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ORIGINAL ARTICLE

Adequacy of Hemodialysis and its relation to Neutrophil-to-Lymphocyte ratio among patients undergoing regular Hemodialysis

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Abstract

Background: ***One of the major concerns for patients with end-stage renal disease (ESRD) who are receiving hemodialysis is the effectiveness of the dialysis treatment. Inflammation levels are elevated in patients with inadequate dialysis. Inflammation can be detected by measuring the neutrophil-to-lymphocyte ratio (NLR).***

Objectives: ***To assess the level of HD sufficiency in (ESRD) patients and how it relates to other factors that impact patient outcomes, such as (NLR), anemia, and blood pressure.***

Methods: ***This cross-sectional study included one hundred ESRD cases from the Hemodialysis Unit at Al-Hussein University Hospital in collaboration with the Allergy and Immunology Center divided into two groups according to dialysis adequacy; group I included 66 cases with Kt/V ≥1.2 (adequate dialysis dose) and group II included 34 cases with Kt/V<1.2 (inadequate dialysis dose).***

Results: ***NLR was significantly higher among ESRD patients with inadequate dialysis dose, 3.8 (2.9-4.6) compared to 2.64 (1.96-3.3) among ESRD patients with adequate dialysis dose. The ROC curve analysis showed that NLR was a diagnostic marker of inadequate dialysis at a cutoff point 3.17, exhibiting a sensitivity of 73.5% and a specificity of 71.2%.***

Conclusion: ***Neutrophil lymphocyte ratio may be a diagnostic marker for inflammation among ESRD patients on regular HD.***

Keywords: ESRD, HD, Inflammation NLR

1. Introduction

With a GFR of 15 mL/min or lower, kidney function has irreversibly declined, indicating end-stage renal disease.[1] After nutritional and pharmaceutical interventions, such as dialysis or kidney transplantation, have been exhausted, the last line of defense against end-stage renal disease (ESRD) is renal replacement therapy (RRT).[2]

Several literatures have demonstrated that ESRD causes significant limitations in different aspects of people's lives, leading to impaired quality of life (QOL). Thanks to the availability of different forms of RRT, the severity of symptoms is diminished. So, life expectancy is increased among ESRD patients.[3] Urinary solute clearance dictates the essential hemodialysis dosage and adequacy. Increasing the duration or frequency of dialysis is one of the effective ways to improve adequacy; nevertheless, both of these treatments rely on patient compliance and expense. Hence, studies should be conducted to enhance dialysis adequacy and quality of life.[4]

Many long-term diseases involve both the immune system and the inflammatory process.[5] The control of adaptive immunity is another key function of neutrophils.[6] One well-known indicator of inflammation is the neutrophil-to-lymphocyte ratio (NLR), which is determined by dividing the neutrophil count in peripheral blood by the lymphocyte count.[7]

Many epidemiological studies have hypothesized the significance of NLR as a marker for chronic low-grade inflammation.[8]

This paper evaluates HD adequacy in ESRD patients in the Hemodialysis Unit at Al-Hussein University Hospital to discover reasons for poor HD and its relationship to NLR, anemia, and blood pressure, which impact patient outcomes.

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2. Patients and methods

This study comprised 100 stable ESRD patients getting regular HD from February to August 2023. Patients recruited at Al-Hussein University Hospital and Imbaba Fever Hospital were on regular HD for at least six months using an arteriovenous fistula (AVF). Traditional hemodialysis has three four-hour sessions each week.

2.1.Inclusion criteria: Patients must be at least 18 years old, have (ESRD) be on regular hemodialysis for at least six months, and be in a medically stable state without a recent, non-access-related emergency hospitalization.

2.2.Exclusion criteria: Patients who had significant infection malignancy.

Ethical consideration: The Al-Azhar University faculty of medicine's regional ethical committee accepted the study. All participants—patients and controls—felt free to discontinue the research voluntarily. Personal privacy was maintained, and the data were only used for research.

