ACPA and Future Onset of Rheumatoid Arthritis Among Individuals With Undifferentiated Arthritis and Arthritis Free Individuals: A Systematic Review of Cohort Studies

Zeinab F.N. Slim[1,2], Mengru Yuwan[1] and Sasha Bernatsky[2,3,*]

[1]*Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada*

[2]*Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, 687 Pine Avenue, V Building, Montreal, Quebec, H3A 1A1, Canada*

[3]*Division of Rheumatology, McGill University Health Centre, 1650 Cedar Ave, Montreal, QC, H3A 1A4, Canada*

Abstract: *Objective*: Antibodies against anti-cyclic citrullinated proteins (ACPA) have been suggested as a risk factor for rheumatoid arthritis (RA). A systematic review of the literature was conducted to determine the relationship between ACPA antibodies and future RA development and to identify the methodological limitations in order to guide the design of any future cohort study in this field.

Materials and Methods: Web of Science, Pub Med, and EMBASE databases were searched. A data extraction and quality assessment form was developed based on the ACROBAT-NRSI ("A Cochrane Risk of Bias Assessment Tool - for Non-Randomized Studies of Interventions) and STROBE statement. Our initial searches produced 1,396 titles, which were reviewed by title and abstract. Thirty seven studies were selected for full text review and eleven studies fulfilled our inclusion criteria.

Results: Qualitative synthesis of the included studies revealed a consistent positive association between ACPA and future RA development. The unadjusted HR comparing ACPA positive and negative groups ranged from 2.46 to 223.1, while the unadjusted OR ranged 1.09 to 46.7. Only one study reported an unadjusted RR of 2.75.

Conclusion: The review indicated that the presence of ACPA in patients with undifferentiated arthritis and healthy subjects predicts future onset of RA.

Keywords: ACPA, Rheumatoid Arthritis onset, Systematic Review, Cohort Studies, Healthy Subjects.

INTRODUCTION

The etiology of RA is still unclear. However, auto-antibodies particularly anti-cyclic citrullinated proteins (ACPA) can be detected in the serum well before disease onset and appears to indicate a higher risk of developing RA. Remarkably, the existence of a long preclinical period provides promise to control the disease before it passes into its clinical stage. This preclinical stage has been the focus of recent research on RA and some studies investigated stored blood samples of RA patients who donated blood prior to development of the disease [1]. One Dutch study followed individuals for several years and showed that the risk of developing RA was associated with positive ACPA at the onset of the study [2]. Another study demonstrated that a positive ACPA is associated with a very high predictive value (100% PPV) for future RA development [3]. On the other hand, one study did not show a conclusive and significant association [4]. Since irreversible damage occurs within the first two years of arthritis onset, biomarkers like ACPA may be very helpful when intervening during a patient's window of opportunity before permanent damage occurs. Additionally, ACPA has been correlated with the most severe forms of RA. In fact, there is a strong correlation between high disease activity and ACPA positivity [5]. In view of the role that this autoantibody plays in either the initiation of RA or its propagation from the autoimmunity state without disease into the chronic inflammatory state, it can be used as a tool to screen for individuals at risk of developing this autoimmune disease. The principle of screening for disease is that for many diseases early detection improves prognosis. This is true for RA whereby early detection and eventually early treatment allows a benefit over later treatment as measured by disability and radiographic progression [6].

The objectives of this paper were to systematically review the literature on the recent evidence of the association between ACPA antibodies and Rheumatoid Arthritis development from cohort studies and to identify the methodological limitations in order to guide the design of any future cohort study in this field.

*Address correspondence to this author at the McGill University Health Centre (MUHC), Division of Clinical Epidemiology, 687 Pine Avenue West, V-Building, Room V2.09, Montreal, Quebec H3A 1A1, Canada; Tel: (514)934-1934 x 44710; Fax: (514)934-8293; E-mail: sasha.bernatsky@mail.mcgill.ca

