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" *Neutrophil to Lymphocyte Ratio and Interleukin-6 Level in Evaluation of Inflammation in Chronic Hemodialysis Patients with and without Residual Kidney Functions* "

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ABSTRACT:

Background: Chronic inflammation is a main characteristic of chronic kidney disease (CKD) and is exacerbated in patients undergoing hemodialysis (HD). Residual kidney function (RKF) plays a vital role in mitigating inflammation. We aimed to assess the utility of neutrophil-to-lymphocyte ratio (NLR) and interleukin-6 (IL-6) as inflammatory markers in HD cases with and without RKF.

Methods: A cross-sectional study was conducted on 100 CKD cases on HD, categorized into two groups based on RKF presence. NLR and IL-6 levels were measured and analyzed in relation to demographic, clinical, and biochemical parameters. Statistical analysis included correlation studies and receiver operating characteristic (ROC) curve analysis.

Results: IL-6 levels and NLR were significantly increased in cases without RKF ($p < 0.05$). ROC analysis revealed IL-6 as a better marker for predicting loss of RKF compared to NLR. Correlations were observed between IL-6 levels, inflammatory markers, and renal parameters.

Conclusions: IL-6 and NLR are useful biomarkers for assessing inflammation in HD patients, with IL-6 demonstrating superior predictive value for RKF status. Monitoring these markers can provide insights into inflammation management in CKD.

Keywords: CKD, Haemodialysis, Residual kidney function, Inflammation, Interleukin-6, Neutrophil-to-lymphocyte ratio.

Background

Chronic kidney disease (CKD) is a disease characterized by extensive and permanent loss of kidney functions. It is considered a major global health problem, eventually culminating in end-stage renal failure (Xie et al., 2018). End-stage kidney disease (ESKD) refers to individuals with a measured GFR below 1 ml/min/1.73 m^2 BSA or those requiring hemodialysis regardless of GFR (Bakris et al., 2020). There is considerable RKF for many HD-initiated cases (Ebrahim et al., 2020). RKF is a condition characterized by a urine volume >100 ml/24 h, and there has been a growing emphasis on the importance of RRF in chronic HD patients (Hu et al., 2018).

Chronic CKD inflammation is characterized by a twofold increase in acute-phase protein and inflammatory mediators, developing gradually, persistently, and with multifaceted origins (Neuen et al., 2016). The NLR has been identified as a new inflammatory marker widely utilized in cardiovascular diseases. Neutrophils reflect the condition of inflammation, whereas lymphocytes are often associated with stressful situations and nutritional status (Mihai et al., 2018). NLR can serve as a novel predictor of microinflammation, which is a potent predictor of cardiovascular disease (CVD) in hemodialysis cases and accelerates atherosclerosis progression (Yuan et al., 2019).

Interleukin-6 (IL-6) is a B-cell stimulatory factor that initiates IgG production (Neirynck et al., 2015). IL-6 is a multifunctional cytokine regulating various biological activities, including organ development, inflammatory conditions, and immune responses (Fujihara et al., 2020). Additionally, IL-6 has a central function in the inflammatory process regulation, particularly in T cell differentiation between Treg and Th17 cells (Bi et al., 2020). IL-6 can also modulate monocyte differentiation into macrophages and dendritic cells (Wang & He, 2020).

Recent studies have revealed that local stimulation of IL-6 is involved in kidney autoimmune and inflammatory disorders (Bhargava et al., 2022). Kidney-resident cells, such as podocytes, mesangial cells, and tubular epithelial cells, could discharge IL-6 under specific conditions (Li et al., 2021). Elevated IL-6 levels are frequently observed in CKD patients secondary to increased free radical formation, chronic inflammation, and fluid overload (Magno et al., 2019). Furthermore, reduced IL-6 clearance due to impaired kidney function contributes to its accumulation. In ESKD patients, hemodialysis and peritoneal dialysis themselves can activate an inflammatory response, further increasing IL-6 production (Ninić et al., 2018).

