Review

Jia-Ning Zhu^a, Liu-Yan Nie^a, Xiao-Yong Lu^a and Hua-Xiang Wu***Meta-analysis: compared with anti-CCP and rheumatoid factor, could anti-MCV be the next biomarker in the rheumatoid arthritis classification criteria?**<https://doi.org/10.1515/cclm-2019-0167>

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Abstract

Background: Previous reviews of the diagnosis for rheumatoid arthritis (RA) have not compared anti-mutated citrullinated vimentin (MCV) with anti-cyclic citrullinated peptide (CCP) and rheumatoid factor (RF) in respect of sensitivity, specificity and the area under the curve (AUC) against disease controls for differential diagnosis. This meta-analysis aims to evaluate the value of anti-MCV in the diagnosis for RA, the combined sensitivity of anti-MCV and anti-CCP, and certain clinical characteristics related to the performance of anti-MCV.

Methods: Medline, Embase, Cochrane Library and Web of Science were searched for articles published up to 25 August 2018. A total of 33 studies including 6044 RA patients and 5094 healthy or disease controls achieved inclusive criteria. QUADAS-2 was applied to evaluate the quality of the included studies. The bivariate random effects model was employed in primary data synthesis to evaluate the diagnostic performance.

Results: The sensitivity of anti-MCV, anti-CCP and RF in RA diagnosis against a disease control group was 0.71, 0.71, 0.77, with the specificity of 0.89, 0.95, 0.73, and the AUC of the SROC of 0.89, 0.95, 0.82, respectively. The predesign of the primary study and diagnostic criteria were statistically significant as sources of heterogeneity. Anti-MCV and anti-CCP tests demonstrated a sensitivity of 0.77 when performed in parallel, with a sensitivity of 0.60 when performed in series; whereas, the combination of anti-MCV and RF presented a sensitivity of 0.64 when used in series.

Conclusions: Anti-MCV demonstrates comparable diagnostic value to anti-CCP and RF, thus it can be an effective diagnostic marker for RA and may be written into the next authoritative criteria.

Keywords: anti-cyclic citrullinated peptide antibodies; anti-mutated citrullinated vimentin antibodies; diagnosis; rheumatoid arthritis; rheumatoid factor.

Introduction

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases, with an incidence of 0.5%–1.0% worldwide [1]. It was estimated to be present in 2.4% of the population aged >65 years, with the prevalence appearing to increase with age [2]. The severe outcome of destructive and deforming arthritis influences impairment of functional capacity and results in low quality of life in patients with RA [3].

Poor as the prognosis of patients with RA is, early diagnosis is regarded as the key role for improvement, and high efficacy is seen with this strategy in reducing joint destruction, retarding radiologic progression and decreasing functional disability [4]. Anti-citrullinated peptide antibodies (ACPAs) and rheumatoid factor (RF) belong to the serum biomarkers involved in the 2010 American College of Rheumatology (ACR)/the European League Against Rheumatism (EULAR) RA classification criteria, no doubt underscoring the serodiagnostic utility of these autoantibodies in RA. Furthermore, ACPAs include anti-cyclic citrullinated peptide (anti-CCP), anti-mutated citrullinated vimentin (anti-MCV), anti-centriolin antibody (anti-CEP-1) and so on, among which anti-CCP is widely used [5].

To date, three published meta-analysis have already tested which is better for diagnosis of RA between anti-MCV and anti-CCP [6–8]. Nevertheless, there is a lack of information on studies concluding the comparison of anti-MCV and anti-CCP with respect to diagnostic accuracy in RA. Restricted by the limited numbers of studies which fulfill the inclusive criteria, these reviews did not

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discuss the specific area of diagnostic accuracy compared to anti-CCP, and it was suggested that anti-MCV could be tested in patients suspected of RA who were seronegative for anti-CCP and RF. Based on previous studies, we decided to evaluate how anti-MCV performs in the diagnosis of RA by increasing the number of included studies and exploring the sensitivity and specificity of anti-MCV, anti-CCP and RF in the diagnosis of RA. Moreover, the efficacy of anti-MCV combined with anti-CCP, and the impact of diagnosis at different cutoff values for anti-MCV were summarized, and receiver operator characteristic curve (ROC) of anti-MCV, anti-CCP and RF were evaluated to identify the best cutoff for diagnosis. In addition, results of studies that assessed the clinical heterogeneity of index testing methods, the gold standard applied for the diagnosis, index cutoff values and the predesign of the primary studies are discussed [8].