Patient consent: All participants were given a thorough description of the study's benefits and risks before they were asked to sign an informed consent form.

2.3.Patient evaluation:

Demographic data and medical history

Clinical examination and vital signs

Laboratory investigation

Complete blood count with its main parameters (hemoglobin, platelet count, leucocyte count, and differential leucocyte count (neutrophils and lymphocytes). Sysmex XS-500i, SYSMEX EUROPE GMBH, Germany performed it. Serum urea and creatinine were assessed via Cobas C 111, Roche Diagnostics, Germany. We used automated methods to measure serum calcium and phosphorus (Roche et al.) serum vitamin D levels. Blood samples were taken and allowed to clot naturally for 30 minutes. Following a 5-minute, 3000 rpm centrifugation, samples were kept at 20 °C. With the help of the Diasorin RIA® assay method, 25-OH levels were determined to measure serum parathyroid hormone, and an electrochemiluminescence immunoassay was used (Cobas et al.).

It was determined that the urea reduction ratio (URR) and the ketone-to-volume ratio (Kt/V) were adequate for hemodialysis. The (URR) was determined by dividing the difference in blood urea nitrogen (BUN) levels before and after dialysis by the BUN levels before. The second-generation logarithmic (Daugirdas) equation was used to determine the Kt/V ratio.[9]

2.4.Statistical analysis: We used the 2013 Released by IBM SPSS Corp. Windows version of IBM SPSS Statistics 22.0 in our data analysis.

In Armonk, New York, IBM Corp. The qualitative data was analyzed using the Chi-Square test after being expressed as percentages and numbers. Parametric data was compared using the Student t-test. In contrast, non-parametric data was characterized using the median and interquartile range, and the Mann-Whitney U test was employed for non-parametric data. By analyzing the test's diagnostic performance using Receiver Operating Characteristic (ROC) curves, we could determine if the results were statistically significant at the (0.05) level.

3. Results

The studied cases were split into 2 groups according to Kt/V values:

Group I (n=66) involved cases with Kt/V ≥1.2 (adequate dialysis dose).

Group II (n=34) included cases with Kt/V <1.2 (inadequate dialysis dose).

Table 1. Analysing demographic information, medical history & blood pressure among the two groups

DEMOGRAPHIC DATA		GROUP I (N=66)		GROUP II (N=34)		TEST OF SIG.	P
AGE (YEAR)	Mean±SD	54.1 ± 10.1		55.5 ± 12.3		t= -0.59	0.55
	Min-Max	27-77		22-71			
		N	%	N	%		
SEX	Male	38	57.6	24	70.6	χ2= 1.61	0.21
	Female	28	42.4	10	29.4		
HTN		37	56.1	17	50	χ2=0.33	0.56
CVD		20	30.3	17	50	χ2=3.74	0.053
DM		14	21.2	13	38.2	χ2=3.3	0.07
SMOKING		10	15.2	4	11.8	χ2=0.21	0.64
BMI (KG/M^2)	Median (IQR)	23.4 (21.4-24.6)		23.5 (22.2-24.4)		U= -1086.5	0.79
	Min-Max	18.9-31.5		19.5-30.5			
DURATION OF DIALYSIS (YEARS)	Median (IQR)	3.41 (2.02-5)		3.58 (2.16-5.74)		U=1115	0.95
	Min-Max	1-10.33		51-264			
SBP (MMHG)	Median (IQR)	140 (130-150)		150 (140-160)		U= 834.5	0.033*
	Min-Max	110-170		120-170			
DBP (MMHG)	Median (IQR)	70 (70-80)		80 (80-90)		U= 628	0.001*
	MIN-MAX	60-100		60-100			

BMI: Body mass index, CVD: Cardiovascular disease, DBP: Diastolic blood pressure, DM: Diabetes mellitus, IQR: Interquartile range, HTN: Hypertension, SD: Standard deviation, SBP: Systolic blood pressure, t: Independent t test, χ2: Chi square test, IQR: Interquartile range, U: Mann-Whitney test, p: p-value >0.05: Non-significant; p-value <0.05: Significant; p-value< 0.01: highly significant.

