PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review and meta-analysis of the risk of rheumatoid arthritis-associated interstitial lung disease related to anti-cyclic citrullinated peptide (CCP) antibody
AUTHORS	Kamiya, Hiroyuki; Panlaqui, Ogee

VERSION 1 – REVIEW

REVIEWER	Yutaro Nakamura Hamamatsu University School of Medicine
REVIEW RETURNED	02-Jul-2020

GENERAL COMMENTS	The authors well statistically reviewed the significance of anti-CCP antibody in RA-ILD. They described the limitation of this study as well. The article will be interesting for the readers. One thing, bronchiolar disease is also reported to be an important association with CCP antibody. Authors may analyze some data or at least discuss or describe this issue in some part.

REVIEWER	Pierre-Antoine Juge Rheumatology Department, Hôpital Bichat Claude Bernard, Inserm UMR1152, Paris, France
REVIEW RETURNED	20-Sep-2020

GENERAL COMMENTS	This study assesses the association between anti-CCP and ILD among RA through a systematic review and meta-analysis of previous cross-sectional and case-control studies. The topic of this meta-anaylis is interesting as the question of an association between ACPA and RA-ILD have been widely discussed. Results of the numerous previous studies are contradictory. the rigorous methodology and the constancy of the signal are the strong points of this study. However there are several limitations that question the interpretation of the study. 1. I am surprised by the low number of studies selected for this review. One reason is that selection criteria are very strict in order to focus on anti-CCP and RA-ILD. Author have only selected studies that reported "anti-CCP positivity" and studies reporting ACPA positivity have been excluded. Outside anti-CCP, other ACPA are usually not tested in clinical routine and many rheumatologic teams use the term ACPA for anti-CCP dosage. If the wish of the authors to perform a anti-CCP specific meta-analysis is more than welcomed, it may have lead to the exclusion of many studies with large population that could have reinforce the strength of this meta-analysis. If authors decide not to include studies that do not precise

	how ACPA status was defined, they should state this limitation in their discussion. 2. One of the main limitation of this study is the heterogeneity of the included studies. If authors have estimated this limitation using appropriate statistical tools, this should be more specifically stated in the discussion and the conclusion part. 1. Anti-CCP positivity and level depends on the temporality of the dosage, received treatment... Authors did not look fo this information in the selected studies. 2. It is stated that patients fulfilled 1987 ACR or 2010 ACR/EULAR criteria for RA but one of the major difference between those 2 classification criteria is that ACPA positivity and high titers are part of 2010 ACR/EULAR criteria and are most of the time required to fulfill the criteria. Thus the use of different criteria for RA may have led to selection bias. 3. ILD screening strategy have not been collected in the selected studies. The ILD definition (symptomatic/non symptomatic) the screening tool (self report, Xray, CT scan, PFTs...) and the temporality of the screening strategy may have influence the classification of RA patients (ie RA-ILD/ RA without ILD). Such bias should have been discussed by the author and ILD definition used by the different studies should have been stated by the authors in Table 1. 4. Another evidence of the heterogeneity is the differences between the RA-ILD and the RA without ILD populations among the selected studies. For example , in Table 1, disease duration varies from 108 months to 14.9 years. ACPA positivity in the RA without ILD population varies from (I guess) 49.1% to 95.8%. A comparison of such different population lead to question the interpretation of the results. Furthermore, a RA population with only 49.1% of patients being positive to anti-CCP is questionable. All those limitation should be more strongly discussed in the discussion and should have lead the authors to lighten their conclusion. I would not say "This systematic review and meta-analysis demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD" but "This systematic review and meta-analysis suggests that the presence of anti-CCP antibody was significantly associated with RA-ILD" and I would lighten the conclusion of the abstract as well. 4. Regarding the flow chart of the study (Figure 1), I do not understand why the authors stopped their chart at 33 studies selected as only 29 studies were included at last. I would add why 4 studies were excluded at the end of the analysis. 5. The authors took into consideration only univariate results because the multivariate results varied deeply on the selected covariate. However, because most of theses studies are cross sectional or case-control studies with a large risk of bias, I wonder if the univariate results may not induce a big limitation on the results. This should be more discussed by the authors. Moreover ion the univariate results, meta-analyses of 17 out of 20 studies were shown in Figure 2 and 12 out of 18 studies were shown in Figure 3. I have not clearly understood why 3 studies were ruled out in Figure 2 and 6 in Figure 3. 6. The authors clearly stated that because of the high positivity frequency of the anti-CCP positivity itself, it could not be enough to

	stratify RA patients according to ILD risk. I would insist on the need to explore composite score that could use clinical features and biological markers to determinate RA patients with high risk to develop ILD. Minor comments : It is stated that included patients age ranged from 45.89 and 63.9. Is it the age at RA diagnosis? ILD diagnosis? Inclusion? Please specify. Table 1. Please specify Disease duration : RA (I guess) or ILD. Please add the ILD and RA criteria used by the studies. Table 2. Proportion and Titres of anti-CCP antibody : please specify which number is RA-ILD and which is RA without ILD.

