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Diagnostic value of third generation anti-cyclic citrullinated peptide antibody (Anti-CCP3) assay in rheumatoid arthritis patients: A cross sectional observational study

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Abstract--Objective: To evaluate the efficacy of anti-CCP3 as a diagnostic marker in Egyptian early rheumatoid arthritis patients. Subjects and Methods: A total of 60 rheumatoid arthritis patients and 30 aged and sex matched volunteers participated in the study. Basic demographic, functional and clinical data were collected alongside laboratory assessment of Anti-cyclic citrullinated peptide 3 (Anti-CCP3) by ELISA. Results: Anti-CCP3 level was significantly higher in RA patients compared to controls (p 0.001) .At cut off value 20.65 (U/mL) and AUC 0.950, Anti-CCP 3 could significantly distinguish between RA patients and controls (p 0.001) .The sensitivity and specificity were 83.33%, and 93.33% respectively. Also, Anti-CCP 3 levels significantly correlated with the number of swollen and tender joints (P 0.05), VAS (P 0.05), DAS-28 (P 0.05), m HAQ (P 0.001), bone erosions (P 0.001), and narrow joint space (P 0.001). Conclusion: Anti-CCP3 is a potent diagnostic as well as prognostic laboratory marker and its positivity resulted in more specific identification of RA patients. Moreover, anti-CCP3 is considered the most acceptable

choice for diagnosing early rheumatoid arthritis especially seronegative type, with 83.33% sensitivity and 93.33% specificity.

Keywords--anti-cyclic citrullinated, peptide antibodies, rheumatoid arthritis, diagnostic biomarker, ACPA.

Introduction

Up to 1.0% of the general population is afflicted by rheumatoid arthritis (RA), a chronic inflammatory illness that causes pain, inflammation, and joint damage. Early RA diagnosis and treatment are essential since they can stop the disease's development and permanent joint damage. ^[1] The efficacy of the citrulline-containing epitope is increased by switching from filaggrin, which was utilized in the first generation anti-CCP test, to peptides specifically developed (mimotypes) to detect ACPA in the second and third generations of anti-CCP antibody tests. ^[2] So, the purpose of this study is to evaluate the efficacy of anti-CCP3 as a diagnostic marker in Egyptian early rheumatoid arthritis patients.

Subjects and Methods

Study design & participants

This observational study was conducted on 60 early RA patients diagnosed according to the ACR/EULAR 2010 criteria for diagnosis of rheumatoid arthritis. ^[3] In addition, 30 volunteers who were of similar age and sex served as the control group. All subjects were chosen from Tanta University Hospitals' Rheumatology, Rehabilitation & Physical Medicine Department outpatient clinics. Any Patient with other connective tissue diseases or rheumatic conditions was excluded.

Methods

All participants were subjected to the following assessment:

- **Complete clinical assessment:** including Complete history taking, general and locomotor systems examination.
- **Disease Activity Score (DAS28):** ^[4] this tool can assess the degree of disease activity in 28 joints at a certain point in time. Clinical remission is attained when a patient's DAS28 score drops below 2.6. A DAS28 over 5.1 denotes high disease activity, below 3.2 denotes low disease activity, between 3.2 and 5.1 denotes moderate disease activity, and below 3.2 denotes low disease activity .
- **Assessment of function :** Using the Modified Health Assessment Questionnaire (MHAQ), ^[5] A functional assessment tool, that examines the response as well as accurately describes the patient's typical skills over the course of the previous week and measures also the disease-related impairment, discomfort, and quality of life in RA patients. The outcome should range from 0.0 to 3.0. A score between 0.3 and 1.3 denotes a minor functional loss, 1.3 to 1.8 a moderate functional loss, etc. When a patient's score increased by 1.8, high functional loss was found.

- **Laboratory assessment:** including Complete blood count (CBC), [6] erythrocyte sedimentation rates (ESR), [7] c-reactive protein (CRP), [8] Rheumatoid factor (RF) titer, [8] kidney and liver functions tests, [9] anti-cyclic citrullinated peptide (Anti-CCP). [10]
- **Anti-cyclic citrullinated peptide 3 (Anti-CCP3) :** it was assessed using the Front Biosci (Elite Ed. USA) kit using the enzyme linked immunosorbent assay (ELISA) method. Each participant provided 2 ml of venous blood, and the specimens were kept at -20°C for a longer period of time before the assay to prevent the loss of bioactive human Anti-CCP3. [11]
- **Radiological assessment:** utilizing plain x-rays of the hands and feet to look for bone erosions and narrowing of joint spaces (Ratingen score). [12]

The approval for conducting this work was taken from the Local Ethics Committee at Faculty of Medicine ,Tanta University and was carried out in compliance with the Declaration of Helsinki. Before receiving their signed informed consents to take part in this study, RA patients and controls were informed about all utilized tests.

