

## Diagnostic Value of Neutrophil to Lymphocyte Ratio in Evaluation of Inflammation in CKD Patients

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### Abstract

**Background:** Neutrophil to Lymphocyte Ratio (NLR) may be a useful and less costly marker in relation to other tests for identifying inflammation in patients with chronic kidney disease at high risk of Cardiovascular Disease (CVD)-related complications. To evaluate the NLR as inflammatory marker among the CKD patients.

**Material and methods:** This is a cross-sectional analytical study was conducted in Chittagong Medical College Hospital during the period of May 2019 to May 2020. Eligible participants were patients of pre- dialysis and haemodialysis CKD patients. Total study duration was one year. Clinical data was obtained from patients through interviews. Complete blood count, serum creatinine, serum albumin, fasting lipid profile and C-Reactive Protein (CRP) were measured. NLR were constructed by dividing neutrophil count to lymphocyte count.

**Results:** Regarding socio-demographic variables, most of the patients were at age group 40-60 years (55.3%) and most were male (75.3%). 46 (54.1%) patients came from rural setting. Among all patients, 84 (98.8%) were hypertensive, (52.9%) were diabetic, 62 (72.9%) patients were at CKD stage 5 and 62 (72.9%) were on dialysis. Among all, 37 (73%) cases of CKD were due to DM, 26 (30.6%) were due to HTN and 18 (21.2%) were due to GN. NLR was raised in 57 (67.1%) cases, and hs-CRP was found raised in 61 (71.8%) cases. There is no relation

with age, gender and residence ration of NLR level among CKD patients. There are no significant association of NLR with HTN, DL and IHD but presence of DM is significantly ( $p < 0.05$ ) associated with raised NLR. There are significant variation of raised NLR with different stages of CKD and dialysis status. There is significant association of raised NLR with raised hs-CRP among CKD patients..

**Conclusion:** Elevated NLR ratio was present in patients both dialysis dependent and non-dialysis patients. Significant associations with well-known markers of inflammation (hs CRP), encourage the use of NLR ratio as a marker of inflammation in this population.

**Key words:** Chronic kidney disease; Inflammation; Neutrophil to lymphocyte ratio.

### Introduction

Patients with Chronic Kidney Disease (CKD) have an annual death rate of about 9% from CVD, which is roughly 10–20 times greater than the general population.<sup>1</sup> This high death rate cannot be adequately explained by conventional cardiovascular risk factors such as diabetes, Hypertension (HTN) and hyperlipidemia. Inflammation is now recognized as one of the primary factors contributing to the development of CVD, since several trials conducted in the last few decades have demonstrated a persistent low-grade inflammatory state in CKD patients.<sup>2,3</sup> It appears that future studies will concentrate on developing treatments to reduce inflammation and ultimately the burden of CVD in this particular population.

Complementary indicators are still needed to evaluate systemic inflammation, despite the introduction of several new markers. Neutrophil to Lymphocyte Ratio (NLR) has been investigated recently as a new indicator of inflammation in many populations and has been demonstrated to have predictive and prognostic effects, particularly in those with systemic inflammation.<sup>4-9</sup> NLR has been shown to be a reasonably priced biomarker to stratify the risk of mortality and recurrence in a number of cancer patients<sup>4-6</sup>. It was also discovered to be a predictor of death in cardiovascular research

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for several patient categories, including myocardial infarction and heart failure.<sup>9</sup> The NLR ratio and other inflammatory indicators in CKD patients have been the subject of a few studies.<sup>10,11</sup> The whole blood count is used to compute the NLR ratio and research on its utility in CKD patients is positive. Thus, the purpose of this study is to ascertain the usefulness of the NLR ratio in the CKD population, comprising pre-dialysis and MHD patients, as a gauge of systemic inflammation.

### Materials and methods

It was a cross sectional analytical study, studied in Department of Nephrology, Chittagong Medical College Hospital, Chattogram, Bangladesh during the period of May 2019 to May 2020 after acceptance of protocol.

The study included patients purposively of both sexes with pre- dialysis CKD patients having eGFRs <60 mL/min/1.73 m<sup>2</sup> [By the Modification of Diet in Renal Disease (MDRD) formula] equating to CKD stage 3 or 4 and the patients receiving Hemodialysis (HD) for more than 3 months who attending in Department of Nephrology, Chittagong Medical College Hospital (CMCH). Inclusion criteria was all patients who are suffering from CKD with or without dialysis. Exclusion criteria were unwilling to give consent, patients with active infection or inflammation like Community Acquired Pneumonia (CAP) patients with hepatitis B and C virus infection and impaired hepatic function, patients with autoimmune disease, patients with current malignancy or history of malignancy, patients on immunosuppressive therapy, patients with history of previous Coronary artery disease, hematological disease and patients with unstable cardiac disease.

