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The value of neutrophil, platelet-to-lymphocyte ratio and lymphocyte to monocyte ratio with disease activity in rheumatoid arthritis

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ORIGINAL STUDY

Value of neutrophil, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio with disease activity in rheumatoid arthritis

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Abstract

For rheumatoid arthritis patients, altering their disease activity is crucial to their treatment plan. Utilizing the platelet/lymphocyte ratio, neutrophil/lymphocyte ratio (NLR), and lymphocyte/monocyte ratio as indicators of inflammation as a result of inflammatory process that led to an alteration in the absolute number of platelets, neutrophils, monocytes, and lymphocyte, we aim to provide an overview of the most recent research on the diagnostic potential of three systemic inflammatory ratios as indicators of rheumatoid activity, platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, and lymphocyte/monocyte ratio. We concentrated on the research that evaluated blood cell parameters' diagnostic usefulness depending on the receiver-operating characteristic, that is area under the curve found in current studies.

Keywords: Disease activity, Lymphocyte/monocyte ratio, Neutrophil/lymphocyte ratio, Platelet/lymphocyte ratio, Rheumatoid arthritis

1. Background

Persistent inflammation is a characteristic feature of rheumatoid arthritis (RA), which is an autoimmune disease. In RA, the synovium is invaded by macrophages, neutrophils, dendritic cells, B cells, and T cells in RA, leading to affected synovial joints, causing progressive cartilage and bone degradation that results in bone loss, disability Also, individuals with RA have a higher susceptibility to cardiac and vascular diseases, with the increased risk of mortality [1]. While the precise origin of RA is unknown, it is thought to arise in those who have susceptible genes and are exposed to environmental triggers that stimulate the immune system [2]. The main argument for RA diagnosis is clinical, and to differentiate it from other conditions is still a very difficult process. In an attempt to improve the likelihood of early diagnosis and treatment, the American College of Rheumatology/European League against Rheumatisms (ACR/EULAR2010) established criteria for RA. This as described by Aletaha *et al*. [3] aims to enhance opportunity for early detection and management of RA. The 2010 ACR/EULAR classification criteria state that the presence of high levels of erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), as well as the positivity of anti-cyclic citrullinated peptide and rheumatoid factor, all greatly contribute to the diagnosis and classification criteria of the disease. The two most widely used indicators of inflammation in clinical practice to evaluate the presence and activity of an inflammatory process are CRP and ESR. These markers, however, have several drawbacks, such as reflecting transient inflammatory activity and having a poor discriminating power. Demographic data, anemia, plasma viscosity with hypergammaglobulinemia, and fibrinogen all have an impact on ESR and evaluate disease activity during the previous weeks [4]. In contrast, these factors are less effective on CRP, which is considered an early indicator of an

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inflammatory state [5]. Thus, the need to create widely used biomarkers that could aid in timely and precise RA detection remains unfulfilled. Neutrophils, monocytes, platelets, and lymphocytes have been shown to participate in inflammation and affect the immune-mediated pathways of chronic inflammatory diseases, including neoplasms [6,7]. Neutrophils have been demonstrated by Cross *et al*. [8] and Rosas *et al*. [9] to activate antigen-presenting cells and to initiate adaptive immunity through neutrophil extracellular traps (noticed by Khandpur *et al*. [10]). Moreover, it is believed that platelets promote the migration of leukocytes to synovium by synovial vasculature of RA [11]. Peripheral blood cell number, shape, and size are altered as a result of the inflammatory process in RA, which is mediated by inflammatory cytokines. Erythropoiesis is modulated by inflammatory cytokines in RA, including tumor necrosis factor alpha interleukins 1 (IL-1) and 6 (IL-6) [12]. In peripheral circulation, 40−75% of leukocytes are neutrophils, while 20−45% of white blood cells are lymphocytes. Among the immune cells, platelets are among the most significant. Both platelets and neutrophils contribute to the synthesis of inflammatory cytokines, which activate both types of cells [13]. The inflammatory situation in RA, marked by elevated inflammatory cytokines, may be responsible for increased neutrophils and platelets [12]. Dysregulation in the cells' ability to undergo apoptosis during this phase could result in reduced production of lymphocytes [12]. Since the inflammatory process influences neutrophils, platelets, and lymphocytes, platelet/lymphocyte (PLR) and neutrophil/lymphocyte ratios (NLR) are considered as inflammatory markers. An easy biomarker of systemic inflammation is the NLR, which also includes the PLR and the lymphocyte/monocyte ratio (LMR) [14]. The link between LMR levels and monocyte counts and variations of ITGA4 and HLA-DRB1 was recently established by a genome-wide association analysis [15]. Interestingly, Han [16] endorsed the use of these genetic polymorphisms as loci that are susceptible to autoimmunity disorders, such as RA. NLR, PLR, as well as LMR are accessible and affordable laboratory indicators of systemic inflammation.

2. Patients and methods

Fifty cases of RA who fulfill the criteria set by ACR and EULAR [16] were recruited from the outpatient clinic of Physical Medicine and Rheumatology at AMTH. In addition, a control group of 30 people, matched for sex and age were included. Before their involvement in the study, all participants in the study groups provided written consent. The GOTHI ethics committee granted ethical approval. Patients with RA were categorized using the ACR 2010 guidelines. Every individual suffering from a systemic illness such as hypertension, renal failure, diabetes mellitus, ischemic heart condition, COPD, oncology, hematological abnormality, infectious conditions, pregnant women or those at puerperium or with chronic granulomatous condition were excluded. Everyone who participated had their complete medical history taken, paying particular consideration to articular symptoms such as the count of inflamed joints (hotness, redness, swelling, pain), morning stiffness and its duration, and any joint deformities. Disease activity was assessed using the modified disease activity score (modified DAS28); manifestations of extra-articular involvements were also noted [17]. The DAS28 was used to divide the patients into two equal groups of 25 patients each: group A, which was considered active, had a DAS28 value of more than or equal to 2.6, while group B, which was considered inactive or in remission, had a score of less than 2.6. Then, 5 ml of blood − 2 ml for complete blood count evaluation and 3 ml for chemistry measurements − were taken from each patient and control. Laboratory investigations included the Westergren method for the first hour ESR, the latex slide test for CRP, and the latex agglutination slide test for rheumatoid factor.

