Diagnostic Accuracy of IL-17A/IL-17F Gene Polymorphism and Anti-Carbamylated Protein Antibody for Rheumatoid Arthritis: Meta-analysis Study (2014-2020)

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Abstract

Background: The anti-CarP antibody is a novel biomarker that might help in the diagnosis of rheumatoid arthritis. Also, the associations between Interleukin-17A and17F gene polymorphism with inflammatory arthritis were inconsistent among previous studies.

Objectives: to evaluate the diagnostic value of the anti-CarP antibody for RA and to determine the relation between IL-17F and IL-17A gene polymorphism with rheumatoid arthritis.

Methods: A literature review of PubMed, PsycINFO, BioMed Central and Medline databases was carried out to identify peer reviewed peer reviewed studies, published between 2014 and 2020.

Results: Fifteen studies were included in total and the pooled sensitivity, specificity, and positive and negative likelihood ratios for anti-CarP antibody were 42% (95% CI, 38% to 45%), 96% (95% CI, 95% to 97%), 10.2 (95% CI, 7.5 to 13.9), and 0.61 (95% CI, 0.57 to 0.65), respectively. The synopsis diagnostic odds ratio was 17 (95% CI, 12 to 24), and the area under summary receiver operator characteristic curve was 80% (95% CI, 77% to 84%). Further, there were significant associations between IL-17rs2275913 G allele with OA, RA susceptibility ($P < 0.05$) but not AS. A significant association between rs763780 and RA susceptibility was detected in Caucasian populations ($P < 0.05$).

Conclusion: The moderate value of Anti-CarP antibody in the diagnosis of RA is relatively low sensitivity and high specificity. As well, IL-17F gene rs763780 C allele confers the increasing in possibility of inflammatory arthritis.

Keywords: Accuracy; IL-17A/IL-17F; Anti-CarP Antibody; Gene polymorphism; Rheumatoid Arthritis; Meta-analysis Study.

DOI: 10.21608/svuijm.2022.146355.1329

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Received: 1 July,2022.

Revised: 31 July,2022.

Accepted: 1 August,2022

Cite this article as: Samar Sayed Ahmed, Mostafa I.El-Amir, Mohamed Ali El-Feky, Eman Ragab Abdelradi (2023). Diagnostic Accuracy of IL-17A/IL-17F Gene Polymorphism and Anti-Carbamylated Protein Antibody for Rheumatoid Arthritis: Meta-analysis Study (2014-2020). *SVU-International Journal of Medical Sciences*. Vol.6, Issue 1, pp: 89- 101.

Introduction

Rheumatoid arthritis (RA) is known as a systemic autoimmune disease, presented by persistent synovitis and systemic inflammation. It is diagnosed by the existence of autoantibodies, particularly anti-cyclic citrullinated peptide (CCP) antibody and rheumatoid factor (RF). Worldwide, the prevalence of RA is about 1% in the general population **(Lee and Weinblatt, 2001)**, and it was 0.5–1.0% in developed countries. Elderly females (> 65 years) are more prone to RA. Genetics and smoking are the main risk factors representing 50% **(Scott et al., 2010)**. Although, it causes irreparable joint damage, early diagnosis and prompt treatment is preventable **(Scott et al., 2010)**.

The 2010 American College of Rheumatology (ACR)/The European League against Rheumatism (EULAR) considered anti-CCP antibody as a part of the RA classification criteria **(Funovits et al., 2010; Neogi et al., 2010)**. The false-negative results represented about one-third, despite the use of the anti-CCP antibody as a marker for diagnosis **(Senolt et al., 2014)**. It is recommended to look for new serological biomarkers to improve predictive value for the diagnosis of RA. The discovery of a novel autoantibody, the anti-CarP antibody, in RA patients helps in the prediction of RA, independent of the other biomarkers **(Shi et al., 2013; Brink et al., 2014)**. High Anti-CarP antibody level has been found in RA patients, especially those with anti-CCP negative **(Jiang et al., 2014)**.

