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Neutrophil-to-Lymphocyte Ratio as a Novel Marker for Early Detection of Hypertensive Nephropathy and as a Predictor of Worsening Renal Functions in Hypertensive Patients

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ABSTRACT

Background: Hypertension (HTN) is one of the most important causes of chronic kidney disease (CKD) and may also be the presenting feature of asymptomatic primary renal disease. However, a progressive reduction in estimated glomerular filtration rate (eGFR) and increased albuminuria indicate progressive loss of renal function, an alteration of renal function is an insensitive marker of renal impairment because a major reduction in renal function is needed before serum creatinine rise. Low-grade inflammation plays crucial pathophysiological role in both hypertension and CKD.

Objective: This work was aimed to study neutrophil-to-lymphocyte ratio (NLR) as a marker for early detection of hypertensive kidney disease and as a predictor of worsening renal function in patients with high normal blood pressure and in hypertensive patients.

Patient and methods: This case control study included a total of 125 hypertensive patients and 50 subjects with normal blood pressure, attending at Department of Internal Medicine, Banha University Hospital. All participants were subjected to careful history taking, clinical examination, and laboratory investigations including NLR.

Results: NLR was significantly higher among HTN group with low eGFR (3.2±1), followed by HTN group with normal eGFR (1.9±0.98) with p value = 0.019, while lymphocyte was significantly lower among HTN group with low eGFR (1.7±0.3) followed by HTN group with normal eGFR (2.2±0.5) with P value 0.005. Neutrophils and NLR were significantly higher among stage IV CKD patients (6.1±2, 3.3±1.1 respectively) followed by stage III patients (5.8±1.4, 2.9±0.99 respectively) with p values were 0.031, 0.022 respectively. There was significant correlation between NLR and blood pressure, urea, creatinine, eGFR, albumin/creatinine ratio, and CRP.

Conclusion: It could be concluded that NLR can be used as a marker with significant sensitivity and specificity for hypertensive nephropathy at different CKD stages.

Keywords: Neutrophil lymphocyte ratio, Chronic kidney disease, Hypertension.

INTRODUCTION

Elevated blood pressure (Bp) was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths [(1)]. Both office BP and out-of-office BP have an independent and continuous relationship with the incidence of several cardiovascular events [haemorrhagic stroke, ischaemic stroke, myocardial infarction, sudden death, heart failure, and peripheral artery disease (PAD)], as well as chronic kidney disease (CKD) [(2)].

Hypertension is defined as office systolic blood pressure (SBP) values ≥140 mmHg and/or diastolic BP (DBP) values > 90 mmHg [(2)]. HMOD (hypertension mediated organ dysfunction) refers to structural or functional changes in arteries or end organs (heart, blood vessels, brain, eyes, and kidney) caused by an elevated blood pressure [(3)]. With wider use of imaging, HMOD is becoming increasingly apparent in asymptomatic patients [(4)]. Hypertension is the second most important cause of CKD after diabetes and hypertension may also be the presenting feature of asymptomatic primary renal disease [(2)].

Chronic kidney disease (CKD) is a major health issue worldwide, which leads to end-stage renal failure and cardiovascular events [(5)]. The diagnosis of hypertension induced renal damage is based on the finding of reduced renal function and or the detection of albuminuria [(6)].

A progressive reduction in eGFR and increased albuminuria indicate progressive loss of renal function, and both are independent and additive predictors of increased cardiovascular risk and progression of renal disease [(6)]. An alteration of renal function is an insensitive marker of renal impairment because a major reduction in renal function is needed before serum creatinine rises[(7)]. Low-grade inflammation plays crucial pathophysiological role in hypertension, as it facilitates the development of essential hypertension and target organ damage [(8)]. Inflammation participates in many processes that contribute to the development of elevated BP: for example, several studies have shown a positive association between hypertension and elevated white blood cell (WBC), C-reactive protein (CRP) and interleukin-6 (IL6) levels [(9)].

The role of inflammation in acute kidney injury and end-stage kidney disease (ESKD) is also well recognized [(10)]. Inflammation has proven to be associated with CKD and CKD patients has shown to possess a low grade inflammatory status [(11)]. Although

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the CRP and IL-6 are recognized inflammation markers, however, detecting of CRP is still not as a routine examination in nephrology clinics worldwide [12].

