The relationship between mean platelet volume and neutrophil/lymphocyte ratio with inflammation and proteinuria in chronic kidney disease

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Background
Mean platelet volume (MPV) and neutrophil/lymphocyte ratio (NLR) are particularly useful as inflammatory markers. The goal of this study was to see if there was a correlation of MPV and NLR with inflammatory markers in patients with chronic kidney disease (CKD) stages II, III, IV, and V.

Patients and methods
We conducted a case–control study with patients with established CKD who were recruited from the Internal Medicine Department's nephrology unit. The participants in this study comprised 120 patients with CKD at various stages and 30 healthy volunteers.

Results
Patients with CKD had a significantly higher NLR than the control group (2.94 ± 0.62 vs. 1.76 ± 0.13, respectively, $P = 0.001$). The average MPV, on the contrary, did not change significantly between the groups ($P = 0.18$). There was no statistically significant difference between stages in terms of MPV, although NLR was much lower in stage II patients than in other stages. NLR had a positive relationship with fibrinogen ($r = 0.23$; $P = 0.001$), C-reactive protein ($r = 0.28$; $P = 0.001$), creatinine ($r = 0.24$; $P = 0.001$), urea ($r = 0.21$; $P = 0.001$), uric acid ($r = 0.11$; $P = 0.05$), and proteinuria ($r = 0.31$; $P = 0.004$).

Conclusion
NLR (rather than MPV) may be employed as a biomarker of inflammation, a risk factor for proteinuria, and a practical predictor of CKD prognosis.

Keywords:
chronic kidney disease, mean platelet volume, neutrophil/lymphocyte ratio, proteinuria

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Introduction

Chronic kidney disease (CKD) is a major global concern, with an increasing incidence. It is a long-term inflammatory condition connected to an increased risk of cardiovascular disease (CVD) and chronic renal failure [1]. In Egypt, the annual frequency of CKD is determined to be about 74 per million, and the overall prevalence of patients undergoing dialysis is 264 per million [2]. Early identification of CKD is crucial because it helps reduce CKD-related comorbidities such as atherosclerosis, which is the primary cause of morbidity and mortality in patients with CKD [3].

Although several pathogenic processes have been linked to the development of CKD, persistent, low-grade inflammation appears to play a key role in the disease's pathogenesis. The specific cause of chronic inflammation in CKD is unknown at this time; nevertheless, it is widely assumed that defective monocytes and endothelial cells are the primary sources of proinflammatory indicators in CKD [4]. Notably, the severity of the inflammatory process in the context of CKD is linked to decreased glomerular filtration rate (GFR), the requirement for dialysis, and even mortality [5].

Mean platelet volume (MPV) and neutrophil/lymphocyte ratio (NLR) are particularly useful as inflammatory signals as they may be detected with a simple blood count. A significant link has been shown in several studies between high MPV and acute myocardial infarction and ischemic stroke [6]. In addition, recent research has found that both MPV and NLR are linked to the severity and progression of CKD [7,8].

Patients and methods

We confirm that the current study complied with the Helsinki Declaration's ethical standards. The protocol for the study was approved by the Assiut University

Hospital's Institutional Review Board with approval number 17101058. All eligible patients signed written informed consent forms.

Adult patients (aged 18–65 years old) with established diagnosis of CKD (stage II–V) were included if they had a GFR of less than 15–89 ml/min/1.73 m2 and a BMI of less than 35 kg/m2. In addition, we included age-matched and sex-matched healthy volunteers. We excluded diabetic patients, patients with malignancy, patients with active infection, patients with history of ischemic heart disease, and patients on steroids and immunosuppressive drugs.

Data collection

The following data were collected from all eligible participants: complete medical history; a comprehensive clinical examination; estimated GFR, which was calculated using the modified modification of diet in renal disease formula [estimated GFR = 186.3×(serum creatinine) [–1.154])×(age [–0.203])×(0.742 if ♀)×(1.21 if African American)] [9]; complete blood count; NLR; MPV; renal function tests; liver function tests; 24-h urine protein; lipid profile; and urine analysis. In addition, the findings of the echocardiography were collected.

MPV is a machine-calculated measurement of the average size of platelets found in blood in routine blood test. Normal value for MPV is 7.2–11.7 fl [10]. NLR is the ratio of absolute neutrophil count to the absolute lymphocyte count, and its normal values are between 0.78 and 3.58 [11].

