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ORIGINAL ARTICLE

Can Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio and Tumor Necrosis Factor Alpha Predict Lupus Nephritis Flares?

[1]Shaimaa H. Fouad*, [1]Mohamed N. Farres, [2]Eman S. A. Mansour, [1]Mayada Moneer
[1]Internal Medicine/ Allergy and Clinical Immunology Department, Faculty of Medicine, Ain-Shams University, Cairo, Egypt
[2]Department of Internal Medicine, Ministry of Health, Cairo, Egypt

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Corresponding Author:
Shaimaa Hani Fouad, Department of Internal Medicine/ Allergy and Clinical Immunology, Ain Shams University, 11566 Abbasia, Cairo, Egypt.
Phone/Fax: +(202) 24346888
Mobile: +(2)01116110004
shaimaahani@med.asu.edu.eg

ABSTRACT

Background: *Systemic Lupus Erythematosus (SLE) is a chronic autoimmune multisystem disease with an array of variable presentations in which the kidney is the most affected organ and influences the overall outcome of the patients.* ***Methodology:*** *The study is a case control study conducted on 90 SLE patients diagnosed according to ACR criteria grouped into three subgroups. It aims at evaluating the role of serum tumor necrosis factor alpha (TNFα), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in diagnosing renal flares and predicting the prognosis in lupus nephritis patients.* ***Results:*** *A highly significant difference was observed between both the SLE starting dialysis group, the SLE nephritis (LN) group, and the control group regarding neutrophil to lymphocyte ratio and TNFα ($p<0.001$ & <0.001, respectively). The median serum Neutrophil/Lymphocyte and TNFα were statistically significantly higher in the SLE starting dialysis patient group than the LN patients and the control group. A cut-off value of ≤ 200 for serum TNFα level and of ≤ 4.8 for Neutrophil/lymphocyte ratio sufficiently differentiated between the LN patients and the SLE patients starting dialysis. TNFα cut-off value showed sensitivity of 76.67%, specificity of 96.67%, positive predictive value of 95.8% and negative predictive value of 80.6 %. Neutrophil/Lymphocyte cut-off showed sensitivity of 70.00%, specificity of 70.00%, positive predictive value of 70.00% and negative predictive value of 70.00 %.* ***Conclusion:*** *NLR and TNFα serum levels appear to be useful biomarkers for disease flares and tissue injury in LN patients. Both can identify disease activities, relapses and remissions in lupus nephritis patients.*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a serious autoimmune disorder with varying clinical presentations and multiorgan involvement. The disease has female predominance and unpredictable courses. [1]

Systemic Lupus Erythematosus diagnosis and activity detection currently include blood markers such as CRP and ESR as acute phase markers and specific serology including anti-double -stranded DNA antibodies (dsDNA), C1q antibodies and complement C3 and C4 levels. [2]

In Systemic Lupus Erythematosus patients, organ involvement can't be predicted. Renal biopsy, an invasive procedure which carries the risk of hematuria, renal hematoma and infection, is the benchmark test for diagnosis of renal involvement. Nonetheless, a biopsy is an inconvenient method for monitoring lupus nephritis since the disease requires continuous monitoring over years to avoid flares and renal function deterioration. [3] Creatinine and albumin serum levels and urinary excretions such as protein: creatinine ratio, 24 hr urine protein collection are used for monitoring disease activity and flares. However, up to the present time there has been no available marker that can demarcate between active and chronic disease. [3,19]

Cytokines association with SLE disease flares and renal involvement have been evaluated by many researchers. Tumor necrosis factor has been in the focus since high serum TNFα levels can be detected in SLE and can also be identified in the kidneys of lupus nephritis patients. Moreover, the use of anti TNF therapy in rheumatoid arthritis patients induces the anti-DNA antibodies though frank lupus is rare. [4]

Two new markers, platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) have been investigated as possible indicators for subclinical inflammation, prognostic indicators in many illnesses such as cancers [4], cardiac [5] and metabolic disorders, [6] and autoimmune inflammatory diseases. [7]

Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are not easily influenced by dehydration or overhydration or by blood sampling techniques, compared to other blood indices such as ESR. [1] The role of both in systemic lupus and whether they can be used to monitor these patients and detect disease flares, especially lupus nephritis, need to be evaluated.