According to Table 1, there is no statistically significant difference in the demographic data or medical history among the two groups. Although group II had considerably higher SBP and DBP.

Table 2. Comparison of biochemical blood test between the two groups

BIOCHEMICAL BLOOD TEST		GROUP I (N=66)	GROUP II (N=34)	TEST OF SIG.	P
PRE-DIALYSIS BUN (MG/DL)	Mean±SD	69.7 ± 10.2	70 ± 9.8	t= -0.12	0.91
	Min-Max	52-90	48-89		
POST-DIALYSIS BUN (MG/DL)	Median (IQR)	21 (18-24)	27.5 (25.75-30)	U= 324	0.001*
	Min-Max	16-31	16-33		
SCR (MG/DL)	Mean±SD	9.5 ± 1.8	9.14 ± 1.5	t= 0.86	0.39
	Min-Max	6.4-16	6.5-12		
S. CA (MG/DL)	Median (IQR)	9.4 (9-9.8)	9.6 (9.2-9.9)	U= 969	0.26
	Min-Max	7.6-10.5	7-10.5		
S. PO_4 (MG/DL)	Mean±SD	4.7 ± 1.2	4.6 ± 1.1	t= 0.187	0.85
	Min-Max	2.2-8.4	2.3-7.3		
PTH (NG/L)	Median (IQR)	170.5 (106.8-433.5)	240.5 (106.8-354.3)	U= 1110	0.93
	Min-Max	33-1546	23-1635		
S. URIC ACID (MG/DL)	Mean±SD	6.3 ± 1.5	8.5 ± 1.9	t= -6.53	0.001*
	Min-Max	3.6-9.7	3.5-11.6		
ALBUMIN (GM/DL)	Median (IQR)	3.9 (3.7-4.1)	3.9 (3.6-4.1)	U= -0.037	0.97
	Min-Max	3.4-4.5	3.3-4.5		
CRP (MG/L)	Median (IQR)	4.5 (3-6.13)	6.1 (3.5-9.3)	U= 819	0.027*
	Min-Max	1.6-17	1.3-25		
URR (%)	Median (IQR)	68.95 (67.8-70.75)	61.4 (59.25-62.65)	U= 1.5	0.001*
	Min-Max	65.4-73.8	57.38-65.5		
KT/V	Median (IQR)	1.38 (1.34-1.47)	1.11 (1.07-1.16)	U=0	0.001*
	MIN-MAX	1.23-1.6	0.98-1.19		

BUN: Blood urea nitrogen, CRP: C-reactive protein, SCr: Serum creatinine, PTH: Parathyroid hormone, t: Independent student t test, U: Mann Whitney test,

Table 2 shows that Post dialysis BUN, serum uric acid and CRP were statistically significantly increased in group II. While URR and Kt/v were statistically significantly declined in group II.

