

# Monocyte/Lymphocyte And Monocyte/ Neutrophil Ratios As Predictors Of Cardiovascular Events In Hemodialysis Patients

Ragaa R. Mohamed <sup>a</sup>, Hend M. Maghraby <sup>a</sup>, Doaa A. Abd El-Fattah <sup>b</sup>, Shereen Y. S. Yousef <sup>c</sup>, Rania F. S. Sayed <sup>a,\*</sup>

<sup>a</sup> Department of Internal Medicine, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt

<sup>b</sup> Department of Clinical Pathology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt

<sup>c</sup> Department of General Internal Medicine and kidney fellow, Ahmed Maher Teaching Hospital, Cairo, Egypt

## Abstract

**Background:** Cases with chronic kidney illness stage 5 who are undergoing dialysis have noticed a rise in their probability of surviving in the past few years.

**Aim:** To assess the monocyte to neutrophil ratio and monocyte to lymphocyte ratio as indicators of cardiovascular events in end-stage renal illness cases on regular hemodialysis.

**Patients and methods:** This cross-sectional research involved 150 stable cases with end-stage renal disease undergoing regular HD for more than six months. Patients were recruited from the Hemodialysis Unit and the Nephrology Unit of EL Zahraa University Hospital, Homayat Imbaba and Ahmed Maher teaching Hospitals over a period of 6 months after oral and written consents and after the agreement of the ethical committee of the university.

**Results:** MLR was statistically significantly higher among group one cases ( $p$ -value= 0.006), and MNR was also statistically significantly higher among group one cases ( $p$ -value= 0.03). MNR was significantly positively correlated with age ( $p$ -value= 0.015,  $r$ -value=0.198), monocytes ( $p$ -value= 0.001,  $r$ =0.79) and LDL ( $p$ -value=0.03,  $r$ =0.18), while MNR showed significant negative correlation with both WBC ( $r$ = -0.29,  $p$ -value=0.001) and neutrophils ( $r$ = -0.51,  $p$ -value=0.001). MLR was a significant predictor for Cardiovascular Events in Hemodialysis Patients,  $p$  0.001.

**Conclusion:** Monocyte to lymphocyte ratio (MLR), and monocyte to neutrophil ratio (MNR) are potential indicators of cardiovascular events in ESRD patients on regular hemodialysis. They show significant correlations with age, monocytes, LDL, and MNR, while being negatively correlated with WBCs and neutrophils.

**Keywords:** Monocyte; Lymphocyte; Neutrophil Ratios; Predictor; Cardiovascular events

## 1. Introduction

Cases with chronic kidney illness stage 5 who are undergoing dialysis have noticed a rise in their probability of surviving in the past few years.<sup>1</sup>

In addition to an elevated occurrence of cardiovascular morbidity, cardiovascular illness is the primary reason for mortality among dialysis patients.<sup>2</sup>

The interaction among subtypes of clinical results and white blood cells is starting to develop, despite the fact that the cause of immune disturbances between these cases is

still not completely clarified. It has been shown that the risk of death in hemodialysis (HD) cases was independently predicted by decreased lymphocyte counts and elevated neutrophil counts.<sup>3</sup>

Li et al.<sup>4</sup> stated that Traditional indicators had limitations of their own. Procalcitonin is usually unavailable, and ferritin has a relatively less level of precision in assessing inflammation in end-stage renal disease (ESRD). Consequently, the predictive value of C-reactive protein (CRP) is rather not particular in its ability to delineate the reason of uremia, as many factors help in the inflammation.

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\* Corresponding author at: Internal Medicine, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.

E-mail address: [mostafarania979@gmail.com](mailto:mostafarania979@gmail.com) (R. F. S. Sayed).

