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OPEN ACCESS **ORIGINAL ARTICLE**

A Cross-Sectional Study for Assessment of Severity of Early Rheumatoid Arthritis in a Tertiary Care Hospital in Eastern India

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ABSTRACT

Rheumatoid Arthritis is a chronic inflammatory multi systemic disorder. In our tertiary care hospital in eastern India, we observed all the patients in both Indoor and Outdoor patients department presenting with Early Rheumatoid Arthritis. We assessed the severity of the disease via DAS 28 score among the patients. It was found that all the patients had moderate to high disease activity during presentation. On further evaluation, it was found that some patients were seronegative. Although seropositive patients have higher disease activity with more progressive disease and multi systemic involvement, DAS 28 score had poor positive correlation with both RA factor and Anti CCP in our study.

Key Words: *Rheumatoid Arthriti; DAS 28; CCP*

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory multisystemic disorder that can cause significant deformity and disability. Common clinical presentation includes symmetrical polyarthritis involving metacarpophalangeal and interphalangeal joints, wrists, elbows, shoulders and knees. The extra-articular manifestations may affect skin, eyes, lungs, heart, bone marrow, salivary glands, nerve tissues and blood vessels. Periods of increased activity, called flares alternate with periods of relative remission- when the swelling and pain fades or disappear [1]. Early Rheumatoid Arthritis is defined when the patient diagnosed with Rheumatoid Arthritis has disease onset of less than 12 months [2]. The pooled sensitivity and specificity for the criteria of diagnosis of Early Rheumatoid Arthritis i.e. disease duration for less than 12 months were 77% (95% confidence interval 68-84) and 77% (95% confidence interval 68-84) respectively, against the gold standard expert opinion of a rheumatologist [3, 4].

According to the 1987 ARA classification criteria for Rheumatoid Arthritis are as follows: 1) morning stiffness in and around joints lasting at least 1 hour before maximal improvement; 2) soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician; 3) swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints; 4) symmetric swelling (arthritis); 5) rheumatoid nodules; 6) the presence of rheumatoid factor; and 7) radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints. Criteria 1 through 4 must have been present for at least 6 weeks. The criteria demonstrated 91-94% sensitivity and 89% specificity for Rheumatoid Arthritis when compared with non-Rheumatoid Arthritis rheumatic disease control subjects when it was first published [5]. But the criteria usually detected Rheumatoid Arthritis in later stages and is predicted to detect more erosive disease [6].

According to the 2010 ACR/EULAR criteria, patients who should be tested for having Rheumatoid Arthritis are those : who have at least 1 joint with definite clinical synovitis and whose synovitis is not better explained by another disease (e.g., lupus, psoriatic arthritis, or gout).The ACR/EULAR classification system is a score-based algorithm for diagnosis of Rheumatoid Arthritis that incorporates the following 4 factors: Joint involvement, Serology test results, Acute-phase reactant test results, Patient self-reporting of the duration of signs and symptoms [7].

The 2010 ACR/EULAR Criteria in details contains: A) Joint involvement: i> 1 large joint- 0 point, ii> 2-10 large joints- 1 point, iii> 1-3 small joints (large joints not counted)- 2 point, iv> 4-10 small joints (large joints not counted) - 3

point, v> more than 10 joints including one small joint- 5 point. B) Serology: i> negative RA Factor and negative Anti CCP- 0 point, ii> Low positive RA Factor or Low positive Anti CCP- 2 point, iii> High positive RA Factor or High positive Anti CCP- 3 point. C) Acute phase reactants: i> Normal ESR and Normal CRP- 0 point, ii> Raised ESR or Raised CRP- 1 point and D) Duration of symptoms: i> less than 6 weeks- 0 point, ii> more than or equal to 6 weeks- 1 point.

The maximum number of points possible is 10. A classification of definitive Rheumatoid Arthritis requires a score of 6/10 or higher. Patients with a score lower than 6/10 should be reassessed over time. If patients already have erosive changes characteristic of Rheumatoid Arthritis, diagnosis of Rheumatoid Arthritis is done even if there is non-contributory blood tests [8]. Despite all the clinical and laboratory evaluations, sometimes diagnosis of Rheumatoid Arthritis specially in early stages is difficult. For that purpose, MRI and ultrasound enable early diagnosis, follow-up, treatment and post-inflammatory joint damage assessment of synovial joints in patients with Rheumatoid Arthritis. MRI additionally shows bone marrow inflammation and axial spine involvement [9].

