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Study of Neutrophil Lymphocyte Ratio in Patient with Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide. The neutrophil - to- lymphocyte ratio (NLR) had been shown as a marker of systemic inflammation. However Studies are inconsistent about NLR and clinical outcome in patients with CKD, so we aimed to clarify the relationship between Neutrophil - lymphocyte ratio and the disease progression in chronic kidney diseases (CKD). This is a prospective observational study conducted on 60 patients with CKD stage 2-4 followed up in the period between March (2021) to November (2021). Patients were divided according to the median level of NLR into high and low NLR groups**.** Our study showed adverse renal outcome in the high NLR group with 13 patients dialyzed versus 2 in the low NLR group. 19 patients showed stationary coarse and 4 was progressed in the low NLR group versus 5 patients showed stationary and 19 was progressed in the high NLR group. We concluded that NLR was a risk factor for progression and poor renal outcome in chronic kidney disease patients with stage 2-4, so it might be a useful predictor marker for renal outcome in CKD patients.

Keywords: Neutrophil Lymphocyte Ratio, Chronic Kidney Disease

1. Introduction

Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide, affecting over 10% of the population worldwide. The problem was ranked 16th among the leading causes of death in 2016 and is expected to rise to 5th ranked by 2040 [1].

Chronic inflammation has an important role in the onset and progression of various diseases such as chronic kidney disease (CKD) diabetes mellitus and cardiovascular disease [2]. Patients with CKD tend to have elevated levels of inflammatory mediators, including C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin (IL) -6. These mediators stimulate mesangial and endothelial glomerular cells and

subsequently cause an increase in production and decreased degradation of the mesangial and endothelial extracellular matrix, leading to glomerular hypertension, tubulointerstitial fibrosis and renal scarring [3]. Because chronic inflammation is a major factor in the progression of CKD, evaluating and alleviating the extent of chronic inflammation is important to attenuate the progression of kidney dysfunction [4].

The neutrophil-to-lymphocyte ratio (NLR), which can be obtained from routine blood tests, has attracted attention because of its wide availability and the low cost of the tests; it has recently emerged as a prognostic marker in various chronic diseases [5]. Studies have demonstrated that NLR is associated with the clinical outcome in patients with CKD; however, these studies are inconsistent [6].

Few studies have addressed the relationship between NLR and kidney disease progression in patients with CKD.

The aim of this study is to clarify the relationship between Neutrophil - lymphocyte ratio and the disease progression in chronic kidney diseases (CKD).

2. Patients and Methods

This study was a prospective observational study conducted on 60 patients with CKD stage from (2-4) categorized according to national kidney foundation disease outcome quality initiative (NKF-K/DOQI) clinical practice guidelines. Patients were collected from Al-Zahraa University Hospital Nephrology clinic and followed up in the period between March (2021) to November (2021) after oral consents of the patients and approval of the ethical committee of the university. According to the median level of NLR the patients were categorized into: High NLR group (NLR above the median level> 3), Low NLR group (NLR below the median level <3). Patients with any malignancy**,** acute or chronic infections, chronic inflammatory disease, patient under treatment with immunosuppressant drugs for previous 3 months and patient with acute exacerbation of CKD and estimated glomerular filtration rate (EGFR)<15 ML/min/1.73 m^2 at baseline were excluded from this study.

2.1 All participants will be subjected to the following:

Complete clinical data including demographic data (age, gender, body mass index (BMI)) and medical history including (diabetes, hypertension, IHD and medications.