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The neutrophil-to-lymphocyte ratio (NLR) was identified as a valuable indicator of immune system activation and inflammation, with greater ratios suggesting a higher level of immune system activation and inflammation.<sup>5</sup>

The cardiovascular risk in patients with CKD stages 3 and 5 is suggested to be assessed using NLR as a complementary prognostic measure. It's hypothesized that death in hemodialysis cases is predicted by a rise in neutrophil count and a decrease in lymphocyte count.<sup>6</sup>

A higher neutrophil-to-lymphocyte ratio correlates with a greater probability of cardiovascular complications in hemodialysis cases and is a powerful indicator of both cardiovascular mortality and all-cause mortality. This suggests that the neutrophil-to-lymphocyte ratio could be an economical and more sensitive prognostic biomarker in hemodialysis cases.<sup>7</sup>

On the other hand, the progression and initiation of atherosclerotic illness are significantly influenced by monocyte-derived macrophages and monocytes. The cardiovascular complications of coronary artery disease (CAD) cases have a strong correlation with an elevated monocyte count or a reduced lymphocyte count, as shown by research results.<sup>8</sup>

The prevailing oxidative stress and systemic inflammation in these people are demonstrated by the general expansion of circulating monocytes, which is accompanied by a rise in basal production of reactive oxygen species (ROS) and cytokines.<sup>9</sup>

Epidemiological research has demonstrated that cases with hemodialysis have increased monocyte counts, which are independently associated with all-cause death and cardiovascular disease.<sup>10</sup>

Monocyte/lymphocyte ratio is a mixed inflammatory biomarker that is calculated by dividing the count of monocytes by the count of lymphocytes, and has received considerable attention for application in CVD.<sup>8</sup>

Additionally, Ji et al.<sup>11</sup> discovered that in cases with a history of CAD, the monocyte/lymphocyte ratio was an indicator of lesion severity and an independent risk factor for the presence of cardiovascular disease.

Additional research by Xiang et al.<sup>12</sup> discovered which in Chinese hemodialysis cases, a greater monocyte to lymphocyte ratio was a significant and independent indicator of all- reason and cardiovascular disease death.

We assume that both monocyte/lymphocyte and monocyte/neutrophil ratios have a prognostic value for CVD in HD patients.

This research objected to assess the monocyte

to neutrophil ratio and monocyte to lymphocyte ratio as predictors of cardiovascular complications in end-stage renal disease cases on regular hemodialysis.

## 2. Patients and methods

This cross-sectional research involved 150 stable cases with end-stage renal disease undergoing regular hemodialysis for more than six months. Cases have been recruited from the Hemodialysis Unit, the Nephrology Unit of EL Zahraa University Hospital, Homayat Imbaba and Ahmed Maher teaching Hospitals, through 6 months after oral and written consents and after the agreement of the ethical committee of the university. Cases have been classified into 2 groups regarding the presence or absence of cardiovascular disease: Group I (number=111): Included patients with CVD, and Group II (number=39): Included cases with no CVD.

Inclusion criteria: Age above eighteen years and cases with ESRD on regular hemodialysis.

Exclusion criteria: Hematological illnesses, current or recent infections, active malignancies, and utilizing any autoimmune illness, immunosuppressant, Patients with diabetes, cancer, acute infections, or acute coronary syndrome at enrollment

### Methods

All cases have been exposed to the following:

#### Assessment

Baseline evaluation: Before enrolment, all subjects have been exposed to full history taking, Complete Clinical investigation and evaluation involving cardiac, chest and abdomen examination. Laboratory investigations: Kidney function test (KFT): Serum creatinine (SCr) and BUN, Serum Ca and Phosphorus, Complete blood counts (CBC), iPTH, CRP, Serum albumin, triglycerides (TG), Serum ferritin, low-density lipoprotein (LDL), Lipid profile including total cholesterol (TC), and high-density lipoprotein (HDL).

#### Clinical outcomes

Patients were evaluated using echocardiography indexes left ventricular mass based on body surface area, while ECG assesses valve morphology, opening movement, and wall thickness.<sup>13,14</sup> Cases with AS found electrocardiographic results included a positive Sokolow-Lyon index and left axis deviation, as well as optional signs like ST depressions, T-wave negativations, and left branch bundle blocks.<sup>15</sup>

#### Ethical consideration

All procedures in this study will follow Al-Azhar University Ethical Committee regulations. All procedures will be done in Al-Zharara University Hospital's nephrology unit. This work is not financially supported by any organization, society or government. Both written and oral consents

were obtained from patients.