The neutrophil to lymphocyte ratio (NLR) is commonly used as a reliable biomarker of systemic inflammatory status [13]. Blood NLR is a simple marker for chronic low grade inflammation that can be easily obtained from a differential WBC count [14].

Many studies have been conducted to demonstrate the value of NLR in various conditions such as hypertension, cardiac disorders, malignancies, and renal failure [15]. It has been hypothesized that NLR is a useful predictive factor for the incidence of hypertension and reflect vascular inflammation in hypertensive patient; however, to date, only few cross-sectional studies have suggested that NLR is positively related to hypertension [16].

This work was aimed to study neutrophil-to-lymphocyte ratio (NLR) as a marker for early detection of hypertensive kidney disease and as a predictor of worsening renal function in patients with high normal blood pressure and in hypertensive patients.

PATIENTS AND METHODS

This case control study included a total of 125 hypertensive patients and 50 subjects with normal blood pressure, attending at Department of Internal Medicine, Banha University Hospital.

Inclusion criteria: Age - 18 years or more.

Exclusion criteria: Age < 18 years, end stage renal disease, diabetes mellitus, pregnancy, malignancy, infection, collagen vascular diseases and liver diseases.

The included subjects were divided into four groups; **Group 1 (control)** consisted of 25 subjects with normal BP and normal eGFR, **Group 2** consisted of 25 subjects with high normal BP and normal eGFR, **Group 3** consisted of 25 patients with HTN and normal eGFR, and **Group 4** consisted of 100 patients with HTN and low eGFR including: (a) HTN & CKD stage1. (b) HTN & CKD stage 2. (c) HTN & CKD stage 3. (d) HTN & CKD stage 4.

History was taken with careful attention to hypertension, smoking, family history of HTN, cardiovascular disease (CVD), stroke, or renal disease, and drug history including nephrotoxic drugs. In addition to complete physical examination and investigations including fasting blood glucose (FBS), HBA1c, Albumin/ creatinine ratio (ACR), serum creatinine, eGFR (ml/min/1.73m2) which calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), serum uric acid, CRP, lipids profile, CBC, and **Neutrophil to lymphocyte ratio (NLR) =** Absolute neutrophil count (**ANC) /** Absolute lymphocyte count (ALC)

- ANC = White blood cells (WBC) count in thousands X (%PMNs+ %Bands)
- **ALC** = WBC count in thousands X (% lymphocyte)

Ethical consent:

An approval of the study was obtained from Benha University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data was computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 26. Data was tested for normal distribution using the Shapiro Walk test. Qualitative data was represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data was expressed as mean and standard deviation. ANOVA and Kruskal Wallis tests were used to calculate difference between quantitative variables in more than two groups for parametric and non-parametric variables. P value < 0.05 was considered significant.

RESULTS

This study included a total of 175 subjects, 72 (42%) males, and 103 (58%) females, aged 60 ±12 years. Demographic data are shown in Table 1.

Table (1): Basic demographic data among the participants

	Control group (n=25)	High normal B.P with normal eGFR (group 1) (n=25)	HTN group with normal eGFR (group 2) (n=25)	HTN group with low eGFR (group 3) (n=100)	P value
Age (years)	55 ±9	60 ±8	59 ±10	60 ±10	0.099[1]
Sex					
Male	9(36%)	10(40%)	13(52%)	40(30%)	0.435[2]
Female	16(64%)	15(60%)	12(48%)	60(60%)	
Smokers	9(36%)	8(32%)	7(28%)	38(38%)	0.586[2]
Family history					
HTN	4(16%)	14(56%)	17(68%)	70(70%)	**<0.001*[2]**
CVD	2(8%)	15(60%)	17(68%)	65(65%)	
Renal disease	1(4%)	7(28%)	9(36%)	40(40%)	
Drug history of nephrotoxic drugs	3(12%)	2(8%)	5(20%)	22(22%)	0.355[2]

[1]ANOVA test used. [2]Chi square test; *p is significant at <0.05

Abbreviations: HTN; hypertension, eGFR; estimated glomerular filtration rate, CVD; cardiovascular disease.

