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Study of neutrophil lymphocyte ratio in patients in different stages of chronic kidney disease attending a tertiary care Centre

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Abstract

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular ration rate (GFR). There is strong evidence that an acute and chronic pro-inflammatory state exists in adults with chronic kidney disease and ESRD and that inflammation contributes to morbidity and mortality.

Several studies have shown that the neutrophil lymphocyte ratio (NLR) is a marker that reflects the state of systemic inflammation. A high neutrophil lymphocyte ratio was reported to be associated with cardiovascular events and mortality. However, little is known about the association between neutrophil lymphocyte ratio and disease severity in patients with chronic kidney disease (CKD). Therefore, the aim of the present study was to determine association between neutrophil lymphocyte ratio and eGFR in CKD patients.

In this hospital based cross sectional study of 1 year duration among 100 chronic kidney disease patients seeking inpatient and outpatient care from departments of General Medicine and Nephrology in Government Medical College, Ernakulam, the primary objective was to estimate the neutrophil lymphocyte ratio in patients with different stages of chronic kidney disease. The secondary objective was to find the correlation between

the neutrophil lymphocyte ratio and estimated GFR in patients with chronic kidney disease.

The data were entered into Microsoft excel sheet and analysed using R software version 4.2.0. Qualitative variables were expressed as proportions and quantitative variables were expressed as mean and standard deviation. Association between qualitative variables was tested using Chi square test. Association between quantitative variables was done by Independent sample t test. Significance level was fixed at a p value ≤ 0.05.

The median neutrophil lymphocyte ratio in chronic kidney disease patients was determined to be 2.4 with IQR 2-3.2 . There was a significant negative correlation between eGFR and neutrophil lymphocyte ratio with a p-value 0.01. It was observed that neutrophil lymphocyte ratio increased as the chronic kidney disease stage progressed, 2.1±0.5 in stage 2 chronic kidney disease, 2.2 ±0.8 in stage 3 chronic kidney disease, 2.4 ±1.2 in stage 4 chronic kidney disease, 2.9 ±1 in stage 5 chronic kidney disease. In this study, neutrophil lymphocyte ratio was found to be higher in chronic kidney disease patients on dialysis (3±1) when compared to chronic kidney disease patients not on dialysis (2.2±0.9).

Keywords: Chronic kidney disease,Glomerular filtration rate , Neutrophil Lymphocyte ratio

Introduction

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular ration rate (GFR).(1)(2). There is strong evidence that an acute and chronic pro-inflammatory state exists in adults with chronic kidney disease and ESRD and that inflammation contributes to morbidity and mortality(3)(4)(5). Studies demonstrated that an increase in neutrophil count coupled with a reduction in lymphocyte counts predicts mortality in hemodialysis patients and peritoneal dialysis patient and indicates the rate of stage 4 chronic kidney disease progressing to dialysis(6)(7). Studies have shown that neutrophil lymphocyte ratio has prognostic potential towards end stage renal disease (ESRD), cardiovascular disease (CVD) and all-cause mortality in patients with stage 1–4 chronic kidney disease other than stage 5 chronic kidney disease(8). Since neutrophil lymphocyte ratio is readily derived from complete blood count tests, its might provide significant information regarding inflammation in chronic kidney disease patients and predictor for progression of disease and cardiovascular outcomes. In this study, I aim to study neutrophil lymphocyte ratio in chronic kidney disease and its correlation with different stages of chronic kidney disease.

Materials and Methods

Study design: Hospital based cross sectional study.

Study setting:

Government Medical College Hospital, Ernakulam.

Study duration: One year from date of final approval by IEC and IRB and clearance of study by the KUHS.

Study subjects: The study will be conducted among inpatients and outpatients of Department of General Medicine and Department of Nephrology and chronic kidney disease patient undergoing dialysis in Dialysis unit of Government Medical College Hospital, Ernakulam.

Inclusion criteria: Patients above the age of 18 years with a diagnosis of chronic kidney disease according to Cockroft Gault equation.