The aim of the present study is to evaluate the role of serum TNFα, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in diagnosing renal flares and to estimate the prognosis of lupus nephritis patients.

METHODOLOGY

The study included patients of lupus nephritis diagnosed according to the American College of Rheumatology (ACR) criteria attending nephrology and rheumatology clinics, dialysis units or admitted as inpatients. Based on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score for disease activity, our patients were divided into 3 groups. The first group included 30 lupus nephritis patients (patient scored ≥ 2). The second group included 30 SLE patients starting dialysis. The third group, which is the control group, included 30 SLE patients in remission (patients scored <2) with no renal affection.

***Exclusion criteria*:**

The following patients were excluded to avoid the presence of other causes of kidney diseases or causes that may affect white blood cells count or the level of TNF∝ .Smokers; pregnant females ,patients with advanced hepatic and pulmonary affection,patients who are already diagnosed malignancy ,patients who have concomitant acute or chronic infections as hepatitis B and/ C viruses; patients who have undergone recent trauma or surgery; Diabetic patients and/or Hypertensive patients, patients having any abnormalities in the white blood cell (WBC) count and patients above the age of 45 to exclude any comorbidities such as diabetes, metabolic syndrome, ISHD.

All participants will be assessed through the followings:

Detailed history and clinical examination ,in addition to the following investigations: complete blood count (CBC) with differential WBC count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), NLR & PLR ratios will be calculated from CBC indices, anti-nuclear antibody (ANA), anti-Double strand DNA, complement 3(C3) & Complement 4(C4), Serum creatinine, blood urea nitrogen (BUN), Urine analysis, protein/creatinine ratio or 24 hours urinary proteins and tumor necrosis factor alpha(TNFα) assay in blood by ELISA.

Statistical analysis of the data:

IBM SPSS software package version 20.0**. (**Armonk, NY: IBM Corp**)** was used to analyze our data. Qualitative data were expressed using number and percent. To verify the normality of distribution, Kolmogorov-Smirnov test was used. A range of (minimum and maximum), mean, standard deviation, median and interquartile range (IQR) were used to describe our quantitative data. Significant results were judged at the 5% level.

RESULTS

Table (1) summarizes the comparison among the three studied groups according to demographic data. SLE on dialysis patient group included 30 patients, 26 females and 4 males, their age ranged between 21.0 – 45.0 years, with a mean age of 36.23 ± 7.03. The SLE nephritis patient group included 30 patients, 26 females and 4 males, whose age ranged between 16.0 – 43.0 years, with a mean age of 31.17 ± 7.08. The control group included 30 patients, 26 females and 4 males, whose age ranged between 21.0 – 43.0 years with a mean age of 31.17 ± 5.80. There was a statistically significant difference among the three groups regarding the mean age. The mean age of the SLE starting dialysis patient group was higher compared to that of the SLE nephritis patient group and the control group.

Table 1: Comparison between the three studied groups according to demographic data

	SLE starting dialysis (n=30)		SLE nephritis patient (n = 30)		Control (n = 30)		P
	No.	%	No.	%	No.	%	
Gender							
Females	26	86.7	26	86.7	26	86.7	$^{MC}p=$ 1.000
Males	4	13.3	4	13.3	4	13.3	
Age (years)							
Min. – Max.	21.0 – 45.0		16.0 – 43.0		21.0 – 43.0		0.004*
Mean ± SD.	36.23 ± 7.03		31.17 ± 7.08		31.17 ± 5.80		
Sig. bet. groups.	p_1=0.011*,p_2=0.011*,p_3=1.000						

χ^2: **Chi square test** MC: **Monte Carlo**

F: **F for ANOVA test**, Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Tukey)**

p: p value for comparing between **the three studied groups**

p_1: p value for comparing between **SLE on dialysis** and **SLE nephritis patient**

p_2: p value for comparing between **SLE on dialysis** and **control**

p_3: p value for comparing between **SLE nephritis patient** and **control**

*: Statistically significant at $p \leq 0.05$

SLE,systemic lupus erythematosus; MIN., minimum; Max., Maximum; Sig., Significance.