Albuminuria, creatinine, A/C ratio, uric acid and CRP were significantly higher among HTN group with low eGFR (35 mg/24h urine, 1.79 mg/dl, 33 mg/g, 6.4±1.7 mg/dl, 1.5±0.31 mg/l respectively) followed by HTN group with normal eGFR (25 mg/24h urine, 1.07±0.22 mg/dl, 24 mg/g, 5.4±0.8 mg/dl, 2.5±0.2 mg/l respectively) with p values were 0.001, while FBS and HA1C showed insignificant differences (table 2).

Table (2): Laboratory data among the participants

	Control group (n=25)	High normal B.P with normal eGFR (n=25)	HTN group with normal eGFR (n=25)	HTN group with low eGFR (n=100)	P value
FBS (mg/dl)	88 ±10	90 ±7	89±8	86±7	0.203[1]
HA1C (%)	4.6±0.8	4.8±.06	4.8±0.7	5±0.2	0.721[1]
Albuminuria (mg/24 hours)	10±1	12.5±0.9	25 ±5.41	35 ± 7.43	**<0.001*[1]**
Creatinine (mg/dl)	0.94 ±0.09	1.01 ±0.23	1.07 ±0.22	1.79 ± 0.4	**<0.001*[1]**
A/C ratio (mg/g)	10.1± 2	12± 1.8	24 ± 5.63	33 ± 8.11	**<0.001*[1]**
Uric acid (mg/dl)	4 ±0.1	4.1±0.2	5.4 ±0.8	6.4±1.3	**<0.001*[1]**
CRP (mg/l)	1.1 ± 0.1	2± 0.11	2.5± 0.20	5 ± 0.31	**<0.001*[1]**

[1]ANOVA test used. *p is significant at <0.05 Abbreviations: FBS; fasting blood sugar, HA1C; hemoglobin A1C, A/C; albumin Creatinine, CRP; C reactive protein

The present study showed that NLR was significantly higher among HTN group with low eGFR (3.2±1), followed by HTN group with normal eGFR (1.9±0.98) with p value = 0.019, while lymphocyte was significantly lower among HTN group with low eGFR (1.7±0.3) followed by HTN group with normal eGFR (2.2±0.5) with P value 0.005. These results are shown in table 3.

Table (3): CBC data among the participants

	Control group (n=25)	High normal B.P with normal eGFR (n=25)	HTN group with normal eGFR (n=25)	HTN group with low eGFR (n=100)	P value
Hb (g/dl)	14.2±1	14.1±1.2	14±1.4	10±1.3	0.223[1]
Leukocytes ($\times 10^3/\mu l$)	6±1.31	6±1.21	6.5±0.7	7.8±1.41	0.802[1]
Platelets ($\times 10^3/\mu l$)	232±19.8	230±21.4	251±18.5	249±21.4	0.062[1]
Neutrophil ($\times 10^3/\mu l$)	3.4± 0.4	3.5± 0.81	4.5 ±1	6± 1.2	**0.010*[1]**
Lymphocyte ($\times 10^3/\mu l$)	2.6± .04	2.5± 0.9	2.2 ±0.5	1.7 ± 0.3	**0.005*[1]**
NLR	1.3± 0.23	1.4± 0.33	1.9 ±0.34	3.2± 0.83	**0.019*[1]**
PLR	89.2±20.5	92±21.5	114.09±27.3	138±33.5	**0.033*[1]**

[1]ANOVA test used. *p is significant at <0.05 Abbreviations: Hb; hemoglobin, NLR; neutrophil lymphocyte ratio, PLR; platelet lymphocyte ratio.

Neutrophils and NLR were significantly higher among stage IV CKD patients (6.1±2, 3.3±1.1 respectively) followed by stage III patients (5.8±1.4, 2.9±0.99 respectively) with p values were 0.031, 0.022 respectively, while lymphocyte was significantly lower among stage IV patients (1.8±0.3) followed by stage III (2.0±0.55) and p value = 0.045. These results are shown in table 4 and also illustrated in figure 1.

