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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040465
Article Type:	Original research
Date Submitted by the Author:	14-May-2020
Complete List of Authors:	Kamiya, Hiroyuki; Tatebayashi Kosei General Hospital, Department of Respiratory Medicine Panlaqui, Ogee; Northern Hospital, Department of Intensive Care Medicine
Keywords:	RHEUMATOLOGY, Thoracic medicine < INTERNAL MEDICINE, Interstitial lung disease < THORACIC MEDICINE

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Title

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

Hiroyuki Kamiya[1], Ogee Mer Panlaqui[2]

[1] Department of Respiratory Medicine, Tatebayashi Kosei General Hospital, Gunma, Japan

[2] Department of Intensive Care Medicine, Northern Hospital, Melbourne, Australia

Correspondence

Hiroyuki Kamiya

Department of Respiratory Medicine, Tatebayashi Kosei General Hospital, Gunma, Japan 374-8533

Phone: +81-276-72-3140

Email: mlb04194@nifty.com

Word count

3960

Keywords

Rheumatoid arthritis, interstitial lung disease, anti-cyclic citrullinated peptide antibody, risk, review

Article Summary

Strengths and limitations of this study

- This systematic review and meta-analysis addressed the risk of RA-ILD related to both the presence and titres of anti-CCP antibody, which was not clarified in previous literature.
- A substantial variance in the results of primary studies, which may have been derived from the diversity of anti-CCP antibody assays and included subjects, may undermine the generalizability of the findings of this study.
- The usefulness of the findings may be limited in clinical practice because of high probability of the autoantibody positivity for RA without ILD and no standard cut-off points for its assays.

ABSTRACT

Objective

To clarify the risk of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) related to anti-cyclic citrullinated peptide (CCP) antibody.

Design

A systematic review and meta-analysis.

Data sources

Medline, EMBASE, Science Citation Index Expanded and Cochrane Central Register of Controlled Trials were searched from the inception through 12 November 2019.

Eligibility criteria for selecting studies

Patients with RA with and without ILD were eligible. All assays for anti-CCP antibody were included although non-specified anti-citrullinated peptide antibody was excluded. The primary outcome was the prevalence or incidence of ILD. Primary studies of any design aside from a case report were eligible.

Data extraction and synthesis

Two reviewers independently selected eligible reports and extracted relevant data. Meta-analysis was conducted using a random-effects model and summarized separately using odds ratios (ORs) or standardized mean differences (SMDs).

Results

29 out of 827 records retrieved through electronic databases and four additional reports identified from other sources were eligible. Finally, 29 of these studies were focused for the review. A total of 10158 subjects were included and the mean age was between 45.8 and 63.9 years. The mean disease duration was between 4.3 and 14.9 years. A number of different anti-CCP antibody tests were employed and its positivity ranged from 50.7% to 95.8%. All studies except for two were deemed as high risk of bias. A pooled analysis of univariate results demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.08 (95%CI: 1.05-2.88). Similarly, the titre of anti-CCP antibody was significantly higher for RA-ILD with an SMD of 0.42 (95%CI: 0.20-0.65). These results were confirmed by multivariate analysis in the majority of studies and consistent by any subgroup and sensitivity analyses.

Conclusion

The presence and higher titres of anti-CCP antibody were significantly associated with an increased risk of RA-ILD.

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that is characterized by a chronic synovial inflammation and eventual joint destruction.[1] Although arthritis is the main manifestation of the disease, it also damages diverse extra-articular organs such as heart, lung, kidney, eye and skin.[2] Interstitial lung disease (ILD) is one of the most common comorbidities of RA and the prevalence of ILD for patients with RA is reported to be 10% to 40% although it varies depending on the target population, a definition of the disease and diagnostic modalities.[3] A complication of ILD deeply affects the prognosis of RA because RA-associated ILD (RA-ILD) is often progressive and only a limited therapeutic option is available.[4] It is also complicated by acute exacerbation and lung cancer.[5-6] As a result, ILD is reported to be the third leading cause of deaths of RA [7] and approximately two thirds of patients with RA-ILD eventually die within 5 years, resulting in a hazard ratio of mortality about 3.0 in comparison to RA without ILD.[8] Moreover, the most common type of ILDs among RA-ILDs, i.e., usual interstitial pneumonia (UIP),[9] demonstrates the worst prognosis, which is similar to the mortality of idiopathic pulmonary fibrosis (IPF).[10] In this context estimating the risk of developing ILD will help clinicians' decision-making and may improve the prognosis of the disease.[11] Historically, a number of studies investigated risk factors for the development of ILD and some clinical information are reported to be associated with an increased risk of RA-ILD, which include male gender,[12] smoking,[13] severe disease [14] and rheumatoid factor (RF).[15] Anti-citrullinated peptide antibody (ACPA) is a specific marker for RA and included in the latest classification criteria for an accurate diagnosis of the disease.[16] Currently,

anti-cyclic citrullinated peptide (CCP) antibody, representing ACPAs is available commercially and usually measured in clinical practice. The autoantibody is also reported to be associated with an increased risk of extra-articular manifestations such as ILD.[17] However, previous studies noted inconsistent results [18-19] and the former systematic review seems to be limited by relatively a small number of studies and unclear definition of ILD and IPF.[20] The aim of this systematic review and meta-analysis was to clarify current evidence regarding the association of anti-CCP antibody with RA-ILD.

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[22]

Patient and public involvement

There was no patient and public involvement in the whole process of conducting this research.

Eligibility

Patients with RA were eligible for this review. RA was diagnosed based on its widely used classification criteria, i.e., the 1987 American College of Rheumatology classification criteria [23] and the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria.[16] ILD was characterized by interstitial inflammatory and fibrotic changes in pulmonary parenchyma and diagnosed based on symptomatic, functional, radiological and/or pathological findings.[24] The

pattern of ILD was classified following the international multidisciplinary classification such as an official American Thoracic Society/European Respiratory Society statement.[25] Other pulmonary lesions associated with RA such as bronchiolitis, bronchiectasis and pleuritis were all excluded. An overlap with other connective tissue diseases was included if RA was the main disease of interest in the study. There was no limitation regarding demographic features of subjects, such as gender and ethnicity, duration of RA and ILD and the severity of the disease unless they were less than the age of 18. Subjects were allowed to participate at any point in time along their clinical course of the disease.

Anti-CCP antibody was examined using Enzyme-Linked Immunosorbent Assay (ELISA).[26] Although measurements of anti-CCP antibody were different among manufacturers and each institution adopted a different test, all kinds of anti-CCP antibody assays were eligible for the review. However, ACPA, which was not specified as anti-CCP antibody, was excluded because it may have represented autoantibodies against different citrullinated peptides.

The outcome of interest in this review was the prevalence or incidence of ILD. Any design of primary studies other than a case report was eligible if it described the association of anti-CCP antibody with RA-ILD. Conference proceedings, letters or editorials and review articles were ineligible. Only reports published in English was considered.

Search strategy

The following electronic databases were searched, Medline, EMBASE, Science Citation Index Expanded and Cochrane Central Register of Controlled Trials, using subject

headings and text words related to study population such as ‘rheumatoid arthritis’, ‘interstitial lung disease’ and ‘anti-cyclic citrullinated peptide antibodies’ (e-Appendix). Search terms were constructed referring to a systematic review in a similar research area identified through the Cochrane Database of Systematic Reviews (CDSR).[27] Methodology filters were not used to avoid limiting the sensitivity of the search. The search was covered from the inception of each database through to the 12th of November 2019. The reference lists of eligible studies and relevant review articles were also hand-searched to identify additional reports. Google Scholar was employed to search grey literature.[28]

Study selection and data collection process

Two reviewers (H.K. and O.M.P.) independently examined titles and abstracts of all retrieved articles to select eligible reports. The same reviewers also extracted relevant data based on a modified data extraction form, which was previously published in a protocol paper for a systematic review.[29] Any uncertainty or disagreement between reviewers arising from these processes was resolved through discussion. The following data was extracted from each eligible study: first author’s name, year of publication, study location, study design, sample size and its demographic features, ILD patterns if available, manufacturers of anti-CCP antibody tests and their cut-off points if available, a proportion of positivity and titres of anti-CCP antibodies for RA with and without ILD, methods for statistical analysis, summary statistics and items associated with a risk of bias.

Risk of bias in individual studies

As all studies investigated the association of anti-CCP antibody with RA-ILD as risk estimates, the Quality in Prognostic Studies (QUIPS) tool was modified and applied to assess a risk of bias in individual studies.[30] However, one of six domains that constitute the tool, i.e., 'the attrition of study population', was considered irrelevant and thus excluded because all studies were designed as cross-sectional or case-control studies. Each domain received an individual bias rating (low, moderate or high), with an overall risk of bias based on a total rating of all domains. For example, a study showing a low risk of bias across all domains was deemed as being subject to a low risk of bias overall.

Statistical analysis

Summary statistics

The effect size of the risk of RA-ILD associated with the presence of anti-CCP antibody was measured using either risk ratios (RRs) or odds ratios (ORs). In a case where titres of anti-CCP antibody were compared between the two comparative groups with or without ILD, the mean difference (MD) was calculated to reveal the difference of the autoantibody titres. If the median was utilized instead of the mean, it was presented for each of the two groups. If the summary statistics were not provided directly, the ORs or RRs were calculated manually based on the absolute number of the outcome across the two comparative groups.

Data synthesis

The effect size of an association between anti-CCP antibody and RA-ILD was statistically combined if it was presented using the same statistics in three or more

studies. The results were summarized using ORs if anti-CCP antibody was reported as binary (positive/negative). If the titre of anti-CCP antibody was reported, a standardized MD (calculated as Hedge's g) was utilized to combine the results.[31] If the median, range or interquartile range was described to report the autoantibody titres, they were converted to the mean and standard deviation, using a formula reported by a previous study, to be summarized as MDs or SMDs.[32] Only the results of univariate analysis were combined whereas those of multivariate analysis were described qualitatively because adjusted variables in multivariate models varied substantially between studies and pooling these data could be misleading. If meta-analysis was feasible from the collated data, it was conducted using a random-effects model employing the DerSimonian and Laird method.[33] Meta-analysis was conducted using the statistical software package, Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical significance was considered with a p-value of <0.05. If combining data was deemed inappropriate due to a small number of studies, the results were to be reported qualitatively.

Heterogeneity between studies

Between-study variance was assessed using both Q statistics and I^2 value. For the assessment of heterogeneity between studies, statistical significance was considered with a p-value of <0.1 due to the low power of the test. Magnitude of heterogeneity was categorised as low (<30%), moderate (≥30%, <50%), considerable (≥50%, <70%) and substantial (≥70%).[34] When heterogeneity was identified, the 95% prediction interval (PI) was presented in addition to the 95% confidence interval (CI).[35] To better interpret sources of heterogeneity, subgroup analysis was conducted based on study

location (Asia or non-Asia) and study design (cross-sectional or case-control). Sensitivity analysis was also considered focusing on the measurements of anti-CCP antibody (same manufacturer and same generation of the autoantibody assay).

Meta-biases

Small study bias (such as publication bias) was examined graphically using a funnel plot and statistically by the Egger's test using Stata 14 (STATA Corp LLC., College Station, TX, USA) if ten or more studies were available for meta-analysis.[36] Statistical significance of the test was considered with a p-value of <0.1 due to the low power of the test.

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) for prognosis [37] was applied to assess the credibility of evidence generated from this review because all studies investigated the association of anti-CCP antibody with RA-ILD as risk estimates.

Results

Search for eligible studies

Out of a total of 827 records identified through a search of five electronic databases, 182 duplicates were removed and 645 records were screened by titles and abstracts. After 320 records consisting of non-English reports (n=16) and 304 articles of ineligible types (conference proceedings (n=153), case reports (n=72), editorials or letters (n=10) and review articles (n=69)) and 265 irrelevant papers were further excluded, the remaining 60 records were retrieved as full-texts. Out of these, 29 reposts/studies were eligible for

the review and additionally four reports were identified through a hand-search of references of eligible studies. As a result, a total of 33 reports were considered for the review (Figure 1). In each of three different groups, which conducted two studies sharing the same cohort, only the study with a larger sample size was included for the review.[38-40] Similarly, among three studies conducted by one group, the study with the largest sample size was included for the review.[41] Furthermore, another study among these three studies was also included because it reported two different cohorts, one of which was not overlapped by the other studies.[42] There was also a study that reported two different cohorts, only one of which was included because it was not overlapped by the other studies.[43] Finally, a total of 29 studies/cohorts were focused for further analysis.[38-66]

Characteristics of included studies

Study location of a total of 29 studies were distributed globally with Asia in the largest number (n=15), which was followed by the Americas (n=7), Europe (n=3), Africa (n=2) and others (n=2). 22 studies were cross-sectional while the remaining seven were case-control studies. A complication of other CTDs was mentioned in 10 studies and ILD patterns were detailed in three studies. The number of subjects enrolled in each study ranged from 41 to 2702, which amounted to 10158 subjects in total and the mean age was between 45.8 and 63.9 years. The proportion of men, smoking history and ILD ranged from 4.0% to 90.1%, 1.9% to 98.9% and 4.9% to 71.6%, respectively. The mean duration of RA was between 4.3 and 14.9 years and the disease activity, which was represented by the mean disease activity score (DAS) 28, was between 2.5 and 5.4 (Table 1). The generation of anti-CCP antibody tests was specified in 14 studies, which

consisted of the second generation in 12 studies and the third generation in two studies. The proportion of positivity of anti-CCP antibody was reported in 21 studies, which ranged from 50.7% to 95.8% while the titre of the autoantibody was described in 18 studies (Table 2).

Risk of bias in individual studies

All studies except for two contained high risk of bias rating in at least one domain and thus was deemed as high risk of bias. Among the five domains constituting the QUIPS tool, the risk of bias for statistical analysis and reporting and ILD confirmation were rated as high in the majority of studies due to no or insufficient information regarding model building process and inconsistent diagnostic procedures. The remaining two studies were rated as moderate risk of bias (Table 3).

Association of anti-CCP antibody with RA-ILD

Univariate result

The association of the positivity of anti-CCP antibody with RA-ILD was reported in 20 studies. Eight out of these studies demonstrated significant results with the ORs ranging from 1.98 to 44.5 (Table 2). Meta-analysis of 17 out of these 20 studies demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.08 (95%CI: 1.05-2.88) with moderate heterogeneity (chi^2=28.6, p=0.03, I^2=44%) (Figure 2).

The titre of anti-CCP antibody was compared between RA with and without ILD in 18 studies. 11 out of these studies demonstrated significant results with higher titres associated with RA-ILD (Table 2). Meta-analysis of 12 out of these 18 studies

demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD with an SMD of 0.42 (95%CI: 0.20-0.65) with considerable heterogeneity (chi^2=36.0, p=0.0002, I^2=69%) (Figure 3).

Multivariate result

Multivariate analysis was conducted in eight studies where detailed results were available in seven studies and adjusted variables were diverse between studies. Six of these seven studies demonstrated a positive association between the presence or higher titres of anti-CCP antibody and RA-ILD and the results were statistically significant in four studies (Table 2). Two studies (Yin 2014 [65] and Rocha-Munoz 2015 [59]) revealed the association of the positivity of anti-CCP antibody with RA-ILD as ORs of 3.50 (95%CI: 1.52-8.04) and 1.06 (95%CI: 1.02-1.10), respectively (Table 2). The association of the titre of anti-CCP antibody with RA-ILD was reported by one study as an OR of 1.08 (95%CI: 1.03-1.12) (Matsuo 2018 [53]) while it was described as 1.41 (95%CI: 1.01-1.97) by another study (Correia 2019 [47]).

Subgroup analysis

Subgroup analysis was conducted based on both study location and study design. There was no significant difference in the effect size of the positivity of anti-CCP antibody with ORs of 1.89 (95%CI: 1.21-2.95) by Asian reports and 2.31 (95%CI: 1.39-3.85) by non-Asian reports (p=0.56) although considerable heterogeneity remained in the latter group (e-Figure 1). Similarly, there was no significant difference in the effect size of the titre of anti-CCP antibody with SMDs of 0.38 (95%CI: 0.04-0.71) by Asian reports and 0.49 (95%CI: 0.24-0.74) by non-Asian reports (p=0.58) although substantial heterogeneity remained in the former group (e-Figure 2). There was no significant

difference in the effect size of the positivity of anti-CCP antibody with ORs of 1.92 (95%CI: 1.32-2.80) by cross-sectional studies and 2.53 (95%CI: 1.26-5.08) by case-control studies (p=0.50) although considerable heterogeneity remained in the latter group (e-Figure 3). Similarly, there was no significant difference in the effect size of the titre of anti-CCP antibody with SMDs of 0.39 (95%CI: 0.11-0.67) by cross-sectional studies and 0.50 (95%CI: 0.12-0.89) by case-control studies (p=0.65) although substantial heterogeneity remained in the former group (e-Figure 4).

Sensitivity analysis

Sensitivity analysis was conducted focusing on the measurements of anti-CCP antibody. A pooled analysis of 10 studies that examined the second generation of anti-CCP antibody test demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.30 (95%CI: 1.34-3.93) although there remained moderate heterogeneity (chi^2=16.7, p=0.05, I^2=46%) (e-Figure 5).

A pooled analysis of three studies that examined the second generation of anti-CCP antibody test by the same manufacture (Euroimmun, Lübeck, Germany) demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 3.81 (95%CI: 1.08-13.5) although there remained considerable heterogeneity (chi^2=4.98, p=0.08, I^2=60%) (e-Figure 6).

These sensitivity analyses were unable to be conducted for the titre of anti-CCP antibody and other generations of the autoantibody test due to a small number of studies.

Additional analysis

Two funnel plots (for both positivity and titre of anti-CCP antibody) were constructed to investigate small study bias, both of which demonstrated no apparent asymmetry (e-Figure 7 and e-Figure 8, respectively). This graphical assessment was confirmed statistically by the Egger's test, which demonstrated no statistical significance (p=0.12 and 0.28, respectively).

Assessment of evidence level

Study limitation was considered present in all of the evidence because no studies were deemed as low risk of bias. Publication bias was also considered present in all of the evidence due to the property of studies of risk estimates [37] although it was not confirmed in both graphical and statistical analyses for univariate results. Overall, the level of evidence derived from this review was rated as low or very low (Table 4).

Discussion

This study demonstrated using a pooled analysis of univariate results that the presence of anti-CCP antibody was significantly associated with RA-ILD and the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD. The results were confirmed by multivariate analyses in the majority of studies that reported it. These findings suggest that anti-CCP antibody is related to an increased risk of ILD for patients with RA. As this review was based on a large number of studies conducted globally and the results were reproduced by any subgroup and sensitivity analyses, these findings will be generalizable to a broader population.

It is desirable and important to identify a high risk group of patients with RA who are likely to develop ILD because it is often progressive and worsens the prognosis of the

disease.[67] If the development of ILD can be predicted, it will help clinicians' decision-making and facilitate an efficient use of limited medical resources to change clinical course of the disease. Much effort has been made to identify clinical information such as serum biomarkers that can easily be obtained and help estimate the risk of ILD for patients with RA.[68] Tests for ACPAs emerged as a tool to diagnose early RA with higher specificity than traditionally employed RF.[69] They date back to the discovery of anti-perinuclear factor and anti-keratin antibody in the sera of patients with RA, which recognized the citrullinated protein filaggrin.[70] Subsequently, cyclic citrullinated peptides (CCP) were synthesized to improve test performance [71] and after further evolution currently the third generation of anti-CCP antibody test is commercially available.[72] Anti-CCP antibody is not only helpful to diagnose RA but also reported to be associated with extra-articular manifestations of the disease.[73] The recent meta-analysis demonstrated an increased risk of RA-ILD as a result of serum anti-CCP antibody positivity.[20] Although a number of specific citrullinated proteins were discovered such as fibrinogen [74] and α-enolase,[75] a diagnostic significance of specific autoantibodies directed against these autoantigens has yet to be established.[76]

RA is classified as a systemic autoimmune disorder although the pathogenesis of the disease has been under dispute for many years.[77] Recent research suggests that the breakdown of immunological tolerance initially occurs in the lungs under the influence of environmental stress such as exposure to cigarette smoke and genetic susceptibility.[78] In short, smoking accelerates the activity of the enzyme peptidylarginine deiminase that catalyses the posttranslational convert of arginine to citrulline, which eventually induces autoimmune reaction and leads to the formation of

autoantibodies against citrullinated peptides under the interplay of both T and B lymphocytes.[79] In these processes, a number of cytokines are generated and may promote fibrotic changes of the lung.[80] Smoking is related to the development of ILD, in particular, UIP, which is the most common type among RA-ILDs [9] and contributes to the formation of ACPAs. Therefore, it is most likely that anti-CCP antibody is closely associated with the development of ILD, in particular for genetically susceptible subjects with smoking history and this relationship was confirmed in this report.

The current study is different from the previous systematic review [20] in that it included a larger number of studies and subjects and thus the result is considered more reliable. It also demonstrated that the titre of anti-CCP antibody was higher for RA-ILD than RA without ILD. This finding is meaningful because anti-CCP antibody may be positive in the majority of patients with RA regardless of the presence of ILD. Indeed, the proportion of positivity of anti-CCP antibody for RA without ILD in this review ranged from 49.1% to 95.8% with the median value of 71.0%. When the group of RA without ILD is positive for anti-CCP antibody with high frequency, the benefit of the autoantibody test for screening patients with RA at a higher risk of developing ILD will be limited. Conversely, the finding of titres may be more informative because it can also be employed to patients with RA without ILD who are tested positive for the autoantibody. Therefore, titres of anti-CCP antibody may be more useful than just its presence to estimate the risk of developing ILD. However, the interpretation of this finding also needs a caution because it was derived from a comparison between RA-ILD and RA without ILD and thus does not indicate any cut-off point that defines a high or low titre of the autoantibody. As a result, in real clinical practice, clinicians need

to assess the implication of the titre of anti-CCP antibody on a case-by-case basis. What makes the issue more complicated is the variability of measurements of anti-CCP antibody, which were produced by a number of manufacturers. The sensitivity and specificity varies depending on the tests and the titres are also different between assays.[81] Although an SMD was employed in this review to enable the comparison of titres derived from different tests, the result may be difficult to be applied in clinical practice. These diversities of anti-CCP antibody tests can explain a large part of the heterogeneity identified in meta-analyses of this review although other factors such as the variability of enrolled subjects may also have been responsible for it.

There are other methodological limitations or caveats that need to be kept in mind to appropriately interpret the results of this study. First, this review was only composed of cross-sectional and case-control studies and thus causality between anti-CCP antibody and RA-ILD cannot be deducted although it is aetiologically plausible. Second, selection bias of subjects in individual studies cannot be ruled out. Patients with RA-ILD at relatively advanced stage may have been included for the review. If this was the case, the findings may not be applicable to an early stage of the disease and become useless for screening purpose. Third, anti-CCP antibody may be most closely related to UIP among other types of ILD complicated with RA. However, the association between anti-CCP antibody and individual ILD patterns could not be elucidated in this review because most of the studies did not report them. Finally, no studies were deemed as low risk of bias. Due to this study limitation, the level of evidence obtained from this review was all rated as low or very low. Therefore, more research with high quality using a

prospective cohort design needs to be accumulated to make a definitive conclusion or solidify the findings of this review.

Conclusion

This systematic review and meta-analysis demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD and the titre of the autoantibody was significantly higher for RA-ILD than RA without ILD. However, an applicability of these findings may be limited due to the diversity of the autoantibody tests and high frequency of their positivity for the control group.

Ethics approval and participant consent

Neither ethics approval nor participant consent was required as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

Data sharing

The dataset used and/or analysed for this review will be available from the corresponding author upon a reasonable request and may become open to the public through a digital repository (such as Dryad) after the final result is published in a journal.

Conflict of interest

None to declare.

Funding

This research received no specific grant from any funding agency in either the public, commercial, or not-for-profit sectors.

Authors' contributions

H.K. planned the entire research project and analysed the data. He also summarized the result and wrote the manuscript. H.K. has full access to the data and takes responsibility for its integrity as well as the accuracy of the analysis.

O.M.P. contributed to the design of the research project and conducted the literature search and data extraction. He was also involved in revising the manuscript.

All researchers provided thoughts and opinions to compile a draft paper and approved of the final version of the manuscript.

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Table 1 Baseline characteristics of included studies[a]

Study	Location	Design	Number (n)	Age (years)	Gender (male) (n (%))	Smoking (n (%))	Proportion of ILD (n (%))[b]	Disease duration (years)	Disease activity[c]	Other CTDs (n)	ILD patterns (on HRCT) (n)
Alunno 2018 [38]	Italy	Cross-sectional	252	61.7±0.8	56 (22.2)	-	37 (20.2) (n=183)	12.6±0.6	-	-	-
England 2019 [39]	US	Cross-sectional[d]	1823	63.5±11.0	(90.1)	(89.5)	90 (4.9)	11.1±11.5	4.0±1.6	-	-
Giles 2014 [40]	US	Cross-sectional[d]	177	59±8[g]	71 (40.1)	105 (59.3)	120 (67.8)	9 (5-19) vs. 8 (4-16)[g]	3.7 (2.9-4.4)[g] (CRP)	-	-
Chen 2013 [41]	China	Cross-sectional	103	49.1±14.7	27 (26.2)	2 (1.9)	63 (61.2)	4.3±5.7	4.4±1.4	-	-
Chen 2015 [42]	China	Cross-sectional	71	60.7±12.1[e]	37 (52.1)	35 (49.3)	49 (69.0)	12.8±10.3 vs. 8.4±8.1 (n=68)	3.7±1.2 vs. 3.3±1.7 (n=43)	-	-
Doyle 2015 [43]	US	Cross-sectional[d]	75	61.5±12.7[e]	11 (14.7)	41 (54.7)	-	-	-	-	-
Abdel-Hamid	Egypt	Cross-sectional	50	45.8±12.3	2 (4.0)	-	19 (38.0)	9.8±6.6	4.7±1.3	0	-

2019 [44]											
Akiyama 2016 [45]	Japan	Cross-sectional	395	58.5±13.1	49 (12.4)	69 (20.3) (n=340)	78 (19.7)	129.4±115.2 (months)	4.9±1.6 (n=372)	38 (SS, SSc, PM/DM, SLE)	-
Alixiou 2008 [46]	Greece	Case-control	136	-	-	-	N/A (ILD 11/no ILD 125)	-	-	-	-
Correia 2019 [47]	US	Cross-sectional	453	59.6±15.7	(19.4)	-	(6.0)	-	-	0	-
Fadda 2018 [48]	Egypt	Cross-sectional	88	50.2±9.0	13 (14.8)	87 (98.9)	63 (71.6)	10.2±6.2	14 (1-32) vs. 12 (3-25) (median (range)) (CDAI)	0	UIP 62%, NSIP 27%, Mixed 1%
Furukawa 2012 [49]	Japan	Case-control	450	63.9±10.9[e]	89 (19.8)	130 (28.9)	N/A (ILD 129/no ILD 321)	14.5±10.9[e]	-	-	-
Kakutani 2019 [50]	Japan	Cross-sectional	2702	62.8±12.5	(17.8)	(28.9)	261 (9.7)	9 (15) vs. 10 (17) (median (IQR))	3.2±1.0 (ESR)	-	-
Kelly 2014	UK	Case-control	460	-	220 (47.8)	-	N/A (ILD 230/no	-	-	-	-

[51]							ILD 230)				
Liu 2019 [52]	China	Cross-sectional	101	54 (17) (median (IQR))	26 (25.7)	-	23 (22.8)	7 (14) (median (IQR)	4.0±1.9	-	-
Matsuo 2018 [53]	Japan	Cross-sectional	312	63.5±12.7	41 (13.1)	95 (30.4)	26 (8.3)	14.9±11.6	2.5±1.1 (CRP)	11 (not specified)	-
Mori 2012 [54]	Japan	Cross-sectional	356	72.5 (12.3) (n=24) vs. 59.0 (16) (n=302) (median (IQR))	85 (23.9)	76 (21.3)	24 (6.7)	1.5 (6.3) (n=24) vs 0 (6) (n=302) (median (IQR))	-	-	UIP 5, NSIP 19
Ortancil 2011 [55]	Turkey	Cross-sectional	67	57.4±13.5	14 (20.9)	-	12 (17.9)	10.2±11.7[e]	-	-	-
Park 2016 [56]	Korea	Cross-sectional	83	53.7±10.1[e]	10 (12.0)	-	7 (8.4)	-	-	-	UIP 6, Indeterminate 1
Paulin 2019	Argentina	Case-control	118	56.7±15.7	26 (22.0)	52 (44.1)	N/A (ILD 52/ no	-	3.4±1.1	-	-

[57]							ILD 66)				
Restrepo 2015 [58]	US	Cross-sectional	779	53.7±13.3 (n=632)[e]	161 (25.5) (n=632)	357 (56.5) (n=632)	69 (8.9)	10.5±10.3[e]	5.4±1.4[e]	-	-
Rocha-Munoz 2015 [59]	Mexico	Case-control	81	51.0 (36.0-72.0) vs. 49.0 (24.0-73.0) (median (range))	-	22 (27.2)	N/A (ILD 39/no ILD 42)	7.0 (1.0-35.0) vs. 6.5 (0.75-25.0) (median (range))	3.9 (1.7-5.3) vs. 2.5 (1.7-5.1) (median (range))	0	-
Sargin 2018 [60]	Turkey	Cross-sectional	83	59.3±12.1	20 (24.1)	9 (10.8)	43 (51.8)	-	-	0	-
Sulaiman 2019 [61]	Malaysia	Cross-sectional	159	48.3±14.1	25 (15.7)	-	21 (13.2)	-	4.7±0.9 (ESR)	0	-
Tian 2016 [62]	China	Cross-sectional	75	-	29 (38.7)	-	37 (49.3)	-	-	-	-
Wang 2015 [63]	China	Cross-sectional	41	60.7±12.4[e]	20 (48.8)	-	25 (61.0)	108 (5-360) vs. 72 (2-552) (months)	-	-	-

								(median (range))			
Yang 2019 [64]	Korea	Case-control	308	57.0±12.0[e]	76 (24.7)	39 (17.7) (n=220)	N/A (ILD 77/ no ILD 231)	11.0±7.3[e]	-	-	-
Yin 2014 [65]	China	Cross-sectional	285	51.7±13.4[e]	74 (26.0)	59 (20.7)	71 (24.9)	9.0 (16.0) vs. 4.0 (9.1) (median (IQR))	5.4±1.7	61[f] (SS 41, SSc 7, PM/DM 4, SLE 16)	-
Zhang 2018 [66]	China	Case-control	75	41-69 vs. 40-70 (range)	30 (40.0)	-	N/A (ILD 28/ no ILD 47)	-	-	0	-

a, Comparisons correspond to RA-ILD vs. RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified;

b, N/A indicates not applicable due to case-control studies;

c, Disease activity was estimated using disease activity score (DAS) 28 unless otherwise specified and a laboratory marker used to calculate the score was described as either ESR or CRP if it was specified;

d, indicates a prospective study while all of the other studies are retrospectively designed;

e, calculated combining the figure in both comparative groups;

f, some patients had multiple CTDs;

g, unknown statistics;

CDAI, clinical disease activity index; CRP, C-reactive protein; CTD, connective tissue disease; ESR, erythrocyte sedimentation rate; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IQR, interquartile range; NSIP, non-specific interstitial pneumonia; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; SSc, systemic sclerosis; UIP, usual interstitial pneumonia;

Table 2 Anti-cyclic citrullinated peptide (CCP) antibody tests and its association with rheumatoid arthritis-associated interstitial lung disease[a]

Study	Measurements of anti-CCP antibody (manufacturer) (cut-off points)	Proportion of anti-CCP antibody	Titres of anti-CCP antibody	Univariate result (positivity)	Univariate result (titre)	Multivariate result (positivity)	Multivariate result (titre)	Adjusted variables
Alunno 2018 [38]	Second generation (Thermo Fisher Scientific or Aesku)	28/37 (75.7) vs. 90/146 (61.6)	-	OR 1.94 (0.85-4.42)	-	-	-	-
England 2019 [39]	Second generation	(86.7) vs. (76.7)	-	**OR 1.98, p=0.03**	-	-	-	-
Giles 2014 [40]	Second generation	51/57 (89.5) vs. 82/120 (68.3)	152 (99-194) (n=32) vs. 89 (11-152) (n=120)[d]	**OR 3.94 (1.57-9.90)**	**p=0.0005[b]**	-	-	-
Chen 2013 [41]	Not specified	-	231.8±178.0 (n=63) vs. 196.8±161.1 (n=40)	-	MD 35.0 (-33.0-103.0)	-	-	-
Chen 2015 [42]	Not specified	-	142.6±151.9 (n=49) vs. 154.6±151.4 (n=22)	-	MD -12.0 (-88.2-64.2)	-	-	-

