Comparison of disease activity by disease activity score-28 C-reactive protein and disease activity score-28 erythrocyte sedimentation rate in established rheumatoid arthritis patients – A comparative study

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ABSTRACT

Objective. To compare disease activity in patients of established Rheumatoid Arthritis estimated by Disease Activity Score-28 (DAS-28) C-reactive protein (CRP) and Disease Activity Score-28 Erythrocyte Sedimentation Rate (ESR).

Material and Methods: This cross-sectional comparative study was conducted at Department of Rheumatology, Pak Emirates Military Hospital Rawalpindi, May 2022 to Oct 2022. Using consecutive non probability sampling, patients of Rheumatoid Arthritis (RA) of 30 to 65 years age of either gender were selected who had the disease for at least 1 year, never received biologics Disease modifying anti-rheumatic drugs (DMARDs) or immunosuppressive therapy and no signs of active infective etiology. DAS28 score was calculated using ESR and CRP to assess disease severity. Sensitivity, specificity, and agreement comparison was done between DAS28-ESR and DAS28-CRP and κ -coefficient was calculated with discordance proportion.

Results. Out of 70 patients, 50 (70%) were female and 20 (28%) were male with mean age of included patients 49.9 ± 7.5 years. Mean disease activity score, calculated using ESR was 4.1 ± 1.25 SD was higher than mean DAS28 score of 3.5 ± 1.12 SD with CRP. Twenty (28.6%) patients had High Disease Activity (HDA) (DAS28 > 5.1) when assessed by DAS28-ESR score as compared to 8 (11.4%) patients by DAS28-CRP score with 17.1% discordance and κ Coefficient of 0.402 corresponding to minimal agreement amid DAS28-ESR and DAS28-CRP for HDA ($p < 0.005$). DAS28 score using ESR as evaluating tool had 35% sensitivity and 98% specificity of detecting RA patients with High Disease Activity.

Conclusion. DAS28-ESR was preferable as compared to DAS28-CRP for monitoring disease activity and treatment decision.

Keywords. C-reactive protein (CRP), Disease activity score (DAS), Erythrocyte sedimentation rate (ESR), Joint pain, Rheumatoid arthritis, Visual analogue scale (VAS)

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INTRODUCTION

Rheumatoid arthritis (RA), a chronic inflammatory autoimmune illness primarily involving joints as idiopathic symmetrical peripheral polyarthritis which affects large as well as small joints of body, causing deformity due to stretching of tendons and ligaments [1]. The overall worldwide prevalence of RA is 1.0 - 1.5% in 3:1 women to men ratio [2]. It progresses from distal to proximal joints causing marked incapacity within 10-20 years after initial presentation in untreated patients [3]. It causes major health risks including higher rates of cardiovascular, pulmonary disease, osteoporosis, and certain types of cancer (e.g. lymphoma) specifically in untreated cases or in patients with poor response to therapy [4]. Moreover, uncontrolled inflammation and joint destruction adversely affect the quality of life causing physical function loss, inability to do routine life activities and shortened life expectancy [5]. According to 2010 American

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College of Rheumatology (ACR) / European Alliance of Associations for Rheumatology (EULAR) classification criteria, definite RA is classified in the patients with manifestation of synovitis in at least one joint, without any alternative diagnosis to explicate synovitis, and criterion score of at least 6 out of 10, from the discrete scores in four features including number and site of affected joints, Rheumatoid Factor (RF) or anti-cyclic citrullinated protein (ACPA) levels, acute phase reactants (including CRP and ESR) and symptoms duration [6].

The Disease Activity Score 28 (DAS28) is among many indices approved by the American College of Rheumatology (ACR) to monitor RA disease severity [7]. The DAS28 is assessed by adding individual score in: tender joints count; swollen joints count; global health score - calculated by visual analogue scale (VAS) and erythrocyte sedimentation rate (ESR) or alternatively Quantitative C-reactive protein (CRP-Q) value [8]. The ESR is an acute phase reactant of inflammation and its level represents disease activity and severity in the earlier weeks and helpful in monitoring the response to therapeutic modality. ESR value is subjective to certain factors like old age, gender, pregnancy, malignancy, fibrinogen levels, hyper-gammaglobulinemia, RF, anemia and polycythemia [9]. Moreover, despite these confounding factors, raised ESR in early RA is predictor and indicator of intense radiographic damage of affected joints in succeeding years despite of treatment with conservative disease-modifying anti-rheumatic drugs (DMARDs). Due to high sensitivity, ESR is believed to be used as marker for disease monitoring but low specificity makes it poor marker for diagnosis [9]. CRP is advocated as measure of RA disease activity and reflect short term changes. CRP levels are not subjective to aforesaid factors, therefore sensitive to disease activity changes. It is noteworthy that ESR and CRP values fluctuate with ongoing pathophysiological processes, hence, DAS28-CRP threshold standards are anticipated to vary from DAS28-ESR [10].

