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Original Article

A Comparative Study of Patients with Seropositive and Seronegative Rheumatoid Arthritis

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Abstract

Objectives: The aim of this study was to analyse and compare the clinical profile, disease activity, extent of disabilities and response to treatment in patients with seropositive and seronegative Rheumatoid Arthritis (RA). **Methods**: A prospective observational study was conducted among 46 patients of RA at the General medicine and Rheumatology OPDs of a tertiary care hospital over a period of 18 months. The clinical profile, disease activity, extent of disabilities and response to treatment of patients with seropositive and seronegative RA was analysed and compared. **Results**: The number of joints involved as well as the outcome indicators (DAS 28 score, HAQ score, SDAI and CDAI) were significantly higher for the seronegative group of patients, indicating more inflammation, higher disease activity and slower response to treatment in the group. Rate of radiological progression of the disease was also higher in seronegative RA. **Conclusion**: Contrary to what was previously believed, patients with seronegative RA have a relatively later disease onset and more active disease at presentation. Physicians should be aware of the considerable clinical burden of seronegative RA, especially at the time of disease onset. However, given the small sample size of this study, these results require validation from larger cohorts.

Keywords: EULAR classification, Polyarthritis, Remission, Rheumatoid factor

Introduction

Rheumatoid Arthritis (RA) is the most common type of inflammatory polyarthritis witnessed in clinical practice. It is an autoimmune disease of insidious onset affecting women more than men and characterized by chronic inflammation, progressive deterioration of joint function, extra-articular manifestations, increased comorbidities and excess mortality[1]. Few patients with early inflammatory arthritis having a classical presentation like RA are negative for both Rheumatoid Factor (RF) and Anti-citrullinated protein/peptide antibodies (ACPA/anti-CCP) and do not seroconvert even for the next few years as per studies. However, these patients behave like seropositive RA in articular manifestations and warrant the same kind of treatment. Thus, RA is typically classified either into seropositive RA or seronegative RA. In 2010, the classification criteria for seronegative patients were revised by the American College of Rheumatology, according to which, they should present with inflammation in at least 10 joints to make a diagnosis of RA[2]. Historically, seropositive RA was thought to be more severe than seronegative RA, but new research suggests otherwise. According to research published in the Annals of the Rheumatic Diseases, in a study of 234 individuals with either a seropositive or seronegative RA diagnosis, the seronegative patients reported greater disease activity than the seropositive patients[3]. This knowledge could be valuable to rheumatologists as well as general physicians, as the presence of anti-CCP antibodies and swelling in joints may not be the most effective criteria in determining the severity of the disease.

About a quarter of cases of RA are found to be seronegative. Irrespective of the seropositivity status, all patients of RA benefit from early diagnosis and treatment. Evidence suggests that there is a therapeutic window of

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Joints involved	Seropositive RA		Seronegative RA	
	Number	Percentage	Number	Percentage
PIP + MCP	1	3.6	0	0
PIP + MCP + Wrist	5	17.9	0	0
PIP + MCP + Shoulder	1	3.6	0	0
PIP + MCP + Wrist + Knee	5	17.9	3	16.7
PIP + MCP + Wrist + Elbow + Knee	5	17.9	0	0
PIP + MCP + Wrist + Shoulder + Knee	5	17.9	2	11.1
PIP + MCP + Wrist +Elbow + Shoulder + Knee	6	21.4	13	72.2
Total	**28**	**100.0**	**18**	**100.0**

Table 1. Distribution of the involved joints in the study participants.

opportunity when starting DMARD (Disease-modifying anti-rheumatic drugs) therapy significantly improves the clinical and reduces joint deterioration. Early RA, on the other hand, can have modest symptoms and hence go untreated in the early stages, when treatment is most effective. ACPA and RF can often be detected before clinical illness starts in seropositive patients. Coffey et al[4]. carried out the first of its kind study to measure the time it takes to meet the criteria and to indicate a delay in starting treatment in people with seronegative RA from the time they first notice joint swelling. However, very few studies in the Indian setup have compared these two types of inflammatory arthritides and there is a lack of data on the clinical picture as well as a therapeutic response on seronegative vis-a-vis seropositive RA patients. The aim of this study was to analyse and compare the clinical profile, disease activity, extent of disabilities and response to treatment in patients with seropositive and seronegative RA.

