

Predictive value of Neutrophil/Lymphocyte ratio and Musculoskeletal ultrasound in detection of early rheumatoid arthritis activity patients

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Abstract

Background: Musculoskeletal ultrasound is available, noninvasive imaging technique with elevated patient acceptability. Gray scale ultrasonography (GSUS) is considered as more sensitive than clinical examination for detecting synovitis and more sensitive than conventional radiography for detecting bone erosions. Neutrophil/lymphocyte ratio (NLR) is defined as the proportion of absolute neutrophilic count to lymphocytic count measured from CBC that used for detection of inflammation in cardiovascular, ulcerative colitis and familial Mediterranean fever diseases.

Objectives: Evaluation of disease activity by the (NLR) and musculoskeletal ultrasound on early rheumatoid arthritis (RA) patients.

Patients and methods: A hospital_ based, cross-sectional research including 50 RA patients obtained from inpatients of the department of Rheumatology and Rehabilitation, Qena University Hospital. All participants were subjected for complete history taking, complete general examination, complete musculoskeletal examination and investigations (CBC , ESR, CRP, RF, anti CCP), (N/L) ratio, Musculoskeletal ultrasound using (the US-7 score) and disease activity assessment using (DAS-28-ESR score)

Results: We found a significant positive correlation between disease activity of RA and NLR ($r = 0.129$ and $p = 0.037$) Also we detected a positive, powerful correlation between disease activity and each of the US-7 score (with Pearson Correlation coefficient of 0.704, 0.764, 0.590 & 0.829 for US-7 gray scale, US-7 Power Doppler, US-7 erosion and US-7 total scores; respectively) and p values of <0.001 for all of these scores.

Conclusion: Musculoskeletal ultrasound was found to be more beneficial than Neutrophil/lymphocyte ratio as a provisional value in detection of disease activity among early RA patients.

Keywords: Neutrophil/lymphocyte ratio; Musculoskeletal ultrasound; Rheumatoid arthritis.

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Introduction

Rheumatoid arthritis (RA) is a widespread long term systemic autoimmune disease, with an estimated prevalence of ~0.25–1% global (Cross et al., 2014)

Early rheumatoid arthritis is most likely to cause erosions of wrists, metacarpophalangeal (MCPs) and interphalangeal (IPs) joints, and synovial pannus can cause destruction of articular cartilage and bony cortex gradually after its formation, so timely diagnosis and effective and accurate treatment is extremely considerable. As the X-rays displays evidence of disease severity and damage lately, additional imaging procedures or modalities like ultrasonography (US) and MRI are used for rheumatoid arthritis to detect the early signs (Botar-Jid et al., 2010 ; Bruyn et al., 2014 ; Bi et al., 2015). MSUS is an easily available, noninvasive imaging technique with elevated patient acceptability. Gray scale ultrasonography (GSUS): is considered as more sensitive than clinical examination for detecting synovitis and more sensitive than conventional radiography for detecting bone erosions (Baillet et al., 2011 ;Smolen et al., 2014 ;Smolen et al., 2023).

Power Doppler US (PDUS) is a special technique which makes it feasible and easy to differentiate between peri-articular and intra-articular blood circulation in small vessels (micro vessels) and displays synovial proliferation, but GSUS principally detects the abnormalities of synovial morphology resulting from synovitis (Tian et al., 2013)

Changes in flow of blood cells amount and formation, typically occur with systemic inflammation like normochromic anemia, thrombocytosis, lymphopenia with increase in neutrophilic count. Hence, components of the circulating blood cells can be used in the evaluation and assessment of inflammatory activity (Kisacik et al., 2008).

Neutrophil/lymphocyte ratio (NLR) is defined as the proportion of absolute neutrophilic count to lymphocytic count, that is measured from (CBC) test which has been used for detection of inflammation in cardiovascular, ulcerative colitis and familial Mediterranean fever diseases (Ahsen et al., 2013; Mercan et al., 2016).

Because of their credibility and cost effectiveness, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are

biomarkers that are hugely used in detecting acute phase reaction. Both of them are influenced by age, sex, and hemoglobin level (Hgb) elements that have no relation to inflammation, but (NLR) does not depend on these elements. (Mercan et al., 2016).

The goal of the current research is the evaluation of disease activity by (NLR) and (MSUS) in early (RA) patients.

Patients and Methods

Type of the research: A hospital-based, cross-sectional research

Research Setting: from inpatient of department of Rheumatology and Rehabilitation of Qena University Hospital.

Research subjects: a total of 50, early RA patients.

Patients' criteria

The Inclusion criteria:-

- Patients were diagnosed as (RA) in accordance to EULAR/ACR 2010 Criteria for classification of (RA) (Aletaha et al., 2010)
- Age > 18 years.

Exclusion criteria

- Other causes of arthritis.
- Diabetes mellitus.
- Thyroid and parathyroid disorders.
- Other autoimmune connective tissue diseases.

