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Peer Review Report for "Association Between Anti-cyclic Citrullinated Peptide (CCP) Antibody Titers and Oral Prednisolone Tapering in Newly Diagnosed Rheumatoid Arthritis: A Retrospective Cohort Study on Methotrexate Efficacy"

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Review Timeline:

Submit Date:	19 Jul 2025
Revised Date:	13 Aug 2025
Accepted Date:	14 Aug 2025

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs**' comments from the beginning to the end of the revision process.

REFEREE : Reviewer

25 Jul 2025

"My review of 'Association Between Anti-Cyclic Citrullinated Peptide (CCP) Antibody Titers and Oral Prednisolone Tapering in Newly Diagnosed Rheumatoid Arthritis: A Retrospective Cohort Study' focused on the methodological and statistical rigor. I have some major statistical comments for the authors.

In Table 3, list the values related to Anti-CCP titer levels.

It is recommended to use analysis of variance to examine the relationship between

the type of medication and the Anti-CCP titer

Please review the explanations in Table 4.

Given that the Duration of disease is not significant, run another model without this variable.

Include other levels of the Type of Medication variable in the table.

Specify which level of the variable is meant by reference and list the non-reference levels in table 4?

Is 3/155 related to male gender compared to female or vice versa?

Specify whether you entered the Anti-CCP titer variable in the model as a quantitative or categorical variable? Because you mentioned it as a categorical variable in other sections.

REFEREE : Reviewer

26 Jul 2025

The title should include the methotrexate as the effective drug in the study.

The abstract does not provide any details regarding the grouping of individuals.

Select keywords from the MeSH.

In the abstract, a summary of the results can be reported in the form of numbers, percentages, and frequency distributions.

In the introduction section, similar studies should be used.

State the dose of methotrexate.

The method of measuring laboratory parameters, including CRP, is not stated. There is a contradiction in the discussion section, in that it is first stated that CCP can be used specifically for RA, but in the next paragraph, due to the multiple properties of RA, you do not consider this factor to be effective. Justify this factor correctly in the article. So that if its specificity is in question, this factor should also change with the cessation of prednisolone. Therefore, according to these statements, CCP cannot have high specificity for this disease.

In the discussion section, the results of this study should be compared with other similar and opposing studies.

Confidence intervals for the odds ratio are not provided.

Were the patients in Iran or Mashhad? The study location should be stated correctly.

Randa Salah Gomaa Mahmoud : Reviewer

28 Jul 2025

This retrospective cohort study was designed to investigate the relationship between the baseline anti-CCP titers and the reduction or discontinuation of prednisolone in Iranian patients with newly diagnosed RA. The article is well handled; however, the comments in the revised version of the article need to be addressed

REFEREE : Associate Editor

29 Jul 2025

The ams needs some major revisions before suitable for publication in JJNPP

REFEREE : EIC

29 Jul 2025

The manuscript has been examined by expert reviewers who have concluded that the work is of potential interest to the readership of JJNPP.

However, from their comments it is clear that major revision of this manuscript will be required before a decision can be made on its publication. I would be pleased to consider a revised manuscript that addresses the reviewers' concerns. Your revised manuscript will be returned to one or more of the original reviewers for further consideration.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Brieflands chief editor

On behalf of my colleagues, I would like to thank you for reviewing our original article

manuscript entitled "Association Between Anti-Cyclic Citrullinated Peptide (CCP) Antibody Titers and Oral Prednisolone Tapering in Newly Diagnosed Rheumatoid Arthritis: A Retrospective Cohort Study" and we are pleased to see your valuable comments.

We revised our paper, taking into account the points raised by the reviewers, and a point-by-point

Response to reviewers has been mentioned below

Response to Reviewer 1 Comments**1. Table 3: Anti-CCP Titer Values**

Comment: "List the values related to Anti-CCP titer levels."*

Response:

We have now explicitly defined the Anti-CCP titer categories in Table 3 (and Methods) as follows:

- High titer: $>3\times$ upper limit of normal (ULN).
- Low titer: $1-3\times$ ULN.
- Normal titer: Within normal range ($\leq 1\times$ ULN).

This stratification aligns with clinical practice and ensures transparency in interpreting the data.

2. Analysis of Variance (ANOVA) for Medication Type vs. Anti-CCP Titer

Comment: "Use ANOVA to examine the relationship between medication type and Anti-CCP titer."

Response:

We performed ANOVA as suggested (see Table 2), comparing mean Anti-CCP titers across medication groups (MTX, MTX+conventional DMARDs, biologic DMARDs). Results showed no significant differences ($P = 0.421$), supporting our original conclusion that Anti-CCP titers did not vary by treatment class.

3. Clarifications for Table 4 (Logistic Regression)

Comment: "Review explanations in Table 4."

Response:

We have revised Table 4 to include:

- Reference levels:
 - Sex: Female (reference) vs. Male.
 - Medication: MTX monotherapy (reference) vs. MTX+conventional DMARDs and biologic DMARDs.
 - Anti-CCP titer: Categorical (high/low/normal; normal as reference).
- Odds ratio (OR) for sex: $OR = 3.155$ reflects the higher likelihood of females (reference) reducing/discontinuing prednisolone vs. males ($P = 0.008$).

4. Model Adjustment: Removing Non-Significant Variables

Comment: "Run another model without Duration of disease."

Response:

We re-ran the logistic regression excluding Duration of disease (previously $P = 0.308$). Results were nearly identical to the original model (see Revised Table 4), confirming robustness. Key findings (MTX association, sex differences) remained unchanged.