Table (4): CBC data among chronic kidney disease stages

	HTN/ Normal GFR	HTN/ CKD-I	HTN/ CKD-II	HTN/ CKD-III	HTN/ CKD-IV	*P* value*
Hb (g/dl)	14± 1.4	12± 1.1	11 .2± 1.1	9.2 ± 0.9	8.4 ± 0.9	0.782
WBCs ($x10^3/\mu l$)	6.7 ± 0.7	7± 1.6	7.3 ± 1.5	7.8 ± 1.8	7.9 ± 1.8	0.423
Neutrophils ($x10^3/\mu l$)	4.5 ± 1	4.7 ± 1	5.2 ± 1.7	5.8 ± 1.2	6.1± 1.31	**0.031**
Lymphocyte ($x10^3/\mu l$)	2.2 ± 0.5	2.3 ± 0.7	2.1 ± 0.6	2.0 ± 0.55	1.8 ± 0.3	**0.045**
Platelets ($x10^3/\mu l$)	251 ± 4.5	247 ± 20	247 ± 18	248 ± 16	251 ± 20	**0.089**
NLR	1.9 ± 0.2	2.04 ± 0.4	2.5 ± 0.45	2.9 ± 0.11	3.3 ± 0.71	**0.022**
PLR	114.5 ± 8.5	112 ± 21.3	117 ± 22.4	124± 22.2	139.3 ± 31	**0.06**

* One way ANOVA. WBC: white blood cells; NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio. HTN: hypertension; GFR: glomerular filtration rate; CKD: chronic kidney disease

There was significant correlation between NLR and blood pressure, urea, creatinine, eGFR, albumin/creatinine ratio, and CRP. These correlations are illustrated in table 5.

Table (5): Correlation of NLR with Blood pressure and other laboratory parameters

Variable	NLR	
	R	P value
Systolic Blood Pressure	0.438	**0.002**
Diastolic Blood Pressure	0.428	**0.004**
Serum urea	0.501	**<0.001**
Serum creatinine	0.544	**<0.001**
Albumin/Creatinine	0.703	**<0.001**
eGFR	-0.562	**<0.001**
Neutrophil count	0.672	**<0.001**
Lymphocyte count	-0.507	**<0.001**
PLT	0.208	0.051
PLR	0.489	**<0.001**
CRP	0.690	**<0.001**

Pearson correlation test

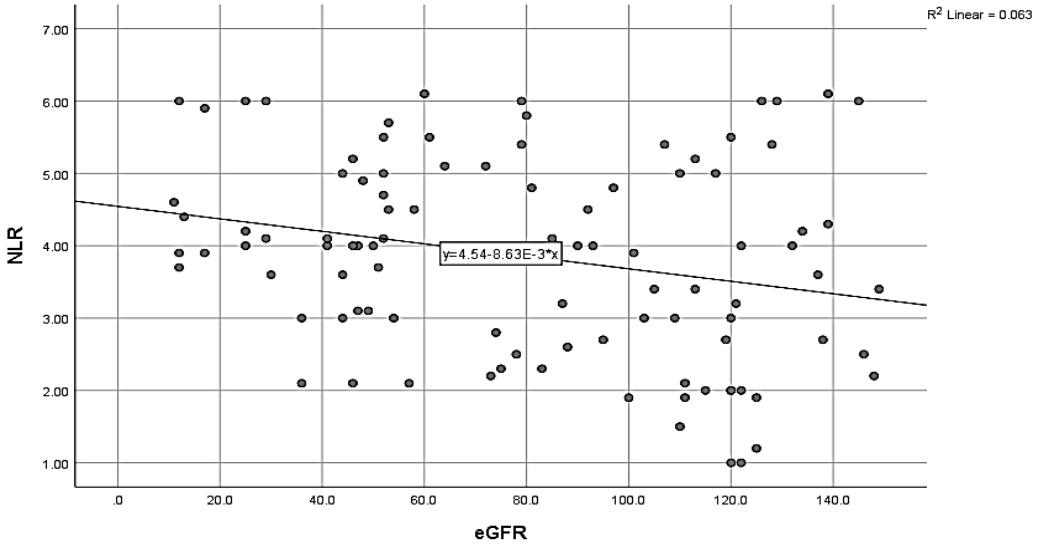

Figure (1): Correlation between eGFR and NLR among HTN with low eGFR group.

In this figure, there was a negative, moderate, but statistically significant correlation between the eGFR and NLR ($r = –0.562$, $p < 0.001$).