Research tools

All patients were subjected to the following:

- Complete history taking including (personal history, drug history, family history , and surgical history)
- Complete general examination.
- Complete musculoskeletal examination.
- Investigations:
 - Laboratory (CBC, ESR, CRP, Rheumatoid factor, Anti-CCP).
 - Routine Lab (Liver enzymes, Renal function tests, Blood Glucose level).
 - Radiographic investigation (MSUS) on both hands and feet and X-Ray on both hands and feet: P-A view and other affected joints.

DAS-28 ESR score

Used for assessment and measurement of disease activity, it was computed utilizing total joint count

(TJC), swollen joint count (SJC), visual analogue scale and erythrocyte sedimentation rate (ESR),

A patient with a DAS28 score of less than 2.6 is in remission; a score greater than or equal to 2.6 and less than 3.1 indicates low activity; a score greater than or equal to 3.1 and <5.1 indicates moderate activity and a score 5.1 or more indicates high activity. (Fuchs et al., 1989)

Musculoskeletal ultrasound

The musculoskeletal ultrasound was done using a linear 12 MHz probe, and a scoring system was applied, using the US-7 scoring system of (Backhaus et al., 2013). According to this system, we measured synovitis both by the gray scale and the Power Doppler, and erosions in 7 joints bilaterally (wrists, 2nd, 3rd and 4th MCPs, and of PIPs joints). The scoring system was applied as follows:

- Gray scale US (US-GS): synovitis takes a value from 0 (no synovitis) to 3 (Severe synovitis) for each joint, giving a maximum score of 42.
- Power Doppler US (US-PDA): Power Doppler Activity (PDA) takes a value of either 0 (no PDA), 1 (one or two dots of PDA), 2 (PDA of more than 2 dots, but less than half of area of the joint space) or 3 (PDA occupying more than half of the joint space area); also giving a maximum score of 42.
- Erosions (US-E): were counted when seen in each of the 7 examined joints.
- The total US-7 score is simply the summation of US-GS, US-PDA and US-E.

Research outcome measures

- Primary (main): Assessment of the disease activity by (NLR) and (MSUS) in early (RA) patients.
- Secondary (subsidiary): Assessment of disease activity by (DAS-28 ESR score) and determination of the relation between (NLR) and (MSUS) findings, and the disease activity in early (RA) patients.

Ethical clearance

- The research protocol was approved and accepted by the local ethical committee of Qena Faculty of Medicine, South Valley University before the beginning of the research.
- A pre-approved written consent was taken from each patient before inclusion in the study.

- **Ethical approval code** :_SVU-MED-PRR022-1-21-12-301

Statistical analysis

The Statistical package for social sciences (IBM-SPSS), version 24 IBM- Chicago, USA (May 2016) was used in the statistical data analysis. Data was demonstrated as mean, standard deviation (SD), number and percentage. The Mean and (SD) were used as descriptive value for quantitative data, but number and percentage were used to assess qualitative data. Student 't test; was used to compare the means between 2 groups, while one way analysis of variance (ANOVA) test; was used to compare means up to 2 groups. and Mann Whitney test; was used rather than Student' t test in case of non-parametric data. The Pearson Chi square was used to compare percentages of qualitative data and Fisher's Exact test was used for non-parametric data. Pearson correlation test was used to compare 2 quantitative variables. For all these tests, a P value of less than 0.5 was considered statistically significant.

Results

This study shows that the mean age of the study population was around 46 years (**Table.1 and Fig.1**)

The vast bulk of the current study cases were females (82%) (**Table.2 and Fig.2**)

The mean disease duration was 8.25±3.09 months (**Table.3 and Fig.3**)

The majority of cases had normal total leucocytic count, with some cases had leucocytosis, with a very wide variation of the (NLR), with a range from 1.045 - 8.875. (**Table.4 and Fig.4**)

Regarding disease activity that measured by DAS-28-ESR score , we found that all of the patients fell in the moderate to high disease activity; with 86% had moderate disease activity (DAS-28 score between 3.2 & 5.1) while the other 14% had high disease activity, none of the cases achieved remission or low disease activity (**Table.5 , Table.6 and Fig.5**)

Regarding ultrasonographic US-7 score, we found that there were wide variations for all of the US-7 items, with a mean synovitis gray scale score of 20.8±9.15 (range 8-42), power Doppler activity score of 7.4±4.99 (range 2-29), mean erosion score of 2.5±2.1 (range 0-7) and a mean Total US-7 score of 30.7±13.86 (range from 14-77) (**Table.7 and Fig.6A- D**)

Regarding the correlation between DAS-28 score and NLR, we found that there is a tenuous but significant correlation between disease activity of RA and NLR (Pearson Correlation coefficient 0.129 and p value 0.037). (Table.8 and Fig.7)

Regarding musculoskeletal ultrasound, we found a positive, powerful and highly significant

correlation between disease activity and each of the US-7 scores (with Pearson Correlation coefficients of 0.704, 0.764, 0.590 and 0.829 for US-7 gray scale, US-7 Power Doppler, US-7 erosions and US-7 total scores; respectively) and p values of <0.001 for all of these scores. (Table.8 and Fig.8)