The complete blood count along with absolute counts of neutrophil, lymphocytes, platelets, and monocytes were determined using peripheral blood; PLR=P/L, NLR=N/L, and the LMR = L/M were also calculated. NLR is derived by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR is estimated by dividing the absolute platelet count by the absolute lymphocyte count.

2.1. Statistical analysis

All statistical calculations were done using the Statistical Package for the Social Sciences (SPSS 20) (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Data were described as mean ± SD, range, or frequencies (number of cases) and percentages when appropriate. For comparing quantitative variables of more than two groups, ANOVA test will be used and for parametric categorical data χ^2 test will be performed. Pearson's correlation test will be conducted. P value less than 0.05 was considered significant.

Table 1. Demographic data.

	Inactive group ($N = 25$)	Active group ($N = 25$)	Normal group ($N = 30$)	Test value	P value	Significance
Age						
Mean ± SD	42.60 ± 3.65	42.52 ± 3.65	41.90 ± 4.02	0.286[a]	0.752	NS
Range	33–48	33–48	33–48			
Sex						
Female	25 (100.0)	25 (100.0)	30 (100.0)	NA	NA	NA

P value more than 0.05: nonsignificant (NS); P value less than 0.05: significant (S); P value less than 0.01: highly significant (HS).
[a] One-way ANOVA test.

Table 2. Demographic and laboratory data of patients.

	Patients group ($N = 50$)
Sex	
Female	50 (100.0)
Age	
Mean ± SD	42.56 ± 3.61
Range	33–48
N/L	
Mean ± SD	1.95 ± 0.94
Range	1.1–4.9
P/L	
Mean ± SD	108.92 ± 34.46
Range	75.9–214
DAS28	
Mean ± SD	2.95 ± 0.99
Range	1.3–5.2
L/M	
Mean ± SD	2.57 ± 0.86
Range	1.3–5.5
ESR	
Mean ± SD	43.86 ± 17.35
Range	21–80
HB	
Mean ± SD	9.93 ± 1.20
Range	7.5–12.3
TLC	
Mean ± SD	7.76 ± 1.04
Range	5.6–10.1
Monocyte	
Mean ± SD	1170.90 ± 901.39
Range	255–3500
Lymphocyte	
Mean ± SD	1593.60 ± 1266.33
Range	320–4100
Platelet	
Mean ± SD	390 480.00 ± 97 825.80
Range	230 000–520 000
Neutrophil	
Mean ± SD	6270.40 ± 2746.72
Range	3100–12000
CRP	
Negative	25 (50.0)
Positive	25 (50.0)

3. Results

Our study included 50 RA patients (25 in group A, i.e. active, and 25 in group B, inactive, i.e. in remission) according to DAS28 as mentioned before and 30 healthy participants as a control group.

The demographic data and laboratory data in all patients are shown.

Table 1: 100% of our patients were female, age ranged from 33 to 48 years.

Table 2: Association according to demographic data and laboratory markers of activity in patients who were involved in the study.

In Group A (active) the CRP was positive and in group B (inactive) patients the CRP was negative.

Table 3 shows the demographic, DAS28, laboratory data of patients, and the control group. As there was no gender difference, all participants in the study were females. Although age and total leukocyte counts showed no significant difference between controls and patients, there was a highly significant difference in the absolute numbers of monocytes, neutrophils, and platelets. High ratios of NLR, PLR, CRP, DAS28, low absolute number of lymphocytes, decreased LMR ratio, and low hemoglobin were recorded between patients and control group.

Tables 4 and 5 show the association between different parameters and disease activity.

The patients were categorized according to DAS28 to group A (active) with a DAS28 score more than or equal to 2.6 and group B with a DAS28 score less than 2.6 (inactive, i.e. in remission) and controls. So Tables 3 and 4 show the comparison between three groups according to clinical articular parameters by the DAS28 scoring system and laboratory data. They show a highly significant difference between the three groups according to the increased absolute number of neutrophils, monocytes, platelets, increased CRP, NLR, PLR, and DAS28. Also there was a highly significant difference in low HB value, low LMR and absolute number of lymphocytes, with nonsignificant difference between the three groups according to TLC.

Tables 6 and 7 provide the post hoc analysis by LSD.

It makes a comparison between active versus inactive group, active versus normal, and inactive versus normal group based on laboratory

Table 3. Demographic, DAS28, laboratory data of patients and control group.

	Normal group ($N = 30$)	Patients group ($N = 50$)	Test value	P value	Significance
Sex					
Female	30 (100.0)	50 (100.0)	NA	NA	NA
Age					
Mean ± SD	41.90 ± 4.02	42.56 ± 3.61	−0.758[a]	0.451	NS
Range	33–48	33–48			
N/L					
Mean ± SD	1.47 ± 0.23	1.95 ± 0.94	−2.723[a]	0.008	HS
Range	1.1–1.9	1.1–4.9			
P/L					
Mean ± SD	91.16 ± 8.00	108.92 ± 34.46	−2.770[a]	0.007	HS
Range	75.6–108	75.9–214			
DAS28					
Mean ± SD	2.14 ± 0.28	2.95 ± 0.99	−4.365[a]	0.000	HS
Range	1.3–2.5	1.3–5.2			
L/M					
Mean ± SD	5.15 ± 2.39	2.57 ± 0.86	6.926[a]	0.000	HS
Range	0.77–11.6	1.3–5.5			
ESR					
Mean ± SD	24.43 ± 3.21	43.86 ± 17.35	−6.055[a]	0.000	HS
Range	20–33	21–80			
HB					
Mean ± SD	11.73 ± 0.49	9.93 ± 1.20	7.799[a]	0.000	HS
Range	10.9–13.1	7.5–12.3			
TLC					
Mean ± SD	7.48 ± 1.12	7.76 ± 1.04	−1.124[a]	0.264	NS
Range	4.5–9.8	5.6–10.1			
Monocyte					
Mean ± SD	558.00 ± 110.00	1170.90 ± 901.39	−3.698[a]	0.000	HS
Range	255–780	255–3500			
Lymphocyte					
Mean ± SD	2896.67 ± 665.65	1593.60 ± 1266.33	5.212[a]	0.000	HS
Range	2000–4300	320–4100			
Platelet					
Mean ± SD	310 333.33 ± 40 555.06	390 480.00 ± 97 825.80	−4.264[a]	0.000	HS
Range	180 000–380 000	230 000–520 000			
Neutrophil					
Mean ± SD	3670.00 ± 511.35	6270.40 ± 2746.72	−5.120[a]	0.000	HS
Range	3200–5000	3100–12 000			
CRP					
Negative	28 (93.3)	25 (50.0)	15.747[b]	0.000	HS
Positive	2 (6.7)	25 (50.0)			

