THE RELATIONSHIP BETWEEN NEUTROPHIL TO LYMPHOCYTE RATIO AND DISEASE PROGRESSION IN PATIENTS WITH STAGE 1-4 CHRONIC KIDNEY DISEASE

Walaa Mayhob[*1], Ibrahim Sulaiman[2] and Suzanne Alshemali[3]

[1]Department of Internal Medicine, Tishreen University, Faculty of Medicine, Lattakia, Syria.
[2]Department of Nephrology, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.
[3]Department of Laboratory Medicine, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.

*Corresponding Author: Walaa Mayhob

Department of Internal Medicine, Tishreen University, Faculty of Medicine, Lattakia, Syria.

ABSTRACT

Objective: The aim of this study is to investigate the association between neutrophil to lymphocyte ratio (NLR) and progression to dialysis in patients with chronic kidney disease(CKD)stage1-4. **Patients and Methods:** Prospective Analytical Study conducted for the period one year(April 2020 – April 2021) at Tishreen University Hospital in Lattakia-Syria. The study included 128 patients with CKD stage 1-4. **Results:** The median age was 64 years, males represented 56.3 % of the patients, and 61.7% were graded in the stage IV with median duration of disease 24 month. Hypertension was the most frequent co-morbidities(82.8%). When the peak NLR reached 4.8, progressive of disease could be predicted with an area under the ROC curve of 0.69(95% CI:0.57-0.76) with sensitivity 67.2% and specificity 62.9%. NLR >4.8 was associated significantly with increased risk of decreasing glomerular filtration rate(GFR). NLR was associated with the risk of occurrence ESRD in patients with stage 4 CKD: HR 2.3(95% CI 0.2-3.9),P:0.01. **Conclusion:** Our study findings demonstrated that progression of kidney disease is significantly associated with inflammation, and NLR could be candidates for predicting renal outcomes in patients with CKD stage 1-4.

KEYWORDS: chronic kidney disease, neutrophil to lymphocyte ratio, NLR.

INTRODUCTION

Chronic kidney disease(CKD)is defined by presence of kidney damage or decreased glomerular filtration rate(GFR) of less than 60 ml/min/1.73 m^2 for three or more months irrespective of the cause.[1] The estimated prevalence is 10.6-13.4%, and 1.2 million people died annually from CKD.[2]

There are different stages of CKD form a continuum. Patients are generally asymptomatic in the stages 1-3, but in stages 4-5 endocrine and metabolic disturbances in water or electrolyte balance become clinically manifest.[3,4]

CKD is a global health problem with high socioeconomic burdens particularly due to progression to end stage renal disease(ESRD), associated cardiovascular events, hospitalization and death.[5]

Various changes will develop during progression of disease including glomerular, tubular an vascular injuries.[6] Persistent Inflammatory processes are common in patients with CKD. It may occur via many mechanisms, and contribute to development of renal fibrosis.[7] CKD- associated inflammation can be assessed by using several biochemical markers including increased levels of interleukin-6(IL-6) and tumor necrosis factor-alpha(TNF-a) which are involved in the inflammatory response and predict poor outcome. Other cytokines such as IL-8, IL-18 has also be linked to renal function decline.[8]

The ratio of neutrophil to lymphocyte (NLR) reflects the balance between adaptive immunity(count of lymphocyte) and both acute and chronic inflammation(count of neutrophil). In recent years, NLR has received as potential new marker which associated with outcome and predict the course of disease among

patients with a variety of medical conditions including CKD.[9] Identification of available, rapid, inexpensive, and reliable prognostic factors can improve the outcome.[10] Therefore, the objective of this review was to determine the association of NLR ratio to renal outcome in patients with CKD stage 1-4.

PATIENTS AND METHODS

This is Prospective Analytical Study of a group of patients with CKD stage 1-4 attending the Nephrology Department's at Tishreen University Hospital in Lattakia-Syria during one year period (April 2020 to April 2021). The exclusion criteria were: patients undergoing emergency hemodialysis, acute infection(white blood cell >11000), patients with cancer, autoimmune diseases, and prescribed corticosteroids in the last month of admission. The following data were recorded: age, sex, co-morbidities, and stages of CKD. Blood samples were collected for measurement of neutrophil(NEUT), lymphocyte(LYM), C-reactive protein(CRP), renal function(urea, creatinine), and creatinine was used to calculate estimated glomerular filtration at admission (eGFR1). After 3 months, patients were reevaluated by estimating eGFR2. NLR was calculated as the ratio of derived neutrophil and lymphocyte counts.