Table (2) compares the three studied groups according to the serum TNFα level. There was a statistically significant difference between the three groups (p=<0.001). The median (IQR) serum TNFα in the SLE starting dialysis patient group was 150 ng/ml (120-200) while in the SLE nephritis patient group was 720 ng/ml (360-960) and in the control group was 85.0ng/ml (30-130). The median serum TNFα was statistically significantly the highest in the lupus nephritis patient group (p=<0.001). It was also statistically significantly higher than the median TNFα in the SLE starting dialysis patient group (p1=<0.001). Moreover, there was a statistically significant higher median serum TNFα in the SLE nephritis patient group than the control group (p3=<0.001). In addition, the median serum TNFα was statistically significantly higher in the SLE starting dialysis patient group than in the control group (p2= <0.041).

Table 2: Comparison between the three studied groups according to Tumor necrosis factor alpha

TNF alpha	SLE starting dialysis (n=30)	SLE nephritis patient (n = 30)	Control (n = 30)	P
Min. – Max. Median (IQR)	90.0 – 960.0 ng/ml 150.0 (120.0–200.0)	180.0 – 960.0 ng/ml 720.0(360.0 – 960.0)	15.0 – 180.0 ng/ml 85.0 (30.0–130.0)	<0.001*
Sig. bet. groups.	p_1<0.001*,p_2=0.002*,p_3<0.001*			

H: H for **Kruskal Wallis test,** Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Dunn's for multiple comparisons test)**

p: p value for comparing between **the three studied groups**

p_1: p value for comparing between **SLE on dialysis** and **SLE nephritis patient**

p_2: p value for comparing between **SLE on dialysis** and **control**

p_3: p value for comparing between **SLE nephritis patient** and **control**

*: Statistically significant at $p \leq 0.05$

SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; MIN., minimum; Max., Maximum; Sig., Significance; IQR, interquartile range

Table (3) illustrates comparison among the three studied groups according to Neutrophil and lymphocyte percentage. Regarding Neutrophil percentage (Neut %), there was a statistically significant difference between the three groups (p=<0.001). The median (IQR) of Neut % in the SLE starting dialysis patient group was 69.27(64.10–73.90), while in the SLE nephritis patient group was 0.65(0.55–0.79) and in the control group was 56.0 (46.0–62.0). The median (IQR) serum Neut % was statistically significantly in the SLE starting dialysis patient group than in the SLE nephritis patient group and in the control group (p=<0.001 and 0.021*, respectively). It was also statistically significantly higher in the control group than in the lupus nephritis patient group (p1=<0.021).

Regarding Lymphocyte percentage (Lymph%), there was a statistically significant difference among the three groups (p=<0.001). The median (IQR) serum Lymph % in the SLE starting dialysis patient group was 21.75 (19.30–29.0), while in the SLE nephritis patient group was 27.25(21.0–41.0) and in the control group was 0.36 (0.30–26.60). The median (IQR) serum Lymph % was statistically significantly the highest in the SLE starting dialysis patient group (p=<0.002*). It was also statistically significantly higher in the control group than the SLE nephritis patient group (p1=<0.001*). The Systemic lupus erythematosus starting dialysis patient group was non- significant with the SLE nephritis patient group (p=0.356).

Table 3: Comparison between the three studied groups according to neutrophil percent (Neut%) and Lymphocyte % (Lymph %)

	SLE starting dialysis (n=30)	SLE nephritis patient (n = 30)	Control (n = 30)	F	p
Neut % Min. – Max. Median (IQR).	 40.20 – 84.0 69.27(64.10–73.90)	 0.39 – 87.0 0.65(0.55–0.79)	 39.0 – 70.0 56.0(46.0–62.0)	58.205*	<0.001*
Sig. bet. groups.	p_1<0.001*,p_2=0.021*,p_3<0.001*				
Lymph % Min. – Max. Median (IQR).	 11.70 – 49.70 21.75(19.30–29.0)	 3.40 – 54.0 27.25(21.0–41.0)	 0.25 – 46.10 0.36(0.30–26.60)	12.973*	<0.001*
Sig. bet. groups.	p_1=0.356,p_2=0.002*,p_3<0.001*				

F: **F for ANOVA test**, Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Tukey)**
p: p value for comparing between **the three studied groups**
p_1: p value for comparing between **SLE on dialysis** and **SLE nephritis patient**
p_2: p value for comparing between **SLE on dialysis** and **control**
p_3: p value for comparing between **SLE nephritis patient** and **control**
*: Statistically significant at $p \leq 0.05$
SLE, Systemic Lupus Erythematosus; Neut%, neutrophil percentage; Lymph%, Lymphocyte percentage; MIN., minimum; Max., Maximum; Sig., Significance; IQR, interquartile range

Table (4) illustrates the comparison among the three studied groups according to median (IQR) neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR).