E-ISSN: 2310-9874/15

Table 1: Search Strategies

Database	Search Strategy
Web of Science	TS=("rheumatoid arthritis" OR RA) AND TS=("anti cyclic citrullinated peptide*" OR "cyclic citrullinated peptide antibod*" OR "anti ccp*") AND TS=(predict*)
PubMed	(((((("Arthritis, Rheumatoid"[Mesh:noexp] OR "rheumatoid arthritis"[tw] OR RA[tw])))) AND ((((cyclic citrullinated peptide*[tw] OR CCP[tw]) AND (antibod*[tw] OR autoantibod*[tw])) OR anticyclic citrullinated peptide*[tw] OR anti cyclic citrullinated peptide*[tw] OR anti CCP*[tw]))))) AND (("predictive value of tests"[MeSH Terms]) OR predict*[Text Word])
EMBASE	-Rheumatoid arthritis as subject search and keyword search; and combining the two by the Boolean operator "OR". -Predictive value as subject search and keyword search; and combining the two by the Boolean operator "OR". -Anticyclic citrullinated peptide antibody as subject search and keyword search; and combining the two by the Boolean operator "OR". -Keyword search for the following: cyclic citrullinated peptide antibod*, anticyclic citrullinated peptide, anti CCP*, anti citrullinated protein antibod*, ACPA, and CCP* antibod*. All the above four searches were combined using "AND".

METHODS

Search Strategy

We searched Web of Science, Pub Med, and EMBASE databases for articles published between January 2006 and March 2015. For PubMed searches, we used the MESH headings: "Arthritis, Rheumatoid" and "predictive value of tests". Several terms were searched for ACPA because of the heterogeneity in reporting this auto-antibody. The terms searched for ACPA included: anti cyclic citrullinated peptide, cyclic citrullinated peptide antibody, anti CCP, anti citrullinated protein antibody, CCP, antibody. Boolean operators "AND" and "OR" were used to combine the different concepts of the research question. The searches were limited to English language studies. Table **1** details the full search strategy for every database.

Study Selection

Our initial searches produced 1,396 titles, which were reviewed by title and abstract. Thirty seven studies were selected for full text review and eleven studies fulfilled our inclusion criteria. Figure **1** shows a flow diagram for our search strategy.

The titles and abstracts of identified publications were screened by one reviewer. All publications identified as potentially relevant were selected for full-text evaluation. If a full text was not found, efforts were done to locate the article online or by contacting the authors. Five articles were conference abstracts and their full article could not be retrieved even after contacting the author. We excluded editorials, letters to the editor, review articles, and meta-analyses. For inclusion in the final analysis, studies had to have a cohort design and be conducted among subjects without an RA diagnosis. The follow-up duration had to be at least one year and the primary outcome had to be RA, with diagnosis based on the 1987 [7] or 2010 [8] American College of Rheumatology (ACR) criteria. All full texts were evaluated by two reviewers, and reasons for exclusion were recorded.

Data Extraction and Quality Assessment

A data extraction and quality assessment form was developed based on the ACROBAT-NRSI ("A Cochrane Risk of Bias Assessment Tool - for Non-Randomized Studies of Interventions)[9] and STROBE statement [10]. The data extraction and quality assessment form was pilot tested on four studies for clarity, efficacy and flow of the questions. Modifications of the form were done accordingly. The full data extraction quality assessment form can be found in appendix A.

Data were extracted independently by two reviewers (ZS and MY). The extracted data included: sex distribution of study participants, mean age and/or range, follow up duration, the nature of the test used for ACPA assessment and its cut off value, total sample size as well as the sample size of each group of ACPA status, the crude effect measure, adjusted effect measure along with their 95% CI, type of regression model that was used to adjust for potential confounders, and the confounders that were adjusted for in the analysis.

RESULTS

A summary of each study included is provided in Table **2**. The study by Castillo-Ortiz *et al*. [11] was

