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# The Relationship between the Levels of Anti Cyclic Citrullinated Protein Antibodies Type2 (ACPA2) and the Severity of Erosive Rheumatoid Arthritis (RA)

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author MJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript, managed the analyses of the study and managed the literature searches. Author KA was supervisor professor. Author HY was assistant supervisor professor. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) is a chronic systemic disease, characterized by autoimmunity. One of the most specific and important diagnostic and prognostic markers of RA are antibodies, Anti Cyclic Citrullinated Protein Antibodies (ACPA).
**Objective:** The purpose of this study was to investigate the association between ACPA (Anti-CCP) levels and radiological damage.
**Methods:** An observational Cross-sectional study included 54 patients fulfilling the ACR-EULAR 2010 criteria for RA, with minimum disease duration of 1 year. Radiographs were scored using a modified Sharp score (Van der Heijde modification of Sharp's score 1989). ACPA levels were determined using immunofluorescence assay.
**Results:** ACPA levels were strongly associated with radiographic severity and there was a significant relationship between ACPA levels and total Sharp score (p=0.0001).

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**Conclusion:** This study concluded that ACPA is an independent severity factor for RA, and our data supports the association between ACPA and radiographic severity.

*Keywords: Anti cyclic citrullinated protein; Type2 (ACPA2); rheumatoid arthritis; chronic systemic disease.*

## ABBREVIATIONS

| | | |
|---|---|---|
| *RA* | *:* | *Rheumatoid Arthritis* |
| *ACPA* | *:* | *Anti citrullinated peptides antibody* |
| *Anti-CCP* | *:* | *Anti Cyclic Citrullinated Protein Antibodies* |
| *ACR* | *:* | *American College of Rheumatology* |
| *EULAR* | *:* | *European League Against Rheumatism* |
| *RF* | *:* | *Rheumatoid Factors* |
| *DMARD* | *:* | *Disease modifying anti rheumatic drugs* |

## 1. INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic systemic disease of unknown origin, characterized by autoimmunity, with the presence of autoantibodies in the blood and joint fluid. One of them is ACPA, which state high disease specificity and may contribute to the pathological process of the disease such as erosiveness and synovitis [1].

If untreated, it usually leads to progressive joint damage and reduction of functional capacity and quality of life [2,3].

Early diagnosis and effective intervention may prevent joint damage, increase the possibility of achieving remission and improve the outcome [4].

Radiography is the most common method for evaluating the existence of structural damage, which results from cumulative disease activity, and determining the effectiveness of treatment by estimating bone erosions and joint space narrowing on conventional radiography [5].

ACPA positive patients are at particularly high risk for developing severe forms of RA and severe radiographic damage, as they are independent severity factor for Rheumatoid Arthritis (RA), and may be very useful biomarkers to predict disease damage [6,7]. There is no research on association between ACPA and structural damage in RA patients in Syria. The objective of the present work was to map the possible association betweenACPA2 and the radiographic severity of the RA patient joints.

## 2. METHODS AND PATIENTS

An observational cross-sectional study included patients (N=54; 45 female, 9 male) with RA (duration more than 1 year) fulfilling the ACR-EULAR 2010 criteria for RA, at the department of Rheumatology, Tishreen University Hospital, Lattakia, Syria. Over 1year period from April 2019 to March 2020, patients having an overlap of RA with other rheumatic disease like gout were excluded from the study.
Radiographs of hand and feet were scored using a modified Sharp score (Van der Heijde modification of Sharp's score).

### 2.1 Antibody Measurement (ACPA/Anti CCP)

Anti CCP were measured, in a blind fashion, at the Immunological laboratory in Tishreen Hospital using an (i-chromα Anti-CCP Plus) kit based on the immunofluorescence assay method. A value of > 5.0 U/ml was considered positive as per the manufacturers' recommendations.

RF was measured using the standard latex agglutination technique.

### 2.2 Measure of Disease Outcome (Structural Damage)

The radiographs were evaluated by two senior rheumatologists in a blind fashion regarding serology and clinical status, with high concordance between them.