Table 1. Age of the study group

Mean	46.12
Median	45.50
Std. Deviation	11.947
Minimum	22
Maximum	69

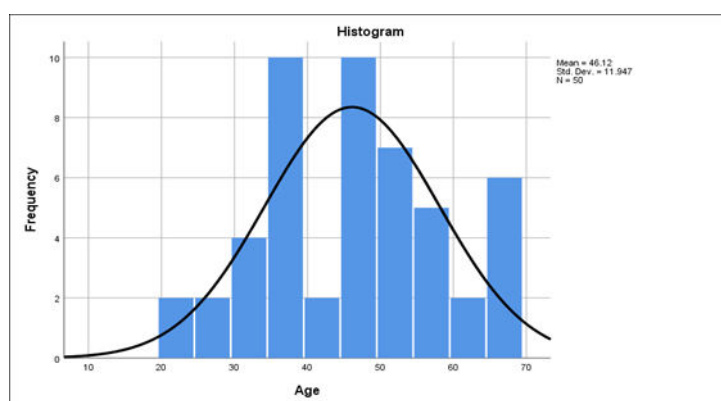


Fig.1.Age of the study group

Table 2. Sex distribution, family history and address of the study group

Variables		No	Percent
Sex	Male	9	18%
	Female	41	82%
Family history	RA	15	30%
	Negative	35	70%
Address	Rural	34	64%
	Urban	16	32%