REVIEWER	Giuseppe Gorini ISPRO, Florence, Italy
REVIEW RETURNED	22-Oct-2020

GENERAL COMMENTS	This is a meaningful and well conducted review and meta-analisys on the risk of rheumatoid arthritis-associated interstitial lung disease related to anti-cyclic citrullinated peptide (CCP) antibody. I suggest that this paper is already ready for publication, with no changes.

REVIEWER	Masanori Nojima The University of Tokyo, Japan
REVIEW RETURNED	23-Oct-2020

GENERAL COMMENTS	The meta-analysis by Kamiya et al. does not show any major problems in the statistical analysis, but there are some points to be addressed as follows. 1. As the authors noted, SMD for quantitative evaluation of antibody titer is difficult to be interpreted. I suggest that studies using the same measurement method should be grouped together and a subgroup analysis of studies using mean differences without variable transformation should be conducted (or, if necessary, depending on the distribution, with appropriate variable transformations such as logarithmic transformation). In many studies, the average values in the RA-ILD group appear to be around 200 and it was around 100 in the non-RA-ILD group (with a few exceptions). If there is a scientific basis for calculating the combined value of these studies, subgroup analyses should be performed as described above. 2. The odds ratio of the multivariate analysis in the Rocha-Munoz et. al. might be a odds ratio for the antibody titer (per 1-unit change) rather than the positivity. The point estimate was small and the confidence interval was too narrow for the number of cases. 3. Is the antibody titer not affected by sex, age or other factors (in other words, are they not a confounding factor)? Is there an association between the variability of the results and the differences in the target population of each study?

VERSION 1 – AUTHOR RESPONSE

Reviewer1
"Bronchiolar disease is also reported to be an important association with CCP antibody. Authors may analyse some data or at least discuss or describe this issue in some part."

Following the comment, this issue was discussed in the Discussion section (5th-10th line on page 20).

Reviewer2
1. "If the wish of the authors to perform an anti-CCP specific meta-analysis is more than welcomed, it may have led to the exclusion of many studies with large population that could have reinforced the strength of this meta-analysis. If authors decide not to include studies that do not precise how ACPA status was defined, they should state this limitation in their discussion".

Following the comment, this limitation was clearly described in the Discussion section (the last sentence on page 20).

2. "One of the main limitations of this study is the heterogeneity of the included studies. If authors have estimated this limitation using appropriate statistical tools, this should be more specifically stated in the discussion and the conclusion part".
a) Temporality and received treatment
b) Criteria for RA
c) ILD screening strategy
d) Disease duration and ACPA positivity in the RA without ILD population

Following the comment, we additionally conducted meta-regression analysis and statistically assessed the effect of all of these factors (3rd-7th line on page 11 in the Methods section and 11th-15th line on page 16 in Result section). Furthermore, the heterogeneity was more strongly discussed as a major limitation of this study (11th-19th line on page 20 in the Discussion section and page 21 in the Conclusion section).

3. "All those limitations should be more strongly discussed in the discussion and should have led the authors to lighten their conclusion. I would not say "This systematic review and meta-analysis demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD" but "This systematic review and meta-analysis suggested that the presence of anti-CCP antibody was significantly associated with RA-ILD" and I would lighten the conclusion of the abstract as well".

Following the comment, the conclusion in both the main text and the abstract was revised as such.

4. "Regarding the flow chart of the study (Figure 1), I do not understand why the authors stopped their chart at 33 studies selected as only 29 studies were included at last. I would add why 4 studies were excluded at the end of the analysis",

Following the comment, the flow chart was revised (Figure 1).

5. "The authors took into consideration only univariate results because the multivariate results varied deeply on the selected covariate. However, because most of these studies are cross-sectional or case-control studies with a large risk of bias, I wonder if the univariate results may not induce a big limitation on the results. This should be more discussed. Moreover, on the univariate results, meta-analyses of 17 out of 20 studies were shown in Figure 2 and 12 out of 18 studies were shown in

Figure 3. I have not clearly understood why 3 studies were ruled out in Figure 2 and 6 in Figure 3".