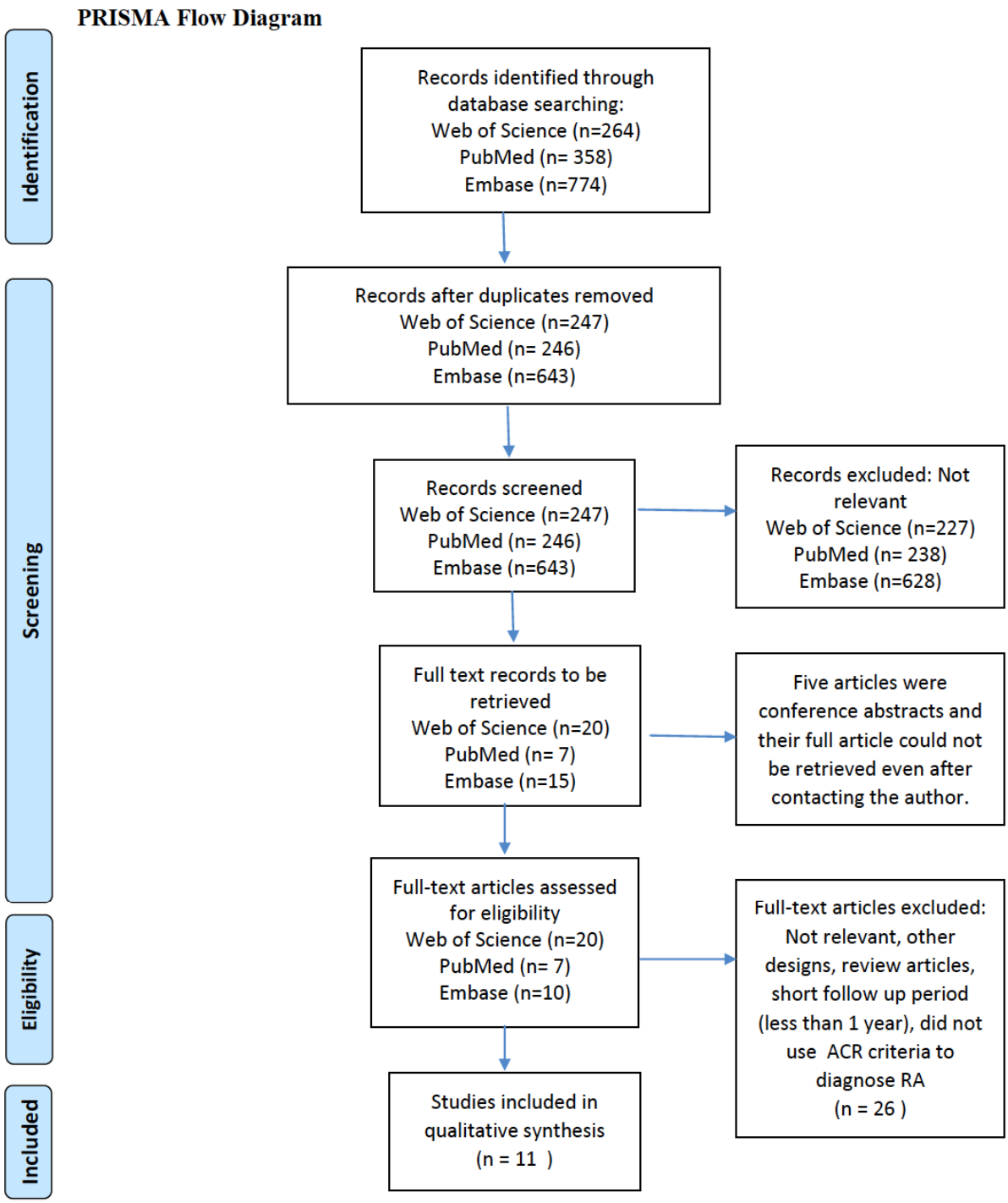

Figure 1: A flow diagram for our search strategy.

conducted on 819 healthy individuals older than 15 years to assess the association of serum IgM-RF and ACPA in the development of RA. The studied cohort were relatives of RA patients. Blood tests were performed and ELISA was used to determine the second-generation anti-cyclic citrullinated peptide IgG (ACPA2) levels. The cut-off for a positive ACPA was >7 IU/mL as per vendor definition. Table **3** summarises the effect measures of every study.

Chen *et al*. [12] conducted a retrospective cohort study to explore predictors contributing to the development of RA from Undifferentiated Arthritis (UA). At baseline, ACPA was assessed by chemiluminescence microparticle immunoassay and the cut-off level was set at 5 RU/ml.

Emad *et al*. [13] intended to find determinants for progression to rheumatoid arthritis (RA) in a group of

Table 2: Characteristics of Studies Investigating the Long Term Predictive Ability of Anticyclic Citrullinated Peptide (Anti-CCP) for the Development of Rheumatoid Arthritis (RA), 2006-2015