First, regarding NLR, there was a statistically significant difference among the three groups (p=<0.001). The median serum NLR in the SLE starting dialysis patient group was 3.25 while in the SLE nephritis patient group was 2.27 and in the control group was 1.63. The median serum NLR was statistically significantly the highest in the SLE starting dialysis patient group compared to the SLE nephritis patient group and the control group (p=<0.010 and 0.024*, respectively). It was also statistically significantly higher in the SLE nephritis patient group than in the control group (p1=<0.001).

Second, Regarding PLR, there was no statistical significance between the three studied groups as the (p = .314). The PLR in the SLE starting dialysis patient group ranged from 45.47 to 290.9, with a median (IQR) 121.6, while in the SLE nephritis patient group it ranged from 32.0 to 431.7, with a median (IQR) 140.9. Plus, in the control group, it ranged from 36.58 to 178.6 with a median (IQR) 121.1.

Table 4: Comparison between the three studied groups according to neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR)

	SLE on dialysis (n=30)	**SLE nephritis patient (n = 30)**	**Control (n = 30)**	**H**	**p**
NLR Min. – Max. Median (IQR)	 0.80 – 6.93 3.25(2.2 – 3.8)	 0.72 – 9.45 2.27(1.3 – 3.4)	 0.86 – 2.80 1.63(1.2 – 2.1)	23.493*	<0.001*
Sig. bet. grps.	p_1=0.024*,p_2<0.001*,p_3=0.010*				
PLR Min. – Max. Median (IQR)	 45.47 – 290.9 121.6(91.1 – 156.4)	 32.0 – 431.7 140.9(92.1 – 181.5)	 36.58 – 178.6 121.1(89.6 – 160.6)	2.317	0.314

H: H for **Kruskal Wallis test,** Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Dunn's for multiple comparisons test)**
p: p value for comparing between **the three studied groups** p_1: p value for comparing between **SLE on dialysis** and **SLE nephritis patient**
p_2: p value for comparing between **SLE on dialysis** and **control**
p_3: p value for comparing between **SLE nephritis patient** and **control**
*: Statistically significant at $p \leq 0.05$
SLE, systemic lupus erythematosus; NLR, neutrophil lymphocyte ratio; PLR, platelet to lymphocyte ratio; MIN., minimum; Max., Maximum; Sig., Significance; IQR, interquartile range

Table (5) illustrates relation between NLR and PLR with ANA, Anti-dsDNA in each group. There was a statistically non-significant relation among the groups regarding NLR and PLR.

Table 5: Relation between Neut/lymph and PLT/lymph with ANA, AntidsDNA in each group

		ANA		AntidsDNA#	
		–ve	+ve	–ve	+ve
Neut/lymph	SLE starting dialysis (n=30)	(n=23)	(n=7)	(n=25)	(n=4)
	Min. – Max.	0.80 – 4.42	1.84 – 6.93	0.80 – 4.80	1.84 – 6.46
	Median	3.23	4.03	3.27	2.96
	U (p)	57.50 (0.266)		47.50 (0.879)	
	SLE nephritis patient (n=30)	(n=7)	(n=23)	(n=15)	(n=14)
	Min. – Max.	1.11 – 6.93	0.72 – 9.45	1.04 – 6.93	0.72 – 9.45
	Median	2.29	2.24	2.78	2.15
	U (p)	78.0 (0.924)		79.0 (0.270)	
PLT/lymph	SLE starting dialysis (n=30)	(n=23)	(n=7)	(n=25)	(n=4)
	Min. – Max.	59.26 – 193.30	45.47–290.90	59.26 – 193.30	45.47 – 127.80
	Median	120.30	129.30	122.50	99.68
	U (p)	61.0 (0.360)		29.0 (0.203)	
	SLE nephritis patient (n=30)	(n=7)	(n=23)	(n=15)	(n=14)
	Min. – Max.	78.70 – 267.09	32.0 – 431.70	75.60 – 392.50	32.0 – 431.70
	Median	177.40	120.14	157.50	117.26
	U (p)	73.0 (0.737)		82.0 (0.331)	