2.2 The following laboratory investigations were collected from all participants:

Complete blood cell count (CBC) with differential leukocyte count, neutrophil lymphocyte ratio, kidney function (serum urea, creatinine, phosphorus)**,** C reactive protein, albumin/creatinine ratio, Lipid profile (cholesterol and triglyceride) and estimated Glomerular filtration (e GFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation**.**

3. Results

As shown in Table .1, the median age of the 60 patients in our study was 53.33 (range 31- 85), 34 (56.7%) patients were female, and 26 (43.3%) patients were male. Their median BMI was 29.71% (range 19-46.9). 27 (45%) of the group of patients studied had diabetes, 56 (93.3%) had hypertension, and 5% (8.3%) had Ischemic patients. Seven patients (11.7%) were CKD stage 2, 33 (55%) patients were CKD stage 3, 20 (33.3%) patients were CKD stage 4. As shown in Table .2, the clinical characteristics of the subjects are summarized according to the values below and above the median NLR value (3), ranging from 1.3 to 5.8. The low NLR group<3, and the high NLR group>3. The higher NLR group had higher male predominance. As shown in Table .3, there was a statistically significant decrease in initial-eGFR in the higher neutrophil lymphocyte group. There was no statistically significant difference in initial

Hb, urea, creatinine, albumin/creatinine ratio, phosphorus, albumin, uric acid, CRP, cholesterol and triglyceride between the 2 groups. As shown in Table .4, there was a statistically significant increase in creatinine and uric acid and a decrease in eGFR in the higher NLR group than the low NLR group after 6 months follow-up. There was no statistically significant difference in Hb, urea, albumin/creatinine ratio, phosphorous, albumin, CRP, cholesterol and triglycerides between the two groups after 6 months follow. As shown in Table .5, after 6 months follow up the high NLR group was associated with more adverse renal outcome. The number of patients who reached composite endpoints was 13, with 2 in the low NLR group and 11 in the high NLR group. 19 patients showed stationary coarse and 4 was progressed in the low NLR group versus 5 patients showed stationary and 19 was progressed in the high NLR group. As shown in Table .6, there was a statistically significant positive correlation found between neutrophil lymphocyte ratio and creatinine and uric acid level and also negative correlation with eGFR. Also, at follow up there was significant positive correlation found between neutrophil lymphocyte ratio and creatinine and a negative correlation with eGFR.

Table (1): Demographic data and clinical characteristics of the patients studied

		No. = 60
Age (years)	Mean ± SD	53.33 ± 12.22
	Range	31 – 85
Gender	Female	34 (56.7%)
	Male	26 (43.3%)
BMI (kg/m2)	Mean ± SD	29.71 ± 5.43
	Range	19 – 46.9
Associated diseases	DM	27 (45.0%)
	HTN	56 (93.3%)
	IHD	5 (8.3%)
CKD stage	Stage 2	7 (11.7%)
	Stage 3	33 (55.0%)
	Stage 4	20 33.3%)

Table (2): Relation between NLR with base baseline clinical parameters of the studied patients

		NLR groups		Test value	P-value	Sig.
		Low NLR (≤3)	High NLR (>3)			
		No. = 25	No. = 35			
Age (years)	Mean ± SD	54.20 ± 14.10	52.71 ± 10.85	0.461•	0.646	NS
	Range	31 – 84	31 – 85			
Gender	Female	18 (72.0%)	16 (45.7%)	4.103*	0.043	S
	Male	7 (28.0%)	19 (54.3%)			
BMI (kg/m2)	Mean ± SD	30.94 ± 6.17	28.83 ± 4.73	1.497•	0.140	NS
	Range	22.2 – 46.9	19 – 42.2			
Associated diseases	DM	12 (48.0%)	15 (42.9%)	0.156*	0.693	NS
	HTN	22 (88.0%)	34 (97.1%)	1.959*	0.162	NS
	IHD	2 (8.0%)	3 (8.6%)	0.006*	0.937	NS
CKD stage	Stage 2	4 (16.0%)	3 (8.6%)	1.063*	0.588	NS
	Stage 3	14 (56.0%)	19 (54.3%)			
	Stage 4	7 (28.0%)	13 (37.1%)			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), *: Chi-square test; •: Independent t-test.