Statistical analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range), whereas nominal data were expressed in the form of frequency (percentage). χ^2 test was used to compare the nominal data of different groups in the study, whereas Student *t* test was used to compare means of two different groups. Spearman correlation was used to determine the correlation between different continuous variables in the current study. A multivariate regression analysis was done to assess significant predictors of CKD. In addition, a receiver operating characteristic curve was drawn to assess the sensitivity and specificity of studied markers in the prediction of CKD. *P* value was significant if less than 0.05.

Results

The demographic data of all studied groups are shown in Table 1, where the mean age of patients with CKD was 42.43 ± 12.96 years. Patients with CKD had significantly higher systolic blood pressure (SBP), diastolic blood pressure, and mean arterial blood pressure. NLR, C-reactive protein (CRP), uric acid, and fibrinogen were higher in patients with CKD than controls, with *P* value less than 0.001. The mean level of MPV was insignificant lower in patients with CKD than controls, with *P* = 0.18. Table 2 shows that the mean SBP was significantly higher among patients with stage IV than stage II, with *P* value less than 0.001. Table 3 shows that the main hemoglobin level was decreased with advanced CKD stages; the lowest level was found in stage V. On the contrary, CRP, uric acid, and fibrinogen were significantly higher in patients with CKD than controls ($P < 0.001$). Fig. 1 shows the main clinical manifestations of studied patients in different CKD stages included gastrointestinal tract manifestations, pruritus, edema, bone pain, pleural effusion, and pericarditis presented in 58 (48.3%), 20 (16.7%), 49 (40.8%), 50 (41.7%), 21 (17.5%), and

Table 1 The demographic and laboratory parameters of the studied groups

Parameters	CKD group (*n*=120)	Control group (*n*=30)	*P*
Age (years)	42.43±12.96	37.32±13.74	0.06
BMI (kg/m^2)	27.33±3.93	26.50±5.05	0.33
DBP (mmHg)	85.01±10.45	76.33±7.42	<0.001
SBP (mmHg)	142.17±14.33	124.80±10.49	<0.001
MBP (mmHg)	103.86±10.95	92.32±6.98	<0.001
CBC			
Hemoglobin (g/dl)	9.22±1.23	13.01±1.23	<0.001
Platelets (×10^9/l)	260.96±85.26	261.43±28.71	0.97
MPV (g/dl)	8.68±0.94	8.32±0.53	0.04
NLR	2.94±0.62	1.76±0.13	<0.001
CRP (mg/l)	10.06±9.05	1.31±0.48	<0.0001
Fibrinogen	3.81±1.36	2.63±0.40	<0.001
KFTs			
Urea (mg/dl)	106.78±49.65	26.94±3.32	<0.001
Creatinine (mg/dl)	3.91±2.23	0.73±0.14	<0.001
Uric acid (mg/dl)	11.11±3.87	4.74±0.56	<0.001
Urine analysis			
Pus cells	117 (97.5)	2 (6.7)	<0.001
Cast	62 (51.7)	10 (33.3)	<0.001
24 h-urine protein (g/day)	701.45±156.98	70.87±13.56	<0.001
LFTs			
Albumin (g/dl)	3.25±0.93	4.80±0.31	<0.001
Lipid profile			
HDL (mg/dl)	47.48±10.35	56.86±5.49	<0.001
LDL (mg/dl)	177.20±46.34	109.83±12.94	<0.001
Cholesterol (mg/dl)	264.34±62.46	184.46±15.45	<0.001
TG (mg/dl)	221.14±73.37	134.06±19.49	<0.001
VLDL (mg/dl)	44.23±14.64	25.90±4.16	<0.001

Data are expressed as *n* (%) and mean±SD. CBC, complete blood count; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; KFT, kidney function test; LDL, low-density lipoprotein; LFT, liver function test; MBP, mean arterial blood pressure; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; SBP, systolic blood pressure; TG, triglycerides; VLDL, very low-density lipoprotein. *P*<0.05.

one (0.80), respectively. Table 4 shows that patients with stage V CKD had a significantly higher frequency of left ventricular hypertrophy (46.7%), dilated left atrium (6.7%), pericardial effusion (13.3%), and diastolic dysfunction (30%) in comparison with other stages.