P value more than 0.05: nonsignificant (NS); P value less than 0.05: significant (S); P value less than 0.01: highly significant (HS).
[a] Independent t test.
[b] Chi square test.

Table 4. Association between different parameters and disease activity.

	Active group ($N = 25$)	Inactive group ($N = 25$)	Normal group ($N = 25$)	Test value[a]	P value	Significance
N/L						
Mean ± SD	2.44 ± 1.12	1.46 ± 0.26	1.47 ± 0.23	18.864	0.000	HS
Range	1.23–4.9	1.1–2.2	1.1–1.9			
P/L						
Mean ± SD	129.71 ± 45.67	92.52 ± 8.25	91.16 ± 8.00	17.800	0.000	HS
Range	75.9–214	75.9–108	75.6–108			
L/M						
Mean ± SD	2.29 ± 0.45	↑2.85 ± 1.07	5.15 ± 2.40	24.896	0.000	HS
Range	1.3–3.6	1.3–5.5	0.77–11.6			
DAS28						
Mean ± SD	3.77 ± 0.67	2.12 ± 0.38	2.14 ± 0.28	107.557	0.000	HS
Range	2.6–5.2	1.3–2.5	1.3–2.5			

(*continued on next page*)

Table 4. (continued)

	Active group ($N = 25$)	Inactive group ($N = 25$)	Normal group ($N = 25$)	Test value[a]	P value	Significance
ESR						
Mean ± SD	58.00 ± 12.91	29.72 ± 5.62	24.43 ± 3.21	129.945	0.000	HS
Range	40–80	21–41	20–33			

P value more than 0.05: nonsignificant (NS); P value less than 0.05: significant (S); P value less than 0.01: highly significant (HS).
[a] One-way ANOVA test.

Table 5. Association between different parameters and disease activity.

	Active group ($N = 25$)	Inactive group ($N = 25$)	Normal group ($N = 25$)	Test value[a]	P value	Significance
HB						
Mean ± SD	8.95 ± 0.74	10.90 ± 0.65	11.73 ± 0.49	138.790	0.000	HS
Range	7.5–10.1	10.2–12.3	10.9–13.1			
TLC						
Mean ± SD	7.96 ± 1.06	7.56 ± 1.00	7.48 ± 1.12	1.538	0.221	NS
Range	6.5–10.1	5.6–9.8	4.5–9.8			
Monocyte						
Mean ± SD	1798.00 ± 909.58	543.80 ± 110.68	558.00 ± 110.00	50.153	0.000	HS
Range	970–3500	255–780	255–780			
Lymphocyte						
Mean ± SD	395.20 ± 73.42	2792.00 ± 525.93	2896.67 ± 665.65	203.408	0.000	HS
Range	320–550	2300–4100	2000–4300			
Platelet						
Mean ± SD	482 000.00 ± 23 629.08	298 960.00 ± 39 119.99	310 333.33 ± 40 555.06	212.220	0.000	HS
Range	420 000–520 000	230 000–360 000	180 000–380 000			
Neutrophil						
Mean ± SD	8800.80 ± 1316.44	3740.00 ± 575.18	3670.00 ± 511.35	301.267	0.000	HS
Range	7100–12 000	3100–5300	3200–5000			
CRP						
Negative	2 (8.0)	23 (92.0)	28 (93.3)	55.193[b]	0.000	HS
Positive	23 (92.0)	2 (8.0)	2 (6.7)			

P value more than 0.05: nonsignificant (NS); P value less than 0.05: significant (S); P value less than 0.01: highly significant (HS).
[a] One-way ANOVA test.
[b] Chi square test.

Table 6. Post hoc analysis by LSD.

	Post hoc analysis by LSD		
	Active group vs. inactive group	Active group vs. normal group	Inactive group vs. normal group
N/L	0.000	0.000	0.951
P/L	0.000	0.000	0.850
L/M	0.222	0.000	0.000
DAS28	0.000	0.000	0.920
ESR	0.000	0.000	0.018

Table 7. Post hoc analysis by LSD.

	Post hoc analysis by LSD		
	Active group vs. inactive group	Active group vs. normal group	Inactive group vs. normal group
HB	0.000	0.000	0.000
Monocyte	0.000	0.000	0.919
Lymphocyte	0.000	0.000	0.446
Platelet	0.000	0.000	0.242
Neutrophil	0.000	0.000	0.765

parameters to identify exactly which groups differ from each other, focusing on the significant differences between them according to the laboratory tests used. So, there was a highly significant difference between active and inactive groups across all laboratory parameters (low HB, low lymphocyte counts, decreased LMR, and high neutrophil, monocyte, platelet counts, PLR, NLR, DAS28, and ESR) and between active and normal groups. However, there was an insignificant difference between inactive and normal groups in laboratory results and DAS28.

Table 8 shows the correlation between DAS28 score with NLR, LMR, PLR, and ESR with laboratory results (all cases, active, and inactive groups).