Table (3): Relationship between NLR and initial laboratory data of the studied patient groups

		NLR groups		Test value	P-value	Sig.
		Low NLR (≤3)	Neutrophil >3			
		No. = 25	No. = 35			
Hb (mg/dl)	Mean ± SD	10.59 ± 1.34	10.85 ± 1.93	-0.581•	0.564	NS
	Range	8 – 12.8	7.3 – 14.9			
Urea (mg/dl)	Mean ± SD	81.50 ± 38.90	74.68 ± 26.32	0.811•	0.421	NS
	Range	30 – 184	34 – 139			
Creatinine (mg/dl)	Mean ± SD	2.20 ± 0.84	2.69 ± 1.03	-1.931•	0.058	NS
	Range	1.3 – 4.2	1.5 – 5.2			
eGFR (ml/min/1.73m2)	Mean ± SD	43.90 ± 16.76	34.92 ± 14.06	2.252•	0.028	S
	Range	17.5 – 76.5	16.1 – 70.8			
Albumin/creatinine Ratio (mg/g)	Median (IQR)	60 (35.8 - 80)	50 (30 - 80)	-0.580	0.562	NS
	Range	10.9 – 333	13.2 – 330			
Phosphorus (mg/dl)	Mean ± SD	4.57 ± 0.77	4.70 ± 0.76	-0.646•	0.521	NS
	Range	3.4 – 6	3.2 – 6			
Uric acid (mg/dl)	Mean ± SD	6.38 ± 1.05	6.87 ± 1.12	-1.731•	0.089	NS
	Range	4.5 – 8	4 – 10			
Albumin (g/dl)	Mean ± SD	4.05 ± 0.26	3.89 ± 0.34	1.998•	0.050	NS
	Range	3.6 – 4.9	3 – 4.5			
CRP	Mean ± SD	7.40 ± 1.22	7.43 ± 0.92	-0.103•	0.918	NS
	Range	5 – 9	5 – 8			
Cholesterol (mg/dl)	Mean ± SD	211.92 ± 60.09	203.86 ± 45.63	0.591•	0.557	NS
	Range	107 – 300	68 – 295			
Triglyceride (mg/dl)	Mean ± SD	190.72 ± 51.56	191.11 ± 72.21	-0.023•	0.981	NS
	Range	88 – 280	30 – 460			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), *: Chi-square test; •: Independent t-test

Table (4): Relationship between neutrophil/lymphocyte ratio and laboratory data of the studied patient groups after 6 months follow up

Follow up		NLR groups		Test value	P-value	Sig.
		Low NLR (≤3)	High NLR (>3)			
		No. = 25	No. = 35			
Hb (mg/dl)	Mean ± SD	10.42 ± 1.41	10.49 ± 1.44	-0.173•	0.863	NS
	Range	6.8 – 13.9	8.1 – 13.3			
Urea (mg/dl)	Mean ± SD	87.40 ± 36.81	99.54 ± 31.74	-1.366•	0.177	NS
	Range	40 – 169	37 – 161			
Creatinine (mg/dl)	Mean ± SD	2.68 ± 1.16	4.20 ± 1.44	-4.357•	0.000	HS
	Range	1.7 – 6.1	1.8 – 7			
eGFR (ml/min/1.73m2)	Mean ± SD	35.93 ± 15.28	21.87 ± 10.78	4.185•	0.000	HS
	Range	11.5 – 58.8	10.3 – 55.4			
Albumin /creatinine Ratio (mg/g)	Median (IQR)	60 (35.3 - 80)	60 (33.9 - 90)	-0.608‡	0.543	NS
	Range	10 – 116	20 – 315			
Phosphorus (mg/dl)	Mean ± SD	4.82 ± 0.73	5.18 ± 1.14	-1.373•	0.175	NS
	Range	3.8 – 6.5	3.3 – 9			
Uric acid (mg/dl)	Mean ± SD	6.38 ± 1.05	7.01 ± 1.08	-2.224•	0.030	S
	Range	3.6 – 8	4.3 – 10			
Albumin (g/dl)	Mean ± SD	4.10 ± 0.36	3.97 ± 0.40	1.296•	0.200	NS
	Range	3.5 – 5	3 – 5			
CRP	Mean ± SD	6.68 ± 1.18	6.77 ± 1.33	-0.275•	0.784	NS
	Range	5 – 9	4 – 10			
Cholesterol (mg/dl)	Mean ± SD	194.80 ± 43.28	195.20 ± 34.10	-0.040•	0.968	NS
	Range	100 – 280	102 – 260			
Triglyceride (mg/dl)	Mean ± SD	166.40 ± 36.89	179.59 ± 43.55	-1.231•	0.223	NS
	Range	98 – 221	36.6 – 300			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), •: One Way ANOVA test; ‡: Kruskal Wallis test