Doyle 2015 [43]	Not specified	-	188±133 vs. 83±113	-	-	-	-	-
Abdel-Hamid 2019 [44]	Third generation	30/50 (60.0)	100 (390) (n=19) vs. 20 (298) (n=31) (median (IQR))	-	**p=0.04**[b]	-	-	-
Akiyama 2016 [45]	Not specified (≥4.5 U/mL)	69/75 (92.0) vs. 245/305 (80.3)	-	**OR 2.82 (1.17-6.81)**	-	OR 1.80 (0.70-4.40) (positive with high titre (>13.5 U/mL))	-	age, sex, smoking, RF
Alexiou 2008 [46]	Second generation (INOVA Diagnostics) (20 IU/mL)	10/11 (90.9) vs. 73/125 (58.4)	152.6±104.5 (n=11) vs. 73.1±114.0 (n=125)	OR 7.12 (0.89-56.9)	**MD 79.5 (9.72-149.3)**	-	-	-
Correia 2019 [47]	Second generation (Euro-Diagnostica) (≥6 U/mL)	-	113.0±5.9 (162.4 vs. 109.9) (mean±SE)	OR 1.51 (0.48-4.74) (low titre), 2.61 (0.59-11.5)(moderate titre), 2.83 (0.96-8.39) (high titre)	**p=0.04**[b]	-	**OR 1.41 (1.01-1.97)/1 group of titre**	age, smoking

Fadda 2018 [48]	Third generation (INOVA Diagnostics) (20 U/mL)	84/88 (95.5)	220 (0-500) (n=63) vs. 120 (30-400) (n=25), (median (range))	-	**MD 67.5 (19.5-115.5), OR1.006 (1.001-1.011) (/1 U/mL)**	-	-	-
Furukawa 2012 [49]	Not specified (Medical & Biological Laboratories)	116/129 (89.9) vs. 278/321 (86.6)	-	OR 1.38 (0.71-2.69)	-	-	-	-
Kakutani 2019 [50]	Not specified	(93.2) vs. (82.9)	-	**OR 2.83, p=0.002**	-	-	-	-
Kelly 2014 [51]	Not specified	-	180 (8-340) vs. 78 (8-340) (median (range))	**OR 4.00 (2.00-7.80)**	**p=0.02[b]**	**OR 0.33, p=0.003**	-	age, sex, smoking, RF
Liu 2019 [52]	Second generation (Euro- Diagnostica) (≥25 U/mL)	77/101 (76.2)	-	OR 0.64 (0.23-1.80)	-	-	-	-

Matsuo 2018 [53]	Not specified	25/26 (96.2) vs. 235/286 (82.2)	199.7±104.6 (n=26) vs. 120.7±112.6 (n=286)	**OR 5.43 (1.11-98.0)**	**MD 79.0 (34.1-123.9), OR 1.06 (1.02-1.10) (/10U/mL)**	-	**OR 1.08 (1.03-1.12) (/10U/mL)**	age, smoking, RF, LDH, CRP, ESR, KL-6, MMP-3, IL18, dose of MTX, dose of PSL
Mori 2012 [54]	Second generation (Axis-Shield Diagnostic) (>4.6 U/mL)	24/24 (100) vs. 294/332 (88.6)	283.5 (695) (n=24) vs. 81.1 (228) (n=302) (median (IQR)	OR 6.41 (0.38-107.8)	**MD 275.2 (184.1-366.3)**	RR 2.73 (0.91-8.23) (positive with high titre (≥90 U/mL))	-	age, sex, smoking, advanced stage, RF, HLA-DRB1*04, HLA-DRB1*1502
Ortancil 2011 [55]	Second generation (Euroimmun)	7/12 (58.3) vs. 27/55 (49.1)	-	OR 1.45 (0.41-5.08)	-	-	-	-
Park 2016 [56]	Not specified (Roche Diagnostics) (≥17.0 U/mL)	69/83 (83.1)	-	-	0.22[c]	-	-	-
Paulin 2019 [57]	Second generation	45/47 (95.7) vs. 46/48 (95.8)	-	OR 0.98 (0.13-7.24)	-	-	-	-

Restrepo 2015 [58]	Not specified (TheraTest) (≥7 IU/mL)	44/69 (63.8) vs. 341/563 (60.6)	5.54±1.49 (n=69) vs. 4.68±1.52 (n=563) (log anti-CCP antibody titre)	OR 1.15 (0.69-1.91)	**MD 0.86 (0.49-1.23) (log anti-CCP antibody titre)**	Not specified	Not specified	age, sex, disease duration, DAS28, RF, HLA-DRB1*SE, PSL use
Rocha-Munoz 2015 [59]	Second generation (Euroimmun) (>20 U/mL)	39/39 (100) vs. 27/42 (64.3)	77.9 vs. 30.2 (median)	**OR 44.5 (2.54-778.3)**	**p<0.001**[b]	**OR 1.06 (1.02-1.10)**	-	age, smoking, disease duration, , DAS28, HAQ-Di, RF, ESR, duration of MTX treatment
Sargin 2018 [60]	Not specified	-	19.5 (139) (n=43) vs. 6.2 (125.4) (n=40) (median (IQR))	-	MD 9.8 (-34.1-53.7)	-	-	-
Sulaiman 2019 [61]	Second generation (Euro-Diagnostica) (≥20.0 U/mL)	13/21 (61.9) vs. 70/138 (50.7)	-	OR 1.58 (0.62-4.05)	-	-	-	-
Tian 2016 [62]	Not specified (Euroimmun) (≥25 RU/mL)	30/37 (81.1) vs. 28/38 (73.7)	475.2±551.8 (n=37) vs. 332.0±418.6 (n=38)	OR 1.53 (0.51-4.59)	MD 143.2 (-78.1-364.5)	-	-	-

Wang 2015 [63]	Not specified	-	296.4 (1.91-500.0) (n=25) vs. 392.9 (7.00-500.0) (n=16) (median (range))	-	MD -49.5 (-132.2-33.2)	-	-	-
Yang 2019 [64]	Not specified (≥5.0 IU/mL)	33/43 (76.7) vs. 95/142 (66.9)	242.8±234.4 (n=43) vs. 125.3±144.3 (n=142)	OR 1.63 (0.74-3.57)	**MD 117.5 (59.7-175.3)**	-	-	-
Yin 2014 [65]	Second generation (Euroimmun) (≥25 U/mL)	207/285 (72.6)	-	**OR 3.83 (1.74-8.43)**	-	**OR 3.50 (1.52-8.04)**	-	age, disease duration
Zhang 2018 [66]	Not specified	-	3.09±0.34 (n=28) vs. 3.05±0.32 (n=47)	-	MD 0.04 (-0.12-0.20)	-	-	-

a, Comparisons correspond to RA-ILD vs. RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified. The value with an interval in the parenthesis indicates 95% confidence interval. Text in bold indicates statistical significance;

b, the difference of the titre of anti-CCP antibody between RA with and without ILD could not be calculated due to unavailability of relevant summary statistics, no information of the number of subjects and/or unknown summary statistics;

c, indicates correlation coefficient between anti-CCP antibody and a total ILD score;

d, unknown statistics;

CCP, cyclic citrullinated peptite; CRP, C-reactive protein; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; HAQ-Di, health assessment questionnaire-disability index; HLA, human leukocyte antigen; IL-18, interleukin-18; ILD, interstitial lung disease; IQR, interquartile range; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MD, mean difference; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; OR, odds ratio; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, risk ratio; SE, shared epitope;

Table 3 Risk of bias in individual studies

Study	Study participation	Anti-CCP antibody measurement	ILD confirmation	Study confounding	Statistical analysis and reporting
Alunno 2018 [38]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
England 2019 [39]	moderate risk	**high risk**	**high risk**	low risk	**high risk**
Giles 2014 [40]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Chen 2013 [41]	low risk	**high risk**	low risk	moderate risk	**high risk**
Chen 2015 [42]	moderate risk	low risk	low risk	moderate risk	**high risk**
Doyle 2015 [43]	moderate risk	moderate risk	low risk	moderate risk	**high risk**
Abdel-Hamid 2019 [44]	moderate risk	moderate risk	**high risk**	moderate risk	**high risk**
Akiyama 2016 [45]	low risk	moderate risk	**high risk**	moderate risk	moderate risk
Alixiou 2008 [46]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
Correia 2019 [47]	moderate risk	low risk	low risk	moderate risk	**high risk**
Fadda 2018 [48]	moderate risk	low risk	low risk	moderate risk	**high risk**
Furukawa2012 [49]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Kakutani 2019 [50]	low risk	**high risk**	**high risk**	moderate risk	**high risk**

Kelly 2014 [51]	moderate risk	**high risk**	low risk	moderate risk	**high risk**
Liu 2019 [52]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Matsuo 2018 [53]	low risk	moderate risk	**high risk**	moderate risk	moderate risk
Mori2012 [54]	low risk	low risk	low risk	moderate risk	moderate risk
Ortancil 2011 [55]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Park2016 [56]	low risk	low risk	low risk	**high risk**	**high risk**
Paulin 2019 [57]	moderate risk	**high risk**	**high risk**	moderate risk	**high risk**
Restrepo 2015 [58]	moderate risk	low risk	**high risk**	moderate risk	moderate risk
Rocha-Munoz 2015 [59]	moderate risk	low risk	**high risk**	moderate risk	low risk
Sargin 2018 [60]	moderate risk	**high risk**	**high risk**	moderate risk	**high risk**
Sulaiman 2019 [61]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
Tian 2016 [62]	**high risk**	low risk	**high risk**	moderate risk	**high risk**
Wang 2015 [63]	moderate risk	**high risk**	low risk	**high risk**	**high risk**
Yang 2019 [64]	moderate risk	**high risk**	moderate risk	moderate risk	moderate risk
Yin 2014 [65]	moderate risk	low risk	low risk	moderate risk	moderate risk

Zhang 2018 [66]	**high risk**	**high risk**	**high risk**	**high risk**	**high risk**

Text in bold indicates high risk of bias

CCP, cyclic citrullinated peptite; ILD, interstitial lung disease;

Table 4 Assessment of quality of evidence by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

Outcome: rheumatoid arthritis-associated interstitial lung disease										
			GRADE factors							
Prognostic factors	Analysis	Phase	Study limitations	Inconsistency	Indirectness	Publication bias	Imprecision	Moderate/large effect size	Dose effect	Overall quality
Anti-CCP antibody positivity	Univariate	1	+	+	-	+	-	-	-	very low
	Multivariate	1	+	+	-	+	-	-	-	very low
Anti-CCP antibody titre	Univariate	1	+	+	-	+	-	-	-	very low
	Multivariate	1	+	-	-	+	-	-	+	low

CCP, cyclic citrullinated peptite;

Figure legends

Figure 1 Study flow diagram

Out of a total of 827 records identified searching through five electronic databases, i.e., Medline, EMBASE, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials and Google Scholar, 645 records were screened by titles and abstracts after removing 182 duplicates. After excluding 320 records consisting of non-English reports (n=16) and articles of ineligible types (n=304) (conference proceedings (n=153), case reports (n=72), editorials or letters (n=10) and review articles (n=69)) and 265 irrelevant reports, 60 records were retrieved as full-texts. Out of these, 31 records were excluded due to no specific pulmonary disease (n=7), no ILD (n=5), no risk estimates (n=11), no anti-CCP antibody (n=7) and no RA (n=1). The remaining 29 reposts/studies were eligible for the review and additionally four reports were identified through a hand-search of references of eligible studies. Finally, a total of 33 reports/studies were selected for the review.

Figure 2 Forrest plot of the result of univariate analysis regarding the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

The results of univariate analyses in 17 studies were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 2.08 (95% confidence interval: 1.50-2.88, $p<0.0001$/95% prediction interval: 0.79-5.49). There was moderate heterogeneity ($chi^2=28.6$, $p=0.03$, $I^2=44\%$).

Figure 3 Forrest plot of the result of univariate analysis regarding the association of the tire of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

The results of univariate analyses in 12 studies were pooled for meta-analysis. The titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with a standardized mean difference (SMD) of 0.42 (95% confidence interval: 0.20-0.65,

p=0.0002/95% prediction interval: -0.33-1.17). There was considerable heterogeneity (chi^2=36.0, p=0.0002, I^2=69%).

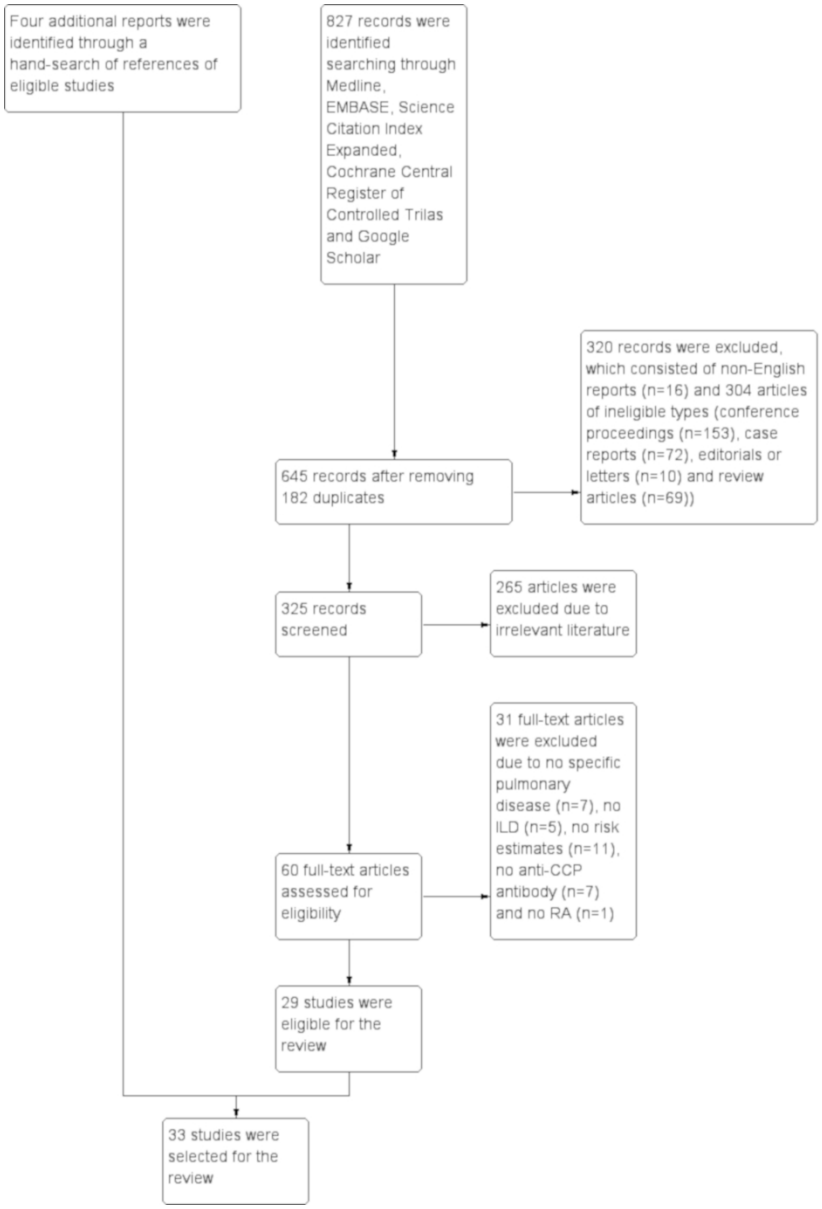


Figure 1

109x161mm (600 x 600 DPI)

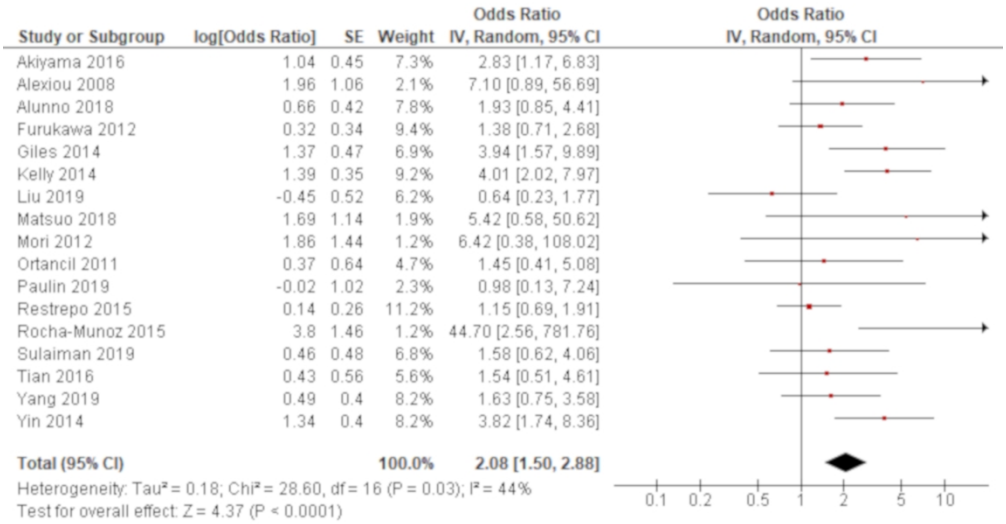


Figure 2

148x80mm (600 x 600 DPI)

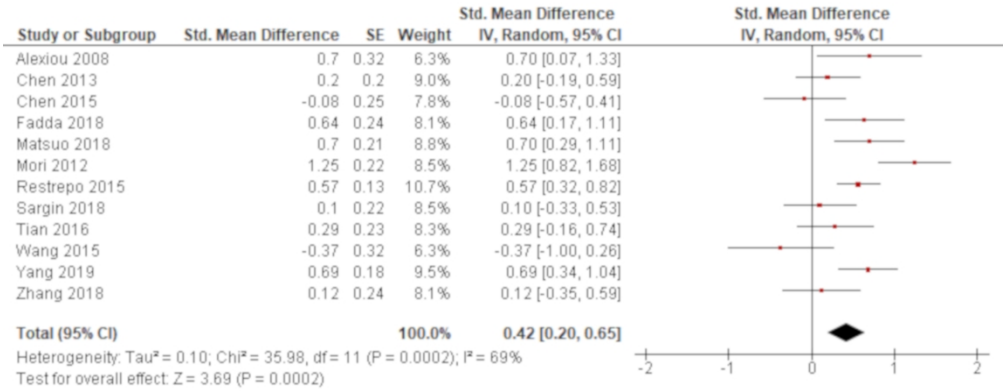
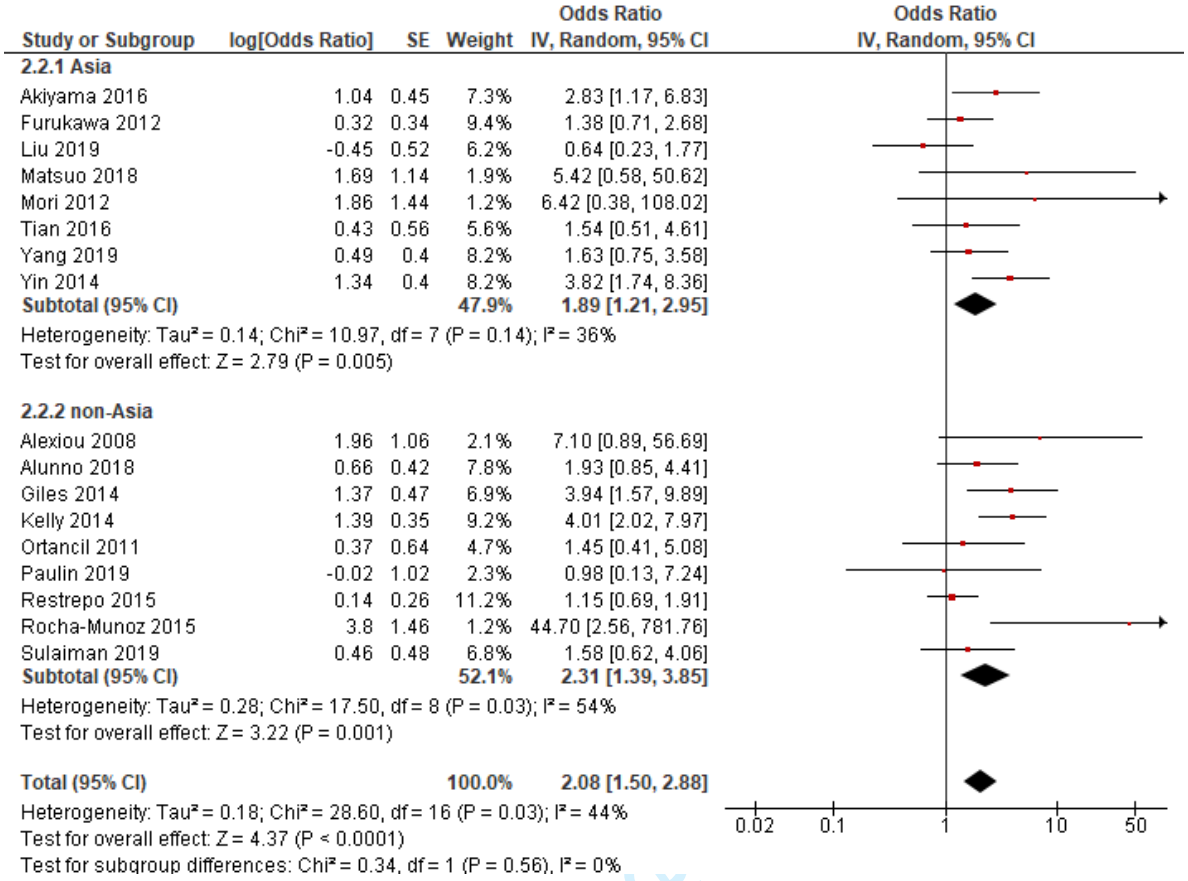


Figure 3

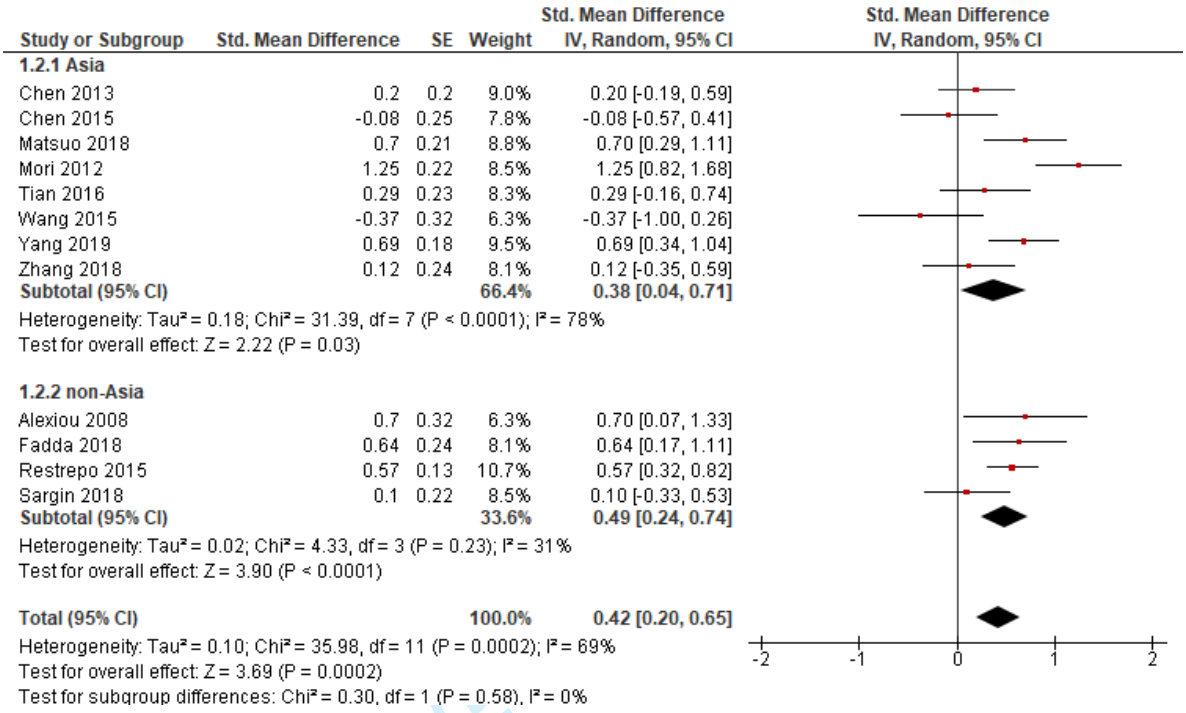
206x83mm (600 x 600 DPI)

Supplementary



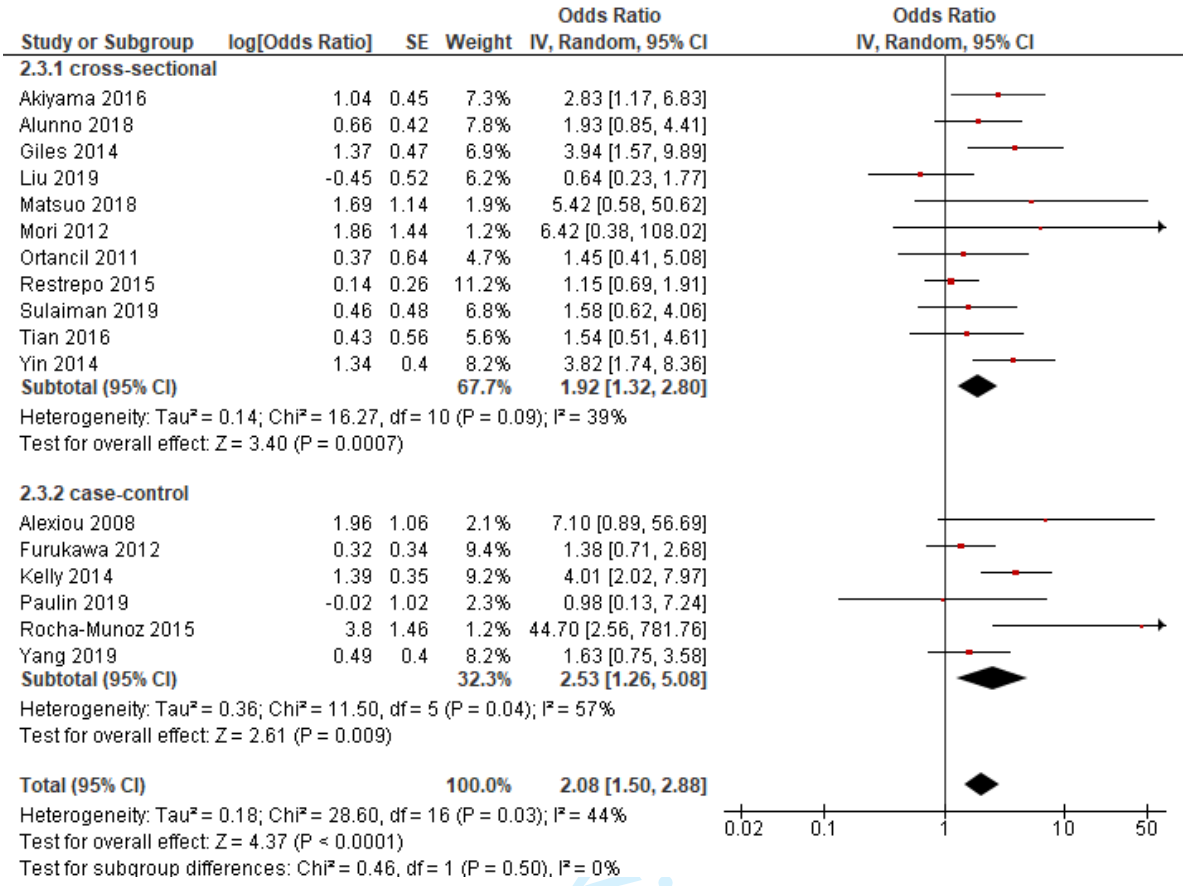
e-Figure 1 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 1.89 (95% confidence interval (CI): 1.21-2.95, p=0.005/95% prediction interval (PI): 0.65-5.52) and 2.31 (95%CI: 1.39-3.85, p=0.001/95%PI: 0.57-9.32), respectively and there was no significant difference in these results (p=0.56). There remained considerable heterogeneity in non-Asian studies (chi^2=17.5, p=0.03, I^2=54%).



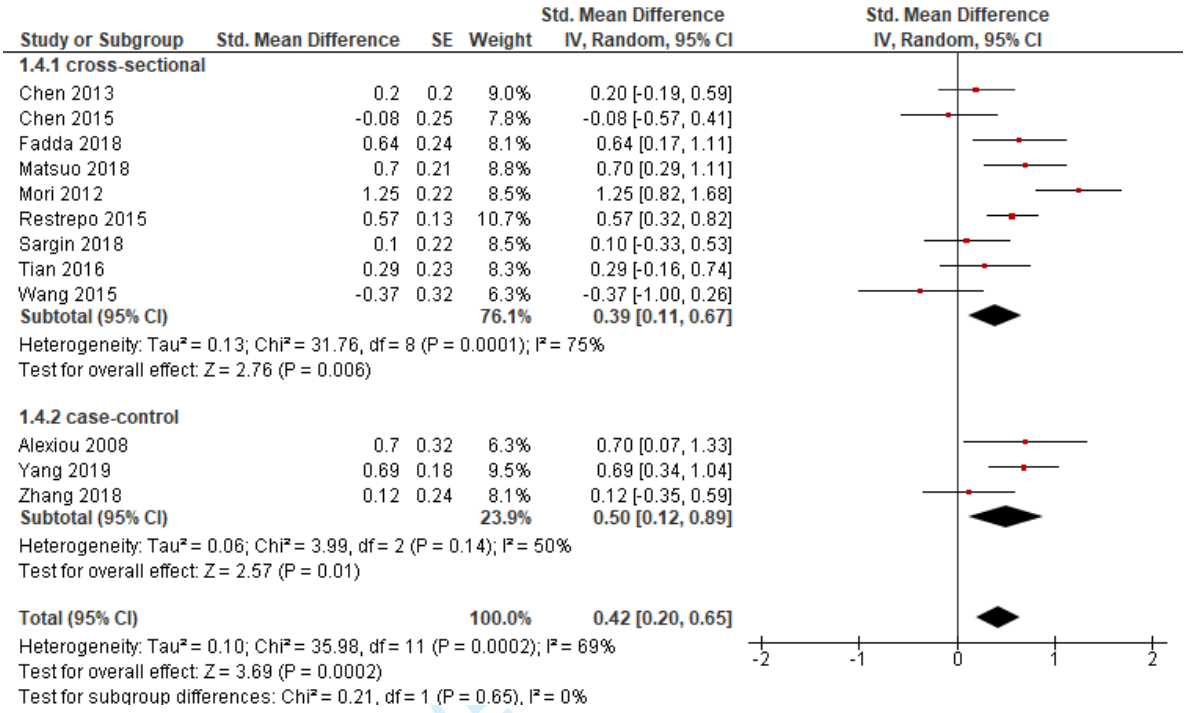
e-Figure 2 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.38 (95% confidence interval (CI): 0.04-0.71, p=0.03/95% prediction interval (PI): -0.74-1.50) and 0.49 (95%CI: 0.24-0.74, p<0.0001/95%PI: -0.33-1.31), respectively and there was no significant difference in these results (p=0.58). There remained substantial heterogeneity in Asian studies (chi^2=31.4, p<0.0001, I^2=78%).



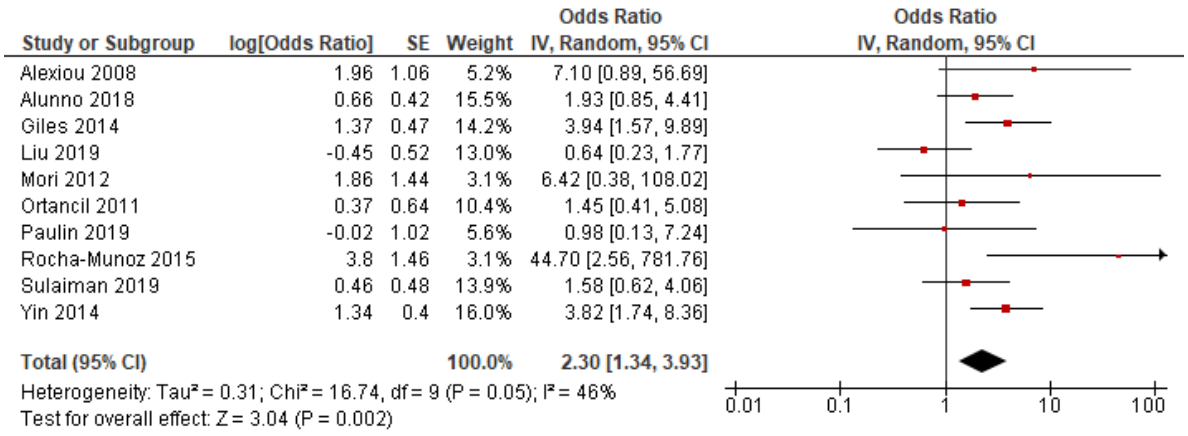
e-Figure 3 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 1.92 (95% confidence interval (CI): 1.32-2.80, p=0.0007/95% prediction interval (PI): 0.74-4.97) and 2.53 (95%CI: 1.26-5.08, p=0.009/95%PI: 0.36-17.5), respectively and there was no significant difference in these results (p=0.50). There remained considerable heterogeneity in case-control studies (chi^2=11.5, p=0.04, I^2=57%).