Another new biomarker, the family members of Interleukin-17 (IL-17) was well-known to have an active role in inflammatory diseases **(Kolls and Linden, 2004)**. The IL-17A to IL-17F, IL-17 cytokines play a pivotal role in the pathogenic activity of T Helper 17 cells **(Paradowska et al., 2007)**. The first discovered member of the IL-17 family was IL-17A in 1993 **(Baeten et al., 2013)**. Some previous studies suggested that the increased risk of RA was related to IL-17A gene rs2275913 A allele in Tunisia and China **(Marwa et al., 2017)**, and rs2275913 wild-type genotype (GG) in Brazil **(Gomes da Silva et al., 2017)**. Conversely, among Caucasians, studies could not find any association between IL-17 gene polymorphism and the occurrence of RA **(Dhaouadi et al., 2018)**.

Consequently, several debates are circulating about the exact role and accuracy of both the anti-CarP antibody and IL-17 gene in the diagnosis and pathogenesis in the literature. This review aimed to explore this relationship.

Method

A literature review of BioMed Central, Medline databases, PsycINFO and PubMed, was carried out to identify reviewed studies that were published between 2014 and 2020, Which was reporting on the role and accuracy of both the anti-CarP antibody and IL-17 gene in the diagnosis and pathogenesis of RA. Searches used keywords such RA, IL-17, IL-17-A, IL-17-F, accuracy, diagnosis, and pathogenesis. Further

articles were added based on the reference lists of the relevant articles.

The Inclusion criteria were:

1) Study sample included exclusively established and early RA cases; 2) Study included an objective to establish the role and accuracy of the anti-CarP antibody in the diagnosis of RA; 3) The study included an aim to establish the role and accuracy of IL-17 (IL-17-A and IL-17-F) gene in the pathogenesis of RA.

The exclusion criteria were:

1) Study didn't report diagnostic accurately; 2) Clinical trials studies 3) The failure to report a relationship between RA and both markers. Year, sample size, study type, country, and research method were abstracted.

A total of 204 citations were retrieved from searches that were confined to those released in the six years. Careful examination of the article headings, abstracts (the article was excluded if there was no abstract), and references of retrieved articles. As a result, 34 articles were included.

A careful reading of these articles led to exclusion of 19 articles as a result of the following justifications: clinical trials without recording detailed methodology and/or relationship (4), the study did not report diagnostic accuracy (4), failure to report a relationship between RA and both markers (5), not aimed to establish the diagnostic role and accuracy of the anti-CarP antibody in RA (2) and not aim to establish role and accuracy of IL-17 (IL-17-A and IL-17-F) gene in the pathogenesis of RA (4). The remaining 15 articles were included and evaluated and discrepancies were resolved through discussion or via consulting professionals.

Results and discussion

A total of 204 published articles were identified after a thorough literature review of the main scientific databases (Pubmed, Psych~~h~~INFO, and Medline), only 15 articles fulfilled the inclusion and exclusion criteria [15–28]. A flow diagram of the selection process of the current study was depicted in (**Fig. 1**).