Table (5): Relationship between neutrophil/lymphocyte ratio and renal outcome of the studied patient groups after 6 months' follow-up

Outcome	Neutrophil groups		Test value	P-value	Sig.
	Low NLR (≤3)	High NLR (>3)			
	No. = 25	No. = 35			
Stationary coarse	19 (76.0%)	5 (14.3%)	23.157	0.000	HS
Progressive coarse	4 (16.0%)	19 (54.3%)			
Dialysis	2 (8.0%)	11 (31.4%)			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), *: Chi-square test.

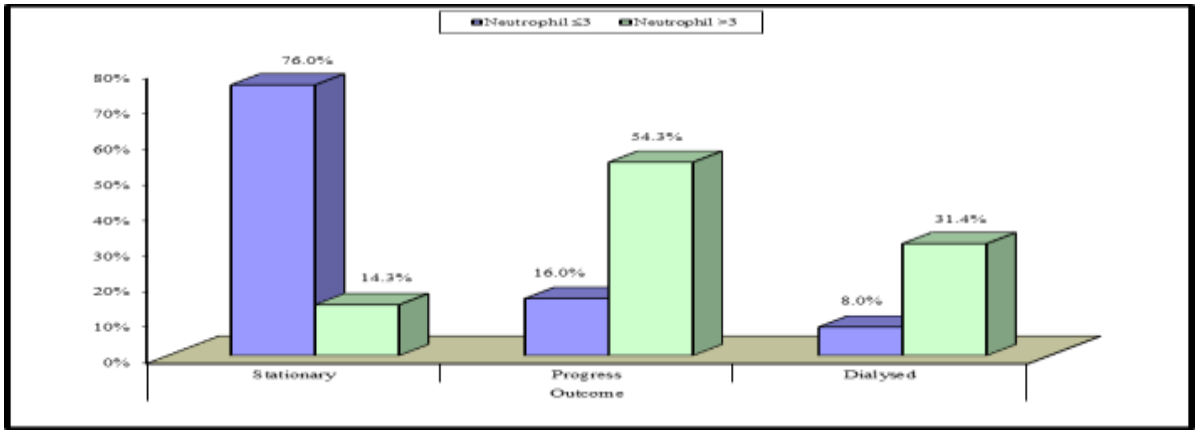

Figure 1: Relation between NLR and renal outcome of the studied patients after 6 months follow up

Table (6): Correlation of neutrophil/lymphocyte ratio with age, BMI, with initial laboratory data and follow up after 6 months