Identification of Early Rheumatoid Arthritis with the beginning of treatment can affect disease course, prevent the development of joint erosions or retard progression of erosive disease [10], can affect disease outcome even to a remission state [11]. Early treatment also slows down the development and progression of the complications of Rheumatoid Arthritis like coronary artery disease, interstitial lung disease, haematological manifestations, vasculitis, neurological manifestations which increases the rate of mortality and morbidity in Rheumatoid Arthritis [12].

REVIEW OF LITERATURE:

Scott et al [13] has performed a study which has shown 50% of the risk for development of Rheumatoid Arthritis is attributable to genetic factors. Smoking is the main environmental risk. Hence, for the development of Rheumatoid Arthritis patient need to have both genetic and environmental risks.

Malaviya et al [14] has performed another study among Indian population which has shown Rheumatoid Arthritis prevalence of 0.75% using the 1987 ARA classification criteria. The prevalence of Rheumatoid Arthritis in India is similar to that reported from the developed countries. These findings are in keeping with the fact that the north Indian population is genetically closer to the Caucasians than to other ethnic groups. Hence, we can refer to studies of European, North African and West Asian populations to compare them with Indian population.

Goemaere et al [15] has performed a study which has shown that median age of onset of symptoms of Rheumatoid Arthritis is 45 years in women and 50 years is male. The female to male ratio of all patients was 2.3; with increasing age the female to male ratio decreased from 3.7 before 30 years of age to 1 after the 6th decade of life, with a peak at the age of 40-44 years. Hence, there can be an effect of age-related changes in sex hormone levels on the pathogenesis of Rheumatoid Arthritis.

Furuta et al [16] has performed another study to compare clinical features of patients of Early Rheumatoid Arthritis and Established Rheumatoid Arthritis (disease duration of more than 3 years). It was concluded there is no significant differences of frequencies of morning stiffness, rheumatoid nodules, elevation of ESR, positivity of CRP and RA factor. However, after treatment marked improvement and remission were more in Early Rheumatoid Arthritis group the Established Rheumatoid Arthritis group. Hence, early initiation of treatment leads to better outcome and control of the disease.

Zhang et al [17] has performed a study on Chinese population which concluded that between Younger onset Rheumatoid Arthritis and Elderly onset Rheumatoid Arthritis- the incidence of male patients, disease severity and the complications are much higher in Elderly onset Rheumatoid Arthritis group than Younger onset Rheumatoid Arthritis. Heidari [18] has performed another study emphasizing the need for early diagnosis and aggressive treatment for Rheumatoid Arthritis. Early initiation of treatment has shown positive results that is expected to prevent the progressive course and can even change the natural course of Rheumatoid Arthritis. Castaneda et al [19] has performed a study regarding the differences of management of Early Rheumatoid Arthritis and Established Rheumatoid Arthritis in Spanish patients. They had concluded that patients of Early Rheumatoid Arthritis showed a much better disease activity response compared to Established Rheumatoid Arthritis patients. Hence, early diagnosis and treatment initiation for Rheumatoid Arthritis are vital for the patient to lead a disability and complication free life.

Grassi et al [20] has performed a study which has shown that Rheumatoid Arthritis can affect any joint but has more predilection to affect metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints, wrists and knees causing pain, early morning stiffness and motion restriction. Hence, for diagnosis we should focus more on the small joints of hand than the big joints which is also mentioned in the classification criterias.