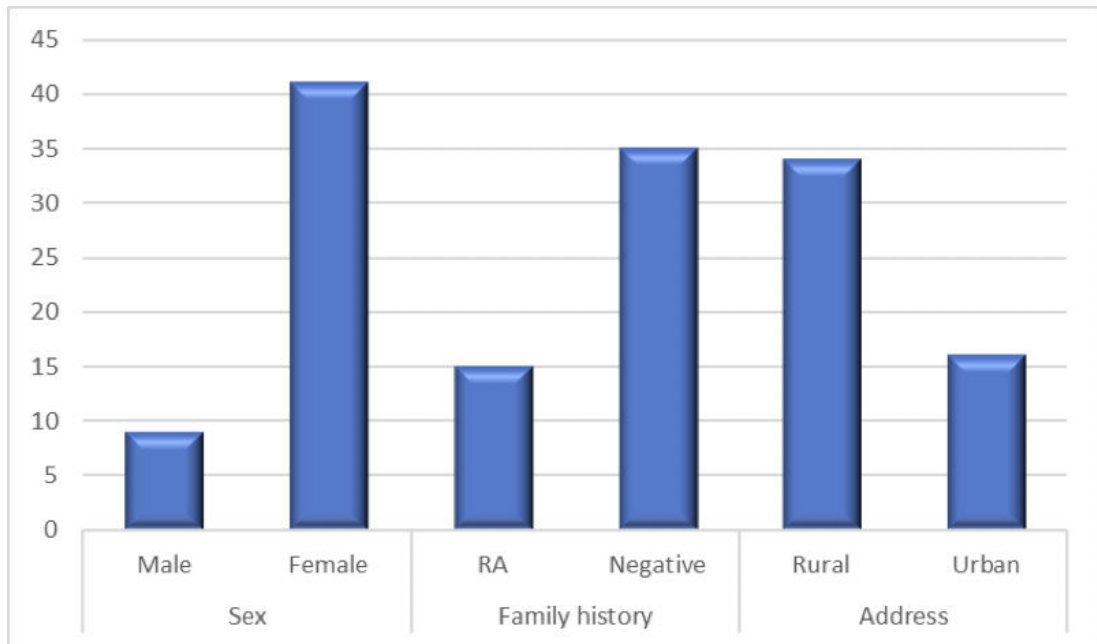


Fig. 2. Sex distribution, family history and address of the study group

Table 3. Disease duration of the study group

Mean	8.050
Median	8.250
Std. Deviation	3.0942
Minimum	2.0
Maximum	13.0

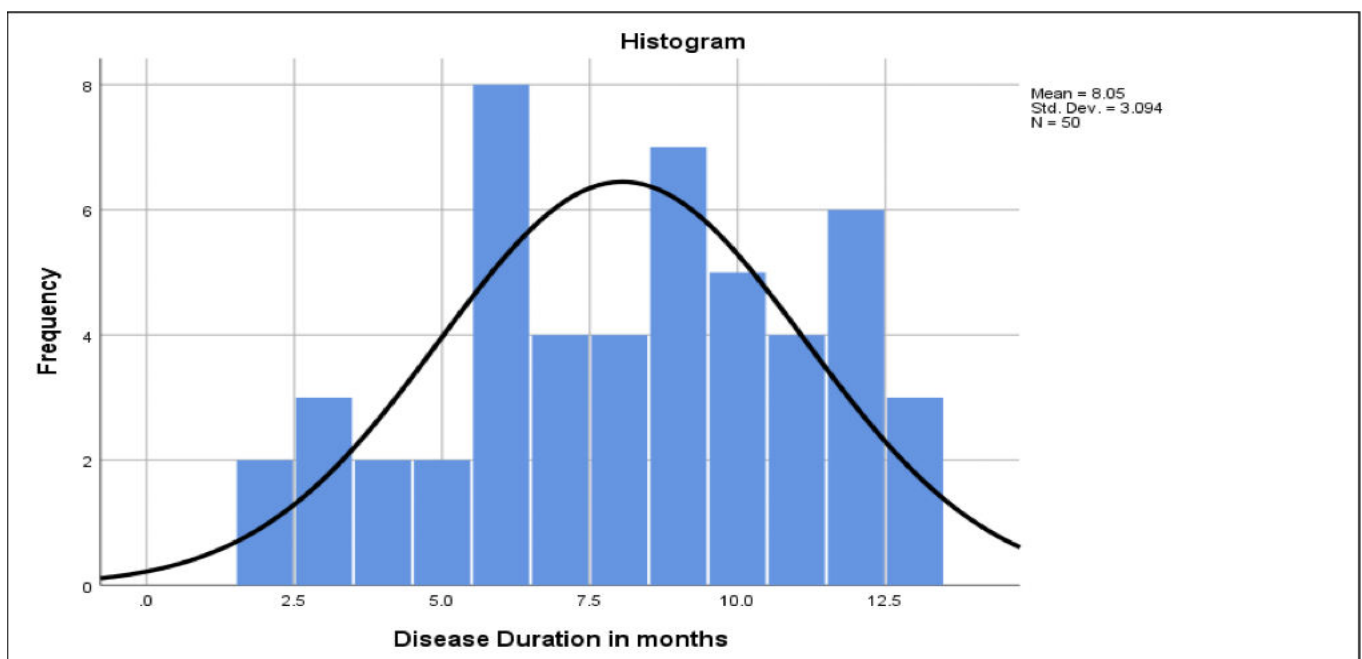


Fig.3. Disease duration of the study group

Table 4.CBC parameters

Variables	Mean	Median	Std. Deviation	Minimum	Maximum
HGB	11.237	11.250	2.176	6.50	15.20
PLT	269.26	246.50	110.687	100	561
TLC	8.032	7.515	2.702	4.20	14.30
Lymphocyte count	2.485	2.355	1.046	0.77	4.60
Neutrophilic count	5.615	5.700	1.768	1.90	9.10
NLR	2.663	2.162	1.638	1.045	8.875

*CBC:Complete Blood Count; *HGB:Hemogloubin; *PLT :Platelet; *TLC: Total Lecuocyte Count *NLR:Neutrophil / Lymphocyte ratio.

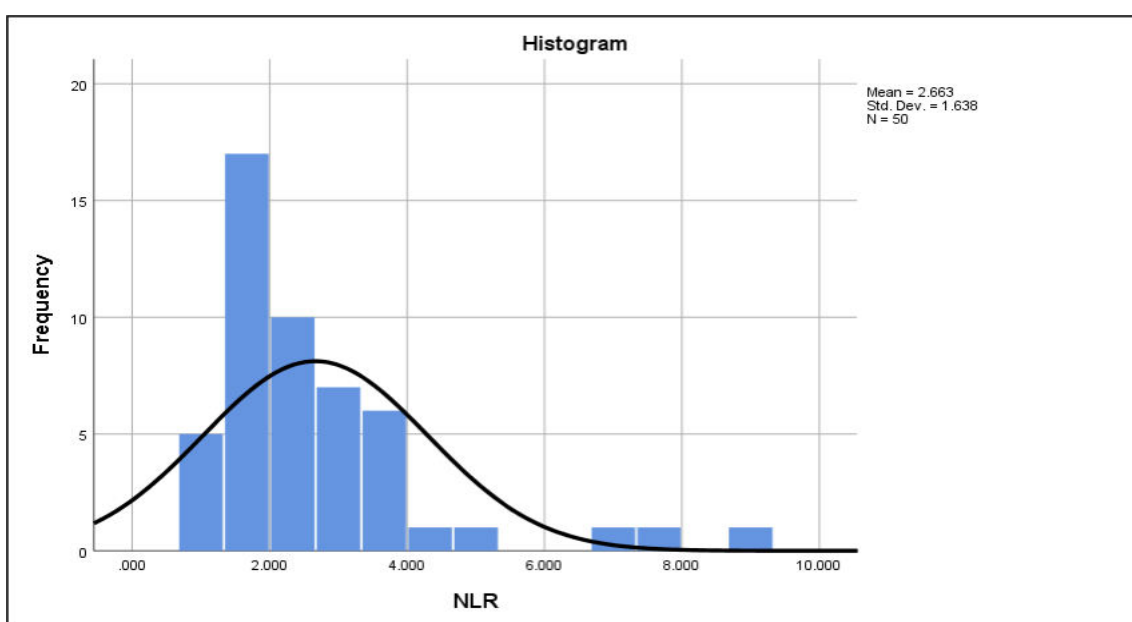


Fig.4 . Neutrophil / Lymphocyte ratio
Table 5. DAS-28 score

Mean	4.666
Median	4.625
Std. Deviation	0.384
Minimum	3.76
Maximum	5.72

Table 6. Disease activity (according to DAS-28 score)