	NLR	
	r	P-value
Age (years)	-0.072	0.583
BMI (kg/m2)	-0.121	0.356
Initial		
Hb (mg/dl)	-0.042	0.747
Urea (mg/dl)	-0.043	0.742
Creatinine (mg/dl)	0.262*	0.043
eGFR (ml/min/1.73m2)	-0.258*	0.046
Albumin/creatinin ratio (mg/g)	0.020	0.879
phosphorus (mg/dl)	0.151	0.249
uric acid (mg/dl)	0.258*	0.046
albumin (g/dl)	-0.182	0.163
CRP	-0.069	0.602
cholesterol (mg/dl)	0.098	0.457
triglyceride (mg/dl)	-0.013	0.923
Follow up		
Hb (mg/dl)	0.015	0.907
urea (mg/dl)	0.169	0.195
Creatinin (mg/dl)	0.518**	0.000
eGFR (ml/min/1.73m2)	-0.425**	0.001
Albumin /creatinin Ratio (mg/g)	0.119	0.364
Phosphorus (mg/dl)	0.210	0.107
uric acid (mg/dl)	0.154	0.240
albumin (g/dl)	-0.099	0.449
CRP	0.011	0.931
Cholesterol (mg/dl)	0.145	0.271
Triglyceride (mg/dl)	0.177	0.177

