The study of possible relationship between NLR (neutrophil to lymphocyte ratio) and PLR (platelet to lymphocyte ratio) along with level of disease activity in patients with SLE (systemic lupus erythematosus)

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease with unknown etiology, and has various clinical manifestations affecting different tissues. Excessive pro-inflammatory cytokine production leads to damage of multiple organ systems. **Methodology:** The study was conducted at Madras Medical College and Rajiv Gandhi Government General Hospital Chennai, for period of one year. 100 patients fulfilling the inclusion exclusion criteria were enrolled in the study. Presenting complaints including the time elapsed from development of the first clinical symptoms; time elapsed after diagnosis; use of regular medication; and the existence of clinical remission will be recorded and Disease activity score will be calculated. **Result:** NLR value of about 4.3141 with a standard deviation of 1.08696 indicates high diseaseactivity. PLR value of about 233.4853 with a standard deviation of 64.74761 indicates high diseaseactivity. Analysis revealed that NLR and PLR were significantly higher in SLE patients and were positively correlated with SLEDAI-2K score which suggests that NLR and PLR could be useful

biomarkers in the management of SLE.
Conclusion: NLR and PLR together with other serum inflammatory markers, were proving as significant clinical tools which could be used as biomarkers for inflammatory response or disease activity in SLE Patients.
Keywords: NLR, PLR, SLE, disease, biomarkers.
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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease with unknown etiology, and has various clinical manifestations affecting different tissues. It is characterized by the deposition of immune complexes due to widespread loss of immune tolerance to nuclear self-antigens, as well as by excessive pro-inflammatory cytokine production, leading to damage of multiple organ systems.[1] Unrestricted hyper-activation of the immune system may lead to the overproduction of autoantibodies, immune complex deposition, inflammatory cytokine release, and eventually disease onset.[2]

Cytokines have a very significant role in the pathogenesis of a great number of inflammatory diseases. Neutrophils and platelets are involved in the production of these cytokines, which in turn contribute to the further activation of these neutrophils and platelets.[3-4] It is known that leukocytes play an important role in inflammatory processes and neutrophils are the most abundant type of the WBC. Activated leukocytes can release superoxide radicals and proteases, all of which promote oxidative stress.[5] At the same time, neutrophils secrete large amounts of inflammatory mediators, and, because of the short neutrophil half-life, neutrophilia may be associated with the acute inflammatory response to tissue injury. Recent studies have shown that the WBC count and its subtypes are also useful for predicting the inflammatory process. NLR represents a combination of these two markers, and is superior to other leucocyte parameters, because its stability is less influenced by physiological, pathological and physical factors.[6-7]

The neutrophil-to-lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have recently been investigated as new prognostic indicators for a large number of malignancy studies.[8-9] Many cancer survival studies have suggested that the NLR is significant predictors of overall and disease-specific survival of patients.[10-13] Moreover, some studies have shown that NLR and PLR are associated with morbidity and mortality in many chronic diseases, such as hypertension, heart failure, infective endocarditis, acute coronary syndromes and type 2 diabetes.[14-18] As a novel marker for inflammation, NLR may be also useful to estimate the activity of autoimmune diseases. Some studies have shown that NLR is associated with psoriasis[19]and rheumatoid arthritis.[20]

A recent study has also shown that NLR is increased in patients with systemic lupus erythematosus (SLE).[21] However, platelets also play an active role in inflammation, while having regulatory effects on the immune system as well.[22-23] Our study is actually very rare that assesses NLR and PLR in patients with SLE, and to investigate their relationship with inflammatory response and disease activity in SLE.