In all cases and in the active group, there was a positive correlation between ESR, NLR, and PLR with the DAS28 score and a negative correlation between DAS28 and LMR.

Also, there was a negative correlation between DAS28 and LMR in the active group.

Figs. 1–4 shows correlations in all cases.

Table 8. Correlation between DAS28 score with NLR, PLR, and LMR & ESR, laboratory parameters (all cases, active, and inactive) groups.

	DAS28					
	All cases		Active group		Inactive group	
	r	*P* value	*r*	*P* value	*r*	*P* value
Age	0.025	0.863	−0.181	0.386	0.227	0.275
N/L	0.583[b]	0.000	0.420[a]	0.037	0.112	0.593
P/L	0.422[b]	0.002	0.505[a]	0.010	−0.331	0.106
L/M	−0.497[b]	0.000	−0.689[b]	0.000	−0.475[a]	0.016
ESR	0.851[b]	0.000	0.542[b]	0.005	0.306	0.137
HB	−0.777[b]	0.000	−0.291	0.159	0.097	0.643
TLC	0.109	0.450	−0.064	0.759	−0.118	0.576
Monocyte	0.802[b]	0.000	0.450[a]	0.024	−0.060	0.774
Lymphocyte	−0.808[b]	0.000	−0.274	0.186	−0.162	0.440
Platelet	0.795[b]	0.000	0.431[a]	0.031	−0.118	0.573
Neutrophil	0.753[b]	0.000	0.311	0.130	−0.326	0.112

P value more than 0.05: nonsignificant (NS); P value less than 0.05: significant (S); P value less than 0.01: highly significant (HS).
[a] Significant.
[b] Highly significant.

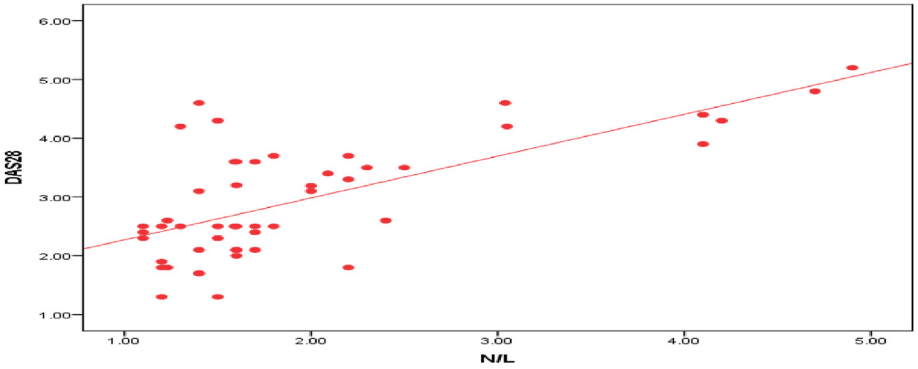

Fig. 1. Correlation between DAS28 and NLR.

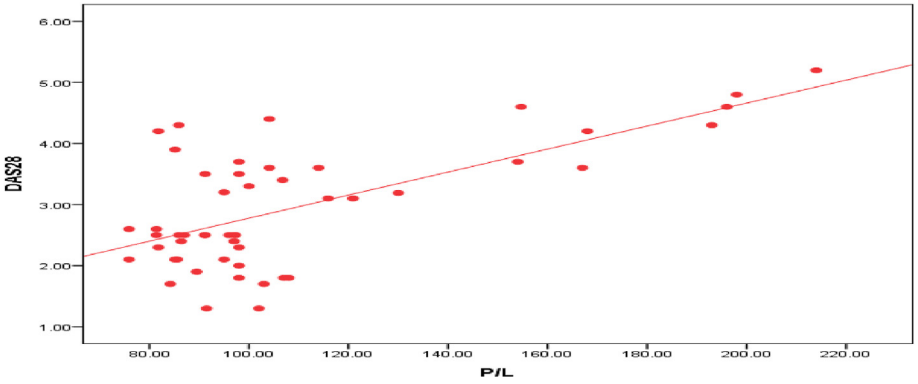

Fig. 2. Correlation between DAS28 and PLR.

Figs. 5–8 shows the correlation in active cases.
Fig. 9 shows the correlation in inactive cases.

Receiver-operating characteristic (ROC) curve) that measures the specificity and sensitivity of P/L, N/L, and L/M ratios for assessing disease activity.

Table 9 and Fig. 10: The present study shows the ROC curve analysis of NLR, PLR, and LMR as predictors of disease activity in patients.

The NLR had an area under the curve (AUC = 0.645, $P < 0.001$) with a sensitivity of 32% and a specificity of 100% at a cutoff of 1.9, while PLR

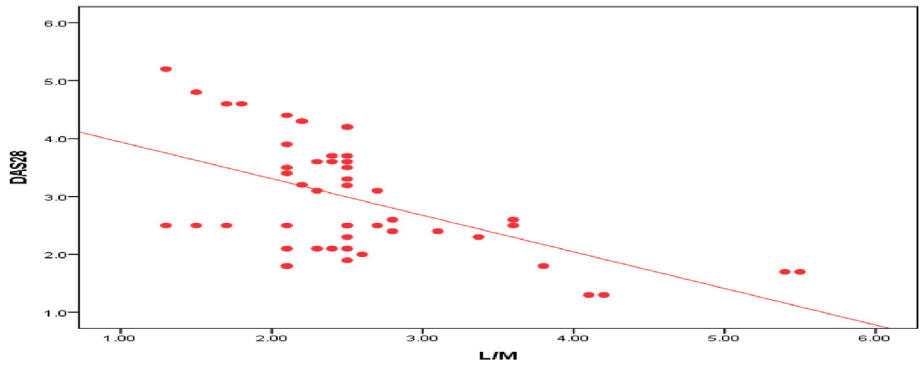

Fig. 3. Correlation between DAS28 and L/M.