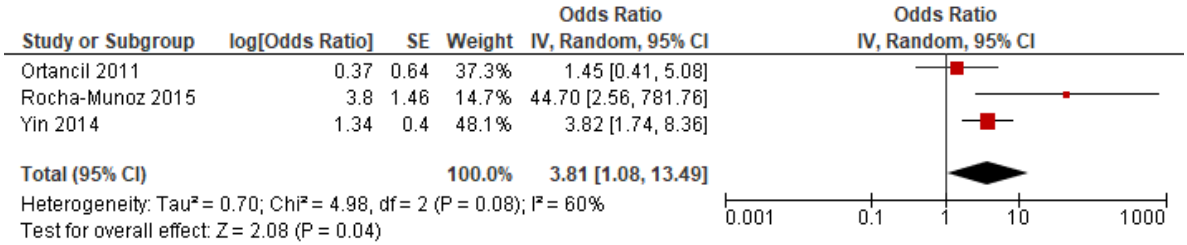
e-Figure 4 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.39 (95% confidence interval (CI): 0.11-0.67, p=0.006/95% prediction interval (PI): -0.53-1.31) and 0.50 (95%CI: 0.12-0.89, p=0.01/95%PI: -3.51-4.51), respectively and there was no significant difference in these results (p=0.65). There remained substantial heterogeneity in cross-sectional studies (chi^2=31.8, p=0.0001, I^2=75%).



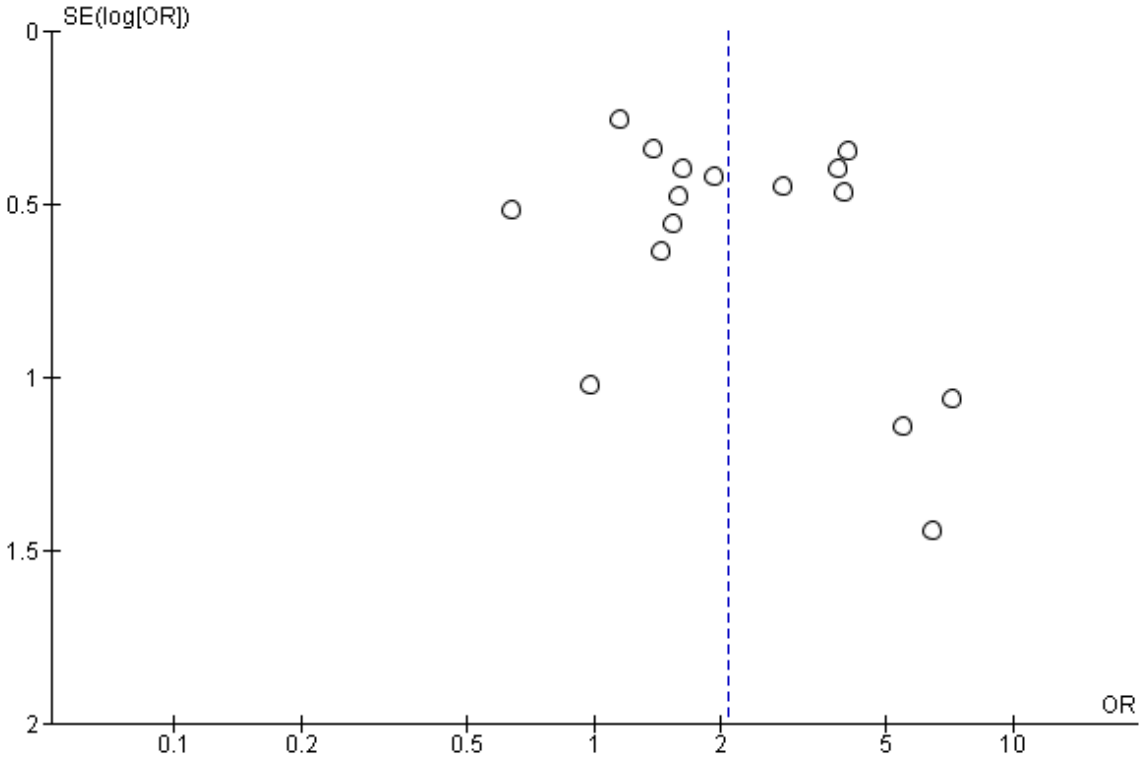
e-Figure 5 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test

The results of univariate analyses in 10 studies that examined the second generation of anti-CCP antibody were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 2.30 (95% confidence interval: 1.34-3.93, p=0.002/95% prediction interval: 0.55-9.61). There remained moderate heterogeneity (chi^2=16.7, p=0.05, I^2=46%).



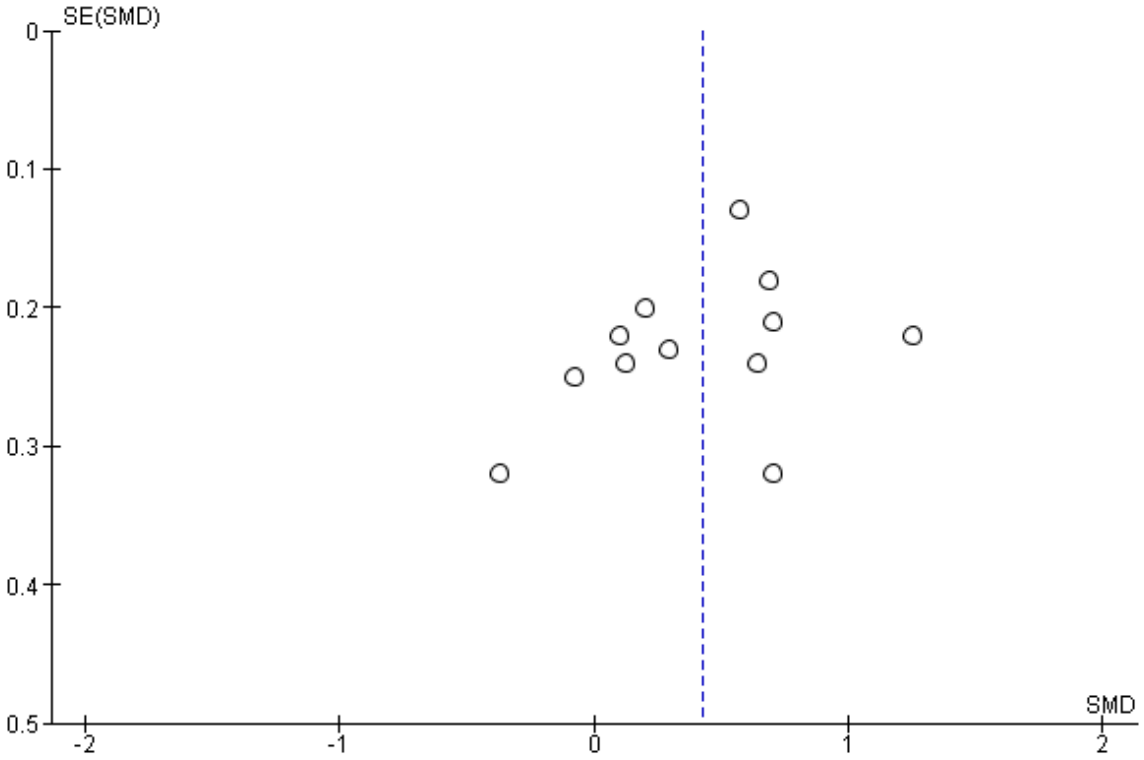
e-Figure 6 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test by the same manufacturer

The results of univariate analyses in three studies that examined the second generation of anti-CCP antibody test by the same manufacturer (Euroimmun, Lübeck, Germany) were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 3.81 (95% confidence interval: 1.08-13.5, p=0.04/95% prediction interval: 0.00->100.0). There remained considerable heterogeneity (chi^2=4.98, p=0.08, I^2=60%).



e-Figure 7 Funnel plot of the effect of the positivity of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.



e-Figure 8 Funnel plot of the effect of the titre of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.

e-Appendix

Search terms for each electronic database

Medline (Ovid) (1946 through 12 November 2019)

1 exp Arthritis, Rheumatoid/ (110375)

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).mp. (60240)

3 exp Lung Diseases, Interstitial/ (57554)

4 exp Pulmonary Fibrosis/ (21497)

5 (interstitial adj3 lung adj3 disease$).mp. (14632)

6 (interstitial adj3 pneumoni$).mp. (10671)

7 alveolitis.mp. (6068)

8 (pulmonary adj3 fibros$).mp. (29467)

9 exp Anti-Citrullinated Protein Antibodies/ (211)

10 cyclic citrullinated protein antibod$.mp. (28)

11 cyclic citrullinated peptide antibod$.mp. (664)

12 citrullinated protein antibod$.mp. (798)

13 citrullinated peptide antibod$.mp. (1001)

14 anti-CCP.mp. (1527)

15 ACPA.mp. (1369)

16 1 or 2 (157282)

17 3 or 4 or 5 or 6 or 7 or 8 (88395)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 (3452)

19 16 and 17 and 18 (64)

EMBASE (Ovid) (1947 through 12 November 2019)

1 exp rheumatoid arthritis/ (218675)

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).mp. (106635)

3 exp interstitial lung disease/ (82134)

4 exp lung fibrosis/ (81580)

5 (interstitial adj3 lung adj3 disease$).mp. (25821)

6 (interstitial adj3 pneumoni$).mp. (22196)

7 alveolitis.mp. (29356)

8 (pulmonary adj3 fibros$).mp. (32054)

9 exp cyclic citrullinated peptide antibody/ (6135)

10 cyclic citrullinated protein antibod$.mp. (78)

11 cyclic citrullinated peptide antibod$.mp. (6299)

12 citrullinated protein antibod$.mp. (1603)

13 citrullinated peptide antibod$.mp. (6704)

14 anti-CCP.mp. (4537)

15 ACPA.mp. (4424)

16 1 or 2 (285679)

17 3 or 4 or 5 or 6 or 7 or 8 (139209)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 (11794)

19 16 and 17 and 18 (452)

Science Citation Index Expanded (Clarivate Analytics) (1900 through 12 November 2019)

#1 TS=(rheumatoid NEAR/3 arthritis or rheumatoid NEAR/3 disease$ or rheumatoid NEAR/3 condition$) (165,017)

#2 TS=("interstitial NEAR/3 lung NEAR/3 disease$") OR TS=("interstitial NEAR/3 pneumoni*") OR TS=(alveolitis) OR TS=("pulmonary NEAR/3 fibros*") (4,751)

#3 TS=(anti cyclic citrullinated protein antibod* or anti cyclic citrullinated peptide antibod* or anti citrullinated protein antibod* or anti citrullinated peptide antibod* or anti CCP or ACPA) (4,483)

#3 #4 AND #5 AND #6 (2)

Cochrane Central Register of Controlled Trials (Cochrane Library) (accessed on the 12th of November 2019)

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees (5530)

#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3(arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab,kw (17434)

#3 MeSH descriptor: [Lung Diseases, Interstitial] explode all trees (738)

#4 MeSH descriptor: [Pulmonary Fibrosis] explode all trees (429)

#5 interstitial near/3 lung near/3 disease*:ti,ab,kw (1017)

#6 interstitial near/3 pneumoni*:ti,ab,kw (619)

#7 alveolitis:ti,ab,kw (732)

#8 pulmonary near/3 fibros*:ti,ab,kw (1440)

#9 MeSH descriptor: [Anti-Citrullinated Protein Antibodies] explode all trees (6)

#10 (cyclic citrullinated protein antibod*):ti,ab,kw (105)

#11 (cyclic citrullinated peptide antibod*):ti,ab,kw (178)

#12 (citrullinated protein antibod*):ti,ab,kw (199)

#13 (citrullinated peptide antibod*):ti,ab,kw (225)

#14 anti-CCP:ti,ab,kw (335)

#15 ACPA:ti,ab,kw (292)

#16 OR #2 (17673)

#17 #3 OR #4 OR #5 OR #6 OR #7 OR #8 (3148)

#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 (728)

#19 #16 AND #17 AND #18 (9)

Google Scholar (accessed on the 12th of November 2019)

("rheumatoid arthritis" OR "rheumatoid disease") ("interstitial lung disease" OR "interstitial pneumonia" OR "pulmonary fibrosis") ("anti cyclic citrullinated protein antibody" OR "anti cyclic citrullinated peptide antibody" OR "anti citrullinated protein antibody" OR "anti citrullinated peptide antibody")

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 9-10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 11-12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 12

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 14
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 13-14
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 15
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 16
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 17-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 18-20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 20
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 28

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Checklist items for Meta-analyses of Observational Studies in Epidemiology (MOOSE)	Reported on Page
Reporting of background should include	
• Problem definition	Page 6-7
• Hypothesis statement	Not described
• Description of study outcome(s)	Page 9
• Type of exposure or intervention used	Page 9
• Type of study designs used	Page 9
• Study population	Page 8
Reporting of search strategy should include	
• Qualifications of searchers (eg, librarians and investigators)	Not described
• Search strategy, including time period included in the synthesis and keywords	Page 9
• Effort to include all available studies, including contact with authors	Page 10
• Databases and registries searched	Page 9
• Search software used, name and version, including special features used (eg, explosion)	Not described
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From Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

BMJ Open

A systematic review and meta-analysis of the risk of rheumatoid arthritis-associated interstitial lung disease related to anti-cyclic citrullinated peptide (CCP) antibody

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040465.R1
Article Type:	Original research
Date Submitted by the Author:	26-Nov-2020
Complete List of Authors:	Kamiya, Hiroyuki; Tatebayashi Kosei Hospital, Department of Respiratory Medicine Panlaqui, Ogee; Northern Hospital, Department of Intensive Care Medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	RHEUMATOLOGY, Thoracic medicine < INTERNAL MEDICINE, Interstitial lung disease < THORACIC MEDICINE

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Title

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

Hiroyuki Kamiya[1], Ogee Mer Panlaqui[2]

[1] Department of Respiratory Medicine, Tatebayashi Kosei Hospital, Gunma, Japan

[2] Department of Intensive Care Medicine, Northern Hospital, Melbourne, Australia

Correspondence

Hiroyuki Kamiya

Department of Respiratory Medicine, Tatebayashi Kosei Hospital, Gunma, Japan

374-8533

Phone: +81-276-72-3140

Email: mlb04194@nifty.com

Word count

4475

Keywords

Rheumatoid arthritis, interstitial lung disease, anti-cyclic citrullinated peptide antibody, risk, review

Article Summary

Strengths and limitations of this study

- This systematic review and meta-analysis addressed the risk of RA-ILD related to both the presence and titres of anti-CCP antibody, which was not clarified in previous literature.
- A substantial variance in the results of primary studies, which may have been derived from the diversity of anti-CCP antibody assays and included subjects, may undermine the generalizability of the findings of this study.
- The usefulness of the findings may be limited in clinical practice because of high probability of the autoantibody positivity for RA without ILD and no standard cut-off points for its assays.

ABSTRACT

Objective

To clarify the risk of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) related to anti-cyclic citrullinated peptide (CCP) antibody.

Eligibility criteria

Patients with RA with and without ILD were eligible. The primary outcome was the prevalence or incidence of ILD. Primary studies of any design aside from a case report were eligible.

Information sources

Medline, EMBASE, Science Citation Index Expanded and Cochrane Central Register of Controlled Trials were searched from the inception through 12 November 2019.

Data extraction and risk of bias

Two reviewers independently selected eligible reports, extracted relevant data and assessed risk of bias using a modified Quality in Prognostic Studies tool.

Data synthesis

Meta-analysis was conducted using a random-effects model.

Quality of evidence

The Grades of Recommendation, Assessment, Development and Evaluation system was applied.

Results

Among 29 out of 827 records retrieved through electronic databases and four additional reports identified from other sources, 29 studies were focused for the review. A total of 10158 subjects were included and the mean age at inclusion was between 45.8 and 63.9 years. The mean RA duration was between 4.3 and 14.9 years. The positivity of anti-CCP antibody ranged from 50.7% to 95.8%. All studies except for two were deemed as high risk of bias. A pooled analysis of univariate results demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.10 (95%CI: 1.59-2.78). Similarly, the titre of anti-CCP antibody was significantly higher for RA-ILD with an SMD of 0.42 (95%CI: 0.20-0.65). These results were confirmed by multivariate analysis in the majority of studies and consistent by any subgroup and sensitivity analyses.

Conclusion

The presence and higher titres of anti-CCP antibody were suggested to be significantly associated with an increased risk of RA-ILD. However, the quality of evidence was rated as low or very low.

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that is characterized by a chronic synovial inflammation and eventual joint destruction.[1] Although arthritis is the main manifestation of the disease, it also damages diverse extra-articular organs such as heart, lung, kidney, eye and skin.[2] Interstitial lung disease (ILD) is one of the most common comorbidities of RA and the prevalence of ILD for patients with RA is reported to be 10% to 40% although it varies depending on the target population, a definition of the disease and diagnostic modalities.[3] A complication of ILD deeply affects the prognosis of RA because RA-associated ILD (RA-ILD) is often progressive and only a limited therapeutic option is available.[4] It is also complicated by acute exacerbation and lung cancer.[5-6] As a result, ILD is reported to be the third leading cause of deaths of RA [7] and approximately two thirds of patients with RA-ILD eventually die within 5 years, resulting in a hazard ratio of mortality about 3.0 in comparison to RA without ILD.[8] Moreover, the most common type of ILDs among RA-ILDs, i.e., usual interstitial pneumonia (UIP),[9] demonstrates the worst prognosis, which is similar to the mortality of idiopathic pulmonary fibrosis (IPF).[10] In this context estimating the risk of developing ILD will help clinicians' decision-making and may improve the prognosis of the disease.[11] Historically, a number of studies investigated risk factors for the development of ILD and some clinical information are reported to be associated with an increased risk of RA-ILD, which include male gender,[12] smoking,[13] severe disease [14] and rheumatoid factor (RF).[15] Anti-citrullinated peptide antibody (ACPA) is a specific marker for RA and included in the latest classification criteria for an accurate diagnosis of the disease.[16] Currently,

anti-cyclic citrullinated peptide (CCP) antibody, representing ACPAs is available commercially and usually measured in clinical practice. The autoantibody is also reported to be associated with an increased risk of extra-articular manifestations such as ILD.[17] However, previous studies noted inconsistent results [18-19] and the former systematic review seems to be limited by relatively a small number of studies and unclear definition of ILD and IPF.[20] The aim of this systematic review and meta-analysis was to clarify current evidence regarding the association of anti-CCP antibody with RA-ILD.

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[22]

Patient and public involvement

There was no patient and public involvement in the whole process of conducting this research.

Eligibility

Patients with RA were eligible for this review. RA was diagnosed based on its widely used classification criteria, i.e., the 1987 American College of Rheumatology classification criteria [23] and the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria.[16] ILD was characterized by interstitial inflammatory and fibrotic changes in pulmonary parenchyma and diagnosed based on symptomatic, functional, radiological and/or pathological findings.[24] The

pattern of ILD was classified following the international multidisciplinary classification such as an official American Thoracic Society/European Respiratory Society statement.[25] Other pulmonary lesions associated with RA such as bronchiolitis, bronchiectasis and pleuritis were all excluded. An overlap with other connective tissue diseases was included if RA was the main disease of interest in the study. There was no limitation regarding demographic features of subjects, such as gender and ethnicity, duration of RA and ILD and the severity of the disease unless they were less than the age of 18. Subjects were allowed to participate at any point in time along their clinical course of the disease.

Anti-CCP antibody was examined using Enzyme-Linked Immunosorbent Assay (ELISA).[26] Although measurements of anti-CCP antibody were different among manufacturers and each institution adopted a different test, all kinds of anti-CCP antibody assays were eligible for the review. However, ACPA, which was not specified as anti-CCP antibody, was excluded because it may have represented autoantibodies against different citrullinated peptides.

The outcome of interest in this review was the prevalence or incidence of ILD. Any design of primary studies other than a case report was eligible if it described the association of anti-CCP antibody with RA-ILD. Conference proceedings, letters or editorials and review articles were ineligible. Only reports published in English was considered.

Search strategy

The following electronic databases were searched, Medline, EMBASE, Science Citation Index Expanded and Cochrane Central Register of Controlled Trials, using subject

headings and text words related to study population such as ‘rheumatoid arthritis’, ‘interstitial lung disease’ and ‘anti-cyclic citrullinated peptide antibodies’ (e-Appendix). Search terms were constructed referring to a systematic review in a similar research area identified through the Cochrane Database of Systematic Reviews (CDSR).[27] Methodology filters were not used to avoid limiting the sensitivity of the search. The search was covered from the inception of each database through to the 12th of November 2019. The reference lists of eligible studies and relevant review articles were also hand-searched to identify additional reports. Google Scholar was employed to search grey literature.[28]

Study selection and data collection process

Two reviewers (H.K. and O.M.P.) independently examined titles and abstracts of all retrieved articles to select eligible reports. The same reviewers also extracted relevant data based on a modified data extraction form, which was previously published in a protocol paper for a systematic review.[29] Any uncertainty or disagreement between reviewers arising from these processes was resolved through discussion. The following data was extracted from each eligible study: first author’s name, year of publication, study location, study design, sample size and its demographic features, ILD patterns if available, manufacturers of anti-CCP antibody tests and their cut-off points if available, a proportion of positivity and titres of anti-CCP antibodies for RA with and without ILD, methods for statistical analysis, summary statistics and items associated with a risk of bias.

Risk of bias in individual studies

As all studies investigated the association of anti-CCP antibody with RA-ILD as risk prediction, the Quality in Prognostic Studies (QUIPS) tool was modified and applied to assess a risk of bias in individual studies.[30] However, one of six domains that constitute the tool, i.e., 'the attrition of study population', was considered irrelevant and thus excluded because all studies were designed as cross-sectional or case-control studies. Each domain received an individual bias rating (low, moderate or high), with an overall risk of bias based on a total rating of all domains. For example, a study showing a low risk of bias across all domains was deemed as being subject to a low risk of bias overall.

Statistical analysis

Summary statistics

The risk of RA-ILD associated with the presence of anti-CCP antibody was measured using either risk ratios (RRs) or odds ratios (ORs). In a case where titres of anti-CCP antibody were compared between the two comparative groups with or without ILD, the mean difference (MD) was calculated to reveal the difference of the autoantibody titres. If the median was utilized instead of the mean, it was presented for each of the two groups. If the summary statistics were not provided directly, the ORs or RRs were calculated manually based on the absolute number of the outcome across the two comparative groups.

Data synthesis

The effect of an association between anti-CCP antibody and RA-ILD was statistically combined if it was presented using the same statistics in three or more studies. The

results were summarized using ORs if anti-CCP antibody was reported as binary (positive/negative). If the titre of anti-CCP antibody was reported, a standardized MD (calculated as Hedge's g) was utilized to combine the results.[31] If the median, range or interquartile range was described to report the autoantibody titres, they were converted to the mean and standard deviation, using a formula reported by a previous study, to be summarized as SMDs.[32] Only the results of univariate analysis were combined whereas those of multivariate analysis were described qualitatively because adjusted variables in multivariate models varied substantially between studies and pooling these data could be misleading. If meta-analysis was feasible from the collated data, it was conducted using a random-effects model employing the DerSimonian and Laird method.[33] Meta-analysis was conducted using the statistical software package, Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical significance was considered with a p-value of <0.05. If combining data was deemed inappropriate due to a small number of studies, the results were reported qualitatively.

Heterogeneity between studies

Between-study variance was assessed using both Q statistics and I^2 value. For the assessment of heterogeneity between studies, statistical significance was considered with a p-value of <0.1 due to the low power of the test. Magnitude of heterogeneity was categorised as low (<30%), moderate (≥30%, <50%), considerable (≥50%, <70%) and substantial (≥70%).[34] When heterogeneity was identified, the 95% prediction interval (PI) was presented in addition to the 95% confidence interval (CI).[35] To better interpret sources of heterogeneity, subgroup analysis was conducted based on study

location (Asia or non-Asia) and study design (cross-sectional or case-control). Sensitivity analysis was also considered focusing on the measurements of anti-CCP antibody (same manufacturer and same generation of the autoantibody assay). A meta-regression analysis was also conducted to assess the effect of other potential confounders, i.e., age, gender, smoking history, RA duration, diagnostic criteria for RA and ILD and a proportion of positivity of anti-CCP antibody. The analysis was conducted using SAS ODA (SAS Institute Inc., Cary, NC, USA).

Meta-biases

Small study bias (such as publication bias) was examined graphically using a funnel plot and statistically by the Egger's test using Stata 14 (STATA Corp LLC., College Station, TX, USA) if ten or more studies were available for meta-analysis.[36] Statistical significance of the test was considered with a p-value of <0.1 due to the low power of the test.

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) for prognosis [37] was applied to assess the credibility of evidence generated from this review because all studies investigated the association of anti-CCP antibody with RA-ILD as risk prediction.

Results

Search for eligible studies

Out of a total of 827 records identified through a search of five electronic databases, 182 duplicates were removed and 645 records were screened by titles and abstracts. After

320 records consisting of non-English reports (n=16) and 304 articles of ineligible types (conference proceedings (n=153), case reports (n=72), editorials or letters (n=10) and review articles (n=69)) and 265 irrelevant papers were further excluded, the remaining 60 records were retrieved as full-texts. Out of these, 29 reposts/studies were eligible for the review and additionally four reports were identified through a hand-search of references of eligible studies. As a result, a total of 33 reports were considered for the review (Figure 1). In each of three different groups, which conducted two studies sharing the same cohort, only the study with a larger sample size was included for the review.[38-40] Similarly, among three studies conducted by one group, the study with the largest sample size was included for the review.[41] Furthermore, another study among these three studies was also included because it reported two different cohorts, one of which was not overlapped by the other studies.[42] There was also a study that reported two different cohorts, only one of which was included because it was not overlapped by the other studies.[43] Finally, a total of 29 studies/cohorts were focused for further analysis.[38-66]

Characteristics of included studies

Study location of a total of 29 studies were distributed globally with Asia in the largest number (n=15), which was followed by the Americas (n=7), Europe (n=3), Africa (n=2) and others (n=2). 22 studies were cross-sectional while the remaining seven were case-control studies. A complication of other CTDs was mentioned in 10 studies and ILD patterns were detailed in three studies. The number of subjects enrolled in each study ranged from 41 to 2702, which amounted to 10158 subjects in total and the mean age at inclusion was between 45.8 and 63.9 years. The proportion of men, smoking

history and ILD ranged from 4.0% to 90.1%, 1.9% to 98.9% and 4.9% to 71.6%, respectively. The mean duration of RA was between 4.3 and 14.9 years and the disease activity, which was represented by the disease activity score (DAS) 28, was between 2.5 and 5.4 as a mean value (Table 1). Other baseline characteristics of included studies were depicted in the supplementary file (e-Table 1). The generation of anti-CCP antibody tests was specified in 14 studies, which consisted of the second generation in 12 studies and the third generation in two studies. The proportion of positivity of anti-CCP antibody was reported in 21 studies, which ranged from 50.7% to 95.8% while the titre of the autoantibody was described in 18 studies (Table 2).

Risk of bias in individual studies

All studies except for two contained high risk of bias rating in at least one domain and thus was deemed as high risk of bias. Among the five domains constituting the QUIPS tool, the risk of bias for statistical analysis and reporting and ILD confirmation were rated as high in the majority of studies due to no or insufficient information regarding model building process and inconsistent diagnostic procedures. The remaining two studies were rated as moderate risk of bias (Table 3).

Association of anti-CCP antibody with RA-ILD

Univariate result

The association of positivity of anti-CCP antibody with RA-ILD was reported in 20 studies. Eight out of these studies demonstrated significant results with the ORs ranging from 1.98 to 44.5 (Table 2). Excluding one study,[47] which conducted a stratified analysis based on the level of the autoantibody titre and thus was not combined, a

meta-analysis of 19 out of these 20 studies demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.10 (95%CI: 1.59-2.78) with moderate heterogeneity (chi^2=29.7, p=0.04, I^2=39%) (Figure 2).

The titre of anti-CCP antibody was compared between RA with and without ILD in 18 studies. Two studies employed the same assay (INOVA Diagnostics) to examine the titre of anti-CCP antibody and reported higher titres associated with RA-ILD with an MD of 79.5 (95%CI: 9.72-149.3) [46] and a median value of 220 for RA-ILD vs. 120 for RA without ILD [48], respectively. Other two studies examined the titre of the autoantibody using another assay (Euroimmun). One of them demonstrated higher titres associated with RA-ILD with a median value of 77.9 for RA-ILD vs. 30.2 for RA without ILD [59] and the other study reported non-significant result with an MD of 143.2 (95%CI: -78.1-364.5).[62] All of the other studies utilized a different or unknown measurement to examine the titre of the autoantibody. Overall, 11 studies demonstrated significant results with higher titres associated with RA-ILD (Table 2). Excluding six studies [40, 44, 47, 51, 56, 59] where MDs were unable to be calculated, a meta-analysis of 12 out of these 18 studies demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD with an SMD of 0.42 (95%CI: 0.20-0.65) with considerable heterogeneity (chi^2=36.0, p=0.0002, I^2=69%) (Figure 3).

Multivariate result

Multivariate analysis was conducted in eight studies where detailed results were available in seven studies and adjusted variables were diverse between studies. Six of these seven studies demonstrated a positive association between the presence or higher titres of anti-CCP antibody and RA-ILD and the results were statistically significant in

four studies (Table 2). One study [65] revealed the association of positivity of anti-CCP antibody with RA-ILD as an OR of 3.50 (95%CI: 1.52-8.04) (Table 2). The association of the titre of anti-CCP antibody with RA-ILD was reported by three studies as ORs of 1.41 (95%CI: 1.01-1.97), 1.08 (95%CI: 1.03-1.12) and 1.06 (95%CI: 1.02-1.10).[47, 53, 59, respectively]

Subgroup analysis

Subgroup analysis was conducted based on both study location and study design. There was no significant difference in the effect size of the positivity of anti-CCP antibody with ORs of 2.02 (95% CI: 1.37-2.99) by Asian reports and 2.22 (95%CI: 1.45-3.39) by non-Asian reports (p=0.75) (e-Figure 1). Similarly, there was no significant difference in the effect size of the titre of anti-CCP antibody with SMDs of 0.38 (95%CI: 0.04-0.71) by Asian reports and 0.49 (95%CI: 0.24-0.74) by non-Asian reports (p=0.58) (e-Figure 2). There was no significant difference in the effect size of the positivity of anti-CCP antibody with ORs of 2.00 (95%CI: 1.48-2.71) by cross-sectional studies and 2.53 (95%CI: 1.26-5.08) by case-control studies (p=0.55) (e-Figure 3). Similarly, there was no significant difference in the effect size of the titre of anti-CCP antibody with SMDs of 0.39 (95%CI: 0.11-0.67) by cross-sectional studies and 0.50 (95%CI: 0.12-0.89) by case-control studies (p=0.65) (e-Figure 4).

Sensitivity analysis

Sensitivity analysis was conducted focusing on the measurements of anti-CCP antibody. A pooled analysis of 10 studies that examined the second generation of anti-CCP antibody test demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.22 (95%CI: 1.42-3.45) (e-Figure 5). A pooled

analysis of three studies that examined the second generation of anti-CCP antibody test by the same manufacture (Euroimmun, Lübeck, Germany) demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 3.81 (95%CI: 1.08-13.5) (e-Figure 6).

Sensitivity analysis was also conducted for the titre of anti-CCP antibody focusing on the same summary statistics. A pooled analysis of seven studies where MDs were available without a conversion of summary statistics demonstrated higher titres associated with RA-ILD with an MD of 52.5 (95%CI: 5.76-99.2) (e-Figure 7).

All of these sensitivity analyses generated no significant difference of the results.

Meta-regression analysis

The effect of the presence of anti-CCP antibody on RA-ILD was not influenced by any other potential confounders. Similarly, the association of the titre of anti-CCP antibody with RA-ILD was not affected by any of them although gender and RA duration were significant in univariate analysis (e-Table 2).

Additional analysis

Two funnel plots (for both positivity and titre of anti-CCP antibody) were constructed to investigate small study bias, both of which demonstrated no apparent asymmetry (e-Figure 8 and e-Figure 9, respectively). This graphical assessment was confirmed statistically by the Egger's test, which demonstrated no statistical significance (p=0.15 and 0.28, respectively).