Exclusion criteria

- Infections (UTI, URTI, LRTI, GI infection, Otitis media, Viral infection, TB Local infection ,Skin infection)

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- Malignancy.
- Congestive heart failure.
- Chronic liver disease
- Acute cerebrovascular accident
- Those not willing to give consent

Sample size

According to Yoshitomi et al, high neutrophil lymphocyte ratio is associated with poor renal outcomes in Japanese patients with chronic kidney disease.The prevalence of high neutrophil lymphocyte ratio in chronic kidney disease was found to be 65%. Using the formula sample size N=4pq/d2. Here p-65 and d =10 (less than 15% of prevalence), Therefore, N=4x 65x35/10x10=91 N= 91(approximate). The sample size for the study is to be fixed at 100.

Sampling method

All consecutive cases of patients satisfying inclusion criteria were included in the study.

Study variables

- Sociodemo graphic variables
- Neutrophil-Lymphocyte ratio
- E-GFR

Data collection

A structured questionnaire was used to collect information on socio- demographic characteristics, the medical history of the participant and investigation results.

Study Procedure

After obtaining Institutional Ethics Committee clearance all patients satisfying the inclusion criteria for the study are taken. After informed written consent from the study participants, a detailed history taking and physical examination including general examination and systemic examination was done and the findings were recorded.

The data was collected from results of various investigations already done as part of treatment and entered into the proforma. The creatinine clearance calculated from Cockcroft – Gault equation.

Then the patients were graded using KDIGO guidelines into different stages.

Stage	Description	GFR(ml/min/1.73m2)
1	Kidney disease with normal or high GFR	>90
2	Kidney damage with mild reduction in GFR	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR	15-29
5	Kidney failure (ESRD)	<15

Table 1: Staging of CKD

The neutrophil lymphocyte ratio in different stage of chronic kidney disease was studied and correlation between neutrophil lymphocyte ratio and eGFR in chronic kidney disease patients was calculated using correlation coefficient.

Data Analysis

Data was entered into MS Excel sheet.

Analysed using R statistical software version 4.2.0.

Qualitative variables were expressed as proportions and quantitative variables were expressed as mean and standard deviation.

Association between qualitative variables was tested using Chi square test. Association between quantitative variables were done by Independent sample t test. Significance level was fixed at a p value $\leq$ 0.05. A correlation between neutrophil

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lymphocyte ratio was calculated using correlation coefficient.

Ethical Considerations

Informed written consent was obtained.

Confidentiality of the subject was maintained throughout the study.

No financial burden imposed on the subjects

Budget

No additional expenses were incurred from the participants during the study.

Observation and Results

Data were entered in Microsoft Excel 365 Software and analysed using R software version 4.2.0.

The continuous variables like age, body weight, haemodynamic parameters, haematological parameters, and biochemical parameters were summarised as mean and standard deviation. Neutrophil lymphocyte ratio and urine protein creatinine ratio and eGFR were summarised as median and IQR. Categorical variables like sex, district, education level, socioeconomic status, residential status, comorbidity status, type of dialysis, frequency of haemodialysis, CVS, CNS, GIT and respiratory system findings, urine albumin level, and stage of chronic kidney disease were summarised as frequency and proportions. Age was also categorised into intervals of 10.

Association between eGFR and neutrophil lymphocyte ratio was assessed using Pearson correlation analysis. The continuous variables like age, body weight, haemodynamic parameters, haematological parameters, and biochemical parameters were summarised as mean and standard deviation. NLR and urine protein creatinine ratio and eGFR were summarised as median and IQR. Categorical variables like sex, district, education level, socioeconomic status, residential status, comorbidity status, type of dialysis, frequency of haemodialysis, CVS, CNS, GIT and respiratory system findings, urine albumin level, and grade of CKD were summarised as frequency and proportions. Age was also categorised into intervals of 10.

Association between eGFR and NLR was assessed using Pearson correlation analysis.