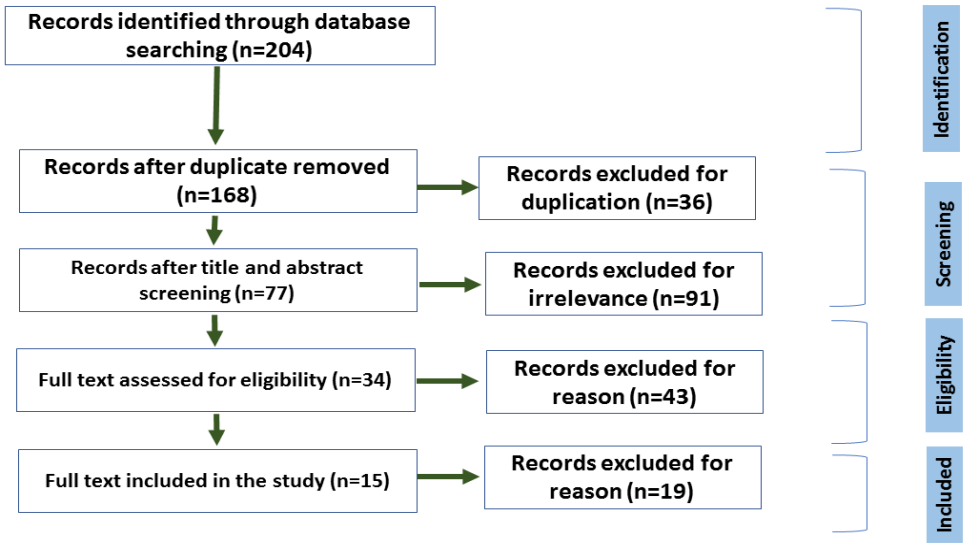

Fig.1. Flow chart of the study records

The main elements and aspects of the retrieved articles (Studies published between 2014 and 2020) were summarized in **Table 1** and **Table 2**.

Table 1. Characteristics of studies included in the Review Analysis for anti-CarP antibody

SN	Study	Year	Study Type	Country	Sample Size
1	Kumar, et al.	2017	Case-control	India	53 RA and 10 Control
2	Li, et al.	2016	Meta-analysis	Worldwide	7 studies
3	Young Ho Lee	2016	Meta-analysis	Worldwide	12 studies
4	Gan, et al:	2015	Case-control	Netherlands	83 RA and 82 Control
5	Shi, et al.	2015	Cross-sectional	Netherlands	2086 RA
6	Yee, et al.	2015	Cross-sectional	Netherlands	120 RA
7	Shi, et al	2014	Case-control	Netherlands	79 RA and 141 Control
8	Jiang, et al.	2013	Case-control	Sweden/Netherlands	Sweden (846) /Netherlands (1985)

Table 2. Characteristics of studies included in the Review Analysis for IL-17

SN	Study	Year	Study Type	Country	Sample Size
1	Shao, et al.	2020	Meta-analysis	Worldwide	19 studies
2	Elsayed, et al.	2019	Case-control	Egypt	70 RA and 34 Control
3	Marwa ,et al.	2017	Case-control	Netherlands	108 RA and 202 Control
4	Gomes da Silva, et al.	2017	Case-control	Brazil	127 RA and 134 Control
5	Marwa, et al.	2016	Case-control	Tunisia	108 RA and 202 Control
6	Pawlik, et al.	2016	Case-control	Tunisia	422 RA and 337 Control
7	Bogunia-Kubik, et al	2015	Case-control	Poland	89 RA and 125 Control

Regarding the role and accuracy of anti-CarP antibody in the diagnosis and prediction of RA; A study by (**Kumar et al., 2017**) carried out on 53 RA cases diagnosed according to ACR 1987 diagnostic criteria. CarP-antibody levels were assessed using ELISA technique and recorded that the anti-

CarP titer was above the cut-off range in 22 RA cases (positive for anti-CarP antibodies). A significantly higher Anti-CarP antibody serum level was detected in those with joint destructive changes. No significant association could be detected between anti-CarP antibodies level and the level of RF.

Moreover, a meta-analysis by **(Li et al., 2016**) searched the Cochrane Library, Embase, PubMed, Web of Science, and Scopus for studies that were published by December 15, 2015. The findings of the study were that anti-CarP antibody had fair validity measures i.e., low sensitivity (42% (95% CI, 38% to 45%)), excellent specificity (96% (95% CI, 95% to 97%)), low positive likelihood ratios (PLR) (10.2 (95% CI, 7.5 to 13.9)) and good negative likelihood ratios (NLR) (0.61 (95% CI, 0.57 to 0.65)). The odds ratio (OR) as a predictive measure was 17 (95% CI, 12 to 24) i.e., patients with positive anti-CARP antibodies had 17 times more likelihood of having RA. Also, the area under the receiver operating characteristic curve (AUC) was 80% (95% CI, 77% to 84%), revealing that anti-CARP antibody had good diagnostic validity for RA.

