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

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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 to 2.78). Similarly, the titre of anti-CCP antibody was significantly higher for RA-ILD with a standardised mean difference of 0.42 (95% CI: 0.20 to 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.

Strengths and limitations of this study

- ► This systematic review and meta-analysis addressed the risk of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) related to both the presence and titres of anti-cyclic citrullinated peptide (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 generalisability 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.

BACKGROUND

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that is characterised 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%–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 (HR) of mortality about 3.0 in comparison to RA without ILD.[8] Moreover, the most common type of ILDs among RA-ILDs, that is, 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] Anticitrullinated 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[21] and the Meta-analysis of Observational Studies in Epidemiology 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, that is, 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 characterised 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.[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 12 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 (HK and OMP) 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 were 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 the six domains that constitute the tool, that is, '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 utilised 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 summarised using ORs if anti-CCP antibody was reported as binary (positive/negative). If the titre of anti-CCP antibody was reported, a standardised MD (SMD) (calculated as Hedge's g) was utilised to combine the results.[31] If the median, range or interquartile range (IQR) was described to report the autoantibody titres, they were converted to the mean and standard deviation (SD), using a formula reported by a previous study, to be summarised 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) V.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 were 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, that is, 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, 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 V.14 (STATA Corp LLC., College Station, TX, USA) if 10 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]

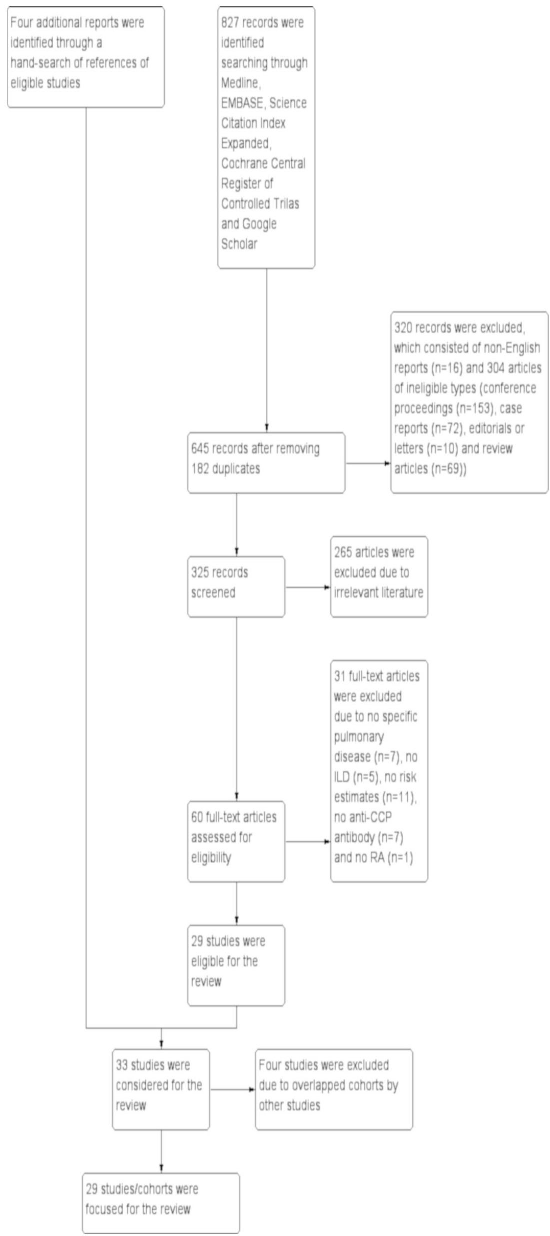

Figure 1 Study flow diagram. Out of a total of 827 records identified searching through five electronic databases, that is, Medline, EMBASE, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials and Google Scholar, 645 records were screened by titles and abstracts after removing 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. CCP, cyclic citrullinated peptide; ILD, interstitial lung disease.

Characteristics of included studies

Study location of a total of 29 studies was 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). Twenty-two 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 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 (online supplemental 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 2 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 to 2.78) with moderate heterogeneity (χ^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 to 149.3)[46] and a median value of 220 for RA-ILD versus 120 for RA without ILD,[48] respectively. Other two studies examined the titre of

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Table 1 Baseline characteristics of included studies*