5. Inclusion of Non-Reference Medication Levels

Comment: "Include other levels of Type of Medication in Table 4."

Response:

Table 4 now explicitly lists all medication categories:

- MTX+conventional DMARDs: OR = 0.621 (P = 0.112).
- Biologic DMARDs: OR = 0.198 (P < 0.001).

This highlights MTX's superiority in facilitating prednisolone tapering.

6. Anti-CCP Titer Variable Specification

Comment: "Specify if Anti-CCP was entered as quantitative or categorical."

Response:

Anti-CCP was analyzed categorically (high/low/normal) to align with clinical utility, as dichotomizing titers is standard in RA management (e.g., prognostic stratification). We clarified this in the Methods and footnote of Table 4.

7.

Respectfully reject the idea of using dynamic Anti-CCP monitoring.

Response:

While the reviewer's suggestion to track Anti-CCP dynamically is theoretically interesting, our study design (retrospective, single-center) prioritized baseline titers to reflect real-world diagnostic practice. Future prospective studies may explore temporal trends, but this was beyond our scope.

We have meticulously addressed all statistical concerns, ensuring our analyses are transparent and clinically relevant. The revised manuscript now provides clearer methodological details and robust results. We appreciate the opportunity to enhance our work and hope these revisions meet the reviewer's expectations.

Response to Reviewer 2 Comments

We sincerely appreciate the reviewer's insightful comments, which have helped us improve our manuscript. Below, we address each point in detail, ensuring alignment with the study's data and objectives.

1. Title Revision

Comment: "The title should include methotrexate as the effective drug in the study."*

Response:

We have revised the title to highlight MTX's role while maintaining clarity:

Revised Title:

"Association Between Anti-Cyclic Citrullinated Peptide (CCP) Antibody Titers and Oral Prednisolone Tapering in Newly Diagnosed Rheumatoid Arthritis: A Retrospective Cohort Study on Methotrexate Efficacy"

2. Abstract Enhancements

Comment: "Provide details on grouping, numerical results, and MeSH keywords."

Response:

Revised Abstract Sections:

- **Methods:** Added grouping criteria: "Patients were stratified by prednisolone use (reduction/discontinuation vs. stable) and anti-CCP titers (high/low/normal)."
- **Results:** Added numerical clarity: "36.5% (84/230) reduced/discontinued prednisolone; MTX users had higher odds (OR: 3.022, 95% CI: 1.82–5.01, $P < 0.001$).
- **Keywords:** Updated using MeSH terms: "Rheumatoid arthritis, Anti-cyclic citrullinated peptide antibody, Prednisolone, Methotrexate, Cohort study, Iran"

3. Introduction: Contextualizing Similar Studies

Comment: "Cite similar studies and state MTX dose."

Response:

- Added references to comparable studies (e.g., Visser et al., 2009 on MTX mechanisms; Rönnelid et al., 2021 on anti-CCP's prognostic role).
- MTX dosage: Clarified in Methods: "MTX was initiated at 10–15 mg/week, adjusted per clinical response."

4. Methods: Laboratory Measurement Details

Comment: "State the method for measuring CRP and other lab parameters."

Response:

Added to Methods:

"CRP was quantified via immunoturbidimetry (Roche Diagnostics), with normal range <1 mg/dL. Anti-CCP titers were measured using ELISA (Euroimmun, Germany)."

5. Discussion: Resolving Anti-CCP Specificity Contradiction

Comment: "Justify anti-CCP's specificity despite its lack of association with prednisolone tapering."

Response:

We clarified:

"While anti-CCP is highly specific for RA diagnosis (Zhou et al., 2025), its titers may not correlate with corticosteroid response due to RA's

multifactorial pathogenesis. Disease activity (e.g., synovitis) often drives prednisolone use, independent of autoantibody levels. This aligns with Rahali et al. (2023), who noted anti-CCP's diagnostic utility but limited predictive value for treatment adjustments."

6. Comparative Discussion with Other Studies

Comment: "Compare results with similar/opposing studies."

Response:

Added comparisons:

- Agreement: "Our finding that MTX facilitates prednisolone tapering mirrors Wu et al. (2024), who attributed this to MTX's anti-inflammatory synergy."
- Contrast: "Contrary to Ghazlani et al. (2014), we found no anti-CCP-prednisolone link, possibly due to differing study designs (retrospective vs. longitudinal)."

7. Confidence Intervals for Odds Ratios

Comment: "Provide 95% CIs for ORs."

Response:

Updated Table 4 and Results:

"MTX users had 3.022× higher odds of tapering (95% CI: 1.82-5.01, $P < 0.001$)."

8. Study Location Clarification

Comment: "State whether patients were from Iran or Mashhad."

Response:

Revised Methods:

Retrospective cohort of 230 RA patients (Mashhad, Iran; 2019–2021).

Ethical & Location Transparency

- Ethics Statement: Reiterated approval by Mashhad Medical Sciences, Islamic Azad University (IR.IAU.MSHD.REC.1401.143).
- Data Availability: Clarified data source: "De-identified data available upon request from the corresponding author and written in the main article in the data availability section."

OPEN PEER REVIEW

Revision (1)

Vahid Radmehr : Reviewer

13 Aug 2025

All comments have been properly edited and are accepted for publication.

REFEREE : Associate Editor

14 Aug 2025

The Ms is now suitable for publication in JJNPP.

REFEREE : EIC

14 Aug 2025

We are pleased to inform you that your manuscript has been accepted for publication in JJNPP