Figus et al [21] has conducted a study for the extra-articular manifestations of Rheumatoid Arthritis which probably occur due to the complex, chronic, inflammatory, and autoimmune features of Rheumatoid Arthritis. Cardiovascular

(CV) disease is the most common cause of death in patients with Rheumatoid Arthritis with twice the risk of myocardial infarction and 50% increased cardiovascular mortality risk. Severe and prolonged disease activity, genetics, and inflammation (e.g. CRP, Anti CCP, cytokines, matrix-degrading enzymes) play important roles in cardiovascular disease and atherosclerotic damage. The second major cause of death in patients with Rheumatoid Arthritis is respiratory disease, which occurs in 30-40% of patients. Rheumatoid Arthritis may affect the lung interstitium, airways, and pleura, while pulmonary vascular involvement is less frequent. Central and peripheral nervous system involvement is usually due to small vessel vasculitis, joint damage, or drug toxicity. There is evidence that microvascular cerebral damage caused by systemic inflammation and is documented to have association with the development of Alzheimer's disease and vascular dementia. Some observational studies have shown Disease Modified Anti-Rheumatic Drugs (DMARDs) and biologics could reduce the incidence of dementia. Primary gastrointestinal and renal involvements are rare and often relate to drug therapy. To minimize morbidity and mortality, physicians must manage Rheumatoid Arthritis disease activity (treat-to-target) and monitor risk factors and concomitant conditions. Hence, DMARDs are useful for prevention of multisystemic involvement and complications in patients of Rheumatoid Arthritis.

Singh et al [22] has performed a study among Indian population which has shown DAS 28 score to be a good clinical indicator to assess the severity of Rheumatoid Arthritis. Hence, our selection to choose DAS 28 score to assess the severity of Early Rheumatoid Arthritis is justified.

England et al [23] has performed a study for the role of ESR with Rheumatoid Arthritis and Pope et al [24] has performed another role for the role of CRP with RA. Both of the studies have shown that increase of ESR and CRP in patients of Rheumatoid Arthritis has an increased risk of cardiovascular disease, metabolic syndrome, diabetes, pulmonary diseases via various mechanisms. Hence, patients with high ESR and CRP should be monitored closely as they are at a higher risk to develop systemic complications.

Aletaha et al [25] and Mimori [26] has performed studies regarding the role of RA factor and Anti CCP on Rheumatoid Arthritis. They have shown that positivity of RA factor and Anti CCP both serve as serologic markers for early diagnosis and prognostic indicator of joint destruction in patients of Rheumatoid Arthritis. Hence, patients with positive RA factor and Anti CCP will have early and more severe joint destruction and requires early and aggressive treatment.

OBJECTIVE: To find out severity of disease for patients presenting with Early Rheumatoid Arthritis.
STUDY DESIGN: Cross-sectional observational study.
STUDY PERIOD: One year.
STUDY POPULATION: All male and female patients with Early Rheumatoid Arthritis.

Exclusion Criteria:

Patients with osteoarthritis, gout, psoriatic arthritis, systemic lupus erythematosus or any other inflammatory arthritis were excluded.

SAMPLE SIZE:

The number of patients recruited in the study was sixty-three.
The formula used to calculate the sample size is as follows

$$n = \frac{z^2 pq}{d^2}$$

where n = sample size
z = the standard normal deviate, which is 1.96 at 95% confidence interval
p = prevalence in the population of the factor under study
Here we take p = .65% = 0.0065 (from previous study)
q = 1-p = 0.9935
d = Absolute precision

Thus, using the formula $n = \frac{z^2 pq}{d^2} = \frac{(1.96)^2 * 0.0065 * 0.9935}{d^2 (0.0004)}$, we getn > 62
Hence, we took at least 63 patients in our study.

CLINICAL AND LABORATORY INVESTIGATIONS:

All patients at both In-patient and Out-patient departments with Early Rheumatoid Arthritis were interviewed regarding personal details of age of onset of symptoms, duration of symptoms, pattern and progression of joint involvement, presence of swelling and severity of pain in the joints and drug history. The laboratory investigations included complete blood counts, serum creatinine, ESR, CRP, uric acid, Rheumatoid Factor, Anti CCP. All the investigations done in the study were according to the normal basic work-up for any patient of Early Rheumatoid Arthritis, no special investigation was done.

METHOD OF MEASUREMENT:

Disease activity score of 28 joints according to the guidelines of American college of Rheumatology. Calculation of DAS28 score was done by following measures:

1. Counting the number of swollen joints (out of 28)
2. Counting the number of tender joints (out of 28)
3. Taking blood to measure the erythrocyte sedimentation rate (ESR)
4. Asking the patient to make a "global assessment of health" (indicated by marking on a 10-point line between very good and very bad).