Statistical Analysis

Statistical Package for Social Science (SPSS)version 19 was used to conduct the study. The results were shown as a mean and standard deviation. The Mann-Whitney U test was used to compare quantitative data that is not regularly distributed, while the Student t test was used to evaluate quantitative data that is normally distributed. The number and percent distributions for qualitative data were computed. Additionally, the Chi-square test was applied to compare qualitative data. Additionally, to examine the relationship between two variables, Pearson's correlation coefficient (r) was determined. It was created a receiver operating characteristic (ROC) curve. The area under the curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and NPV), and cutoff value were provided. P-values (probability values) below 0.05 were regarded as statistically significant.

Results

There were 60 RA patients, with a mean age of (43.83 + 8.78) years, a mean disease duration of (1.30 + 0.96), 48 females and 12 men (F:M 4:1), the majority of whom were active, and a mean DAS28 of (4.34 + 1.04). 10 (16.66%), 10 (16.66%), and 40 (66.67%) of the patients had moderate disease activity, low disease activity, and high disease activity, respectively. The majority of patients (26.7%) were receiving methotrexate and leflunomide combination therapy, which was administered to almost all patients who were taking conventional DMARDs. Table 1 displays the demographic and clinical traits of our patients. At cut off value 20.65 (U/mL) and AUC 0.950, Anti-CCP 3 could significantly distinguish between RA patients and controls (p 0.001) . Anti-CCP 3 was detected with a sensitivity and specificity of 83.33% and 93.33%, respectively, in patients compared to controls (p 0.001). Fig. 1, Table 2,3. Furthermore, in our study, we found a significant positive correlation between anti CCP 3 and tender joints count (r 0.476, P 0.007), swollen joints count (r 0.412, P 0.024), VAS (r 0.684, P 0.001), DAS-28 (r 0.467, P 0.009), mHAQ (r 0.569, p 0.001), ESR (r 0.517, P

<0.001), RF (r 0.478, P 0.007), Bone erosions (r 0.623 , P <0.001), and narrow joint space (r 0.581, p <0.001) was reported in our study . Table 4

Discussion

Even though the majority of RA diagnoses are based on a clinical basis, a number of disease-specific markers are of great additional value in its early detection. [13] Recently, antibodies against variety of citrullinated peptides, including anti-cyclic citrullinated peptide (anti-CCP), are firmly established as sensitive as well as specific diagnostic and prognostic markers for detection of RA. [14] Thirty age- and sex-matched apparently healthy volunteers served as controls in addition to the sixty rheumatoid arthritis patients who were recruited for our study. All subjects underwent thorough history taking & clinical examinations, as well as laboratory evaluation (CBC, ESR, CRP, and RF, renal and liver function tests, anti-CCP and anti-CCP3).

The results of the current study showed that there was no statistically significant difference in age or gender between RA patients and controls (P 0.17). These results are consistent with those of Vos et al., [15] who studied 127 RA patients to evaluate the performance of anti-CCP2 with anti-CCP 3 as a diagnostic marker as well as the two tests combined. Their findings showed that neither age nor gender between the RA and control groups differed significantly. Recently, distinct diagnostic and prognostic biomarkers for RA have been shown to be anti-citrullinated protein antibodies. [16]. Likewise, the outcomes of the existing study revealed that anti-CCP levels in the RA patients were considerably greater than in the controls (P 0.001). These results are in line with those of Mutlu et al., [17] who reported the greatest anti-CCP positive ratio (88.5% for early and 77.6% for established RA) in comparison to controls. The results of Mutlu et al.'s study, [17] which found that anti-CCP had moderate diagnostic performance at a 16 U/ml cutoff with a sensitivity value of 57% and specificity of 92.9%, were slightly different from our findings in that they were observed at a cutoff value of 134U/mL, where the sensitivity and specificity were observed to be 76.67% and 87%, respectively (P 0.001).