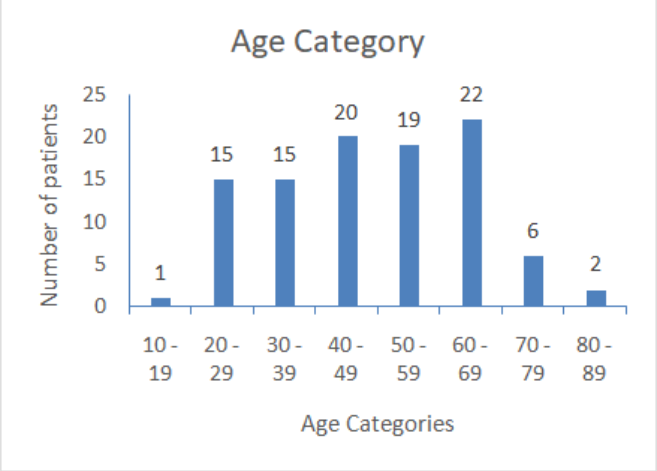

Fig. 1: Age distribution of study participants

The mean age (SD) of the study participants was 48.6 (16.1) years.

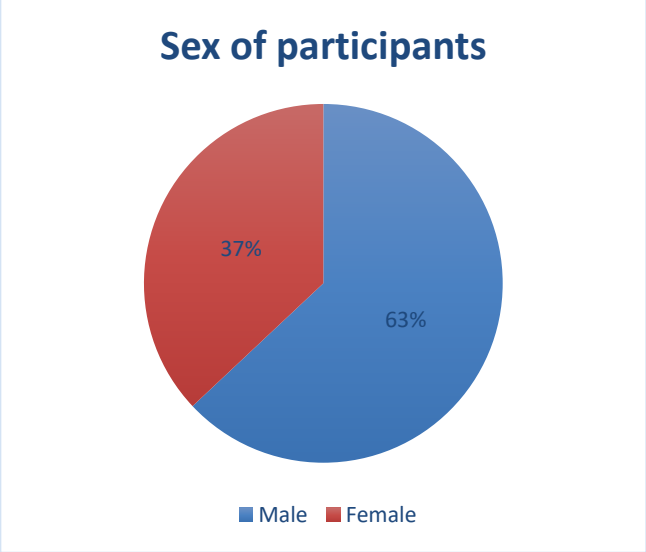

Fig. 2: Sex distribution of study participants

Out of the 100 participants, 63 (63%) were males

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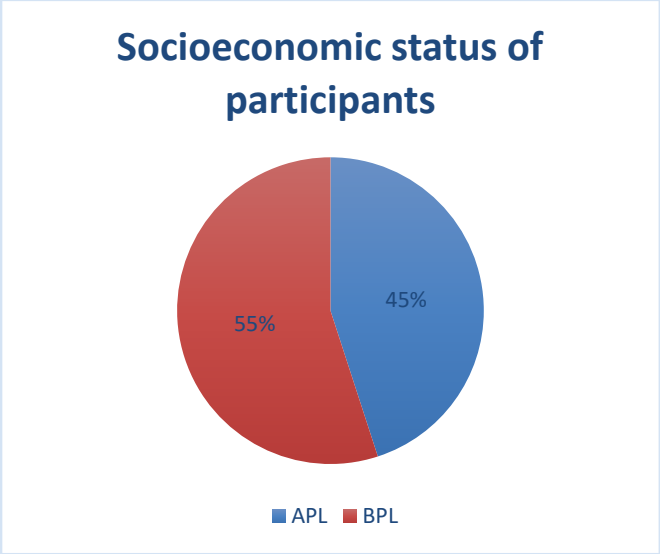

Fig. 3: Socioeconomic status of study participants

Out of the 100 participants, 55 (55%) belonged to BPL category.

Table 2: Body weight of the participants

	Mean	SD
Body weight (kg)	60.6	7.1

The mean body weight was found to be 60.6+7.1

Table 3: 1 Comorbidity status of the patients

Comorbidity	N	%
Diabetes Mellitus	55	55.0
Hypertension	56	56.0
Coronary Artery Disease	27	27.0
Thyroid dysfunction	15	15.0

The majority of participants were suffering from diabetes mellitus (55%) and hypertension (56%).