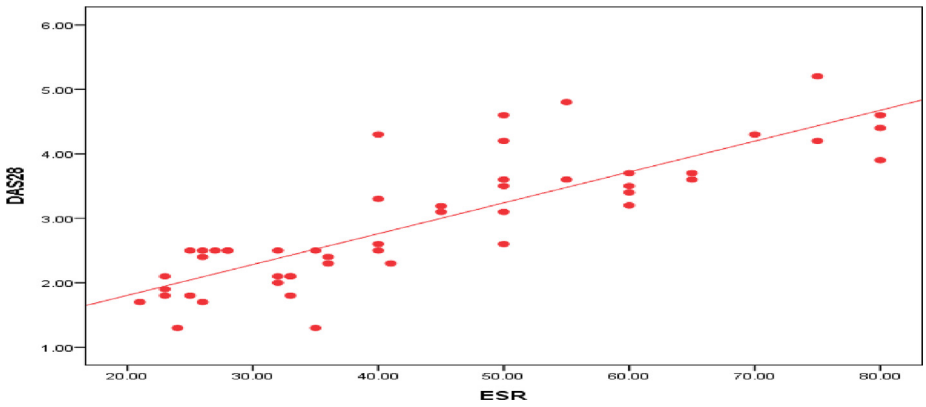

Fig. 4. Correlation between DAS28 and ESR.

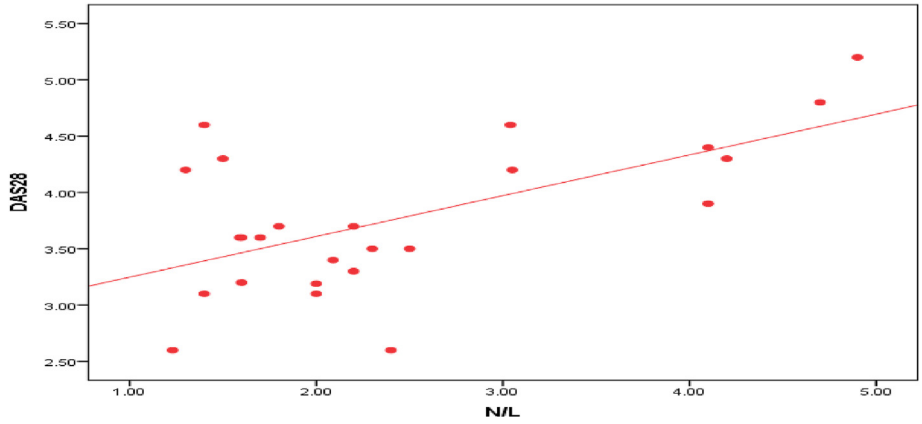

Fig. 5. Correlation between DAS28 and NLR.

had an AUC of 0.662 ($P < 0.001$) with a sensitivity of 34% and a specificity of 96.6% at a cutoff of 103, and LMR had an AUC of 0.901 ($P < 0.001$), with 72.0% sensitivity and 96.6% specificity with a cutoff of 2.5.

Table 10 and Fig. 11: ROC curve of NLR and PLR as a predictor of active groups versus inactive group.

NLR had an AUC f 0.829 ($P < 0.001$) with a sensitivity of 64% and a specificity of 92.0% with cutoff of 1.7. PLR had an AUC of 0.751 ($P < 0.001$) with a sensitivity of 64% and a specificity of 92% with a cutoff of 103.

Table 11 and Fig. 12: ROC curve of NLR, PLR, a LMR as a predictor of active group versus normal group.

NLR had an area under the curve (AUC = 0.821, $P < 0.001$) with a sensitivity of 60% and a specificity of 100% at a cutoff of 1.9, while PLR had an AUC of 0.775 ($P < 0.001$) with a sensitivity of 60% and a

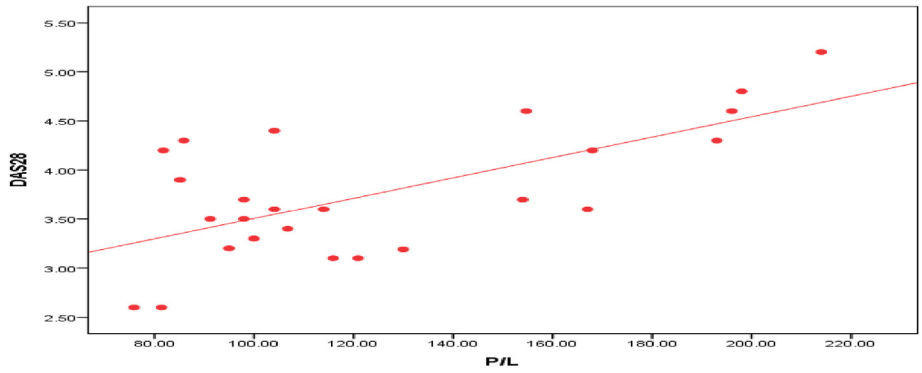

Fig. 6. Correlation between DAS28 and PLR.

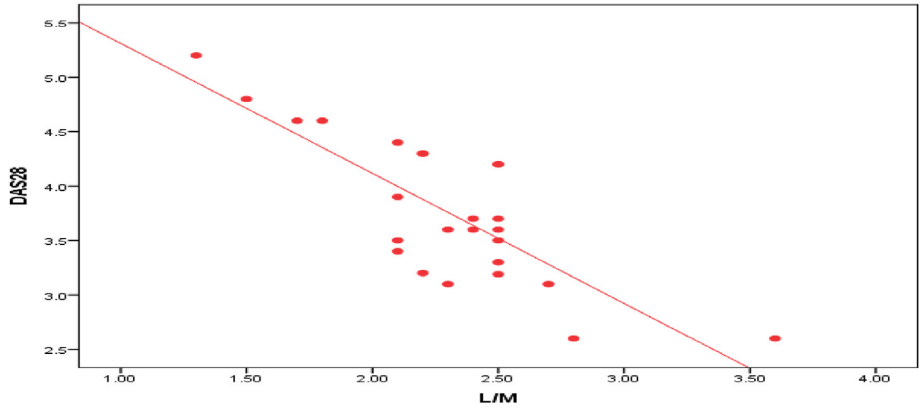

Fig. 7. Correlation between DAS28 and L/M.