MATERIALS AND METHODS

The Cross Sectional Observational Study was carried out at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai after getting permission from the Institutional ethics committee. Study was conducted for one year. 100 patients were included in the study. Patients belonging to the age group 15 to 45 (median – 27 years), both genders, fulfilling the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) criteria (2019) for SLEand ready to give consent were

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included in the study. Patients with hypertension, diabetes, chronic liver and kidney diseases, cerebrovascular diseases, cardiovascular diseases, infectious diseases, immune compromised patients such as HIV/AIDS, malignancy, and those associated with other autoimmune diseases: such as Rheumatoid arthritis, Sjogren's syndrome, grave's disease were excluded from the study. Written informed consent was taken from the patient in their local language.

Relevant demographic details like age, gender, residence, occupation and other life style details will be recorded. Presenting complaints including the time elapsed from development of the first clinical symptoms; time elapsed after diagnosis; use of regular medication; and the existence of clinical remission will be recorded and disease activity score will be calculated. The relevant past history, drug history, associated comorbidities, family history will be recorded. General and Systemic examination and vitals will be examined and recorded. Venous blood was drawn from each patient into tubes for laboratory work up. Counts of white blood cells (WBC), neutrophils (NEU) and lymphocytes (LYM), platelets will be obtained from the analyser and neutrophil to lymphocyte ratio (NLR) and the Platelet to lymphocyte ratio (PLR) will be calculated. The levels of C-reactive protein (CRP) and ESR will also be measured. An Attempt will be made to find the association platelet to lymphocytes ratio and neutrophil to lymphocyte ratio and the level of disease activity. Further the association between these haematological markers with the other inflammatory markers like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) will also be evaluated. Data will be collected in the proforma and entered in an excel sheet.

RESULT

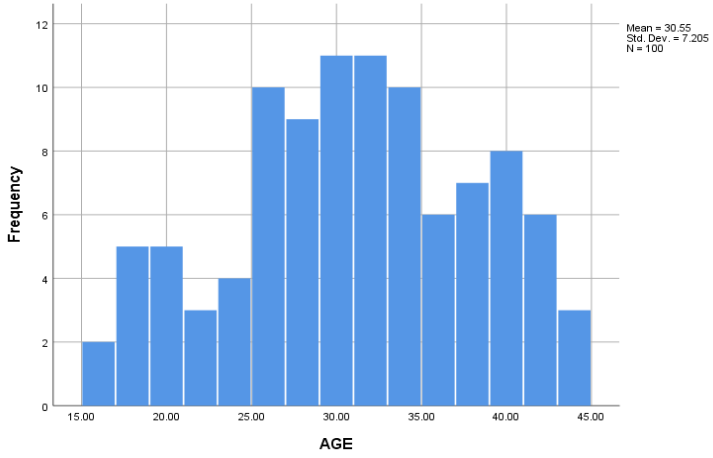

Fig.1 Age Distribution

Table 1: AGE vs. DISEASE ACTIVITY

		Mean	Std. Deviation	95% CI for Mean		Minimum	Maximum	F value	P Value
				Lower Bound	Upper Bound				
AGE	**Low (n=66)**	30.9242	7.32606	29.1233	32.7252	16	43	0.521	0.472
	High (n=34)	29.8235	7.01285	27.3766	32.2704	17	43		
	Total (n=100)	30.55	7.20462	29.1204	31.9796	16	43		

Table2: DISEASE ACTIVITY AMONG TOTAL NUMBER OF PATIENTS

DISEASE ACTIVITY SCORE	**Frequency**	**Percent**
Low	66	66.0
High	34	34.0
Total	**100**	**100.0**

		Mean	**Std. Deviation**	**95% CI for Mean**		**Minimum**	**Maximum**	**F value**	**P Value**
				Lower Bound	**Upper Bound**				
NLR	**Low (n=66)**	1.8171	0.1793	1.773	1.8612	1.4	2.1	333.785	<0.001
	High (n=34)	4.3141	1.08696	3.9349	4.6934	2.71	7.94		
	Total (n=100)	2.6661	1.35211	2.3978	2.9344	1.4	7.94		