Variables	No	Percent
Disease activity	Moderate disease activity	43 86.0
	High disease activity	7 14.0

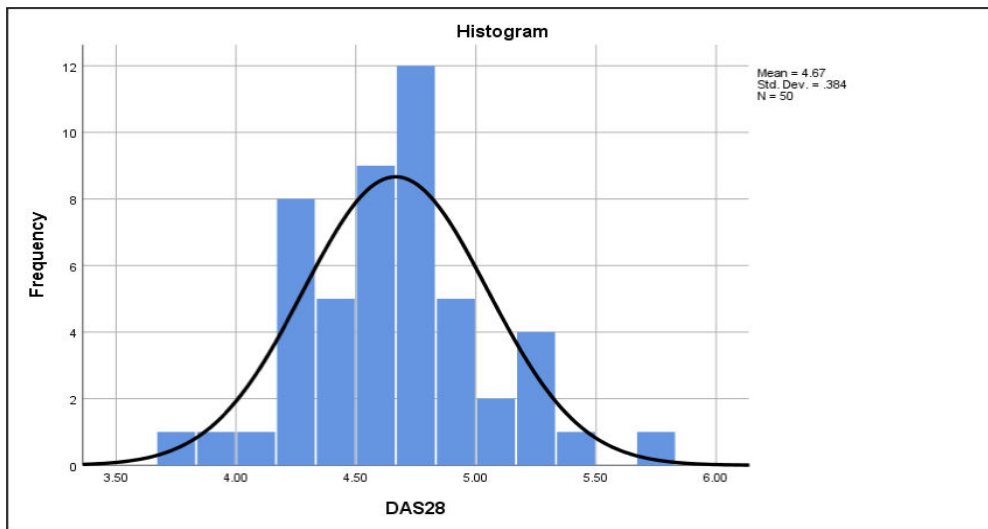


Fig. 5. DAS-28 score

Table 7.US-7 score

Variables	Mean	Median	Std. Deviation	Minimum	Maximum
US7-GS	20.800	19.500	9.150	8.00	42.00
US7-PDA	7.400	6.000	4.994	2.00	29.00
US7-Erosions	2.500	2.000	2.102	0.00	7.00
US7-Total	30.700	27.000	13.860	14.00	77.00

*US7-GS: Ultrasonography 7 Gray scale score; *US7-PDA: Ultrasonography 7 power Doppler Activity score

