CLINICO-PATHOLOGICAL CORRELATION IN PATIENTS OF RHEUMATOID ARTHRITIS

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Abstract:

Introduction: Rheumatoid arthritis (RA) is an inflammatory arthritis of unknown etiology characterized by a symmetric polyarthritis with varied extra-articular manifestations. Autoantibody production with the formation of immune complexes that fix complement contribute to these extra-articular findings. Among the composite indices to measure disease activity, the DAS-28(Disease Activity Score) score system is the most commonly used parameter to measure the disease activity. **Objectives:** To study correlation of seropositive and seronegative patients with articular manifestations by Disease Activity Score-28. To study correlation of seropositive and seronegative patients with regards to extra-articular manifestations in Rheumatoid Arthritis. **Material and Methods:** This study was conducted on 72 patients of Rheumatoid arthritis as per the 2010 American College of Rheumatology (ACR) classification criteria attending our institute on Out Patient and In-Patient Department basis with age >= 18 years. Patients not giving consent were excluded from study. **Results:** 57 patients were seropositive (SP) and 15 patients were seronegative (SN). Sero-Positive Rheumatoid Arthritis patients manifested more active disease as they had elevated C-Reactive Protein and higher Swollen Joint Count than Sero-Negative Rheumatoid Arthritis. Extra Articular Manifestations were observed in 6 seronegative patients and 32 seropositive patients. Erythrocyte Sedimentation Rate was significantly elevated in the patients with Extra Articular Manifestations. After 6 months, change in mean Tender Joint Count, Erythrocyte Sedimentation Rate and Patient Global Assessment Score was higher in seronegative patients as compared to seropositive patients but statistically not significant. DAS-28 score was significantly reduced in seronegative patients than in the seropositive patients. **Conclusion:** Seropositive patients have more active disease when assessed on the basis of disease activity index at presentation. The seronegative patients showed better response to treatment indicating a low disease activity. The extra-articular manifestations develop frequently in patients with seropositivity. The DAS-28 score can be used as a guide in the suppression of disease activity with Disease Modifying Anti-Rheumatic Drugs.

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KeyWords: Seropositive and Seronegative, Extra-articular manifestations, DAS- 28 score

Introduction:

Rheumatoid arthritis (RA) is perhaps the most common inflammatory arthritis, affecting 0.5% to 1% of the general population worldwide. It is a chronic inflammatory disease of unknown etiology characterized by a symmetric polyarthritis which may also lead to a variety of extra articular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities, which must be managed accordingly.

Serum antibodies to cyclic citrullinated peptides (anti-CCPs) are routinely included with rheumatoid factor (RF) in the diagnostic evaluation of patients with suspected RA and serve as biomarkers of prognostic significance.

The articular manifestations are primarily driven by active synovitis that result in joint swelling, stiffness, pain and palpable warmth. Extra-articular manifestations are observed in up to 50% of patients with RA and portend a poor prognosis. Several composite indices have been developed to assess clinical disease activity like SDAI (Simplified Disease Activity Index), CDAI (Clinical Disease Activity Index), DAS 28 (Disease Activity Score) and RAPID 3(Routine Assessment of Patient Index Data 3).[1] Among these, the DAS 28 score system is the most commonly used parameter to measure the disease activity. The DAS28 is a composite score developed to measure the progress and improvement of Rheumatoid Arthritis.[2] To calculate the DAS28 score:

a) count the number of swollen joints (out of the 28),
b) count the number of tender joints (out of the 28),
c) measure the erythrocyte sedimentation rate (ESR) or C reactive protein (CRP).
d) ask the patient to make a 'global assessment of health' using a 100 mm visual analogue scale.

These results are then fed into a complex mathematical formula:

DAS28=0.56 * sqrt (no of tender joints) + 0.28 * sqrt (no. of swollen joints) + 0.70 log (ESR)+0.014(global assessment in mm).

- A DAS28 value of greater than 5.1 implies high disease activity.
- A DAS28 value between 3.2 and 5.1 corresponds to moderate a moderate disease activity.
- A DAS28 value between 2.6 and 3.2 corresponds to a low disease activity.
- A DAS28 value less than 2.6 corresponds to remission.

The current study was intended to find out the association of the serum antibodies with articular and extra-articular manifestations of RA. Seropositive patients are patients with serum RF or anti-CCP antibodies or both detected in their serum while seronegative patients are patients without antibodies.