Definitions
Staging of CKD: The stages of CKD are classified as follows:
Stage 1: kidney damage with normal or increased GFR(>90 mL/min/1.73 m2)
Stage2: Mild reduction in GFR(60-89 mL/min/1.73 m2)
Stage3a: Moderate reduction in GFR(45-59 mL/min/1.73 m2)
Stage3b: Moderate reduction in GFR(30-44 mL/min/1.73 m2)
Stage4: severe reduction in GFR(15-29 mL/min/1.73 m2)

Stage5: kidney failure(GFR<15 mL/min/1.73 m2 or dialysis).[11]

Statistical Analysis
Statistical analysis was performed by using IBM SPSS version20. Basic Descriptive statistics included means, standard deviations(SD), median, Frequency and percentages. Independent t student test or Mann Whitney test was used to compare 2 independent groups. Differences among different groups were examined with using chi- square test or Fisher exact test. The receiver operating characteristics(ROC) curves were constructed, and the area under curve(AUC) was established to assess the ability of peak NLR in predicting progressive of disease. Multiple logistic regression analysis was performed to estimate independent predictive factors. This model included risk factors first identified through univariate analysis. p value <0.05 was considered as statistically significant.

Ethical consideration: All patients were provided a complete and clear informed consent after discussion about the study. This study was performed in accordance with the Declaration of Helsinki.

RESULTS

A total of 128 patients with CKD stage 1-4 were included in the study, the baseline characteristics of patients were as shown in Table(1). The median age of patients was 64 years(range 32-91 years), 56.30% were males, and 35.2% were smokers. Hypertension was the most frequent co-morbidities(82.8%),followed by diabetes mellitus(72.1%).The patients were classified as follows: stage II: 6.3%, stage III: 32%, and stage IV: 61.7%, with median duration of disease 24 months(range 5-120 month).

Table 1: Demographic characteristics of the study population.

Variables	Patients
Age (years)	64(32-91)
Sex	
Female	56(43.80%)
Male	72(56.30%)
Duration of disease(months)	24(5-120)
Stages of CKD	
II	8(6.3%)
III	41(32%)
IV	79(61.7%)
Co-morbidities	
Hypertension	106(82.8%)
Diabetes mellitus	93(72.1%)
Ischemic heart disease	19(14.8%)
Smoking	45(35.2%)

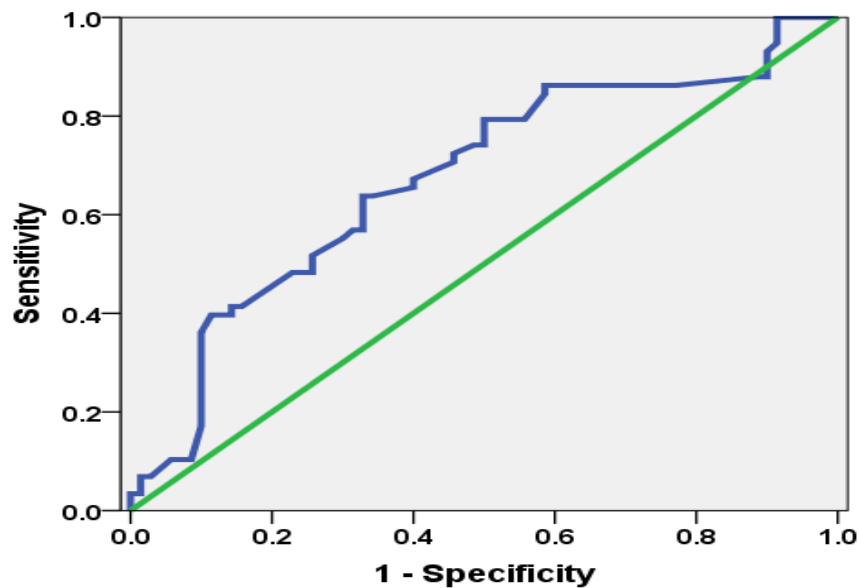The AUC of ROC was 0.69(95% CI:0.57-0.76), Figure1.

Figure 1: Receiver operating characteristics curve presenting ability of peak NLR in predicting progressive of disease.