Assessment of evidence level

Study limitation was considered present in all of the evidence because no studies were deemed as low risk of bias. Publication bias was also considered present in all of the evidence due to the property of studies of risk prediction [37] although it was not confirmed in both graphical and statistical analyses regarding univariate results. Overall, the level of evidence derived from this review was rated as low or very low (Table 4).

Discussion

This study demonstrated using a pooled analysis of univariate results that the presence of anti-CCP antibody was significantly associated with RA-ILD and the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD. The results were confirmed by multivariate analyses in the majority of studies that reported it. These findings suggest that anti-CCP antibody is related to an increased risk of ILD for patients with RA. As this review was based on a large number of studies conducted globally and the results were reproduced by any subgroup and sensitivity analyses, these findings will be generalizable to a broader population.

It is desirable and important to identify a high risk group of patients with RA who are likely to develop ILD because it is often progressive and worsens the prognosis of the disease.[67] If the development of ILD can be predicted, it will help clinicians' decision-making and facilitate an efficient use of limited medical resources to change clinical course of the disease. Much effort has been made to identify clinical information such as serum biomarkers that can easily be obtained and help estimate the risk of ILD for patients with RA.[68] Tests for ACPAs emerged as a tool to diagnose early RA with higher specificity than traditionally employed RF.[69] They date back to the discovery of anti-perinuclear factor and anti-keratin antibody in the sera of patients

with RA, which recognized the citrullinated protein filaggrin.[70] Subsequently, cyclic citrullinated peptides (CCP) were synthesized to improve test performance [71] and after further evolution currently the third generation of anti-CCP antibody test is commercially available.[72] Anti-CCP antibody is not only helpful to diagnose RA but also reported to be associated with extra-articular manifestations of the disease.[73] The recent meta-analysis demonstrated an increased risk of RA-ILD as a result of serum anti-CCP antibody positivity.[20] Although a number of specific citrullinated proteins were discovered such as fibrinogen [74] and α-enolase,[75] a diagnostic significance of specific autoantibodies directed against these autoantigens has yet to be established.[76]

RA is classified as a systemic autoimmune disorder although the pathogenesis of the disease has been under dispute for many years.[77] Recent research suggests that the breakdown of immunological tolerance initially occurs in the lungs under the influence of environmental stress such as exposure to cigarette smoke and genetic susceptibility.[78] In short, smoking accelerates the activity of the enzyme peptidylarginine deiminase that catalyses the posttranslational convert of arginine to citrulline, which eventually induces autoimmune reaction and leads to the formation of autoantibodies against citrullinated peptides under the interplay of both T and B lymphocytes.[79] In these processes, a number of cytokines are generated and may promote fibrotic changes of the lung.[80] Smoking is related to the development of ILD, in particular, UIP, which is the most common type among RA-ILDs [9] and contributes to the formation of ACPAs. Therefore, it is most likely that anti-CCP antibody is closely associated with the development of ILD for genetically susceptible subjects with smoking history and this relationship was confirmed in this report.

The current study is different from the previous systematic review [20] in that it included a larger number of studies and subjects and thus the result is considered more reliable. It also demonstrated that the titre of anti-CCP antibody was higher for RA-ILD than RA without ILD. This finding is meaningful because anti-CCP antibody may be positive in the majority of patients with RA regardless of the presence of ILD. Indeed, the proportion of positivity of anti-CCP antibody for RA without ILD in this review ranged from 49.1% to 95.8% with the median value of 71.0%. When the group of RA without ILD is positive for anti-CCP antibody with high frequency, the benefit of the autoantibody test for screening patients with RA at a higher risk of developing ILD will be limited. Conversely, the finding of titres may be more informative because it can also be employed to patients with RA without ILD who are tested positive for the autoantibody. Therefore, titres of anti-CCP antibody may be more useful than just its presence to estimate the risk of developing ILD. However, the interpretation of this finding also needs a caution because it was derived from a comparison between RA-ILD and RA without ILD and thus does not indicate any cut-off point that defines a high or low titre of the autoantibody. As a result, in usual clinical practice, clinicians need to assess the implication of the titre of anti-CCP antibody in the context of a total evaluation. If the titre of the autoantibody is combined with clinical features such as age, gender and smoking history alongside with other biomarkers such as Krebs von den Lungen-6 (KL-6), creating composite scores, it would be more beneficial to identify a group with a higher risk of developing ILD. However, what makes the issue more complicated is the variability of measurements of anti-CCP antibody, which was produced by a number of manufacturers. The sensitivity and specificity varies depending on the tests and the titres are also different between assays.[81] Although an

SMD was employed in this review to enable the comparison of titres derived from different tests, the result may be difficult to be applied in clinical practice. Furthermore, anti-CCP antibody is reported to be closely associated with bronchiolar disease, which is also a common pulmonary complication associated with RA alongside with ILD.[54] Although bronchiolar disease was excluded in this review, it is possible that the disease was missed by the researcher or not selectively reported. If this was the case, the precise association of anti-CCP antibody with RA-ILD will be compromised. Anti-CCP antibody may also be affected by a number of other potential confounders such as age, gender, smoking history, RA duration, diagnostic criteria for RA and ILD and the proportion of positivity of anti-CCP antibody, which were diverse between studies. Although none of these confounders were found to be significantly associated with the heterogeneity of the results, it may possibly have been influenced by other clinical factor such as previous treatment. Therefore, the findings of this review may not be directly applicable to usual clinical practice and clinicians should consider all of the factors that can affect the presence or titres of anti-CCP antibody and assess the risk of ILD for patients with RA on a case-by-case basis.

There are other methodological limitations or caveats that need to be kept in mind to appropriately interpret the findings of this study. First, this review specifically focused on anti-CCP antibody and excluded ACPAs, which were not specified as anti-CCP antibody since it may have represented autoantibodies against different citrullinated peptides. However, ACPAs other than anti-CCP antibody are not usually used in clinical practice and many rheumatologic teams may use the term ACPA for anti-CCP antibody. Therefore, this narrow inclusion criterion may have excluded some studies

with a large number of subjects that could have reinforced the strength of meta-analysis. Second, this review was only composed of cross-sectional and case-control studies and thus causality between anti-CCP antibody and RA-ILD cannot be deducted although it is aetiologically plausible. Third, selection bias of subjects in individual studies cannot be ruled out. Patients with RA-ILD at relatively advanced stage may have been included for the review. If this was the case, the findings may not be applicable to an early stage of the disease and become useless for screening purpose. Fourth, anti-CCP antibody may be most closely related to UIP among other types of ILD complicated with RA. However, the association between anti-CCP antibody and individual ILD patterns could not be elucidated in this review because most of the studies did not report them. Finally, no studies were deemed as low risk of bias given that most of them were retrospectively designed cross-sectional or case-control studies. Due to this study limitation, the level of evidence obtained from this review was all rated as low or very low although univariate results in relatively a larger number of studies were combined to generate an average estimate. Therefore, more research with high quality using a prospective cohort design needs to be accumulated to make a definitive conclusion or solidify the findings of this review.

Conclusion

This systematic review and meta-analysis suggested that the presence of anti-CCP antibody was significantly associated with RA-ILD and the titre of the autoantibody was significantly higher for RA-ILD than RA without ILD. However, an applicability of these findings may be limited due to the heterogeneity of included studies.

Ethics approval and participant consent

Neither ethics approval nor participant consent was required as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

Data sharing

The dataset used and/or analysed for this review will be available from the corresponding author upon a reasonable request and may become open to the public through a digital repository (such as Dryad) after the final result is published in a journal.

Conflict of interest

None to declare.

Funding

This research received no specific grant from any funding agency in either the public, commercial, or not-for-profit sectors.

Authors' contributions

H.K. planned the entire research project and analysed the data. He also summarized the result and wrote the manuscript. H.K. has full access to the data and takes responsibility for its integrity as well as the accuracy of the analysis.

O.M.P. contributed to the design of the research project and conducted the literature search and data extraction. He was also involved in revising the manuscript.

All researchers provided thoughts and opinions to compile a draft paper and approved of the final version of the manuscript.

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Table 1 Baseline characteristics of included studies[a]

Study	Location	Design	Number (n)	Age at inclusion (years)	Gender (male) (n (%))	Smoking (n (%))	Proportion of ILD (n (%))[b]	Disease duration (RA) (years)	Disease activity[c]	Other CTDs (n)	ILD patterns (on HRCT) (n)
Alunno 2018 [38]	Italy	Cross-sectional	252	61.7±0.8	56 (22.2)	-	37 (20.2) (n=183)	12.6±0.6	-	-	-
England 2019 [39]	US	Cross-sectional[d]	1823	63.5±11.0	(90.1)	(89.5)	90 (4.9)	11.1±11.5	4.0±1.6	-	-
Giles 2014 [40]	US	Cross-sectional[d]	177	59±8[g]	71 (40.1)	105 (59.3)	120 (67.8)	9 (5-19) vs. 8 (4-16)[g]	3.7 (2.9-4.4)[g] (CRP)	-	-
Chen 2013 [41]	China	Cross-sectional	103	49.1±14.7	27 (26.2)	2 (1.9)	63 (61.2)	4.3±5.7	4.4±1.4	-	-
Chen 2015 [42]	China	Cross-sectional	71	60.7±12.1[e]	37 (52.1)	35 (49.3)	49 (69.0)	12.8±10.3 vs. 8.4±8.1 (n=68)	3.7±1.2 vs. 3.3±1.7 (n=43)	-	-
Doyle 2015 [43]	US	Cross-sectional[d]	75	61.5±12.7[e]	11 (14.7)	41 (54.7)	-	-	-	-	-

Abdel-Hamid 2019 [44]	Egypt	Cross-sectional	50	45.8±12.3	2 (4.0)	-	19 (38.0)	9.8±6.6	4.7±1.3	0	-
Akiyama 2016 [45]	Japan	Cross-sectional	395	58.5±13.1	49 (12.4)	69 (20.3) (n=340)	78 (19.7)	129.4±115.2 (months)	4.9±1.6 (n=372)	38 (SS, SSc, PM/DM, SLE)	-
Alexiou 2008 [46]	Greece	Case-control	136	-	-	-	N/A (ILD 11/no ILD 125)	-	-	-	-
Correia 2019 [47]	US	Cross-sectional	453	59.6±15.7	(19.4)	-	(6.0)	-	-	0	-
Fadda 2018 [48]	Egypt	Cross-sectional	88	50.2±9.0	13 (14.8)	87 (98.9)	63 (71.6)	10.2±6.2	14 (1-32) vs. 12 (3-25) (median (range)) (CDAI)	0	UIP 62%, NSIP 27%, Mixed 1%
Furukawa 2012 [49]	Japan	Case-control	450	63.9±10.9[e]	89 (19.8)	130 (28.9)	N/A (ILD 129/no ILD 321)	14.5±10.9[e]	-	-	-
Kakutani 2019 [50]	Japan	Cross-sectional	2702	62.8±12.5	(17.8)	(28.9)	261 (9.7)	9 (15) vs. 10 (17) (median (IQR))	3.2±1.0 (ESR)	-	-

Kelly 2014 [51]	UK	Case-control	460	-	220 (47.8)	-	N/A (ILD 230/no ILD 230)	-	-	-	-
Liu 2019 [52]	China	Cross-sectional	101	54 (17) (median (IQR))	26 (25.7)	-	23 (22.8)	7 (14) (median (IQR)	4.0±1.9	-	-
Matsuo 2018 [53]	Japan	Cross-sectional	312	63.5±12.7	41 (13.1)	95 (30.4)	26 (8.3)	14.9±11.6	2.5±1.1 (CRP)	11 (not specified)	-
Mori 2012 [54]	Japan	Cross-sectional	356	72.5 (12.3) (n=24) vs. 59.0 (16) (n=302) (median (IQR))	85 (23.9)	76 (21.3)	24 (6.7)	1.5 (6.3) (n=24) vs 0 (6) (n=302) (median (IQR))	-	-	UIP 5, NSIP 19
Ortancil 2011 [55]	Turkey	Cross-sectional	67	57.4±13.5	14 (20.9)	-	12 (17.9)	10.2±11.7[e]	-	-	-
Park 2016 [56]	Korea	Cross-sectional	83	53.7±10.1[e]	10 (12.0)	-	7 (8.4)	-	-	-	UIP 6, Indeterminate 1

Paulin 2019 [57]	Argentina	Case-control	118	56.7±15.7	26 (22.0)	52 (44.1)	N/A (ILD 52/ no ILD 66)	6 (8) (median (IQR))	3.4±1.1	-	-
Restrepo 2015 [58]	US	Cross-sectional	779	53.7±13.3 (n=632)[e]	161 (25.5) (n=632)	357 (56.5) (n=632)	69 (8.9)	10.5±10.3[e]	5.4±1.4[e]	-	-
Rocha-Munoz 2015 [59]	Mexico	Case-control	81	51.0 (36.0-72.0) vs. 49.0 (24.0-73.0) (median (range))	-	22 (27.2)	N/A (ILD 39/no ILD 42)	7.0 (1.0-35.0) vs. 6.5 (0.75-25.0) (median (range))	3.9 (1.7-5.3) vs. 2.5 (1.7-5.1) (median (range))	0	-
Sargin 2018 [60]	Turkey	Cross-sectional	83	59.3±12.1	20 (24.1)	9 (10.8)	43 (51.8)	-	-	0	-
Sulaiman 2019 [61]	Malaysia	Cross-sectional	159	48.3±14.1	25 (15.7)	-	21 (13.2)	-	4.7±0.9 (ESR)	0	-
Tian 2016 [62]	China	Cross-sectional	75	-	29 (38.7)	-	37 (49.3)	-	-	-	-
Wang 2015	China	Cross-sectional	41	60.7±12.4[e]	20 (48.8)	-	25 (61.0)	108 (5-360) vs. 72	-	-	-

[63]								(2-552) (months) (median (range))			
Yang 2019 [64]	Korea	Case-control	308	57.0±12.0[e]	76 (24.7)	39 (17.7) (n=220)	N/A (ILD 77/ no ILD 231)	11.0±7.3[e]	-	-	-
Yin 2014 [65]	China	Cross-sectional	285	51.7±13.4[e]	74 (26.0)	59 (20.7)	71 (24.9)	9.0 (16.0) vs. 4.0 (9.1) (median (IQR))	5.4±1.7	61[f] (SS 41, SSc 7, PM/DM 4, SLE 16)	-
Zhang 2018 [66]	China	Case-control	75	41-69 vs. 40-70 (range)	30 (40.0)	-	N/A (ILD 28/ no ILD 47)	-	-	0	-

a, Comparisons correspond to RA-ILD vs. RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified;

b, N/A indicates not applicable due to case-control studies;

c, Disease activity was estimated using disease activity score (DAS) 28 unless otherwise specified and a laboratory marker used to calculate the score was described as either ESR or CRP if it was specified;

d, indicates a prospective study while all of the other studies are retrospectively designed;

e, calculated combining the figure in both comparative groups;

f, some patients had multiple CTDs;

g, unknown statistics;

CDAI, clinical disease activity index; CRP, C-reactive protein; CTD, connective tissue disease; ESR, erythrocyte sedimentation rate; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IQR, interquartile range; NSIP, non-specific interstitial pneumonia; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; SSc, systemic sclerosis; UIP, usual interstitial pneumonia;

Table 2 Anti-cyclic citrullinated peptide (CCP) antibody tests and its association with rheumatoid arthritis-associated interstitial lung disease[a]

Study	Measurements of anti-CCP antibody (manufacturer) (cut-off points)	Proportion of anti-CCP antibody	Titres of anti-CCP antibody	Univariate result (positivity)	Univariate result (titre)	Multivariate result (positivity)	Multivariate result (titre)	Adjusted variables
Alunno 2018 [38]	Second generation (Thermo Fisher Scientific or Aesku)	28/37 (75.7) vs. 90/146 (61.6)	-	OR 1.94 (0.85-4.42)	-	-	-	-
England 2019 [39]	Second generation	(86.7) vs. (76.7)	-	**OR 1.98, p=0.03**	-	-	-	-
Giles 2014 [40]	Second generation	51/57 (89.5) vs. 82/120 (68.3)	152 (99-194) (n=32) vs. 89 (11-152) (n=120)[d]	**OR 3.94 (1.57-9.90)**	**p=0.0005[b]**	-	-	-
Chen 2013 [41]	Not specified	-	231.8±178.0 (n=63) vs. 196.8±161.1 (n=40)	-	MD 35.0 (-33.0-103.0)	-	-	-
Chen 2015 [42]	Not specified	-	142.6±151.9 (n=49) vs. 154.6±151.4 (n=22)	-	MD -12.0 (-88.2-64.2)	-	-	-

Doyle 2015 [43]	Not specified	-	188±133 vs. 83±113	-	-	-	-	-
Abdel-Hamid 2019 [44]	Third generation	30/50 (60.0)	100 (390) (n=19) vs. 20 (298) (n=31) (median (IQR))	-	**p=0.04**[b]	-	-	-
Akiyama 2016 [45]	Not specified (≥4.5 U/mL)	69/75 (92.0) vs. 245/305 (80.3)	-	**OR 2.82 (1.17-6.81)**	-	OR 1.80 (0.70-4.40) (positive with high titre (>13.5 U/mL))	-	age, sex, smoking, RF
Alexiou 2008 [46]	Second generation (INOVA Diagnostics) (20 IU/mL)	10/11 (90.9) vs. 73/125 (58.4)	152.6±104.5 (n=11) vs. 73.1±114.0 (n=125)	OR 7.12 (0.89-56.9)	**MD 79.5 (9.72-149.3)**	-	-	-
Correia 2019 [47]	Second generation (Euro-Diagnostica) (≥6 U/mL)	-	113.0±5.9 (162.4 vs. 109.9) (mean±SE)	OR 1.51 (0.48-4.74) (low titre), 2.61 (0.59-11.5)(moderate titre), 2.83 (0.96-8.39) (high titre)	**p=0.04**[b]	-	**OR 1.41 (1.01-1.97)/1 group of titre**	age, smoking

Fadda 2018 [48]	Third generation (INOVA Diagnostics) (20 U/mL)	84/88 (95.5)	220 (0-500) (n=63) vs. 120 (30-400) (n=25), (median (range))	-	**MD 67.5 (19.5-115.5)[c], OR1.006 (1.001-1.011) (/1 U/mL)**	-	-	-
Furukawa 2012 [49]	Not specified (Medical & Biological Laboratories)	116/129 (89.9) vs. 278/321 (86.6)	-	OR 1.38 (0.71-2.69)	-	-	-	-
Kakutani 2019 [50]	Not specified	(93.2) vs. (82.9)	-	**OR 2.83, p=0.002**	-	-	-	-
Kelly 2014 [51]	Not specified	-	180 (8-340) vs. 78 (8-340) (median (range))	**OR 4.00 (2.00-7.80)**	**p=0.02[b]**	**OR 0.33, p=0.003**	-	age, sex, smoking, RF
Liu 2019 [52]	Second generation (Euro- Diagnostica) (≥25 U/mL)	77/101 (76.2)	-	OR 0.64 (0.23-1.80)	-	-	-	-

Matsuo 2018 [53]	Not specified	25/26 (96.2) vs. 235/286 (82.2)	199.7±104.6 (n=26) vs. 120.7±112.6 (n=286)	**OR 5.43 (1.11-98.0)**	**MD 79.0 (34.1-123.9), OR 1.06 (1.02-1.10) (/10U/mL)**	-	**OR 1.08 (1.03-1.12) (/10U/mL)**	age, smoking, RF, LDH, CRP, ESR, KL-6, MMP-3, IL18, dose of MTX, dose of PSL
Mori 2012 [54]	Second generation (Axis-Shield Diagnostic) (>4.6 U/mL)	24/24 (100) vs. 294/332 (88.6)	283.5 (99.0-794.0) (n=24) vs. 81.1 (21.0-249.0) (n=302) (median (1st-3rd quartile)	OR 6.41 (0.38-107.8)	**MD 275.2 (184.1-366.3)[e]**	RR 2.73 (0.91-8.23) (positive with high titre (≥90 U/mL))	-	age, sex, smoking, advanced stage, RF, HLA-DRB1*04, HLA-DRB1*1502
Ortancil 2011 [55]	Second generation (Euroimmun)	7/12 (58.3) vs. 27/55 (49.1)	-	OR 1.45 (0.41-5.08)	-	-	-	-
Park 2016 [56]	Not specified (Roche Diagnostics) (≥17.0 U/mL)	69/83 (83.1)	-	-	0.22[c]	-	-	-
Paulin 2019 [57]	Second generation	45/47 (95.7) vs. 46/48 (95.8)	-	OR 0.98 (0.13-7.24)	-	-	-	-

Restrepo 2015 [58]	Not specified (TheraTest) (≥7 IU/mL)	44/69 (63.8) vs. 341/563 (60.6)	5.54±1.49 (n=69) vs. 4.68±1.52 (n=563) (log anti-CCP antibody titre)	OR 1.15 (0.69-1.91)	**MD 0.86 (0.49-1.23) (log anti-CCP antibody titre)**	Not specified	Not specified	age, sex, disease duration, DAS28, RF, HLA-DRB1*SE, PSL use
Rocha-Munoz 2015 [59]	Second generation (Euroimmun) (>20 U/mL)	39/39 (100) vs. 27/42 (64.3)	77.9 vs. 30.2 (median)	**OR 44.5 (2.54-778.3)**	**p<0.001**[b]	**-**	**OR 1.06 (1.02-1.10)**	age, smoking, disease duration, , DAS28, HAQ-Di, RF, ESR, duration of MTX treatment
Sargin 2018 [60]	Not specified	-	19.5 (1.8-140.8) (n=43) vs. 6.2 (0.5-15.9) (n=40) (median (1st-3rd quartile))	-	MD 9.8 (-34.1-53.7)[e]	-	-	-
Sulaiman 2019 [61]	Second generation (Euro-Diagnostica) (≥20.0 U/mL)	13/21 (61.9) vs. 70/138 (50.7)	-	OR 1.58 (0.62-4.05)	-	-	-	-
Tian 2016 [62]	Not specified (Euroimmun) (≥25	30/37 (81.1) vs. 28/38 (73.7)	475.2±551.8 (n=37) vs. 332.0±418.6 (n=38)	OR 1.53 (0.51-4.59)	MD 143.2 (-78.1-364.5)	-	-	-

	RU/mL)							
Wang 2015 [63]	Not specified	-	296.4 (1.91-500.0) (n=25) vs. 392.9 (7.00-500.0) (n=16) (median (range))	-	MD -49.5 (-132.2-33.2)[e]	-	-	-
Yang 2019 [64]	Not specified (≥5.0 IU/mL)	33/43 (76.7) vs. 95/142 (66.9)	242.8±234.4 (n=43) vs. 125.3±144.3 (n=142)	OR 1.63 (0.74-3.57)	**MD 117.5 (59.7-175.3)**	-	-	-
Yin 2014 [65]	Second generation (Euroimmun) (≥25 U/mL)	207/285 (72.6)	-	**OR 3.83 (1.74-8.43)**	-	**OR 3.50 (1.52-8.04)**	-	age, disease duration
Zhang 2018 [66]	Not specified	-	3.09±0.34 (n=28) vs. 3.05±0.32 (n=47)	-	MD 0.04 (-0.12-0.20)	-	-	-

a, Comparisons correspond to RA-ILD vs. RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified. The value with an interval in the parenthesis indicates 95% confidence interval. Text in bold indicates statistical significance;

b, the difference of the titre of anti-CCP antibody between RA with and without ILD could not be calculated due to unavailability of relevant summary statistics, no information of the number of subjects and/or unknown summary statistics;

c, indicates correlation coefficient between anti-CCP antibody and a total ILD score;

d, unknown statistics;

e, MDs (95% confidence interval) were calculated converting the median, range or interquartile range to the mean and standard deviation, using a formula reported by a previous study;[32]

CCP, cyclic citrullinated peptite; CRP, C-reactive protein; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; HAQ-Di, health assessment questionnaire-disability index; HLA, human leukocyte antigen; IL-18, interleukin-18; ILD, interstitial lung disease; IQR, interquartile range; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MD, mean difference; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; OR, odds ratio; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, risk ratio; SE, shared epitope;

Table 3 Risk of bias in individual studies

Study	Study participation	Anti-CCP antibody measurement	ILD confirmation	Study confounding	Statistical analysis and reporting
Alunno 2018 [38]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
England 2019 [39]	moderate risk	**high risk**	**high risk**	low risk	**high risk**
Giles 2014 [40]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Chen 2013 [41]	low risk	**high risk**	low risk	moderate risk	**high risk**
Chen 2015 [42]	moderate risk	low risk	low risk	moderate risk	**high risk**
Doyle 2015 [43]	moderate risk	moderate risk	low risk	moderate risk	**high risk**
Abdel-Hamid 2019 [44]	moderate risk	moderate risk	**high risk**	moderate risk	**high risk**
Akiyama 2016 [45]	low risk	moderate risk	**high risk**	moderate risk	moderate risk
Alexiou 2008 [46]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
Correia 2019 [47]	moderate risk	low risk	low risk	moderate risk	**high risk**
Fadda 2018 [48]	moderate risk	low risk	low risk	moderate risk	**high risk**
Furukawa2012 [49]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Kakutani 2019 [50]	low risk	**high risk**	**high risk**	moderate risk	**high risk**

Kelly 2014 [51]	moderate risk	**high risk**	low risk	moderate risk	**high risk**
Liu 2019 [52]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Matsuo 2018 [53]	low risk	moderate risk	**high risk**	moderate risk	moderate risk
Mori2012 [54]	low risk	low risk	low risk	moderate risk	moderate risk
Ortancil 2011 [55]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Park2016 [56]	low risk	low risk	low risk	**high risk**	**high risk**
Paulin 2019 [57]	moderate risk	**high risk**	**high risk**	moderate risk	**high risk**
Restrepo 2015 [58]	moderate risk	low risk	**high risk**	moderate risk	moderate risk
Rocha-Munoz 2015 [59]	moderate risk	low risk	**high risk**	moderate risk	low risk
Sargin 2018 [60]	moderate risk	**high risk**	**high risk**	moderate risk	**high risk**
Sulaiman 2019 [61]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
Tian 2016 [62]	**high risk**	low risk	**high risk**	moderate risk	**high risk**
Wang 2015 [63]	moderate risk	**high risk**	low risk	**high risk**	**high risk**
Yang 2019 [64]	moderate risk	**high risk**	moderate risk	moderate risk	moderate risk
Yin 2014 [65]	moderate risk	low risk	low risk	moderate risk	moderate risk

Zhang 2018 [66]	**high risk**	**high risk**	**high risk**	**high risk**	**high risk**

Text in bold indicates high risk of bias

CCP, cyclic citrullinated peptite; ILD, interstitial lung disease;

Table 4 Assessment of quality of evidence by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

Outcome: rheumatoid arthritis-associated interstitial lung disease										
			GRADE factors							
Prognostic factors	Analysis	Phase	Study limitations	Inconsistency	Indirectness	Publication bias	Imprecision	Moderate/large effect size	Dose effect	Overall quality
Anti-CCP antibody positivity	Univariate	1	+	+	-	+	-	-	-	very low
	Multivariate	1	+	+	-	+	-	-	-	very low
Anti-CCP antibody titre	Univariate	1	+	+	-	+	-	-	-	very low
	Multivariate	1	+	-	-	+	-	-	+	low

CCP, cyclic citrullinated peptite;

Figure legends

Figure 1 Study flow diagram

Out of a total of 827 records identified searching through five electronic databases, i.e., Medline, EMBASE, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials and Google Scholar, 645 records were screened by titles and abstracts after removing 182 duplicates. After excluding 320 records consisting of non-English reports (n=16) and articles of ineligible types (n=304) (conference proceedings (n=153), case reports (n=72), editorials or letters (n=10) and review articles (n=69)) and 265 irrelevant reports, 60 records were retrieved as full-texts. Out of these, 31 records were excluded due to no specific pulmonary disease (n=7), no ILD (n=5), no risk estimates (n=11), no anti-CCP antibody (n=7) and no RA (n=1). The remaining 29 reposts/studies were eligible for the review and additionally four reports were identified through a hand-search of references of eligible studies. As a result, a total of 33 reports/studies were considered for the review. Among them, four studies were excluded due to overlapped cohorts by other studies and finally a total of 29 studies/cohorts were focused for further analysis.

Figure 2 Forrest plot of the result of univariate analysis regarding the association of positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

The results of univariate analyses in 19 studies were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds

ratio (OR) of 2.10 (95% confidence interval: 1.59-2.78, p<0.00001/95% prediction interval: 0.93-4.76). There was moderate heterogeneity (chi^2=29.7, p=0.04, I^2=39%).

Figure 3 Forrest plot of the result of univariate analysis regarding the association of the tire of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

The results of univariate analyses in 12 studies were pooled for meta-analysis. The titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with a standardized mean difference (SMD) of 0.42 (95% confidence interval: 0.20-0.65, p=0.0002/95% prediction interval: -0.33-1.17). There was considerable heterogeneity (chi^2=36.0, p=0.0002, I^2=69%).