These results were incorporated into a mathematical formula to produce the overall disease activity score:
$DAS28 = 0.56\sqrt{(28TJC)} + 0.28\sqrt{(28SJC)} + 0.70 \text{ Ln } (ESR) + 0.014VAS$
(Here TJC = Tender joint count, SJC = Swollen joint count, Ln = log, VAS = Visual analog scale)

Disease severity was assessed according to the value of DAS28 score as follows:

- Remission: DAS28 ≤2.6
- Low disease activity: 2.6 <DAS28 ≤3.2
- Moderate disease Activity: 3.2 <DAS28 ≤5.1
- High disease Activity: DAS28 >5.1

The 28 joints that are included in DAS28 score are- proximal interphalangeal joints, metacarpophalangeal joints, wrist joint, elbow joint, shoulder joint and knee joint of both sides.

RESULTS

Result 1: Distribution of Age in group

Table 1: Distribution of age in group

Age in group (in years)	Frequency	Percent
≤30	4	6.3%
31-40	13	20.6%
41-50	21	33.3%
51-60	14	22.2%
>61	11	17.5%
Total	63	100.0%

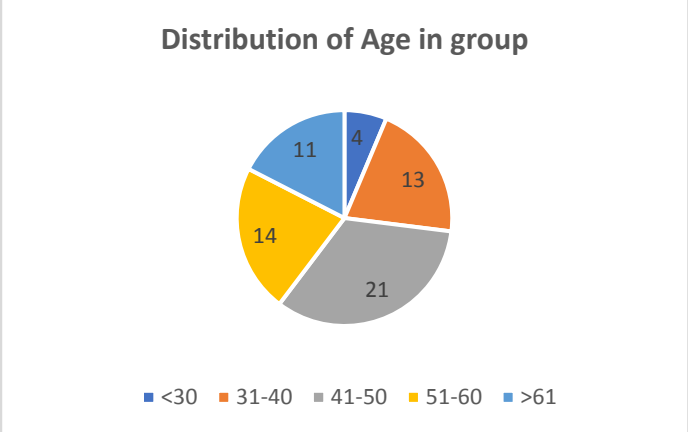

Figure 1: Distribution of age in group

Result 2: Distribution of mean AGE

Table 2: Distribution of mean AGE

	Number	Mean	SD	Minimum	Maximum	Median
AGE	63	47.9206	11.7326	25.0000	71.0000	48.0000

Result 3: Distribution of SEX

Table 3: Distribution of Sex

Sex	Frequency	Percent
Female	51	81.0%

Male	12	19.0%
Total	63	100.0%

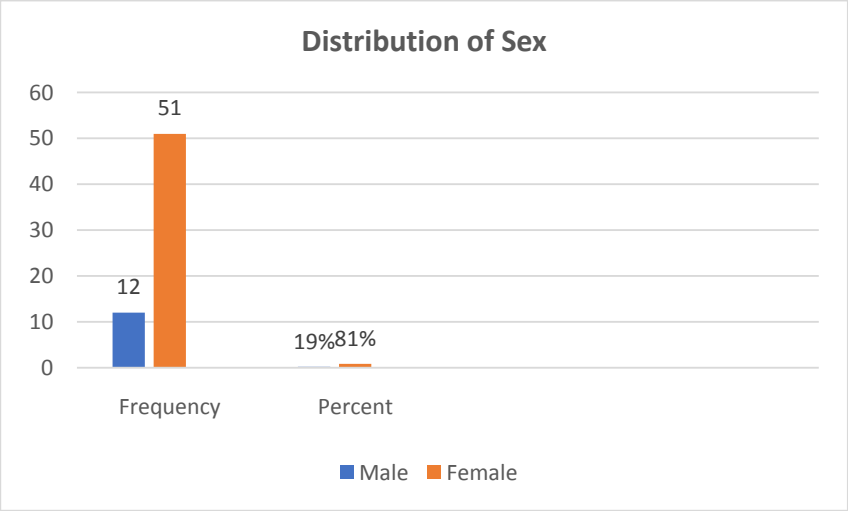

Figure 2: Distribution of Sex

Result 4: Distribution of Disease duration

Table 4: Distribution of Disease Duration

Disease Duration in group (in months)	Frequency	Percent
0-3	6	9.52%
4-6	28	44.44%
7-9	22	34.92%
10-12	7	11.11%
Total	63	100%