Statistical analysis and data interpretation

Data were input into the computer and examined with IBM SPSS Corp., which became available in 2013. Version 22.0 of IBM SPSS Statistics for Windows. IBM Corp., Armonk, NY. Percentages and numbers were utilized to express qualitative data. The median and interquartile range have been utilized for presenting quantitative data for non-parametric data, and the standard deviation and mean were used for parametric data, following the Kolmogorov-Smirnov test, which was performed to determine normality. The outcomes were assessed for significance at the 0.05 level. Data analysis” Qualitative data: Chi-Square test for comparison of 2 or more groups.

### 3. Results

Table (1) shows that statistically insignificant was discovered among both groups according to sex, age, BMI, Smoking and Duration of dialysis  $p > 0.05$ .

Table (2) demonstrates which the difference among both groups according to kidney function test, serum phosphorus, serum calcium, albumin, serum ferritin, CRP and parathyroid hormone, statistically significant wasn't observed  $p > 0.05$ .

CVD has been prevalent within 111 patients (74%), while 39 patients (26%) were free from CVD. The most common CVD among the patients was LVH (52.3%), followed by wall motion abnormality (47.7%), then AF (30.6%), then MS (26.1%), then AS (23.4%) and bradycardia (14.4%) (Table 3).

WBCs, neutrophils, monocytes were statistically significantly elevated among group I as WBC was 6.9 (5.6-8.0)  $\times 10^3/\text{mm}^3$  versus 5.9 (4.9-7.2)  $\times 10^3/\text{mm}^3$  among group II,  $p$ -value= 0.02. Neutrophil count recorded 4.4 (3.4-5.7)  $\times 10^3/\text{mm}^3$  versus 3.9 (3.0-4.8)  $\times 10^3/\text{mm}^3$ ,  $p$ -value= 0.05 and monocyte count recorded 4.1 (3.0-7.0)  $\times 10^3/\text{mm}^3$  versus 3.2 (2.1-4.0)  $\times 10^3/\text{mm}^3$  among group one and group two, respectively,  $p$ -value=0.02. (Table 4)

MLR was statistically significantly higher among group one cases ( $p$ -value= 0.006) and MNR was also statistically significantly higher among group one cases ( $p$ -value= 0.03). (Table 5)

MNR was significantly positively correlated with age ( $p$ -value= 0.015,  $r$ -value=0.198), monocytes ( $p$ -value= 0.001,  $r$ =0.79) and LDL ( $p$ -value=0.03,  $r$ =0.18), While MNR showed significant negative correlation with both WBC ( $p$ -value=0.001,  $r$ = -0.29) and neutrophils ( $p$ -value=0.001,  $r$ = -0.51). (Table 6)

MLR was a significant predictor for Cardiovascular Events In Hemodialysis Patients  $p = 0.001$ . (Table 7)

Table 1. Demographic data between the two groups

DEMOGRAPHIC DATA		GROUP ONE (NUMBER=111)		GROUP TWO (NUMBER=39)		TEST OF SIG.	P-VALUE
AGE (YEAR)	Mean±SD	53.86 ± 10.79		52.72± 8.13		t=	0.55
	Min-Max	22-77		37-71		-0.61	
SEX	Male	N 69	% 62.2	N 23	% 59	χ2=0.124	0.725
	Female	42	37.8	16	41		
SMOKING		9	8.1	5	12.8	χ2=0.757	0.384
BMI (KG/M <sup>2</sup> )	Median (IQR)	26.8 (24.5-30.2)		25.6 (22.9-29.7)		U=1834.5	0.16
	Min-Max	19.7-40.7		19.5-34.8			
DURATION OF DIALYSIS (MONTHS)	Median (IQR)	34 (18-46)		33 (17-45)		U=1920.5	0.235
	MIN-MAX	6-110		6-109			

SD: Standard deviation, U: Mann-Whitney test, t: Independent t test, BMI: Body mass index, IQR: Interquartile range,  $\chi^2$ : Chi square test,  $p$ -value  $< 0.05$ : Significant;  $p$ :  $p$ -value  $> 0.05$ : Non-significant;  $p$ -value  $< 0.01$ : highly significant.