Study	Location	Design	Number (n)	Age at inclusion (years)	Gender (male) (n (%))	Smoking (n (%))	Proportion of ILD (n (%))†	Disease duration (RA) (years)	Disease activity‡	Other CTDs (n)	ILD patterns (on HRCT) (n)
Alunno *et al* 2018[38]	Italy	Cross-sectional	252	61.7±0.8	56 (22.2)	–	37 (20.2) (n=183)	12.6±0.6	–	–	–
England *et al* 2019[39]	USA	Cross-sectional§	1823	63.5±11.0	(90.1)	(89.5)	90 (4.9)	11.1±11.5	4.0±1.6	–	–
Giles *et al* 2014[40]	USA	Cross-sectional§	177	59±8¶	71 (40.1)	105 (59.3)	120 (67.8)	9 (5–19) vs 8 (4–16)¶	3.7 (2.9–4.4)¶ (CRP)	–	–
Chen *et al* 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 *et al* 2015[42]	China	Cross-sectional	71	60.7±12.1**	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 *et al* 2015[43]	USA	Cross-sectional§	75	61.5±12.7**	11 (14.7)	41 (54.7)	–	–	–	–	–
Abdel-Hamid *et al* 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 *et al* 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 *et al* 2008[46]	Greece	Case–control	136	–	–	–	N/A (ILD 11/ no ILD 125)	–	–	–	–
Correia *et al* 2019[47]	USA	Cross-sectional	453	59.6±15.7	(19.4)	–	(6.0)	–	–	0	–
Fadda *et al* 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 *et al* 2012[49]	Japan	Case–control	450	63.9±10.9**	89 (19.8)	130 (28.9)	N/A (ILD 129/no ILD 321)	14.5±10.9**	–	–	–
Kakutani *et al* 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 *et al* 2014[51]	UK	Case–control	460	–	220 (47.8)	–	N/A (ILD 230/no ILD 230)	–	–	–	–
Liu *et al* 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 *et al* 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 *et al* 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 *et al* 2011[55]	Turkey	Cross-sectional	67	57.4±13.5	14 (20.9)	–	12 (17.9)	10.2±11.7**	–	–	–
Park *et al* 2016[56]	Korea	Cross-sectional	83	53.7±10.1**	10 (12.0)	–	7 (8.4)	–	–	–	UIP 6, indeterminate 1
Paulin *et al* 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 *et al* 2015[58]	USA	Cross-sectional	779	53.7±13.3 (n=632)**	161 (25.5) (n=632)	357 (56.5) (n=632)	69 (8.9)	10.5±10.3¶	5.4±1.4**	–	–

Continued

Table 1 Continued

Study	Location	Design	Number (n)	Age at inclusion (years)	Gender (male) (n (%))	Smoking (n (%))	Proportion of ILD (n (%))†	Disease duration (RA) (years)	Disease activity‡	Other CTDs (n)	ILD patterns (on HRCT) (n)
Rocha-Munoz *et al* 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 *et al* 2018[60]	Turkey	Cross-sectional	83	59.3±12.1	20 (24.1)	9 (10.8)	43 (51.8)	–	–	0	–
Sulaiman *et al* 2019[61]	Malaysia	Cross-sectional	159	48.3±14.1	25 (15.7)	–	21 (13.2)	–	4.7±0.9 (ESR)	0	–
Tian *et al* 2016[62]	China	Cross-sectional	75	–	29 (38.7)	–	37 (49.3)	–	–	–	–
Wang *et al* 2015[63]	China	Cross-sectional	41	60.7±12.4**	20 (48.8)	–	25 (61.0)	108 (5–360) vs 72 (2–552) (months) (median (range))	–	–	–
Yang *et al* 2019[64]	Korea	Case–control	308	57.0±12.0**	76 (24.7)	39 (17.7) (n=220)	N/A (ILD 77/ no ILD 231)	11.0±7.3**	–	–	–
Yin *et al* 2014[65]	China	Cross-sectional	285	51.7±13.4**	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 (SS 41, SSc 7, PM/DM 4, SLE 16)††	–
Zhang *et al* 2018[66]	China	Case–control	75	41–69 vs 40–70 (range)	30 (40.0)	–	N/A (ILD 28/ no ILD 47)	–	–	0	–

*Comparisons correspond to RA-ILD vs RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified.
†N/A indicates not applicable due to case–control studies.
‡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.
§A prospective study while all of the other studies were retrospectively designed.
¶Unknown statistics.
**Calculated combining the figure in both comparative groups.
††Some patients had multiple CTDs.
CDAI, clinical disease activity index; CRP, C-reactive protein; CTD, connective tissue disease; ESR, erythrocyte sedimentation rate; HRCT, high-resolution CT; ILD, interstitial lung disease; 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*