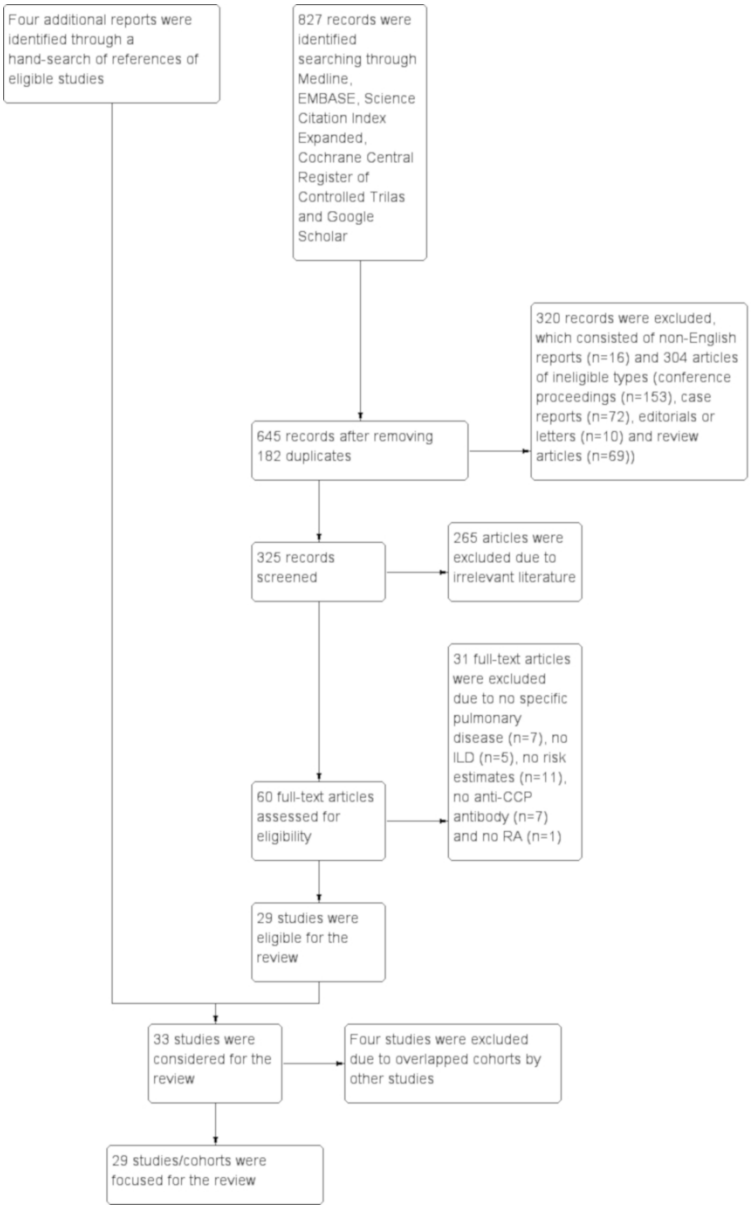

Figure 1

102x165mm (600 x 600 DPI)

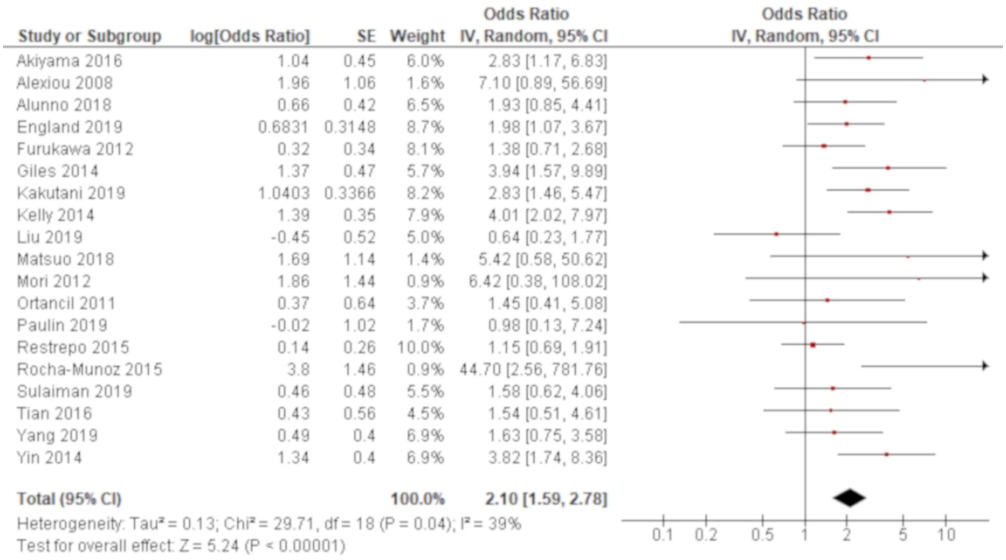

Figure 2

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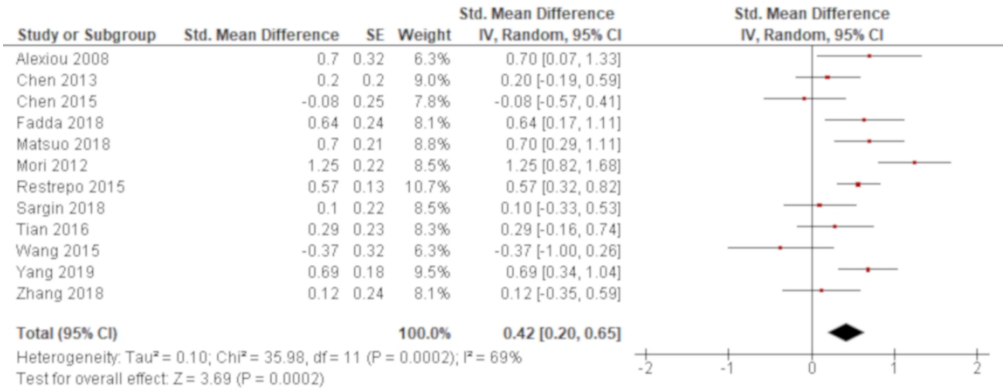


Figure 3

206x83mm (1100 x 1100 DPI)

Supplementary file

e-Table 1 Other baseline characteristics of included studies

Study	RA diagnostic criteria	ILD diagnostic criteria	Treatment received[a]
Alunno 2018 [38]	ACR/EULAR 2010	X-ray and HRCT in symptomatic cases	-
England 2019 [39]	ACR 1987	1)Pulmonologist diagnosis and imaging, 2)non-pulmonologist diagnosis and two of the followings; imaging, pathology or PFT	PSL 63.0% vs. 42.8%, MTX 21.0% vs. 51.2%, Biologics 30.0% vs. 20.1%
Giles 2014 [40]	ACR 1987	Cardiac MDCT	PSL 51% vs. 32%, MTX 58% vs. 68%, TNF-αI 56% vs. 40%
Chen 2013 [41]	ACR 1987	HRCT	-
Chen 2015 [42]	ACR 1987	HRCT	PSL 57% vs. 68%, MTX 63% vs. 67%, TNF-αI 18% vs. 9%
Doyle 2015 [43]	-	HRCT	PSL 93.5% vs. 83%, MTX 78.5% vs. 76%, TNF-αI 73.5% vs. 55%
Abdel-Hamid 2019 [44]	ACR/EULAR 2010	HRCT	-
Akiyama 2016 [45]	ACR/EULAR 2010	HRCT in symptomatic cases or abnormal radiograph	PSL 51.3% vs. 33.1%, MTX 24.4% vs. 61.8%, Biologics 50.0% vs. 43.2%
Alixiou 2008 [46]	-	-	-
Correia 2019 [47]	ACR/EULAR 2010	CT or radiograph and DLCO or pulmonologist	-

		diagnosis	
Fadda 2018 [48]	ACR/EULAR 2010	HRCT	MTX 6.9±4.2 vs. 7.9±4.3 years (duration)
Furukawa 2012 [49]	ACR 1987	Radiograph or CT	-
Kakutani 2019 [50]	ACR 1987 ACR/EULAR 2010	HRCT	PSL 77.8% vs. 58.1%, MTX 44.4% vs. 66.5%, non- TNF-αI Biologics 10.7% vs. 4.8%
Kelly 2014 [51]	ACR/EULAR 2010	HRCT	-
Liu 2019 [52]	ACR 1987	-	-
Matsuo 2018 [53]	-	CT in abnormal radiograph	PSL 65.4% vs. 41.6%, MTX 57.7% vs. 72.7%, Biologics 19.2% vs. 30.4%
Mori 2012 [54]	ACR 1987	HRCT	MTX 12.5% vs. 12.8%, TNF-αI 0% vs. 0.2%
Ortancil 2011 [55]	ACR 1987	-	-
Park 2016 [56]	ACR/EULAR 2010	CT	-
Paulin 2019 [57]	ACR/EULAR 2010	HRCT	MTX 51.9% vs. 74.2%, TNF-αI 11.5% vs. 24.2%
Restrepo 2015 [58]	ACR 1987	Clinical, PFT, imaging and pathology	PSL 63.7% vs. 46.5%, MTX 50.7% vs. 60.7%, TNF-αI 4.3% vs. 2.7%
Rocha-Munoz 2015 [59]	ACR 1987	Symptoms, PFT and HRCT	PSL 94.9% vs. 88.1%, MTX 100.0% vs. 97.6%
Sargin 2018 [60]	ACR/EULAR 2010	Symptoms, PFT, X-ray and HRCT	-
Sulaiman 2019	ACR/EULAR 2010	Radiograph and HRCT in	-

[61]		positive clinical exam	
Tian 2016 [62]	ACR/EULAR 2010	Clinical, PFT, imaging and/or pathology	-
Wang 2015 [63]	ACR 1987	HRCT	PSL 68.0% vs. 81.3%, MTX 64.0% vs. 81.3%
Yang 2019 [64]	ACR 1987	Clinical, PFT, imaging and/or pathology	MTX 39.0% vs. 76.2%, TNF-αI 5.2% vs. 5.2%
Yin 2014 [65]	ACR 1987	HRCT	PSL 81.7% vs. 82.2%, MTX 53.5% vs. 66.4%, Biologics 8.5% vs. 15.0%
Zhang 2018 [66]	-	-	-

a, Comparisons correspond to RA-ILD vs. RA without ILD;

ACR, American College of Rheumatology; DLCO, diffusing capacity of the lung for carbon monoxide; EULAR, European League Against Rheumatism; HRCT, high resolution computed tomography; ILD, interstitial lung disesae; MDCT, multi-detector computed tomography; MTX, methotrexate, PFT, pulmonary function test; PSL, prednisolone; RA, rheumatoid arthritis; TNF-αI, tumor necrosis factor-α inhibitor;

e-Table 2 Meta-regression analysis[a]

Potential confounder	Positivity of anti-CCP antibody		Titre of anti-CCP antibody	
	Univariate	Multivariate[b]	Univariate	Multivariate[b]
Age (at inclusion) (/year)	0.02 (-0.04-0.07)	0.06 (-0.03-0.16)	-0.01 (-0.08-0.06)	-0.01 (-0.09-0.06)
Gender (male) (/percentage)	0.003 (-0.009-0.02)	0.003 (-0.009-0.02)	**-0.02 (-0.04--0.004)**	0.004 (-0.04-0.05)
Smoking history (/percentage)	-0.008 (-0.02-0.005)	-0.0005 (-0.03-0.02)	0.001 (-0.01-0.01)	0.0008 (-0.006-0.008)
RA duration (/year)	0.02 (-0.19-0.23)	0.03 (-0.20-0.26)	**0.05 (0.01-0.09)**	0.06 (-0.03-0.14)
RA diagnostic criteria (ACR/EULAR 2010 vs. ACR 1987)	0.36 (-0.22-0.94)	0.47 (-0.25-1.18)	-0.17 (-0.94-0.59)	0.06 (-1.24-1.36)
ILD diagnostic criteria (CT for all subjects vs. others)	0.02 (-0.60-0.64)	-0.48 (-1.66-0.71)	-0.24 (-1.26-0.78)	0.20 (-0.21-0.61)
Proportion of positivity of anti-CCP antibody in subjects with RA alone (/percentage)	0.009 (-0.01-0.03)	0.02 (-0.02-0.06)	0.01 (-0.01-0.04)	-[c]

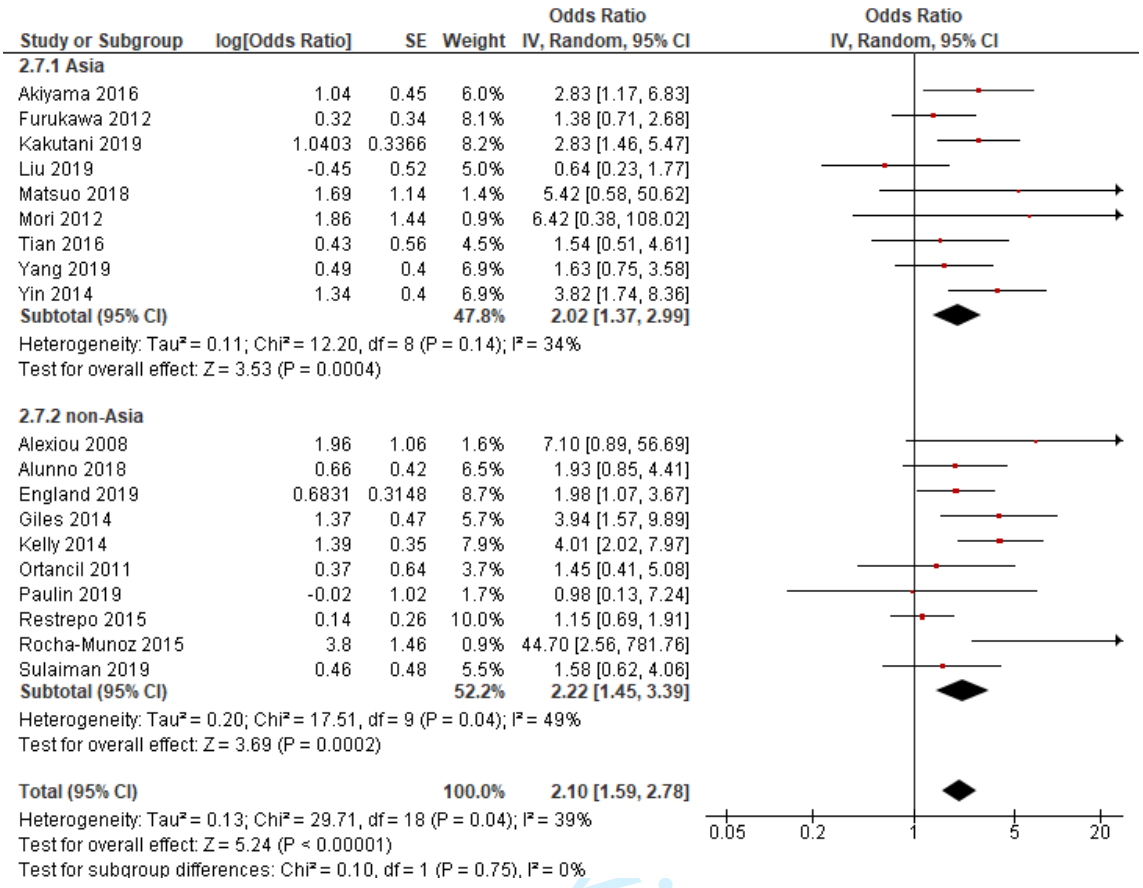
Text in bold indicates statistical significance;

a, The effect of the association of positivity and titres of anti-CCP antibody with RA-ILD was regressed against each potential confounder;

b, Each potential confounder was adjusted for RA duration and the effect of RA duration was estimated allowing for gender;

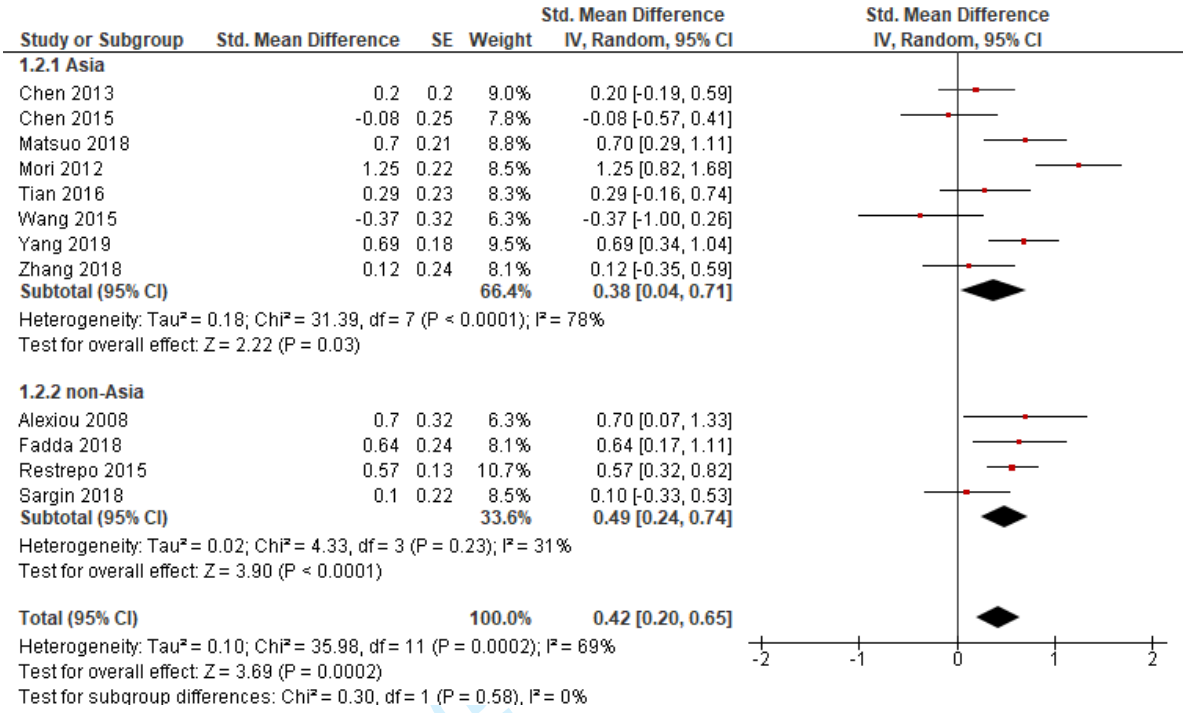
c, The effect was unable to be estimated due to a small number of studies;

ACR, American College of Rheumatology; CCP, cyclic citrullinated peptide; EULAR, European League Against Rheumatism; ILD, interstitial lung disease; HRCT, high resolution computed tomography; RA, rheumatoid arthritis;



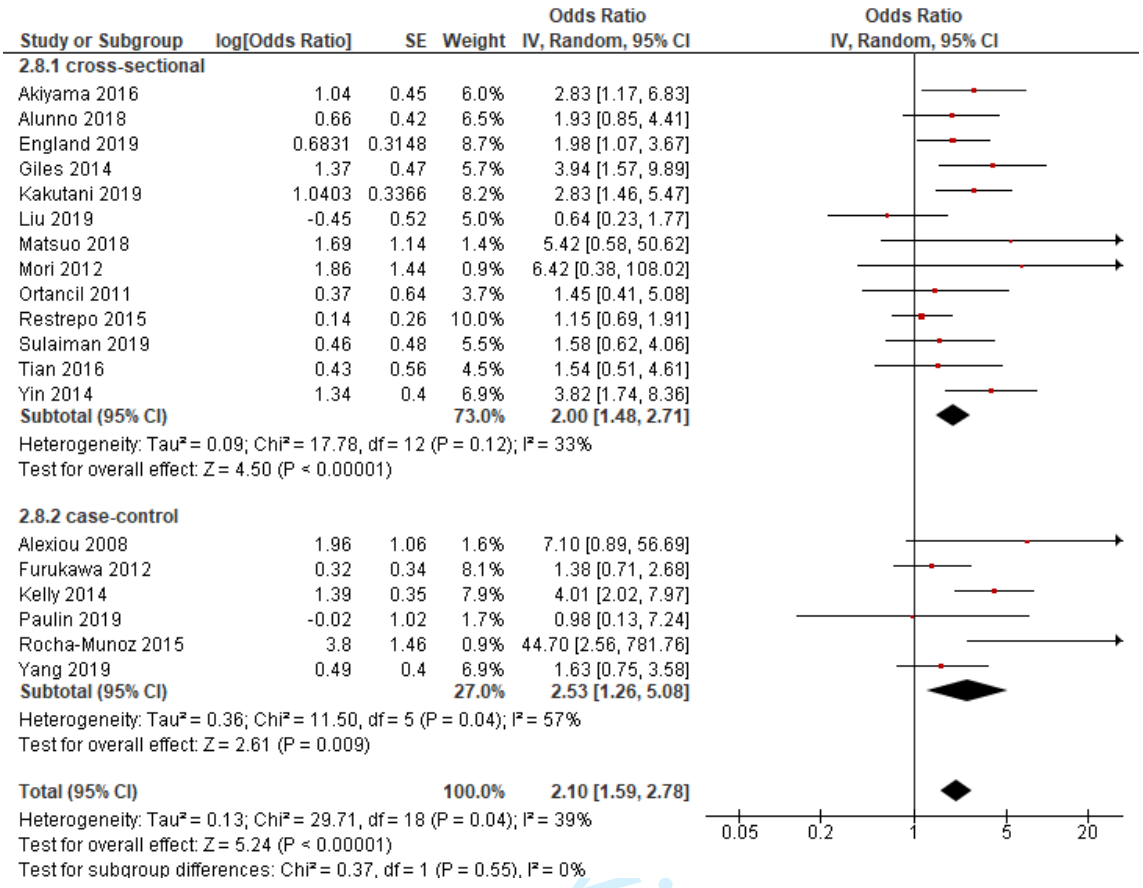
e-Figure 1 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 2.02 (95% confidence interval (CI): 1.37-2.99, p=0.0004/95% prediction interval (PI): 0.81-5.05) and 2.22 (95%CI: 1.45-3.39, p=0.0002/95%PI: 0.71-6.98), respectively and there was no significant difference in these results (p=0.75). There remained moderate heterogeneity in both Asian and non-Asian studies.



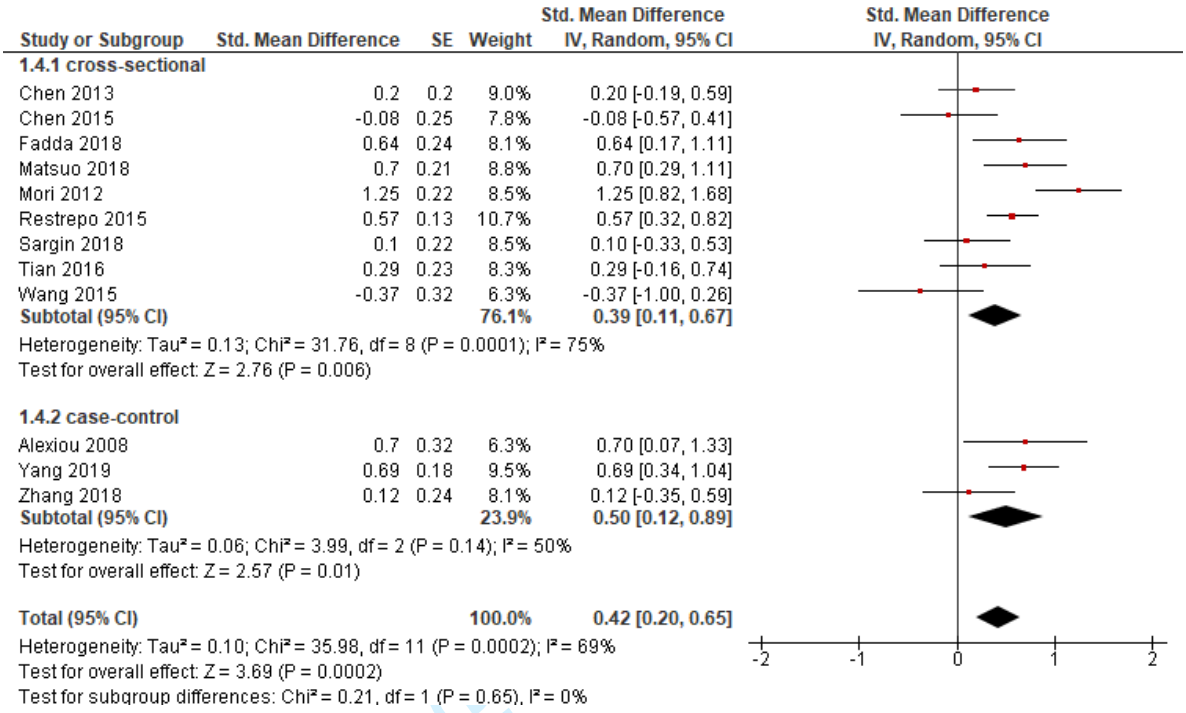
e-Figure 2 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.38 (95% confidence interval (CI): 0.04-0.71, p=0.03/95% prediction interval (PI): -0.74-1.50) and 0.49 (95%CI: 0.24-0.74, p<0.0001/95%PI: -0.33-1.31), respectively and there was no significant difference in these results (p=0.58). There remained substantial heterogeneity in Asian studies (chi^2=31.4, p<0.0001, I^2=78%).



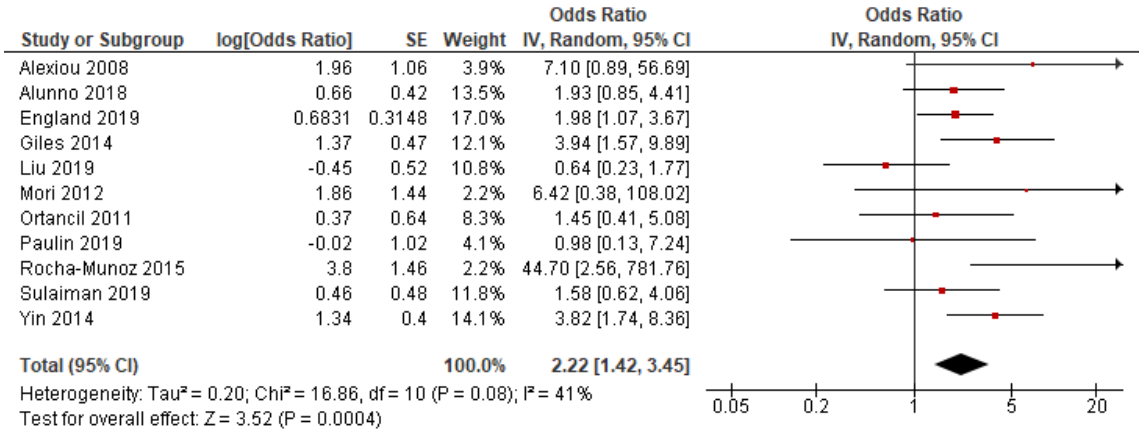
e-Figure 3 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 2.00 (95% confidence interval (CI): 1.48-2.71, p<0.00001/95% prediction interval (PI): 0.95-4.21) and 2.53 (95%CI: 1.26-5.08, p=0.009/95%PI: 0.36-17.5), respectively and there was no significant difference in these results (p=0.55). There remained considerable heterogeneity in case-control studies (chi^2=11.5, p=0.04, I^2=57%).



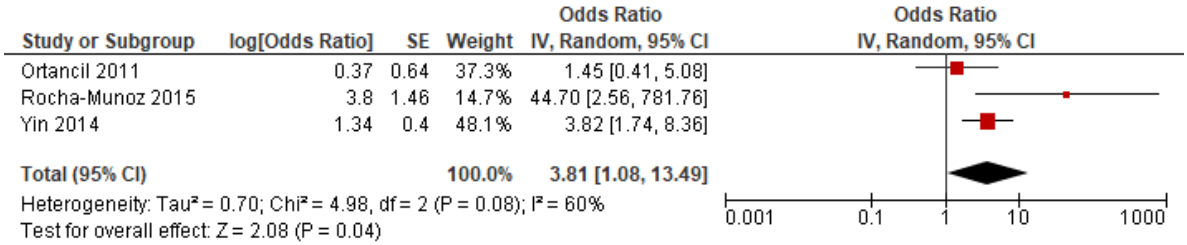
e-Figure 4 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.39 (95% confidence interval (CI): 0.11-0.67, p=0.006/95% prediction interval (PI): -0.53-1.31) and 0.50 (95%CI: 0.12-0.89, p=0.01/95%PI: -3.51-4.51), respectively and there was no significant difference in these results (p=0.65). There remained substantial heterogeneity in cross-sectional studies (chi^2=31.8, p=0.0001, I^2=75%).



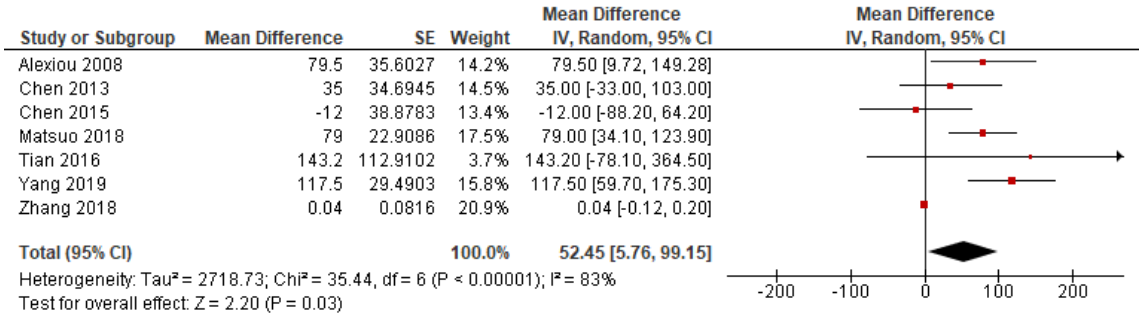
e-Figure 5 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test

The results of univariate analyses in 11 studies that examined the second generation of anti-CCP antibody were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 2.22 (95% confidence interval: 1.42-3.45, p=0.00041/95% prediction interval: 0.72-6.89). There remained moderate heterogeneity (chi^2=16.9, p=0.08, I^2=41%).



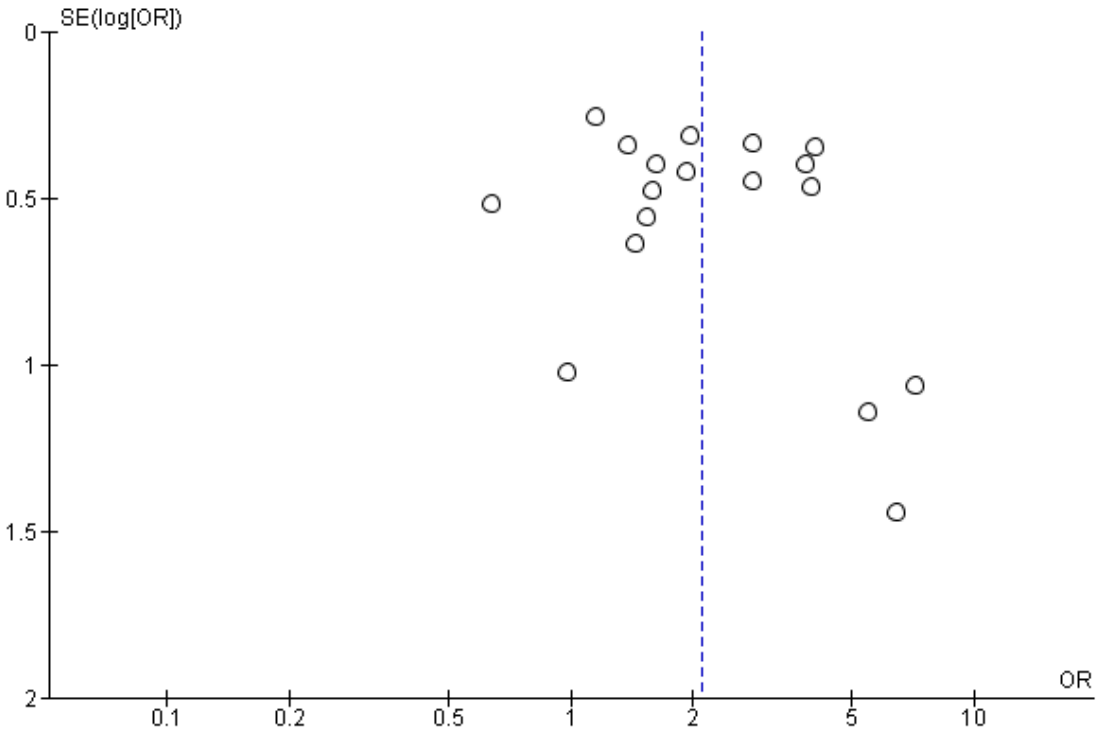
e-Figure 6 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test by the same manufacturer

The results of univariate analyses in three studies that examined the second generation of anti-CCP antibody test by the same manufacturer (Euroimmun, Lübeck, Germany) were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 3.81 (95% confidence interval: 1.08-13.5, p=0.04/95% prediction interval: 0.00->100.0). There remained considerable heterogeneity (chi^2=4.98, p=0.08, I^2=60%).



