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ORIGINAL ARTICLE

Diagnostic Accuracy of Anti-Carbamylated Protein Antibodies in Rheumatoid Arthritis: a Systematic Review and Meta-Analysis

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SUMMARY

Background: **The purpose of this study was to estimate the diagnostic accuracy of anti-carbamylated protein (anti-CarP) antibodies in rheumatoid arthritis.**
Methods: **We searched the PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus databases for studies published before January 1, 2019. Two investigators independently evaluated studies to determine their inclusion in the analysis, assess their quality, and extract the relevant data. The articles were assessed with the Quality Assessment of Diagnostic Accuracy Studies tool, and a bivariate mixed effects model was used to estimate the diagnostic indexes across studies.**
Results: **We included 16 published studies in this meta-analysis. The pooled sensitivity and specificity of anti-CarP were 43.1% and 94.4%, respectively. The area under the summary receiver operator characteristic curve was 0.55. The specificity estimates were highly heterogeneous, which could be partly explained by the higher specificity in the healthy control group (43.0%, 96.8%) than in the other disease group (43.4%, 89.8%).**
Conclusions: **Anti-CarP antibodies have a relatively low sensitivity and high specificity for rheumatoid arthritis. However, the specificity was lower in the other disease subgroups than in the healthy controls.**
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Supplementary Tables and Figures

Table 1. The list of the search strategy.

1. Pubmed: 76

Search (((((((((antibody to carbamylated protein [Title/Abstract]) OR antibody to CarP [Title/Abstract]) OR autoantibody to carbamylated protein [Title/Abstract]) OR autoantibody to CarP [Title/Abstract]) OR anti-carbamylated protein antibody [Title/Abstract]) OR anti-carp antibody [Title/Abstract]) OR anti carbamylated protein antibody [Title/Abstract]) OR anti carp antibody [Title/Abstract])) AND (("Arthritis, Rheumatoid" [Mesh]) OR ((rheumatoid arthritis [Title/Abstract]) OR RA [Title/Abstract])).

2. Embase: 207

1	'rheumatoid arthritis'/exp OR 'rheumatoid arthritis'	226,953
2	rheumatoid AND ('arthritis'/exp OR arthritis)	227,982
3	'ra'	136,103
4	#1 or #2 or #3	296,109
5	'antibody'/exp OR antibody AND to AND carbamylated AND ('protein'/exp OR protein)	207
6	'antibody'/exp OR antibody AND to AND ('carp'/exp OR carp)	848
7	'autoantibody'/exp OR autoantibody AND to AND carbamylated AND ('protein'/exp OR protein)	140
8	'autoantibody'/exp OR autoantibody AND to AND ('carp'/exp OR carp)	142
9	anti AND carbamylated AND ('protein'/exp OR protein) AND ('antibody'/exp OR antibody)	193
10	'anti carbamylated' AND ('protein'/exp OR protein) AND ('antibody'/exp OR antibody)	135
11	anti AND ('carp'/exp OR carp) AND ('antibody'/exp OR antibody)	375
12	'anti carp' AND ('antibody'/exp OR antibody)	179
13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	957
14	#4 and #13	207

3. Cochrane library databases: 6.

#1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees	5,286
#2	rheumatoid arthritis: ti, ab, kw (Word variations have been searched)	10,785
#3	RA: ti, ab, kw (Word variations have been searched)	7,888
#4	#1 or #2 or #3	13,360
#5	antibody to carbamylated protein: ti, ab, kw (Word variations have been searched)	6
#6	antibody to CarP: ti, ab, kw (Word variations have been searched)	2
#7	autoantibody to carbamylated protein: ti, ab, kw (Word variations have been searched)	5
#8	autoantibody to CarP: ti, ab, kw (Word variations have been searched)	1
#9	anti-carbamylated protein antibody: ti, ab, kw (Word variations have been searched)	6
#10	anti-carp antibody: ti, ab, kw (Word variations have been searched)	0
#11	anti-carbamylated protein antibody: ti, ab, kw (Word variations have been searched)	6
#12	anti-carp antibody: ti, ab, kw (Word variations have been searched)	3
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	7
#14	#4 and #13	6

4. Web of Science: 208.

TS = (antibody to carbamylated protein OR antibody to CarP OR autoantibody to carbamylated protein OR autoantibody to CarP OR anti carbamylated protein antibody OR anti-carbamylated protein antibody OR anti CarP antibody OR anti-CarP antibody) AND TS = (rheumatoid arthritis OR RA).

5. Scopus: 74.

(TITLE-ABS-KEY ("antibody to carbamylated protein" OR "antibody to CarP" OR "autoantibody to carbamylated protein" OR "autoantibody to CarP" OR "anti carbamylated protein antibody" OR "anti-carbamylated protein antibody" OR "anti CarP antibody" OR "anti-CarP antibody") AND TITLE-ABS-KEY ("rheumatoid arthritis" OR ra)).

Table 2. A list of the article not included in the study (and the reasons).

No.	Studies	Reasons for exclusion	Number of studies
1	Shi 2013 [1], Willemze 2012 [2]	Reviews without patients to diagnose.	2
2	Boeters 2018 [3], Truchetet 2017 [4]	The whole patients or part did not meet the diagnostic criteria.	2
3	Myrthe 2018 [5], Regueiro 2018 [6], Hutchinson 2017 [7], De Moel 2017 [8], Kumar 2017 [9], Othman 2017 [10], Dekkers 2017 [11], Dekkers 2016[12], Verheul 2016 [13], Vidal-Bralo 2016[14], Regueiro 2016 [15], Van Wesemael 2015 [16], Jiang 2014 [17]	It did not report the number of responders and non-responders to anti-carp, in which case we could not calculate the sensitivity and specificity.	14
4	Regueiro 2018 [18], Romero-Sanchez 2018 [19], Brink 2016 [20], Marcos 2016 [21], Gan 2015 [22], Brink 2014 [23], Shi 2014 [24], De Smit 2013 [25]	The participates were not rheumatoid arthritis or just individuals who were identified before onset of symptoms of RA.	8
5	Kaneko 2018 [26]	The number of patients were less than 50 people, which could not ensure the diagnostic accuracy.	1
6	De Moel 2018 [27], de Moel 2018 [28], Ponikowska 2018 [29], Ajeganova 2017 [30], Boeters 2017 [31], Derksen 2015 [32], HAjeganova 2016 [33], van Wesemael 2016 [34], Ajeganova 2016 [35], Hunt 2014 [36], Yee 2014 [37],	It didn't report the sufficient positive/negative data at baseline in control groups. As a result, there was no way to calculate the specificity.	11
7	Castellanos-Moreira 2018 [38], Lac 2018 [39], Hayrynen 2015 [40], Turunen 2015 [41]	The antigen of the homocitrulinated peptide was not fetal calf serum.	4
8	van Delft 2017 [42], Bartosiewicz [43]	The data was duplicated report in two articles, and we exclude one of them.	2

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