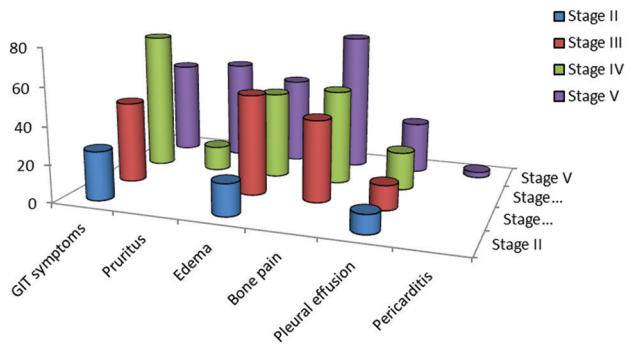
Notably, the diastolic dysfunction had statistically significant differences regarding mean levels of MPV and NLR in comparison with those without diastolic dysfunction. However, left ventricular hypertrophy had insignificant differences regarding MPV and NLR in comparison with those without left ventricular hypertrophy (Table 5).

At cutoff point more than 1.98, the NLR had 95% sensitivity and 100% specificity for prediction of CKD, with an area under curve of 0.97, whereas at a cutoff point more than 8.8 MPV had 47.5% sensitivity and 80% specificity for prediction of CKD, with an area under curve of 0.63 (Fig. 2).

Correlation between studied markers and other variables is shown in Table 6. The MPV level significantly correlated with CRP (r=–0.32; P < 0.001). However, NLR had a positive correlation with fibrinogen (r = 0.23; P < 0.001), CRP (r = 0.28; P < 0.001), creatinine (r = 0.24; P < 0.001), urea (r = 0.21; P < 0.001), uric acid (r = 0.11; P = 0.05), and proteinuria (r = 0.31; P = 0.004).

The multivariate regression analysis demonstrated that NLR more than 1.98 was an independent predictor of CKD with odds ratio of 2.11 (95% confidence interval 1.09–4.56; P < 0.001) (Table 7).

Figure 1

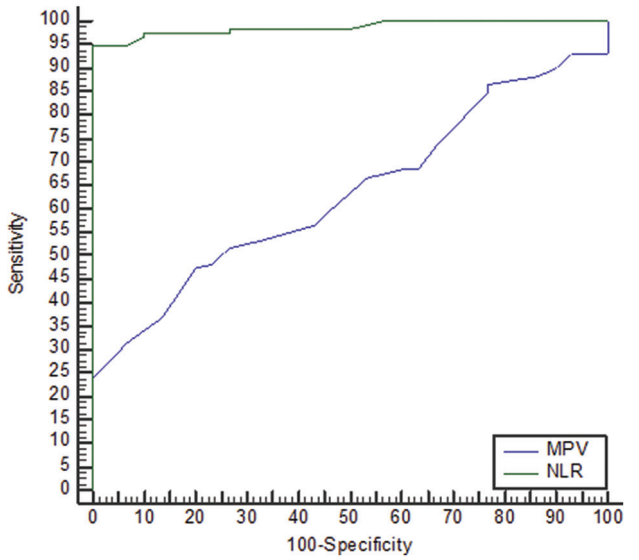


The main clinical data of studied patients based on stage of CKD. CKD, chronic kidney disease.

Discussion

Early detection and treatment of CKD can help to lessen the negative consequences of the disease and potentially stop it from progressing [3]. Inflammation develops in the early stages of CKD, when neutrophil numbers rise but lymphocyte counts fall [12]. The NLR is a new, inexpensive, and readily available predictor of inflammation and atherosclerosis that can be used to predict clinical outcomes [13].

Figure 2



The ROC curve for diagnostic accuracy of MPV and NLR for prediction of CKD. CKD, chronic kidney disease; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; ROC, receiver operating characteristic.

Table 2 Demographic and clinical data of studied patients in different chronic kidney disease stages

Parameters	Stage II (n=30) GFR=60-89 ml/min	Stage III (n=30) GFR=30-59 ml/min	Stage IV (n=30) GFR=15-29 ml/min	Stage V (n=30) GFR <15 ml/min	P1	P2	P3	P4	P5	P6
Age (years)	33.86±12.59	38.80±13.66	46.40±10.48	50.66±7.65	0.33	<0.001	<0.001	0.05	<0.001	0.46
Sex										
Male	14 (46.70)	9 (30)	16 (53.3)	16 (53.3)	0.98	0.24	0.24	0.09	0.09	0.65
Female	16 (53.3)	21 (70)	14 (46.70)	14 (46.70)						
BMI (kg/m^2)	26.90±2.65	27.40±4.23	28.18±4.64	26.79±3.96	0.94	0.59	0.99	0.89	0.91	0.52
DBP (mmHg)	80.66±8.68	88.33±9.85	86±11.91	85±10.08	0.02	0.18	0.35	0.81	0.58	0.98
SBP (mmHg)	136.67±12.68	141.67±12.3	148.66±15.25	141.67±14.87	0.50	<0.001	0.50	0.21	0.99	0.21
MBP (mmHg)	99.14±9.02	105.93±9.74	106.68±12.52	103.70±11.13	0.07	0.03	0.35	0.99	0.85	0.70