Author	Year	Journal	Country	Population	Sample Characteristics
Castillo-Ortiz *et al*.	Unpublished paper	-	Mexico	Healthy relatives of RA patients	Mean age: 36 ± 12 years Male: 31% Female: 69% Other: 41% offspring
Chen *et al*.	2013	Rheumatology International	China	Patients of undifferentiated arthritis attending Rheumatoid Immunology Department of the First Affiliated Hospital of Sun Yatsen University	Mean age of those who developed RA at the end of the follow up period: 44.73 ± 15.81 years Mean age of those who did not develop RA at the end of the follow up period: 39.07 ± 12.58 years Male: 28% Female: 72%
Emad *et al*.	2014	Clinical Rheumatology	Egypt	Patients attending physician's clinic	Mean age: 39.14 ± 9.004 years Male: 44% Female: 56%
Feitsma *et al*.	2007	Rheumatology	Denmark	Patients attending physician's clinic	Mean age and sex distribution were not reported in this study.
Goeb *et al*.	2008	Rheumatology	France	Patients studied are those of the VERA cohort that comprises patients with very early arthritis.	Mean age: 52.0 years (range 19–84 years) Female/Male ratio was 2.17.
Rojas-Serrano *et al*.	2009	Clinical Rheumatology	Mexico	Patients attending physician's clinic	Mean age: 35.5 years (range 16-76 years) Male: 12% Female: 88%
Chen *et al*.	2010	Journal of Medical Ultrasound	China	Patients attending rheumatology outpatient clinic	Mean age was not reported in this study. Male: 33.3% Female: 66.7%
Sanmartí *et al*.	2012	The Journal of Rheumatology	Spain	Patients attending physician's clinic	Mean age: 52.4 + 12.5 years Male: 23.9% Female: 76.1%
Tamai *et al*.	2010	Scandinavian Journal of Rheum-atology	Japan	Patients attending physician's clinic	Median age: 47 years (range 22-71 years) Male: 28.6% Female: 71.4%)
Bizzaro *et al*.	2013	Arthritis Research & Therapy	Italy	Patients attending physician's clinic	Mean age: 52±16 years Male: 23.4% Female:76.6%
Van der Helm-van Mil *et al*.	2007	Arthritis & Rheumatology	Netherlands	Patients attending physician's clinic	Mean age was not reported for the total sample, but for those who progressed to RA (56.3±15.3 years) as well as those who did not progress to RA (48.6±17.0 years). Male: 42.3% Female: 57.7%

Egyptian patients with palindromic rheumatism (PR). Baseline ACPA was assessed using commercially available second-generation ELISA kits with values more than 5 U/ml considered as positive.

Feitsma *et al*. [14] conducted a study on a subset (n=394) of a large cohort (N= 1944) of white Dutch patients with recent-onset arthritis to investigate whether the combination of Anti-citrullinated peptide

Table 3: Results of Studies Assessing the Long Term Predictive Ability of Anticyclic Citrullinated Peptide (Anti-CCP) for the Development of Rheumatoid Arthritis (RA), 2006-2015

Author	Total sample size, anti-CCP positive sample size, anti-CCP negative sample size	Crude measure of association (95% CI)	Adjusted measure of association (95% CI)
Castillo-Ortiz *et al*.	819, 23, 796	Hazard Ratio (HR): 223.1 (63.8 – 779.9)	HR: 207.3 (54.8-784.8)
Chen *et al*.	218, 26, 192	Odds Ratio (OR): 1.09 (1.03–1.17)	OR: 1.07 (1.00–1.15)
Emad *et al*.	90, 34, 56	Reported as B coefficient B= -0.253	Reported as B coefficient B= -0.262
Feitsma *et al*.	394, 105, 289	Relative Risk (RR): 2.75 (95% CI 2.15–3.53)	OR: 6.3, 95% CI 3.9–10.3
Goeb *et al*.	284, 110, 174	For ≥10 AU Anti-CCP titer compared to ≤ 10 AU: OR= 16.7 (5.9, 65.8) For ≥50 AU Anti-CCP titer compared to ≤ 10 AU: OR=24.2 (6.0, 209.9)	For a positive anti-CCP titer i.e. ≥10 AU compared to ≤ 10 AU: OR= 3.58 (1.16, 13.43)
Rojas-Serrano *et al*.	78, 29, 47	Not reported but was calculated from the numbers provided in table 3, OR= 32.95	OR: 52.6 (3.27-843)
Chen *et al*.	84, 11, 73	OR: 36.27 (7.26–181.06)	OR: 28.99 (4.52–185.91)
Sanmartí *et al*.	71, 37, 34	HR: 2.46 (0.77 – 7.86)	Not reported
Tamai *et al*.	28, 13, 15	OR: 46.7 (95 % CI was not reported)	HR: 27.26 (1.85 – 401.23)
Bizzaro *et al*.	192, 80, 112	HR for low level positive group: 3.36 (1.412 – 7.998) HR for high positive level group: 4.613 (2.698, 7.887)	HR for low level positive group: 3.187 (1.257 – 8.077) HR for high positive level group: 4.324 (2.023, 9.245)
Van der Helm-van Mil *et al*.	570, 121, 449	Not reported but was calculated from the numbers provided in table 1, OR= 8.25	OR: 8.1 (4.2–15.8)

antibodies (ACPA) and the C1858T missense single-nucleotide polymorphism (SNP) in the PTPN22 gene yielded better prediction for progression from undifferentiated arthritis (UA) to RA compared with ACPA alone. ELISA was used to assess ACPA levels and the cut-off level for ACPA positivity was set at 25 arbitrary units.