The local action of peptidyl arginine deiminases (PAD) on peptide residues that induces citrullination may help to explain the high specificity of anti-CCP antibodies in RA patients. There are at least five genetically distinct kinds of PAD, and monocytes and macrophages from inflamed synovium have been reported to have the PAD2 and PAD4 isotypes. It was believed that during rheumatic synovitis, PAD is released into the extracellular space, causing local citrullination of arginine residues in a number of proteins (vimentin, fibrinogen & fibrin , keratin, fibronectin).[18] Depending on the current study, anti-CCP3 levels in RA patients were found to be considerably greater than in controls (p 0.001). This is consistent with Vos et al.'s finding [15] that the anti-CCP3 level in the RA group was noticeably higher than in the control group. Additionally, similar findings were reported by Mutlu et al. [17] who found that anti-CCP3 statistically more significant in RA patients than in the control group. This may be explained by the anti-CCP3 ELISA test's greater sensitivity, which is due to the presence of a particular peptide with several citrullinated epitopes exhibited in a conformational

structure to maximize epitope exposure and hence immunoreactivity, especially for early RA. ^[19]

In addition, simultaneous testing of the IgG and IgA anti-CCP isotypes is of considerably greater utility and may boost the sensitivity of RA detection. ^[16] One of our study's most notable outcomes is the diagnostic capability of anti-CCP3 for rheumatoid arthritis. Anti-CCP3 demonstrated a great sensitivity and specificity in individuals with early rheumatoid arthritis (83.33 % and 93.33 %, respectively) at a cutoff value of 20.65 U/mL. Vos et al. ^[15] evaluated the diagnostic performance of the anti-CCP3 in patients with RA and reported that the sensitivity for anti-CCP3 was 79.4%, while the specificity was 61.0%. Our results are consistent with their findings. The anti-CCP3 has also been evaluated by Santiago et al., ^[16] and Wu et al., ^[17] who discovered that it is both more sensitive and more specific than CCP2. Additionally, Anjos et al., ^[20] observed that although CCP2 and CCP3 both had good diagnostic performance and the same specificity, CCP3 was 4.3% more sensitive than CCP2 in their investigation of 70 RA patients from Southern Brazil.

Nevertheless, other authors have noted that anti CCP2 and CCP3 assays function fairly similarly in terms of diagnosis ⁽²⁴⁾. The anti-CCP3 epitope diversity idea may be able to explain this. Patients in the pre-diagnostic period have antibodies to only one or a very small number of epitopes, and the titer of anti-CCP3 is connected with the epitope spreading in early RA. Anti-citrullinated protein antibodies (ACPA) assay performance features have been shown to be most strongly influenced by the epitope. ⁽²⁵⁾ Interestingly, the present study exhibited also that there was a positive significant correlation between anti-CCP3 and count of swollen & tender joints, as well as the VAS, DAS-28, mHAQ, ESR, CRP, RF, bone erosions, and narrow joint space. However, Sockalingam, et al. ⁽²⁶⁾ did not discover a relationship between anti-CCP levels and the number of painful or swollen joints in their study. Additionally, no association between anti-CCP antibody levels and ESR or CRP was identified (p value > 0.05). Although, they did discover that anti-CCP levels significantly correlated with rheumatoid factor.

In addition, Onder, et al. ⁽²⁷⁾ observed that anti-CCP positive was not associated with disease duration, VAS, HAQ, ESR, CRP, or haemoglobin, but was associated with higher DAS-28 scores, serum RF positivity, and longer duration of morning stiffness. Aside from RF titers, Shah B.G. et al. ⁽²⁸⁾ discovered no correlation between serum anti-CCP antibodies and DAS-28 or any other parameters of disease activity. Our results closely matched those of Vanichapuntu, et al. ⁽²⁹⁾, who discovered that anti-CCP levels significantly correlated with various inflammation-related parameters but not with DAS 28. Yee et al. ^(30, 31) also conducted a study to assess the relationship between joint erosions in RA patients and antibodies against carbamylated antigens and anti-CCP3 antibodies. Their findings revealed a substantial positive correlation between anti-CCP3 and joint space narrowing and bone erosions. Additionally, Chen et al. ⁽³²⁾ found a strong association between RF and anti-CCP3 in RA patients in a recent study to identify citrullinated antigens for early detection of RA patients.