Table3:NEUTROPHIL TO LYMPHOCYTE RATIO vs DISEASE ACTIVITY

Table4:PLATELET TO LYMPHOCYTE RATIO vs DISEASE ACTIVITY

		Mean	**Std. Deviation**	**95% CI for Mean**		**Minimum**	**Maximum**	**F value**	**P Value**
				Lower Bound	**Upper Bound**				
PLR	**Low (n=66)**	86.203	9.05865	83.9761	88.4299	63.8	99.7	332.026	<0.001
	High (n=34)	233.4853	64.74761	210.8938	256.0768	174.9	395.8		
	Total (n=100)	136.279	79.80077	120.4448	152.1132	63.8	395.8		

Table 5:C- REACTIVE PROTEIN (CRP) vs DISEASE ACTIVITY

		Mean	**Std. Deviation**	**95% CI for Mean**		**Minimum**	**Maximum**	**F value**	**P value**
				Lower Bound	**Upper Bound**				
CRP (mg)	**Low (n=66)**	4.3939	0.65348	4.2333	4.5546	3	5	759.402	<0.001
	High (n=34)	9.2353	1.10258	8.8506	9.62	7	12		
	Total (n=100)	6.04	2.44916	5.554	6.526	3	12		

		Mean	**Std. Deviation**	**95% CI for Mean**		**Minimum**	**Maximum**	**F value**	**P Value**
				Lower Bound	**Upper Bound**				

SLEDAI-2K	**Low (n=66)**	1.8485	0.3613	1.7597	1.9373	1	2	554.102	<0.001
	High (n=34)	15.9706	4.87097	14.271	17.6702	7	26		
	Total (n=100)	6.65	7.2938	5.2028	8.0972	1	26		

Table.6 SLEDAI-2K vs. DISEASE ACTIVITY

Table7: NEUTROPHIL (mm^3) vs. DISEASE ACTIVITY

		Mean	Std. Deviation	95% CI for Mean		Minimum	Maximum	**F value**	**P Value**
				Lower Bound	Upper Bound				
NEUT	**Low (n=66)**	4383.6061	814.94507	4183.2676	4583.9446	2800	6006	9.778	0.002
	High (n=34)	5179.1176	1733.39089	4574.309	5783.9263	1790	8456		
	Total (n=100)	4654.08	1257.39412	4404.5857	4903.5743	1790	8456		

TABLE8: CORRELATION OF SLEDAI-2K with NLR, PLR, CRP

Correlations										
			NLR	**PLR**	**CRP**	**SLEDAI-2K**		**NLR**	**PLR**	**CRP**	**SLEDAI-2K**
NLR	Pearson Correlation		1	-.251*	-0.011	-0.09		1	.470**	.403*	.592**
	p Value			0.042	0.929	0.473			0.005	0.018	0
	N		66	66	66	66		34	34	34	34
PLR	Pearson Correlation		-.251*	1	.366**	0.218		.470**	1	.802**	.709**
	p Value		0.042		0.003	0.078		0.005		0	0
	N		66	66	66	66		34	34	34	34
CRP	Pearson Correlation		-0.011	.366**	1	.257*		.403*	.802**	1	.735**
	p Value		0.929	0.003		0.037		0.018	0		0
	N		66	66	66	66		34	34	34	34
SLEDAI-2K	Pearson Correlation		-0.09	0.218	.257*	1		.592**	.709**	.735**	1
	p Value		0.473	0.078	0.037			0	0	0	
	N		66	66	66	66		34	34	34	34

DISCUSSION

Figure 1: shows the age distribution among the participants.

Among 100 patients, the mean age was around 30 years with minimum being 16 years and maximum being 43 years.

Table 1: AGE vs disease activity.

Mean age of high disease activity is about 29 years and mean age of low disease activity is about 30 years. Is not significantly correlate

with disease activity.

Table.2: disease activity among total number of patients.

Among the 100 patients, 66% were in low disease activity and 33% were in high disease activity.