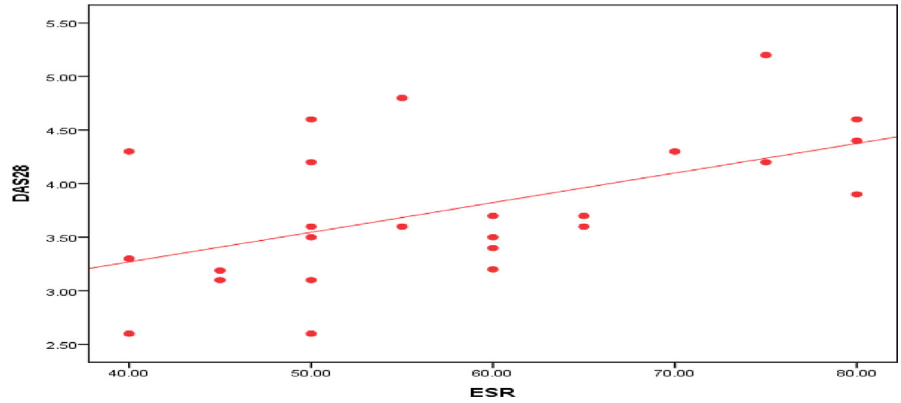

Fig. 8. Correlation between DAS28 and ESR.

specificity of 96.6% with a cutoff of 103, and LMR had an AUC of 0.951 ($P < 0.001$), with 88.0% sensitivity and 96.6% specificity with a cutoff of 2.5.

Table 12 and Fig. 13: ROC curve of LMR as a predictor of inactive group versus normal group.

The LMR had an area under the curve (AUC = 0.852, $P < 0.001$) with a sensitivity of 72% and a specificity of 83.33% with a cutoff of 1.9. PLR had an AUC of 3.1.

4. Discussion

Assessment of the level of RA disease activity remains difficult [18]. While the DAS28 score, ESR, and CRP are currently considered markers of the activity of the RA illness, prior research has shown certain limitations. Nevertheless, assessing the inflammatory response is crucial to determining the effectiveness of treatment [19]. Even though a

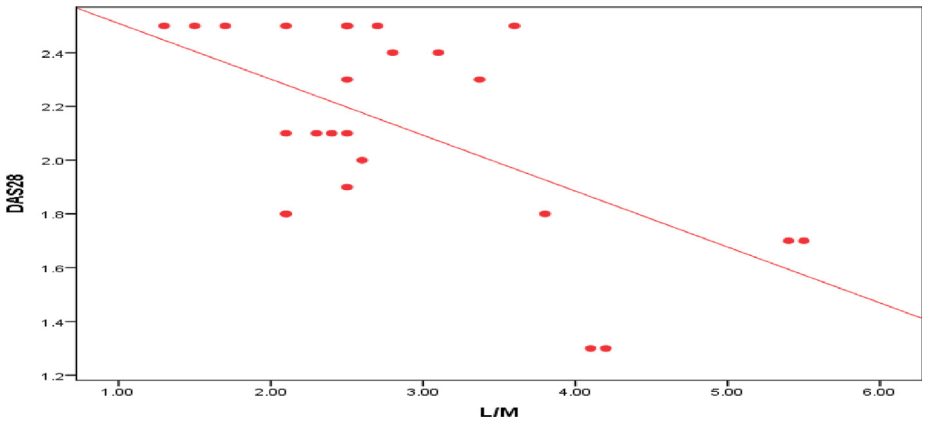

Fig. 9. Correlation between DAS28 and LMR.

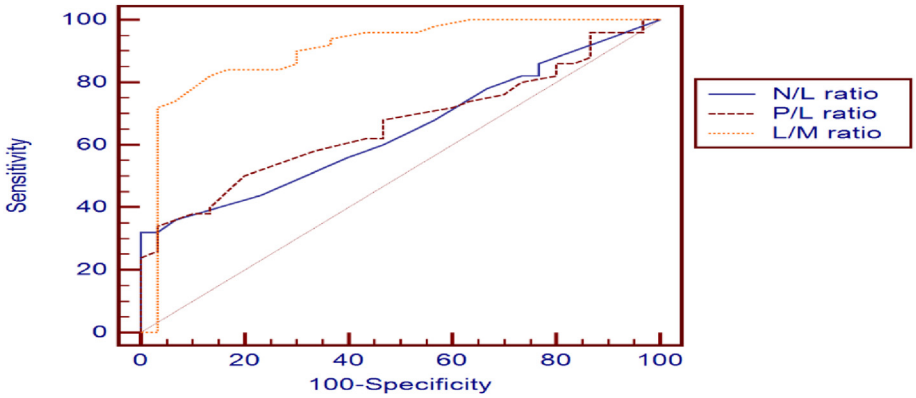

Fig. 10. The present study shows the ROC curve analysis of NLR, PLR, and LMR as predictors of disease activity in patients.

Table 9. ROC curve analysis of NLR,PLR& LMR as predictor of disease activity in patients.

Parameters	AUC	Cut of point	Sensitivity	Specificity	PPV	NPV
N/L	0.645	>1.9	32.0	100.0	100.0	46.9
P/L	0.662	>103	34.0	96.67	94.4	46.8
L/M	0.901	≤2.5	72.0	96.67	97.3	67.4

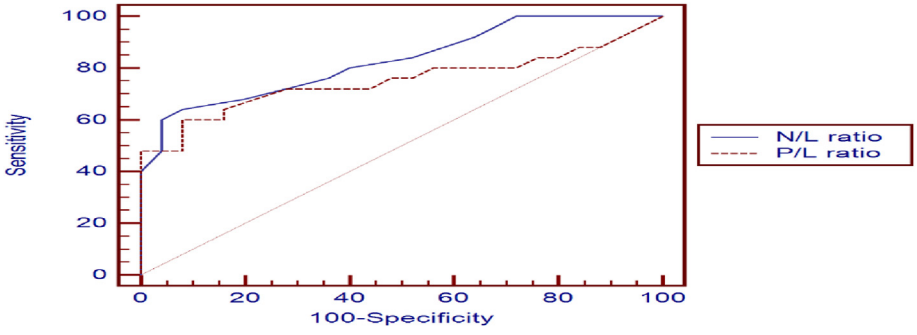

Fig. 11. ROC curve of NLR and PLR as a predictor of active groups versus inactive group.