U: Mann Whitney test
p: p value for comparing between **the two categories**
#: Excluded from the comparison due to small number of **equivocal cases** (n = 1)
*: Statistically significant at $p \leq 0.05$
ANA, anti-nuclear antibody; Anti dsDNA, anti-double stranded nucleic acid antibody; SLE; systemic lupus erythematosus; MIN., minimum; Max., Maximum

The multivariate analysis identified only two risk factors significantly associated with higher odds of starting dialysis in SLE nephritis: TNFα ≤ 200 and NLR ≤ 4.8 (Table 6). Age and Neutrophil percent were found to be potential risk factors (p value =0.001 & 0.011, respectively), but they were excluded from the final model.

Table (6): Univariate and multivariate logistic regression analysis for age, Tumor necrosis factor alpha, Neutrophil percentage and Neutrophil to lymphocyte ratio between Systemic lupus erythematosus patients and Systemic lupus erythematosus starting dialysis

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Age (years) >35	**0.001**	6.571	2.109	20.479	**0.026**	18.562	1.411	244.224
TNF α ≤ 200 ng/ml	**0.000**	95.286	10.928	830.856	**0.001**	279.181	11.699	6662.339
Neut % >66.1	**0.011**	4.000	1.367	11.703	0.097	6.093	0.72	51.567
NLR ≤ 4.8	**0.003**	5.444	1.804	16.427	**0.019**	21.689	1.649	285.262

NLR, neutrophil to lymphocyte ratio; TNFα , tumor necrosis factor alpha, Neut%, neutrophil percentage
*: Statistically significant at $p \leq 0.05$

The receiver operating characteristic (ROC) curve shows that a cut-off value of ≤ 200 for serum TNF alpha level sufficiently differentiated between the SLE nephritis patient group and the lupus nephritis starting dialysis patient group with sensitivity of 76.67 percent, specificity of 96.67 percent, positive predictive value (PPV) of 95.8 percent, and negative predictive value (NPV) of 80.6 percent. The NLR's cut off value of ≤ 4.80 significantly differentiate between the SLE nephritis patient group and the SLE nephritis starting dialysis patient group with sensitivity of 70 percent, specificity of 70 percent, positive predictive value (PPV) of 70 percent, and negative predictive value (NPV) of 70 percent. (Figure 1, table 7)