Table 2. Biochemical blood test between the two groups

BIOCHEMICAL BLOOD TEST		GROUP ONE (NUMBER=111)	GROUP TWO (NUMBER=39)	TEST OF SIG.	P-VALUE
BUN (MG/DL)	Median (IQR)	70 (60-83)	75 (61-84)	U= 2022.5	0.54
	Min-Max	14-175	48-89		
SCR (MG/DL)	Mean $\pm$ SD	8.64 $\pm$ 2.13	9.26 $\pm$ 1.96	t= 0.579	0.117
	Min-Max	3.9-16	4.2-12.3		
S. CA (MG/DL)	Median (IQR)	9.3 (8.7-9.7)	9 (8.4-9.7)	U= 1814.5	0.133
	Min-Max	5.8-10.5	5.8-10.1		
S. PO <sub>4</sub> (MG/DL)	Mean $\pm$ SD	4.7 $\pm$ 1.2	4.6 $\pm$ 1.1	t= 0.593	0.554
	Min-Max	2.2-8.4	2.3-7.3		
PTH (NG/L)	Median (IQR)	244 (123-421)	238 (141-530)	U= 2030	0.56
	Min-Max	5-1239	5-1635		
ALBUMIN (GM/DL)	Median (IQR)	3.9 (3.6-4.3)	3.9 (3.7-4.1)	U= 2054.0	0.63
	Min-Max	3.2-4.5	3.4-4.5		
CRP (MG/L)	Median (IQR)	5 (3.1-8)	6.0 (4.5-8)	U= 1828.5	0.15
	Min-Max	1.3-21	2-25		
SERUM FERRITIN (NG/ML)	Median (IQR)	343 (192-722)	405 (146-714)	U= -0.289	0.77
	MIN-MAX	11-2180	40-1320		

Scr: Serum creatinine, PTH: Parathyroid hormone, BUN: Blood urea nitrogen, CRP: C-reactive protein

**Table 3. Diagnosis of CVD and ECHO findings among the studied population**

DIAGNOSIS		ALL PATIENTS (N = 111)	
		N	%
CVD	Yes	111	74
	No	39	26
ECHO FINDINGS			
LVH		58	52.3
WALL MOTION ABNORMALITY		53	47.7
MS		29	26.1
AS		26	23.4
ECG FINDINGS			
AF		34	30.6
BRADYCARDIA		16	14.4

ECHO: Echocardiography, ECG: Electrocardiography, IHD: Ischemic heart disease, LVH: Left ventricular hypertrophy, MS: Mitral stenosis, AF: Atrial fibrillation, AS: Aortic stenosis.

**Table 4. Complete blood cell count between the two groups**

CBC		GROUP ONE (NUMBER=111)	GROUP TWO (NUMBER=39)	TEST OF SIG.	P- VALUE
HB (GM/DL)	Mean±SD	10.22 ± 1.52	10.61 ± 1.73	t=	0.187
	Min-Max	6.2-14.3	7.3-13.6	1.327	
PLATELET COUNT (X10 <sup>3</sup> /MM <sup>3</sup> )	Median (IQR)	205 (154-259)	184 (155-236)	U=	0.33
	Min-Max	80-440	105-390	1935.0	
WBC (X10 <sup>3</sup> /MM <sup>3</sup> )	Median (IQR)	6.9 (5.6-8.0)	5.9 (4.9-7.2)	U=	0.02*
	Min-Max	3.7-14.3	2.0-14.5	1629.5	
NEUTROPHILS (X10 <sup>3</sup> /MM <sup>3</sup> )	Median (IQR)	4.4 (3.5-5.7)	3.9 (3.0-4.8)	U=	0.05*
	Min-Max	1.8-10.3	0.66-12.47	1712.5	
MONOCYTES (X10 <sup>3</sup> /MM <sup>3</sup> )	Median (IQR)	4.1 (3.0-7.0)	3.2 (2.1-4.0)	U=	0.002*
	Min-Max	0.2-2.4	0.4-0.91	1447.0	
LYMPHOCYTES (X10 <sup>3</sup> /MM <sup>3</sup> )	Median (IQR)	1.46 (1.2-1.8)	1.45 (1.14-1.81)	U=	0.92
	MIN-MAX	0.18-2.8	0.16-4.8	2141	