In South Asian countries including Pakistan, Qualitative and Semi-Quantitative CRP test is available and being used to monitor disease activity in primary health care setups instead of Quantitative (CRP-Q) and high sensitivity (hs-CRP) which are more sensitive in assessing joint inflammation and is closest to age adjusted ESR values [11]. Hence, it has been observed in repeated research data that, ESR is considered preferred marker to assess disease activity as compared to CRP as ESR is cost effective 900-1350 PKR (average $3 - $4.5) and readily available as compared to CRP-Q which is a bit costly 1500-2700 (average $5 - $9).

It has been noted from the data and studies that there is discordance between DAS28 scores assessed by ESR and CRP values. The rationale of our study was to observe and assess disease severity and activity in local population by comparing DAS28-ESR and DAS28-CRP scores in the light of standard values of disease activity in relation to clinical disease severity.

MATERIAL AND METHODS

This cross-sectional comparative study was conducted in Rheumatology Department of Pak-Emirates Military Hospital, Rawalpindi after seeking approval from Institutional Ethical Committee (IEC-A/28/EC/391/2022). Sample size was 70, calculated with WHO calculator keeping confidence interval 95%, margin of error 5%, and reported global prevalence of RA 0.5-1.0% [12]. Sampling was done by consecutive non-probability method.

Patients of either gender aged 30 to 65 years with diagnosed RA since at least 1 year, treated with low dose steroids (< 10mg Prednisone) or non-biologic DMARDs, no associated underlying comorbid condition and no active infection were selected for study.

RA patients with age < 30 and > 65 years, associated anemia or polycythemia and other autoimmune disease i.e. Sjogren`s syndrome, Systemic Sclerosis, Osteoarthritis, used high dose steroids (> 10mg Prednisone),

received biologic DMARDs or immune-suppressive therapy, history of infective illness active or in preceding 1-month, chronic liver or kidney disease, pregnancy, BMI > 30 kg/m^2, terminal illness or malignancy were all excluded from this study.

The study was conducted after taking informed consent from all patients included in the study. Patients with diagnosed RA were advised base line investigation including CRP and ESR on outdoor basis and DAS28 score was calculated by measuring both ESR and CRP levels. Patients who had recently received high dose steroids or previously treated with biologic DMARDs or immunosuppressive therapy were dropped from study as immunosuppressive agents can reduce or alter the ESR or CRP disproportionately without controlling overall disease activity. The activity of disease is assessed by DAS28 score and categorized as high disease activity (HDA) with DAS28 score > 5.1, moderate disease activity (MDA) score > 3.2 to < 5.1, low disease activity (LDA) score > 2.6 to < 3.2 and remission with score of < 2.6 [9].

Patient`s age, gender, disease duration, ESR and CRP values, and DAS28 scoring were noted in all patients for analysis. Categorical data were presented as numbers and percentages whereas continuous variables were as mean ± SD. Data were analyzed using Statistical Package for Social Sciences version 23 (SPSS v 23). The normality of data was tested by the Kolmogorov-Smirnov test. For analysis, the t-test was used, sensitivity and specificity for detecting high disease activity was calculated, agreement level between DAS28-ESR and CRP was calculated with κ -coefficient and discordance proportion. A p-value of ≤ 0.05 was taken as a statistically significant.