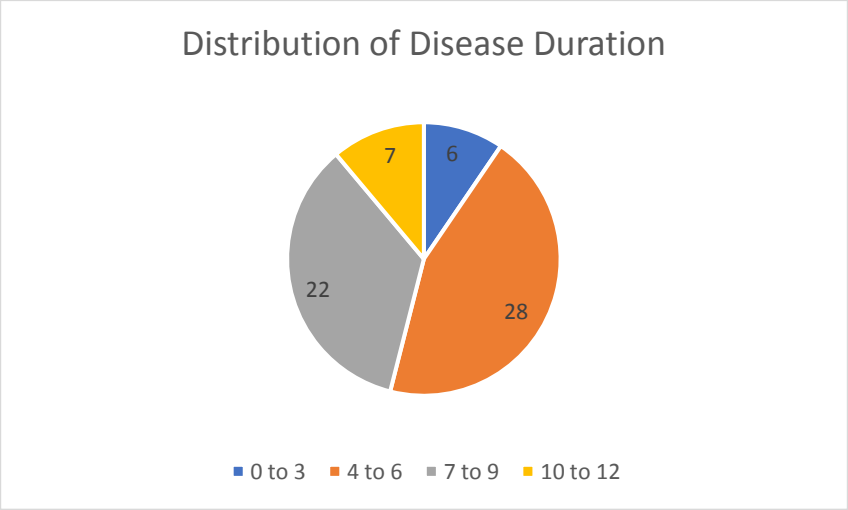

Figure 3: Distribution of disease duration

Result 5: Distribution of mean NUMBER OF JOINTS TENDER

Table 5: Distribution of mean number of joints tender

	Number	Mean	SD	Minimum	Maximum	Median
Number of Joints Tender	63	8.3651	2.9474	4.0000	16.0000	8.0000

Result 6: Distribution of mean NUMBER OF JOINTS SWOLLEN

Table 6: Distribution of mean number of joints swollen

	Number	Mean	SD	Minimum	Maximum	Median
Number of Joints Swollen	63	4.8889	2.8234	0.0000	14.0000	5.0000

Result 7: Distribution of mean DEGREE OF PAIN (VISUAL ANALOG SCALE)

Table 7: Distribution of mean Degree of Pain (Visual Analog Scale)

	Number	Mean	SD	Minimum	Maximum	Median
Degree of Pain (Visual Analog Scale)	63	5.9841	1.9551	2.0000	10.0000	6.0000

Result 8: Distribution of ESR

Table 8: Distribution of ESR

ESR	Frequency	Percent
Normal	6	9.52%
Raised	57	90.48%
Total	63	100%

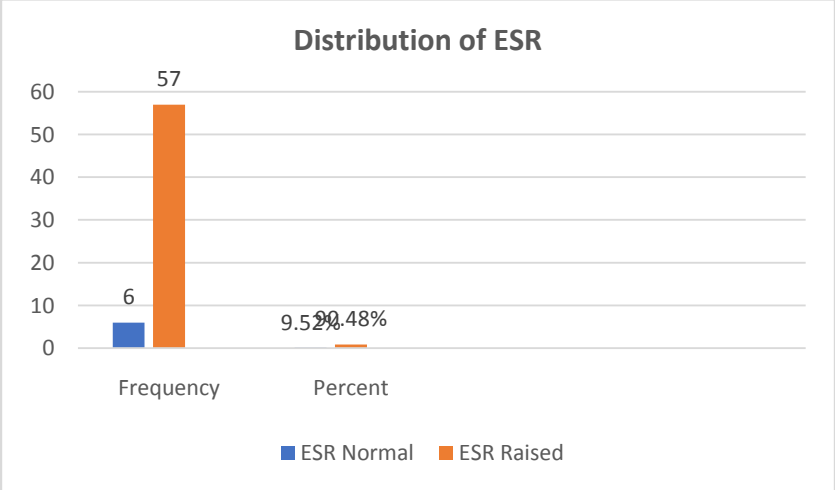

Figure 4: Distribution of ESR

Result 9: Distribution of mean ESR

Table 9: Distribution of mean ESR

	Number	Mean	SD	Minimum	Maximum	Median
ESR	63	42.2857	25.5850	12.0000	161.0000	36.0000