Hb: Hemoglobin, CBC: Complete blood count, WBC: White blood cell

**Table 5. MLR and MNR between the two groups**

		GROUP ONE (NUMBER=111)	GROUP TWO (NUMBER=39)	TEST OF SIG.	P- VALUE
MLR	Median (IQR)	0.25 (0.19-0.52)	0.21 (0.13-0.29)	U=	0.006*
	Min-Max	0.01-3.48	0.02-5.68	1525.5	
MNR	Median (IQR)	0.09 (0.07-0.19)	0.09 (0.05-0.011)	U=	0.03*
	MIN-MAX	0.02-0.63	0.01-0.26	1670.0	

**Table 6. Correlation between MNR with each of demographic and laboratory data**

PARAMETERS	MNR	
	R	P
AGE (YEAR)	0.198*	0.015*
BMI (KG/M <sup>2</sup> )	0.09	0.25
DURATION OF DIALYSIS (YEARS)	0.007	0.93
BUN (MILLIGRAM PER DECILITERS)	-0.138	0.09
SCR (MILLIGRAM PER DECILITERS)	0.075	0.36
S. CA (MILLIGRAM PER DECILITERS)	0.02	0.97
S. PO <sub>4</sub> (MILLIGRAM PER DECILITERS)	-0.11	0.17
PTH (NG/L)	0.13	0.11
ALBUMIN (GM/DL)	0.003	0.97
CRP (MG/L)	-0.03	0.703
SERUM FERRITIN (NG/L)	-0.008	0.92
HB (MG /DL)	-0.14	0.87
PLATELET COUNT (X10 <sup>3</sup> /MM <sup>3</sup> )	0.018	0.09
WBC (X10 <sup>3</sup> /MM <sup>3</sup> )	-0.29**	0.001*
NEUTROPHILS (X10 <sup>3</sup> /MM <sup>3</sup> )	-0.51**	0.001*
MONOCYTES (X10 <sup>3</sup> /MM <sup>3</sup> )	0.79**	0.001*
LYMPHOCYTES (X10 <sup>3</sup> /MM <sup>3</sup> )	-0.04	0.64
TC (MILLIGRAM PER DECILITERS)	0.14	0.09
TG (MILLIGRAM PER DECILITERS)	0.11	0.18
HDL (MILLIGRAM PER DECILITERS)	0.05	0.534
LDL (MILLIGRAM PER DECILITERS)	0.18*	0.03*

**Table 7. Logistic regression of independent marker predicting CVD.**

PARAMETERS	MNR	
	P value	ODDS RATIO (95% CI)
MLR	.001	11.023 (6.235 – 28.652)
MNR	0.323	0.13 (0.002 – 7.459)

#### 4. Discussion

In our study, statistically insignificant was observed among both groups according to sex, age, BMI, Smoking and dialysis period  $p>0.05$ .

Our study has been agreed with, Xiang F et al.,<sup>12</sup> who examined the predictive value of monocyte to lymphocyte ratio for all-reason and cardiovascular death within hemodialysis cases and comparing it with neutrophil-to-lymphocyte ratio. A total of 355 cases (220 males and 135 females) had been included in the investigation. The average age was 58.0 years, with a median time on hemodialysis of twenty months. (10, 53).