RESULTS

A total of 70 patients with established RA were included in study. Amongst them, 50 (70%) were females and 20 (28%) were males. Mean age of patients was 49.9 ± 7.5 years. Disease duration was also noted by detailed history and previous documentation which showed that 34 (48.6%) had RA since 1-3 years, 30 (42.9%) had RA for last 3-5 years and 6 (8.6%) had disease for > 5 years. ESR measurements showed that ESR were raised (> 20 mm/hour) in 61 (87.1%) patients and 9 (12.9%) had ESR in normal range whereas CRP were raised (> 10mg/L) in 62 (88.6%) patients and 8 (11.4%) had CRP in normal range. It was appreciated in final analysis that mean DAS28 score using ESR was 4.1 ± 1.25 SD which is higher than mean score 3.5 ± 1.12 SD using CRP levels. Out of total 70 patients in our study, 20 (28.6%) met the criteria for HDA (DAS28 > 5.1), 28 (40.0%) were in MDA (DAS28 > 3.2 to < 5.1), 17 (24.3%) were in LDA (DAS28 2.6 - 3.2) and 5 (7.1%) were in remission (DAS28 < 2.6) when assessed using DAS28-ESR score. On other hand, when disease activity calculated by DAS28-CRP, fewer were in HDA 8 (11.4%) and more in remission 13 (18.6%) in comparison to DAS28-ESR score (Table-I & Figure-I).

Multivariate analysis of DAS28 scores was done by assessing DAS score using ESR and CRP levels in relation with age, gender and duration of disease. It was observed that out of 70 selected patients, 35 (50%) were of < 50 years age, among which more patients were in high disease activity (HDA) in DAS28 ESR score as compared to DAS28 CRP 7 (20.0%) versus 1 (2.8%) respectively (Table-II, III).

It was also seen that DAS28-CRP score showed out of 35 (50%) patients of < 50 years age more patients 10 (28.6%) were categorized in remission (DAS28 < 2.6) as compared to 3 (8.5%) when assessed using DAS28-ESR. (Table-II, III)

DAS28 score showed that more patients 20 (28.6%) were in high disease activity (> 5.1) using DAS28-ESR as compared to DAS28-CRP 8 (11.4%) patients with 17.1% discordance and κ Coefficient of 0.402, corresponding to minimal agreement proportion between DAS28 ESR > 5.1 and DAS28 CRP > 5.1 indication high

disease activity among RA patients ($p < 0.005$) (Table-IV).

Sensitivity and specificity of DAS28 scoring using ESR and CRP was done for detection patients with high disease activity (HDA). It was observed that DAS28 score using ESR as evaluating tool had 35% sensitivity and 98% specificity of detecting RA patients with HDA

Table-I: Basic parameters of studied patients (70).

Parameter		Results n (%)
Age (mean years ± SD)		49.9 ± 7.5
Gender	Female	50 (71.4%)
	Male	20 (28.6%)
DAS28-ESR	HDA (>5.1)	20 (28.6%)
	MDA (> 3.2 to < 5.1)	28 (40.0%)
	LDA (> 2.6 to < 3.2)	17 (24.3%)
	Remission (< 2.6)	5 (7.1%)
DAS28-CRP	HDA (>5.1)	8 (11.4%)
	MDA (> 3.2 to < 5.1)	25 (35.7%)
	LDA (> 2.6 to < 3.2)	24 (34.3%)
	Remission (< 2.6)	13 (18.6%)

Table-II: Disease activity by DAS28-ESR with relation to disease duration.

		DAS28-ESR			
	Severity →	**HDA > 5.1**	**MDA: > 3.2 - < 5.1**	**LDA: > 2.6 - < 3.2**	**Remission < 2.6**
Duration of RA	**1 - 3 years** 34/70 (48.6%)	9 (26.5%)	10 (29.4%)	11 (32.4%)	4 (11.8%)
	3 - 5 years 30/70 (42.9%)	8 (26.7%)	15 (50.0%)	6 (20.0%)	1 (3.3%)
	> 5 years 6/70 (8.6%)	3 (50.0%)	3 (50.0%)	0	0

Table-III: Disease activity by DAS28 CRP with relation to disease duration.

		DAS28-CRP			
Parameter	**Severity →**	**HDA > 5.1**	**MDA: > 3.2 - < 5.1**	**LDA: > 2.6 - < 3.2**	**Remission < 2.6**
Duration of RA	**1 - 3 years** 34/70 (48.6%)	2 (5.9%)	12 (35.3%)	9 (26.5%)	11 (32.4%)
	3 - 5 years 30/70 (42.9%)	5 (16.7%)	11 (36.7%)	12 (40.0%)	2 (6.7%)
	> 5 years 6/70 (8.6%)	1 (16.7%)	2 (33.3%)	3 (50.0%)	0

Table-IV: Agreement comparison of DAS28 ESR and DAS28 CRP.