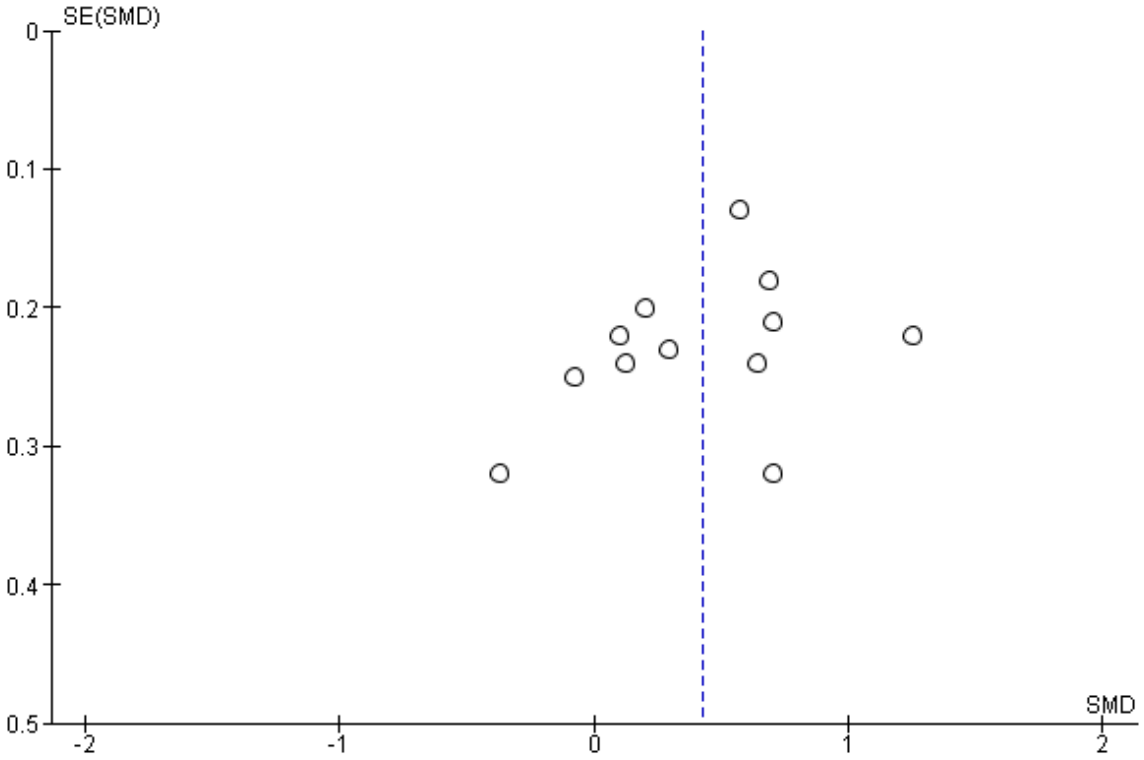
e-Figure 7 Sensitivity analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same summary statistics

A pooled analysis of seven studies where mean differences (MDs) were available without a conversion of summary statistics demonstrated that higher titres of anti-CCP antibody was significantly associated with RA-ILD with an MD of 52.5 (95% confidence interval: 5.76-99.2, p=0.03/95% prediction interval: -94.9-199.9). There remained substantial heterogeneity (chi^2=35.4, p<0.00001, I^2=83%).



e-Figure 8 Funnel plot of the effect of the positivity of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.



e-Figure 9 Funnel plot of the effect of the titre of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.

e-Appendix

Search terms for each electronic database

Medline (Ovid) (1946 through 12 November 2019)

1 exp Arthritis, Rheumatoid/ (110375)

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).mp. (60240)

3 exp Lung Diseases, Interstitial/ (57554)

4 exp Pulmonary Fibrosis/ (21497)

5 (interstitial adj3 lung adj3 disease$).mp. (14632)

6 (interstitial adj3 pneumoni$).mp. (10671)

7 alveolitis.mp. (6068)

8 (pulmonary adj3 fibros$).mp. (29467)

9 exp Anti-Citrullinated Protein Antibodies/ (211)

10 cyclic citrullinated protein antibod$.mp. (28)

11 cyclic citrullinated peptide antibod$.mp. (664)

12 citrullinated protein antibod$.mp. (798)

13 citrullinated peptide antibod$.mp. (1001)

14 anti-CCP.mp. (1527)

15 ACPA.mp. (1369)

16 1 or 2 (157282)

17 3 or 4 or 5 or 6 or 7 or 8 (88395)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 (3452)

19 16 and 17 and 18 (64)

EMBASE (Ovid) (1947 through 12 November 2019)

1 exp rheumatoid arthritis/ (218675)

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).mp. (106635)

3 exp interstitial lung disease/ (82134)

4 exp lung fibrosis/ (81580)

5 (interstitial adj3 lung adj3 disease$).mp. (25821)

6 (interstitial adj3 pneumoni$).mp. (22196)

7 alveolitis.mp. (29356)

8 (pulmonary adj3 fibros$).mp. (32054)

9 exp cyclic citrullinated peptide antibody/ (6135)

10 cyclic citrullinated protein antibod$.mp. (78)

11 cyclic citrullinated peptide antibod$.mp. (6299)

12 citrullinated protein antibod$.mp. (1603)

13 citrullinated peptide antibod$.mp. (6704)

14 anti-CCP.mp. (4537)

15 ACPA.mp. (4424)

16 1 or 2 (285679)

17 3 or 4 or 5 or 6 or 7 or 8 (139209)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 (11794)

19 16 and 17 and 18 (452)

Science Citation Index Expanded (Clarivate Analytics) (1900 through 12 November 2019)

#1 TS=(rheumatoid NEAR/3 arthritis or rheumatoid NEAR/3 disease$ or rheumatoid NEAR/3 condition$) (165,017)

#2 TS=("interstitial NEAR/3 lung NEAR/3 disease$") OR TS=("interstitial NEAR/3 pneumoni*") OR TS=(alveolitis) OR TS=("pulmonary NEAR/3 fibros*") (4,751)

#3 TS=(anti cyclic citrullinated protein antibod* or anti cyclic citrullinated peptide antibod* or anti citrullinated protein antibod* or anti citrullinated peptide antibod* or anti CCP or ACPA) (4,483)

#3 #4 AND #5 AND #6 (2)

Cochrane Central Register of Controlled Trials (Cochrane Library) (accessed on the 12th of November 2019)

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees (5530)

#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3(arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab,kw (17434)

#3 MeSH descriptor: [Lung Diseases, Interstitial] explode all trees (738)

#4 MeSH descriptor: [Pulmonary Fibrosis] explode all trees (429)

#5 interstitial near/3 lung near/3 disease*:ti,ab,kw (1017)

#6 interstitial near/3 pneumoni*:ti,ab,kw (619)

#7 alveolitis:ti,ab,kw (732)

#8 pulmonary near/3 fibros*:ti,ab,kw (1440)

#9 MeSH descriptor: [Anti-Citrullinated Protein Antibodies] explode all trees (6)

#10 (cyclic citrullinated protein antibod*):ti,ab,kw (105)

#11 (cyclic citrullinated peptide antibod*):ti,ab,kw (178)

#12 (citrullinated protein antibod*):ti,ab,kw (199)

#13 (citrullinated peptide antibod*):ti,ab,kw (225)

#14 anti-CCP:ti,ab,kw (335)

#15 ACPA:ti,ab,kw (292)

#16 OR #2 (17673)

#17 #3 OR #4 OR #5 OR #6 OR #7 OR #8 (3148)

#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 (728)

#19 #16 AND #17 AND #18 (9)

Google Scholar (accessed on the 12th of November 2019)

("rheumatoid arthritis" OR "rheumatoid disease") ("interstitial lung disease" OR "interstitial pneumonia" OR "pulmonary fibrosis") ("anti cyclic citrullinated protein antibody" OR "anti cyclic citrullinated peptide antibody" OR "anti citrullinated protein antibody" OR "anti citrullinated peptide antibody")

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 7-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 13-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 15-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Checklist items for Meta-analyses of Observational Studies in Epidemiology (MOOSE)	Reported on Page
Reporting of background should include	
• Problem definition	Page 5-6
• Hypothesis statement	Not described
• Description of study outcome(s)	Page 7
• Type of exposure or intervention used	Page 7
• Type of study designs used	Page 7
• Study population	Page 6-7
Reporting of search strategy should include	
• Qualifications of searchers (eg, librarians and investigators)	Not described
• Search strategy, including time period included in the synthesis and keywords	Page 7-8
• Effort to include all available studies, including contact with authors	Page 8
• Databases and registries searched	Page 7
• Search software used, name and version, including special features used (eg, explosion)	Not described
• Use of hand searching (eg, reference lists of obtained articles)	Page 8
• List of citations located and those excluded, including justification	Figure 1
• Method of addressing articles published in languages other than English	Page 7
• Method of handling abstracts and unpublished studies	Page 7
• Description of any contact with authors	Not described
Reporting of methods should include	
• Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Not described
• Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Not described

• Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Not described
• Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Not described
• Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Page 8-9
• Assessment of heterogeneity	Page 10-11
• Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 9-10
• Provision of appropriate tables and graphics	Figure 1 (study flow diagram)
Reporting of results should include	
• Graphic summarizing individual study estimates and overall estimate	Figure 2-3
• Table giving descriptive information for each study included	Table 1, 2
• Results of sensitivity testing (eg, subgroup analysis)	Page 15-16
• Indication of statistical uncertainty of findings	Page 13-15
Reporting of discussion should include	
• Quantitative assessment of bias (eg, publication bias)	Page 21
• Justification of exclusion (eg, exclusion of non-English-language citations)	Not described
• Assessment of quality of included studies	Page 21
Reporting of conclusions should include	
• Consideration of alternative explanations for observed results	Page 22
• Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Page 22
• Guidelines for future research	Page 21
• Disclosure of funding source	Page 22

From Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

BMJ Open

A systematic review and meta-analysis of the risk of rheumatoid arthritis-associated interstitial lung disease related to anti-cyclic citrullinated peptide (CCP) antibody

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040465.R2
Article Type:	Original research
Date Submitted by the Author:	11-Jan-2021
Complete List of Authors:	Kamiya, Hiroyuki; Tatebayashi Kosei Hospital, Department of Respiratory Medicine Panlaqui, Ogee; Northern Hospital, Department of Intensive Care Medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	RHEUMATOLOGY, Thoracic medicine < INTERNAL MEDICINE, Interstitial lung disease < THORACIC MEDICINE

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Title

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

Hiroyuki Kamiya[1], Ogee Mer Panlaqui[2]

[1] Department of Respiratory Medicine, Tatebayashi Kosei Hospital, Gunma, Japan

[2] Department of Intensive Care Medicine, Northern Hospital, Melbourne, Australia

Correspondence

Hiroyuki Kamiya

Department of Respiratory Medicine, Tatebayashi Kosei Hospital, Gunma, Japan

374-8533

Phone: +81-276-72-3140

Email: mlb04194@nifty.com

Word count

4475

Keywords

Rheumatoid arthritis, interstitial lung disease, anti-cyclic citrullinated peptide antibody, risk, review

Article Summary

Strengths and limitations of this study

- This systematic review and meta-analysis addressed the risk of RA-ILD related to both the presence and titres of anti-CCP antibody, which was not clarified in previous literature.
- A substantial variance in the results of primary studies, which may have been derived from the diversity of anti-CCP antibody assays and included subjects, may undermine the generalizability of the findings of this study.
- The usefulness of the findings may be limited in clinical practice because of high probability of the autoantibody positivity for RA without ILD and no standard cut-off points for its assays.

ABSTRACT

Objective

To clarify the risk of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) related to anti-cyclic citrullinated peptide (CCP) antibody.

Eligibility criteria

Patients with RA with and without ILD were eligible. The primary outcome was the prevalence or incidence of ILD. Primary studies of any design aside from a case report were eligible.

Information sources

Medline, EMBASE, Science Citation Index Expanded and Cochrane Central Register of Controlled Trials were searched from the inception through 12 November 2019.

Data extraction and risk of bias

Two reviewers independently selected eligible reports, extracted relevant data and assessed risk of bias using a modified Quality in Prognostic Studies tool.

Data synthesis

Meta-analysis was conducted using a random-effects model.

Quality of evidence

The Grades of Recommendation, Assessment, Development and Evaluation system was applied.

Results

Among 29 out of 827 records retrieved through electronic databases and four additional reports identified from other sources, 29 studies were focused for the review. A total of 10158 subjects were included and the mean age at inclusion was between 45.8 and 63.9 years. The mean RA duration was between 4.3 and 14.9 years. The positivity of anti-CCP antibody ranged from 50.7% to 95.8%. All studies except for two were deemed as high risk of bias. A pooled analysis of univariate results demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.10 (95%CI: 1.59-2.78). Similarly, the titre of anti-CCP antibody was significantly higher for RA-ILD with an SMD of 0.42 (95%CI: 0.20-0.65). These results were confirmed by multivariate analysis in the majority of studies and consistent by any subgroup and sensitivity analyses.

Conclusion

The presence and higher titres of anti-CCP antibody were suggested to be significantly associated with an increased risk of RA-ILD. However, the quality of evidence was rated as low or very low.

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that is characterized by a chronic synovial inflammation and eventual joint destruction.[1] Although arthritis is the main manifestation of the disease, it also damages diverse extra-articular organs such as heart, lung, kidney, eye and skin.[2] Interstitial lung disease (ILD) is one of the most common comorbidities of RA and the prevalence of ILD for patients with RA is reported to be 10% to 40% although it varies depending on the target population, a definition of the disease and diagnostic modalities.[3] A complication of ILD deeply affects the prognosis of RA because RA-associated ILD (RA-ILD) is often progressive and only a limited therapeutic option is available.[4] It is also complicated by acute exacerbation and lung cancer.[5-6] As a result, ILD is reported to be the third leading cause of deaths of RA [7] and approximately two thirds of patients with RA-ILD eventually die within 5 years, resulting in a hazard ratio of mortality about 3.0 in comparison to RA without ILD.[8] Moreover, the most common type of ILDs among RA-ILDs, i.e., usual interstitial pneumonia (UIP),[9] demonstrates the worst prognosis, which is similar to the mortality of idiopathic pulmonary fibrosis (IPF).[10] In this context estimating the risk of developing ILD will help clinicians' decision-making and may improve the prognosis of the disease.[11] Historically, a number of studies investigated risk factors for the development of ILD and some clinical information are reported to be associated with an increased risk of RA-ILD, which include male gender,[12] smoking,[13] severe disease [14] and rheumatoid factor (RF).[15] Anti-citrullinated peptide antibody (ACPA) is a specific marker for RA and included in the latest classification criteria for an accurate diagnosis of the disease.[16] Currently,

anti-cyclic citrullinated peptide (CCP) antibody, representing ACPAs is available commercially and usually measured in clinical practice. The autoantibody is also reported to be associated with an increased risk of extra-articular manifestations such as ILD.[17] However, previous studies noted inconsistent results [18-19] and the former systematic review seems to be limited by relatively a small number of studies and unclear definition of ILD and IPF.[20] The aim of this systematic review and meta-analysis was to clarify current evidence regarding the association of anti-CCP antibody with RA-ILD.

Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[22]

Patient and public involvement

There was no patient and public involvement in the whole process of conducting this research.

Eligibility

Patients with RA were eligible for this review. RA was diagnosed based on its widely used classification criteria, i.e., the 1987 American College of Rheumatology classification criteria [23] and the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria.[16] ILD was characterized by interstitial inflammatory and fibrotic changes in pulmonary parenchyma and diagnosed based on symptomatic, functional, radiological and/or pathological findings.[24] The

pattern of ILD was classified following the international multidisciplinary classification such as an official American Thoracic Society/European Respiratory Society statement.[25] Other pulmonary lesions associated with RA such as bronchiolitis, bronchiectasis and pleuritis were all excluded. An overlap with other connective tissue diseases was included if RA was the main disease of interest in the study. There was no limitation regarding demographic features of subjects, such as gender and ethnicity, duration of RA and ILD and the severity of the disease unless they were less than the age of 18. Subjects were allowed to participate at any point in time along their clinical course of the disease.

Anti-CCP antibody was examined using Enzyme-Linked Immunosorbent Assay (ELISA).[26] Although measurements of anti-CCP antibody were different among manufacturers and each institution adopted a different test, all kinds of anti-CCP antibody assays were eligible for the review. However, ACPA, which was not specified as anti-CCP antibody, was excluded because it may have represented autoantibodies against different citrullinated peptides.

The outcome of interest in this review was the prevalence or incidence of ILD. Any design of primary studies other than a case report was eligible if it described the association of anti-CCP antibody with RA-ILD. Conference proceedings, letters or editorials and review articles were ineligible. Only reports published in English was considered.

Search strategy

The following electronic databases were searched, Medline, EMBASE, Science Citation Index Expanded and Cochrane Central Register of Controlled Trials, using subject

headings and text words related to study population such as ‘rheumatoid arthritis’, ‘interstitial lung disease’ and ‘anti-cyclic citrullinated peptide antibodies’ (e-Appendix). Search terms were constructed referring to a systematic review in a similar research area identified through the Cochrane Database of Systematic Reviews (CDSR).[27] Methodology filters were not used to avoid limiting the sensitivity of the search. The search was covered from the inception of each database through to the 12th of November 2019. The reference lists of eligible studies and relevant review articles were also hand-searched to identify additional reports. Google Scholar was employed to search grey literature.[28]

Study selection and data collection process

Two reviewers (H.K. and O.M.P.) independently examined titles and abstracts of all retrieved articles to select eligible reports. The same reviewers also extracted relevant data based on a modified data extraction form, which was previously published in a protocol paper for a systematic review.[29] Any uncertainty or disagreement between reviewers arising from these processes was resolved through discussion. The following data was extracted from each eligible study: first author’s name, year of publication, study location, study design, sample size and its demographic features, ILD patterns if available, manufacturers of anti-CCP antibody tests and their cut-off points if available, a proportion of positivity and titres of anti-CCP antibodies for RA with and without ILD, methods for statistical analysis, summary statistics and items associated with a risk of bias.

Risk of bias in individual studies

As all studies investigated the association of anti-CCP antibody with RA-ILD as risk prediction, the Quality in Prognostic Studies (QUIPS) tool was modified and applied to assess a risk of bias in individual studies.[30] However, one of six domains that constitute the tool, i.e., 'the attrition of study population', was considered irrelevant and thus excluded because all studies were designed as cross-sectional or case-control studies. Each domain received an individual bias rating (low, moderate or high), with an overall risk of bias based on a total rating of all domains. For example, a study showing a low risk of bias across all domains was deemed as being subject to a low risk of bias overall.

Statistical analysis

Summary statistics

The risk of RA-ILD associated with the presence of anti-CCP antibody was measured using either risk ratios (RRs) or odds ratios (ORs). In a case where titres of anti-CCP antibody were compared between the two comparative groups with or without ILD, the mean difference (MD) was calculated to reveal the difference of the autoantibody titres. If the median was utilized instead of the mean, it was presented for each of the two groups. If the summary statistics were not provided directly, the ORs or RRs were calculated manually based on the absolute number of the outcome across the two comparative groups.

Data synthesis

The effect of an association between anti-CCP antibody and RA-ILD was statistically combined if it was presented using the same statistics in three or more studies. The

results were summarized using ORs if anti-CCP antibody was reported as binary (positive/negative). If the titre of anti-CCP antibody was reported, a standardized MD (calculated as Hedge's g) was utilized to combine the results.[31] If the median, range or interquartile range was described to report the autoantibody titres, they were converted to the mean and standard deviation, using a formula reported by a previous study, to be summarized as SMDs.[32] Only the results of univariate analysis were combined whereas those of multivariate analysis were described qualitatively because adjusted variables in multivariate models varied substantially between studies and pooling these data could be misleading. If meta-analysis was feasible from the collated data, it was conducted using a random-effects model employing the DerSimonian and Laird method.[33] Meta-analysis was conducted using the statistical software package, Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Statistical significance was considered with a p-value of <0.05. If combining data was deemed inappropriate due to a small number of studies, the results were reported qualitatively.

Heterogeneity between studies

Between-study variance was assessed using both Q statistics and I^2 value. For the assessment of heterogeneity between studies, statistical significance was considered with a p-value of <0.1 due to the low power of the test. Magnitude of heterogeneity was categorised as low (<30%), moderate (≥30%, <50%), considerable (≥50%, <70%) and substantial (≥70%).[34] When heterogeneity was identified, the 95% prediction interval (PI) was presented in addition to the 95% confidence interval (CI).[35] To better interpret sources of heterogeneity, subgroup analysis was conducted based on study

location (Asia or non-Asia) and study design (cross-sectional or case-control). Sensitivity analysis was also considered focusing on the measurements of anti-CCP antibody (same manufacturer and same generation of the autoantibody assay). A meta-regression analysis was also conducted to assess the effect of other potential confounders, i.e., age, gender, smoking history, RA duration, diagnostic criteria for RA and ILD and a proportion of positivity of anti-CCP antibody. The analysis was conducted using SAS ODA (SAS Institute Inc., Cary, NC, USA).

Meta-biases

Small study bias (such as publication bias) was examined graphically using a funnel plot and statistically by the Egger's test using Stata 14 (STATA Corp LLC., College Station, TX, USA) if ten or more studies were available for meta-analysis.[36] Statistical significance of the test was considered with a p-value of <0.1 due to the low power of the test.

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) for prognosis [37] was applied to assess the credibility of evidence generated from this review because all studies investigated the association of anti-CCP antibody with RA-ILD as risk prediction.

Results

Search for eligible studies

Out of a total of 827 records identified through a search of five electronic databases, 182 duplicates were removed and 645 records were screened by titles and abstracts. After

320 records consisting of non-English reports (n=16) and 304 articles of ineligible types (conference proceedings (n=153), case reports (n=72), editorials or letters (n=10) and review articles (n=69)) and 265 irrelevant papers were further excluded, the remaining 60 records were retrieved as full-texts. Out of these, 29 reposts/studies were eligible for the review and additionally four reports were identified through a hand-search of references of eligible studies. As a result, a total of 33 reports were considered for the review (Figure 1). In each of three different groups, which conducted two studies sharing the same cohort, only the study with a larger sample size was included for the review.[38-40] Similarly, among three studies conducted by one group, the study with the largest sample size was included for the review.[41] Furthermore, another study among these three studies was also included because it reported two different cohorts, one of which was not overlapped by the other studies.[42] There was also a study that reported two different cohorts, only one of which was included because it was not overlapped by the other studies.[43] Finally, a total of 29 studies/cohorts were focused for further analysis.[38-66]

Characteristics of included studies

Study location of a total of 29 studies were distributed globally with Asia in the largest number (n=15), which was followed by the Americas (n=7), Europe (n=3), Africa (n=2) and others (n=2). 22 studies were cross-sectional while the remaining seven were case-control studies. A complication of other CTDs was mentioned in 10 studies and ILD patterns were detailed in three studies. The number of subjects enrolled in each study ranged from 41 to 2702, which amounted to 10158 subjects in total and the mean age at inclusion was between 45.8 and 63.9 years. The proportion of men, smoking

history and ILD ranged from 4.0% to 90.1%, 1.9% to 98.9% and 4.9% to 71.6%, respectively. The mean duration of RA was between 4.3 and 14.9 years and the disease activity, which was represented by the disease activity score (DAS) 28, was between 2.5 and 5.4 as a mean value (Table 1). Other baseline characteristics of included studies were depicted in the supplementary file (e-Table 1). The generation of anti-CCP antibody tests was specified in 14 studies, which consisted of the second generation in 12 studies and the third generation in two studies. The proportion of positivity of anti-CCP antibody was reported in 21 studies, which ranged from 50.7% to 95.8% while the titre of the autoantibody was described in 18 studies (Table 2).

Risk of bias in individual studies

All studies except for two contained high risk of bias rating in at least one domain and thus was deemed as high risk of bias. Among the five domains constituting the QUIPS tool, the risk of bias for statistical analysis and reporting and ILD confirmation were rated as high in the majority of studies due to no or insufficient information regarding model building process and inconsistent diagnostic procedures. The remaining two studies were rated as moderate risk of bias (Table 3).

Association of anti-CCP antibody with RA-ILD

Univariate result

The association of positivity of anti-CCP antibody with RA-ILD was reported in 20 studies. Eight out of these studies demonstrated significant results with the ORs ranging from 1.98 to 44.5 (Table 2). Excluding one study,[47] which conducted a stratified analysis based on the level of the autoantibody titre and thus was not combined, a

meta-analysis of 19 out of these 20 studies demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.10 (95%CI: 1.59-2.78) with moderate heterogeneity (chi^2=29.7, p=0.04, I^2=39%) (Figure 2).

The titre of anti-CCP antibody was compared between RA with and without ILD in 18 studies. Two studies employed the same assay (INOVA Diagnostics) to examine the titre of anti-CCP antibody and reported higher titres associated with RA-ILD with an MD of 79.5 (95%CI: 9.72-149.3) [46] and a median value of 220 for RA-ILD vs. 120 for RA without ILD [48], respectively. Other two studies examined the titre of the autoantibody using another assay (Euroimmun). One of them demonstrated higher titres associated with RA-ILD with a median value of 77.9 for RA-ILD vs. 30.2 for RA without ILD [59] and the other study reported non-significant result with an MD of 143.2 (95%CI: -78.1-364.5).[62] All of the other studies utilized a different or unknown measurement to examine the titre of the autoantibody. Overall, 11 studies demonstrated significant results with higher titres associated with RA-ILD (Table 2). Excluding six studies [40, 44, 47, 51, 56, 59] where MDs were unable to be calculated, a meta-analysis of 12 out of these 18 studies demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD with an SMD of 0.42 (95%CI: 0.20-0.65) with considerable heterogeneity (chi^2=36.0, p=0.0002, I^2=69%) (Figure 3).

Multivariate result

Multivariate analysis was conducted in eight studies where detailed results were available in seven studies and adjusted variables were diverse between studies. Six of these seven studies demonstrated a positive association between the presence or higher titres of anti-CCP antibody and RA-ILD and the results were statistically significant in

four studies (Table 2). One study [65] revealed the association of positivity of anti-CCP antibody with RA-ILD as an OR of 3.50 (95%CI: 1.52-8.04) (Table 2). The association of the titre of anti-CCP antibody with RA-ILD was reported by three studies as ORs of 1.41 (95%CI: 1.01-1.97), 1.08 (95%CI: 1.03-1.12) and 1.06 (95%CI: 1.02-1.10).[47, 53, 59, respectively]

Subgroup analysis

Subgroup analysis was conducted based on both study location and study design. There was no significant difference in the effect size of the positivity of anti-CCP antibody with ORs of 2.02 (95% CI: 1.37-2.99) by Asian reports and 2.22 (95%CI: 1.45-3.39) by non-Asian reports (p=0.75) (e-Figure 1). Similarly, there was no significant difference in the effect size of the titre of anti-CCP antibody with SMDs of 0.38 (95%CI: 0.04-0.71) by Asian reports and 0.49 (95%CI: 0.24-0.74) by non-Asian reports (p=0.58) (e-Figure 2). There was no significant difference in the effect size of the positivity of anti-CCP antibody with ORs of 2.00 (95%CI: 1.48-2.71) by cross-sectional studies and 2.53 (95%CI: 1.26-5.08) by case-control studies (p=0.55) (e-Figure 3). Similarly, there was no significant difference in the effect size of the titre of anti-CCP antibody with SMDs of 0.39 (95%CI: 0.11-0.67) by cross-sectional studies and 0.50 (95%CI: 0.12-0.89) by case-control studies (p=0.65) (e-Figure 4).

Sensitivity analysis

Sensitivity analysis was conducted focusing on the measurements of anti-CCP antibody. A pooled analysis of 10 studies that examined the second generation of anti-CCP antibody test demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.22 (95%CI: 1.42-3.45) (e-Figure 5). A pooled

analysis of three studies that examined the second generation of anti-CCP antibody test by the same manufacture (Euroimmun, Lübeck, Germany) demonstrated that the presence of anti-CCP antibody was significantly associated with RA-ILD with an OR of 3.81 (95%CI: 1.08-13.5) (e-Figure 6).

Sensitivity analysis was also conducted for the titre of anti-CCP antibody focusing on the same summary statistics. A pooled analysis of seven studies where MDs were available without a conversion of summary statistics demonstrated higher titres associated with RA-ILD with an MD of 52.5 (95%CI: 5.76-99.2) (e-Figure 7).

All of these sensitivity analyses generated no significant difference of the results.

Meta-regression analysis

The effect of the presence of anti-CCP antibody on RA-ILD was not influenced by any other potential confounders. Similarly, the association of the titre of anti-CCP antibody with RA-ILD was not affected by any of them although gender and RA duration were significant in univariate analysis (e-Table 2).

Additional analysis

Two funnel plots (for both positivity and titre of anti-CCP antibody) were constructed to investigate small study bias, both of which demonstrated no apparent asymmetry (e-Figure 8 and e-Figure 9, respectively). This graphical assessment was confirmed statistically by the Egger's test, which demonstrated no statistical significance (p=0.15 and 0.28, respectively).

Assessment of evidence level

Study limitation was considered present in all of the evidence because no studies were deemed as low risk of bias. Publication bias was also considered present in all of the evidence due to the property of studies of risk prediction [37] although it was not confirmed in both graphical and statistical analyses regarding univariate results. Overall, the level of evidence derived from this review was rated as low or very low (Table 4).

Discussion

This study demonstrated using a pooled analysis of univariate results that the presence of anti-CCP antibody was significantly associated with RA-ILD and the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD. The results were confirmed by multivariate analyses in the majority of studies that reported it. These findings suggest that anti-CCP antibody is related to an increased risk of ILD for patients with RA. As this review was based on a large number of studies conducted globally and the results were reproduced by any subgroup and sensitivity analyses, these findings will be generalizable to a broader population.

It is desirable and important to identify a high risk group of patients with RA who are likely to develop ILD because it is often progressive and worsens the prognosis of the disease.[67] If the development of ILD can be predicted, it will help clinicians' decision-making and facilitate an efficient use of limited medical resources to change clinical course of the disease. Much effort has been made to identify clinical information such as serum biomarkers that can easily be obtained and help estimate the risk of ILD for patients with RA.[68] Tests for ACPAs emerged as a tool to diagnose early RA with higher specificity than traditionally employed RF.[69] They date back to the discovery of anti-perinuclear factor and anti-keratin antibody in the sera of patients

with RA, which recognized the citrullinated protein filaggrin.[70] Subsequently, cyclic citrullinated peptides (CCP) were synthesized to improve test performance [71] and after further evolution currently the third generation of anti-CCP antibody test is commercially available.[72] Anti-CCP antibody is not only helpful to diagnose RA but also reported to be associated with extra-articular manifestations of the disease.[73] The recent meta-analysis demonstrated an increased risk of RA-ILD as a result of serum anti-CCP antibody positivity.[20] Although a number of specific citrullinated proteins were discovered such as fibrinogen [74] and α-enolase,[75] a diagnostic significance of specific autoantibodies directed against these autoantigens has yet to be established.[76]

RA is classified as a systemic autoimmune disorder although the pathogenesis of the disease has been under dispute for many years.[77] Recent research suggests that the breakdown of immunological tolerance initially occurs in the lungs under the influence of environmental stress such as exposure to cigarette smoke and genetic susceptibility.[78] In short, smoking accelerates the activity of the enzyme peptidylarginine deiminase that catalyses the posttranslational convert of arginine to citrulline, which eventually induces autoimmune reaction and leads to the formation of autoantibodies against citrullinated peptides under the interplay of both T and B lymphocytes.[79] In these processes, a number of cytokines are generated and may promote fibrotic changes of the lung.[80] Smoking is related to the development of ILD, in particular, UIP, which is the most common type among RA-ILDs [9] and contributes to the formation of ACPAs. Therefore, it is most likely that anti-CCP antibody is closely associated with the development of ILD for genetically susceptible subjects with smoking history and this relationship was confirmed in this report.

The current study is different from the previous systematic review [20] in that it included a larger number of studies and subjects and thus the result is considered more reliable. It also demonstrated that the titre of anti-CCP antibody was higher for RA-ILD than RA without ILD. This finding is meaningful because anti-CCP antibody may be positive in the majority of patients with RA regardless of the presence of ILD. Indeed, the proportion of positivity of anti-CCP antibody for RA without ILD in this review ranged from 49.1% to 95.8% with the median value of 71.0%. When the group of RA without ILD is positive for anti-CCP antibody with high frequency, the benefit of the autoantibody test for screening patients with RA at a higher risk of developing ILD will be limited. Conversely, the finding of titres may be more informative because it can also be employed to patients with RA without ILD who are tested positive for the autoantibody. Therefore, titres of anti-CCP antibody may be more useful than just its presence to estimate the risk of developing ILD. However, the interpretation of this finding also needs a caution because it was derived from a comparison between RA-ILD and RA without ILD and thus does not indicate any cut-off point that defines a high or low titre of the autoantibody. As a result, in usual clinical practice, clinicians need to assess the implication of the titre of anti-CCP antibody in the context of a total evaluation. If the titre of the autoantibody is combined with clinical features such as age, gender and smoking history alongside with other biomarkers such as Krebs von den Lungen-6 (KL-6), creating composite scores, it would be more beneficial to identify a group with a higher risk of developing ILD. However, what makes the issue more complicated is the variability of measurements of anti-CCP antibody, which was produced by a number of manufacturers. The sensitivity and specificity varies depending on the tests and the titres are also different between assays.[81] Although an

SMD was employed in this review to enable the comparison of titres derived from different tests, the result may be difficult to be applied in clinical practice. Furthermore, anti-CCP antibody is reported to be closely associated with bronchiolar disease, which is also a common pulmonary complication associated with RA alongside with ILD.[54] Although bronchiolar disease was excluded in this review, it is possible that the disease was missed by the researcher or not selectively reported. If this was the case, the precise association of anti-CCP antibody with RA-ILD will be compromised. Anti-CCP antibody may also be affected by a number of other potential confounders such as age, gender, smoking history, RA duration, diagnostic criteria for RA and ILD and the proportion of positivity of anti-CCP antibody, which were diverse between studies. Although none of these confounders were found to be significantly associated with the heterogeneity of the results, it may possibly have been influenced by other clinical factor such as previous treatment. Therefore, the findings of this review may not be directly applicable to usual clinical practice and clinicians should consider all of the factors that can affect the presence or titres of anti-CCP antibody and assess the risk of ILD for patients with RA on a case-by-case basis.

There are other methodological limitations or caveats that need to be kept in mind to appropriately interpret the findings of this study. First, this review specifically focused on anti-CCP antibody and excluded ACPAs, which were not specified as anti-CCP antibody since it may have represented autoantibodies against different citrullinated peptides. However, ACPAs other than anti-CCP antibody are not usually used in clinical practice and many rheumatologic teams may use the term ACPA for anti-CCP antibody. Therefore, this narrow inclusion criterion may have excluded some studies

with a large number of subjects that could have reinforced the strength of meta-analysis. Second, this review was only composed of cross-sectional and case-control studies and thus causality between anti-CCP antibody and RA-ILD cannot be deducted although it is aetiologically plausible. Third, selection bias of subjects in individual studies cannot be ruled out. Patients with RA-ILD at relatively advanced stage may have been included for the review. If this was the case, the findings may not be applicable to an early stage of the disease and become useless for screening purpose. Fourth, anti-CCP antibody may be most closely related to UIP among other types of ILD complicated with RA. However, the association between anti-CCP antibody and individual ILD patterns could not be elucidated in this review because most of the studies did not report them. Finally, no studies were deemed as low risk of bias given that most of them were retrospectively designed cross-sectional or case-control studies. Due to this study limitation, the level of evidence obtained from this review was all rated as low or very low although univariate results in relatively a larger number of studies were combined to generate an average estimate. Therefore, more research with high quality using a prospective cohort design needs to be accumulated to make a definitive conclusion or solidify the findings of this review.

Conclusion

This systematic review and meta-analysis suggested that the presence of anti-CCP antibody was significantly associated with RA-ILD and the titre of the autoantibody was significantly higher for RA-ILD than RA without ILD. However, an applicability of these findings may be limited due to the heterogeneity of included studies.

Ethics approval and participant consent

Neither ethics approval nor participant consent was required as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

Data sharing

The dataset used and/or analysed for this review will be available from the corresponding author upon a reasonable request and may become open to the public through a digital repository (such as Dryad) after the final result is published in a journal.

