.26	0.01
Total C (mmol/L)	0.28	0.31	0.25	0.62

Spearman correlation analysis; r correlation coefficient; NLR, Neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Total C = Total cholesterol, Hb, hemoglobin. BUN, blood urea nitrogen.

### Relationship between NLR, PLR and different RFD stages

In order to explore the relationship between NLR, PLR and different RFD stages, and eliminate the effects of dialysis on blood parameters blood, we only analyzed the stage 1, 2, 3, 4. Notably, we found NLR, PLR significantly increased across worsening CKD stages, the NLR and PLR of stage 2, 3, 4 significantly increased compared with control group and stage 1, and there was no significant difference between whether NLR or PLR of stage 1 and control group ( $P > 0.05$ ) (Figure 2). Therefore, we can draw a conclusion that the level of NLR

and PLR were trend to increase when ADPKD patients developed RFD stage.

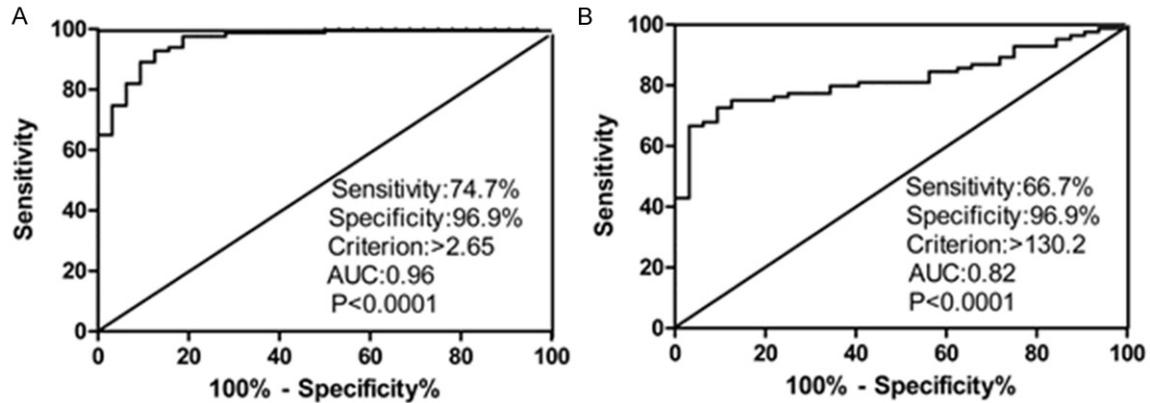
### Correlation analysis

In the bivariate correlation analysis, NLR, PLR were positively correlated with blood urea nitrogen (BUN) ( $r = 0.34$ ,  $P = 0.0005$ ,  $r = 0.26$ ,  $P = 0.01$ , respectively), but were negatively with albumin ( $r = -0.36$ ,  $P = 0.032$ ,  $r = -0.41$ ,  $P = 0.04$ , respectively) and the NLR was negatively with hemoglobin ( $r = -0.2$ ,  $P = 0.05$ ), however, PLR had no correlation with hemoglobin ( $r = -0.04$ ,  $P = 0.7$ ) (Table 3).

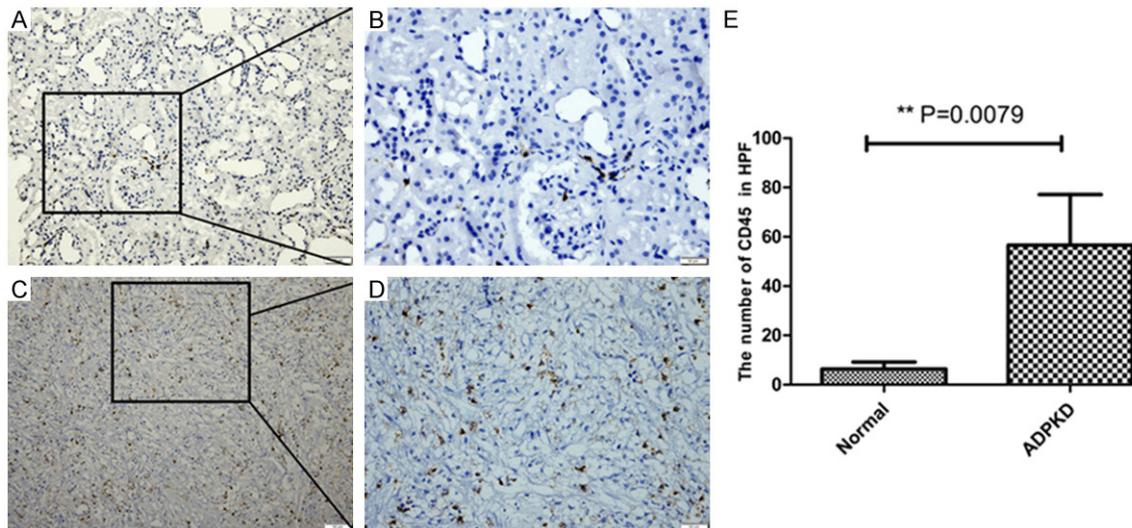
### Receiver operator characteristics analysis