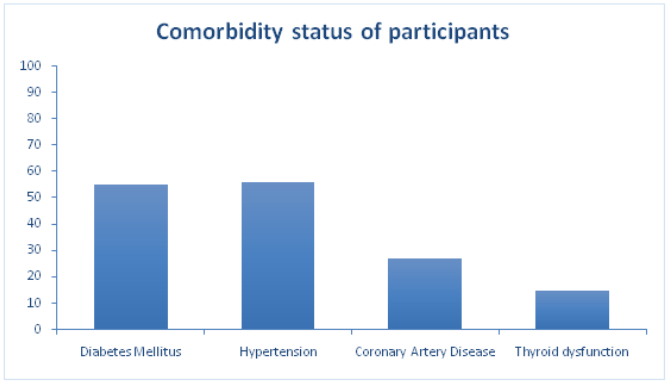

Figure 4: Comorbidity status of study participants

Table 4: Type of dialysis of the patients

Type of dialysis	N	%
Peritoneal Dialysis	1	1.0
Haemodialysis	46	46.0

46 (46%) were undergoing haemodialysis and one (1%) patient was undergoing peritoneal dialysis among the participants.

Table 5: Frequency of haemodialysis of the patients (N = 46)

Frequency of HD	N	%
2	37	80.4
3	9	19.6

The majority (80.4%) were undergoing procedures two times a week among the participants undergoing haemodialysis (N = 46).

Table 6: Hemodynamic parameters of the participants

Hemodynamic parameters	Mean	SD
Pulse Rate	81.1	11.1
Systolic Blood Pressure	136.4	18.3
Diastolic Blood Pressure	85.0	12.1

Table 7 : CVS findings of the participants

CVS findings	N	%
ESM	5	5.0
PSM	6	6.0
Normal	89	89.0

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The majority (89.0%) of participants had normal CVS findings.

Table 8: CNS findings of the participants

CNS findings	N	%
Flap	1	1.0
Normal	99	99.0

The CNS findings of the majority (99.0%) of participants were within normal limits.

Table 9: Respiratory system findings of the participants

Respiratory system findings	N	%
Rhonchi	1	1.0
Crepitations	16	16.0
Clear	83	83.0

The respiratory system findings of the majority (83.0%) of participants were within normal limits.

All participants in the study had normal findings in the gastro-intestinal examination.

Table 10: Haematological parameters of the patients

Haematological parameters	Mean	SD
Haemoglobin (mg/dl)	10.4	2.0
PCV	32.9	7.6
Total Count	7350.4	2054.5
Differential count (%) – Polymorphs	60.0	9.2
Differential count (%) – Lymphocytes	25.5	7.3
Absolute Neutrophil Count	4468.8	1640.4
Absolute Lymphocyte Count	1872.5	715.5
ESR (mm in first hour)	39.0	22.8
Platelet count (in Lakhs)	2.4	0.8
MPV	8.4	1.4
PDW	15.8	0.6
Platelet – Large Cell Ratio	22.8	4.3

Table 2 Biochemical parameters of the participants

Biochemical parameters	Mean	SD
Urea	82.0	47.6
Creatinine	6.6	4.6
Total Protein	6.9	0.5
Albumin	3.6	0.5
Serum Sodium	136.4	5.0
Serum Potassium	4.4	0.8
Random Blood Sugar	185.4	83.8

Table 3 Urine albumin of the participants

Urine Albumin	N	%
Nil	18	18.0
Trace	5	5.0
1+	33	33.0
2+	31	31.0
3+	7	7.0
4+	6	6.0

The majority (83.0%) of participants had normal respiratory system findings.

Table 13: Urine protein creatinine ratio of the participants

	Median	IQR
Urine protein creatinine Ratio	1.4	0.7, 2.4

Table 4 e GFR of the participants

	Median	IQR
eGFR	11	6, 39

Table 5 Grade of CKD of the participants

Grade of CKD	N	%
2	8	8.0
3	25	25.0
4	12	12.0
5	55	55.0

The majority of the participants (55%) in the study had grade 5 CKD.

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Table 16: Neutrophil lymphocyte ratio of the participants

	Median	IQR
Neutrophil Lymphocyte Ratio	2.4	2.0, 3.2

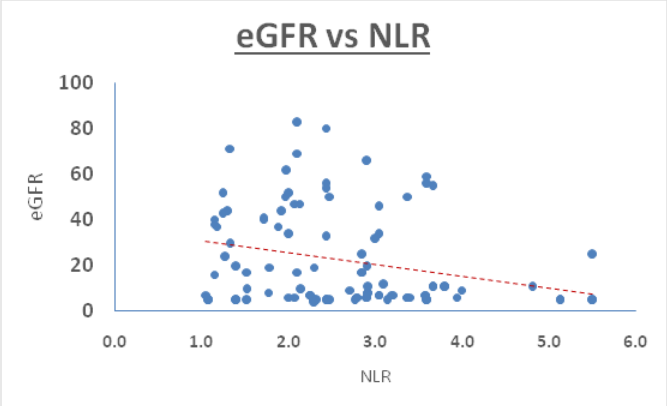

Figure 5: eGFR with Neutrophil Lymphocyte Ratio

Pearson correlation coefficient of eGFR with NLR is -0.25. There was a significant correlation between eGFR and NLR with a p-value 0.01.