Table (3): Evaluation of the two groups' CBC

CBC		GROUP I (N=66)	GROUP II (N=34)	TEST OF SIG.	P
HB (GM/DL)	Mean±SD	10.51 ± 1.39	10.62 ± 1.69	t= -0.33	0.74
	Min-Max	7.5-13.4	7.5-14.3		
PLATELET COUNT ($X10^3/MM^3$)	Mean±SD	207.2 ± 69.1	200.3 ± 64.61	t= 0.48	0.63
	Min-Max	100-440	105-390		
WBC ($X10^3/MM^3$)	Median (IQR)	6.25 (5.1-7.23)	7.45 (5.2-8.2)	U= 810	0.02*
	Min-Max	2-10.5	3.7-14.5		
NEUTROPHILS ($X10^3/MM^3$)	Median (IQR)	4.3 (3.3-4.9)	5.5 (4.0-6.2)	U= 706	0.002*
	Min-Max	6.6-7.8	2.2-12.47		
LYMPHOCYTES ($X10^3/MM^3$)	Median (IQR)	1.47 (1.29-1.78)	1.39 (1.17-1.62)	U= 845	0.04*
	Min-Max	1.04-3.6	6.2-2.4		
NLR (NORMAL RANGE 1-2)	Median (IQR)	2.64 (1.96-3.3)	3.8 (2.9-4.6)	U= 548.5	0.001*
	Min-Max	0.4-4.88	1.57-8.6		
SERUM IRON (MCG/DL)	Median (IQR)	59 (50.5-65)	57 (41.8-64.3)	U= 1002.5	0.384
	Min-Max	29-81	31-72		
SERUM FERRITIN (NG/ML)	Median (IQR)	317.5 (168.3-735.3)	354.5 (198-529.3)	U= 1071.0	0.711
	Min-Max	40-1631	54-1180		
TIBC (MCG/DL)	Median (IQR)	210.5 (187.8-246.5)	197.5 (179-231.8)	U= 874.5	0.07
	Min-Max	151-348	106-311		
TSAT (%)	Median (IQR)	26.8 (21.3-34.9)	24 (18.1-28.3)	U= 853.5	0.06
	MIN-MAX	9.7-55	1.9-42		

TIBC: Total iron binding capacity; TSAT: transferrin saturation, WBC: White blood cell, U: Mann Whitney test,

Table 3 shows that WBC, neutrophils, lymphocytes & NLR were statistically significantly higher in group II.

Table 4. Correlation between NLR and each of demographic & laboratory data

PARAMETERS	NLR	
	R	P
AGE (YEAR)	0.034	0.74
BMI (KG/M^2)	0.019	0.85
DURATION OF DIALYSIS (YEARS)	0.142	0.16
SBP (MMHG)	0.057	0.57
DBP (MMHG)	0.102	0.31
PRE-DIALYSIS BUN (MG/DL)	0.041	0.69
POST-DIALYSIS BUN (MG/DL)	0.322*	0.001*
SCR (MG/DL)	-0.095	0.35
S. CA (MG/DL)	0.109	0.28
S. PO_4 (MG/DL)	-0.123	0.224
PTH (NG/L)	0.066	0.51
S. URIC ACID (MG/DL)	0.23*	0.02*
ALBUMIN (GM/DL)	-0.062	0.54
CRP (MG/L)	0.405*	0.001*
HB (MG /DL)	-0.129	0.2
PLATELET COUNT (X103/MM3)	0.057	0.57
WBC (X103/MM3)	0.462	0.001*
NEUTROPHILS (X103/MM3)	0.684**	0.001*
LYMPHOCYTES (X103/MM3)	-0.475*	0.001*
SERUM IRON (MCG/DL)	-0.091	0.369
SERUM FERRITIN (NG/L)	-0.024	0.815
TIBC (MCG/DL)	-0.076	0.451
TSAT (%)	-0.143	0.155
URR (%)	-0.469*	0.001*
KT/V	-0.413*	0.001*

r: Spearman correlation coefficient, *: weak correlation; **: moderate correlation; ***: strong correlation,

Table 4 showed that each of post dialysis BUN, uric acid, CRP, WBC and neutrophils were significantly positively correlated with NLR. While lymphocytes, URR and Kt/v showed significant negative correlation with NLR.