The study by Goeb *et al*. [15] evaluated the association between several genetic markers one of them was ACPA and development of RA in a sample of 284 French Caucasians with very early arthritis. The presence of ACPA was detected using second generation commercially available kits with ACPA levels ≥10 arbitrary units considered as positive.

Rojas-Serrano *et al*. [16] conducted a prospective cohort study on incident cases of self-reported arthritis to assess the association between RA development and baseline ACPA as well as rheumatologist's predictive ability. Baseline serum samples were collected from all patients and the samples were frozen until the end of the follow up. ELISA was used to assess ACPA levels and cut-off was set at 25 IU/ml.

Chen *et al*. [17] aimed at investigating the predictive value of sonography and ACPA antibodies for development of RA among Chinese patients with PR. Not all patients with PR were included. Only patients with active episodes were selected, thus rendering the study sample a highly selective one. Baseline ACPA was assessed using enzyme-linked immunosorbent assay with 20 IU/mL as the cut-off value.

Sanmartí *et al*. [4] intended to analyze long term progression to rheumatoid arthritis (RA) and the predictive value of anti-citrullinated peptide/protein antibodies (ACPA) in PR patients. Serum ACPA was measured by ELISA using the citrullinated filaggrin-based cyclic citrullinated peptide (CCP1) test up to 2002 and the CCP2 test afterwards, with 50 IU/mL as the cut-off value for both tests.

Tamai *et al*. [18] conducted a cohort study on twenty eight Japanese patients with palindromic

Rheumatism (PR) to investigate several variables, among which is ACPA, that are predictive for the development of rheumatoid arthritis (RA). Serological tests were done to assess for ACPA antibodies and the cut-off value was 4.5 IU/mL.

Bizzaro *et al*. [19] conducted a two-year prospective study to analyze the prognostic significance of ACPA titer on RA onset in patients with recent onset UA in Italy. Patients (n=192) with UA were recruited in the study from nine different rheumatology units belonging to an association of hospital and university professionals in the field of autoimmune diseases. ACPA assessments were determined by CCP2-based assays which were different among the nine centers. As such, ACPA2 levels were expressed as a ratio to facilitate comparison between the centers. Low and high titer categorized based on levels less than, or more than three times the cut-off, respectively.

The study by Van der Helm-van Mil *et al*. [20] aimed at developing a model that predicts progression from UA to RA. The authors investigated the predictive value of nine clinical variables for RA development. Among the nine variables, ACPA was obtained at baseline and was assessed by ELISA with the cut-off value of 25 arbitrary units.

DISCUSSION

Main Findings

This systematic review assessed the literature on the association between ACPA and RA development from cohort study designs. The review showed that there has been interest in this auto-antibody as a marker for future development of RA. Overall, it revealed a consistent positive association between ACPA and future RA development albeit there was a non-significant positive result in one of the studies [4]. There was heterogeneity in the reported results as some studies used hazard ratios (HR), while the majority reported odds ratio (OR). One study reported unadjusted risk ratio (RR) and adjusted OR. The unadjusted HR comparing ACPA positive and negative groups ranged from 2.46 to 223.1, while the unadjusted OR ranged 1.09 to 46.7. Only one study reported an unadjusted RR of 2.75 [14]. Furthermore, important differences were seen in the characteristics of patients of the included studies such as age, symptom duration and genetic predisposition. There was also heterogeneity in the type of ACPA tests as well as cut off value used to define a positive ACPA test. These differences may explain the wide range of effect measures.

Critical appraisal of the included cohort studies demonstrated potential methodological issues which require attention. Most studies lacked information on the proportion of eligible subjects that was actually included into the study and not all studies thoroughly explained their exclusion and inclusion criteria. Further, selection bias was hard to assess in many studies because of the absence of comparison between the ACPA positive and ACPA negative groups at study onset as well as during study follow up period after loss to follow up occurred. In the studies that compared the two ACPA groups, the ACPA positive group was different from ACPA negative groups in some aspects such as age. For example, in the study conducted by Castillo-Ortiz *et al*. [11], the ACPA2 positive groups were on average 8 years older compared with the seronegative and RF-positive/ACPA2-negative groups. This difference may overestimate the risk among ACPA positive group since older age is associated with both ACPA positivity and RA development.