Data were started to collect after approval from Ethical Review Committee of Chittagong Medical College. After selection, the aim, objectives and procedure of the study were explained in details to the subjects. They were encouraged for voluntary participation and were also be allowed to withdraw themselves from the study even after participation whenever they want. An informed

written consent was taken from all study patients. Patients were selected purposively. Patient interviews provided clinical data on baseline features and medical history. Age, gender, height, body weight, and blood pressure readings were noted for every participant. For patients awaiting dialysis, the estimated glomerular filtration rate was computed using the MDRD formula.<sup>12</sup> HD patients received conventional bi-carbonate dialysate and biocompatible synthetic membranes twice a week for four hours of dialysis. All individuals were fasted for the whole night before having venous blood samples taken. In specifically, sampling was done in the morning of a midweek dialysis session before HD patients were heparinized. Automated methods at the Department of Clinical Biochemistry, CMCH, identified the complete blood count and biochemistry analyses [Creatinine, serum albumin, total cholesterol, triglyceride, LDL cholesterol and high-density lipoprotein (HDL) cholesterol]. A full blood count test included the determination of the white blood cell differential. By dividing the neutrophil count by the lymphocyte count, NLR was created. A high sensitivity turbidimetry assay was used to quantify high sensitivity C-reactive Protein (hs CRP). The characteristics that were classified as clinical and demographic were age, sex, hypertension, diabetes, and dyslipidemia. The distribution of NLR among various sociodemographic characteristics, risk factors, variables associated to dialysis, and inflammatory marker (High-sensitivity CRP) were the outcome variables.

Statistical analyses were performed using data analysis software 'IBM SPSS Statistics' version 20.0 for Windows. Data were presented as mean and Standard Deviation (SD) or median (Interquartile range) for continuous/numerical variables and as frequency distribution and percentages for categorical variables. Continuous variables were compared by independent t-test and ANOVA test. Categorical variables were compared by Chi-square test. Pearson correlation test was done to see correlation. Statistical significance was defined as  $p < 0.05$ .

## Results

**Table 1** Distribution of socio-demographic variables and risk factors (base-line characteristics) among the study subjects (n = 85)

Variables		Frequency	Percentage (%)
Age (Years): Mean±Standard Deviation (SD)		52.44 ± 12.35	
Age Groups	< 40 Years	14	16.5
	40 – 60 Years	47	55.3
	> 60 Years	24	28.2
Gender	Male	64	75.3
	Female	21	24.7
Residence	Rural	46	54.1
	Urban	39	45.9
Hypertension	Present	84	98.8
	Absent	01	1.2
Diabetes Mellitus	Present	45	52.9
	Absent	40	47.1
Dyslipidaemia	Present	27	31.8
	Absent	58	68.2
Ischaemic Heart Disease	Present	23	27.1
	Absent	62	72.9

Socio-demographic variables where most of the patients were at age group 40-60 years (55.3%) and most were male (75.3%) and 46 (54.1%) patients came from rural area. Different risk factors of CKD were also showed where 84 (98.8%) were hypertensive and 45(52.9%) were diabetic. Dyslipidemia and ischemic heart disease were present in 31.8% and 27.1% patients respectively (Table I).

**Table II** Distribution of CKD related variables, hs CRP of the study subjects (n = 85)

Variables		Frequency	Percentage (%)
Dialysis Status	Yes	62	72.9
	No	23	27.1
Causes of CKD	Diabetes	37	43.5
	Hypertension	26	30.6
	Glomerulonephritis	18	21.2
	Others	04	4.7
hs-CRP (mg/l) : Median (Interquartile Range)		5.4 (2.3 – 14.0)	
High-sensitive CRP (hs-CRP)			
Status	High Risk (> 3 mg/l)	61	71.8
	Low Risk (≤3 mg/l)	24	28.2
NLR : Mean ± SD		3.56 ± 1.76	
Neutrophil to Lymphocyte Ratio (NLR) Status	Raised (≥3)	57	67.1
	Normal (< 3)	28	32.9

10.6%, 16.5% and 72.9% patients were at CKD stage 3, 4 and 5 respectively. 62(72.9%) patients were on dialysis. Among all 37(73%) cases of CKD were due to DM, 26(30.6%) were due to HTN and 18(21.2%) were due to GN. Median (IQR) of hs CRP was 5.4 (2.3 - 14.0) mg/l and 71.8% had higher risk. NLR was raised in 57(67.1%) cases and mean±SD value was 3.56 ± 1.76 (Table II).

**Table III** Distribution of Neutrophil to Lymphocyte Ratio (NLR) according to the socio-demographic variables and risk factors among the study subjects (n = 85)

Variables	NLR (Mean ± SD)	p value
Gender	Male	3.20 ± 1.93
	Female	2.91 ± 1.80
		p > 0.05*
		Not Significant
Residence	Rural	3.23 ± 2.00
	Urban	3.01 ± 1.77
		p > 0.05*
		Not Significant
Age Groups	< 40 Years	3.41 ± 1.64
	40 – 60 Years	3.05 ± 1.81
	> 60 Years	3.12 ± 2.21
		p > 0.05†
		Not Significant
Hypertension	Present	3.14 ± 1.90
	Absent	2.6
		p > 0.05*
		Not Significant
Diabetes mellitus	Present	3.61 ± 2.20
	Absent	2.59 ± 1.29
		p < 0.05*
		Significant
Dyslipidemia	Present	3.49 ± 2.45
	Absent	2.96 ± 1.56
		p > 0.05*
		Not Significant
Ischemic heart disease	Present	3.5 ± 1.4
	Absent	3.6 ± 2.0
		p > 0.05*
		Not Significant

\*Independent t test, †ANOVA test.