Methods

Study Design and Population A cross-sectional study was conducted on 60 adult CKD patients undergoing maintenance HD at a tertiary care center. Patients were stratified into two groups based on RKF status (with or without).

Inclusion and Exclusion Criteria

- Inclusion: Adult CKD patients on HD for >6 months, with stable clinical status.
- Exclusion: Active infections, recent surgeries, malignancies, or autoimmune diseases.

Data Collection Demographic data, history, and laboratory investigations were recorded. Blood samples were collected pre-dialysis for IL-6 measurement using enzyme-linked immunosorbent assay (ELISA). NLR was measured as the ratio of absolute neutrophil to lymphocyte counts.

Statistical Analysis Continuous variables were expressed as mean±SD, while categorical data were presented as percentages. The two-sample t-test and chi-square tests were used for comparisons. Correlation coefficients assessed relationships between variables. ROC curves determined the predictive ability of IL-6 and NLR for RKF status.

Results

The study included 60 patients on hemodialysis (HD) divided into 2 groups based on the presence or absence of residual renal function (RRF): Group 1: comprised HD cases with preserved RKF (urine volume more than 100 ml/24 h). Group 2: comprised HD cases without preserved RKF (urine volume less than 100 ml/24 h).

Insignificant difference was recorded between both groups concerning age, BMI, or sex. The mean age in the preserved RRF was 53.53 ± 11.85 years and 55.03 ± 12.64 years in those with unpreserved RRF. Males represented 63.3% and 50% in the preserved and unpreserved RRF cases, respectively.**(table 1)**

The commonest cause of CKD was HTN nephropathy, followed by DM nephropathy.

Insignificant difference was recorded between both groups concerning the cause of CKD. The duration of dialysis was statistically significantly longer in those with unpreserved RRF. **(table 2)**

AVF was the most common means for dialysis. There was no significant difference between both groups concerning: kidney functions including creatinine before and after dialysis, urea before and after dialysis, and URR.hemoglobin level, albumin level, fasting blood glucose, sodium level, calcium level, potassium level, and phosphorous level. neutrophil count, lymphocyte count, and NLR **(table 3)**

The IL-6 level in those with preserved RRF was 32.41 ± 10.71 pg/ml, which was statistically significantly higher than those with unpreserved RRF (12.84 ± 2.69 pg/ml). The best cutoff point of IL-6 to detect cases with unpreserved RRF was < 17.245 pg/ml with 93.3% sensitivity and 83.3% specificity. The area under the curve was 0.881.**(table 4)**

The best cutoff point of NLR to detect those with unpreserved RRF was < 1.985 pg/ml with 73.3% sensitivity and 43.3% specificity. The area under the curve was 0.580 and showed a non-statistically significant value**.(figure 1).**

In those with preserved RRF, there was a statistically significant negative relationship between NLR and: interdialytic urine volume, RKF and Na. **(table 5).** A statistically significant positive correlation was recorded between IL-6 and neutrophil count. In those with unpreserved RRF, a statistically significant positive correlation was recorded between NLR and UPR.

A statistically significant positive correlation was recorded between IL-6 and urea before dialysis, and a negative correlation with albumin level. **(table 6)**

Table (1): Analysis of the demographic data between both study groups

Variable	**Preserved RRF (N= 30)**	**Unpreserved RRF (N= 30)**	**Test of sig.**
Age (years)	53.53 ± 11.85	55.03 ± 12.64	t = - 0.474 P = 0.637
BMI (Kg/m^2)	24.80 ± 4.39	25.05 ± 4.26	t = - 0.230 P = 0.819
Sex			
Males	19 (63.3%)	15 (50%)	χ2= 1.086 P = 0.279
Females	11 (36.7%)	15 (50%)	

t: The two-sample t-test χ^2 : Chi-square test

Table (2): Analysis of the cause of CKD in the two study groups

Variable	**Preserved RRF (N= 30)**	**Unpreserved RRF (N= 30)**	**Test of sig.**
Chronic glomerulonephritis	0 (0%)	1 (3.3%)	MC= 10.959 P = 0.36
Chronic pyelonephritis	2 (6.7%)	1 (3.3%)	
DM nephropathy	6 (16.7%)	11 (33.3%)	
HTN nephropathy	8 (26.7%)	11 (36.7%)	
NSAIDS	2 (6.7%)	2 (6.7%)	
Obstructive nephropathy	3 (10%)	0 (0%)	
Polycystic kidney	4 (13.3%)	2 (6.7%)	
Unknown	5 (16.7%)	2 (6.7%)	