Result 10: Distribution of CRP

Table 10: Distribution of CRP

CRP	Frequency	Percent
Normal	14	22.22%
Raised	49	77.78%
Total	63	100%

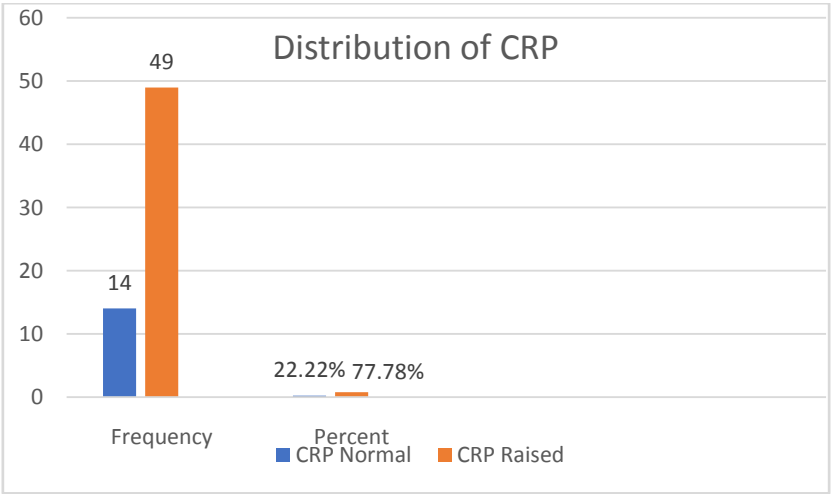

Figure 5: Distribution of CRP

Result 11: Distribution of mean CRP

Table 11: Distribution of mean CRP

	Number	Mean	SD	Minimum	Maximum	Median
CRP	62	8.5795	10.1058	0.3000	49.4000	5.4000