Materials and Methods:

Approval to conduct the study from Institutional Review Board was taken. This prospective observational study was conducted at a tertiary care hospital, SVP Hospital Ahmedabad with a sample size of 72 over a period of 18 months.

The selected patients were evaluated with detailed history, general examination, systemic examination, Laboratory and radiological parameters (like Complete haemogram count, Serum Creatinine, ESR, CRP, Rheumatoid factor, Anti-cyclic citrullinated peptide, Chest x-ray and joint x-rays and additional investigations as needed-HRCT Thorax, 2D Echocardiography, ANA Blot, Fluid analysis).

DAS-28 score was calculated on the basis of tender joint count (TJC) and swollen joints count (SJC), ESR and patient's global assessment activity (PGAS) using a 100 mm visual analogue scale. The DAS-28 score was calculated on the initial visit and on a follow up visit after 6 months. The majority of the patients were on DMARDS or steroids.
The statistical analysis was done by EPI INFO.Ver.7 software. Qualitative data was presented as frequency and percentage and compared by chi square test. Quantitative data of two groups was presented with mean and standard deviation and compared by Z test. The "p" values equal to or less than 0.05 was considered as significant.

Results: Total 72 patients were enrolled in this study.

Table 1: Serological status of RA patients

Rheumatoid arthritis		**Frequency**	**Percentage (%)**
Seropositive 57 (79.1%)	ACPA+RF–	9	15.8
	ACPA–RF+	3	4.2
	ACPA+RF+	45	62.5
Seronegative (ACPA–RF–)		15	20.8
Total		72	100.0

(Where 1: ACPA+RF, 2: ACPA–RF+, 3: ACPA+RF+ while 4: ACPA–RF–) (rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)

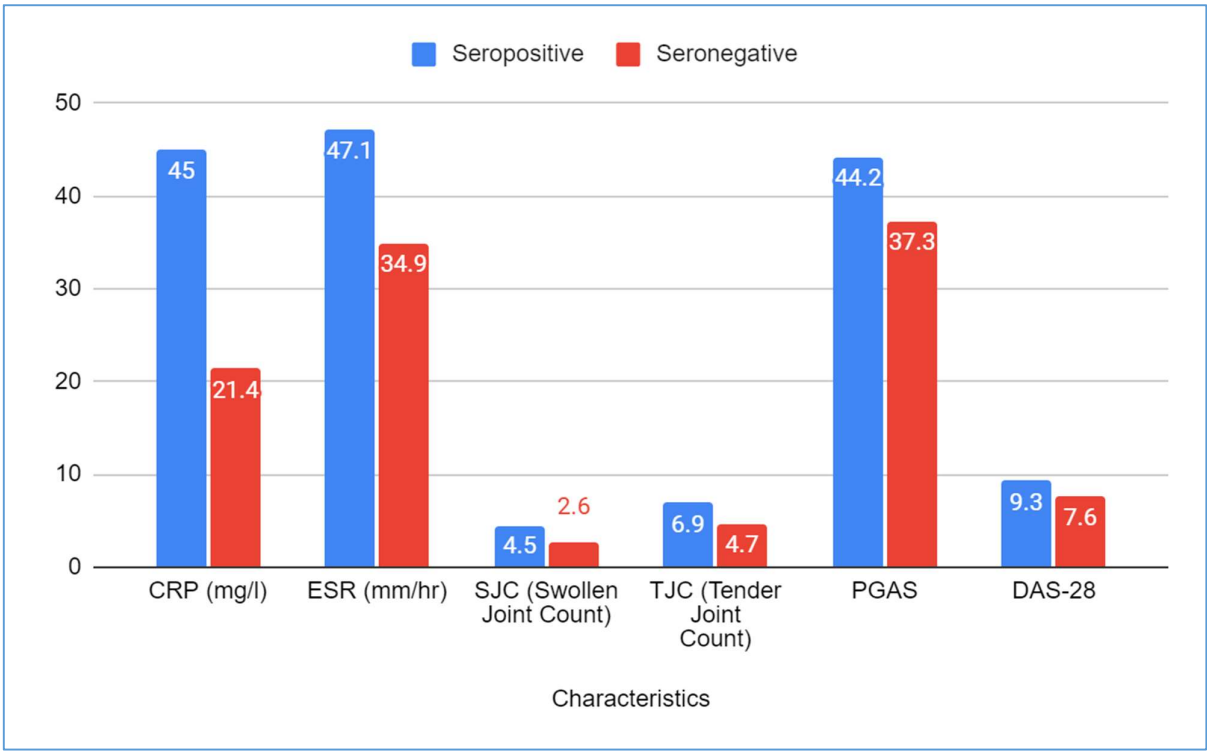
There were 15 seronegative patients (20.8% ACPA–RF–); 9 were ACPA+RF– (15.8%), 3 were ACPA–RF+ (4.2%), and 45 were ACPA+RF+ (62.5%).