Total (n)	DAS28 ESR > 5.1 n (%)	DAS28 CRP > 5.1 n (%)	Discordance Proportion n (%)	κ - Coefficient	p-value
70	20/70 (28.6%)	8/70 (11.4%)	12/70 (17.1%)	0.402	< 0.005

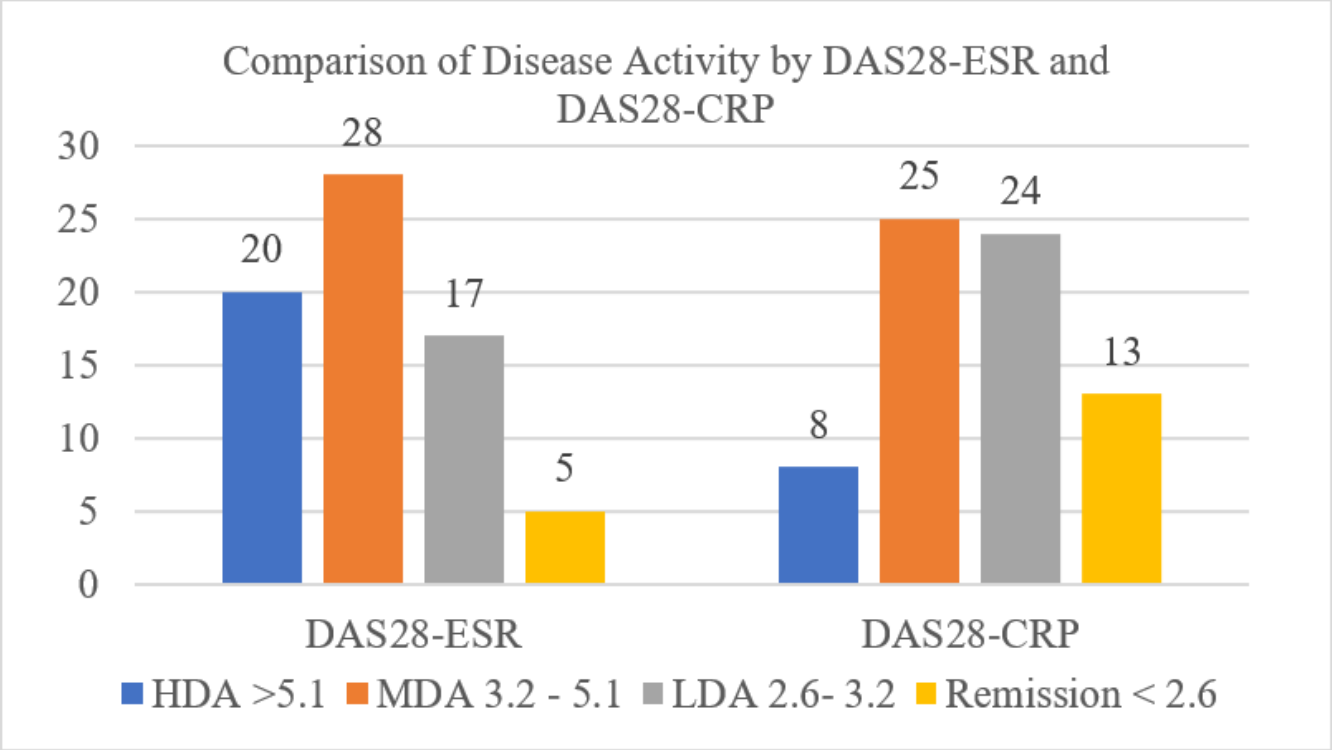

Figure-I: Comparison of disease activity by DAS28-ESR and DAS28-CRP.