Moreover, numerous studies have demonstrated that early RA patients who test positive for anti-CCP3 may experience a more erosive course of the illness ⁽³³⁾.

This has been supported by other researchers' investigations, which also claim that anti-CCP3 is a better predictor of an erosive illness course than IgM RF. These results demonstrate that anti-CCP is an independent predictor of radiological damage and illness progression. ⁽³⁴⁾ Consequently, elevated levels of acute phase reactants, bone erosion, and radiological abnormalities are all closely correlated with elevated levels of anti-CCP3. Hence, it might serve as a prognostic indicator in people with early RA.

Conclusion

Anti-CCP3 is a potent prognostic and diagnostic indicator, and the most accurate early detection of RA patients was made possible by its positivity. With 83.33% sensitivity and 93.33% specificity, it is regarded as the most reliable option for diagnosing rheumatoid arthritis, especially the sero-negative type. To obtain more conclusive findings about the unique diagnostic and prognostic performance of anti-CCP3, longer, multicenter prospective studies are necessary. Additionally, more research is required to determine whether anti-CCP3 can be used as a screening test for families of RA patients to identify disease susceptibility.

References

1. Shrivastava AK, Pandey A Inflammation and rheumatoid arthritis. *J Physiol Biochem.* 2013; 69:335-347.
2. Dos Anjos LM, Pereira IA, d 'Orsi E et al: A comparative study of IgG second- and third-generation anti-cyclic citrullinated peptide (CCP) ELISAs and their combination with IgA third-generation CCP ELISA for the diagnosis of rheumatoid arthritis. *Clin Rheumatol*; 28:153-158 (2009).
3. Neogi T, Aletaha D, Silman AJ, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. *Arthritis Rheum.* 2010; 62:2582-2591.
4. Van L, Renskers L. The Disease Activity Score (DAS) and the Disease Activity Score using 28 joint counts (DAS28) in the management of rheumatoid arthritis. *Clin Exp Rheumatol.* 2016; 34:40-44.
5. Ono K, Ohashi S, Oka H, et al. The impact of joint disease on the Modified Health Assessment Questionnaire scores in rheumatoid arthritis patients: A cross-sectional study using the National Database of Rheumatic Diseases by iR-net in Japan. *Mod Rheumatol.* 2016; 26:529-533.
6. Akkececi NS, Cetin GY, Gogebakan H, et al. The C-reactive protein/albumin ratio and complete blood count parameters as indicators of disease activity in patients with Takayasu arteritis. *Med Sci Monit.* 2019; 25:1401.
7. Ying P, Lu T, Xu Y, et al. Preoperative erythrocyte sedimentation rate in patients with rheumatoid arthritis predicts deep vein thrombosis following total knee arthroplasty. *Clin Hemorheol Microcirc.* 2021;1-9.
8. Tyker A, Ventura IB, Lee CT, et al. High-titer rheumatoid factor seropositivity predicts mediastinal lymphadenopathy and mortality in rheumatoid arthritis-related interstitial lung disease. *Sci Rep.* 2021; 11:1-8.
9. Khadim R, Al-Fartusie F. editors. Evaluation of Liver Function and Lipid profiles in Iraqi patients with Rheumatoid Arthritis. *Journal of Physics:*