A receiver operator characteristics curve analysis showed that the plot of the NLR and PLR levels yielded significant specificity and sensitivity for predicting the risk of RFD events in patients with ADPKD. When an ROC analysis was completed for the relationship between NLR and RFD events in patients with ADPKD, the results were AUC: 0.96,  $P < 0.0001$ ; cut-off value 2.65, confidence interval 83.8%-99.1%. A cutoff value for NLR of 2.65 could predict development of RFD events with 74.7% sensitivity and 96.9% specificity (Figure 3A), and analyzed for the relationship between PLR and RFD events in patients with ADPKD, the results

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**Figure 3.** A. Receiver operator curve (ROC) plot showing the sensitivity and specificity of NLR in ADPKD (AUC: 0.96,  $P < 0.0001$ ; a best cut-off value of 2.65 for NLR gave 74.7% sensitivity and 96.9% specificity). B. ROC plot showing the sensitivity and specificity of PLR in ADPKD (AUC: 0.82, a best cut-off value of 130.2 for PLR gave 66.7% sensitivity and 96.9% specificity  $P < 0.0001$ ). ADPKD, autosomal dominant polycystic kidney disease; NLR, Neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.



**Figure 4.** Positive expression of CD45 in normal renal tissue and ADPKD tissue. Representative immunohistochemistry images for the expression of CD45 are presented. A and B. Section is from the normal renal tissue. C and D. Section comes from the ADPKD tissue. E. Quantitative analysis of the positive CD45 in high power field, data are mean  $\pm$  SD of 10 non-overlapping fields from 6 normal renal tissue and 6 ADPKD patients, Normal vs ADPKD,  $*P = 0.0079$ . Scale bar = 50  $\mu$ m. ADPKD, autosomal dominant polycystic kidney disease; HPF, high power field.

were AUC: 0.82,  $P < 0.0001$ ; cut-off value 130.2, confidence interval 78.6%-85.8%. A cut-off value for PLR of 130.2 could predict development of RFD events with 66.7% sensitivity and 96.9% specificity (**Figure 3B**).

### Immunohistochemical analysis

Furthermore, we analyzed the inflammatory characteristic of ADPKD tissue by immunohistochemical means. CD45 known as leuko-

cyte common antigen (LCA), which was one of inflammatory cell markers [17]. We found that the ADPKD patients with CD45 positive cells were obviously higher than the control group ( $6.4 \pm 2.8$  vs  $56.6 \pm 20.6$ ,  $P = 0.0079$ ) (**Figure 4**).

### Discussion

In the present study, we found that the level of neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in ADPKD patients

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were related to poor prognosis. The main findings of this study were: (1) NLR and PLR were significantly increased in the ADPKD patients with dialysis or not; (2) NLR and PLR significantly increased across worsening RFD stages 2-4; (3) NLR and PLR could predict the occurrence of RFD events, and showed a significant positive correlation with blood urea nitrogen, while a significant negative with albumin; (4) the inflammatory cell marker CD45 significantly expressed on the ADPKD capsule wall tissue.

Several studies found that the level of NLR or PLR was increased in patients with chronic kidney disease or end-stage renal disease (ESRD) [11, 18, 19]. However, whether the level of NLR was boosted in ADPKD patients, it was remain controversy at present. Turkmen et al. [12] reported that the ADPKD patients had higher levels of NLR than healthy group, but Gul et al. revealed that the NLR level had no significant differences compared with healthy volunteers [20]. We found higher NLR levels in ADPKD patients than that in controls which were in conformity with the Turkmen study corresponding data [19], and our also found that the PLR level also increased in ADPKD patients as compared with control. Especially, both NLR and PLR were steadily increased whatever the ADPKD patients without dialysis or with dialysis, and the ADPKD patients with dialysis had higher NLR and PLR than without dialysis patients, which agreement with the corresponding data in the literature [19].