Conflict of interest

None to declare.

Funding

This research received no specific grant from any funding agency in either the public, commercial, or not-for-profit sectors.

Authors' contributions

H.K. planned the entire research project and analysed the data. He also summarized the result and wrote the manuscript. H.K. has full access to the data and takes responsibility for its integrity as well as the accuracy of the analysis.

O.M.P. contributed to the design of the research project and conducted the literature search and data extraction. He was also involved in revising the manuscript.

All researchers provided thoughts and opinions to compile a draft paper and approved of the final version of the manuscript.

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Table 1 Baseline characteristics of included studies[a]

Study	Location	Design	Number (n)	Age at inclusion (years)	Gender (male) (n (%))	Smoking (n (%))	Proportion of ILD (n (%))[b]	Disease duration (RA) (years)	Disease activity[c]	Other CTDs (n)	ILD patterns (on HRCT) (n)
Alunno 2018 [38]	Italy	Cross-sectional	252	61.7±0.8	56 (22.2)	-	37 (20.2) (n=183)	12.6±0.6	-	-	-
England 2019 [39]	US	Cross-sectional[d]	1823	63.5±11.0	(90.1)	(89.5)	90 (4.9)	11.1±11.5	4.0±1.6	-	-
Giles 2014 [40]	US	Cross-sectional[d]	177	59±8[g]	71 (40.1)	105 (59.3)	120 (67.8)	9 (5-19) vs. 8 (4-16)[g]	3.7 (2.9-4.4)[g] (CRP)	-	-
Chen 2013 [41]	China	Cross-sectional	103	49.1±14.7	27 (26.2)	2 (1.9)	63 (61.2)	4.3±5.7	4.4±1.4	-	-
Chen 2015 [42]	China	Cross-sectional	71	60.7±12.1[e]	37 (52.1)	35 (49.3)	49 (69.0)	12.8±10.3 vs. 8.4±8.1 (n=68)	3.7±1.2 vs. 3.3±1.7 (n=43)	-	-
Doyle 2015 [43]	US	Cross-sectional[d]	75	61.5±12.7[e]	11 (14.7)	41 (54.7)	-	-	-	-	-

Abdel-Hamid 2019 [44]	Egypt	Cross-sectional	50	45.8±12.3	2 (4.0)	-	19 (38.0)	9.8±6.6	4.7±1.3	0	-
Akiyama 2016 [45]	Japan	Cross-sectional	395	58.5±13.1	49 (12.4)	69 (20.3) (n=340)	78 (19.7)	129.4±115.2 (months)	4.9±1.6 (n=372)	38 (SS, SSc, PM/DM, SLE)	-
Alexiou 2008 [46]	Greece	Case-control	136	-	-	-	N/A (ILD 11/no ILD 125)	-	-	-	-
Correia 2019 [47]	US	Cross-sectional	453	59.6±15.7	(19.4)	-	(6.0)	-	-	0	-
Fadda 2018 [48]	Egypt	Cross-sectional	88	50.2±9.0	13 (14.8)	87 (98.9)	63 (71.6)	10.2±6.2	14 (1-32) vs. 12 (3-25) (median (range)) (CDAI)	0	UIP 62%, NSIP 27%, Mixed 1%
Furukawa 2012 [49]	Japan	Case-control	450	63.9±10.9[e]	89 (19.8)	130 (28.9)	N/A (ILD 129/no ILD 321)	14.5±10.9[e]	-	-	-
Kakutani 2019 [50]	Japan	Cross-sectional	2702	62.8±12.5	(17.8)	(28.9)	261 (9.7)	9 (15) vs. 10 (17) (median (IQR))	3.2±1.0 (ESR)	-	-

Kelly 2014 [51]	UK	Case-control	460	-	220 (47.8)	-	N/A (ILD 230/no ILD 230)	-	-	-	-
Liu 2019 [52]	China	Cross-sectional	101	54 (17) (median (IQR))	26 (25.7)	-	23 (22.8)	7 (14) (median (IQR)	4.0±1.9	-	-
Matsuo 2018 [53]	Japan	Cross-sectional	312	63.5±12.7	41 (13.1)	95 (30.4)	26 (8.3)	14.9±11.6	2.5±1.1 (CRP)	11 (not specified)	-
Mori 2012 [54]	Japan	Cross-sectional	356	72.5 (12.3) (n=24) vs. 59.0 (16) (n=302) (median (IQR))	85 (23.9)	76 (21.3)	24 (6.7)	1.5 (6.3) (n=24) vs 0 (6) (n=302) (median (IQR))	-	-	UIP 5, NSIP 19
Ortancil 2011 [55]	Turkey	Cross-sectional	67	57.4±13.5	14 (20.9)	-	12 (17.9)	10.2±11.7[e]	-	-	-
Park 2016 [56]	Korea	Cross-sectional	83	53.7±10.1[e]	10 (12.0)	-	7 (8.4)	-	-	-	UIP 6, Indeterminate 1

Paulin 2019 [57]	Argentina	Case-control	118	56.7±15.7	26 (22.0)	52 (44.1)	N/A (ILD 52/ no ILD 66)	6 (8) (median (IQR))	3.4±1.1	-	-
Restrepo 2015 [58]	US	Cross-sectional	779	53.7±13.3 (n=632)[e]	161 (25.5) (n=632)	357 (56.5) (n=632)	69 (8.9)	10.5±10.3[e]	5.4±1.4[e]	-	-
Rocha-Munoz 2015 [59]	Mexico	Case-control	81	51.0 (36.0-72.0) vs. 49.0 (24.0-73.0) (median (range))	-	22 (27.2)	N/A (ILD 39/no ILD 42)	7.0 (1.0-35.0) vs. 6.5 (0.75-25.0) (median (range))	3.9 (1.7-5.3) vs. 2.5 (1.7-5.1) (median (range))	0	-
Sargin 2018 [60]	Turkey	Cross-sectional	83	59.3±12.1	20 (24.1)	9 (10.8)	43 (51.8)	-	-	0	-
Sulaiman 2019 [61]	Malaysia	Cross-sectional	159	48.3±14.1	25 (15.7)	-	21 (13.2)	-	4.7±0.9 (ESR)	0	-
Tian 2016 [62]	China	Cross-sectional	75	-	29 (38.7)	-	37 (49.3)	-	-	-	-
Wang 2015	China	Cross-sectional	41	60.7±12.4[e]	20 (48.8)	-	25 (61.0)	108 (5-360) vs. 72	-	-	-

[63]								(2-552) (months) (median (range))			
Yang 2019 [64]	Korea	Case-control	308	57.0±12.0[e]	76 (24.7)	39 (17.7) (n=220)	N/A (ILD 77/ no ILD 231)	11.0±7.3[e]	-	-	-
Yin 2014 [65]	China	Cross-sectional	285	51.7±13.4[e]	74 (26.0)	59 (20.7)	71 (24.9)	9.0 (16.0) vs. 4.0 (9.1) (median (IQR))	5.4±1.7	61[f] (SS 41, SSc 7, PM/DM 4, SLE 16)	-
Zhang 2018 [66]	China	Case-control	75	41-69 vs. 40-70 (range)	30 (40.0)	-	N/A (ILD 28/ no ILD 47)	-	-	0	-

a, Comparisons correspond to RA-ILD vs. RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified;

b, N/A indicates not applicable due to case-control studies;

c, Disease activity was estimated using disease activity score (DAS) 28 unless otherwise specified and a laboratory marker used to calculate the score was described as either ESR or CRP if it was specified;

d, indicates a prospective study while all of the other studies are retrospectively designed;

e, calculated combining the figure in both comparative groups;

f, some patients had multiple CTDs;

g, unknown statistics;

CDAI, clinical disease activity index; CRP, C-reactive protein; CTD, connective tissue disease; ESR, erythrocyte sedimentation rate; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IQR, interquartile range; NSIP, non-specific interstitial pneumonia; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren syndrome; SSc, systemic sclerosis; UIP, usual interstitial pneumonia;

Table 2 Anti-cyclic citrullinated peptide (CCP) antibody tests and its association with rheumatoid arthritis-associated interstitial lung disease[a]

Study	Measurements of anti-CCP antibody (manufacturer) (cut-off points)	Proportion of anti-CCP antibody	Titres of anti-CCP antibody	Univariate result (positivity)	Univariate result (titre)	Multivariate result (positivity)	Multivariate result (titre)	Adjusted variables
Alunno 2018 [38]	Second generation (Thermo Fisher Scientific or Aesku)	28/37 (75.7) vs. 90/146 (61.6)	-	OR 1.94 (0.85-4.42)	-	-	-	-
England 2019 [39]	Second generation	(86.7) vs. (76.7)	-	**OR 1.98, p=0.03**	-	-	-	-
Giles 2014 [40]	Second generation	51/57 (89.5) vs. 82/120 (68.3)	152 (99-194) (n=32) vs. 89 (11-152) (n=120)[d]	**OR 3.94 (1.57-9.90)**	**p=0.0005[b]**	-	-	-
Chen 2013 [41]	Not specified	-	231.8±178.0 (n=63) vs. 196.8±161.1 (n=40)	-	MD 35.0 (-33.0-103.0)	-	-	-
Chen 2015 [42]	Not specified	-	142.6±151.9 (n=49) vs. 154.6±151.4 (n=22)	-	MD -12.0 (-88.2-64.2)	-	-	-

Doyle 2015 [43]	Not specified	-	188±133 vs. 83±113	-	-	-	-	-
Abdel-Hamid 2019 [44]	Third generation	30/50 (60.0)	100 (390) (n=19) vs. 20 (298) (n=31) (median (IQR))	-	**p=0.04**[b]	-	-	-
Akiyama 2016 [45]	Not specified (≥4.5 U/mL)	69/75 (92.0) vs. 245/305 (80.3)	-	**OR 2.82 (1.17-6.81)**	-	OR 1.80 (0.70-4.40) (positive with high titre (>13.5 U/mL))	-	age, sex, smoking, RF
Alexiou 2008 [46]	Second generation (INOVA Diagnostics) (20 IU/mL)	10/11 (90.9) vs. 73/125 (58.4)	152.6±104.5 (n=11) vs. 73.1±114.0 (n=125)	OR 7.12 (0.89-56.9)	**MD 79.5 (9.72-149.3)**	-	-	-
Correia 2019 [47]	Second generation (Euro-Diagnostica) (≥6 U/mL)	-	113.0±5.9 (162.4 vs. 109.9) (mean±SE)	OR 1.51 (0.48-4.74) (low titre), 2.61 (0.59-11.5)(moderate titre), 2.83 (0.96-8.39) (high titre)	**p=0.04**[b]	-	**OR 1.41 (1.01-1.97)/1 group of titre**	age, smoking

Fadda 2018 [48]	Third generation (INOVA Diagnostics) (20 U/mL)	84/88 (95.5)	220 (0-500) (n=63) vs. 120 (30-400) (n=25), (median (range))	-	**MD 67.5 (19.5-115.5)[c], OR1.006 (1.001-1.011) (/1 U/mL)**	-	-	-
Furukawa 2012 [49]	Not specified (Medical & Biological Laboratories)	116/129 (89.9) vs. 278/321 (86.6)	-	OR 1.38 (0.71-2.69)	-	-	-	-
Kakutani 2019 [50]	Not specified	(93.2) vs. (82.9)	-	**OR 2.83, p=0.002**	-	-	-	-
Kelly 2014 [51]	Not specified	-	180 (8-340) vs. 78 (8-340) (median (range))	**OR 4.00 (2.00-7.80)**	**p=0.02[b]**	**OR 0.33, p=0.003**	-	age, sex, smoking, RF
Liu 2019 [52]	Second generation (Euro- Diagnostica) (≥25 U/mL)	77/101 (76.2)	-	OR 0.64 (0.23-1.80)	-	-	-	-

Matsuo 2018 [53]	Not specified	25/26 (96.2) vs. 235/286 (82.2)	199.7±104.6 (n=26) vs. 120.7±112.6 (n=286)	**OR 5.43 (1.11-98.0)**	**MD 79.0 (34.1-123.9), OR 1.06 (1.02-1.10) (/10U/mL)**	-	**OR 1.08 (1.03-1.12) (/10U/mL)**	age, smoking, RF, LDH, CRP, ESR, KL-6, MMP-3, IL18, dose of MTX, dose of PSL
Mori 2012 [54]	Second generation (Axis-Shield Diagnostic) (>4.6 U/mL)	24/24 (100) vs. 294/332 (88.6)	283.5 (99.0-794.0) (n=24) vs. 81.1 (21.0-249.0) (n=302) (median (1st-3rd quartile)	OR 6.41 (0.38-107.8)	**MD 275.2 (184.1-366.3)[e]**	RR 2.73 (0.91-8.23) (positive with high titre (≥90 U/mL))	-	age, sex, smoking, advanced stage, RF, HLA-DRB1*04, HLA-DRB1*1502
Ortancil 2011 [55]	Second generation (Euroimmun)	7/12 (58.3) vs. 27/55 (49.1)	-	OR 1.45 (0.41-5.08)	-	-	-	-
Park 2016 [56]	Not specified (Roche Diagnostics) (≥17.0 U/mL)	69/83 (83.1)	-	-	0.22[c]	-	-	-
Paulin 2019 [57]	Second generation	45/47 (95.7) vs. 46/48 (95.8)	-	OR 0.98 (0.13-7.24)	-	-	-	-

Restrepo 2015 [58]	Not specified (TheraTest) (≥7 IU/mL)	44/69 (63.8) vs. 341/563 (60.6)	5.54±1.49 (n=69) vs. 4.68±1.52 (n=563) (log anti-CCP antibody titre)	OR 1.15 (0.69-1.91)	**MD 0.86 (0.49-1.23) (log anti-CCP antibody titre)**	Not specified	Not specified	age, sex, disease duration, DAS28, RF, HLA-DRB1*SE, PSL use
Rocha-Munoz 2015 [59]	Second generation (Euroimmun) (>20 U/mL)	39/39 (100) vs. 27/42 (64.3)	77.9 vs. 30.2 (median)	**OR 44.5 (2.54-778.3)**	**p<0.001**[b]	**-**	**OR 1.06 (1.02-1.10)**	age, smoking, disease duration, , DAS28, HAQ-Di, RF, ESR, duration of MTX treatment
Sargin 2018 [60]	Not specified	-	19.5 (1.8-140.8) (n=43) vs. 6.2 (0.5-15.9) (n=40) (median (1st-3rd quartile))	-	MD 9.8 (-34.1-53.7)[e]	-	-	-
Sulaiman 2019 [61]	Second generation (Euro-Diagnostica) (≥20.0 U/mL)	13/21 (61.9) vs. 70/138 (50.7)	-	OR 1.58 (0.62-4.05)	-	-	-	-
Tian 2016 [62]	Not specified (Euroimmun) (≥25	30/37 (81.1) vs. 28/38 (73.7)	475.2±551.8 (n=37) vs. 332.0±418.6 (n=38)	OR 1.53 (0.51-4.59)	MD 143.2 (-78.1-364.5)	-	-	-

	RU/mL)							
Wang 2015 [63]	Not specified	-	296.4 (1.91-500.0) (n=25) vs. 392.9 (7.00-500.0) (n=16) (median (range))	-	MD -49.5 (-132.2-33.2)[e]	-	-	-
Yang 2019 [64]	Not specified (≥5.0 IU/mL)	33/43 (76.7) vs. 95/142 (66.9)	242.8±234.4 (n=43) vs. 125.3±144.3 (n=142)	OR 1.63 (0.74-3.57)	**MD 117.5 (59.7-175.3)**	-	-	-
Yin 2014 [65]	Second generation (Euroimmun) (≥25 U/mL)	207/285 (72.6)	-	**OR 3.83 (1.74-8.43)**	-	**OR 3.50 (1.52-8.04)**	-	age, disease duration
Zhang 2018 [66]	Not specified	-	3.09±0.34 (n=28) vs. 3.05±0.32 (n=47)	-	MD 0.04 (-0.12-0.20)	-	-	-

a, Comparisons correspond to RA-ILD vs. RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified. The value with an interval in the parenthesis indicates 95% confidence interval. Text in bold indicates statistical significance;

b, the difference of the titre of anti-CCP antibody between RA with and without ILD could not be calculated due to unavailability of relevant summary statistics, no information of the number of subjects and/or unknown summary statistics;

c, indicates correlation coefficient between anti-CCP antibody and a total ILD score;

d, unknown statistics;

e, MDs (95% confidence interval) were calculated converting the median, range or interquartile range to the mean and standard deviation, using a formula reported by a previous study;[32]

CCP, cyclic citrullinated peptite; CRP, C-reactive protein; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; HAQ-Di, health assessment questionnaire-disability index; HLA, human leukocyte antigen; IL-18, interleukin-18; ILD, interstitial lung disease; IQR, interquartile range; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MD, mean difference; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; OR, odds ratio; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, risk ratio; SE, shared epitope;

Table 3 Risk of bias in individual studies

Study	Study participation	Anti-CCP antibody measurement	ILD confirmation	Study confounding	Statistical analysis and reporting
Alunno 2018 [38]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
England 2019 [39]	moderate risk	**high risk**	**high risk**	low risk	**high risk**
Giles 2014 [40]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Chen 2013 [41]	low risk	**high risk**	low risk	moderate risk	**high risk**
Chen 2015 [42]	moderate risk	low risk	low risk	moderate risk	**high risk**
Doyle 2015 [43]	moderate risk	moderate risk	low risk	moderate risk	**high risk**
Abdel-Hamid 2019 [44]	moderate risk	moderate risk	**high risk**	moderate risk	**high risk**
Akiyama 2016 [45]	low risk	moderate risk	**high risk**	moderate risk	moderate risk
Alexiou 2008 [46]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
Correia 2019 [47]	moderate risk	low risk	low risk	moderate risk	**high risk**
Fadda 2018 [48]	moderate risk	low risk	low risk	moderate risk	**high risk**
Furukawa2012 [49]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Kakutani 2019 [50]	low risk	**high risk**	**high risk**	moderate risk	**high risk**

Kelly 2014 [51]	moderate risk	**high risk**	low risk	moderate risk	**high risk**
Liu 2019 [52]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Matsuo 2018 [53]	low risk	moderate risk	**high risk**	moderate risk	moderate risk
Mori2012 [54]	low risk	low risk	low risk	moderate risk	moderate risk
Ortancil 2011 [55]	moderate risk	low risk	**high risk**	moderate risk	**high risk**
Park2016 [56]	low risk	low risk	low risk	**high risk**	**high risk**
Paulin 2019 [57]	moderate risk	**high risk**	**high risk**	moderate risk	**high risk**
Restrepo 2015 [58]	moderate risk	low risk	**high risk**	moderate risk	moderate risk
Rocha-Munoz 2015 [59]	moderate risk	low risk	**high risk**	moderate risk	low risk
Sargin 2018 [60]	moderate risk	**high risk**	**high risk**	moderate risk	**high risk**
Sulaiman 2019 [61]	moderate risk	low risk	**high risk**	**high risk**	**high risk**
Tian 2016 [62]	**high risk**	low risk	**high risk**	moderate risk	**high risk**
Wang 2015 [63]	moderate risk	**high risk**	low risk	**high risk**	**high risk**
Yang 2019 [64]	moderate risk	**high risk**	moderate risk	moderate risk	moderate risk
Yin 2014 [65]	moderate risk	low risk	low risk	moderate risk	moderate risk

Zhang 2018 [66]	**high risk**	**high risk**	**high risk**	**high risk**	**high risk**

Text in bold indicates high risk of bias

CCP, cyclic citrullinated peptite; ILD, interstitial lung disease;

Table 4 Assessment of quality of evidence by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

Outcome: rheumatoid arthritis-associated interstitial lung disease										
			GRADE factors							
Prognostic factors	Analysis	Phase	Study limitations	Inconsistency	Indirectness	Publication bias	Imprecision	Moderate/large effect size	Dose effect	Overall quality
Anti-CCP antibody positivity	Univariate	1	+	+	-	+	-	-	-	very low
	Multivariate	1	+	+	-	+	-	-	-	very low
Anti-CCP antibody titre	Univariate	1	+	+	-	+	-	-	-	very low
	Multivariate	1	+	-	-	+	-	-	+	low

CCP, cyclic citrullinated peptite;

Figure legends

Figure 1 Study flow diagram

Out of a total of 827 records identified searching through five electronic databases, i.e., Medline, EMBASE, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials and Google Scholar, 645 records were screened by titles and abstracts after removing 182 duplicates. After excluding 320 records consisting of non-English reports (n=16) and articles of ineligible types (n=304) (conference proceedings (n=153), case reports (n=72), editorials or letters (n=10) and review articles (n=69)) and 265 irrelevant reports, 60 records were retrieved as full-texts. Out of these, 31 records were excluded due to no specific pulmonary disease (n=7), no ILD (n=5), no risk estimates (n=11), no anti-CCP antibody (n=7) and no RA (n=1). The remaining 29 reposts/studies were eligible for the review and additionally four reports were identified through a hand-search of references of eligible studies. As a result, a total of 33 reports/studies were considered for the review. Among them, four studies were excluded due to overlapped cohorts by other studies and finally a total of 29 studies/cohorts were focused for further analysis.

Figure 2 Forrest plot of the result of univariate analysis regarding the association of positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

The results of univariate analyses in 19 studies were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds

ratio (OR) of 2.10 (95% confidence interval: 1.59-2.78, p<0.00001/95% prediction interval: 0.93-4.76). There was moderate heterogeneity (chi^2=29.7, p=0.04, I^2=39%).

Figure 3 Forrest plot of the result of univariate analysis regarding the association of the tire of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

The results of univariate analyses in 12 studies were pooled for meta-analysis. The titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with a standardized mean difference (SMD) of 0.42 (95% confidence interval: 0.20-0.65, p=0.0002/95% prediction interval: -0.33-1.17). There was considerable heterogeneity (chi^2=36.0, p=0.0002, I^2=69%).

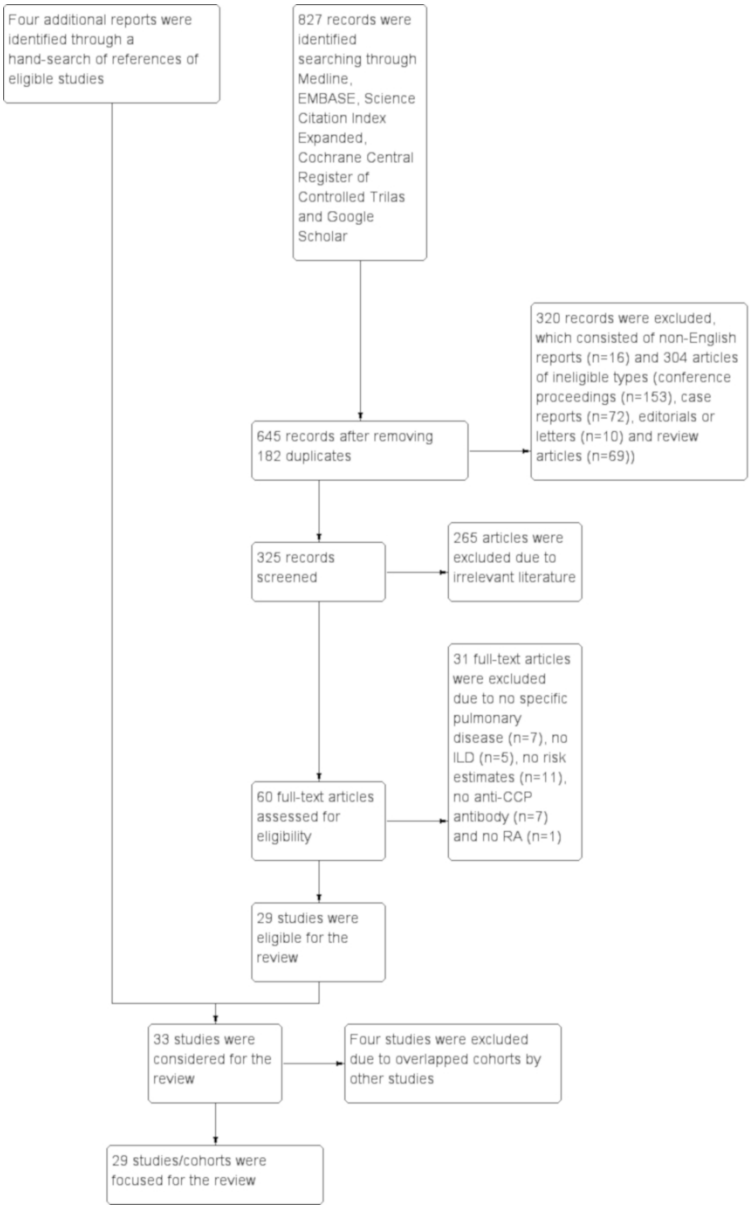


Figure 1

102x165mm (1100 x 1100 DPI)

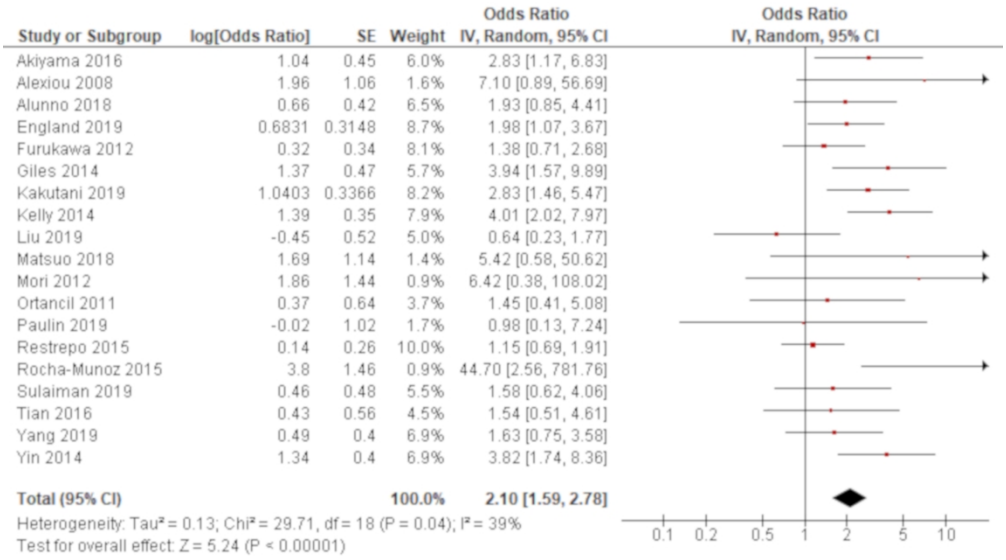


Figure 2

174x100mm (1200 x 1200 DPI)

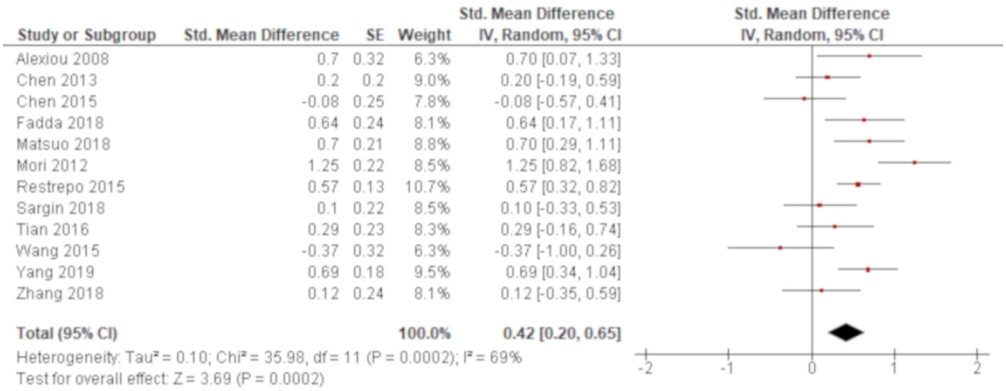


Figure 3

206x83mm (1100 x 1100 DPI)

Supplementary file

e-Table 1 Other baseline characteristics of included studies

Study	RA diagnostic criteria	ILD diagnostic criteria	Treatment received[a]
Alunno 2018 [38]	ACR/EULAR 2010	X-ray and HRCT in symptomatic cases	-
England 2019 [39]	ACR 1987	1)Pulmonologist diagnosis and imaging, 2)non-pulmonologist diagnosis and two of the followings; imaging, pathology or PFT	PSL 63.0% vs. 42.8%, MTX 21.0% vs. 51.2%, Biologics 30.0% vs. 20.1%
Giles 2014 [40]	ACR 1987	Cardiac MDCT	PSL 51% vs. 32%, MTX 58% vs. 68%, TNF-αI 56% vs. 40%
Chen 2013 [41]	ACR 1987	HRCT	-
Chen 2015 [42]	ACR 1987	HRCT	PSL 57% vs. 68%, MTX 63% vs. 67%, TNF-αI 18% vs. 9%
Doyle 2015 [43]	-	HRCT	PSL 93.5% vs. 83%, MTX 78.5% vs. 76%, TNF-αI 73.5% vs. 55%
Abdel-Hamid 2019 [44]	ACR/EULAR 2010	HRCT	-
Akiyama 2016 [45]	ACR/EULAR 2010	HRCT in symptomatic cases or abnormal radiograph	PSL 51.3% vs. 33.1%, MTX 24.4% vs. 61.8%, Biologics 50.0% vs. 43.2%
Alixiou 2008 [46]	-	-	-
Correia 2019 [47]	ACR/EULAR 2010	CT or radiograph and DLCO or pulmonologist	-

		diagnosis	
Fadda 2018 [48]	ACR/EULAR 2010	HRCT	MTX 6.9±4.2 vs. 7.9±4.3 years (duration)
Furukawa 2012 [49]	ACR 1987	Radiograph or CT	-
Kakutani 2019 [50]	ACR 1987 ACR/EULAR 2010	HRCT	PSL 77.8% vs. 58.1%, MTX 44.4% vs. 66.5%, non- TNF-αI Biologics 10.7% vs. 4.8%
Kelly 2014 [51]	ACR/EULAR 2010	HRCT	-
Liu 2019 [52]	ACR 1987	-	-
Matsuo 2018 [53]	-	CT in abnormal radiograph	PSL 65.4% vs. 41.6%, MTX 57.7% vs. 72.7%, Biologics 19.2% vs. 30.4%
Mori 2012 [54]	ACR 1987	HRCT	MTX 12.5% vs. 12.8%, TNF-αI 0% vs. 0.2%
Ortancil 2011 [55]	ACR 1987	-	-
Park 2016 [56]	ACR/EULAR 2010	CT	-
Paulin 2019 [57]	ACR/EULAR 2010	HRCT	MTX 51.9% vs. 74.2%, TNF-αI 11.5% vs. 24.2%
Restrepo 2015 [58]	ACR 1987	Clinical, PFT, imaging and pathology	PSL 63.7% vs. 46.5%, MTX 50.7% vs. 60.7%, TNF-αI 4.3% vs. 2.7%
Rocha-Munoz 2015 [59]	ACR 1987	Symptoms, PFT and HRCT	PSL 94.9% vs. 88.1%, MTX 100.0% vs. 97.6%
Sargin 2018 [60]	ACR/EULAR 2010	Symptoms, PFT, X-ray and HRCT	-
Sulaiman 2019	ACR/EULAR 2010	Radiograph and HRCT in	-

[61]		positive clinical exam	
Tian 2016 [62]	ACR/EULAR 2010	Clinical, PFT, imaging and/or pathology	-
Wang 2015 [63]	ACR 1987	HRCT	PSL 68.0% vs. 81.3%, MTX 64.0% vs. 81.3%
Yang 2019 [64]	ACR 1987	Clinical, PFT, imaging and/or pathology	MTX 39.0% vs. 76.2%, TNF-αI 5.2% vs. 5.2%
Yin 2014 [65]	ACR 1987	HRCT	PSL 81.7% vs. 82.2%, MTX 53.5% vs. 66.4%, Biologics 8.5% vs. 15.0%
Zhang 2018 [66]	-	-	-

a, Comparisons correspond to RA-ILD vs. RA without ILD;