Table 2: Comparison of baseline characteristics between Seropositive and Seronegative patients

Characteristics	**Seropositive**		**Seronegative**		**p value**
	Mean	**SD**	**Mean**	**SD**	
CRP (mg/l)	45.0	27.3	21.40	18.60	<0.001
ESR (mm/hr)	47.1	24.04	34.9	22.85	0.08
SJC	4.5	4.62	2.6	2.59	0.04
TJC	6.9	6.02	4.7	4.27	0.20
PGAS	44.2	19.92	37.3	20.86	0.24
DAS-28	9.3	4.16	7.6	3.85	0.15

(Tender Joint Count (TJC), Swollen Joints Count (SJC)

Figure 1: Characteristics of involved joints as per their status in serological test



CRP and SJC were significantly elevated in seropositive patients as compared to seronegative patients (p value < 0.001). ESR was also higher in the seropositive patients than seronegative patients but statistically not significant (p=0.08). Other markers of disease severity like TJC, PGAS and DAS-28 were also increased in seropositive compared to seronegative patients but not statistically significant.

Table 3: Association Between Extra Articular (EA) Features and Serological status in RA patients

Extra-articular features	**RA**		**Total**	**p value**
	Seronegative	Seropositive		
Present	6 (40.0%)	32 (56.1%)	38 (52.8%)	0.24
Absent	9 (60.0%)	25 (43.9%)	34 (47.2%)	
Total	15 (100.0%)	57(100.0%)	72(100.0%)	

Extra-articular manifestations were observed in 6 seronegative patients (40.0%) and 32 seropositive patients (56.1%) (p=0.24).

Table 4: Association between different Extra Articular (EA) Features and Serological status in RA patients

Extraarticular Features	RA		Total	p value
	Seronegative	Seropositive		
Anaemia	6 (40.0%)	21 (36.8%)	27 (37.5%)	0.82
Subcutaneous Nodule	2 (13.3%)	16 (28.1%)	18 (25.0%)	0.24
Osteoporosis	4 (26.7%)	9 (15.8%)	13 (18.1%)	0.32
ILD*	1 (6.7%)	8 (14.0%)	9 (12.5%)	0.44
Secondary sjogren's disease	2 (13.3%)	5 (8.8%)	7 (9.7%)	0.59
LVF	1 (6.7%)	3 (5.3%)	4 (5.6%)	0.83
Vasculitis	0 (0.0%)	1 (1.8%)	1 (1.4%)	0.60
Pericarditis	0 (0.0%)	1 (1.8%)	1 (1.4%)	0.60
Pleural effusion	0 (0.0%)	1 (1.8%)	1 (1.4%)	0.60
Scleritis	0 (0.0%)	1 (1.8%)	1 (1.4%)	0.60
No	9 (60.0%)	25 (43.9%)	34 (58.3%)	
Total	**15 (100.0%)**	**57 (100.0%)**	**72 (100.0%)**	

*ILD: Interstitial Lung Disease

Anaemia, osteoporosis, Secondary sjogren's disease and LVF were commonly observed in seronegative patients as compared to seropositive patients but it was statistically not significant. [SNRA v/s SPRA; Anaemia: 40.0% v/s 36.8%, p =0.82; Osteoporosis: 26.7% v/s 15.8%, p= 0.32; secondary sjogren's disease: 13.3% v/s 8.8%, p= 0.59; LVF: 6.7% v/s 5.3%, p= 0.83]. ILD and Subcutaneous nodules were observed more in subjects of seropositive patients than seronegative patients but statistically not significant. [SNRA v/s SPRA ILD: 6.7% v/s 14.0%, p =0.44; Subcutaneous nodules: 13.3% v/s 28.1%, p = 0.24]. Vasculitis, pericarditis, pleural effusion and scleritis were observed only in seropositive patients (1.4% for each).