Data are expressed as n (%) and mean±SD. DBP, diastolic blood pressure; GFR, glomerular filtration rate; MBP, mean arterial blood pressure; SBP, systolic blood pressure. P<0.05. P1 compared between stage II and stage III. P2 compared between stage II and stage IV. P3 compared between stage II and stage V. P4 compared between stage III and stage IV. P5 compared between stage III and stage V. P6 compared between stage IV and stage V.

Table 3 The main laboratory investigations of studied patients in different chronic kidney disease stages

Parameters	Stage II (*n*=30)	Stage III (*n*=30)	Stage IV (*n*=30)	Stage V (*n*=30)	*P*1	*P*2	*P*3	*P*4	*P*5	*P*6
CBC										
Hb (g/dl)	10.11±0.79	9.22±0.95	8.85±1.22	8.71±1.41	0.01	<0.001	<0.001	0.56	0.29	0.96
Platelet (×10^9/l)	255.73±96.29	283.8±99.08	256.9±69.87	247.36±71.27	0.09	0.06	0.67	0.17	0.32	0.54
MPV (g/dl)	8.34±0.89	8.36±0.77	8.40±1.06	8.34±1.01	0.99	0.50	0.99	0.44	0.99	0.35
NLR	2.55±0.47	3.01±0.59	3.14±0.62	3.07±0.64	0.01	<0.001	<0.001	0.78	0.95	0.97
CRP (mg/l)	8.05±3.42	8.83±3.12	9.98±2.36	14.33±4.46	0.18	0.03	<0.001	0.04	<0.001	<0.001
Fibrinogen (g/l)	3.25±1.01	3.88±1.03	4.49±1.75	4.54±1.20	0.19	<0.001	0.01	0.02	<0.001	0.05
KFTs										
Urea (mg/dl)	72.16±18.96	88.7±17.67	95.78±17.89	180.5±38.32	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Creatinine (mg/dl)	1.63±0.07	2.50±0.36	4.31±0.79	7.19±38.32	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Uric acid (mg/dl)	7.93±1.47	7.66±2.01	7.87±2.22	7.98±3.01	0.98	0.09	0.11	0.32	0.19	0.76
Urine analysis										
Pus cells	30 (100)	30 (100)	29 (96.7)	28 (93.3)	-	0.09	0.08	0.09	0.08	0.16
Cast	26 (86.7)	28 (93.3)	8 (26.7)	0	0.05	<0.001	<0.001	<0.001	<0.001	<0.001
24 h-urine protein	655.56±122.45	1024.45±389.5	1325.67±334.56	1012.56±545.67	0.04	<0.001	<0.001	0.19	0.01	0.01
LFTs										
Albumin (g/dl)	3.37±1.54	2.92±1.04	2.75±0.81	2.47±0.64	0.15	0.09	<0.001	0.13	0.01	0.08
Lipid profile										
HDL (mg/dl)	52.73±10.48	50.50±10.50	43.46±8.81	43.23±8.34	0.89	0.02	0.01	<0.001	<0.001	0.99
LDL (mg/dl)	168.93±36.89	160.90±56.77	174.63±52.08	184.33±32.21	0.08	0.62	0.98	0.95	0.19	0.84
Chol. (mg/dl)	245.23±48.39	254.26±68.15	255.83±74.93	297.03±45.68	0.04	0.06	0.03	0.99	0.99	0.99
TG (mg/dl)	190.43±69.09	201.3±70.90	238.2±62.1	252.63 76.44	0.95	0.18	0.02	0.06	<0.001	0.85
VLDL (mg/dl)	38.13±13.73	40.44±14.14	47.64±12.42	50.52±15.28	0.95	0.18	0.03	0.07	<0.001	0.65

CBC, complete blood count; CRP, C-reactive protein; HDL, high-density lipoprotein; KFT, kidney function test; LDL, low-density lipoprotein; LFT, liver function test; MPV, mean platelet volume; VLDL, very low-density lipoprotein.