The most important finding of this study was that  $NLR \geq 4.3$  was associated with a 1.5-fold increased risk of dialysis, and when  $PLR \geq 174$ , the rate of dialysis increased significantly. Previous studies had shown NLR and PLR utility in predicting unfavorable progression and prognosis [21]. Furthermore, previous studies had been suggested that higher levels of inflammatory markers were associated with faster progression of chronic kidney disease (CKD) in patients [5, 22, 23]. Thereby, NLR may be considered as a marker for evaluating the systemic inflammation [24].

This study indicated that white blood cell count, absolute neutrophil count and NLR, PLR were significantly higher, but absolute lymphocyte count and absolute platelet count were significantly lower in patients with ADPKD compared to healthy subjects. These data were in accor-

dance with previous reports suggesting increased inflammatory markers in ADPKD [3, 12, 25]. It is known that lymphocytopenia is a common finding in chronic inflammatory conditions and lymphocyte count reduction may be an early marker of physiologic stress and systemic inflammation response [26]. Moreover, we found the NLR, PLR level of ADPKD patients with RFD were significant higher than healthy objects and ADPKD patients with normal glomerular filtration rate, and even ADPKD patients with CKD stage 4 had higher NLR, PLR level than the CKD stage 3. Menon et al. [3] showed that ADPKD eGFR of 25 to 60 group had higher levels of C-reactive protein and IL-6 than controls, normotensive ADPKD with eGFR of  $> 60$ , and hypertensive ADPKD with eGFR of  $> 60$ . Inflammation was evident early in ADPKD even with preserved kidney function [3, 27].

The NLR and PLR have emerged as simple, inexpensive and useful markers of inflammation related to various renal diseases, inflammatory and cardiovascular [11, 19, 28]. Previous studies have demonstrated that an association between the NLR and PLR and worsening renal function in diabetic patients or hypertensive patients [21, 29, 30]. In the present study, we found that ADPKD patients with NLR values greater than 2.65 were found to be associated with renal function deficit with a higher sensitivity and specificity (74.7%, 96.9%, respectively), and ADPKD patients with PLR values greater than 130.2 were more feasible to predict renal function deficit (66.7%, 96.9%, respectively).

In addition, we found CD45-positive was abundant in the renal interstitium of ADPKD patients, which were significantly higher than the normal renal tissue. Previous studies have shown that macrophages and other inflammatory cells constitute the interstitial infiltrates in human and animal models of polycystic kidney diseases. Karihaloo et al. [31] shown that higher number of F4/80+ CD45+ Cd11c- macrophages presented in mice model of polycystic kidney disease (PKD). Recent studies in animal models demonstrated that the chronic interstitial inflammation in PKD contributed to cyst development and renal impairment [32]. Ibrahim et al. [33] found that CD 45-positive lymphocytes were dense in cyst of human with ADPKD. Several studies indicated that macrophages migrated to cystic areas and contribute

to promote cyst cell proliferation, cyst growth, and fibrosis [34, 35]. Therefore, interruption of macrophages and other inflammatory cells of homing and proliferative signals could alleviate the disadvantageous progression of the ADPKD.

The present study has several limitations. First, this study has a retrospective cross-sectional design with a single-center data. Due to the retrospective retrieval of the patient data, we could not execute the statistical significance concerning the correlation of NLR, PLR and other inflammatory markers (i.e., erythrocyte sedimentation rate, IL-6 and C-reactive protein). Second, the cross-sectional design made it impossible to establish any causes and effect relationships. Third, using NLR, PLR in a single preoperative blood sample does not allow for assessing the stability of this variable over time. Finally, the cyst tissue from ADPKD patients is relatively small, which limits us to analyze the correlation between the inflammatory score and clinical parameters. Nevertheless, despite these certain limitations, given the paucity of the solid information available on this area, our findings represent a valuable contribution to the literature.

In conclusion, this study demonstrated that NLR and PLR were significantly higher in ADPKD patients with renal insufficiency, and we found that NLR and PLR significantly increased across worsening CKD stages. Higher level of NLR, PLR was easier to develop hemodialysis. The positive inflammatory markers in cyst tissue from ADPKD patients significantly increased compared to healthy adults. Herein, as NLR, PLR are readily available in routine blood count analysis, they may be used as a cost-effective predictor association with ADPKD poor progression. Our data suggested that lower NLR and PLR level in circulation, might be potential and novel preventive and therapeutic options for patients with ADPKD.