Following the comment, the limitation of univariate results was added in the discussion section (14th-18th line on page 21 in the Discussion section). The reason why some studies were excluded from meta-analysis was also added in the result section (the last sentence on page 13 and the last sentence in the Univariate result section on page 14).

6. "I would insist on the need to explore composite score that could use clinical features and biological markers to determine RA patients with high risk to develop ILD".

Following the comment, the need to combine clinical features and biological markers to better identify a group with a higher risk of ILD was additionally described and emphasized in the discussion section (the last sentence on page 19 in the Discussion section).

Minor comments:
1. It is stated that included patients age ranged 45.8 and 63.9. Is it the age at RA diagnosis? ILD diagnosis? Inclusion? Please specify.

Following the comment, it was specified as "at inclusion" in the main text (the last two lines on page 12) and Table 1.

2. Table 1.
Please specify Disease duration.

Following the comment, it was specified in Table 1.

Please add the ILD and RA criteria used by the studies.

Following the comment, it was specified in e-Table 1.

3. Table 2. Proportion and titres of anti-CCP antibody: please specify which number is RA-ILD and which is RA without ILD.

Following the comment, it was specified in the foot note of Table 2.

Reviewer3
Thank you for the comment.

Reviewer4
1. "As the authors noted, SMD for quantitative evaluation of antibody titre is difficult to be interpreted. I suggest that studies using the same measurement method should be grouped together and a subgroup analysis of studies using mean differences without variable transformation should be conducted"

Following the comment, the results of studies using the same measurement method were analysed as a group although it ended up with a description instead of statistical analysis due to the small number of studies (6th-14th line on page 14 in the Result section). In addition, sensitivity analysis of studies using mean differences without variable transformation was additionally conducted and presented in the Result section (6th-9th line on page 16).

“In many studies, the average values in the RA-ILD group appear to be around 200 and it was around 100 in the non-RA-ILD group. If there is a scientific basis for calculating the combined value of these studies, subgroup analyses should be performed as described above.”

Following the comment, sensitivity analysis of studies using mean differences without variable transformation was additionally conducted and presented in the Result section (6th-9th line on page 16).

2. The odds ratio of the multivariate analysis in the Rocha-Munoz et al might be an odds ratio for the antibody titre rather than the positivity.

I agree with the comment. It was revised as such (Table 2).

3. “Is the antibody titre not affected by sex, age or other factors? Is there an association between the variability of the results and the differences in the target population of each study.”

Following the comment, we additionally conducted meta-regression analysis and statistically assessed the effect of all of these factors (3rd-7th line on page 11 in the Methods section and 11th-15th line on page 16 in Result section). Furthermore, the heterogeneity was more strongly discussed as a major limitation of this study (11th-19th line on page 20 in the Discussion section and page 21 in the Conclusion section).

VERSION 2 – REVIEW

REVIEWER	Pierre-Antoine Juge Service de Rhumatologie, Hôpital Bichat Claude - Bernard, Paris, France
REVIEW RETURNED	26-Dec-2020

GENERAL COMMENTS	The authors have made important efforts to answer all of my previous comments. Due to the heterogeneity of the included studies, conclusion of this meta-analysis may be weak but this have been well discussed by the authors in the discussion part.

REVIEWER	Masanori Nojima The Institute of Medical Science, The University of Tokyo
REVIEW RETURNED	17-Dec-2020

GENERAL COMMENTS	Overall, the review comments have been adequately addressed. Please respond to just one point below. Comment: It is great that the authors have implemented meta-regression (e-Table 2). However, it is difficult to understand what is the dependent variable in each regression, and it is also difficult to interpret the coefficients: is the positive proportion in the RA-ILD cases, or the antibody titer in the RA-ILD cases the dependent variable? Or, the group differences in positive proportion and antibody titer with/without RA-ILD?

VERSION 2 – AUTHOR RESPONSE

Reviewer 2
Thank you for the comment.

Reviewer 4
“It is difficult to understand what is the dependent variable in each regression and it is also difficult to interpret the coefficients.”

We agree with the comment.
Following the opinion, two additional explanations were attached in the footnote in the e-Table 2 for clarity:
a, The positivity of anti-CCP antibody for RA-ILD against RA alone (dependent variable) was regressed against each potential confounder and the value in each cell indicates a change of an OR with one unit increase of each covariate;
b, The difference of titres of anti-CCP antibody between RA-ILD and RA alone (dependent variable) was regressed against each potential confounder and the value in each cell indicates a change of an SMD with one unit increase of each covariate;