Table 5: Comparison of baseline characteristics of the patients with extra-articular manifestations (EAM) and patients without extra-articular manifestations

Characteristics	Extra articular manifestation (EAM)				P value
	Present		Absent		
	Mean	SD	Mean	SD	
SJC	5.0	5.07	3.2	3.30	0.07
TJC	7.3	6.44	5.4	4.73	0.14
CRP	42.8	24.80	36.9	30.05	0.34
ESR	51.0	21.97	37.3	24.75	0.01
PGAS	43.3	21.85	42.2	18.39	0.81
DAS-28	9.6	4.45	8.2	3.69	0.17

ESR was significantly elevated in the subjects with extra-articular manifestations (51.0 ± 21.97 mm/hr) as compared to patients without them (37.3 ± 24.75 mm/hr, p =0.01). SJC was also higher in patients with extra-articular manifestations (5.0 ± 5.07) as compared to patients without them (3.2 ± 3.30) but the difference was near to significant level (p = 0.07). Other disease severity measures such as TJC, CRP, PGAS and DAS-28 were not significantly different between two groups.

Table 6: Change from baseline in measures of disease severity for seropositive and seronegative patients at 6 months follow up:

Characteristics	Seropositive					Seronegative				
	Baseline		After 6 month		p value	Baseline		After 6 Month		p Value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
SJC	4.5	4.62	3.2	3.79	0.10	2.6	2.59	1.3	1.63	0.12
TJC	6.9	6.02	5.1	5.28	0.10	4.7	4.27	2.6	2.5	0.14
ESR (mm/hr)	47.1	24.04	33.7	18.76	0.001	34.9	22.85	19.2	12.05	0.002
PGAS	44.2	19.92	28.3	12.18	<0.001	37.3	20.86	18.6	9.15	0.005
DAS-28	9.3	4.16	7.7	5.47	0.04	7.6	3.85	5.54	2.82	0.04

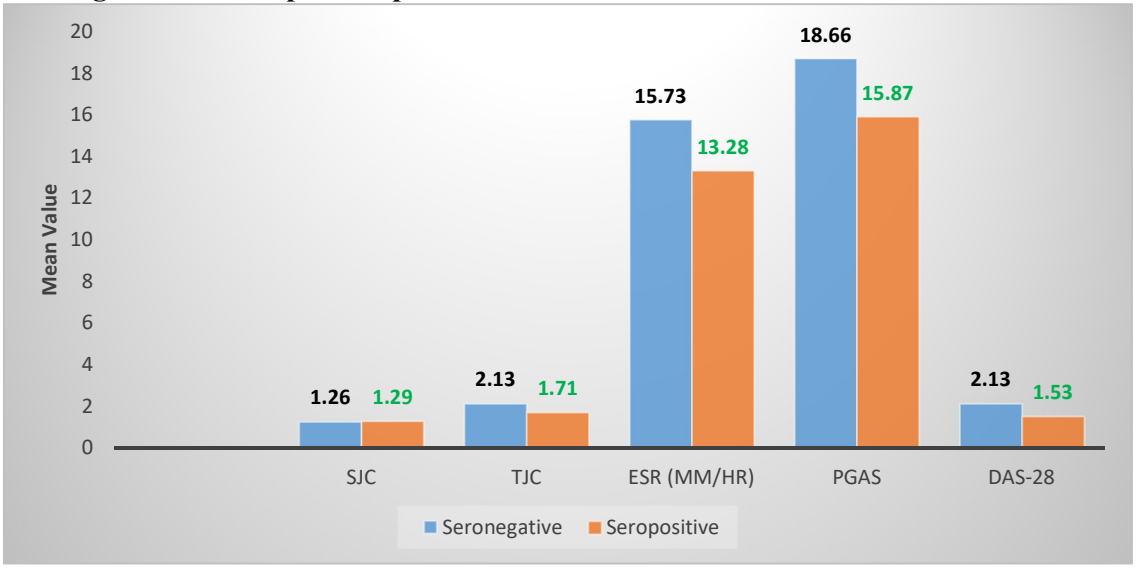
In seropositive patients, mean SJC and TJC after 6 months were lower than baseline value but not statistically significant ESR, PGAS and DAS-28 was significantly reduced after 6 months as compared to baseline.

In seronegative patients, mean SJC and TJC after 6 months were lower than baseline value but not statistically significant. ESR, PGAS and DAS-28 were significantly reduced after 6 months as compared to baseline.