The best cutoff value of NLR that can be used to predict progressive of disease was 4.8 with sensitivity 67.2 % and specificity 62.9%. Based on this cutoff value, patients were divided into two groups: <4.8 and ≥4.8. As shown in table(2), patients in the high NLR group were older (66.3±11.1 vs. 61.1±9.2, p: 0.006), with higher rate of hypertension(90.4% vs. 72.7%, p: 0.009), diabetes mellitus(82.2% vs. 60%, p: 0.005), and ischemic heart disease(20.5% vs. 7.3%, p: 0.03). There were no significant differences between the two groups regarding to sex, presence of smoking, and duration of disease(p>0.05).

Table 2: Demographic characteristics of the study population according to NLR.

Variable	<4.8	≥4.8	P value
Sex Female Male	28(50.9%) 27(49.1%)	28(38.4%) 45(61.6%)	0.1
Age	61.1±9.2	66.3±11.1	0.006
Smoking	18(32.7%)	27(37%)	0.6
Co-morbidities Hypertension Diabetes mellitus Ischemic heart disease	40(72.7%) 33(60%) 4(7.3%)	66(90.4%) 60(82.2%) 15(20.5%)	0.009 0.005 0.03
Duration of disease	2.8±2.6	2.5±1.8	0.5

Patients in the high NLR group had significantly higher mean neutrophil (6.73±1.7 vs. 5.85±1.5, p: 0.004), NLR(6.40±1.3 vs. 3.83±0.5, p: 0.0001), urea(126.06±43.9 vs. 98±37.7, p: 0.0001), and significantly lower eGFR1(25.96±7.1 vs. 35.78±14.4,p: 0.002) and eGFR 2(21.90±8.2 vs. 29.80±12.1, p: 0.001). There were significant differences between the two groups regarding eGFR, in which eGFR was 15-30 in 72.6% of the patients in the high NLR group.

Table 3: Laboratory parameters of the study population according to NLR.

Variable	<4.8	≥4.8	P value
Lymphocyte	1.50±0.4	1.23±1.03	0.07
Neutrophil	5.85±1.5	6.73±1.7	0.004
NLR	3.83±0.5	6.40±1.3	0.0001
CRP	18.2±14.88	17.07±14.08	0.8
Urea	98±37.7	126.06±43.9	0.0001
eGFR 1	35.78±14.4	25.96±7.1	0.002
eGFR 2	29.80±12.1	21.90±8.2	0.001

eGFR grades			
eGFR≥ 60	8(14.5%)	0(0%)	
30 ≤ eGFR<60	21(38.2%)	20(27.4%)	0.001
15≤ eGFR<30	26(47.3%)	53(72.6%)	

During follow up period, there were 58 ESRD event occurred, higher incidence rate of ESRD events was observed with increase in NLR(41(56.2%) vs. 17(30.9%), p:0.004). The mean value of NLR was significantly higher in patients who developed ESRD compared to those who didn't(5.85±1.7 vs. 4.84±1.4,p: 0.004).

After adjustment the factors associated with increased progression to ESRD, NLR was associated independently with occurrence of ESRD in patients with stage 4 CKD, with HR value 2.3(95% CI 0.2-3.9) compared with lower NLR, P:0.01, table(4).

Table 4: Association of NLR with ESRD events among CKD patients according to the stage.

NLR(Ratio)	HR	P value	Confidence interval
eGFR≥ 60			
<4.8	Ref	0.8	[0.2-3.1]
≥4.8	0.9		
30 ≤ eGFR<60			
<4.8	Ref	0.09	[0.9-4.1]
≥4.8	1.6		
15≤ eGFR<30			
<4.8	Ref	0.01	[0.2-3.9]
≥4.8	2.3		

DISCUSSION

Although neutrophil and lymphocyte count are routinely evaluated under simple laboratory conditions among patients with CKD, the clinical importance of NLR in progression the disease remains unclear.

The current study of 128 patients with CKD stage 1-4 shows that majority of patients were elderly, and approximately two third were CKD stage 4. The most frequent co-morbidities were hypertension followed by diabetes mellitus. It is also demonstrated that NLR levels carry important prognostic information in CKD patients regarding their outcomes, in which the cutoff value of NLR 4.8 was a significant independent predictor for progression to ESRD. Elevated levels of NLR correlated significantly with lower eGFR, with HR 2.3 times for occurrence of ESRD in patients with stage 4.