Table.3: Neutrophil to lymphocyte ratio was calculated and it was compared to the disease activity scoring of SLEDAI-2K. It was found that the Neutrophil to Lymphocyte ratio was increased in patients with high disease activity and the ratio was low in patients with low disease activity. For patients with high disease activity index it was found that NLR was 4.3141 with a standard deviation of 1.08696 and for patients with low disease activity index NLR was 1.8171 with a standard deviation of about 0.1793. The p-value obtained in this correlation study was <0.001 proving its significance. Thus the NLR ratio and disease activity calculated using SLEDAI-2K activity showed correlation with high disease activity having higher ratio.

Table.4:Platelet to Lymphocyte ratio was calculated and it was compared to the disease activity scoring of SLEDAI-2K. It was found that the Platelet to Lymphocyte ratio was increased in patients with high disease activity and ratio was low in patients with low disease activity. For patients with high disease activity index it was found that PLR was about 233.4853 with a standard deviation of about 64.74761 and for patients with low disease activity index PLR was 86.203 with a standard deviation of about 9.05865. The p-value obtained is <0.001 further proving its significance. Thus the PLR ratio and disease activity calculated using SLEDAI-2K activity showed correlation with high disease activity having higher ratio.

Table.5: Similarly in this study **CRP** level was analyzed against the disease activity index. It was clear that patients with high disease activity had higher values of CRP about 9.2353 with a standard deviation of about 1.10258 and patients with low disease activity had lower values of about 4.3939 with a standard deviation of about 0.65348. The p-value in this analysis was <0.001 thus proving the strongassociation of elevated CRP levels in patients with high disease activity index.

Table.6: Disease activity was analyzed via **SLEDAI-2K** scoringwhich had showed that patients with high disease activity have higher disease activity index and those with low disease activity had lower disease activity index. For patients with high disease activity, SLEDAI-2K had a mean value of 15.9706 with standard deviation of 4.87097 and for patients with low disease activity had a mean value of 1.8485 with a standard deviation of 0.3613. The p-value in this analysis was <0.001. Thus, proving its significance.

Table.7: Further in this study, an analysis was made between **Neutrophil** count and the disease activity index. It was found that patients with high disease activity had higher neutrophil count with mean value of about 5179.1176 with a standard deviation of 1733.39089. Patients with low disease activity had lower neutrophil count with mean of about 4383.6061 and standard deviation of 814.94507. The p-value in this analysis was calculated to be 0.002 proving its stastistically significant. Thus, it can be concluded that patients with high disease activity have higher polymorphs compare to those with low disease activity who have lower polymorphs count.

Table.8: Finally NLR and PLR correlated with SLEDAI-2 K, it showed NLR and PLR was positively correlated with SLEDAI-2 K , p-value of about <0.001.Similar study conducted by Yunxiu Wu, Yanjuan Chen, Xianming Yang, Lishu Chen, Yihua Yang[24] found the association between NLR and PLR and their impact in disease activity. Also study conducted by Lisha ma, Aiping zeng, Binxuan chen, Ying chen, Renfang zhou[25] also proved the association between the hematological markers and disease activity.

CONCLUSION

NLR and PLR can be calculated easily, cost effective, available in all simple laboratories and reporting time will be short compared to other inflammatory markers. And hence we

can take NLR and PLR as a poor man's inflammatory marker. In addition, NLR and PLR were relatively stable as compared with individual white blood cells parameters, which are easily influenced by dehydrations, diluted blood specimens and blood specimen handling. These might be useful in clinical practice. NLR and PLR together with other serum inflammatory markers, were proving as significant clinical tools which could be used as biomarkers for inflammatory response or disease activity in SLE Patients.

Analysis revealed that NLR and PLR were significantly higher in SLE patients and were positively correlated with SLEDAI-2K score which suggests that NLR and PLR could be useful biomarkers in the management of SLE.

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