Materials and methods

This study was a prospective observational study conducted at General medicine and Rheumatology OPDs (Outpatient Departments) of a tertiary care hospital in a time period of 18 months (March 2020 to August 2021). The sample size comprised of 46 patients of RA. Consenting patients older than 18 years of age, who were diagnosed as having RA according to ACR-EULAR 2010 criteria and were treatment naïve, were included in the study. Patients with mixed connective tissue disease or overlap syndromes and pregnant patients were excluded from the study. A pre-tested validated proforma was developed in line with the study objectives to collect data. The study was commenced after obtaining permission from the Institutional Ethics Committee of Seth Gordhandas Sunderdas Medical College & King Edward Memorial Hospital (EC/151/2019). Depending on their seropositivity status, eligible subjects were divided into seropositive and seronegative RA groups. Detailed history was taken and physical examination was carried out for each patient. Laboratory investigations, imaging studies and treatment carried out by the treating rheumatologist were also noted. Patient were assessed for Disease Activity Score 28 5 (DAS 28), Health Assessment Questionnaire[6] (HAQ) score, Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI)[7,8] and Sharp score[9]. Patients were followed up after 3 months and 6 months for a repeat assessment for all parameters.

Written informed consent for participation in this study was taken from all participants. The confidentiality of the patient's data was ensured. Data entry was done in Microsoft Excel 2016 and analyzed using SPSS version 21.0 (IBM). Descriptive statistics included measures like mean, standard deviation, range, and proportions. The results were represented in tabular and graphical formats. Association between categorical variables was seen using Chi-square test. Independent sample t-test was used to see difference between continuous variables in two groups. P value of <0.05 was considered as the level of statistical significance.

Results

Out of the 46 patients included in the study, 28 (60.9%) patients belonged to the seropositive group and 18 (39.1%) patients belonged to the seronegative group. Majority of the patients in the seropositive RA group belonged to 36-45 years (42.95%) and those in the seronegative RA group belonged to 46-55 years (72.2%). On applying independent sample t-test, mean age of patients in seropositive RA group (41.50±8.61) was found to be significantly lower than that in the seronegative RA group (51.72±5.13). No significant association between gender and seropositivity was seen. Female preponderance was seen in the seropositive group of patients (M:F :: 1:2.11). The mean number of joints involved was found to be significantly higher in seronegative group as compared to that in the seropositive group for every visit, indicating higher inflammatory activity in

Co-morbifities	Seropositive RA		Seronegative RA	
	Number	Percentage	Number	Percentage
Diabetes Mellitus	8	28.57	5	27.77
Hypertension	5	17.85	5	27.77
Hypothyroidism	2	7.14	2	11.11
COPD/Tuberculosis	2	7.14	1	5.56
Ischemic heart disease	1	3.57	1	5.56
Tobacco chewing	1	3.57	1	5.56
Smoking	0	0	2	11.11
Osteoarthritis of knee joint	0	0	2	11.11
Seizure disorder	1	3.57	0	0
Obstructive Airway Disease	1	3.57	0	0
Chronic Kidney Disease	0	0	1	5.56
Varicose Vein status post-surgery	0	0	1	5.56
None	14	50.0	8	44.44

Table 2. Co-morbidities present in study participants.