Table 10. ROC curve of NLR and PLR as a predictor of active groups versus inactive group.

Parameters	AUC	Cutoff point	Sensitivity	Specificity	PPV	NPV
N/L	0.829	>1.7	64.0	92.0	88.9	71.9
P/L	0.751	>103	60.0	92.0	88.2	69.7

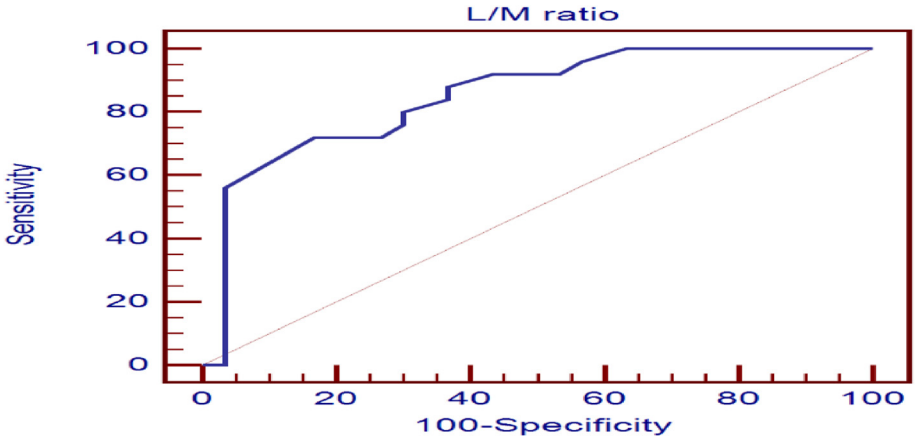

Fig. 12. ROC curve of NLR, PLR, a LMR as a predictor of active group versus normal group.

Table 11. ROC curve of NLR, PLR, a LMR as a predictor of active group versus normal group.

Parameters	AUC	Cut of point	Sensitivity	Specificity	PPV	NPV
L/M	0.852	≤3.1	72.0	83.33	78.3	78.1

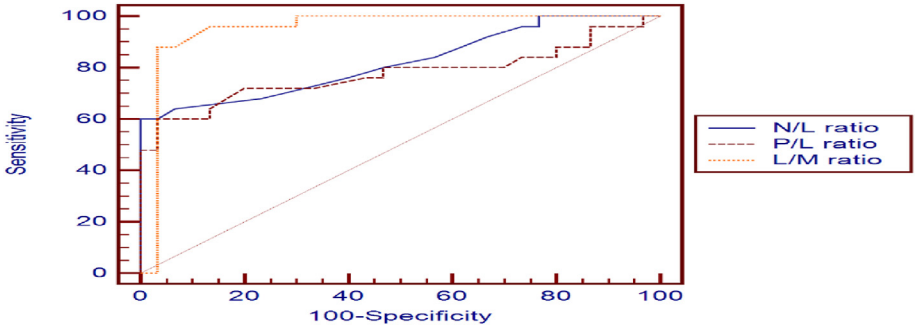

Fig. 13. ROC curve of LMR as a predictor of inactive group versus normal group.

Table 12. ROC curve of LMR as predictor of inactive group vs normal group.

Parameters	AUC	Cutoff point	Sensitivity	Specificity	PPV	NPV
N/L	0.821	>1.9	60.0	100.0	100.0	75.0
P/L	0.775	>103	60.0	96.67	93.7	74.4
L/M	0.951	≤2.5	88.0	96.67	95.7	90.6

patient's CRP, ESR, CDAI, and DAS28 score are below a certain threshold, they may still have joint injury and synovial inflammation [20]. The subjective and time-consuming character of the DAS28 score remains one of its major shortcomings, despite its widespread use in clinical practice. Because of this, it is imperative to develop a quick, easy, dependable, efficient, and objective method for determining a patient's level of RA activity. Neutrophils, platelets and lymphocytes are important regulators of inflammatory processes in RA people. Also, the concentration of them in the blood helps in measuring the activity of RA [3]. The results of the current study indicated that, although