Materials and methods

Search strategies

This meta-analysis was performed following the guidelines of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Four databases were searched for this study: Medline, Embase, Cochrane Library and Web of Science, with publication time up to 25 August 2018. A combination of MeSH terms and keywords pertaining to RA (“Arthritis, Rheumatoid” OR “rheumatoid arthr*” OR “RA”), AND anti-MCV (“MCV” OR “mutated citrullinated vimentin”) were applied to the search strategies. The reference lists of all the included studies were searched to identify any additional eligible studies.

Study selection

Titles and abstracts were independently screened by two reviewers (Zhu and Nie). Full articles were retrieved and reviewed for the following inclusion criteria:

1. studies were prospective or retrospective or cross-sectional study of the diagnostic value of MCV, with or without CCP and/or RF in RA study with human subjects;
2. studies included a healthy and/or other diseases control groups for comparison;
3. RA patients fulfilled either the 1987 ACR classification criteria or the 2010 ACR/EULAR classification criteria, as which have been approved by the professional and scientific authorities;

4. studies evaluated MCV, with or without CCP and/or RF levels in serum, and were quantitative tests;
5. studies provided the necessary data, e.g. the number of true positive, true negative, false positive, and false negative, sensitivity, specificity, or likelihood ratios, to construct 2×2 contingency tables of levels of MCV, with or without CCP and/or RF for the diagnosis of RA.

Studies were excluded if they were not available in English or included duplicate data. No age restriction on participants was applied here.

Data extraction

Two reviewers (Zhu and Nie) individually extracted the data, with discrepancies resolved by discussion. When it was difficult to reach an agreement, a third reviewer (Lu) was consulted. When results of different cutoff values were reported on an index test, data from the recommended cutoff value according to the manufacturers' instructions were extracted. Where there was more than one type of assay for the same index test, the more frequently used one among included studies was extracted. Where more than one subtype of the same kind of index test was available from the study, the more widely used one was included for the review, to be more specific, anti-CCP2 IgG and RF IgM were chosen as the representation.

Quality assessment

The quality of each included study was independently assessed by the two reviewers (Zhu and Nie), using the revised version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Any disagreements were resolved through discussion.

Statistical analysis

Data analysis was performed using Stata 12 software (Midas commands) (StataCorp LP, College Station, TX, USA), Revman 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

The bivariate random effects model based on the binomial distribution for sensitivity and specificity

was employed in primary data synthesis, with inferences made about summary estimates of sensitivity and specificity and their 95% confidence intervals (CIs). Derived logit estimates of sensitivity, specificity based on parameters estimated by the bivariate model were used to plot a hierarchical summary ROC curve, with a summary point estimate, 95% confidence region and 95% prediction region presented. The area under the curve (AUC) is the average TPR over the entire range of FPR values.

I^2 is viewed as the index to assess the heterogeneity, which calculates the percentage of total variation across studies caused by heterogeneity rather than chance. I^2 ranges from 0% to 100%, with 0% indicating no observed heterogeneity, and values greater than 50% suggesting substantial heterogeneity. Covariates regarding any test performance that may contribute to the heterogeneity were introduced into a regression as the dependent variable.

To investigate publication bias, the funnel plot with a superimposed regression line of diagnostic log odds ratio against $1/\sqrt{n}$ (effective sample size), weighting by effective sample size was conducted, and $p < 0.10$ for the slope coefficient suggests significant asymmetry.

Results

Search results

The initial search identified 704 articles, of which 300 were duplicates and 302 were excluded according to the title and abstract (Figure 1). One hundred and two full-text articles were reviewed, of which 25 were excluded as we were unable to extract sufficient information to construct 2×2 tables, 15 were excluded as they did not include a control group, seven were excluded due to a lack of a golden diagnostic tool, specifically, neither the 1987 ACR classification criteria nor the 2010 ACR/EULAR classification criteria for RA was adopted in these studies, 15 were conference abstracts, two were systematic reviews, two were duplicate reports and another two were not available in English. Therefore, the meta-analysis was conducted based on the remaining 33 studies [9–41] (Table 1).

Methodological quality of included studies

QUADAS-2 was selected as the guide for methodological quality evaluation for the included studies, this evaluates

Figure 1: Flowchart of selection of studies for inclusion in the meta-analysis.

Table 1: Characteristics of individual studies included in the meta-analysis.