ACR, American College of Rheumatology; DLCO, diffusing capacity of the lung for carbon monoxide; EULAR, European League Against Rheumatism; HRCT, high resolution computed tomography; ILD, interstitial lung disesae; MDCT, multi-detector computed tomography; MTX, methotrexate, PFT, pulmonary function test; PSL, prednisolone; RA, rheumatoid arthritis; TNF-αI, tumor necrosis factor-α inhibitor;

e-Table 2 Meta-regression analysis

Potential confounder	Positivity of anti-CCP antibody[a]		Titre of anti-CCP antibody[b]	
	Univariate (95%CI)	Multivariate (95%CI)[c]	Univariate (95%CI)	Multivariate (95%CI)[c]
Age (at inclusion) (/year)	0.02 (-0.04-0.07)	0.06 (-0.03-0.16)	-0.01 (-0.08-0.06)	-0.01 (-0.09-0.06)
Gender (male) (/percentage)	0.003 (-0.009-0.02)	0.003 (-0.009-0.02)	**-0.02 (-0.04--0.004)**	0.004 (-0.04-0.05)
Smoking history (/percentage)	-0.008 (-0.02-0.005)	-0.0005 (-0.03-0.02)	0.001 (-0.01-0.01)	0.0008 (-0.006-0.008)
RA duration (/year)	0.02 (-0.19-0.23)	0.03 (-0.20-0.26)	**0.05 (0.01-0.09)**	0.06 (-0.03-0.14)
RA diagnostic criteria (ACR/EULAR 2010 vs. ACR 1987)	0.36 (-0.22-0.94)	0.47 (-0.25-1.18)	-0.17 (-0.94-0.59)	0.06 (-1.24-1.36)
ILD diagnostic criteria (CT for all subjects vs. others)	0.02 (-0.60-0.64)	-0.48 (-1.66-0.71)	-0.24 (-1.26-0.78)	0.20 (-0.21-0.61)
Proportion of positivity of anti-CCP antibody in subjects with RA alone (/percentage)	0.009 (-0.01-0.03)	0.02 (-0.02-0.06)	0.01 (-0.01-0.04)	-[d]

Text in bold indicates statistical significance;

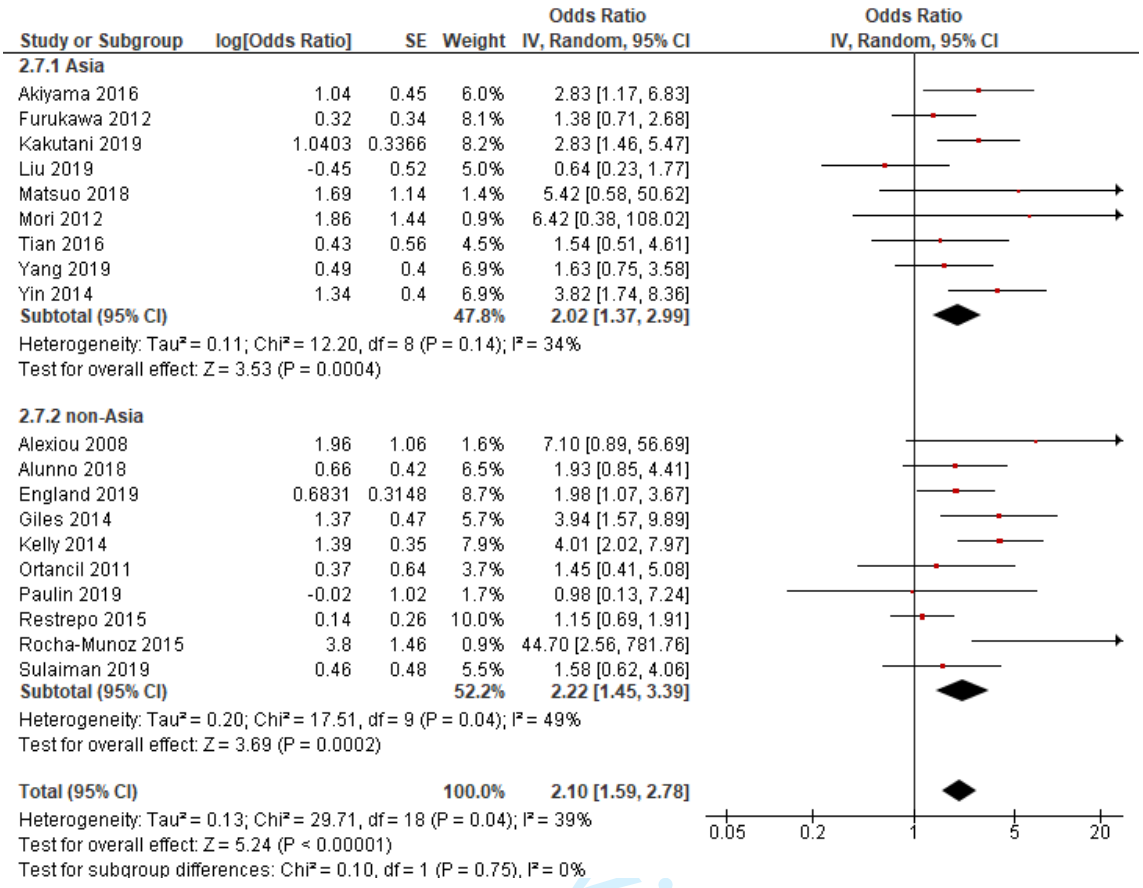
a, The positivity of anti-CCP antibody for RA-ILD against RA alone (dependent variable) was regressed against each potential confounder and the value in each cell indicates a change of an OR with one unit increase of each covariate;

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;

c, Each potential confounder was adjusted for RA duration and the effect of RA duration was estimated allowing for gender;

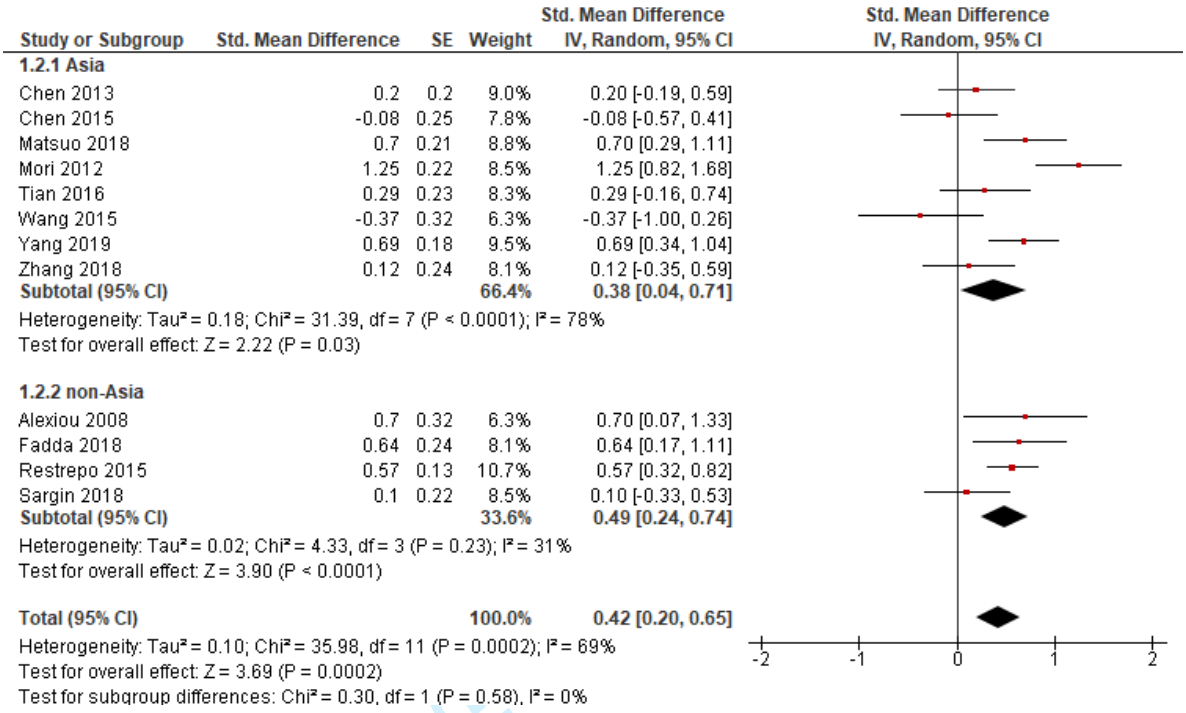
d, The effect was unable to be estimated due to a small number of studies;

ACR, American College of Rheumatology; CCP, cyclic citrullinated peptide; CI, confidence interval; EULAR, European League Against Rheumatism; ILD, interstitial lung disease; HRCT, high resolution computed tomography; OR, odds ratio; RA, rheumatoid arthritis; SMD, standardized mean difference;



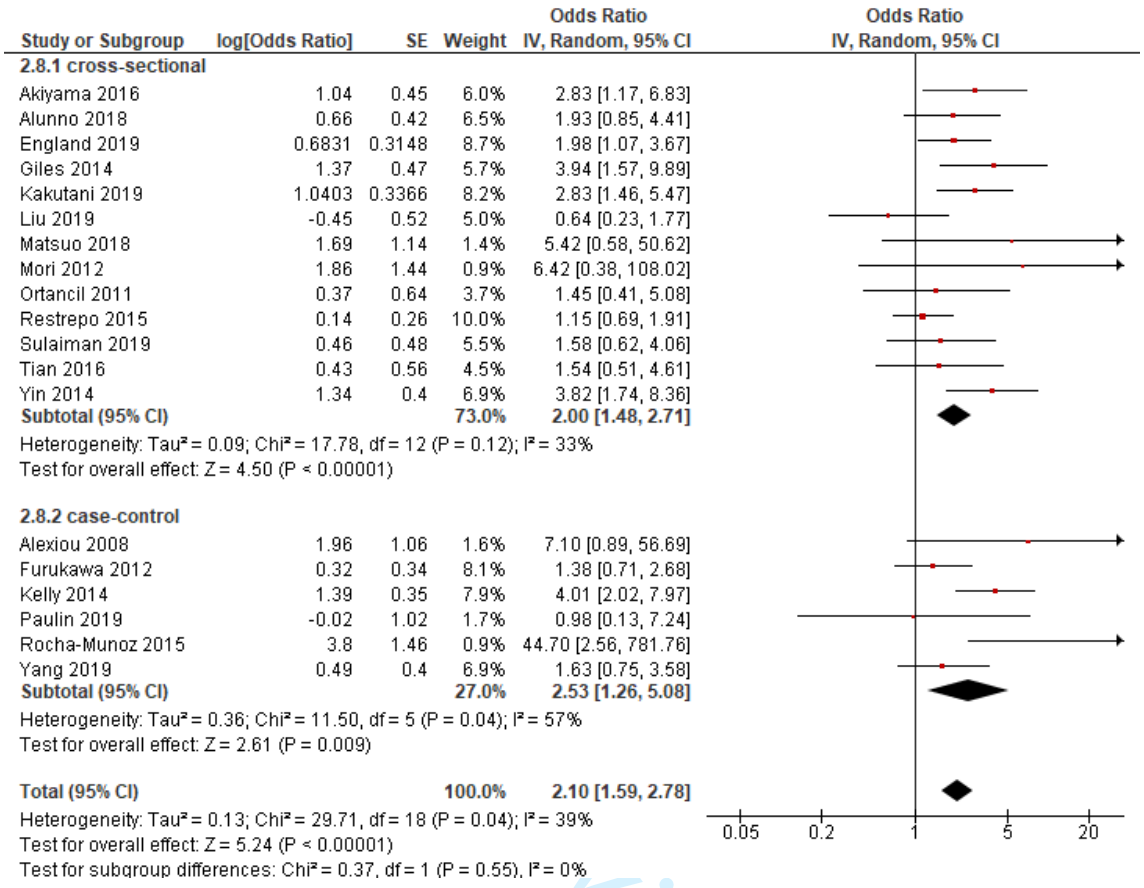
e-Figure 1 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 2.02 (95% confidence interval (CI): 1.37-2.99, p=0.0004/95% prediction interval (PI): 0.81-5.05) and 2.22 (95%CI: 1.45-3.39, p=0.0002/95%PI: 0.71-6.98), respectively and there was no significant difference in these results (p=0.75). There remained moderate heterogeneity in both Asian and non-Asian studies.



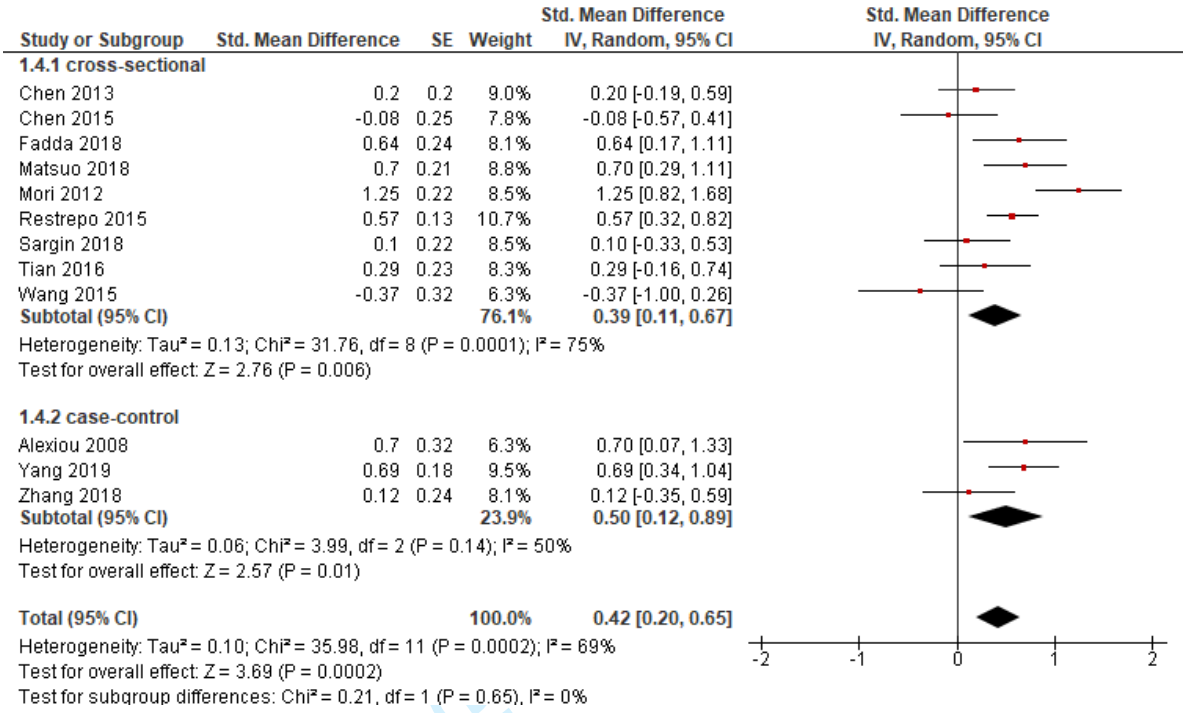
e-Figure 2 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study location

A pooled analysis of studies in Asia and non-Asia individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.38 (95% confidence interval (CI): 0.04-0.71, p=0.03/95% prediction interval (PI): -0.74-1.50) and 0.49 (95%CI: 0.24-0.74, p<0.0001/95%PI: -0.33-1.31), respectively and there was no significant difference in these results (p=0.58). There remained substantial heterogeneity in Asian studies (chi^2=31.4, p<0.0001, I^2=78%).



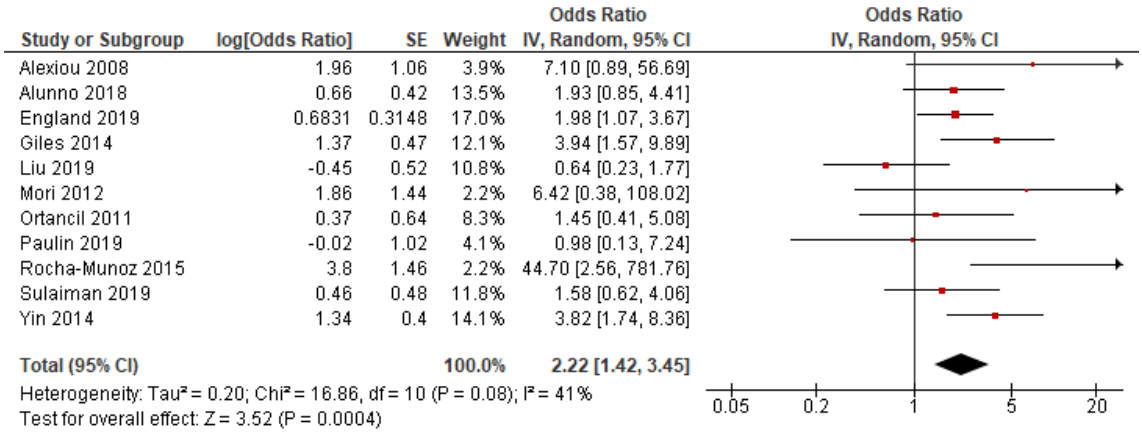
e-Figure 3 Subgroup analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the positivity of anti-CCP antibody was significantly associated with RA-ILD with odds ratios (ORs) of 2.00 (95% confidence interval (CI): 1.48-2.71, p<0.00001/95% prediction interval (PI): 0.95-4.21) and 2.53 (95%CI: 1.26-5.08, p=0.009/95%PI: 0.36-17.5), respectively and there was no significant difference in these results (p=0.55). There remained considerable heterogeneity in case-control studies (chi^2=11.5, p=0.04, I^2=57%).



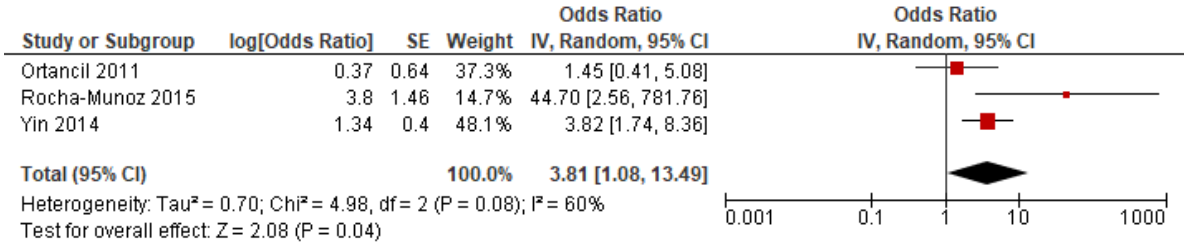
e-Figure 4 Subgroup analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) based on study design

A pooled analysis of cross-sectional and case-control studies individually demonstrated that the titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with standardized mean differences (SMDs) of 0.39 (95% confidence interval (CI): 0.11-0.67, p=0.006/95% prediction interval (PI): -0.53-1.31) and 0.50 (95%CI: 0.12-0.89, p=0.01/95%PI: -3.51-4.51), respectively and there was no significant difference in these results (p=0.65). There remained substantial heterogeneity in cross-sectional studies (chi^2=31.8, p=0.0001, I^2=75%).



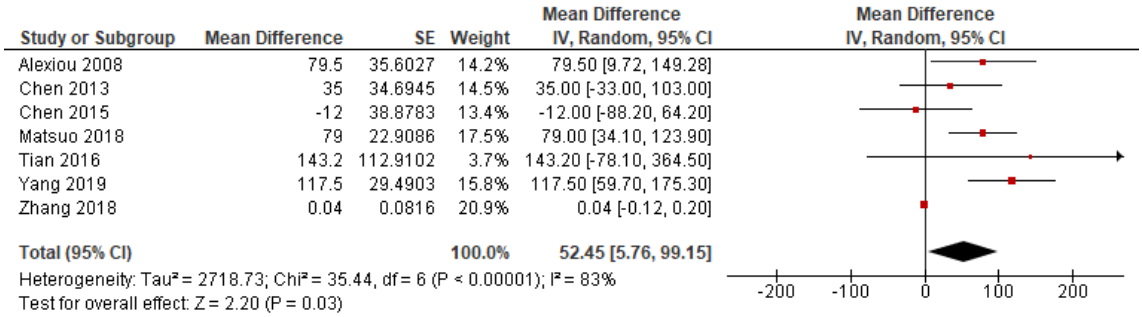
e-Figure 5 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test

The results of univariate analyses in 11 studies that examined the second generation of anti-CCP antibody were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 2.22 (95% confidence interval: 1.42-3.45, p=0.00041/95% prediction interval: 0.72-6.89). There remained moderate heterogeneity (chi^2=16.9, p=0.08, I^2=41%).



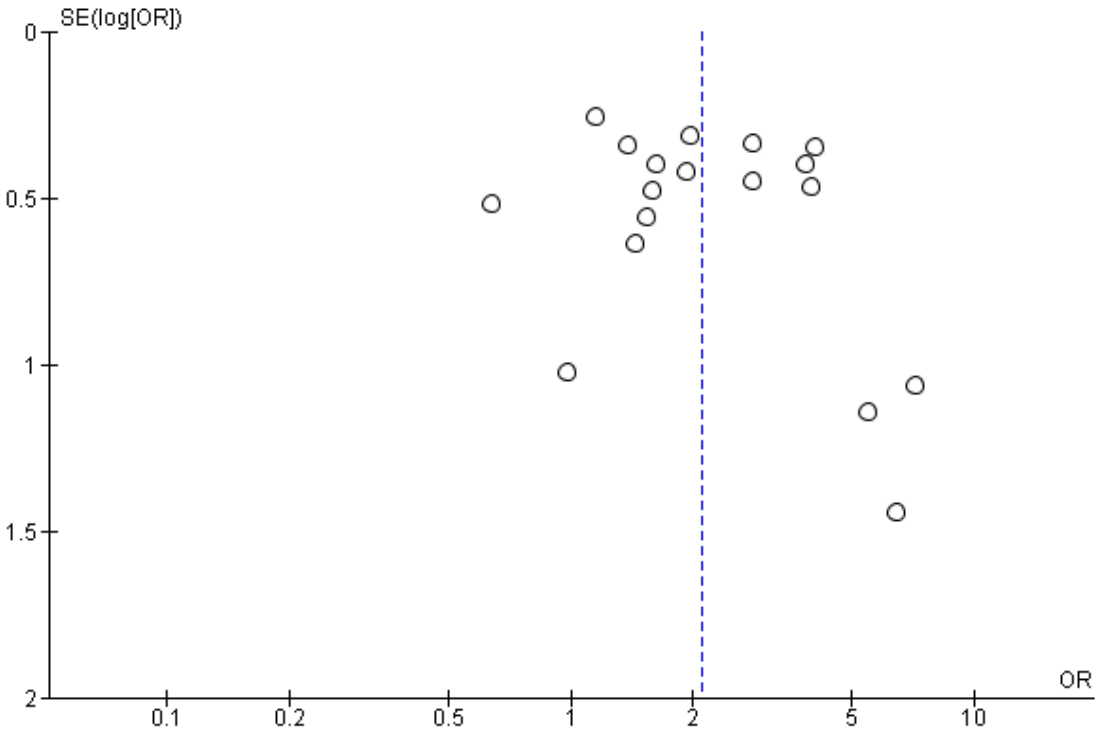
e-Figure 6 Sensitivity analysis of the association of the positivity of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same generation of the autoantibody test by the same manufacturer

The results of univariate analyses in three studies that examined the second generation of anti-CCP antibody test by the same manufacturer (Euroimmun, Lübeck, Germany) were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an odds ratio (OR) of 3.81 (95% confidence interval: 1.08-13.5, p=0.04/95% prediction interval: 0.00->100.0). There remained considerable heterogeneity (chi^2=4.98, p=0.08, I^2=60%).



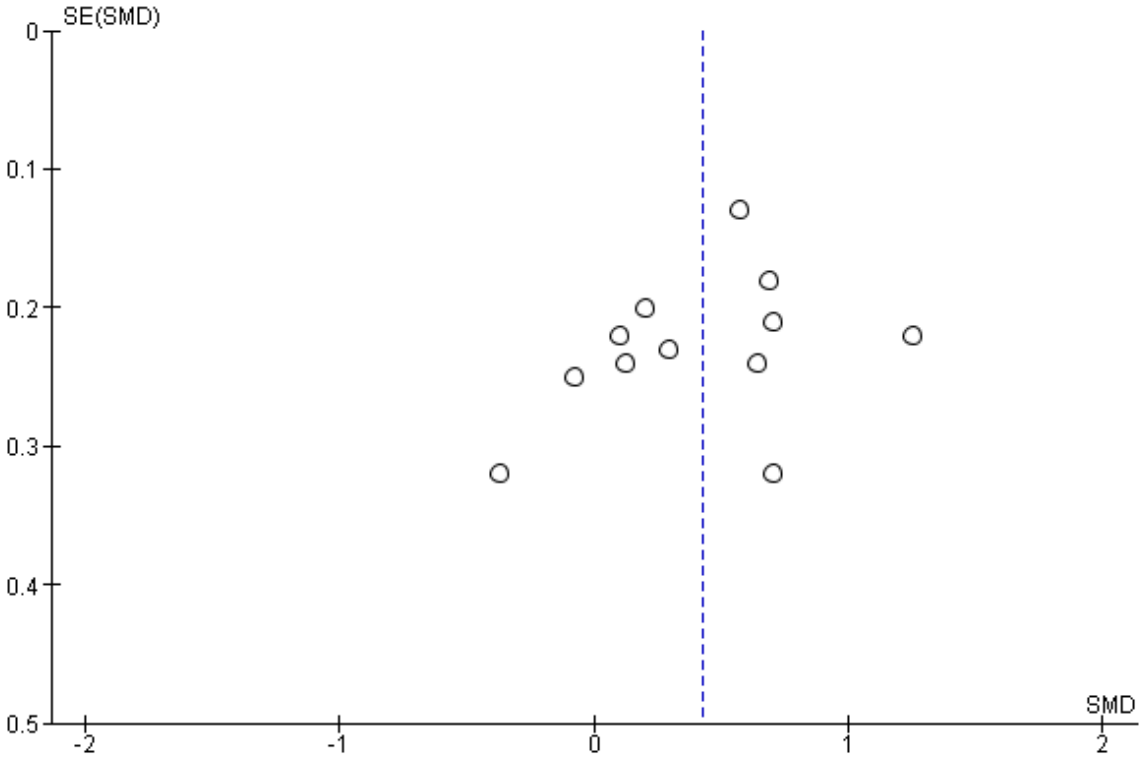
e-Figure 7 Sensitivity analysis of the association of the titre of anti-citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) focusing on the same summary statistics

A pooled analysis of seven studies where mean differences (MDs) were available without a conversion of summary statistics demonstrated that higher titres of anti-CCP antibody was significantly associated with RA-ILD with an MD of 52.5 (95% confidence interval: 5.76-99.2, p=0.03/95% prediction interval: -94.9-199.9). There remained substantial heterogeneity (chi^2=35.4, p<0.00001, I^2=83%).



e-Figure 8 Funnel plot of the effect of the positivity of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.



e-Figure 9 Funnel plot of the effect of the titre of anti-citrullinated peptide (CCP) antibody against its standard error

The graphical inspection demonstrated no apparent asymmetry.

e-Appendix

Search terms for each electronic database

Medline (Ovid) (1946 through 12 November 2019)

1 exp Arthritis, Rheumatoid/ (110375)

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).mp. (60240)

3 exp Lung Diseases, Interstitial/ (57554)

4 exp Pulmonary Fibrosis/ (21497)

5 (interstitial adj3 lung adj3 disease$).mp. (14632)

6 (interstitial adj3 pneumoni$).mp. (10671)

7 alveolitis.mp. (6068)

8 (pulmonary adj3 fibros$).mp. (29467)

9 exp Anti-Citrullinated Protein Antibodies/ (211)

10 cyclic citrullinated protein antibod$.mp. (28)

11 cyclic citrullinated peptide antibod$.mp. (664)

12 citrullinated protein antibod$.mp. (798)

13 citrullinated peptide antibod$.mp. (1001)

14 anti-CCP.mp. (1527)

15 ACPA.mp. (1369)

16 1 or 2 (157282)

17 3 or 4 or 5 or 6 or 7 or 8 (88395)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 (3452)

19 16 and 17 and 18 (64)

EMBASE (Ovid) (1947 through 12 November 2019)

1 exp rheumatoid arthritis/ (218675)

2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$or artrit$ or diseas$ or condition$ or nodule$)).mp. (106635)

3 exp interstitial lung disease/ (82134)

4 exp lung fibrosis/ (81580)

5 (interstitial adj3 lung adj3 disease$).mp. (25821)

6 (interstitial adj3 pneumoni$).mp. (22196)

7 alveolitis.mp. (29356)

8 (pulmonary adj3 fibros$).mp. (32054)

9 exp cyclic citrullinated peptide antibody/ (6135)

10 cyclic citrullinated protein antibod$.mp. (78)

11 cyclic citrullinated peptide antibod$.mp. (6299)

12 citrullinated protein antibod$.mp. (1603)

13 citrullinated peptide antibod$.mp. (6704)

14 anti-CCP.mp. (4537)

15 ACPA.mp. (4424)

16 1 or 2 (285679)

17 3 or 4 or 5 or 6 or 7 or 8 (139209)

18 9 or 10 or 11 or 12 or 13 or 14 or 15 (11794)

19 16 and 17 and 18 (452)

Science Citation Index Expanded (Clarivate Analytics) (1900 through 12 November 2019)

#1 TS=(rheumatoid NEAR/3 arthritis or rheumatoid NEAR/3 disease$ or rheumatoid NEAR/3 condition$) (165,017)

#2 TS=("interstitial NEAR/3 lung NEAR/3 disease$") OR TS=("interstitial NEAR/3 pneumoni*") OR TS=(alveolitis) OR TS=("pulmonary NEAR/3 fibros*") (4,751)

#3 TS=(anti cyclic citrullinated protein antibod* or anti cyclic citrullinated peptide antibod* or anti citrullinated protein antibod* or anti citrullinated peptide antibod* or anti CCP or ACPA) (4,483)

#3 #4 AND #5 AND #6 (2)

Cochrane Central Register of Controlled Trials (Cochrane Library) (accessed on the 12th of November 2019)

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees (5530)

#2 ((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3(arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab,kw (17434)

#3 MeSH descriptor: [Lung Diseases, Interstitial] explode all trees (738)

#4 MeSH descriptor: [Pulmonary Fibrosis] explode all trees (429)

#5 interstitial near/3 lung near/3 disease*:ti,ab,kw (1017)

#6 interstitial near/3 pneumoni*:ti,ab,kw (619)

#7 alveolitis:ti,ab,kw (732)

#8 pulmonary near/3 fibros*:ti,ab,kw (1440)

#9 MeSH descriptor: [Anti-Citrullinated Protein Antibodies] explode all trees (6)

#10 (cyclic citrullinated protein antibod*):ti,ab,kw (105)

#11 (cyclic citrullinated peptide antibod*):ti,ab,kw (178)

#12 (citrullinated protein antibod*):ti,ab,kw (199)

#13 (citrullinated peptide antibod*):ti,ab,kw (225)

#14 anti-CCP:ti,ab,kw (335)

#15 ACPA:ti,ab,kw (292)

#16 OR #2 (17673)

#17 #3 OR #4 OR #5 OR #6 OR #7 OR #8 (3148)

#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 (728)

#19 #16 AND #17 AND #18 (9)

Google Scholar (accessed on the 12th of November 2019)

("rheumatoid arthritis" OR "rheumatoid disease") ("interstitial lung disease" OR "interstitial pneumonia" OR "pulmonary fibrosis") ("anti cyclic citrullinated protein antibody" OR "anti cyclic citrullinated peptide antibody" OR "anti citrullinated protein antibody" OR "anti citrullinated peptide antibody")

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 7-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 9-10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 13-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 15-16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Checklist items for Meta-analyses of Observational Studies in Epidemiology (MOOSE)	Reported on Page
Reporting of background should include	
• Problem definition	Page 5-6
• Hypothesis statement	Not described
• Description of study outcome(s)	Page 7
• Type of exposure or intervention used	Page 7
• Type of study designs used	Page 7
• Study population	Page 6-7
Reporting of search strategy should include	
• Qualifications of searchers (eg, librarians and investigators)	Not described
• Search strategy, including time period included in the synthesis and keywords	Page 7-8
• Effort to include all available studies, including contact with authors	Page 8
• Databases and registries searched	Page 7
• Search software used, name and version, including special features used (eg, explosion)	Not described
• Use of hand searching (eg, reference lists of obtained articles)	Page 8
• List of citations located and those excluded, including justification	Figure 1
• Method of addressing articles published in languages other than English	Page 7
• Method of handling abstracts and unpublished studies	Page 7
• Description of any contact with authors	Not described
Reporting of methods should include	
• Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Not described
• Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Not described

• Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Not described
• Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Not described
• Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Page 8-9
• Assessment of heterogeneity	Page 10-11
• Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Page 9-10
• Provision of appropriate tables and graphics	Figure 1 (study flow diagram)
Reporting of results should include	
• Graphic summarizing individual study estimates and overall estimate	Figure 2-3
• Table giving descriptive information for each study included	Table 1, 2
• Results of sensitivity testing (eg, subgroup analysis)	Page 15-16
• Indication of statistical uncertainty of findings	Page 13-15
Reporting of discussion should include	
• Quantitative assessment of bias (eg, publication bias)	Page 21
• Justification of exclusion (eg, exclusion of non-English-language citations)	Not described
• Assessment of quality of included studies	Page 21
Reporting of conclusions should include	
• Consideration of alternative explanations for observed results	Page 22
• Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Page 22
• Guidelines for future research	Page 21
• Disclosure of funding source	Page 22

From Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.