Most did not consistently identify all potentially important confounders such as smoking, age, sex, family history of RA, rheumatoid factor (RF) and shared HLA epitope alleles. Some studies did consider clinical factors [12,13, 20,17], positive RF-IgM [12, 13, 15, 17, 19] and/or IgA RF, IgG RF [15,16], HLA-DRB1*SE, HLA-DRB1*0405 allele, RA-susceptible PADI4 haplotype homozygote, PIP [18], CRP level [13, 19, 20], age [11-13, 20], family history [11], sex [12, 13, 20], PTPN22 1858T allele [14]. However, some studies used retrospective data which limited the assessment of all potential confounders. One of the confounders that was considered in some studies was smoking. It is associated with both ACPA and RA [21, 22]. However, in the study by Castillo-Ortiz *et al*. [11] and Van der Helm-van Mil *et al*. [20], smoking was not significant at the univariate analysis, and was not considered in the multivariable model. It is important to note that smoking was reported as a binary categorical variable (Yes/No question). In diseases like RA and exposures such as ACPA, duration and intensity of smoking need to be taken into account and failing to do so may cause misclassification of the smoking variable, and eventually improper adjustment for this confounder. The study by Emad *et al*. [13] used linear regression to assess association between ACPA and RA development, and another model choice may have been better.

Some studies mentioned the blinding of the outcome assessor to baseline ACPA status, while others did not. Additionally, information on the presence of missing data and the methods used to deal with it was lacking in all studies.

Strengths and Limitations

Our systematic review has several strengths. The preferred reporting items for systematic reviews guidelines using ACROBAT-NRSI ("A Cochrane Risk of Bias Assessment Tool - for Non-Randomized Studies of Interventions) [9] and STROBE statement [10] were followed in data extraction. Also, published and unpublished studies were included to reduce publication bias. The unpublished papers were tracked down and authors were contacted to retrieve the necessary information for data extraction and quality assessment.

Our systematic review has potential limitations. First, only English studies were included. Second, despite the fact that our review included unpublished articles; we were able to retrieve only one unpublished study. Therefore, the possibility of publication bias exists.

CONCLUSION

In conclusion, we provide an updated systematic review of the recent literature on cohort studies and the predictive ability of ACPA and RA development. The review confirms that the presence of ACPA in patients with undifferentiated arthritis and healthy subjects predicts future onset of RA.

APPENDIX A

Data Extraction and Quality Assessment form

SECTION A: BASIC INFORMATION

1) STUDY ID	
2) Article title	
3) First Author name	
4) Journal title	
5) Final Status	1- Included 2- Excluded, if excluded provide the reason:_____ 3- Incomplete
6) Author contacted:	1- Yes, if yes provide the date: _____ 2- No 3- Responded, provide the date:_____
7) Email of the author who was contacted	
8) Data Extracted by	1- ZS 2- MY
9) Date Completed	
10) Notes	

SECTION B: STUDY CHARACTERISTICS

1) Type of Publication	1- Peer-reviewed paper 2- Unpublished paper
2) Publication Year	
3) Country of study	
4) Aim of the study	

5) Study design	1- Case-control (traditional) 2- Nested case-control 3- Case-cohort 4- Prospective cohort 5- Retrospective cohort 6- Other _____
6) Is the study population a subgroup or general population?	1- General 2- Patients attending physician's clinics 3- Elderly 4- Males 5- Females 6- Other _____
7) Age groups included (e.g. mean age/range of study participants)	
8) Sex distribution of study participants	1- Male 2- Female
9) Was the follow-up duration ≥ 1 year?	1- Yes 2- No-----If no, then exclude the study.
10) Follow-up duration (write the exact duration of follow up for this study).	
11) Was Rheumatoid Arthritis diagnosis based on ACR criteria?	1- Yes 2- No-----If no, then exclude the study.
12) How was the main exposure (ACPA) assessed?	
13) What was the ACPA cut-off used in this study?	
14) Notes:	

SECTION C: STUDY QUALITY

1) Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome), i.e. In arthritis-free individuals as well as individuals with undifferentiated arthritis, does Anti-Cyclic Citrullinated Peptide (ACPA) antibodies predict future onset of Rheumatoid Arthritis?	1- Yes 2- No
2) The study addresses an appropriate and clearly focused question.	1- Yes 2- No 3- Unable to tell
SELECTION OF SUBJECTS (Selection bias)	
3) The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. In other words, those with positive ACPA and those with negative ACPA are selected from the same study base?	1- Yes 2- No 3- Unable to tell
4) Was loss to follow-up similar in ACPA positive and negative individuals?	1- Yes 2- No 3- Unable to tell
5) What was the loss to follow-up overall rate?	
6) Was there comparison between full participants and those lost to follow up?	1- Yes 2- No 3- Unable to tell
7) Notes	
ASSESSMENT OF EXPOSURE AND OUTCOME (Information Bias)	
8) Were there some eligible subjects who might have the outcome at the time of enrolment?	1- Yes 2- No 3- Unable to tell