Author, year	Country	Age, years	Patient, n RA (F/M)	NRA (Health, Disease control [F/M])	Method	Gold standard	Study design	Cutoff, U/mL			Duration of RA
								Anti-MCV	-Anti-CCP	RF	
Zahrán et al., 2013 [9]	Egypt	RA: 25–65 DC: 34–74 HC: 33–48	22/8	DC: 30/10 HC: 13/7	ELISA	1987 ACR	Cross-sectional	20	5	20	UC
Yousefghahari et al., 2013 [10]	Iran	RA: 49.6 ± 11.8 DC: 48.8 ± 12	116/34	DC: 58/17	ELISA	1987 ACR	Cross-sectional	20	5	N	6 months to 6 years
Damjanovska et al., 2010 [11]	Holland	RA: 56.9 ± 15 DC: 45.9 ± 16.8	376/187	DC: 184/167 HC: 99	ELISA	1987 ACR	Prospective	20	20	N	<2 years
Iwaszkiewicz et al., 2015 [12]	Poland	RA: 51.7 ± 11.8 DC: 46.1 ± 15.2	32/9	DC: 98/30	ELISA	2010 ACR	Cross-sectional	20	5	N	MT: 9.0 (0.2–41.0) years
Nicaise-Roland et al., 2008 [13]	France	N	156	DC: 158 HC: 50	ELISA	1987 ACR	Cross-sectional	20	25	20	>1 year: 136 <1 year: 20
Besada et al., 2011 [42]	Norway	RA: 64 ± 15	59/16	DC: 28/41	ELISA	1987 ACR	Cross-sectional	20	20	6	UC
Liu et al., 2009 [15]	China	RA: 16–83	119/51	DC: 76 HC: 60	ELISA	1987 ACR	Cross-sectional	11.85	25	20	1–12 months
Nicaise-Roland et al., 2013 [16]	France	RA: 49.06 ± 11.95	452/139	DC: 93	ELISA	1987 ACR	Prospective	20	25	N	<6 months
Bizzaro et al., 2007 [17]	Italy	RA: 64 (40–86) HC: 63(36–74)	90/10	DC: 202 HC: 70/4	ELISA	1987 ACR	Cross-sectional	20	20	20	<1 year: 22 2–18 years: 78
Kim et al., 2013 [18]	Korea	RA: 53.6 ± 10.7 FDR: 26.3 ± 11.1	135/0	FDR: 153/49	ELISA	1987 ACR	Cross-sectional	20	5	10	<10 years: 68 >10 years: 67
Maraina et al., 2010 [19]	Malaysia	RA: 50.0 DC: 49.9	87/13	DC: 125/28	ELISA	1987 ACR	Cross-sectional	20	15	20	UC
Kaptanoglu et al., 2010 [20]	Turkey	RA: 48.91 ± 11.64 DC: 57.73 ± 11.62	23/11	DC: 22/8	ELISA	1987 ACR	Cross-sectional	20	12	20	MT: 5.56 ± 4.50 years
Mutlu et al., 2009 [21]	Turkey	RA: 53.8 (26–76) HC: 51 (25–71)	77/16	DC: 58/25 HC: 15/2	ELISA	1987 ACR	Prospective	20	20	15	<6 months: 15 0.7–26 years: 78
Diaz-Toscano et al., 2014 [22]	Mexico	RA: 49 ± 10.69	135/7	DC: 86 HC: 56	ELISA	1987 ACR	Cross-sectional	20	5	N	MT: 9 ± 8.07 years
Zhu and Feng, 2013 [23]	China	RA: 45 (19–71) DC: 47 (26–68) HC: 46 (23–69)	39/17	DC: 30/12 HC: 15/5	ELISA	1987/2010 ACR	Cross-sectional	20	12	20	1–10 years
Svard et al., 2011 [24]	Sweden	UC	215	DC: 52	ELISA	1987 ACR	Prospective	150	25	N	UC
Soos et al., 2007 [25]	America	RA: 52.7 ± 12.5	100/19	DC: 64/10 HC: 29/13	ELISA	1987 ACR	Cross-sectional	20	20	25	MT: 10.2 ± 9.1 years
Dejaco et al., 2006 [26]	Austria	RA: 60.4 ± 12.0 DC: 58.5 ± 15.7	140/24	DC: 231/72	ELISA	1987 ACR	Cross-sectional	20	10	N	<1 year: 23 1–5 years: 45 >5 years: 85

Table 1 (continued)