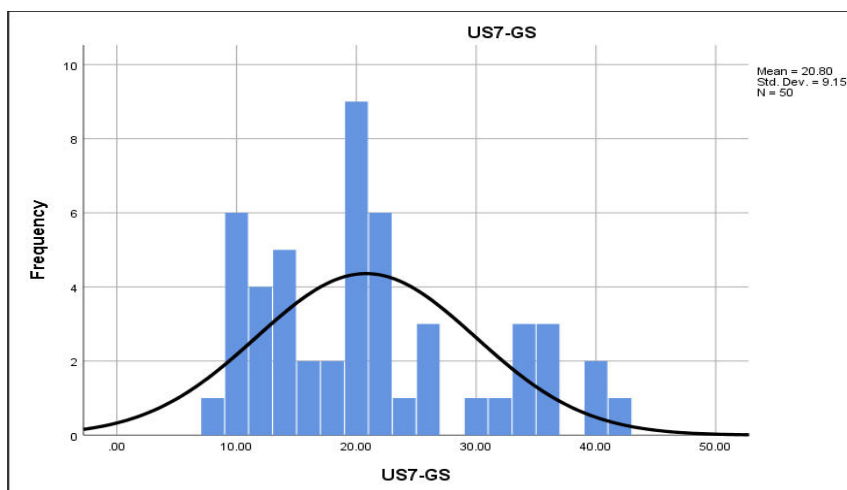


Fig. 6.A. US-7-GS score

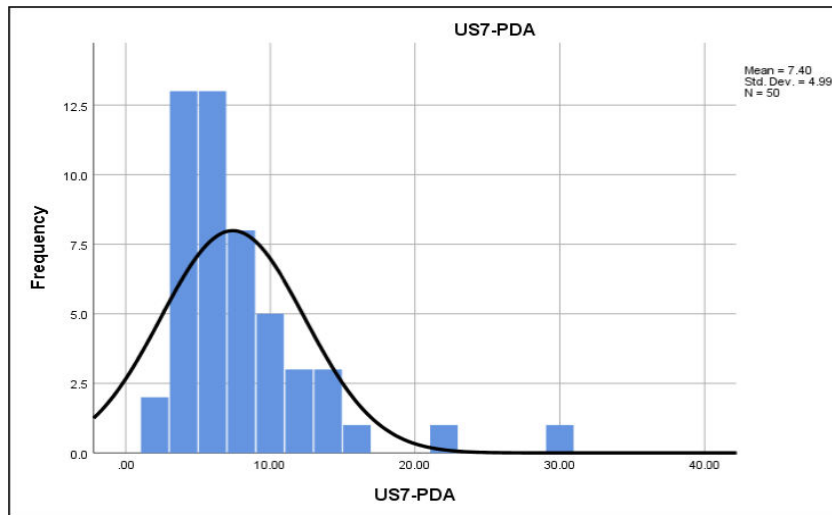


Fig.6.B.US-7-PDA score

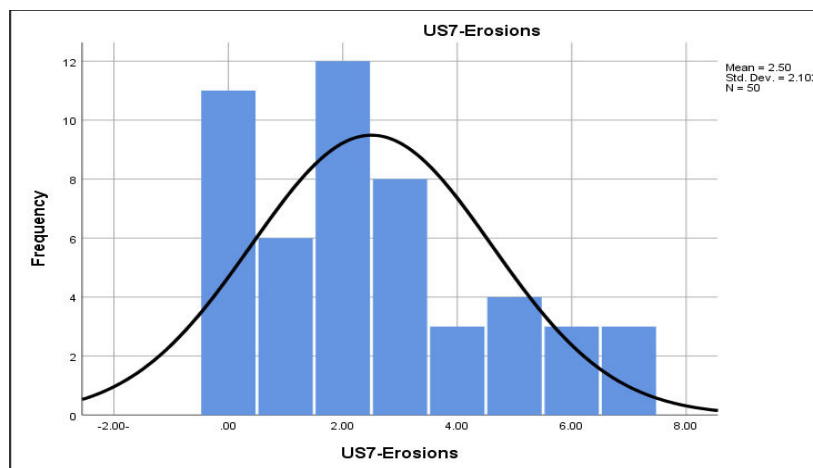


Fig. 6.C. US-7-Erosion Score

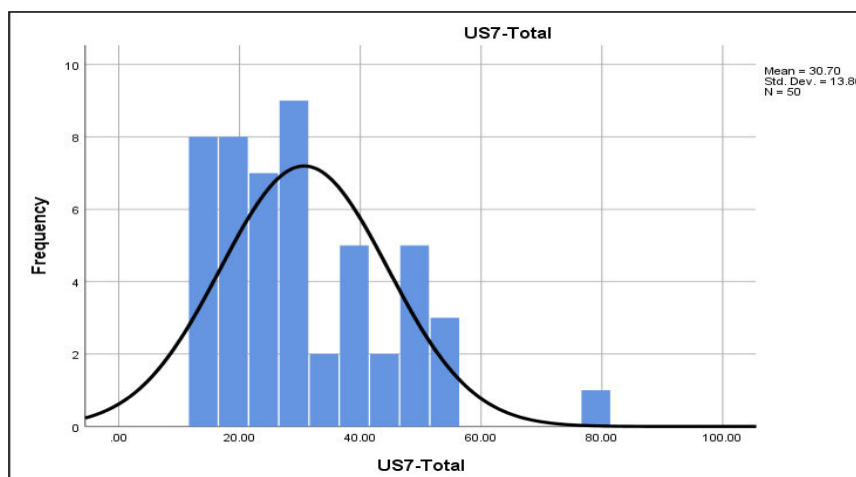


Fig.6.D. US-7-Total score

Table 8. Correlation between DAS-28 score and each of NLR and US-7

Variables	Pearson Correlation coefficient	P value
NLR	-0.129	0.037
US7-GS	0.704	<0.001
US7-PDA	0.764	<0.001
US7-Erosions	0.590	<0.001
US7-Total	0.829	<0.001