Table 4 Echocardiographic findings based on stages of chronic kidney disease

Parameters	Stage II (*n*=30)	Stage III (*n*=30)	Stage IV (*n*=30)	Stage V (*n*=30)	*P*1	*P*2	*P*3	*P*4	*P*5	*P*6
EF (%)	67.2±3.57	65.50±5.09	59.80±9.55	60.4±11.1	0.09	0.22	0.03	0.07	0.04	0.05
LV dimension										
Normal	30 (100)	28 (93.3)	25 (83.3)	19 (63.3)						
Hypertrophy	0	1 (3.3)	4 (13.3)	9 (30)	0.45	0.01	0.01	0.07	0.02	0.01
Dilated	0	0	1 (3.3)	2 (6.7)						
Concentric	0	1 (3.3)	0	0						
Contractility										
Good	30 (100)	30 (100)	28 (93.3)	23 (87.3)	0.45	0.18	0.09	0.13	0.23	0.40
Fair	0	0	2 (16.7)	7 (13.7)						
Dilated left atrium	0	0	6 (20)	11 (36.7)	-	0.03	0.01	0.03	0.01	0.03
Pericardial effusion	0	0	2 (6.7)	4 (13.3)	-	0.06	0.01	0.06	0.01	0.05
Diastolic dysfunction	1 (3.3)	2 (6.7)	8 (26.7)	9 (30)	0.06	0.01	0.01	0.01	0.01	0.98

Table 5 The mean level of mean platelet volume and neutrophil/lymphocyte ratio in patient groups based on diastolic dysfunction and left ventricular hypertrophy in echocardiography

Parameters	NLR	*P*	MPV	*P*
With diastolic dysfunction	3.21±0.33	<0.001	9.05±0.13	<0.001
Without diastolic dysfunction	1.23±0.98		3.55±0.19	
With LVH	3.01±0.60	0.45	8.87±0.14	0.45
Without LVH	2.81±0.34		7.90±0.55	

LVH, left ventricular hypertrophy; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio.

In the present study, the mean age of our patients was 42.43 ± 12.96 years with no sex difference. However, Yu *et al*. [14] found that the prevalence of CKD increased with age after 55 years in both sexes. This difference could be attributed to genetic or social differences between the Egyptian and other communities.

In this study, patients with CKD had significantly higher diastolic blood pressure, SBP, and mean arterial blood pressure than controls, with the highest mean level of SBP ascending and the GFR steadily decreasing. These findings were in line with those of Heerspink *et al*. [15], who found that patients with stage IV had much higher SBP than those with stage II, indicating that renal function had deteriorated more.

In the present study, gastrointestinal tract symptoms were significantly increasing with advanced stages of CKD mainly at stages III, IV, and V. As interesting findings in our study also the pruritus and bone pain occurred with more advancing stages, not in earlier stages, such as stage IV and stage V. This was in accordance with the National Kidney Foundation,

Table 6 Correlations of the mean levels of neutrophil/lymphocyte ratio and mean platelet volume with the parameters of patients with chronic kidney disease

Parameters	NLR		MPV	
	r	*P*	*r*	*P*
Demographic data				
Age	0.15	0.08	0.19	0.58
BMI	0.19	0.56	0.12	0.17
MBP	0.17	0.67	0.21	0.45
Laboratory data				
Fibrinogen	0.23	<0.001	0.21	0.56
C-reactive protein	0.28	<0.001	-0.32	<0.001
Creatinine	0.24	<0.001	0.18	0.44
Urea	0.21	<0.001	0.13	0.66
Uric acid	0.11	0.05	-0.11	0.19
24 h-urine protein	0.311	0.004	0.12	0.46
HDL	0.05	0.52	0.06	0.46
LDL	-0.05	0.53	-0.07	0.39
MPV	0.11	0.22	-	
NLR	-		0.11	0.22

HDL, high-density lipoprotein; LDL, low-density lipoprotein; MBP, mean arterial blood pressure; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; *r*, strength of correlation. *P* indicates significance of correlation and considered significant if less than 0.05.