Posterior - anterior radiographs of the hands, wrists, and feet were obtained and were examined blind by a two rheumatologists, and graded according to modified Sharp score (Van der Heijde modification of Sharp's score) in comparison with standard reference films.

The scoring system included erosion score: 16 locations in each hand and wrist, and 12 location in each foot were scored. Each location in the hand/wrist and foot was scored individually using a 6-point scale from 0 to 5 based on the number and size of discrete erosions in each location.

Joint space narrowing (JSN) score: 15 locations in each hand and wrist, and 6 locations in each foot were scored using a 5-point scale (from 0 to 4).

The maximum erosion score is 160 for hands and wrists, and 120 for feet. The maximum JNS score is 120 for hands and wrists, and 48 for feet. The total score ranges from 0 to 448 [8].

### 2.3 Statistics

All data were analyzed using the Statistical Package for Social Sciences (SPSS, Version 20). Data were presented in simple measures of frequency, percentage, mean, and standard deviation.

Non-parametric test Mann Whitney used for non-normally distributed data, while correlation between quantitative data were tested using Person Correlation. Results were considered statistically significant with a p-value<5%.

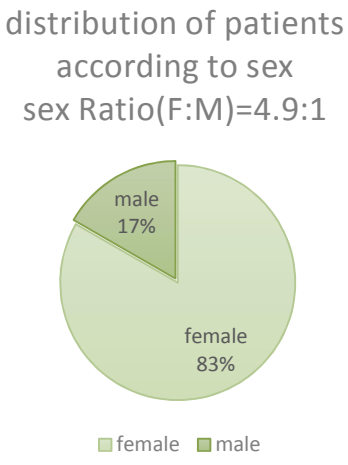


**Fig. 1. Distribution of patients according to sex**

## 3. RESULTS

The cross-sectional study includes 54 patients (45 female, 9 male) with RA, the median (IQR, Interquartile range) age was 50.5 (27-80) yr. The median (IQR, Interquartile range) disease duration was 2.7 year (1-20) yr, the proportion of females in the study was 83.3%. 94.4% of the patients were treated with DMARDs. About 68.5 per cent (n=38) patients were seropositive (positive for RF), and 81.5 per cent (n=44) patients had erosive disease.

On bivariate analysis, patients with erosive disease had a significantly higher disease duration, DMARD naïve period, RF positivity and ACPA titers than patients with non-erosive disease (Table 1).

### 3.1 Association among Radiographic Outcome and Anti-$CCP_2$ (ACPA) Status

In our study ACPA titers were strongly associated with radiographic severity as measured using Sharp van der Heijde score (p-value=0.0001).

## 4. DISCUSSION

- We founded that disease duration, DMARD naïve period, RF titers, and ACPA titers were significantly higher in patients with erosive disease compared with non-erosive disease (Table 1). The most significant and important factor of them all was ACPA titers (p=0.001). This result compatible with the study that was done by Shankar et al [9].
- The long duration without compatible treatment with DMARDs can be attributed in Syria to the lack of medications in the light of the economic situation.
- The most significant difference was in ACPA, RF titers between patients with erosive and non-erosive disease, what confirms that the combination of ACPA and RF are associated with more aggressive articular disease and that the association of both RF and ACPA is independent factor for more severe destructive disease [10,1,6].
- The high positive correlation between ACPA titers and Sharp scores (r=0.7, p=0.0001) (Fig. 2) indicates that ACPA has a significant role in predicting the radiographic and structural damage in rheumatoid patients, and that corresponds with a previous study by Meyer et al. that included 191 patients with recent oncet RA followed for 5 years. Their serum samples were examined for ACPA, and erosions

were scored using Sharp scores modified as described by van der Heijde. Their results suggested that odds of a complete Sharp score increase after 5 years was significantly higher in patients with ACPA [11].

- It confirms that patients with erosive disease had significantly higher ACPA titers than those with non-erosive disease; consequently, high titers of ACPA antibodies are associated with more aggressive disease, as measured by significantly higher Sharp scores[6].
- Finally, this study showed the effect of DMARD naïve period and the disease duration on erosion formation, as the median of DMARD naïve period and the median disease duration were significantly higher in patients with erosive disease compared to patients with non-erosive disease [12].