9) Were these eligible subjects who had the outcome at the start of the study assessed and taken into account in the analysis?	1- Yes 2- No 3- Unable to tell 4- Not applicable
10) How was ACPA status categorized?	
11) Did all participants get the same ACPA test?	1- Yes 2- No 3- Unable to tell
12) Was Rheumatoid Arthritis assessment done independent of ACPA status (i.e. blinded to exposure information; or done in the same way in both exposed and unexposed groups)?	1- Yes 2- No 3- Unable to tell
13) Notes	
CONFOUNDING	
14) Were the main potential confounders identified? Potential confounders: Smoking, age, sex, family history of Rheumatoid Arthritis (RA), baseline joint symptoms or tenderness, Rheumatoid Factor and Shared Epitope alleles.	1- Yes 2- No 3- Unable to tell
15) How were the confounders accounted for?	1- In the design 2- In the analysis
16) What kind of regression model was used to account for confounding?	1- Cox model 2- Poisson regression 3- Logistic regression 4- Other:
17) List additional confounding variables, if any, specific to the setting of this particular study.	
18) Notes	
MISSING DATA	
19) Are outcome data reasonably complete?	1- Yes 2- No 3- Unable to tell
20) Are data reasonably complete for other variables in the analysis?	1- Yes 2- No 3- Unable to tell
21) Are the proportion of participants and reasons for missing data similar across the two groups of ACPA status?	1- Yes 2- No 3- Unable to tell
22) Were appropriate statistical methods used to account for missing data?	1- Yes 2- No 3- Unable to tell
23) Notes	
BIAS IN SELECTION OF THE REPORTED RESULT	
24) Is the reported effect estimate unlikely to be selected on the basis of the results, from multiple outcome measurements within the outcome domain, or from multiple analyses of the exposure-outcome relationship or from different subgroups?	1- Yes 2- No 3- Unable to tell
25) Most important design flaws:	
26) Notes:	

SECTION D: RESULTS

1) What is the total sample size	
2) What is the sample size of the exposed	
3) What is the sample size of the unexposed	

CRUDE EFFECT MEASURE	
4) What is the measure of crude effect	a. Odds ratio b. Risk Ratio c. Rate Ratio d. Hazard ratio e. Kaplan–Meier method f. Other:
5) Estimate of measure of effect and 95% CI:	
6) Other comments	
ADJUSTED EFFECT MEASURE	
7) For this study, is an adjusted effect measure available	1- Yes….If yes, proceed to 8) 2- No 3- Unable to tell
8) What is the adjusted effect	a. Odds ratio b. Risk Ratio c. Rate Ratio d. Hazard ratio
9) Estimate of adjusted measure of effect and 95% CI (or SE/variance)	
10) What regression model was used to generate the above adjusted measure	
11) What covariates/confounders were adjusted for in this analysis (list)	
12) Other comments	

REFERENCES

[1] Kokkonen H, Söderström I, Rocklöv J, Hallmans G, Lejon K, Rantapää Dahlqvist S. Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. Arthritis & Rheumatism 2010; 62(2): 383-91. http://dx.doi.org/10.1002/art.27186

[2] van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Annals of the Rheumatic Diseases 2012: Annrheumdis-2012-202127.

[3] Rantapää-Dahlqvist S, de Jong BA, Berglin E, *et al*. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis & Rheumatism 2003; 48(10): 2741-9. http://dx.doi.org/10.1002/art.11223

[4] Sanmarti R, Cabrera-Villalba S, Gomez-Puerta JA, *et al*. Palindromic rheumatism with positive anticitrullinated peptide/protein antibodies is not synonymous with rheumatoid arthritis. A longterm followup study. The Journal of Rheumatology 2012; 39(10): 1929-33. http://dx.doi.org/10.3899/jrheum.120568

[5] Pinheiro GC, Scheinberg MA, Aparecida dSM, Maciel S. Anti-cyclic citrullinated peptide antibodies in advanced rheumatoid arthritis. Annals of Internal Medicine 2003; 139(3): 234-5. http://dx.doi.org/10.7326/0003-4819-139-3-200308050-00023

[6] Stenger A, Van Leeuwen M, Houtman P, *et al*. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Rheumatology 1998; 37(11): 1157-63. http://dx.doi.org/10.1093/rheumatology/37.11.1157

[7] Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis & Rheumatism 1988; 31(3): 315-24. http://dx.doi.org/10.1002/art.1780310302

[8] Aletaha D, Neogi T, Silman A, Funovits J, Felson D, Bingham C. An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative 2010 Rheumaotid arthritis classification criteria. Arthritis and Rheumatism 2010; 62: 2569-81. http://dx.doi.org/10.1002/art.27584

[9] Sterne JAC HJ, Reeves BC on behalf of the development group for ACROBAT-NRSI. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) 2014 [cited 2015 June 1]. Version 1.0.0: [Available from: http: //www.riskofbias.info

[10] Von Elm E AD, Egger M, Pocock SJ, Gøtzsche PC, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. PLoS Med 2007; 4: e296.