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 *et al* 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 *et al* 2019[39]	Second generation	(86.7) vs (76.7)	–	**OR 1.98, p=0.03**	–	–	–	–
Giles *et al* 2014[40]	Second generation	51/57 (89.5) vs 82/120 (68.3)	152 (99–194) (n=32) vs 89 (11–152) (n=120)†	**OR 3.94 (1.57–9.90)**	**p=0.0005‡**	–	–	–
Chen *et al* 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 *et al* 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 *et al* 2015[43]	Not specified	–	188±133 vs 83±113	–	–	–	–	–
Abdel-Hamid *et al* 2019[44]	Third generation	30/50 (60.0)	100 (390) (n=19) vs 20 (298) (n=31) (median (IQR))	–	**p=0.04‡**	–	–	–
Akiyama *et al* 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 *et al* 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 *et al* 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‡**	–	**OR 1.41 (1.01–1.97)/1 group of titre**	Age, smoking
Fadda *et al* 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 *et al* 2012[49]	Not specified (Medical and Biological Laboratories)	116/129 (89.9) vs 278/321 (86.6)	–	OR 1.38 (0.71–2.69)	–	–	–	–
Kakutani *et al* 2019[50]	Not specified	(93.2) vs (82.9)	–	**OR 2.83, p=0.002**	–	–	–	–
Kelly *et al* 2014[51]	Not specified	–	180 (8–340) vs 78 (8–340) (median (range))	**OR 4.00 (2.00–7.80)**	**p=0.02‡**	**OR 0.33, p=0.003**	–	Age, sex, smoking, RF

Continued

Table 2 Continued

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
Liu *et al* 2019[52]	Second generation (Euro- Diagnostica) (≥25 U/mL)	77/101 (76.2)	–	OR 0.64 (0.23–1.80)	–	–	–	–
Matsuo *et al* 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) (10 U/mL)**	–	**OR 1.08 (1.03–1.12) (10 U/mL)**	Age, smoking, RF, LDH, CRP, ESR, KL-6, MMP-3, IL18, dose of MTX, dose of PSL
Mori *et al* 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)**§	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 *et al* 2011[55]	Second generation (Euroimmun)	7/12 (58.3) vs 27/55 (49.1)	–	OR 1.45 (0.41–5.08)	–	–	–	–
Park *et al* 2016[56]	Not specified (Roche Diagnostics) (≥17.0 U/mL)	69/83 (83.1)	–	–	0.22¶	–	–	–
Paulin *et al* 2019[57]	Second generation	45/47 (95.7) vs 46/48 (95.8)	–	OR 0.98 (0.13–7.24)	–	–	–	–
Restrepo *et al* 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 *et al* 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**‡	–	**OR 1.06 (1.02–1.10)**	Age, smoking, disease duration, DAS28, HAQ-Di, RF, ESR, duration of MTX treatment
Sargin *et al* 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)§	–	–	–
Sulaiman *et al* 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 *et al* 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 *et al* 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)§	–	–	–

Continued

Table 2 Continued

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
Yang *et al* 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 *et al* 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 *et al* 2018[66]	Not specified	–	3.09±0.34 (n=28) vs 3.05±0.32 (n=47)	–	MD 0.04 (−0.12–0.20)	–	–	–

Text in bold indicates statistical significance.
*Comparisons correspond to RA-ILD vs RA without ILD and the values are expressed as mean±SD or number (proportion) unless otherwise specified.
†Unknown statistics.
‡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.
§MDs (95% CI) were calculated converting the median, range or IQR to the mean and standard deviation, using a formula reported by a previous study.[32]
¶Correlation coefficient between anti-CCP antibody and a total ILD score.
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 leucocyte antigen; IL-18, interleukin-18; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; MD, mean difference; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, risk ratio; SE, shared epitope.;

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 versus 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 to 364.5).[62] All of the other studies utilised 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 to 0.65) with considerable heterogeneity (χ^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 to 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 to 1.97), 1.08 (95% CI: 1.03 to 1.12) and 1.06 (95% CI: 1.02 to 1.10).[47 53 59]

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 to 2.99) by Asian reports and 2.22 (95% CI: 1.45 to 3.39) by non-Asian reports (p=0.75) (online supplemental 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 to 0.71) by Asian reports and 0.49 (95% CI: 0.24 to 0.74) by non-Asian reports (p=0.58) (online supplemental 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 to 2.71) by cross-sectional studies and 2.53 (95% CI: 1.26 to 5.08) by case–control studies (p=0.55) (online supplemental 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 to 0.67) by cross-sectional studies and 0.50 (95% CI: 0.12 to 0.89) by case–control studies (p=0.65) (online supplemental 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 to 3.45) (online supplemental e-Figure 5). A pooled analysis of three studies that examined the second