Similar to our results, Sethi et al.<sup>16</sup> studied the quality of life among ESRD patients and reported a mean age of  $54.44 \pm 14.19$  years. There was a preponderance of male patients, which constituted 74% of the total patients.

As for BMI, Inagaki et al.<sup>17</sup> studied the correlation between all-cause death and BMI and reported a mean BMI of  $23.3 \pm 4.24$  kg/m<sup>2</sup> at the first HD session.

In our study, we found that WBCs, neutrophils and monocytes were significantly higher among



ESRD patients with CVD. We also found that both MLR and MNR were statistically significantly higher among the CVD group compared to the patient group without CVD, *p*-value 0.006 and 0.03, respectively.

In accordance with our outcomes, Muto et al.<sup>18</sup> stated a significantly higher number of CVD events among the great monocyte to lymphocyte ratio group than the reduced monocyte to lymphocyte ratio group.

Furthermore, Xiang et al.<sup>12</sup> conducted a single-center research with 355 hemodialysis cases and observed which an elevated monocyte to lymphocyte ratio demonstrated lesser survival rates compared with lesser monocyte to lymphocyte ratio and which monocyte to lymphocyte ratio was independently correlated with cardiovascular disease mortality.

In cases with chronic kidney disease and cardiovascular comorbidities, the expression of membrane-bound angiotensin-converting enzyme (ACE) was observed to rise, which leads to a more complete characterization of monocytes.<sup>19</sup>

In contrast, a diminished lymphocyte count has been observed in end-stage renal disease cases and identified as a predictor of mortality and morbidity among these people.<sup>20</sup>

Within the current research, CVD was prevalent in 111 cases (74%), while 39 patients (26%) were free from CVD. The most common CVD among the patients was LVH (52.3%), followed by wall motion abnormality (47.7%), then AF (30.6%), then MS (26.1%), then AS (23.4%) and bradycardia (14.4%).

Consistent with our study, Xiang F et al.,<sup>12</sup> who reported that of the 355 cases, 107 (30.1%) had a history of cardiovascular disease, which included eleven angina pectoris, eight myocardial infarction, forty-nine cases of cerebral infarction, thirty-seven cases of congestive heart failure, three peripheral vascular illnesses and nine cerebral hemorrhage.

In our study, MLR and MNR were significantly positively correlated with age and LDL, while MLR was significantly negatively correlated with phosphorus.

This was in line with Gao et al.<sup>21</sup>, who observed that MLR is positively associated with age.

This could be owing to the fact that aging is a natural physiological process that elevates the probability of cardiovascular illnesses, including ischemic heart disease, hypertension, and additional comorbidities.<sup>22</sup>

In regard to the association with LDL, intermediate monocytes are elevated when atherogenic lipids, including Lp(a) and small dense (sd)LDL, are present at higher concentrations.<sup>23</sup>

Although we could not find previous reports of

correlation between monocytes count and phosphorus, Raggi et al.<sup>24</sup> interestingly demonstrated that valvular calcification progression was related to alteration of mineral metabolism that can be reduced by interventions targeting the metabolism of parathyroid hormone and phosphorus, calcium within cases undergoing hemodialysis. This might be the reason for this correlation.

In brief, The neutrophil-to-lymphocyte ratio and monocyte to lymphocyte ratio are two immune pathways that are likely less influenced by confounding conditions and can be more accurate for assessing inflammation compared to monocytes, neutrophils, lymphocytes or platelets, taken separately.

#### 4. Conclusion

Monocyte to lymphocyte ratio and monocyte to neutrophil ratio could be useful indicators of cardiovascular complications within cases with ESRD on regular hemodialysis. The MLR and MNR showed significant correlations with age, monocytes, LDL, and MNR, while being negatively correlated with WBCs and neutrophils. These findings suggest that MLR and MNR could be valuable biomarkers for identifying hemodialysis patients at increased probability of cardiovascular complications.

#### Disclosure

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

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All authors have a substantial contribution to the article

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There are no conflicts of interest.

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