DISCUSSION

Hypertension is an important cause of cardiovascular diseases, if left untreated; hypertension can be life-threatening due to the comorbidities including cardiac arrhythmogenesis (sudden death), atherosclerosis, heart failure, brain hemorrhagic stroke, and kidney failure [17].

It has been well established that inflammation plays critical roles in the pathogenesis of hypertension and its comorbidities. For example, transferring lymphocytes of diseased animals to recipient animals induces high blood pressure, whereas immunosuppression lowers blood pressure, indicating that inflammation is the upstream of blood pressure elevation. Therefore, inflammation is indispensable for the initiation of hypertension and hypertension-associated organ damages [18].

Hypertension is the second most important cause of chronic kidney disease (CKD) after diabetes and hypertension may also be the presenting feature of asymptomatic primary renal disease (2018 ESC/ESH Guidelines for the management of hypertension). Chronic kidney disease (CKD) is a major health issue worldwide, which leads to end-stage renal failure and increasing cardiovascular morbidity and mortality [5].

Nonmicrobial inflammation contributes to CKD progression and fibrosis. The neutrophil count reflects inflammation, while the lymphocyte count indicates the status of general stress and nutrition. The neutrophil-to-lymphocyte ratio (NLR) in CKD patients provides information on the inflammation status. It is suggested that NLR is a complementary prognostic marker for evaluating the cardiovascular risk in CKD3-5 patients. Studies demonstrated that an increase in neutrophil count coupled with a reduction in lymphocyte counts predicts mortality in hemodialysis patients and peritoneal dialysis patient. Also, NLR indicates the rate of stage 4 chronic kidney disease progressing to dialysis [19].

The aim of this study was to study the Neutrophil-to-Lymphocyte ratio (NL R) as a novel marker for early detection of hypertensive kidney disease and NLR as a Predictor of Worsening Renal Function in patients with high normal blood pressure and in hypertensive Patients.

The study included four groups: Control group (group 1), High normal B.P with normal eGFR (group 2), HTN group with normal eGFR (group 3) & HTN group with low eGFR (group 4), which subdivided to 4 subgroups from CKD stage 1 to 4 according to eGFR.

There were statistical insignificant differences between study groups in age, sex smoking and drug history as p value >0.05, while family history showed significant difference between study groups as p<0.001 as hypertensive group with low eGFR had the highest risk of family history of HTN, CVD and renal diseases.

Our results were supported by study of **Yuan *et al.*** [20] who reported that there were no statistically significant differences between study groups as regard sex and smoking.

This was in concordance with the prospective observational study of **Akase *et al.*** [21], which included 184 men aged 73 ± 11 years and 174 women aged 76 ± 10 years at baseline. There were no inter-group differences based on gender, smoking status, daily alcohol consumption.

The present study showed that both systolic and diastolic blood pressure were significantly higher among HTN group with low eGFR (group 3) followed by HTN group with normal eGFR (group 2) (p=-0.002 and 0.011, respectively), while BMI showed insignificant difference p=0.608.

In concordance with our results, a study of **Jaaban *et al.*** [22] which studied the relationship between NLR and level of albuminuria. They reported that there was highly significant difference between their studied groups as regard systolic and diastolic blood pressure and there was no significant difference between their studied groups as regard BMI.

Regarding laboratory measures, the current study showed that albuminuria, creatinine, A/C ratio, uric acid and CRP were significantly higher among HTN group with low eGFR (group 3) followed by HTN group with normal eGFR (group 2) (p<0.001, respectively), while FBS and $HA1_C$ showed insignificant differences (p=0.203, 0.721, respectively).

Our results were supported by study of **Chen *et al.*** [23] which was carried out on a total of 15219 individuals, and out of them 4997 were hypertensive, they reported that an estimate of kidney function (BUN and CREA) was significantly higher in HTN compared with those in non-HTN (P < .0001).

In our study, total cholesterol, triglycerides, and LDL were significantly higher among HTN group with low eGFR (group 3) followed by HTN group with normal eGFR (group 2) (p=0.038, 0.010 and, 0.002, respectively), while HDL was significantly lower among group 3 followed by group 2 (p=0.029).

Our results were supported by study of **Karagoz *et al.*** [24] which was carried on 82 patients as they reported that serum low density lipoprotein (LDL), and triglyceride levels significantly higher in hypertensive patient with diastolic dysfunction (p < 0.05).

