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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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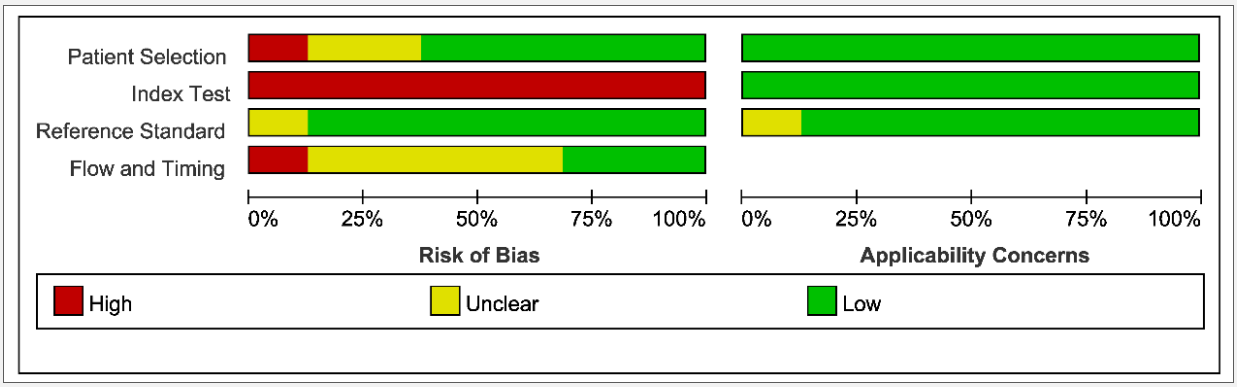
Supplementary Tables and Figures

Table 1. The study quality of QUADAS-1.

Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	study quality
Shi et al.	2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	11
Montes et al.	2014	Y	Y	Y	U	Y	Y	Y	N	Y	N	Y	Y	N	Y	10
Shi et al.	2015	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	11
Pecani et al.	2015	Y	Y	Y	U	Y	Y	Y	N	Y	N	Y	Y	N	Y	10
Alessandri et al.	2015	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	N	Y	11
Brink et al.	2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	12
Janssen et al.	2015	Y	Y	U	U	Y	Y	Y	N	N	N	Y	Y	N	Y	9
Verheul et al.	2015	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	11
Pecani et al.	2016	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	11
Koppejan et al.	2016	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	N	Y	11
Challener et al.	2016	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	11
Verheul et al.	2016	Y	Y	Y	U	Y	Y	Y	N	Y	N	Y	Y	N	N	9
Nakabo et al.	2017	Y	Y	U	U	Y	Y	Y	Y	N	N	Y	Y	N	Y	10
Van Delf et al	2017	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	N	Y	11
Spinelli et al.	2017	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	11
Verheul et al.	2017	Y	Y	Y	U	Y	Y	Y	Y	Y	N	Y	Y	N	Y	11

QUADAS - Quality Assessment of Diagnostic Accuracy Studies, Y - Yes, N - No, U - Unclear. Item 1. Was the patient spectrum representative of the patients who will receive the test in practice? 2. Were selection criteria clearly described? 3. Is the reference standard likely to correctly classify the target condition? 4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? 5. Did the whole study population or a random selection of the sample, receive verification using a reference standard for diagnosis? 6. Did patients receive the same reference standard regardless of the index test result? 7. Was the reference standard independent of the index test? 8. Was the execution of the index test described in sufficient detail to permit replication of the test? 9. Was the execution of the reference standard described in sufficient detail to permit its replication? 10. Were the index test results interpreted without the knowledge of the results of the reference standard? 11. Were the reference standard results interpreted without knowledge of the index test results? 12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? 13. Were uninterpretable / intermediate test results reported? 14. Were withdrawals from the study explained?

Table 2. The study quality of QUADAS-2 and a list of studies that did not meet some items.



Item	Study (unclear)	Study (no)
Was a consecutive or random sample of patients enrolled?	Montes 2014, unclear; Janssen 2015, unclear; Nakabo 2017, unclear	Verheul 2017, no
Did the study avoid inappropriate exclusions?	Shi 2011, unclear; Verheul 2016, unclear	Janssen 2015, no
Could the selection of patients have introduced bias?	Shi 2011, unclear risk; Montes 2014, unclear risk; Verheul 2016, unclear risk; Nakabo 2017, unclear risk	Janssen 2015, high risk; Verheul 2017, high risk
Could the reference standard, its conduct, or its interpretation have introduced bias?	Janssen 2015, unclear risk; Nakabo 2017, unclear risk	-
Are there concerns that the target condition as defined by the reference standard does not match the question?	Janssen 2015, unclear concern; Nakabo 2017, unclear concern	-
Was there an appropriate interval between index test and reference standard?	Montes 2014, unclear; Pecani 2015, unclear; Alessandri 2015, unclear; Koppejan 2016, unclear; Verheul 2016, unclear; Nakabo 2017, unclear; Van Delf 2017, unclear; Verheul 2017, unclear	Pecani 2016, no; Challener 2016, no; Spinelli 2017, no
Were all patients included in the analysis?	-	Shi 2011, no
Could the patient flow have introduced bias?	Montes 2014, unclear risk; Pecani 2015, unclear risk; Alessandri 2015, unclear risk; Koppejan 2016, unclear risk; Verheul 2016, unclear risk; Nakabo 2017, unclear risk; Van Delf 2017, unclear risk; Verheul 2017, unclear risk	Challener 2016, high risk; Spinelli 2017, high risk

Table 3. Sensitivity analysis of this meta-analysis. A: mixed control; B: healthy control group; C: disease control group.

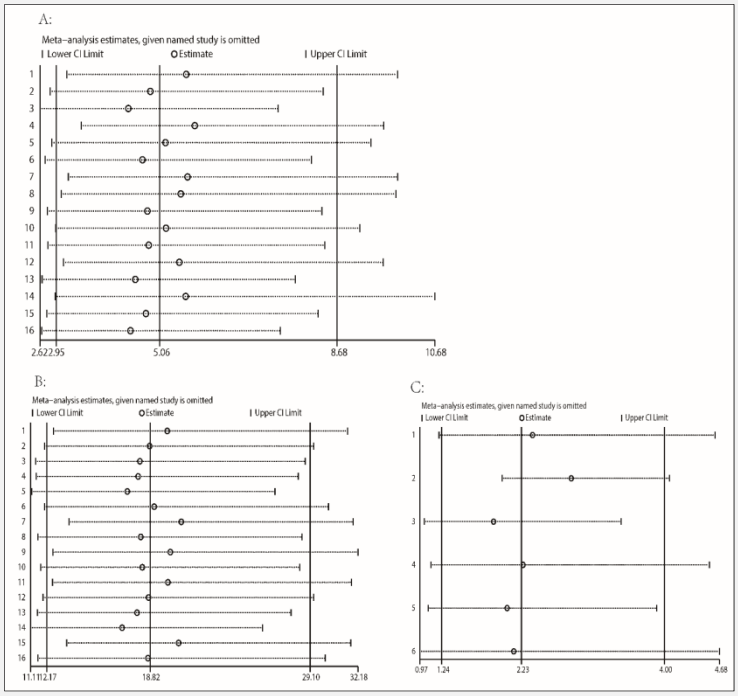


Table 4. The single rate analysis of the sensitivity for the anti-CarP antibody in the anti-CCP positive (A)/negative (B) or the RF IgM positive (C)/negative RA patients (D).