Author, year	Country	Age, years	Patient, n RA (F/M)	NRA (Health, Disease control [F/M])	Method	Gold standard	Study design	Cutoff, U/mL			Duration of RA
								Anti-MCV	-Anti-CCP	RF	
Wagner et al., 2009 [27]	Austria	RA: 65.30(36–89) DC: 59 (30–83) UC	156/37	DC: 243/89	ELISA	1987 ACR	Cross-sectional	20	5	50	MT: 11.9 (0.5–40) years
Zehairy et al., 2012 [28]	Egypt	UC	30	55	Immunological assays	1987 ACR	Cross-sectional	20	25	15	UC
Bang et al., 2007 [29]	Germany	UC	1151	DC: 257 HC: 232	ELISA	1987 ACR	Cross-sectional	25	25	UC	UC
Barouta et al., 2017 [30]	Greece	RA: 60.91 ± 10.87 DC: 53.0 ± 15.34 HC: 60.05 ± 7.35	98/43	DC: 31/22 HC: 20/20	ELISA	1987 ACR	Prospective	42	UC	N	<3 months
Sizova, 2012 [31]	Russian	RA: 46.12 ± 11.81	211/39	6	ELISA	1987 ACR	Prospective	20	20	N	MT: 4.92 ± 3.32 months
Lima et al., 2013 [32]	Brazil	RA: 55 ± 13 DC: 48 ± 17 HC: 35 (28–42)	47/3	DC: 26/24 HC: 8/12	ELISA	1987 ACR	Cross-sectional	20	20	25	MT: 13 years
Sghiri et al., 2008 [33]	Tunisia	RA: 17–78	139/31	DC: 250 HC: 59	ELISA	1987 ACR	Cross-sectional	172	UC	UC	<1 year: 59 >1 year: 111
Sahin et al., 2011 [34]	Turkey	RA: 50 (23–76) HC: 45 (28–61)	23/11	HC: 19/5	ELISA	1987 ACR	Cross-sectional	20	12	20	4 (1–20) years
Reyes-Castillo et al., 2015 [35]	Mexico	RA: 47 ± 12	149/21	HC: 103	ELISA	1987 ACR	Cross-sectional	20	5	30	5 ± 6
Renger et al., 2010 [36]	Germany	RA: 57.9 ± 13.8 DC: 57.1 ± 14 HC: 47.4 ± 19.1	87/21	DC: 84/38 HC: 139/61	ELISA	1987/2010 ACR	Cross-sectional	40	N	30	UC
Mathsson et al., 2008 [37]	Sweden	RA: 57.0	193/80	HC: 100	ELISA	1987 ACR	Cross-sectional	20	25	UC	MT: 5 months
El-Barbary et al., 2011 [38]	Egypt	RA: 51 (37–65) HC: 48 (36–61)	75/25	HC: 80/20	ELISA	1987 ACR	Cross-sectional	20	20	15	0.4 (0.3–0.6) months
Bartoloni et al., 2013 [39]	Italy	N	285	DC: 136 HC: 91	ELISA	1987 ACR	Cross-sectional	55	5	N	<3 years
Al-Shukaili et al., 2012 [40]	Oman	RA: 41.6 ± 14.5 HC: 35 ± 7	71/9	HC: 70/63	ELISA	1987 ACR	Cross-sectional	20	5	30	10.3 ± 18.7 years
Meyer et al., 2018 [41]	South Africa	RA: 48 (19) HC: 46	61/14	HC: 19/11 DC: 46	ELISA	1987 ACR	Prospective	91	10	UC	9 (12) months

RA, rheumatoid arthritis; NRA, non-rheumatoid arthritis, include health control and disease control; anti-MCV, anti-mutated citrullinated vimentin; anti-CCP, anti-cyclic citrullinated peptide; RF, rheumatoid factor; HC, health control; DC, disease control; N, no information; UC, unclear; FDR, first-degree relatives; ELISA, enzyme-linked immunosorbent assay; ACR, American College of Rheumatology; MT, median time.

the risk of bias of each study cohort on four categories (patient selection, index test, reference standards, flow and timing), and the concerns regarding applicability on three categories (patient selection, index test, reference standards). The risk was graded as high, low or unclear, and an overall risk grades for each category mentioned were estimated (Figure 2). About half of the studies showed

a high risk for patient selection because a case-control design was often difficult to avoid and a consecutive or random sample of cohorts was difficult to satisfy (see Supplementary material, Figure 1). Around 50% of the studies presented an unclear risk for flow and timing, based on the fact that except for the gold standard of diagnosis for RA, the reference standards for other rheumatic diseases were unclear, therefore making it challenging to decide whether the disease control groups received the same gold standard. Nearly all the studies demonstrated a low risk among all three categories of the concerns regarding applicability.