Table 6 : Neutrophil lymphocyte ratio of the participants with dialysis status

	Predialysis n = 53	Under Dialysis n = 47	p-value
Neutrophil Lymphocyte Ratio	2.2 (0.9)	3.0 (1.0)	<.001
Mean (SD)			

NLR levels were found higher in dialysis patient than in predialysis patient indicating the disease progression.

Table 7 : NLR with Grade of CKD of the participants

Grade of CKD	NLR Mean (SD)	p-value
2	2.1 (0.5)	.007
3	2.2 (0.8)	
4	2.4 (1.2)	
5	2.9 (1.0)	

One way ANOVA test showed significant association of NLR with grade of CKD with p-value .007. Post hoc analysis found significant difference between patients in grade 3 and grade 5 CKD, with p-value .02.

Discussion

Early on in CKD, inflammation starts to develop. Recent studies have stressed that NLR could be used as a marker for inflammation because inflammation causes an increase in neutrophil numbers while a decrease in lymphocyte counts.(6) Other investigations demonstrated that NLR is elevated in inflammatory conditions associated with cardiovascular problems and can be utilised as a prognostic marker(9)(10).Ghaffari et al. demonstrated that NLR is a predictor of myocardial infarction prognosis and risk of significant postinfarction events(11). NLR and lifespan are connected, according to studies on patients with cardiovascular disease and cancer (12).

In the present hospital based cross sectional study conducted among patients of General Medicine and Nephrology department of Government Medical College Ernakulam during March 2021- February 2022, the total number of cases were 100 out of which 63 were males and 37 were females with a male to female ratio 1.7:1. The mean age of the study participants was 48.6 ±16.1 years**.** 90% of patient were from Ernakulam district.

In this study, Hypertension was the most common comorbidity seen in 56% of patients followed by Diabetes mellitus(55%).Numerous studies suggest that the risk factors for progression of CKD include diabetes mellitus, systemic hypertension, smoking, dyslipidaemia, atherosclerotic disease, presence of inflammatory markers, obesity, and male sex (13)(14). In spite of the large number of risk factors, several studies have recently focused on the relationship

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between inflammation and CKD. Bash et al found that inflammation and homeostasis are important preceding pathways in the progression of kidney disease independent of the major traditional risk factors. (15)

46% of patients underwent haemodialysis of which 80.4% patients had twice weekly dialysis. One patient underwent peritoneal dialysis and rest were managed conservatively without dialysis. The majority of participants in this study i.e., about 55% of patients had stage 5 CKD ; 25% had stage 3 CKD, 12% had stage 4 CKD and 8% had stage 2 CKD.

The median NLR in CKD patient was found to be 2.4 with IQR 2-3.2. thus NLR is considerably higher in CKD patients, and that NLR rises as renal disease progresses.(9) These findings provide that a simple calculation of N/L ratio might be a surrogate marker for evaluation of inflammation in CKD patients.

This study also showed that, in comparison to predialysis and dialysis patients with CKD had higher levels of N/L ratio, similar to Okyay et al (10) study where healthy, predialysis and dialysis patients with CKD had higher levels of N/L ratio, IL-6, and hs-CRP, and N/L ratio exhibited positive relationships with these inflammatory biomarkers.

Conclusion

NLR was higher in ckd patient than in healthy individuals

Median nlr ratio in CKD patient was found to be 2.4 with IQR 2.4-3

Limitations

The population for study was 100, it should have been assessed in a larger population.

Many factors affect N/L ratio such as infection, inflammatory diseases, cancer, and cardiovascular events. However, we tried to exclude these factors; some subclinical cases could be incorporated into the study population.

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