[11] Castillo-Ortiz JD, Ramos-Remus C. Predictive Value Of Anti Cyclic Citrullinated Peptide and Rheumatoid Factor To The Development Of Rheumatoid Arthritis In a Cohort Of Healthy Relatives Of Patients With Rheumatoid Arthritis. Arthritis and Rheumatism 2013; 65: S155-S.

[12] Chen DY, Li H, Liang LQ, *et al*. Clinical features and independent predictors in the further development of rheumatoid arthritis in undifferentiated arthritis. Rheumatology International 2013; 33(11): 2827-32. http://dx.doi.org/10.1007/s00296-013-2799-8

[13] Emad Y, Anbar A, Abo-Elyoun I, *et al*. In palindromic rheumatism, hand joint involvement and positive anti-CCP antibodies predict RA development after 1 year of follow-up. Clinical Rheumatology 2014; 33(6): 791-7. http://dx.doi.org/10.1007/s10067-014-2569-3

[14] Feitsma AL, Toes REM, Begovich AB, *et al*. Risk of progression from undifferentiated arthritis to rheumatoid arthritis: the effect of the PTPN22 1858T-allele in anti-citrullinated peptide antibody positive patients. Rheumatology 2007; 46(7): 1092-5. http://dx.doi.org/10.1093/rheumatology/kem006

[15] Goeb V, Dieude P, Daveau R, *et al*. Contribution of PTPN22 1858T, TNFRII 196R and HLA-shared epitope alleles with

rheumatoid factor and anti-citrullinated protein antibodies to very early rheumatoid arthritis diagnosis. Rheumatology 2008; 47(8): 1208-12.
http://dx.doi.org/10.1093/rheumatology/ken192

[16] Rojas-Serrano J, Burgos-Vargas R, Perez LL, Garcia CG, Moctezuma F, Vazquez-Mellado J. Very recent onset arthritis: the value of initial rheumatologist evaluation and anti-cyclic citrullinated peptide antibodies in the diagnosis of rheumatoid arthritis. Clinical Rheumatology 2009; 28(10): 1135-9.
http://dx.doi.org/10.1007/s10067-009-1206-z

[17] Chen HH, Chen DY, Hsieh TY, *et al*. Predicting the Progression of Palindromic Rheumatism to Rheumatoid Arthritis: The Role of Ultrasonography and Anti-cyclic Citrullinated Peptide Antibodies. Journal of Medical Ultrasound 2010; 18(1): 17-26.
http://dx.doi.org/10.1016/S0929-6441(10)60003-3

[18] Tamai M, Kawakami A, Iwamoto N, Arima K, Aoyagi K, Eguchi K. Contribution of anti-CCP antibodies, proximal interphalangeal joint involvement, HLA-DRB1 shared epitope, and PADI4 as risk factors for the development of rheumatoid arthritis in palindromic rheumatism. Scandinavian Journal of Rheumatology 2010; 39(4): 287-91.
http://dx.doi.org/10.3109/03009741003604534

[19] Bizzaro N, Bartoloni E, Morozzi G, *et al*. Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis Research & Therapy 2013; 15(1).
http://dx.doi.org/10.1186/ar4148

[20] van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis and Rheumatism 2007; 56(2): 433-40.
http://dx.doi.org/10.1002/art.22380

[21] Heliövaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. The Journal of Rheumatology 1993; 20(11): 1830-5.

[22] Verpoort KN, Papendrecht-van der Voort EA, van der Helm-van Mil AH, *et al*. Association of smoking with the constitution of the anti-cyclic citrullinated peptide response in the absence of HLA-DRB1 shared epitope alleles. Arthritis and Rheumatism 2007; 56(9): 2913-8.
http://dx.doi.org/10.1002/art.22845

Received on 17-08-2015 Accepted on 28-08-2015 Published on 11-09-2015

DOI: http://dx.doi.org/10.12970/2310-9874.2015.03.02.2