### Disclosure of conflict of interest

None.

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### References

- [1] Heffernan KS, Kuvin JT, Sarnak MJ, Perrone RD, Miskulin DC, Rudym D, Chandra P, Karas RH and Menon V. Peripheral augmentation index and vascular inflammation in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2011; 26: 2515-2521.
- [2] Ecker T and Schrier RW. Cardiovascular abnormalities in autosomal-dominant polycystic kidney disease. *Nat Rev Nephrol* 2009; 5: 221-228.
- [3] Menon V, Rudym D, Chandra P, Miskulin D, Perrone R and Sarnak M. Inflammation, oxidative stress, and insulin resistance in polycystic kidney disease. *Clin J Am Soc Nephrol* 2011; 6: 7-13.
- [4] Meuwese CL, Stenvinkel P, Dekker FW and Carrero JJ. Monitoring of inflammation in patients on dialysis: forewarned is forearmed. *Nat Rev Nephrol* 2011; 7: 166-176.
- [5] Tonelli M, Sacks F, Pfeffer M, Jhangri GS and Curhan G. Biomarkers of inflammation and progression of chronic kidney disease. *Kidney Int* 2005; 68: 237-245.
- [6] Sari I, Sunbul M, Mammadov C, Durmus E, Bozbay M, Kivrak T and Gerin F. Relation of neutrophil to lymphocyte and platelet to lymphocyte ratio with coronary artery disease severity in patients undergoing coronary angiography. *Kardiol Pol* 2015; 73: 1310-6.
- [7] Yu XY, Li XS, Li Y, Liu T and Wang RT. Neutrophil-lymphocyte ratio is associated with arterial stiffness in postmenopausal women with osteoporosis. *Arch Gerontol Geriatr* 2015; 61: 76-80.
- [8] Balta S, Celik T, Mikhailidis DP, Ozturk C, Demirkol S, Aparci M and Iyisoy A. The Relation Between Atherosclerosis and the Neutrophil-Lymphocyte Ratio. *Clin Appl Thromb Hemost* 2016; 22: 405-11.
- [9] Arruda-Olson AM, Reeder GS, Bell MR, Weston SA and Roger VL. Neutrophilia predicts death and heart failure after myocardial infarction: a community-based study. *Circ Cardiovasc Qual Outcomes* 2009; 2: 656-662.
- [10] Tamhane UU, Aneja S, Montgomery D, Rogers EK, Eagle KA and Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol* 2008; 102: 653-657.
- [11] Ahabap E, Sakaci T, Kara E, Sahutoglu T, Koc Y, Basturk T, Sevinc M, Akgol C, Kayalar AO, Ucar ZA, Bayraktar F and Unsal A. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in evaluation of inflammation in end-stage renal disease. *Clin Nephrol* 2016; 85: 199-208.