In another meta-analysis by **(Lee Y., 2016**) 12 articles were retrieved after searching the Embase, Pubmed, and Cochrane library databases on the anti-CarP and ACF antibodies RA diagnostic accuracy. Seven out of the 12 studies, which included 1,749 patients and 1,044 controls, examined anti-CarP antibodies. The pooled validity criteria for anti-CarP antibody in diagnosis of RA were contrasting i.e., low sensitivities (43.9%) and very high specificities (94.5%). Additionally, PLR and NLR were 9.9 and 0.6, with a 14.5 diagnostic odds ratio (DOR).

Furthermore, A case-control study by **(Gan et al., 2015**) using serum samples from 76 RA cases tested for several diagnostic antibodies including anti-CarP fetal calf serum (FCS) using IgM, IgG, and IgA. Using AUC, validity measures of Anti-CarP-FCS were contrasting, with low sensitivity (26%) and very high specificity (95%). Also, those with positive Anti-CarP-FCS were at higher risk of future RA. The antibody combination after adding Anti-CarP-FCS had a significant higher AUC (0.72) compared with that without Anti-CarP-FCS (0.71).

As well, **(Shi et al., 2015)** conducted a study where Anti-CarP FCS antibodies and Anti-CCP2 antibodies were measured using ELISA, IgM, and RF as part of routine assessment. Patients from the Leiden Early Arthritis Clinic, Leiden, the Netherlands were recruited. Among a total of 2086 patients with early arthritis, the validity of anti-CarP antibodies in the early prediction of RA was as follows: 44% sensitivity and 89% specificity. For Anti-CCP2 antibodies as a reference, sensitivity was 54% and specificity was 96%.

Additionally, **(Yee et al., 2015)** researched patients diagnosed with RA (n=120) and examined for the presence of anti-CCP antibodies and anti-CarP FCS antibodies. It was concluded that

when using anti-CarP FCS antibodies in combination with anti-CCP antibodies, a significant association was detected with DAS-28 i.e., a positive significant correlation between DAS-28 and combined antibody level (p=0.026).

Further, (**Shi et al., 2014**) in a study on asymptomatic early RA cases against age-and sex-matched controls for the comparison of the levels of anti-CarP FCS, Ca-Fib, cyclic citrullinated-peptide 2, and IgM-RF. The findings of this study were that Anti-CarP FCS was detected in 27% of asymptomatic early RA cases before a diagnosis of RA and Anti-CarP FCS could be detected years before diagnosis of RA. Also, Anti-CarP FCS could be discovered earlier than IgM-RF.

Another study was carried out in two centers, Leiden Early Arthritis Clinic, Leiden, the Netherlands (n=846) and the Swedish Epidemiological Investigation of Rheumatoid Arthritis (n=1985) by (**Jiang et al., 2013**) who reported the presence of Anti-CarP FCS and CarP-Fib antibody using ELISA among RA cases. Similar results were noticed in both cohorts. Although positive Anti-CarP antibody was found in 49% and 73% of those with positive anti-CCP antibodies, it was also found in 8% and 14% of those with negative anti-CCP antibodies.

As regards the role and accuracy of IL-17 gene polymorphism in the pathogenesis of RA**:** A meta-analysis by (**Shao et al., 2020**) using OR (95% CI) in the determination of the association between IL-17A and F gene polymorphism with susceptibility to inflammatory arthritis including RA. A total of 19 studies (5298 cases and 5675 controls) were included. The likelihood of RA was significant associations between rs2275913 G allele ($P < 0.05$). Subgroup analysis by ethnicity indicated that the rs763780 C allele was not related to RA.

In addition, in a case-control study by **El-Sayed et al.(2019)** on seventy RA patients and 34 controls, ELISA technique was used for anti-CarP and ACPA antibody detection.