Table 5. Validity of NLR in differentiating inadequate HD

LAB PARAMETER	AUC	P	SENSITIVITY (%)	SPECIFICITY (%)	95% CI	CUTOFF	PPV (%)	NPV (%)
NLR	0.763	0.001*	73.5	71.2	0.66-0.86	3.17	55.3	83.6

AUC: Area Under curve, CI: Confidence interval, , NPV: Negative predictive value, PPV: positive predictive value

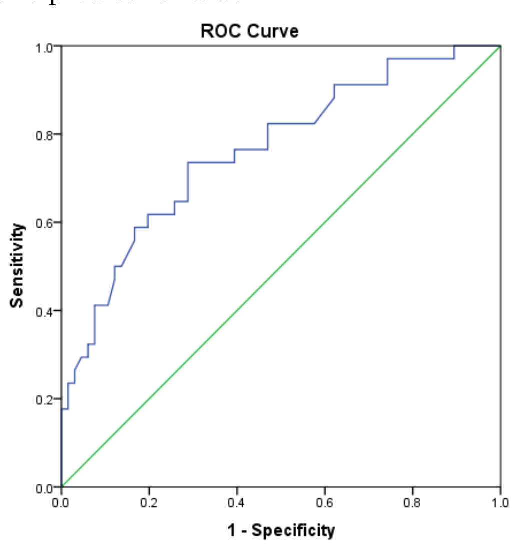

Figure 1. ROC curve of NLR for prediction of inadequate HD

Table 5 and Figure 1 show that the area under ROC curve for NLR in differentiating inadequate HD is 0.76 with the best detected cut off point is 3.17 yielding total accuracy of 71%.

4. Discussion

The adequacy of hemodialysis has a major impact on patients' overall health. Therefore, as dialysis adequacy improves, this will positively affect survival.[10] Many studies have suggested that a cutoff of Kt/V larger than 1.2 is associated with better outcomes. Hemodialysis Clinical Practice Guidelines from the Kidney Disease Outcomes Quality Initiative (KDOQI) Adequacy, in contrast, indicates a URR minimum dosage greater than 65%.[11]

Indeed, dialysis has been associated with elevated levels of inflammatory mediators and proinflammatory cytokines.[12] In chronic hemodialysis patients, inflammation may worsen due to inadequate dialysis (lower Kt/V levels).[13] There has been recent news linking the (NLR) to the inflammatory process in (ESRD) patients after beginning HD or PD treatment.[14]

Among our patients, the mean age was 54.6 ± 10.8 years, with male predominance (62%) versus 38% females. The median BMI was 23.5 (21.4-24.6) kg/m2. The median duration of dialysis was 3.5 (2.08-5) years. HTN was the most common morbidity (54%), followed by CVD (37%), then DM (27%) and smoking (14%).

Similar to our results, Sethi et al.[15] reported a mean age among 100 patients with ESRD to be 54.44 ± 14.19 years and the majority of men cases, which constituted 74% of the total patients 15. As for BMI, Inagaki et al. (2021) reported that the mean BMI among HD patients was 23.3 ± 4.24 kg/m2.[16]

Wu et al. studied 120 ESRD patients; the mean time on hemodialysis was 5.68 ± 4.37 years.[17] The most common comorbidities, which recorded 49.2%, were congestive heart failure (34.2%) and diabetes (47.5%). While Jacob et al.[18] reported the hypertension prevalence to be 59.54%.

Regarding the vital signs, both SBP and DBP were significantly elevated among ESRD patients who had inadequate doses of dialysis.

Similarly, Panagoutsos et al. [20] indicated a relation between blood pressure reduction and dialysis dose enhancement, suggesting a central role of dialysis dose in blood pressure control among patients.19This could be due to ineffective sodium solute removal that results in excess fluid intake and hypertension.

A complex etiology is responsible for the inflammatory state produced by the hemodialysis procedure. In addition to vascular access, poor dialyzer membrane biocompatibility, dialysate contamination, dialysis age, oxidative stress, infections, and comorbidities, the variables that are associated with HD include chronic kidney disease.[21]

In individuals with (ESRD), the presence of uremia is responsible for the promotion of low-grade inflammation.[22] There is a strong correlation between the white blood cell count in the blood and the presence of systemic inflammation. For example, neutrophils have a role in the development of atherosclerosis and vascular endothelial damage.[23]

Our results demonstrated that post-dialysis BUN, serum uric acid, CRP, WBC, neutrophil count, and NLR were significantly elevated between ESRD cases with inadequate dialysis. In contrast, lymphocyte count was significantly lower among them.