MC : Monte-Carlo test

Table (3): Analysis of the kidney functions in the two study groups

Variable	Preserved RRF (N= 30)	Unpreserved RRF (N= 30)	Test of sig.
Creatinine before (mg/dl)	8.80 ± 2.37	8.81 ± 2.05	t = - 0.023 P = 0.981
Creatinine after (mg/dl)	3.63 ± 1.08	3.48 ± 0.72	t = 0.648 P = 0.519
Urea before (mg/dl)	139.77 ± 30.41	148.37 ± 24.42	t = -1.208 P = 0.232
Urea after (mg/dl)	48.88 ± 13	51.87 ± 11.06	t = - 0.959 P = 0.341
URR	64.42 ± 5.68	64.67 ± 6.06	t = - 0.160 P = 0.873

t: The two-sample t-test

Table (4): Analysis of the interleukin-6 (pg/mL) level in the two study groups

Variable	Preserved RRF (N= 30)	Unpreserved RRF (N= 30)	Test of sig.
Interleukin-6 (pg/mL)	32.41 ± 10.71	12.84 ± 2.69	**t = 7.768** **P < 0.001***

t: The two-sample t-test *: Statistically significant (P< 0.05)

Figure (10): ROC Curve of interleukin-6 (pg/mL) to identify cases with unpreserved kidney functions

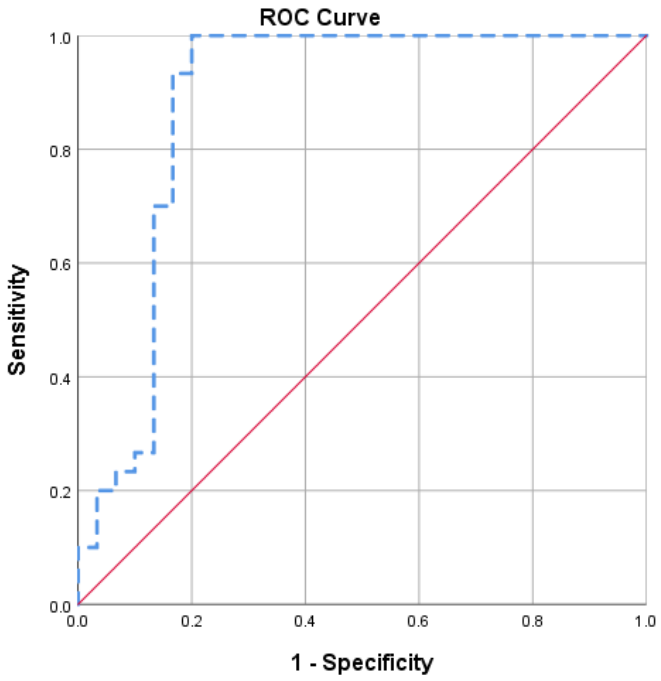

Figure (1): ROC Curve of interleukin-6 (pg/mL) to identify cases with unpreserved kidney functions

Table (5): Diagnostic value of NLR to identify cases with unpreserved kidney functions

Diagnostic criteria	**NLR**
AUC	0.580
Cut off point	> 1.985
Sensitivity	73.3 %
Specificity	43.3 %
NPV	50.6 %
PPV	68.3 %
Accuracy	58.7 %
P	0.280
AUC: area under the curve. NPV: Negative predictive value **PPV: Positive predictive value** P: probability. *: significant p value (< 0.05).	