Table 3 Risk of bias in individual studies

Study	Study participation	Anti-CCP antibody measurement	ILD confirmation	Study confounding	Statistical analysis and reporting
Alunno *et al* 2018[38]	Moderate risk	Low risk	**High risk**	**High risk**	**High risk**
England *et al* 2019[39]	Moderate risk	**High risk**	**High risk**	Low risk	**High risk**
Giles *et al* 2014[40]	Moderate risk	Low risk	**High risk**	Moderate risk	**High risk**
Chen *et al* 2013[41]	Low risk	**High risk**	Low risk	Moderate risk	**High risk**
Chen *et al* 2015[42]	Moderate risk	Low risk	Low risk	Moderate risk	**High risk**
Doyle *et al* 2015[43]	Moderate risk	Moderate risk	Low risk	Moderate risk	**High risk**
Abdel-Hamid *et al* 2019[44]	Moderate risk	Moderate risk	**High risk**	Moderate risk	**High risk**
Akiyama *et al* 2016[45]	Low risk	Moderate risk	**High risk**	Moderate risk	Moderate risk
Alexiou *et al* 2008[46]	Moderate risk	Low risk	**High risk**	**High risk**	**High risk**
Correia *et al* 2019[47]	Moderate risk	Low risk	Low risk	Moderate risk	**High risk**
Fadda *et al* 2018[48]	Moderate risk	Low risk	Low risk	Moderate risk	**High risk**
Furukawa *et al* 2012[49]	Moderate risk	Low risk	**High risk**	Moderate risk	**High risk**
Kakutani *et al* 2019[50]	Low risk	**High risk**	**High risk**	Moderate risk	**High risk**
Kelly *et al* 2014[51]	Moderate risk	**High risk**	Low risk	Moderate risk	**High risk**
Liu *et al* 2019[52]	Moderate risk	Low risk	**High risk**	Moderate risk	**High risk**
Matsuo *et al* 2018[53]	Low risk	Moderate risk	**High risk**	Moderate risk	Moderate risk
Mori *et al* 2012[54]	Low risk	Low risk	Low risk	Moderate risk	Moderate risk
Ortancil *et al* 2011[55]	Moderate risk	Low risk	**High risk**	Moderate risk	**High risk**
Park *et al* 2016[56]	Low risk	Low risk	Low risk	**High risk**	**High risk**
Paulin *et al* 2019[57]	Moderate risk	**High risk**	**High risk**	Moderate risk	**High risk**
Restrepo *et al* 2015[58]	Moderate risk	Low risk	**High risk**	Moderate risk	Moderate risk
Rocha-Munoz *et al* 2015[59]	Moderate risk	Low risk	**High risk**	Moderate risk	Low risk
Sargin *et al* 2018[60]	Moderate risk	**High risk**	**High risk**	Moderate risk	**High risk**
Sulaiman *et al* 2019[61]	Moderate risk	Low risk	**High risk**	**High risk**	**High risk**
Tian *et al* 2016[62]	**High risk**	Low risk	**High risk**	Moderate risk	**High risk**
Wang *et al* 2015[63]	Moderate risk	**High risk**	Low risk	**High risk**	**High risk**
Yang *et al* 2019[64]	Moderate risk	**High risk**	Moderate risk	Moderate risk	Moderate risk
Yin *et al* 2014[65]	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk
Zhang *et al* 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.;

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 to 13.5) (online supplemental 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 to 99.2) (online supplemental 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 (online supplemental 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 (online supplemental e-Figure 8 and 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