Spearman correlation coefficients

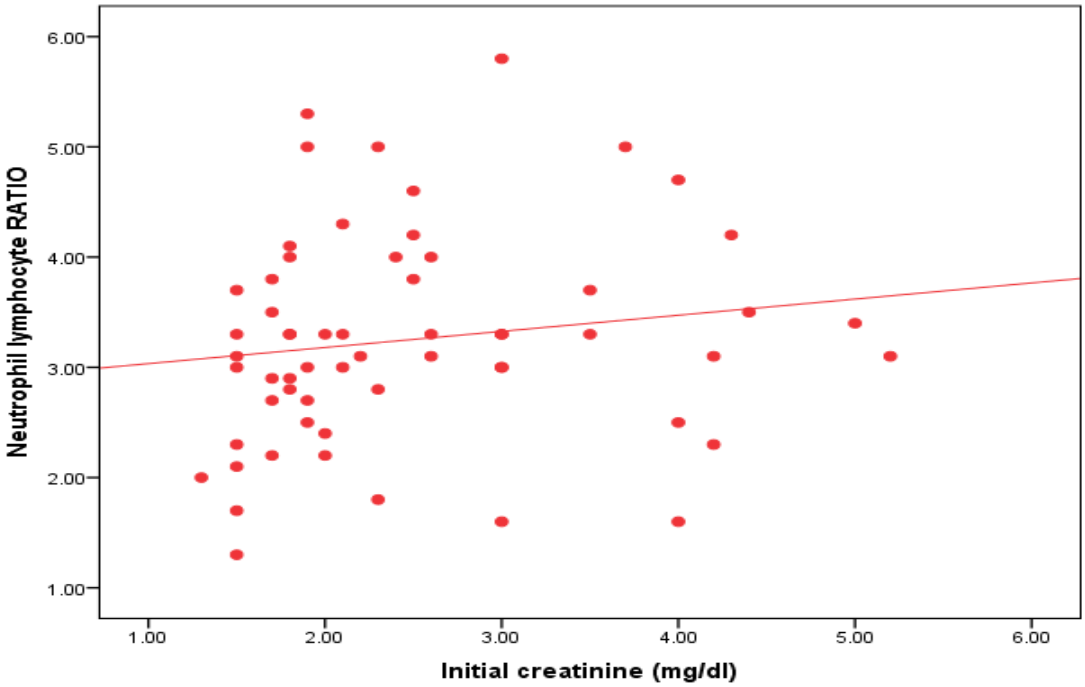

Figure 2: Correlation between neutrophil/lymphocyte ratio and initial creatinine

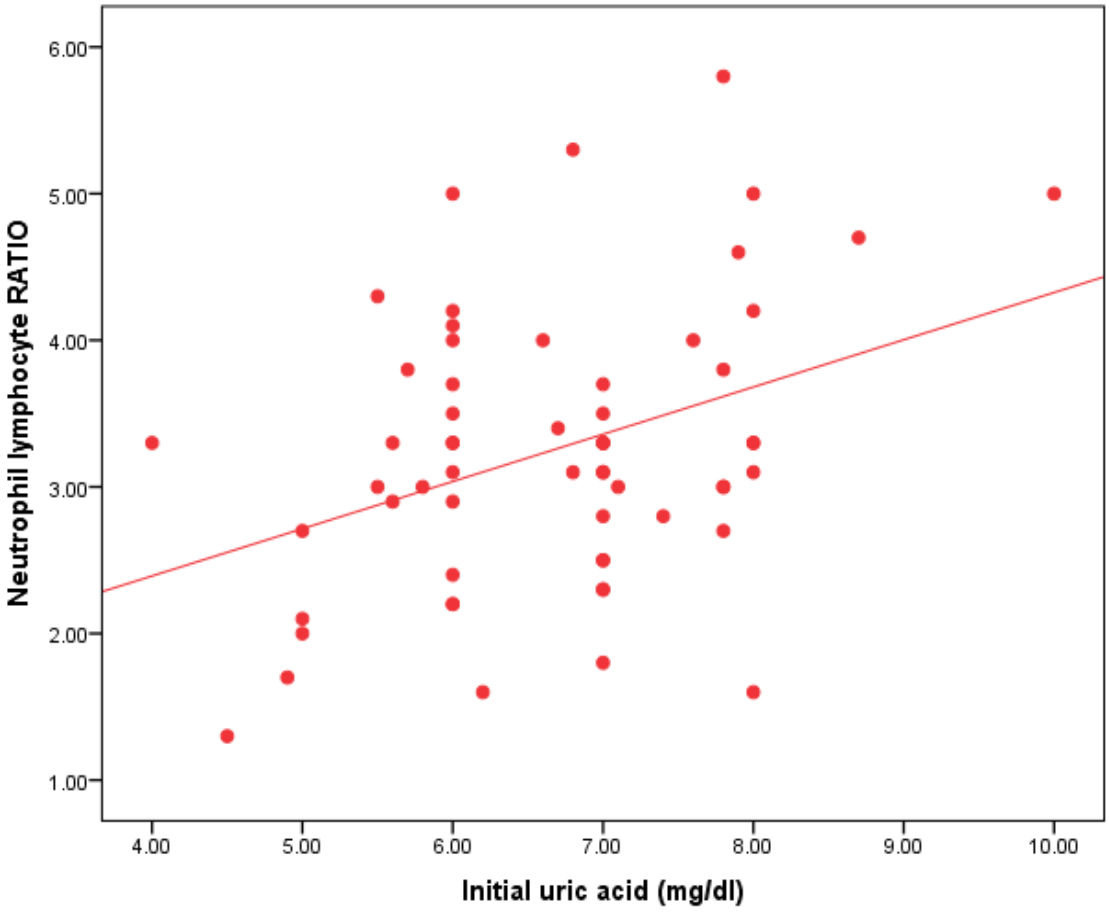

Figure 3: Correlation between neutrophil/lymphocyte ratio and initial uric acid**.**

4. Discussion

CKD is a worldwide health problem because of the significant rate of morbidity and mortality. The most important cause of mortality in CKD is atherosclerosis, which is mostly due to inflammation that develops in early stages of CKD [1].

NLR is a marker used for assessing inflammation. NLR is a marker that related to immune pathways. NLR has been used widely to evaluate the patients with different illness. It calculated from differential WBC counts [7].

Our present prospective study investigated the relationship of NLR and chronic kidney disease. It is demonstrated that the high NLR group had a significantly increased risk for poor renal outcomes, in patients with CKD stages 2–4.

The main mechanism of the underlying relationship between NLR and these poor outcomes was thought to be an increase in chronic inflammation, probably related to higher NLR [8].

This is in agreement with Yoshitomi et al. (2019) [3] who demonstrated that that a high NLR was associated with poor renal outcomes, suggesting that NLR may be a useful marker for prognostic prediction in patients with CKD.

This comes also in agreement with Tatar et al. (2016) [9] who investigated 165 elderly patients with CKD 3-5 and showed that mortality rate and renal replacement therapy was higher among high NLR group versus low NLR group.