Result 12: Distribution of RA Factor

Table 12: Distribution of RA Factor

RA Factor	Frequency	Percent
Positive	47	74.6%
Negative	16	25.4%
Total	63	100%

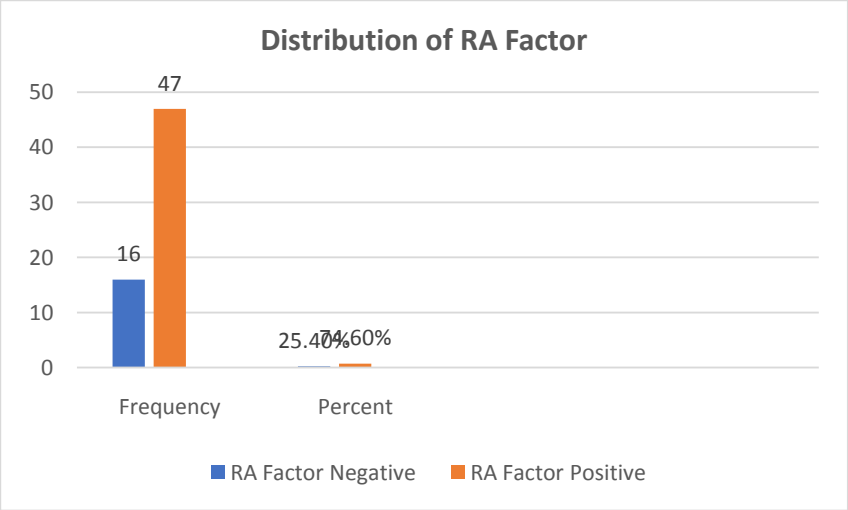

Figure 6: Distribution of RA Factor

Result 13: Distribution of Anti CCP

Table 13: Distribution of Anti CCP

Anti CCP	Frequency	Percent
Positive	47	74.6%
Negative	16	25.4%
Total	63	100%

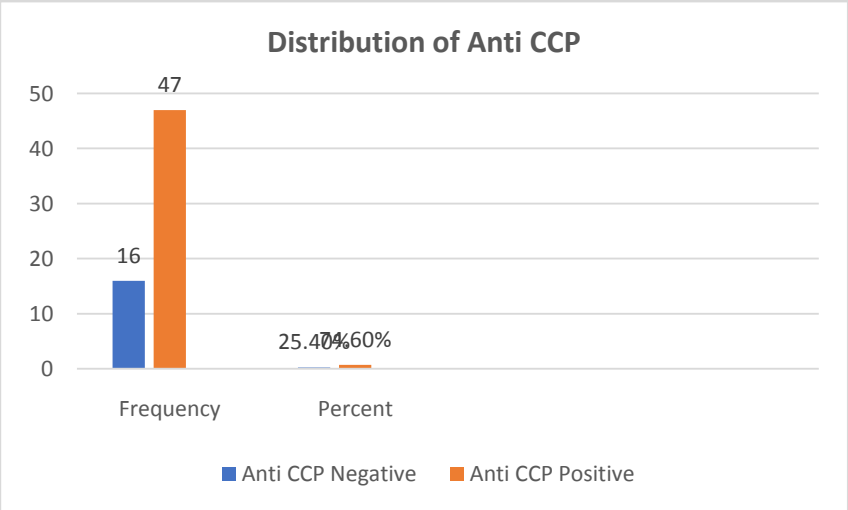

Figure 7: Distribution of Anti CCP

Result 14: Distribution of DAS28 Score

Table 14: Distribution of DAS 28 Score

DAS 28 SCORE	Frequency	Percent
Remission	0	0%
Low Disease Activity	0	0%
Moderate Disease Activity	17	26.98%
High Disease Activity	46	73.02%
Total	63	100%

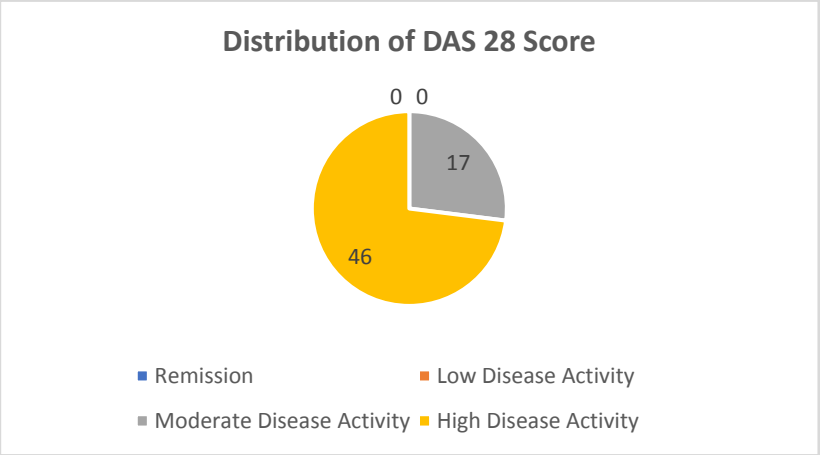

Figure 8: Distribution of DAS 28 Score

Result 15: Distribution of mean DAS 28 Score

Table 15: Distribution of mean DAS 28 Score

	Number	Mean	SD	Minimum	Maximum	Median
DAS 28 SCORE	63	5.5190	.7440	3.5000	7.2000	5.4000

RESULT 16: CORRELATION OF DAS 28 WITH RA FACTOR AND ANTI CCP

		DAS 28 SCORE
RA FACTOR	**Pearson Correlation**	.150
	Sig. (2-tailed)	.240
	N	63
ANTI CCP	**Pearson Correlation**	.229
	Sig. (2-tailed)	.071
	N	63

DISCUSSION

From the above set of results, it was found that out of total 63 patients, 21 patients (33.33%) were from the 41-50 years of age group with a mean age of 47.9206 years with standard deviation of 11.7326 years and median of 48 years which could indicate that onset of Rheumatoid Arthritis maybe related to menopause and hormonal changes as described by Wong et al [27].

In our study, 81% percent of patients (51) were female and 19% of patients (12) were male with a ratio of 4.25 which was slightly higher than the previously documented ratio of 3 as described by Favalli et al [28].