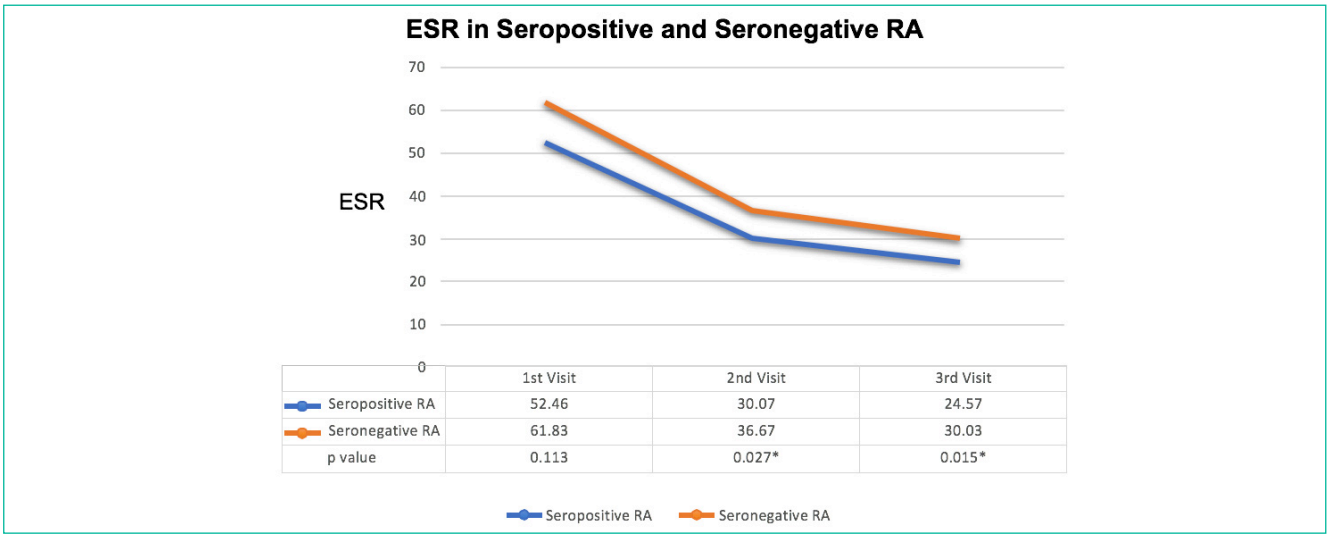

Figure 1. ESR values in seropositive and seronegative patients during all three hospital visits (* = p value < 0.05, statistically significant).

seronegative RA. The Proximal Interphalangeal joint (PIP) and Metacarpophalangeal joint (MCP) were involved in all the cases. The next most commonly involved joints were wrist, followed by knee joints. The involvement of all joints was found to be symmetrically distributed (Table 1).

The mean duration of symptoms in the seropositive group (8.07 months) did not significantly differ from that in the seronegative group (7.78 months). The mean number of tender and swollen joints was found to be significantly more in the seronegative group of patients. While small joint involvement was found to be comparable in both the groups, involvement of large joints was found to be significantly more in seronegative patients (6) as compared to seropositive patients (2.43). Diabetes mellitus was found to be the most common co-morbidity in seropositive group. Hypertension and Diabetes mellitus were equally common in the seronegative group. The presence of co-morbidities in different patients is depicted in Table 2 (no statistically

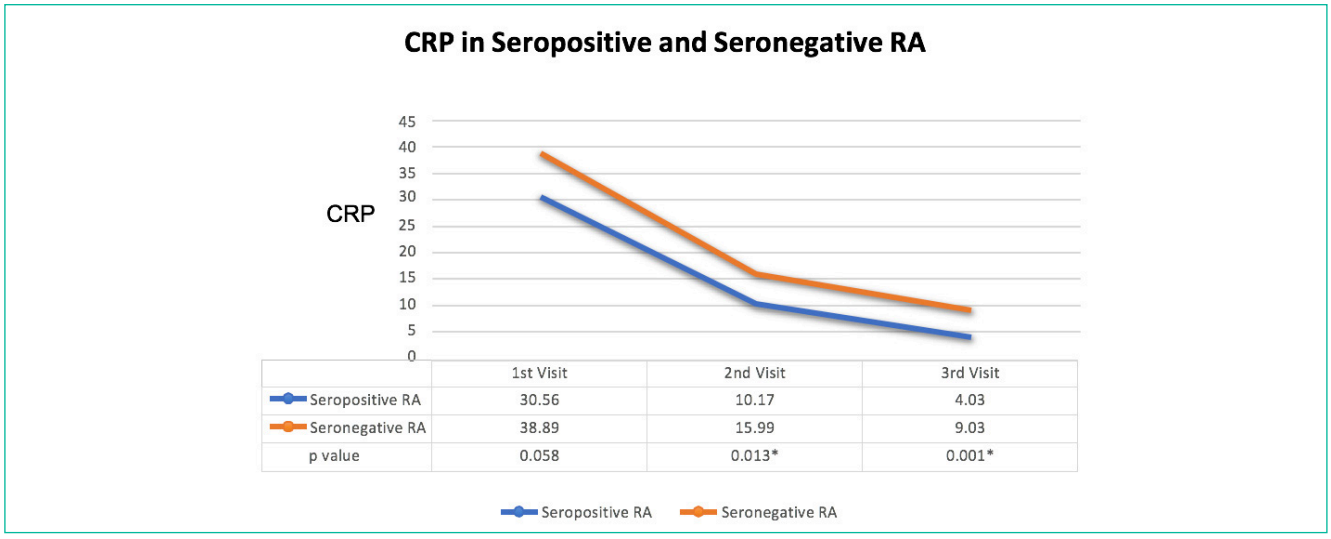

Figure 2. CRP values in seropositive and seronegative patients during all three hospital visits (* = p value < 0.05, statistically significant).