Nevertheless, recent evidence indicates that NLR was not an independent predictor of CKD progression in CKD stage 2–4 patients. Altunoren et al. (2019) [10] showed that patients with high NLR had significantly lower mean renal survival (86.5 months) than patients with low NLR (105 months) However, the percent of patient reaching the end point (renal disease requiring dialysis and death) was not different between the groups with high and low baseline NLR. This is in disagreement with our study, which revealed a higher percentage of reaching endpoint dialysis among the high NLR (84.6%) group than the low NLR group (15.4%).

In a study of a large chinese CKD population for the relationship between NLR, ESRD, CVD, and all-cause mortality Yuan et al. (2019) [4] revealed NLR as an independent risk factor of ESRD only in patients with stage 4 CKD after adjusting for classic risk factors of CKD including ACR and eGFR. They did not observe any significant associations between abnormal NLR and the risk of either CVD or all-cause mortality in CKD patients in general and CKD patients grouped according to the disease stages in particular.

This also in disagreement with our study as we found a statistically significant difference in renal outcome among all stages of CKD in higher NLR group versus low NLR group.

In the present study multivariable analysis showed significant positive correlation of NLR with serum creatinine while negative correlation with eGFR denoting that NLR increase with progression of CKD stages. This is in agreement with Yoshitomi et al. (2019) [3] showed that NLR was correlated with eGFR.

This comes also in agreement with Farag-Allah et al. (2019) [11] who studied 50 CKD patient versus 50 healthy persons as control group and found a significant correlation between NLR and serum creatinine and eGFR.

Multiple Clinical studies have shown that reducing proteinuria can delay the progression of renal disease with a reno-protective effect. Apart from the progress of kidney disease, proteinuria is an important indicator of arteriosclerotic cardiovascular diseases that increase the risk of cardiovascular incidents and mortality in patients both with and without DM. However, multivariable analysis in our study showed the non-significant correlation between NLR and proteinuria (albumin/creatinine ratio), which comes in agreement with Yoshitomi et al. (2019) [3].

Our findings disagree with Farag-Allah et al. (2019) [11] who demonstrated significant positive correlation between NLR and 24h urinary protein.

Our study also disagreed with Kahraman et al. (2017) [12] his study showed that 112 patients with type-2 diabetes mellitus with proteinuria, there was positive correlation between NLR and 24h urine protein excretion.

Also, Yilmaz et al, (2017) [13] a statistically significant positive correlation between NLR and 24 h urine micro-albumin in chronic kidney disease.

Our study showed non-significant correlation between NLR and CRP, which is in disagreement with Yoshitomi et al. (2019) [3] who demonstrated that NLR levels were positively correlated with CRP level denoting that high NLR is associated with oxidative stress associated with cardiovascular disease. Unfortunately, we do not include other inflammatory markers in our study.

Also, we are in disagreement with Yilmaz et al, (2017) [14] who found that NLR is significantly correlated with CRP. Another study, Solak et al. (2013) [14] found that NLR independently related to endothelial dysfunction and could predict composite cardiovascular endpoints independent of hsCRP patients with moderate to severe CKD with 80.3 % sensitivity and 91.8 % specificity.

Indeed, it was reported that high NLR levels were associated with the development of IHD in pre-dialysis_and dialysis patients. However, our study showed a non-significant correlation between NLR and IHD which is in disagreement with [15] and [14].

Our study had some limitations. First, the study subjects were recruited in a single regional hospital. Second was the small number of the study population. Some of our patients were on erythropoietin therapy that may influence NLR and also, we did not investigate the effect of smoking. A further larger-scale population observational study is needed to clarify the association between NLR and renal function decline, cardiovascular morbidity and mortality in CKD patients.

We concluded that NLR is a risk factor for progression and poor renal outcome in chronic kidney disease patients with stage 2-4 so it might be a useful predictor marker for renal outcome in CKD patients.

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