the total leukocytic count had no significant difference between the controls and patients, the differential count showed highly significant differences between them. Also, our patients showed a highly significant difference with low lymphocyte counts and high counts of both neutrophils and monocytes, which matches the findings of Du and Tsukamoto [18,21], who demonstrated that RA patients showed a low absolute count of lymphocytes and high absolute counts of monocytes than controls. Orr [21] suggests that elevated apoptotic components such as caspase and heat-shock proteins and increased lymphocyte accumulation in inflammatory joints could be the cause of RA patients' lower lymphocyte count. Berezne *et al*. [22], however, linked lymphopenia to changes in lymphocyte distribution or immunosuppressive therapy-related increased destruction and decreased lymphocyte production. The recognition that neutrophils are involved in the synthesis of lytic enzymes suggests a function for them in the pathophysiology of RA. Pro-oxidative mediators in the joints, antigen-presenting cell activation, and neutrophil extracellular trap release − which releases large quantities of citrullinated proteins − all contribute to this process [23]. Proteases produced from neutrophils and reactive oxygen species have a significant role in the degradation of cartilage as well as the post-translational alteration of proteins and DNA [24]. Furthermore, neutrophil-derived cytokines and chemokines control immunity, induce autoantibody presentation, and prevent neutrophils in synovial joints from apoptosis, which results in persistent inflammation [24]. Our results showed that the differential count of white blood cells was influenced by the activity of the RA disease, as patients who were actively ill had higher levels of neutrophils and monocytes and reduced number of lymphocytes. The DAS28 score showed a positive correlation with PLT, neutrophils, monocytes, ESR, and CRP and had a negative correlation with lymphocytes and hemoglobin. This is in agreement with Cascao *et al.'s* [25] findings that individuals with active illness had higher neutrophils, decreased lymphocyte count, and increased neutrophil and platelet count He explained that the increased neutrophil count is due to increased antiapoptotic cytokine secretion and also myeloid cell and neutrophil activation by granulocyte colony-stimulating factor. According to Kouri *et al*. [26], neutrophils contribute to RA disease activity in the joint cavity through protease production, reactive oxygen species, and the release of prostaglandins into it. They also stimulate other cells by secreting stimulators to B lymphocytes, tumor necrosis factor alpha, IL-17, and several mediators of inflammation. Comparison between the remission group and active patients had higher platelet counts, which agreed with Tekeoğu *et al*. [27], who observed that thrombocytosis delays the remission according to its controversial role in RA pathogenesis [28]. According to DU [29], the anti-inflammatory role of platelets is mediated through white blood cells (macrophages, lymphocytes, and monocytes) cell-to-cell interaction CD40, platelet glycoprotein 1 bα, and p-selectin. However, Boilard [11] noticed that the proinflammatory process is done through recruiting leukocytes into vascular inflamed synovium. Numerous proinflammatory chemicals found in platelets can release active microparticles, which are crucial in the onset of autoimmune diseases [30]. Through lipoxygenase expression and eicosanoid pathway activation, the microparticles produced by neutrophils interact with activated platelets [31]. Based on research, the PLR is considered a useful indicator of changes in lymphocyte and platelet counts as a result of inflammatory as well as prothrombotic conditions [18,32]. NLR and PLR are considered to be novel inflammatory indicators and are linked to cancer and cardiovascular illnesses; nevertheless, only a small number of studies with restricted sample sizes have been published to date that demonstrate their involvement in RA [31]. Furthermore, as a result of few studies with a range of cutoff values used, the impact of NLR and PLR as indicators of flare RA activity remains insufficiently studied Abd Elazeem [17,33]. Although LMR is one of the markers of inflammation for the onset and the course of the disease, its specific effect has not fully discovered till now [29]. In line with Jin *et al.'s* [34] findings that in RA patients, the NLR and PLR are higher than in healthy controls. Our investigation also showed that there were considerably higher ratios of NLR and PLR with low LMR in comparison to controls. Through his meta-analysis research, Lee [35] concluded that patients with RA had higher N/L and P/L ratios than control groups. PLR and NLR are important biomarkers for diagnosis in individuals with rheumatic disease, particularly RA, according to several studies [36,37]. LMR was observed at lower level in rheumatoid inpatients than in control by Du [29]. Our results showed that compared with inactive patients and active patients there were high N/L and P/L ratios, while L/M ratio was low. We noticed that, when comparing groups with varying disease activities and a control group, higher disease activity was linked to higher PLR, higher NLR, and lower LMR. Furthermore, we observed that the correlation was negative between

LMR and DAS28 scores, while the correlation was positive between PLR, NLR, and DAS28. Our results agree with those of Abd-Elazeem and Sargin Abdelazeem [17,33,38], who found that ratios of N/L and P/L had been elevated in active patients and correlated positively with the DAS28. As reported by Lee [35], PLR and NLR correlated positively with the active state of RA. Du *et al*. [29] discovered that LMR correlated negatively as well as its levels are lower level in individuals with active state of disease. NLR was found to be substantially linked to both tenosynovitis images which were noticed by ultrasound as well as DAS28 in rheumatoid activity, according to Gaballah *et al.'s* [39] studies. Thus, these ratios should be the primary goal of future research as biomarkers for extra-articular and articular inflammatory activity in RA patients. In our current study, the LMR is highly sensitive to active rheumatoid state both N/L and P/L ratios and according to ROC curve analysis and his results are not in agreement with the Elsayed *et al*. [40] study, which found that NLR is highly sensitive to rheumatoid active patients than both P/L and L/M ratios, but can be explained by Tan [41] who noticed that LMR, NLR, and PLR are influencing independently on the activity of rheumatoid. Also, the difference in ranking of our ratios to other studies may be due to the smaller numbers of patients and the mono gender as all participants were female. In terms of specificity, we noticed that NLR was the greatest and then LMR and PLR, which is compatible with the result of Zhang and Elsayed [41,42]. Regarding specificity, NLR was the greatest, followed by LMR and then PLR. ROC curve analysis was used by Zhang *et al*. [42] to ascertain that integrating PLR and NLR improves the accuracy of distinguishing between patients in remission and those with rheumatoid activity, a finding that is also supported by Elsayed *et al*. [40]. To effectively assess disease activity and inform treatment decisions, it is necessary to examine the patient clinically and assess his laboratory and radiological findings. However, our results imply that lymphocyte/monocyte, PLR, and NLR could be valuable indicators for the evaluation of RA activity.

4.1. Conclusion

Apart from possessing accepted specificity and sensitivity for detecting RA disease activity, the other makers LMR, NLR, and PLR, correlated with significance with the DAS28 score. Patients' differences from controls were also noted when comparing varying degrees of disease activity. In addition to the DAS28 score, they could be simple, dependable, affordable, and time-efficient indicators for the evaluation of RA disease activity.

4.2. Limitation

Further research with bigger sample sizes, male gender, and longer follow-up periods with patient medication monitoring is required to validate these markers' effectiveness in measuring the activity of rheumatoid illness.

Ethics information

The institutional committee's ethical criteria were followed during all proceedings. The Ethics Committee of the Scientific Research, GOTHI, Ministry of Health, Egypt approved the study (No. HAM00148.). Following an explanation of the purpose, procedures, and nature of the study to all participants, signed informed consent was obtained from each participant.

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Author's contribution

Data collection, scientific writing and statistical analysis: Lamis Safwat, Shaimaa M. Abd El Aziz.

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Conflict of interest

Authors declare no conflict of interest.

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