Treatment	Seropositive RA		Seronegative RA	
	Number	Percentage	Number	Percentage
HCQ + NSAID + Steroid	0	0	1	5.6
Methotrexate + HCQ + NSAID + Steroid	16	57.1	6	33.3
Methotrexate + HCQ + SAAZ + NSAID + Steroid	8	28.6	7	38.9
Methotrexate + HCQ + Tofacitinib + NSAID + Steroid	4	14.3	3	16.7
Methotrexate+ HCQ+ SAAZ + NSAID + Steroid+ Leflunomide	0	0	1	5.6
Total	**28**	**100.0**	**18**	**100.0**

Table 3. Pharmacotherapy received by the study participants (NSAID - Non-steroidal anti-inflammatory drug, HCQ – hydroxychloroquine, SAAZ – Sulfasalazine).

significant association was found between the type of RA and presence of any comorbidity).

Among other hematological parameters, Hemoglobin, WBC count and platelet count did not differ significantly among the two groups in any of the visits. However, ESR (Figure 1) and CRP (Figure 2) were significantly higher in seronegative groups during the 2nd and 3rd visits, indicating higher inflammatory activity and a slower response to treatment in patients with seronegative RA.

Joint space narrowing was seen in all patients of both the groups. Periarticular osteopenia, erosions and deformities were the other changes seen on X ray. The treatment record of the patients is depicted in Table 3.

In each visit, the outcome indicators (DAS 28 score, HAQ score, SDAI and CDAI) were significantly higher for the seronegative group of patients, indicating more inflammation, higher disease activity and slower response to treatment in the group. Rate of radiological progression of the disease was also higher in seronegative RA. At the end of 6-months, number of patients achieving remission and those with low disease activity was significantly higher in patients with seropositive RA, indicating better response to treatment than those with seronegative RA (Table 4).

Discussion

In a study by Lena Bugge Nordberg et al[3], a total of 234 patients (84.6% seropositive and 15.4% seronegative) were included to study and compare clinical profile of both groups of rheumatoid arthritis. This study concluded that mean age of seropositive patients (50.7 years) was significantly lower

Outcome Indicators		Seropositive RA		Seronegative RA		Independent t-test
		Mean	SD	Mean	SD	
DAS 28 score	1st visit	6.69	0.63	7.63	0.37	t=-5.7 **p=0.002**
	2nd visit	5.06	0.76	6.48	0.35	t=-7.4 **p<0.001**
	3rd visit	3.63	0.83	5.70	0.47	t=-8.5 **p<0.001**
HAQ score	1st visit	1.24	0.38	1.83	0.47	t=-4.6 **p=0.002**
	2nd visit	0.80	0.44	1.57	0.28	t=-6.4 **p<0.001**
	3rd visit	0.53	0.38	1.50	0.37	t=-8.5 **p<0.001**
SDAI	1st visit	41.26	10.21	55.33	6.41	t = -5.2 **p =0.002**
	2nd visit	21.00	8.29	39.48	4.89	t=-8.5 **p<0.001**
	3rd visit	7.99	6.22	29.74	6.65	t=-11.2 **p<0.001**
CDAI	1st visit	38.19	9.54	51.44	5.78	t=-5.2 **p=0.002**
	2nd visit	20.04	8.00	37.83	4.71	t=-8.5 **p<0.001**
	3rd visit	7.59	6.03	28.75	6.54	t=-11.22 **p<0.001**
Sharp score	1st visit	93.07	42.74	165.39	33.68	t=-6.06 **p=0.002**
	2nd visit	110.64	44.93	190.66	39.74	t=-6.1 **p<0.001**
	3rd visit	124.00	48.86	211.50	39.28	t=-6.3 **p<0.001**

Table 4. Outcome Indicators in each visit among the study participants.

than that of those in the seronegative group (55.8 years). This was consistent with observations made in the present study. Among other studies, Yan Geng et al.[11] and Sang-Tae Choi et al.[12] observed that there was no significant difference in age of two groups. However, both these studies used the 1987 ACR/EULAR classification criteria for rheumatoid arthritis for inclusion of patients in the study. Yan Geng et al.[11] also observed that age of onset was earlier in seropositive (47.4 years) as compared to the seronegative group (52.4 years) which was similar to this study.