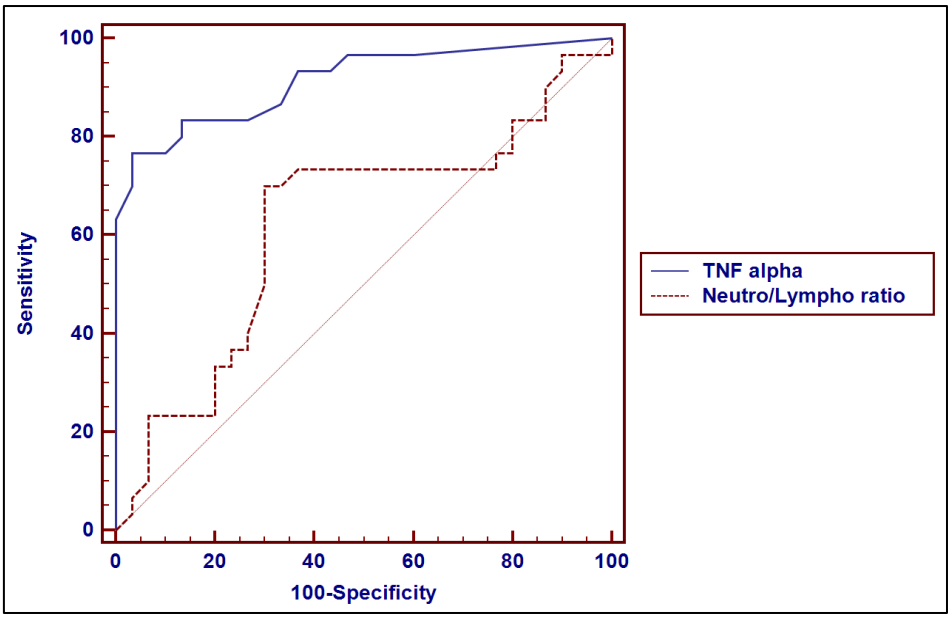

Fig. 1: Receiver operating characteristic (ROC) curve for Tumor necrosis factor alpha and Neutrophil to lymphocyte ratio between Systemic lupus erythematosus nephritis patients and Systemic lupus erythematosus starting dialysis

Table 7: Cut off point for Tumor necrosis factor alpha and Neutrophil to lymphocyte ratio between Systemic lupus erythematosus nephritis patients and Systemic lupus erythematosus starting dialysis

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
TNF alpha ng/ml	≤ 200	0.913	76.67	96.67	95.8	80.6
Neut/Lymph ratio	≤ 4.8	0.622	70.00	70.00	70.0	70.0

TNF alpha, Tumor necrosis factor alpha; Neut/lymph, neutrophil/lymphocyte; AUC, area under the curve;+PV, positive predictive value; -PV, negative predictive value

DISCUSSION

Lupus is an incurable autoimmune disease with remitting–relapsing paths. Accompanied co morbidities and fatalities might be reduced if practitioners spotted the early signs of clinical relapse. Systemic lupus erythematosus has a diversity of symptoms and targets many body systems such as the urinary, respiratory and central nervous systems, the skin and muscles. Lupus nephritis (LN) occurs in 50% or more of SLE patients, most of whom end in chronic kidney disease and finally long life extracorporeal renal replacement therapy or renal transplantation, hence increasing the risk of mortality [8].

Concerning sociodemographic data, the SLE starting dialysis patient group included 30 patients, 26 females and 4 males, with a mean age of 36.23 ± 7.03. The lupus nephritis patient group included 30 patients, 26 females and 4 males, with a mean age of 31.17 ± 7.08. The Control group included 30 patients, 26 females and 4 males, with a mean age of 31.17 ± 5.80. There was a statistically significant difference among the three groups regarding the mean of age. The mean age of the SLE on the dialysis patient group was higher than that of the lupus nephritis patient group and that of the control group. On the contrary, Soliman et al., [9] reported that disparities in age and sex between studied populations were of no significant differences.

Lately, neutrophil, lymphocyte, and platelet levels have been a point of convergence in research communities as potential markers of tissue inflammation in several medical disorders. Scientists incorporated NLR with many other inflammatory markers and cytokines to predict systemic inflammation in both autoimmune and non -autoimmune conditions. Platelet to lymphocyte ratio has been studied in multiple medical conditions including cardiac disorders, myeloproliferative diseases, different malignancies, chronic inflammatory disorders and many infections. [10, 11]

In our current study, Neut %, Lymph% and NLR showed statistically significant difference among the three groups (p=<0.001) being the highest in the SLE starting dialysis patient group. Additionally, the median serum NLR was statistically significantly higher in the SLE on dialysis patient group than in the lupus nephritis patient and in the control (p=<0.010 and 0.024*, respectively). It was also statistically significantly higher in the lupus nephritis patient group than in the control (p1=<0.001). Neutrophil to lymphocyte ratio cut off value of ≤ 4.80 differentiated between the lupus nephritis patient group and the lupus nephritis patients starting dialysis group with sensitivity of 70 percent, specificity of 70 percent, positive predictive value (PPV) of 70 percent and negative predictive value (NPV) of 70 percent. Regarding PLT/Lympho ratio, there was no significant difference between the SLE starting dialysis group, the lupus nephritis group and the control group (p=0.314).

These data are in concordance with several studies as regards NLR but they disagree with those studies as regards PLR. Torman et al. [11] work results coincide with the current results. They studied CBC parameters with advanced renal disease. In their work, higher creatinine levels were associated with increased PLR and NLR.

Furthermore, Ata Bora et al., [12] demonstrated that mean MPV and NLR values were significantly higher in SLE nephritis group (p=0.001 and p<0.001, respectively). Similarly, Abdulrahman et al., [13] revealed that the NLR and PLR ratios were significantly higher in patients compared to controls (p = 0.007 for both). Lupus nephritis patients showed higher values for both NLR and PLR compared to non-nephritis patients (p < 0.001).