Table 7: Comparison of change in mean of various disease severity parameters in seronegative and seropositive patients

Change in mean after 6 months	Seronegative		Seropositive		p value
	Mean	SD	Mean	SD	
SJC	1.26	1.10	1.29	1.22	0.92
TJC	2.13	1.95	1.71	1.08	0.27
ESR (mm/hr)	15.73	11.60	13.28	10.02	0.42
PGAS	18.66	15.05	15.87	10.56	0.41
DAS-28	2.13	1.20	1.53	0.65	0.01

Figure 2: Comparison of change in mean of various disease severity parameters in Seronegative and seropositive patients



Change in SJC after 6 months was similar in both groups. Changes in TJC, ESR and PGAS were higher in seronegative patients as compared to seropositive patients but statistically not significant. DAS-28 score was greatly reduced by 2.13 ± 1.20 in seronegative patients. This change was significantly higher than in the seropositive patients (1.53 ± 0.65, p =0.01).

Discussion:

In the present study, 72 patients of rheumatoid arthritis were included. There were 15 seronegative patients (20.8% ACPA–RF–); 9 were ACPA+RF– (15.8%), 3 were ACPA–RF+ (4.2%), and 45 were ACPA+RF+ (62.5%). Barra et al.[3]reported 26.0% seronegative patients, 12.0% ACPA+RF–, 17.0% ACPA–RF+, and 45.0% ACPA+RF+.

CRP and SJC were significantly higher in SPRA as compared to SNRA. ESR was also higher in the SPRA subjects than SNRA patients but statistically not significant (p=0.08). Other severity markers were comparable between SPRA and SNRA subjects. This finding was consistent with Mouterde et al.[4] who reported that SNRA had low disease activity at baseline than SPRA patients.

Extra-articular features were observed in 6 seronegative patients (40.0%) and 32 seropositive patients (56.1%) (p=0.24). Cimmino et al.[5] in 587 patients with RA confirmed a higher frequency of EAM in seropositive patients.

Anaemia, osteoporosis, secondary sjogren's disease and LVF were commonly observed in seronegative patients as compared to seropositive patients but it was statistically not significant. ILD and Subcutaneous nodules were commonly observed in seropositive patients as compared to seronegative patients. Vasculitis, pericarditis, pleural effusion and scleritis were observed only in seropositive patients. Most common EAM in the study of Sahatçiu-Meka Vet al.[6] in both subsets were muscular weakness and anemia. Diffuse lung fibroses, central and peripheral nervous system injuries were higher in seropositive patients, while osteoporosis in seronegative. Balbir-Gurman et al.[7]found that pleural effusion was seen with positive rheumatoid factor. Wallberg et al.[8] have found that mortality as a consequence of cardiovascular diseases, was increased in case of seropositive RA.

In the present study, ESR was significantly elevated in the patients with EAM as compared to patients without EAM. SJC was also higher in patients with EAM as compared to patients without EAM but the difference was near to significant level (p = 0.07). Other disease severity measures such as TJC, CRP, PGAS and DAS-28 were not significantly different between two groups.

After 6 months of treatment in SPRA and SNRA patients, mean SJC and TJC did not show any significant difference. However, ESR, PGAS and DAS 28 were significantly reduced after 6 months.

After 6 months of treatment, mean reduction rate of SJC, TJC, PGAS and ESR were similar in both groups. However, DAS-28 score was significantly reduced by in SNRA patients as compared to SPRA patients (p =0.01). Choi ST et al.[9] revealed that both group of patients (SNRA and SPRA) better responded to treatment after 1 year. Barra et al.[3]also stated that treatment was similar between the 2 groups as after 12 months treatment, there was no significant difference in Δ DAS 28 and ΔESR. However, compared to SPRA subjects, SNRA patients had greater mean value change in ΔSJC and ΔTJC.

Conclusion:

Seropositive patients have more active disease when assessed on the basis of disease activity index at presentation as compared to the seronegative patients. The seronegative patients showed better response to treatment which indicate they have a low disease activity going on. The extra-articular manifestations develop frequently in patients who were positive for serum RF or anti-ccp antibodies and those who have an early onset of significant physical disability. But significant differences were not observed with regards to the serological status between the 2 groups. The DAS-28 score can be used as a guide in the suppression of RA disease activity with DMARDs. The extraarticular activity in RA mimics the disease activity going on in joints. Hence, control of the disease activity will help in preventing or controlling the extra-articular manifestations.

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