Table 7 Multivariate regression analysis for prediction of chronic kidney disease

Parameters	Odd's ratio	95% confidence interval	*P*
High NLR	2.11	1.09-4.56	<0.001
Urinary cast	1.99	1.39-2.22	<0.001
Proteinuria	4.33	2.34-8.98	<0.001
High triglyceride	1.11	1.10-2.01	<0.001

NLR, neutrophil/lymphocyte ratio.

which stated that uremic manifestations in patients with CKD stage IV–V are believed to be secondary to an accumulation of multiple toxins [16].

Our study shows that patients with stage II or III CKD had significantly higher mean level of hemoglobin in comparison with those with stage IV or V, which is in agreement with El-Kateb and Provenzano [17], who documented that many factors contribute to declining hemoglobin as CKD progresses, but impaired production of erythropoietin by failing kidneys is a central cause.

Interestingly, our findings demonstrated a significant reduction in the high-density lipoproteins levels and significant elevation in the triglycerides and very low-density lipoprotein in patients with advanced stages of CKD. This finding supports the association between CKD and cardiovascular-related comorbidities, and the severity of dyslipidemia correlates with the degree of renal dysfunction [18]. Deepak *et al*. [19] showed that there was a significant rise in low-density lipoprotein and very low-density lipoprotein and a significant reduction in high-density lipoprotein from stage III to V, suggesting that dyslipidemia is a common complication of CKD and is associated with increased risk of CVD and renal disease progression.

In the current study, we discovered that patients with CKD had significantly higher mean levels of fibrinogen and CRP than controls. These findings matched those of Goicoechea *et al*. [20], who discovered that higher CRP and serum fibrinogen levels are associated with chronic inflammation in individuals with chronic renal illness, resulting in an increase in inflammatory markers.

Notably, our study showed that there was significantly more prevalence of ventricular hypertrophy, dilated left atrium, pericardial effusion, and diastolic dysfunction in patients with stage V in comparison with other stages according to echocardiographic findings. These finding could be explain by that cardiac diastolic dysfunction was secondary to severe renal impairment associated with stage V, in concordance with Balananda *et al*. [21].

In the current study, we found insignificant lower mean level of MPV in patients with CKD compared with controls, with insignificant progressive decline of their levels with advanced deterioration of CKD up to stage V. These could be owing to platelet counts and volume decreased along with estimated GFR owing to uremic toxin. Moreover, there were insignificant correlations between mean level of MPV and proteinuria and fibrinogen in patients with CKD. In agreement with our result, Yilmaz *et al*. [22] found that MPV was lower in patients with CKD compared with healthy individuals, but this was not statistically significant. MPV was also not found to be associated with proteinuria. These finding were in contrary with Afsar *et al*. [23], who reported that MPV was significantly increased with progression of CKD and suggested that MPV could be considered as an useful indicator of increased risks of CVD in patients with CKD. This difference could be related to the large sample size of the study by Afsar and colleagues (553 patients with CKD) and their nonexclusion of ischemic cardiac diseases, as our study did. However, Ju *et al*. [24] reported that there was a negative linear correlation between GFR and MPV in patients with chronic kidney failure and MPV was higher in patients with cardiovascular or cerebrovascular disorders.

Regarding NLR, we found that the lowest NLR as seen in patients with stage II in comparison with other stages, indicating the evidence of the pathophysiological role of inflammation in CKD and thus it could be help in progression of disease. NLR had a positive correlation with increased level of fibrinogen, CRP, creatinine, urea, and proteinuria.

In agreement with our result, El-Hafeez *et al.* [13] and Yilmaz *et al.* [22] showed that NLR ratio might provide significant information regarding inflammation in CKD and NLR is a marker with prognostic value for the presence and degree of proteinuria.

An interesting finding in our study was the increased levels of NLR in patients with CKD with left ventricular diastolic dysfunction compared with patients with CKD without diastolic dysfunction, which is in agreement with Gromadziński *et al.* [25].

Our study showed that the following variables could be predictors for CKD: creatinine, high NLR, urinary casts, and proteinuria.

At a cutoff point more than 1.98, NLR had 95% sensitivity and 100% specificity for prediction of CKD, with an area under curve of 0.97, whereas at a cutoff point more than 8.8, MPV had 47.5% sensitivity and 80% specificity for prediction of CKD, with an area under curve of 0.63. To the best of our knowledge, the current study was the first one to evaluate the validity of NLR as a predictor of proteinuria in patients with CKD; moreover, no other studies support our finding.

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Conflicts of interest

There are no conflicts of interest.

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