Moreover, Soliman et al., [9] work revealed that NLR showed a significant increase in both the active SLE group, and the LN subgroups compared to the remitting patients and the control groups. However, it failed to discriminate between the remitting and control groups (P=0.2). In addition, Qin et al. [8], reported higher levels of PLR and NLR in the SLE patients compared to the healthy controls.

The results of Wu et al. [14] showed that PLR and NLR levels had higher levels in the SLE patients compared to those of the healthy controls. Both ratios were equated to lupus activity index 2000 (SLEDAI-2K), moreover; NLR was significantly increased in LN and NLR cutoff value of 2.26 which was able to correctly identify SLE patients with more severe disease with 75 percent sensitivity and 50 percent specificity, where the PLR cutoff value 203.85 identified patients with intense disease coarse with 42.3 percent sensitivity and 83.9 percent specificity.

Other studies such as Ayna et al. [15] reported a parallely significant increase in NLR in the Lupus nephritis patients and in the SLE patients without renal involvement. This study and many antecedent studies disclosed the role of NLR and PLR as useful tools to track SLE disease flares specially in lupus nephritis patients and they correlate to SLEDAI -2k [12].

Tumor necrosis factor alpha is a powerful pro-inflammatory cytokine with a key role in the immune system responses during inflammation, cell proliferation, differentiation and apoptosis. It is well established now that lupus patients have higher levels of circulating TNFα. Moreover, many researchers have reported a strong correlation between TNFα level and SLE activity index ([16,17]. Data from several research results have disclosed that even with the use of aggressive immunosuppressives, TNF α and other cytokines levels are not affected.

Our results showed that as regards serum TNF α, there was a statistically significant difference among the three groups (p=<0.001). The median (IQR) serum TNF alpha was significantly higher in the lupus nephritis patient group than in the SLE starting dialysis patient group and in the control group. It was also higher in SLE starting dialysis than in the control group. Serum level ≤ 200 ng/ml was the cut-off point between the control group and the two other groups

These data are consistent with Adhya et al., who evaluated the ability of 6 different cytokines in detecting SLE disease activity. In his work, serum TNF-alpha was able to demarcate between active and inactive LN and also between active LN versus SLE patients without renal affection. It should, therefore, be considered a promising marker in this field. [18]

Recommendations

In our study, we did not compare blood indices to renal biopsy results since many patients did not have renal biopsies, especially the mild cases. Some of our patients who had prior renal biopsies, lost their results, while others refused to have another renal biopsy at the time of study. Moreover, we did not stratify our SLE nephritis patients into subgroups according to severity due to our small study population.

More studies with larger sample size are needed. More prospective cohort studies should be performed to assess the role of NLR and serum TNF alpha in predicting lupus flare.

CONCLUSION

Being easily obtained and cheap, NLR and serum TNF alpha levels appear to be promising biomarkers for disease flares and tissue injury in LN patients. NLR and TNF levels identified precisely SLE nephritis patients with higher disease activity scores.

List of Abbreviations:
ANA; Anti- nuclear antibody, Anti-DNA; Anti double stranded nucleic acid antibody,CBC; Complete blood count , ESR; erythrocyte sedimentation rate,ESRD ; End stage renal disease,ISHD; Ischemic heart disease IQR; Interquartile range,LN; lupus nephritis,Lymph%; Lymphocyte percentage,NPV; Negative predictive value,Neutrophil percentage, NLR; Neutrophil to lymphocyte ratio,Neut%; PLR; Platelet to lymphocyte ratio,ROC; Receiver operating characteristic,SLE; Systemic lupus erythematosus,TNF; Tumor necrosis factor.

Ethics approval and consent to participate:
The work was authorized by Ain Shams University's Research Ethics Committee, FWA 00017585 FMASU MSO 10/2022, and followed the Helsinki Declaration. Each participant or their first-degree relative gave written informed consent after being told of the study's purpose and protocol. All patient data was kept confidential.

Consent for publication
Not applicable

Availability of data and material
Data are available upon request

Competing interests
The author declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article any.

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