Also, **Chen *et al.*** [23] demonstrated that triacylglycerols (TG), cholesterol (Chol), and low-density lipoprotein (LDL) levels were all significantly higher in HTN group (P < 0.0001).

The present study showed that neutrophil, NLR and PLR were significantly higher among HTN group with low eGFR (group 3) followed by HTN group with normal eGFR (group 2) (p=0.010, 0.019 and 0.033, respectively), while lymphocyte was significantly

lower among group 3 followed by group 2 (p=0.005). Neutrophils and NLR were significantly higher among stage IV group followed by stage III (p=0.031, and 0.022, respectively), while lymphocyte was significantly lower among stage IV group followed by stage III (p=0.045).

Our results were in line with study of **Kutlugun *et al.*** [25] who stated that there was a positive correlation between the urine albumin level and NLR in the whole study groups ($r = 0.214$, $p < 0.005$). In non-diabetic patients there was a significant positive correlation between NLR and albuminuria ($r = 0.324$, $p = 0.013$).

Our results were supported by study of **Chen *et al.*** [23] as they reported that WBCs counts were significantly higher in HTN group ($P < .0001$; $P < .0001$). Median Hemoglobin and NEU, MON, EOS, & BAS counts, which were within the normal ranges, were significantly higher in HTN than in non-HTN ($P < .0001$). PLT was significantly lower ($P < .001$).

Whereas, in the study of **Karagoz *et al.*** [24], patients with diastolic dysfunction had significantly higher values of NLR when compared to control group (those with no diastolic dysfunction). Mean NLR value was found to be 2.07±0.82 in the study group while the control group had a mean value of 1.69±0.60 ($p = 0.020$). Other parameters of complete blood count (CBC) were also evaluated. Red cell distribution width (RDW-SD), mean platelet volume (MPV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), did not differ significantly between two groups ($p > 0.05$).

Similarly, in the study of **Sevencan & Ozkan**[26]**,** The NLR, albuminuria and uric acid levels of the patients with stage 3 CKD were higher than those with stages 1 and 2 ($p = 0.013$, $p = 0.001$ and $p = 0.001$, respectively). However, no statistically significant difference was detected for the PLR.

Furthermore, in the study of **Wang *et al.*** [27]**,** in which all patients were distributed into a high group ($NLR \geq 2.67$) and low group ($NLR < 2.67$). Compared with the low group, patients in the high NLR group had a higher incidence of proteinuria ($p < 0.001$), higher incidence of hypertension ($p = 0.003$), and worse renal function.

The current study showed that there was significant correlation between NLR and of blood pressure, urea, creatinine, eGFR, albumin/creatinine ratio, PLR, and CRP.

The areas under the ROC curves were 64.2, 69.8, 72.0 and 78.4 % for the NLR in CKD stages. The areas under the ROC curves for the NLR had statistically significant sensitivity and specificity was detected in different CKD stages.

Our results were supported by study of **Sevencan & Ozkan**[26]**,** as the areas under the ROC curves were 64.3% for the NLR, 63.4% for the albuminuria and 74.3% for the uric acid. The areas under the ROC curves for the NLR and albuminuria were very similar to each other, whereas the area for uric acid was larger.

This was in line with a study of **Yuan *et al.*** [20]**,** in which, the associations between NLR and ESRD are shown. After adjustment for demographic and traditional ESRD risk factors, as well as the baseline eGFR categories and ACR, baseline NLR was independently associated with the occurrence of ESRD in CKD stage 4 patients, with an HR value 2.12 (95% CI 1.10–4.10) compared with the lower NLR ($p = 0.025$).

Furthermore, **Chen *et al.*** [23]**,** analyzed the correlation between NLR and kidney functional parameters. NLR was positively correlated with BUN and CREA in HTN ($r = 0.09$, $P < 0.0001$; $r = 0.142$, $P < 0.0001$, respectively).

CONCLUSION

It could be concluded that NLR can be used as a marker with significant sensitivity and specificity for hypertensive nephropathy at different CKD stages. There was significant correlation between NLR and blood pressure, urea, creatinine, eGFR, albumin/creatinine ratio, and CRP.

Conflict of interest: The authors declare no conflict of interest.

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Author contribution: Authors contributed equally in the study.

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