Table (6): Correlation between IL-6 with other clinical and laboratory data in the cases with preserved kidney functions

		IL-6
NLR	rs	0.167
	P	0.377
Duration of dialysis	rs	-0.210
	P	0.266
Urine urea concentration	rs	0.022
	P	0.908
Mean BUN	rs	0.009
	P	0.964
Interdialytic urine volume	rs	0.080
	P	0.675
RKF	rs	0.040
	P	0.834
Creatinine before	rs	-0.134
	P	0.480
Creatinine after	rs	-0.023
	P	0.905
Urea before	rs	-0.009
	P	0.964
Urea after	rs	0.225
	P	0.231
URR	rs	-0.254
	P	0.175
Hemoglobin	rs	-0.017
	P	0.927
Albumin	rs	-0.100
	P	0.598
FBG	rs	-0.105
	P	0.579
Na	rs	-0.028
	P	0.882
Ca	rs	-0.307
	P	0.099
K	rs	-0.331
	P	0.074
Ph	rs	-0.201
	P	0.288
Neutrophils	rs	**0.391***
	P	**0.033**
lymphocytes	rs	0.137
	P	0.471

rs: Spearman's correlation

P: probability *: significant p value (< 0.05).

Discussion

The incidence of CKD is rising worldwide. RRF provides numerous benefits for hemodialysis patients, including improved solute clearance, better phosphate excretion, enhanced nutritional markers, endogenous vitamin D and erythropoietin formation, and elimination of uremic toxins (500-60,000 Da). Preserving RRF is critical in managing hemodialysis patients; however, identifying early RRF loss during HD, especially with minimal urine output, is challenging (Kalantar-Zadeh et al., 2014).

This study aimed to evaluate inflammation in CKD patients on HD with or without RRF using NLR and IL-6 levels as inflammatory markers. Different studies have used various cutoff points to define RRF. This study used a 100 ml/day cutoff, while others defined RRF as urine volume >200 ml/day, >100 mL during the interdialytic interval, or >250 mL/day (Shafi et al., 2010).

The study found no significant differences in age or gender between groups with and without RRF, consistent with findings by Ahsan et al. (2020) and Elgendy et al. (2022). Hypertension was the most common comorbidity, followed by diabetes mellitus, which aligns with prior research (Ahsan et al., 2020; Abdel-Azim et al., 2017). The leading cause of CKD was hypertension, followed by diabetes and polycystic kidney disease. Dialysis duration was significantly longer in the group with unpreserved RRF, consistent with Elgendy et al. (2022).

The IL-6 level was significantly higher in cases with preserved RRF compared with those without. This contradicts earlier studies that reported higher IL-6 levels in patients with reduced RRF (Murt et al., 2022). The discrepancy might stem from the impact of inflammation on RRF loss, as persistent inflammation can lead to progressive nephron loss and reduced IL-6 production. No significant differences were noticed between both groups concerning neutrophil count, lymphocyte count, and NLR. Other studies, however, found NLR to be associated with inflammation in both peritoneal dialysis and HD patients (Turkmen et al., 2012).

A positive relationship was observed between IL-6 and neutrophil count in patients with preserved RRF, as well as between IL-6 and urea before dialysis, and a negative correlation with albumin levels in patients with unpreserved RRF. These findings align with El-Hafeez et al. (2019), who revealed a positive relationship between NLR and IL-6.

The study identified a cutoff point for IL-6 to distinguish between preserved and unpreserved RRF. This significant contribution highlights IL-6 as a potential non-invasive biomarker for this purpose. However,

further research is needed to understand why higher IL-6 levels are accompanied by preserved renal function in some cases. For instance, Wueest and Konrad (2020) suggested that higher IL-6 could result from elevated physiological IL-6 levels in adipose tissue.

Clinical Implications: Regular monitoring of IL-6 and NLR can guide inflammation management strategies, potentially preserving RKF and improving patient outcomes. Future research should explore interventional approaches targeting IL-6-mediated inflammation.

Conclusions

IL-6 and NLR are effective markers for inflammation in CKD patients on HD. IL-6 outperforms NLR in predicting RKF status, emphasizing its role in clinical monitoring and therapeutic decision-making.

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