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- [12] Turkmen K, Tufan F, Selcuk E, Akpınar T, Oflaz H and Ecder T. Neutrophil-to-lymphocyte ratio, insulin resistance, and endothelial dysfunction in patients with autosomal dominant polycystic kidney disease. *Indian J Nephrol* 2013; 23: 34-40.
- [13] Akkaya E, Gul M and Ugur M. Platelet to lymphocyte ratio: a simple and valuable prognostic marker for acute coronary syndrome. *Int J Cardiol* 2014; 177: 597-598.
- [14] Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P and Danks DM. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. *Lancet* 1994; 343: 824-827.
- [15] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW and Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; 145: 247-254.
- [16] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39: S1-266.
- [17] Torkko KC, Wilson RS, Smith EE, Kusek JW, van Bokhoven A and Lucia MS. Prostate Biopsy Markers of Inflammation are Associated with Risk of Clinical Progression of Benign Prostatic Hyperplasia: Findings from the MTOPS Study. *J Urol* 2015; 194: 454-461.
- [18] Solak Y, Yilmaz MI, Sonmez A, Saglam M, Cakir E, Unal HU, Gok M, Caglar K, Oguz Y, Yenicesu M, Karaman M, Ay SA, Gaipov A, Turk S, Vural A and Carrero JJ. Neutrophil to lymphocyte ratio independently predicts cardiovascular events in patients with chronic kidney disease. *Clin Exp Nephrol* 2013; 17: 532-540.
- [19] Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, Demirtas L, Turk S and Tonbul HZ. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. *Hemodial Int* 2013; 17: 391-396.
- [20] Gul CB, Yildiz A, Ersoy A, Kahvecioglu S, Asiltas B, Yildirim F, Ermurat S, Sag S, Oruc A, Gullulu S and Gullulu M. Correlation between arterial stiffness and inflammatory markers in autosomal dominant polycystic kidney disease patients with preserved renal function. *Int Urol Nephrol* 2015; 47: 1187-1194.
- [21] Akbas EM, Demirtas L, Ozcicek A, Timuroglu A, Bakirci EM, Hamur H, Ozcicek F and Turkmen K. Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. *Int J Clin Exp Med* 2014; 7: 1794-1801.
- [22] Rees AJ. The role of infiltrating leukocytes in progressive renal disease: implications for therapy. *Nat Clin Pract Nephrol* 2006; 2: 348-349.
- [23] Turkmen K. Platelet-to-Lymphocyte Ratio: One of the novel and valuable platelet indices in hemodialysis patients. *Hemodial Int* 2013; 17: 670.
- [24] Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, Meghani M, Akhtar M and Costantino T. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Rev Cardiovasc Ther* 2013; 11: 55-59.
- [25] Chen L, Zhou X, Fan LX, Yao Y, Swenson-Fields KI, Gadjeva M, Wallace DP, Peters DJ, Yu A, Grantham JJ and Li X. Macrophage migration inhibitory factor promotes cyst growth in polycystic kidney disease. *J Clin Invest* 2015; 125: 2399-2412.
- [26] Ommen SR, Gibbons RJ, Hodge DO and Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. *Am J Cardiol* 1997; 79: 812-814.
- [27] Kocyigit I, Eroglu E, Orscelik O, Unal A, Gungor O, Ozturk F, Karakukcu C, Imamoglu H, Sipahioglu MH, Tokgoz B and Oymak O. Pentraxin 3 as a novel bio-marker of inflammation and endothelial dysfunction in autosomal dominant polycystic kidney disease. *J Nephrol* 2014; 27: 181-186.
- [28] Ergelen M, Uyarel H, Altay S, Kul S, Ayhan E, Isik T, Kemaloglu T, Gul M, Sonmez O, Erdogan E and Turfan M. Predictive value of elevated neutrophil to lymphocyte ratio in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. *Clin Appl Thromb Hemost* 2014; 20: 427-432.
- [29] Azab B, Daoud J, Naeem FB, Nasr R, Ross J, Ghimire P, Siddiqui A, Azzi N, Rihana N, Abdallah M, Azzi N, Patel P, Kleiner M and El-Sayegh S. Neutrophil-to-lymphocyte ratio as a predictor of worsening renal function in diabetic patients (3-year follow-up study). *Ren Fail* 2012; 34: 571-576.
- [30] Braga FL, Arruda IK, Diniz Ada S, Cabral PC, Lemos Mda C, Braga MD and Chaves Hde C Jr. Renal dysfunction and inflammatory markers in hypertensive patients seen in a university hospital. *Arq Bras Cardiol* 2013; 100: 538-545.
- [31] Karihaloo A, Korashy F, Huen SC, Lee Y, Merrick D, Caplan MJ, Somlo S and Cantley LG. Macrophages promote cyst growth in polycystic kidney disease. *J Am Soc Nephrol* 2011; 22: 1809-1814.
- [32] Grantham JJ, Mulamalla S and Swenson-Fields KI. Why kidneys fail in autosomal dominant

## Neutrophil-lymphocyte ratio and polycystic kidney disease

- polycystic kidney disease. *Nat Rev Nephrol* 2011; 7: 556-566.
- [33] Ibrahim S. Increased apoptosis and proliferative capacity are early events in cyst formation in autosomal-dominant, polycystic kidney disease. *ScientificWorldJournal* 2007; 7: 1757-1767.
- [34] Swenson-Fields KI, Vivian CJ, Salah SM, Peda JD, Davis BM, van Rooijen N, Wallace DP and Fields TA. Macrophages promote polycystic kidney disease progression. *Kidney Int* 2013; 83: 855-864.
- [35] Ta MH, Harris DC and Rangan GK. Role of interstitial inflammation in the pathogenesis of polycystic kidney disease. *Nephrology (Carlton)* 2013; 18: 317-330.