There were no significant of NLR with age, gender and residence among CKD patients. Regarding risk factors, there were no significant association of NLR with hypertension, dyslipidemia and ischemic heart disease but presence of diabetes mellitus is significantly (p<0.05) associated with raised NLR (Table III).

**Table IV** Distribution of Neutrophil to Lymphocyte Ratio (NLR) according to the CKD related variables among the study subjects (n = 85)

Variables	NLR (Mean ± SD)	p value
CKD stages	Stage 3	1.71 ± 0.59
	Stage 4	2.70 ± 0.95
	Stage 5	4.02 ± 1.77
		p < 0.001†
		Very Highly Significant
Dialysis status	Yes	4.02 ± 1.77
	No	2.31 ± 0.95
		p < 0.001*
		Very Highly Significant

\*Independent t test, †ANOVA test.

There were significant variation of raised NLR with different stages of CKD and dialysis status ( $p < 0.001$ ) (Table IV).

**Table V** Association between hs CRP and NLR status (n = 85)

NLR Status□ □	hs-CRP Status□		p value*
	High Risk□	Low Risk□	
Raised□	47 (77.0)□	10 (41.7)□	p<0.001
Normal□	14 (23.0)□	14 (58.3)	

Data were presented as frequency (percentage). \*Chi-square test.

There was significant association of raised NLR with raised hs-CRP among CKD patients ( $p < 0.001$ ) (Table V).

### Discussion

Among 85 patients socio-demographic variable evaluated where most of the patients were at age group 40-60 years (55.3%) with mean age were  $52.44 \pm 12.35$  years and most were male (75.3%) and 46 (54.1%) patients came from rural setting. Regarding different risk factors of CKD where 84(98.8%) were hypertensive and 45 (52.9%) were diabetic. Analysis of etiology of CKD were done where 62 (72.9%) patients were at CKD stage 5, 62 (72.9%) were on dialysis. Among all 37(73%) cases of CKD were due to DM, 26(30.6%) were due to HTN and 18 (21.2%) were due to GN. This results were consistent with a previous study.<sup>13</sup>

It was found that 67.1% patients had higher NLR and mean NLR was  $3.56 \pm 1.76$ . Moreover, 71.8% of our patients had high hs-CRP. Korevaar et al. and Shaarawy et al. had similar result like this study.<sup>14</sup> N/L ratio, a novel biomarker for assessing inflammation, has been getting widely used to identify patients with various illnesses. It can be calculated routinely without additional cost from the complete blood count, Neutrophil-to-Lymphocyte Ratio (NLR) is obtained by dividing neutrophil to lymphocyte count.<sup>15</sup>

In this study there was also more significant higher NLR ( $3.61 \pm 2.20$ ) in DM patients with CKD which was higher from above study which was supported by previous study.<sup>16</sup> Also in our study there is no statistically significant relation of dyslipidaemia and hypertension with NLR and this comes in similar to Okyay et al.<sup>17</sup>

Our study results goes in favour with the chronic inflammatory state present in CKD patients specially in ESRD and advanced stages of CKD which supported by previous studies.<sup>13,18,19</sup>

By using pearson's correlation, there was also statistically significant positive correlation between NLR and hs-CRP with p value<0.001. So NLR can be used as a inflammatory marker.<sup>20,21</sup>

N/L ratio is a newer marker for inflammation and higher value have an effect in CKD progression, CVS outcome and mortality. This study demonstrated that higher value of N/L ratio is found in DM, advanced CKD and ESRD patients.<sup>14,22-25</sup> Moreover, it positively correlate with inflammatory marker hs-CRP.

### Limitations

The study was for short duration and single centered. There were relatively small number of the study population and all the lab investigation were not supported by single centre.

### Conclusions

N/L ratio is higher in diabetic patients, advanced CKD and dialysis patients. It is positively correlate with well-known inflammatory marker hs-CRP. Moreover, N/L ratio has strong association with inflammation as it strongly associated with hs-CRP.

### Recommendation

N/L ratio can be used as marker of inflammation in CKD patients. But, this was a single center study with a small population. So, a large scale multicenter study should be carried out to assess its importance in CKD patients.

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### Contribution of authors

MAK-Conception, acquisition of data, interpretation of data, drafting the article and final approval.

BKB-Acquisition of data, revision of content & final approval.

SMI-Data analysis, critical revision and final approval.

MA-Design, drafting and final approval.

MMR-Acquisition of data and revision of content and final approval.



MFR-Interpretation of data, critical revision & final approval.

MNH-Conception, critical revision of content & final approval.

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### Disclosure

All the authors declared no conflict of interest.

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