Similar to the present study, Lena Bugge Nordberg et al.[3], concluded that gender distribution was similar between seropositive and seronegative group. Yan Geng et al.[11], and Sang-Tae Choi et al.[12], also observed that there was no significant difference in gender distribution between the two groups.

In the present study, the involvement of greater number of joints in seronegative RA in all visits reflected higher inflammatory activity in the seronegative group. This finding was similar to those of the studies by Lena Bugge Nordberg et al.[3] (p<0.001) and Sang-Tae Choi et al.[12] (p<0.001).

In the present study, the most common individually affected joints were PIP and MCP joints, which were involved in all patients. Lena Bugge Nordberg et al.[3] observed the wrist to be the most commonly involved joint. However, they used ultrasound to determine synovitis in the joints, whereas joint involvement was determined clinically in this study. Mean duration of symptoms at the time of diagnosis

was 8.07 (±6.36) months in seropositive and 7.78 (±5.16) months in seronegative patients. No significant difference was observed in the mean duration of symptoms in both the groups. This was consistent with studies by Lena Bugge Nordberg et al.[3], Yan Geng et al.[11], and Sang-Tae Choi et al.[12], which also observed no significant difference in the mean duration in both the groups.

Sang-Tae Choi et al.[12] also observed significantly higher number of tender joints in the seronegative group (p=0.004). Yan Geng et al.[11], did not find any difference between the two groups. Our study and the one by Sang-Tae Choi et al.[12] used TJC-28 (Tender Joint Count 28) for assessment whereas Yan Geng et al.[11], did not used any specific parameter. During all three visits, the number of swollen joints involved in both groups was substantially different (p<0.05). In the seronegative group, the average number of swollen joints was higher. Studies by Lena Bugge Nordberg et al.[3] (p<0.001) and Sang-Tae Choi et al.[12], (p<0.001) concluded that the number of swollen joints was significantly higher in the seronegative group. Sang-Tae Choi et al.[12] used SJC-28 (Swollen Joint Count-28), which was also used in the present study. Lena Bugge Nordberg et al.[3], used used SJC-44 (Swollen Joint Count-44). Small joint involvement was similar in both groups without any statistical difference. A significant difference was observed in mean number of large joints involved {seropositive v/s seronegative=2.43 (±2.13) V/S 6.0 (±0)} with p<0.001. Despite thorough literature reviews, the authors were unable to find any studies that compared small joint against large joint involvement in both the groups.

The slower reduction in mean ESR in seronegative RA group in this study highlighted the group's slower response to treatment and prolonged underlying inflammatory activity. Studies by Lena Bugge Nordberg et al.[3], Yan Geng et al.[11], and Sang-Tae Choi et al.[12] observed no difference in ESR in both the groups. But these studies analyzed ESR values only at the time of the 1st assessment . Similar to the present study, no significant difference was observed in ESR values during the 1st visit in any of these studies. But none of these studies analyzed ESR values at the time of follow up visits. The ARCTIC trial[10] concluded that mean ESR between the two groups was similar at the 1st visit and after 24 months. Mean CRP levels did not differ significantly at 1st visit (p=0.058) but were significantly higher in seronegative group at 2nd (p=0.013) and 3rd (p<0.001) visit. Lena Bugge Nordberg et al.[3], (p=0.48) and Sang-Tae Choi et al.[12], (p=0.135) observed in their study that mean CRP levels were similar between two groups at the 1st assessment, but these studies didn't follow up with their patients and hence data in further course of disease was not available. The ARCTIC trial[10] found that the mean CRP levels in the two groups were similar at the 1st visit and at 24 months. CRP levels were significantly higher in seronegative group at 1st assessment in the study by Yan Geng et al.[11], (p=0.017). Thus, it is clear that levels of ESR and CRP were similar among both groups at the time of diagnosis. But they were significant higher in seronegative RA group for initial 6 months even after treatment and attained same level as seropositive RA at 24 months. Thus, treatment response is slow in seronegative RA in initial 6 months after diagnosis and initiation of treatment, again highlighting higher inflammatory activity in seronegative RA. Out of 28 patients of seropositive RA, 23 (82.1%) were positive for RF and 27 (96.4%) were positive for ACPA titres, highlighting its high specificity in the diagnosis of RA.