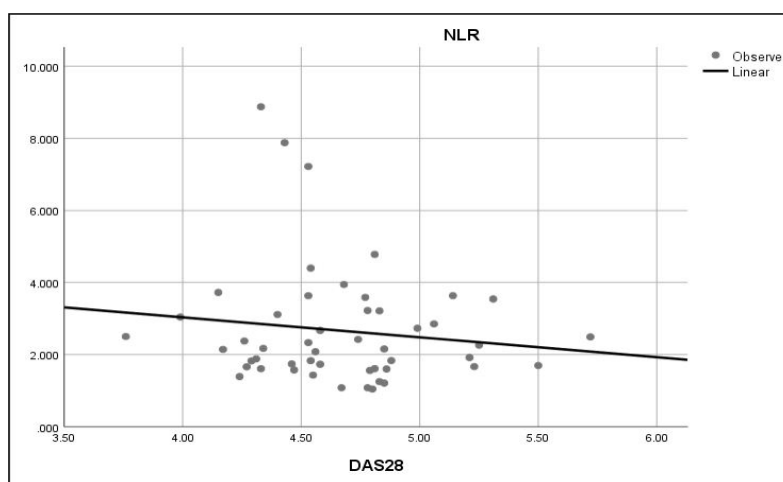


Fig. 7. Correlation between DAS-28 score and NLR

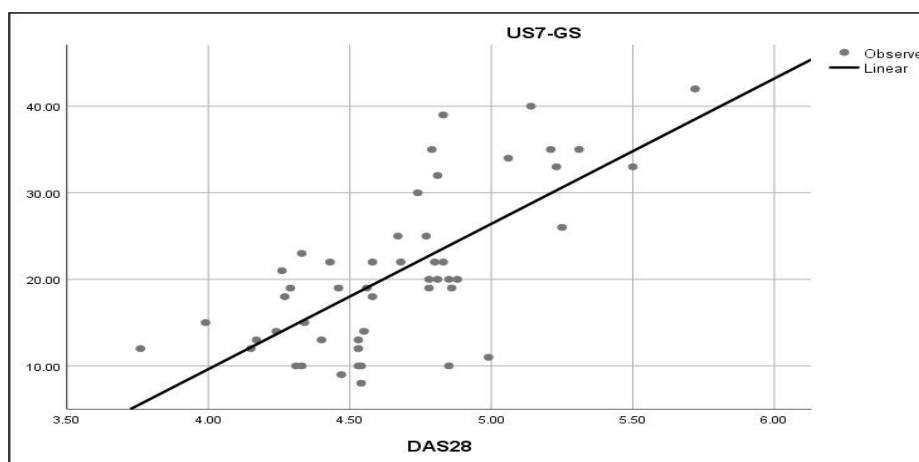


Fig. 8. Correlation between DAS-28 score and US-7-GS

Discussion

Rheumatoid arthritis is the commonest autoimmune systemic disease all over the world. Its incidence is about 1%. RA is an inflammatory disease that occurs principally in females. In the character of disease, synovial inflammation leads

to erosion and deformity in joints. (Assayag et al., 2014 ;Sas, 2019).

MSUS is a viable imaging technique in rheumatic joint diseases for assessment of soft tissue changes like synovitis and tenosynovitis, and bony changes. The validated Ultrasound-Score ‘US7’ is a time-

efficient, standardized alternative to more time consuming total joint screens. It was found that the 'US7 Score' is quite appropriate for document therapy-response in RA compared to the DAS28 (Backhaus et al., 2009 ; Alcalde et al., 2012 ;Backhaus et al., 2013).

The goal of current research is the evaluation of disease activity by (NLR) and (MSUS) in early (RA) patients.

The current study shows that the mean age of the research population was about 46 year, with a wide range from 22-69 year. This is somewhat similar to the research of (Mendonca et al., 2011) where the mean age of their cases was 42 year & (Mitran et al., 2015) with a mean age of around 48 year . Our cases were somewhat younger than those studied by (Lijuan et al., 2021) and (Sas, 2019) where the mean age of their cases were around 55 and 56 years; respectively and the study of (Lautwein et al., 2022) where the mean age was 52 years. However, mean age of the research done by (Mohammed et al., 2019) was much younger, around 36 years only.

The vast majority of the current study cases were females (82%). This female predominance was similar to studies of (Lijuan et al., 2021 ;Mitran et al., 2015) and (Mendonca et al., 2011). In the studies done by (Sas, 2019) and (Mohammed et al., 2019); the female predominance was less prominent (around 75%) and that of (Lautwein et al., 2022) who found that females accounted for 72% Of the total cases.

The disease duration of research cases ranging from 2-13 months, with a mean of 8.25 ± 3.09 months. This was comparable to the research of (Mendonca et al., 2011) where the mean disease duration of their cases was 14 month. On the other hand, this was different from the research that was done by (Lijuan et al., 2021) where the mean disease duration of their cases was around 9-10 years. Also, the study of (Sas, 2019) stated that mean disease duration was eight year.

In the current study, the majority of the cases had normal total leucocytic count, with some cases had leucocytosis, with a range of white blood cells (WBCs) from 4.2 to $14.3 \times 10^3/\text{ml}$. This wide variation was also seen for neutrophilic count ($1.9-9.1 \times 10^3/\text{ml}$) and lymphocytic count ($0.77-4.6 \times 10^3/\text{ml}$). This was reflected to the very wide variation of the (NLR), with a range from 1.045 to 8.875. In the study of (Quaiser and Khan, 2020),

they found similar wide variations of NLR between 0.64 to 10.2.

Rheumatoid factor was positive in 76% of the cases and anti CCP in 64% of them. In fact, 95% of the cases had either positive (RF) or positive anti CCP, with 54% of them had positive both (RF) & anti-CCP, while only 5 cases had negative both RF and anti CCP. In study of (Mitran et al., 2015), RF was positive in 72.4% of their cases and anti -CCP in 58.6% of them.

Regarding disease Activity measured by DAS-28-ESR score we found that all of patients fell on the moderate to High disease activity; with 86% had moderate disease activity (DAS-28 score between 3.2 & 5.1) while the other 14% Had high disease activity. None of the cases attained remission or low disease activity . In a study done by (Lijuan et al., 2021), around 13% of the cases were in remission and another 10% were in low disease activity, while 18% were in moderate disease activity and 59% were in high disease activity. Also, the study of (Sas, 2019) showed that around 26% of their patients were in remission while only 58% had either moderate or high disease activity. The study of (Mitran et al., 2015) showed the mean DAS-28 was 5.11 which means that the vast bulk of their cases had high RA disease activity. The study done by (Mohammed et al., 2019) was designed from the start to include equal numbers of active RA cases and RA cases in remission (20 cases for each group). The study done by (Mendonca et al., 2011) included only active RA cases, with DAS-28 score of at least 3.2.