- Conference Series; 2021; IOP Publishing: DOI:10.1088/1742-6596/1853/1/012040.
10. Chinnadayala SR, Cho S. Electrochemical immunosensor for the early detection of rheumatoid arthritis biomarker: anti-cyclic citrullinated peptide antibody in human serum based on avidin-biotin system. *Sensors*. 2021; 21:124.
 11. Demoruelle MK, Wang H, Davis RL, et al. Anti-peptidylarginine deiminase-4 antibodies at mucosal sites can activate peptidylarginine deiminase-4 enzyme activity in rheumatoid arthritis. *Arthritis Res Ther*. 2021; 23:1-8.
 12. Salaffi F, Carotti M, Beci G, et al. Radiographic scoring methods in rheumatoid arthritis and psoriatic arthritis. *Radiol Med*. 2019; 124:1071-1086.
 13. Hodkinson B, Meyer PWA, Musenge E, et al. The diagnostic utility of the anti-CCP antibody test is no better than rheumatoid factor in South Africans with early rheumatoid arthritis. *Clinical Rheumatology*. 2010;29(6):615-8.
 14. Santiago M, Baron M, Miyachi K, et al. A comparison of the frequency of antibodies to cyclic citrullinated peptides using a third generation anti-CCP assay (CCP3) in systemic sclerosis, primary biliary cirrhosis and rheumatoid arthritis. *Clinical Rheumatology*. 2008; 27(1):77-83.
 15. Vos I, Van Mol C, Trouw LA, et al. Anti-citrullinated protein antibodies in the diagnosis of rheumatoid arthritis (RA): diagnostic performance of automated anti-CCP-2 and anti-CCP-3 antibodies assays. *Clinical Rheumatology*. 2017; 36(7):1487-92.
 16. Santiago M, Baron M, Miyachi K, Fritzler MJ, Abu-Hakima M, Leclercq S et al. A comparison of the frequency of antibodies to cyclic citrullinated peptides using a third generation anti-CCP assay (CCP3) in systemic sclerosis, primary biliary cirrhosis and rheumatoid arthritis. *Clin Rheumatol* 2008; 27(1):77-83.
 17. Wu R, Shovman O, Zhang Y, Gilburd B, Zandman-Goddard G, Shoenfeld Y. Increased prevalence of anti-third generation cyclic citrullinated peptide antibodies in patients with rheumatoid arthritis and CREST syndrome. *Clin Rev Allergy Immunol* 2007; 32(1):47-56.
 18. Luis Caro-Oleas J, Fernández-Suárez A, Reneses Cesteros S, Porrino C, Núñez-Roldán A, Wichmann Schlipf I. Diagnostic usefulness of a third-generation anti-cyclic citrulline antibody test in patients with recent-onset polyarthritis. *Clin Chem Lab Med* 2007; 45(10):1396-401.
 19. Lutteri L, Malaise M, Chapelle JP. Comparison of second- and third-generation anti-cyclic citrullinated peptide antibodies assays for detecting rheumatoid arthritis. *Clin Chim Acta* 2007; 386(1-2):76-81.
 20. Szekanecz Z, Szabó Z, Zeher M, et al. Superior performance of the CCP3.1 test compared to CCP2 and MCV in the rheumatoid factor-negative RA population. *Immunol Res*. 2013;56(2-3):439-43.
 21. Mutlu N, Bicakcigil M, Tasan DA, et al. Comparative performance analysis of 4 different anti-citrullinated protein assays in the diagnosis of rheumatoid arthritis. *J Rheum.* 2009;36(3):491-500.
 22. Predeteanu D, Varzaru L, Balanescu A, et al. Anti-cyclic citrullinated peptide antibodies--activity markers in rheumatoid arthritis. *Journal of medicine and life*. 2009;2(1):36-41.
 23. Swart A, Burlingame RW, Gürtler I, et al. Third generation anti-citrullinated peptide antibody assay is a sensitive marker in rheumatoid factor negative rheumatoid arthritis. *Clinica chimica acta*. 2012;414:266-72.

24. Sockalingam S, Khuan CS and Sthaneshwar P. Prevalence of anticyclic citrullinated peptide antibodies in Malaysian rheumatoid arthritis patients and its correlation with disease activity. *Int. J. Rheum.* 2009, 12: 211-5.
25. Onder B, Kurtaran A, Kimyon S, Selcuk B and Akyuz, M. Association of anti-CCP positivity with serum ferritin and DAS-28. *Rheumatol Int.*2009;30: 223-7.
26. Shah B G , Quershi H.J, Zafar U. Serum Anti-CCP Antibody and its Correlation with Disease Activity in Local Pakistani Rheumatoid Arthritis Patients. *Pak J. Med and Health Sci.* 2014, (8); 1041-44.
27. Vanichapuntu M, Phuekfon P, Suwannalai P, Verasertniyom O, Nantiruj K. and Janwityanujit, S. Are anti-citrulline autoantibodies better serum markers for rheumatoid arthritis than rheumatoid factor in Thai population? *Rheumatol Int.*2010;30: 755-9.
28. Rydell E, Forslind K, Nilsson J-Å, et al. Predictors of radiographic erosion and joint space narrowing progression in patients with early rheumatoid arthritis: a cohort study. *Arthritis research & therapy.* 2021;23(1):1-13.
29. Yee A, Webb T, Seaman A, et al. Anti-CarP antibodies as promising marker to measure joint damage and disease activity in patients with rheumatoid arthritis. *Immunologic research.* 2015;61(1):24-30.
30. Chen Z, Fang W, Qin Y, et al. Citrullinated Antigens with Multiple Citrulline Similar Motif in the Diagnosis of Rheumatoid Arthritis: A Preliminary Single-Center Study. *Journal of Immunology Research.* 2021;2021.
31. Kroot E, De Jong B, Van Leeuwen M, et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with onset rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 1831-35 22.
32. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). *Ann Rheum Dis* 2004; 63:1090-95