DAS 28 score was significantly higher in seronegative group than seropositive group at every visit (p<0.05). The ARCTIC trial[10] also observed in their study that DAS 28 score was higher in seronegative RA (p=0.03) indicating higher inflammatory activity and slow treatment response in the seronegative group. ARCTIC trial[10] also observed that there was no significant difference in DAS 28 score at the end of 24 months, which indicated similar treatment outcome after a period of 2 years though response was slower in initial 6 months in seronegative RA. According to DAS 28 score, out of 28 seropositive patients, 3.6% (n=1) and 39.3% (n=11) achieved remission and low disease activity respectively at the end of 6 months. No patient was in remission or low activity in the seropositive group, highlighting slower treatment response in seronegative patients. But DAS 28 score was similar in ARCTIC trial[10] at the end of 24 months. It concluded that treatment response was slow in initial 6 months in seronegative group, but eventually, both the groups responded equally well to treatment.

At each visit, the HAQ score in the seronegative group was substantially higher than in the seropositive group (p<0.05). Indian adaptation of Health Assessment Questionnaire was used in this study. No other Indian study has used the same for comparing disease activity between the two groups. Higher HAQ score in seronegative RA is indicative of slower treatment response and worse quality of life in seronegative group than seropositive group.

Mean SDAI and CDAI at enrollment, 3rd month and 6th month was significantly higher in seronegative RA than seropositive RA (p<0.05) concluding that disease activity is significantly higher in seronegative RA. None of the other studies used SDAI and CDAI as outcome indicators to compare two subtypes of rheumatoid arthritis. According to SDAI 28.6% (n=8) patients achieved remission and 46.4% (n=13) had low disease activity at the end of 6 month in seropositive group and none of seronegative patient was in remission or low disease activity. 25% (n=7) and 50% (n=14) of patients were in remission and low disease activity respectively in seropositive group as per CDAI and none from seronegative group. This highlights high disease activity and high inflammation along with slower response to treatment in the seronegative group.

Significantly higher Sharp score was observed in seronegative group compared to seropositive group (p<0.05), denoting that more joint inflammation and destruction took place in patients of seronegative arthritis.

However, according to the study by Lena Bugge Nordberg et al.[3], there was no difference in joint damage radiologically in both groups. ARCTIC trial[10] also concluded that there was no significant difference in radiological damage at the end of 2 years. Van der Heijde-modified Sharp score was used in these studies in contrast to Sharp score being used in our study. As the ARCTIC trial[10] was conducted in Norway, further studies are warranted to investigate underlying differences in genetic composition and ethnicity affecting joint inflammation. Yan Geng et al.[11], concluded in their study, using bone erosions score, that radiological disease progressed faster in the seronegative group of patients. However, it is possible that the scales used to measure disease activity of RA encompass pain and disability in older patients not only from RA but also from Osteoarthritis and other age-related changes in soft tissue, thus having a negative impact on pain and remission criteria[13]. This may have a confounding effect on the results, given that the mean age of seropositive patients was found to be significantly lower than that of the patients in the seronegative group.

Limitations

Due to the Covid-19 pandemic, the ideal sample size of 66 patients could not be achieved. Instead, 46 patients were included in the study depending on availability of patients. Patients were followed up only for a period of 6 months and hence long-term outcome could not be compared between two groups. Sharp score based on X-ray, as advised by treating rheumatologist, was used to study the radiological progression of disease, although better investigations like ultrasound or MRI would have given more reliable results. Extra articular manifestations were not studied and compared between the two groups.

Conclusion

Contrary to what was previously believed, patients with seronegative RA have a relatively later disease onset and more active disease at presentation, evident by the greater number of joints affected as compared to those with seropositive RA, which may reflect the requirement of higher number of joints to be involved for seronegative patients to fulfill the 2010 ACR/EULAR classification criteria for RA. Seronegative RA also has a slower treatment response as compared to seropositive RA. However, given the small sample size of this study, these results require validation from larger cohorts. It is possible that delay in labeling the patients as RA due to negative antibodies could lead to delay in initiating the DMARDS in these patients. Physicians should be aware of the considerable clinical burden of seronegative RA, especially at the time of disease onset. The authors would further like to emphasize that seronegative and seropositive RA are probably two distinct disease subtypes driven by different mechanisms and investigating their differences is an important step for reaching an early diagnosis along with the need for an aggressive and individualized treatment.

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