Both post-dialysis BUN and serum uric acid elevation were mainly caused by inadequate dialysis and lower URR. Elevation of CRP, WBC, neutrophil, and NLR was induced by increased inflammation among patients with inadequate dialysis doses.

Reportedly, the NLR among patients with inadequate dialysis ranged from 1.57 to 8.6, with a median NLR of 3.8 (2.9-4.6), compared to 0.4 to 4.88 and a median NLR of 2.64 (1.96-3.3) among patients with adequate dialysis dose.

Consistent with our findings, Ahbab et al.[24] stated that ESRD cases on HD had higher values for NLR in patients (3.7 ± 0.2 versus 2.7 ± 0.2, $p < 0.01$).

Our results demonstrated an adequate dose of dialysis in 66% of total patients, while 34% had an inadequate dose. The Urea reduction ratio and Kt/V were significantly lower among ESRD patients with inadequate dialysis. The URR was estimated to be 61.4% (59.25-62.65) versus 68.95% (67.8-70.75), while Kt/V was 1.11 (1.07-1.16) compared to 1.38 (1.34-1.47) among inadequate hemodialysis group versus adequate dialysis group, respectively, p-value=0.001.

This was parallel to the consequences of Rezaiee et al., who presented that more than half of the patients (56.4%) had desirable hemodialysis adequacy.[25]

(URR>65%), 29.7% of the patients had relatively favorable (URR=55–64.99%), and the rest (13.9%) had unfavorable hemodialysis adequacy (URR<55%).

However, Somji et al.[10] reported a lower prevalence of dialysis adequacy as (34.3%) and 40.6% received target URR (≥65%) and Kt/V (>1.2), respectively. The difference regarding hemodialysis adequacy among regions may be due to the availability of high-flux dialysis.

Among our patients, the NLR correlation showed a significantly positive correlation with post-dialysis BUN, uric acid, CRP, WBC, and neutrophils. Conversely, it showed a significantly negative correlation with lymphocytes, URR, and Kt/v. Nevertheless, we could not identify a significant correlation between dialysis adequacy and anemia profile.

Accordingly, Neuen et al.[26] stated that the correlation between NLR and CRP was also significant and positive correlation ($r = 0.24$, $p = 0.0023$).

Furthermore, Rashid et al.[27] demonstrated a significant inverse relationship between URR and serum CRP. Borazan et al.[28] stated that there was a significant -ve relationship between CRP levels Kt/V.

Our study reported that ROC curve analysis of NLR to differentiate inadequate HD cases from adequate dialysis ones showed an AUC of 0.74, a sensitivity of 73.5%, a specificity of 71.2%, PPV of 55.3%, and NPV of 83.6% at a cutoff point of 3.17 yielding total accuracy of 71%.

Many conditions allegedly impact NLR. Adults' values above 3.0 and below 0.7 are considered abnormal, whereas a typical range is between 1-2. It is possible that NLR in the range of 2.3 to 3.0 could serve as an early indicator of a pathological condition.[29]

Our findings are in line with those of Ahbab et al.,[24] who documented a sensitivity of 65.7% and specificity of 63.3% when estimating an NLR cutoff point of 2.82 to distinguish inflammatory cases among HD patients.

In conclusion, NLR is an easy-to-use, widely accessible, and low-cost method that provides a workable plan for assessing inflammation in patients with end-stage renal disease (ESRD) in clinical practice.

4. Conclusion

Insufficient hemodialysis elevated CRP and NLR, indicating inflammation. Neutrophil lymphocyte ratio may indicate inflammation in ESRD on HD. The Kt/V and URR correlations between NLR and dialysis adequacy were negative.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

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There are no conflicts of interest.

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