Table 1
Demographic & Clinical characteristics of the RA patients

Variables	Range	Mean ± S.D.
Age(years)	25-60	43.83 ± 8.78
Duration of disease (years)	1-2.5	1.30 ± 0.9
Number of tender Joints	0-20	3.27 ± 4.52
Number of swollen Joints	0-20	1.67 ± 3.72
VAS (1-100) mm	30-87	52.83 ± 14.76
DAS 28	2.6-7.87	4.34 ± 1.04
mHAQ	0.1-2.2	1.15 ± 0.59
Morning stiffness(min.)	30-120	54.50 ± 19.49

VAS: Visual analog scale, DAS-28: Disease activity score-28, mHAQ: Modified health assessment questionnaire, RA: Rheumatoid arthritis.

Table 2
Anti-CCP3 levels in RA patients and controls

		Range	Median - IQR	Mann Whitney Z	p. value
Anti CCP 3 (U/mL)	Patients	18.52-29.52	23.49-5.19	-4.87	<0.001*
	Controls	14.29-22.63	17.64-1.86		

RA: Rheumatoid arthritis, Anti-CCP 3: Anti-cyclic citrullinated peptides 3rd generation, *Statistically significant as $P \leq 0.05$

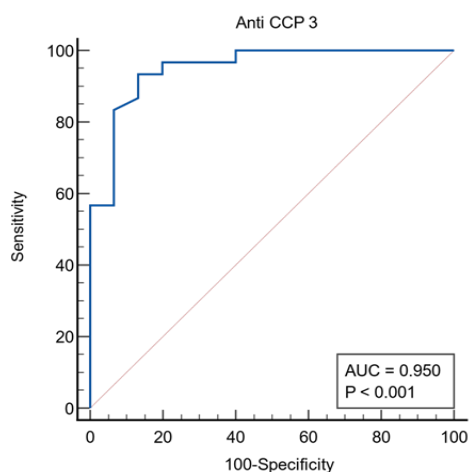


Figure 1. ROC curve of anti-CCP 3 in RA patients

Table 3
Sensitivity and specificity of anti-CCP 3 in RA patients

Anti CCP 3		Patients	Controls	Total	
Negative	N	4	26	30	
	%	6.67	86.67	33.33	
Positive	N	56	4	60	
	%	93.33	13.33	66.67	
Total	N	60	30	90	
	%	100	100	100	
Chi-square	X ²	25.31			
	P-value	<0.001*			
Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
20.65	83.33	93.33	96.2	73.7	88.33

RA: Rheumatoid arthritis, Anti-CCP 3: Anti-cyclic citrullinated peptides 3rd generation, PPV :Positive predictive value ,NPV :Negative predictive value, *Statistically significant as $P \leq 0.05$

Table 4
Correlation between demographic data (age), clinical, laboratory, radiological data versus anti-CCP3

Variables	Anti CCP 3	
	r	p-value
Age(years)	0.143	0.349
Duration of disease (years)	0.03	0.88
Number of tender Joints	0.476	0.007*
Number of swollen Joints	0.412	0.024*
VAS (1-100)	0.684	<0.001*
DAS-28	0.467	0.009*
mHAQ	0.569	0.001*
ESR (mm/h)	0.517	<0.001*
CRP	0.496	0.005*
RF	0.478	0.007*
Bone erosions	0.623	<0.001*
Narrow joint space	0.581	<0.001*

Anti-CCP 3: Anti-cyclic citrullinated peptides 3rd generation, VAS: Visual analog scale, DAS-28: Disease activity score-28, mHAQ: Modified health assessment questionnaire, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, *Statistically significant as $P \leq 0.05$