The exact mechanisms that can explain the association between inflammation and observed progression of disease is not fully understood, and there are many supposed mechanisms. Inflammation contributes by inducing the release of cytokines and increased production and activity of adhesion molecules which lead together to T cell adhesion and migration into interstitium, subsequently attracting profibrotic factors.[12] The results of our study are consistent with the previous studies that found that NLR value played a predictive role in CKD progression.

Kocyigit *et al*., (2013) showed high progression rate of stage 4 CKD to dialysis in patients with NLR ratio> 3 compared with low level. The sensitivity and specificity of NLR were 79% and 69% respectively.[13]

Tonyali S *et al*., (2018) demonstrated that NLR is correlated negatively with GFR and positively correlated with CKD stage(p:0.02 for both correlations).[14]

Yuan *et al*., (2019) demonstrated that NLR is associated independently with the risk of ESRD in patients with stage 4 CKD with HR value 2.12(95% CI 1.10-4.10) compared with lower NLR(p:0.02).[15]

Yoshitomi *et al*., (2019) also showed that a high level of NLR was associated with poor renal outcomes with an HR value 1.67(95% CI 1.02-2.77) compared with lower NLR(p:0.01), suggesting that NLR may be a useful marker for prognostic prediction in patients with CKD.[16]

In summary, NLR is a marker for progression disease in CKD patients with independent prognostic value.

REFERENCES

1. de Boer I(2012). Chronic kidney disease-a challenge for all ages. JAMA, 308: 2401-2.
2. Bikbov B, Levey A, Smith M(2020). Global, regional, and national burden of chronic kidney disease, 1990-2017: A systematic analysis for the Global burden of disease study 2017. Lancet. 395: 709-733. 3- Levey A, Coresh J(2012).
3. Chronic kidney disease. Lancet, 379: 165.
4. Kazancioglu R(2013). Risk factors for chronic kidney disease: An update. Kidney Int., 3: 368-371.
5. Murray C, Vos T, Lozano R(2012). Disability adjusted life years(DALYs) for 291diseases and injuries in 21 regions, 1990-2010: a systematic

analysis for the Global Burden of Disease Study 2010. Lancet, 380: 2197.

6. Albertus P, Saran R, Robinson B(2016). Risk of ESRD in the United States. A m J Kidney Dis., 68: 862-72.

7. Gupta J, Mitra N, Kanetsky P(2012). Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrol, 7: 1938-1946.

8. Amdur R, Feldman H, Gupta J(2016). Inflammation and progression of CKD: the CRIC study. Clin J Am Soc Nephrol, 11: 1546-1556.

9. Solak Y, Yilmaz M, Sonmez A(2013). Neutrophil to lymphocyte ratio independently predicts cardiovascular events in patients with chronic kidney disease. Clin Exp Nephrol, 17: 532-40.

10. Sevencan N, Ozkan A(2019). Associations between neutrophil/lymphocyte, platelet/ lymphocyte ratio, albuminuria and uric acid and the estimated glomerular filtration rate in hypertensive patients with chronic kidney disease stages 1-3. A rch Med Sci., 15: 1232-1239.

11. Levey A, Coresh J, de Jong P(2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGI Controversies Conference report. Kidney Int., 80: 17.

12. Mihai S, Popescu I, Necula L(2018). Inflammation-Related Mechanisms in chronic kiney disease prediction, progression, and outcome. J Immunol Res., 6: 2180373.

13. Kocyigit I, Eroglu E, Unal A(2013). Role of Neutrophil to lymphocyte ratio in prediction of disease progression in patients with stage 4 chronic kidney disease. J Nephrol, 26: 358-365.

14. Tonyali S, Ceylan C, Yahsi S(2018). Does neutrophil to lymphocyte ratio demonstrate deterioration in renal function. Renal Failure, 40: 209-212.

15. Yuan Q, Wang J, Tao L(2019). Neutrophil to lymphocyte ratio and incident end stage renal disease in Chinese patients with chronic kidney disease: results from Chinese Cohort Study of Chronic kidney Disease(C-STRIDE). J Transl Med., 17: 86.

16. Yoshitomi R, Tsuda S, Seki M(2019). High neutrophil/lymphocyte ratio is associated with poor renal outcomes in Japanese patients with chronic kidney disease. Renal Failure, 41: 238-243.