Regarding the ultrasonographic US-7 score, we found that there were wide variations for all of the US-7 items, with a mean synovitis gray scale score of 20.8 ± 9.15 (range 8-42), Power Doppler Activity score of 7.4 ± 4.99 (range 2-29), mean erosion score of 2.5 ± 2.1 (range 0-7) and a mean total US-7 score of 30.7 ± 13.86 (range from 14-77). In the study done by (Mendonca et al., 2011), they found that synovitis was assessed by GSUS in 66.6% (N=14) & 61.9% (N=13) of Right and Left wrists, incessantly. In the Rt wrist, the synovitis is determined by GSUS was 28.5% (N=6) grade 1, 19% (N=4) grade 2 & 19% (N=4) grade 3. In the Lt wrist, synovitis was 33.3% (N=7) grade 1, 14.2% (N=3) grade 2, & 14.2% (N=3) grade 3. PDUS was seen in 23.8% (N=5) of the Rt and Lt wrists. In the Rt wrist, 9.5% (N=1) were grade 2 and 19% (N = 4) were grade 3. In the Lt wrist,

16% (N = 4) were grade 2 & 4.76% (N = 1) were grade 3.

Regarding the correlation between DAS-28 score and NLR, we found that there was a tenuous and significant correlation between disease activity of RA and NLR (Pearson Correlation coefficient 0.129 and p value 0.037).

According to study done by (Quaiser and Khan, 2020), (NLR) was significantly high in RA patients and they concluded that it could be used as a potential method for detection of disease activity in RA patients, particularly in resource poor settings that the cost of other validated indices & expertise is very scarce. The study of (Sas, 2019) reached similar conclusion.

The study done with (Lijuan et al., 2021) concluded that; in spite of patients with disease activity presented elevated NLR and platelet/lymphocyte ratio (PLR) that compared to patients on remission, both the NLR & PLR viewed lower discrimination power than CRP & ESR in detecting disease activity & combining NLR or PLR can not significantly improved the diagnostic value of ESR and CRP. So, NLR, PLR and LMR may not be useful independent diagnostic or complementary biomarkers for disease activity on patients with RA.

In the study of (Mohammed et al., 2019), they found that NLR was highly associated with disease activity with sensitivity of 90%, specificity of 85% and P- value Of <0.001.

We revised some meta-analyses studying the relation between NLR and RA. The first study done by (Erre et al., 2019) and concluded that the NLR was highly associated with the presence of RA, which means that a NLR was significantly more higher among RA subjects in comparison to control subjects. According to the second meta-analysis done by (Lee, 2018), the NLR was significantly higher on the RA patients and positively but weakly correlated with the RA activity. More recently, the systematic review and meta-analysis done by (Zinellu and Mangoni, 2022) achieved similar conclusions.

Regarding (MSUS) in the current study, we found that there are positive, powerful and highly significant correlations between disease activity and each of the US-7 scores (with Pearson Correlation coefficients of 0.704, 0.764, 0.590 and 0.829 for US-7 gray scale, US-7 Power Doppler,

US-7 erosions and US-7 total scores; respectively) and p values of <0.001 for all of these scores.

In the study of (Mendonca et al., 2011), they found that the MSUS of both wrists showed significant correlation to disease activity among cases with early RA, results which are very identical to the current study results. Also, the research that was done by (Mitran et al., 2015) found similar significant correlation between MSUS of the hands and wrists and disease activity of their RA patients.

The study done by (Lautwein et al., 2022) concluded that MSUS makes diagnosis of RA easy. But low US7 sum score (1-5) was more frequently found in healthy persons, scores ≥ 5 were more highly predictive for initial diagnosis and follow up of disease activity of (RA).

Study limitations: In this study, we met some limitations like small sample size, the absence of control group and the medical treatment of the patients didn't considered in our study.

Conclusion

The (MSUS) found to be more beneficial than (NLR) as a provisional value of disease activity among early RA patients.

List of abbreviations

GSUS: Gray Scale Ultrasonography Score

NLR: Neutrophil to Lymphocyte ratio

CBC: Complete Blood Count

ESR : Erythrocyte Sedimentation Rate

CRP: C-Reactive Protein

RF: Rheumatoid Factor

Anti-ccp : anti cyclic citrullinated peptide

MSUS: Musculoskeletal Ultrasonography

MCPs: Metacarpophalangeals

IPs: Interphalangeals

MRI: Magnetic resonance imaging

RA: Rheumatoid Arthritis

PDUS: Power Doppler Ultrasound

HGB: Hemoglobin

EULAR: European Alliance of Associations for Rheumatology

ACR: American collage of Rheumatology

P.A: Postero_Anterior view

PIPs: Proximal Interphalangeals

PDA: Power Doppler Activity

US-E: Ultrasound Erosion score

SD: Standerd Deviation

ANOVA: Analysis Of Variance test

DAS28: Disease Activity Score

WBCs; White Blood Cells

PLR: Platelet to Lymphocyte Ratio

PLT: Platelet count

TLC: Total Leucocytic Count

TJC: Total Joint Count

SJC: Swollen Joint Count

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