On further evaluation of clinical history of 63 patients, 6 of them (9.52%) presented between 0 to 3 months of disease onset, 28 of them (44.44%) presented to the clinic between 4 to 6 months of disease onset, 22 of them (34.92%) presented between 7 to 9 months of disease onset and 7 of them (11.11%) presented between 10 to 12 months of disease onset. As per a study by Gomes et al [29] in Brazil, the mean duration of disease of rheumatoid arthritis diagnosis was 28 months with diagnosis up to 3 and 12 months was 27.7% and 64.8%, respectively. Hence, the proportion of patients with Very Early Rheumatoid Arthritis i.e. disease duration of 0 to 3 months in our study were significantly lower than the previously documented data, can be attributed to inadequate awareness regarding the disease and the fact that the study was undertaken during the COVID pandemic period.

On examination of 63 patients during interview, the minimum number of tender joints were 4 and maximum were 16 with a mean of 8.3651 joints with standard deviation of 2.9474 joints and median of 8 joints. The minimum number of swollen joints were 0 and maximum were 14 with a mean of 4.8889 joints with standard deviation of 2.8234 joints and median of 5 joints. The pain described by patient in visual analog scale out of 63 patients, was minimum of 2 points and maximum of 10 points with a mean of 5.9841 points with standard deviation of 1.9551 points and median of 6 points which indicates significant joint involvement associated with uncontrolled pain in most of the patients at presentation which can be calculated by DAS 28 score.

On estimation of acute phase reactants, ESR was found to be raised in 57 patients (90.48%) and normal in 6 patients (9.52%) with a mean of 42.2857 mm in 1st hour with standard deviation of 25.5850 in mm 1st hour and median of 36 mm in 1st hour; CRP was found to be raised in 49 patients (77.78%) and normal in 14 patients (22.22%) with a mean of 8.5795 mg/dl with standard deviation of 10.1058 mg/dl and median of 5.4 mg/dl in the study. Both of them are higher as compared to a previous study by Wolfe [30]. Hence, our study population is probably at a higher risk of developing multi systemic involvement and complications as discussed from the review of literature.

Serological markers of Rheumatoid Arthritis are RA factor and Anti CCP, their reports designate patients as Seropositive or Seronegative Rheumatoid Arthritis. RA Factor and Anti CCP were positive in 47 patients (74.6%) and negative in 16 patients (25.4%) was found in our study. It is slightly lower the Anti CCP positivity rate as described by Sghiri et al [31]. In the same study, RA Factor isotype positivity rate was determined- 61.4% patients had positive IgA RA Factor, 58.2% had positive IgG RA Factor, 71.2% had positive IgM RA Factor. Since RA Factor isotype determination requires special and expensive investigations, it was not done in our study. RA factor and Anti CCP both are predictors for progressive and erosive joint disease. So, we can predict that most of the patients we had interviewed will probably have significant disease if not treated adequately. But when RA factor and Anti CCP were compared to DAS 28 score, it showed weak positive correlation to both of them.

After tabulation of DAS 28 score of 63 patients, there were no patients in remission and low disease activity group. There were 17 patients (26.98%) in moderate disease activity group and 46 patients (73.02%) in high disease activity group with a mean of 5.5190 with standard deviation of 0.7440 and median of 5.4 which is lower than the median DAS 28 score of 6 at presentation in Rheumatoid Arthritis patients done in South India by Kumar et al [32]. DAS 28 score in both the studies indicate that most of the patients during presentation had high disease activity at presentation which is maybe due to as all the patients were naïve to any treatment.

CONCLUSION

Through this study, it was observed that most of the patients were female, and they had symptoms onset at peri-menopausal age with moderate to high disease activity. All patients were interviewed on their first visit to the clinic, naïve to any treatment- hence can be attributed to have moderate to high disease activity during interview.

SCOPE OF FURTHER STUDY:

From the above study, we can follow-up the patients after starting treatment and observe the effect of the treatment and check if we can predict the response to treatment after re-evaluating all the clinical parameters.

Patient Consent: Taken.
Institutional Ethical Clearance: Taken
Conflict Of Interest: None
Funded Study: No

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