**Table 1. Characteristics of patients with erosive and non-erosive disease**

| Characteristics | Erosive Disease(n=44) | Non erosive disease(n=10) | Test used | P-value | The statistical significance |
|---|---|---|---|---|---|
| Disease duration (yr) Median (IQR) | 3.5 (1-20) | 2 (1-3) | Mann Whitney | 0.03 | S |
| DMARD Naïve period (month) Median (IQR) | 12 (0-60) | 10.5 (0-24) | Mann Whitney | 0.04 | S |
| RF positivity (%) | 31 (70.45) | 6 (60) | Chi-square | 0.07 | N.S |
| RF positivity (U/ml) Median (IQR) | 47 (1-192) | 30 (10-210) | Mann Whitney | 0.002 | S |
| Median ACPA titer (U/ml) Median (IQR) | 16.2 (5.1-300) | 7.5 (5.4-38) | Mann Whitney | 0.001 | S |

*DMARD: disease modifying anti rheumatic drugs ACPA: anti citrullinated peptides antibody S: Statistically significant N.S: Statistically not significant*

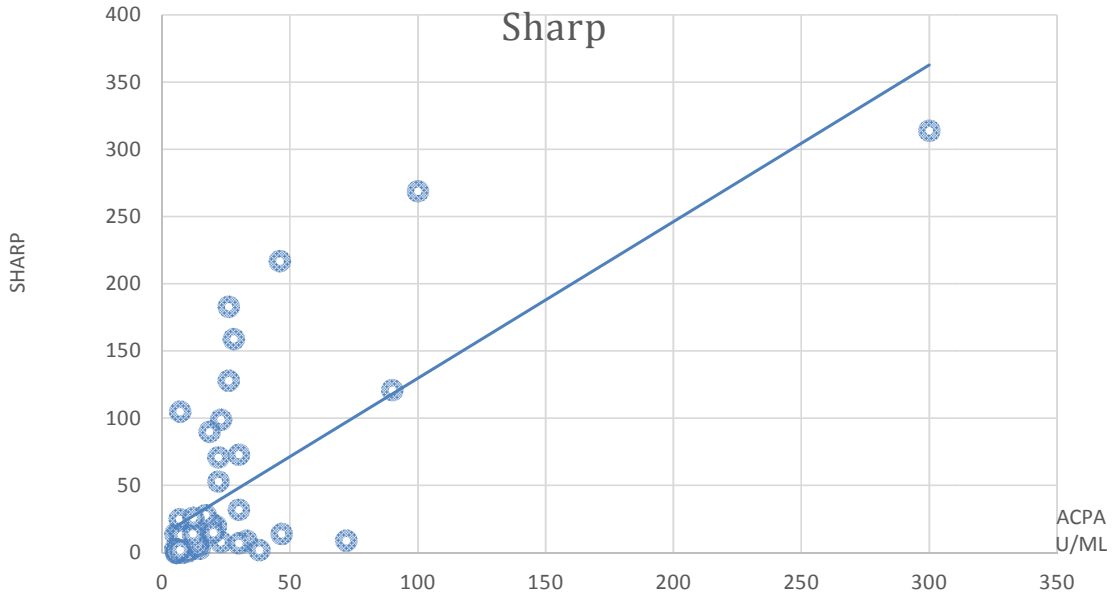


**Fig. 2. Showing high positive correlation between ACPA titers and SHARP scores. R=0.7, p=0.0001**

## 5. CONCLUSION

- ACPA titers are reliable predictors of erosive disease, in addition to the fact of their ability to predict the cumulative structural and radiological damage is superior to RF [6,13].

- ACPA is very important serological marker in identifying patients with worse prognosis who may develop more severe structural damage, and need early aggressive treatment and consequently improves their clinical outcome and reduce joint damage and disability[14].

- Determination of ACPA are extremely valuable marker which is especially useful in RF negative patients with early arthritis who did not yet fulfill the diagnostic criteria of RA [1,14].

## CONSENT AND ETHICAL APPROVAL

This study was reviewed and approved by the moral Committee of the Tishreen University Hospital. As per international standard or university standard guideline participant consent has been collected and preserved by the authors.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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