DISCUSSION

RA is a chronic debilitating disease and its outcome is meticulously correlated to disease activity, which is usually assessed by markers including CRP and ESR [13]. Therefore, disease activity is consistently assessed in RA patients in decision making regarding treatment modality and assessing therapeutic response and efficacy of routinely used therapeutic approach and in clinical trials [14]. Our study results also showed that more patients fall into high disease activity when assessed by DAS28-ESR in comparison to patients assessed by DAS28-CRP with discordance proportion of 12 (17.1%). In a review study directed by Greenmyer *et al* [2020, North Dakota] concluded that 48.5% patients fall into criteria for HDA measured by DAS28-ESR compared to 14.6% patients in DAS28-CRP score with 33.9% discordance [15]. In a study conducted in Agha Khan University Hospital Karachi done by Nasir *et al* [2022, Pakistan], it was concluded that DAS28-ESR is preferred choice when assessing disease activity for initiation or maintaining therapy when combined with modified Health Assessment Questionnaire (mHAQ) [16].

In our study it was seen that there was minimal proportion of agreement between DAS28 score in detecting high disease activity (> 5.1) using DAS28-ESR as compared to DAS28-CRP with κ Coefficient of 0.402, and 17.1% discordance. Also it was observed in this study that using DAS28-ESR as evaluating tool had 35% sensitivity and 98% specificity of detecting RA patients with HAD. In a comparative study done by Kuriya *et al* [2014, Canada] and published in Clinical and Experimental Rheumatology Journal it was highlighted that intended standards for DAS28-CRP were lower for remission, LDA and HDA with 2.5, 2.9 and 4.6 respectively and showing moderate level agreement with DAS28-ESR values (κ = 0.70) [17]. Similarly, in another study by Shivacheva *et al* [2020, Bulgaria] it was concluded that there was low level of agreement (κ = 0.235-0.464) and discrepancy between DAS28-ESR and DAS28-CRP when estimating activity of disease [18].

As high levels of circulating CRP in RA patients usually associated with disease activity and directly proportional to each other. Therefore, CRP levels declines with treatment representing low disease activity as explained by Pope *et al* [2021, UK] in his study that CRP is a regulator of systemic inflammation in RA that appears to play a role in pathological effects of RA. Also, reducing levels of CRP with DMARDs treatment contribute towards reduction in disease activity [19].

It was observed in our study that sensitivity and specificity of DAS28-ESR for detecting patients with high disease activity was 35 % and 95% respectively. Similarly, Hamann *et al* [2019, UK] reported that DAS28-CRP was 0.3 points lower than the DAS28-ESR for corresponding cohort when estimating activity of disease [20]. Moreover it is has been explained in a study by Hensor *et al* [2010, UK] that age-adjusted ESR (age/2 for male and age + 10/2 for female) and age-adjusted CRP (Q) (age/50 for male and age/50 + 0.5 for female) can be applied to correlate DAS28-ESR and DAS28-CRP more accurately to disease activity simultaneously [21]. Ranganath *et al* [2005, California] concluded in a study that apparent discrepancy between DAS28-ESR and DAS8-CRP scores can be minimized or removed using age adjusted values for ESR and CRP [22].

CONCLUSION

DAS28-CRP score was pointedly lower and underestimated the patients at high and moderate end of disease activity who would be undertreated whereas in actual they could have been in need of aggressive treatment. Similarly, DAS28-CRP score overestimated patients in remission who would actually need maintenance or up titration of therapy. DAS28-ESR is preferable while assessing disease activity for treat-to-target approach. Hence, ESR would be used to assess and monitor RA disease activity for treatment optimization, as it is available even at smaller setups.

LIMITATIONS

The authors of this study are well aware of its limitations, the most important being the single center study and limited sample size. Also, results could have been different, if high sensitivity CRP (hsCRP-Q) and age-adjusted ESR had been used as activity markers.

RECOMMENDATION

Further studies like RCTs including different populations of different ethnic group are required for more accurate results and comparison due to genetic polymorphism in each population. In addition, effect of anemia, co-existing infection and systemic disease on RA disease should be observed before implication of results on larger scales.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Declared none

AUTHORS CONTRIBUTION

Amna Butt: Conception, study design, data acquisition, manuscript writing, analysis and interpretations, final approval, accountable for all aspects of the work

Khalid Raja, Fahad Javed Awan: Conception and study design, Analysis and interpretation, critical review, final approval, accountable for all aspects of the work

Wajahat Ahmed Khan: Analysis and interpretations, final approval, accountable for all aspects of the work

Farhan Zaid: Conception, data acquisition, critical review, accountable for all aspects of the work

Fahad Ul Hassan: Study design, Analysis and interpretation, final approval, accountable for all aspects of the work

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