The study proposed that about one-third of cases (35.7%) and only about 6% of controls screened positive for anti-CarP. Also, about one-quarter (24%) and one-third (30%) were RF and ACAP-negative. In detail, about one-third (29.4%) and about one-fifth (19%) of the negative RF and ACPA-negative groups were positive for anti-CarP. The severity of RA disease (DAS-28 and Larsen scores) was positively correlated with anti-CarP titer. Also, joint erosion was strongly related to anti-CarP antibody titer at baseline and follow-up.

A Tunisian case-control study (n=108 RA cases and 202 control) by **(Marwa et al., 2017)** aimed to study the IL-17A and F genes polymorphisms using PCR and RFLP. The results indicated that IL17F 7488 and 7383 A/G polymorphisms were significantly associated with RA probability. On the contrary, IL17A-152 G/A was not associated with the risk of RA. Subgroup analysis based on demographic and clinical criteria revealed significant

associations of IL17A and F A/G polymorphisms in RA patients. IL17A-152 and F 7383 and 7488 G/A polymorphism showed a better response to biologic treatment. Compared with controls, gene expression of IL-17 in RA patients was significantly higher ($P < 0.001$). Also, there was a dose-response relationship between the gene expression of IL-17 with the disease severity. Again, there was a steady increase in the IL-17 levels in the anti-TNF-treated patients from baseline to3 years ($P<0.05$).

A Brazilian study (127 RA and 134 controls) by Gomez da silva et al., 2017 was performed using RFLP-PCR for IL17 genotyping. Patients with CC genotype for the IL-23R polymorphism had 80% lower RA risk (OR 0.2; $p = 0.004$), as well cases with variant C allele had 40% lower risk (OR 0.6; $p = 0.002$). Regarding the IL-17A 197 G/A polymorphism, patients with GG (wild) had triple the risk of having RA (OR 3.18; $p = 0.033$). For IL-17F the 7488 A/G polymorphism, comparable percentages were recorded for cases and controls ($p>0.05$). Further, no association was reported between IL-17F gene polymorphisms and clinical features.

Pawlik et al.(2016) examined the IL17A-rs2275913 and IL17F-rs763780, rs11465553, and rs2397084 polymorphism among (422 RA cases and 337 Controls) using TM-typing assays. Insignificant differences were reported in the IL17A and IL17F genotypes and alleles distribution between cases and controls. Likewise, insignificant associations between disease duration, destructive disease, extra-articular symptomatology, and IL genotypes.

Finally, a case-control study by **Bogunia-Kubik et al. (2015)** recruited 89 RA patients and 125 controls to explore the association between IL17A expression and treatment response. There was a positive association between IL-17A polymorphism and both progression and response to anti-TNF treatment among RA cases. RA Females with IL-17A GG (wild-type) had higher stages (stage IV) and more active disease (DAS28 score) at the end of follow-up of TNF inhibitors treatment. Notably, a strong association between IL-17 F polymorphism and RA disease probability.

One of the major causes of functional disability is RA as it hinders the life quality. Early diagnosis and prompt treatment exhibited a major role in adverse consequences i.e., massive erosions and deformities in the inflamed joints of RA patients. Several laboratory investigations were identified to support the early diagnosis of the disease. Early RA recognition using valid biomarkers was enrolled to increase the benefits from early management. Anti-CarP antibody was recently introduced as one of the later newly discovered autoantibodies in the sera of patients with RA. Shi J et al showed that anti-CCP and anti-CarP antibodies are different, but some cross-reactivities may exist **(Shi et al., 2014)**.