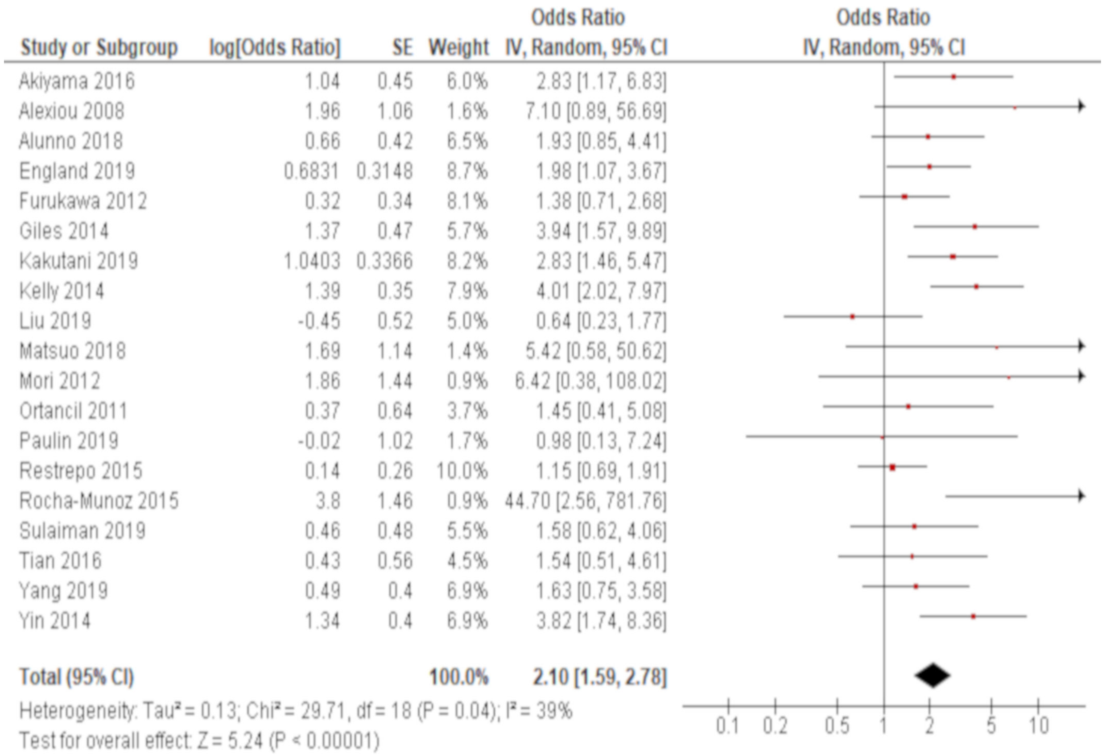

Figure 2 Forrest plot of the result of univariate analysis regarding the association of positivity of anti-cyclic citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) The results of univariate analyses in 19 studies were pooled for meta-analysis. The positivity of anti-CCP antibody was significantly associated with RA-ILD with an OR of 2.10 (95% CI: 1.59 to 2.78, p<0.00001/95% prediction interval: 0.93 to 4.76). There was moderate heterogeneity (χ^2=29.7, p=0.04, I^2=39%).

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 generalisable to a broader population.

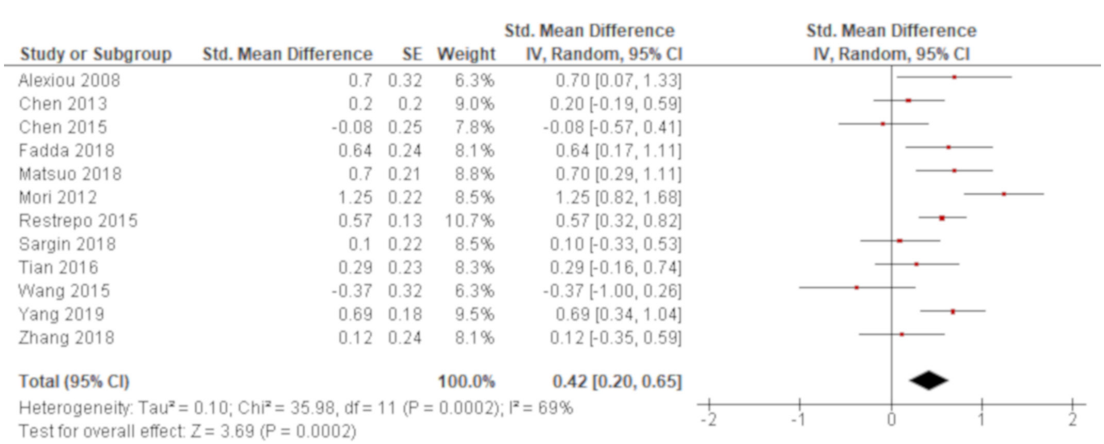

Figure 3 Forrest plot of the result of univariate analysis regarding the association of the tire of anti-cyclic citrullinated peptide (CCP) antibody with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). The results of univariate analyses in 12 studies were pooled for meta-analysis. The titre of anti-CCP antibody was significantly higher for RA-ILD than RA without ILD with a standardised mean difference (SMD) of 0.42 (95% CI: 0.20 to 0.65, p=0.0002/95% prediction interval: −0.33 to 1.17). There was considerable heterogeneity (χ^2=36.0, p=0.0002, I^2=69%).

Table 4 Assessment of quality of evidence by the Grades of Recommendation, Assessment, Development and Evaluation 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; ;GRADE, Grades of Recommendation, Assessment, Development and Evaluation.

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 recognised the citrullinated protein filaggrin.[70] Subsequently, CCP were synthesised 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 both helpful to diagnose RA and 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 post-translational 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 vary 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 would 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 that 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 large 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.

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Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those

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