Until now, the anti-CarP antibody may supply additional benefits in the diagnosis of RA as several studies reported especially for those with anti-CCP-negative diseases **(Senolt et al., 2014; Ajeganova and Huizinga, 2015)**. The anti-CarP antibodies are also detected in psoriatic arthritis, systemic sclerosis, and juvenile idiopathic arthritis. As well, the anti-CarP antibody level was correlated with RA disease progression among cases and the ACPA-negative subgroup **(Ajeganova et al., 2016)**. Anti-CarP antibody may be used to forecast radiographic progression within the RA population. So, the detection of the anti-CarP antibody may be a useful serological test for the identification and sub-classification of patients with RA. Moreover, there is increasing evidence that some specific IL-17A and IL-17F gene polymorphisms were functional, suggesting that they may play important roles in disease susceptibility.

This review analysis aimed to assess the diagnostic value of the anti-CarP antibody for RA. Additionally, this review aimed to investigate the association of IL-17A and IL-17F gene polymorphisms with inflammatory arthritis susceptibility.

A total of 15 studies were included in this review. The probable validity of the anti-CarP antibody was mainly attributed to its high validity measures specificity (96%) and PLR (10.2). This suggested that RA cases had about a ten-fold increase in the likelihood of becoming positive for the anti-CarP antibody. On the other hand, it had lower sensitivity (42%), while the NLR was not low enough (<0.1) to exclude RA when the anti-CarP antibody tests were negative. Likely, the test had 80% AUC, this demonstrated that the anti-CarP antibody had very good diagnostic power for RA. Furthermore, five larger sample studies (n=100) **(Shi et al., 2011; Challener et al., 2015; Verheul et al., 2015)** were analyzed independently to test the predictive and diagnostic power of anti-CarP antibody for RA disease. Validity measures were as follows: sensitivity (41%), specificity (96%), PLR (11.4%) and NLR (61%).

Regarding IL-17 gene polymorphism, the results suggested that the gene rs2275913 polymorphism allele was significantly correlated with RA probability in Caucasians but not Mongolians race. The results concluded that there was a significant positive relationship between IL17 rs2275913 G allele and increased possibility of RA. In contrast to several previous studies that cannot detect such association, validity analysis revealed that the findings of this meta-analysis were robust. Regarding the IL-17F rs763780, the C allele was found to increase the RA likelihood among Caucasians. Till now, the probability of RA affection was found to be associated with IL17F rs763780 polymorphisms in two different meta-analysis studies (**Eskandari-Nasab et al., 2017; Chen et al., 2017**), supporting this conclusion.

A plausible explanation was that IL-17A and F were proposed to trigger the

pro-inflammatory responses, and this was crucial for the pathogenesis of RA diseases **(Pappu et al., 2010)**. Also, IL-17 gene mutation was claimed to provoke RA diseases by the initiation of the IL-17 cytokine activation and pro-inflammatory functions and hence leads to the production and expression of TNF-alpha **(Jin et al., 2015; Li et al., 2014)**. Multiple previous research illustrated that IL-17F cytokines possessed pro-inflammatory roles **(Espinoza et al., 2011; Kapoor et al., 2011)**. Collectively, variations in both the Anti-CarP antibody level and the IL-17 gene polymorphism play a major role possibility of having inflammatory arthritis including RA (**Kapoor et al., 2011**).

This study faced several limitations. First, genetic variations of IL-17 polymorphism and the risk of RA were heterogenic, this may be due to the difference in the environmental conditions, genetic basis, and lifestyle that were not included in the analysis. Secondly, As the parameters used for assessment were not controlled for all studies, they should have been precisely assessed after adjustment of the major confounders (age, BMI, smoking, and other socio-demographic factors. Finally, only one study included in the review was conducted in a similar population (Arab, Caucasian, EMR-region (the Tunisian study)).

Conclusion

In conclusion, the anti-CarP antibody was found to possess moderate diagnostic power for the risk of RA disease, with relatively low sensitivity and high specificity. In Addition, this review suggested that there was a strong positive association between the increased risk of RA and gene polymorphism of IL-17A and F among Caucasians. Even though, the relation between the IL-17 gene and RA likelihood in Mongolians was still inconclusive. Future studies with a larger sample and high standardized quality assessment for the role of Anti-CarP antibody and IL-17 in RA are required.

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