Diagnostic value of anti-MCV with RA

The diagnostic value of MCV to RA vs. the disease control group mainly consisted of other rheumatic diseases, some infectious diseases with similar clinical features to RA, one study with unaffected first-degree relatives from RA families is also reported here. Among the 33 studies included in the present meta-analysis, eight of which provided information only on healthy controls rather than disease controls. According to the forest plot, the remaining 25 included studies [9–13, 15–30, 32, 41, 42] showed a combined sensitivity of 0.71 [0.64–0.77] (95% CI), specificity of 0.89 [0.85–0.92] (Figure 3). The SROC curve showed an AUC of 0.89 [0.86–0.91] (Figure 4).

The I^2 of combined sensitivity was 94.73 [93.42–96.03], with $p=0.00$ for Q test; similarly, the I^2 of combined specificity was 88.32 [84.66–91.98], with $p=0.00$ for Q test. A meta-regression was performed due to the obvious heterogeneity, with covariates including testing methods of MCV with its cutoff value, disease duration, diagnostic criteria and predesign of the primary study. As a result, the predesign of the primary study presents as a significant contributor to the heterogeneity for both sensitivity and specificity, with $p=0.00$ and $p=0.01$ respectively, while diagnostic criteria contribute to the heterogeneity for specificity ($p=0.05$).

Publication bias was examined using the Deeks' funnel plot asymmetry test, symmetry in the data and a low likelihood of publication bias are observed in the present study ($p=0.20$).

Clinical subgroup analysis

The predesign of the study and the diagnostic criteria were observed to be statistically significant as sources of heterogeneity by meta-regression among the 25 studies where

Figure 2: Risk of bias and applicability concerns summary. Each item in the graph was described with + (low risk of bias), – (high risk of bias) and ? (unclear).

Figure 3: Forest plot of coupled sensitivity and specificity for anti-MCV in the diagnosis of RA vs. DC.

The point estimate of sensitivity and specificity of each study is shown as a solid square on a line that represents the CI. The continuous vertical line represents the weighted average sensitivity and specificity and dotted vertical lines represent the CI.

the information on the disease control group was available, therefore, these two covariates were investigated by subgroup analysis. Clinical subgroups of different testing

methods of MCV with its cutoff value and disease duration were also analyzed, because of their clinical importance in RA diagnosis.

Seven studies [11, 16, 21, 24, 30, 31, 41] with a prospective study predesign were distributed into one subgroup. The results of this subgroup suggested that according to the forest plot, the combined sensitivity was 0.57 [0.46–0.68], the specificity was 0.90 [0.86–0.94] (see Supplementary material, Figure 2). Among those 25 studies, only Iwazskiewicz et al. [12] used the ACR/EULAR 2010 criteria as its diagnostic criteria for RA, while the rest adopted ACR 1987. Nineteen studies that used an enzyme-linked immunosorbent assay (ELISA) as its testing method for MCV, with the cutoff set to 20 U/mL were assigned to one subgroup. The subgroup of uniform cutoff demonstrated a combined sensitivity of 0.70 [0.62–0.77], specificity of 0.90 [0.85–0.93] according to the forest plot (see Supplementary material, Figure 3).

Overall, the subgroup of the prospective study predesign demonstrated the lowest heterogeneity for both sensitivity and specificity and compared with all the

Figure 4: SROC curve for anti-MCV in diagnosis of RA vs. DC.

Each circle represents a study and the asterisk represents the global estimate.

other results in the present review, the value of I^2 can be reduced by up to 10% for sensitivity, and 30% for specificity. The heterogeneity of the combined sensitivity among these two subgroups ranged from 81.56% to 93.69%, represented by I^2 ; the I^2 of specificity ranged from 57.47% to 89.92%, and Q test suggested $p=0.00$, except for the specificity of the prospective study predesign subgroup ($p=0.04$).

Comparison between MCV, CCP and RF

Among the 33 studies included for the present meta-analysis, the results of anti-CCP tests from the disease control group were not available for nine of them [11, 29, 31, 33–38]. The remaining 24 included studies [9–28, 30, 32, 39, 41, 42] which showed a combined sensitivity of 0.71 [0.64–0.77] and a specificity of 0.95 [0.94–0.97] (Figure 5)

for anti-CCP according to the forest plot. The SROC curve showed an AUC of 0.95 [0.92–0.96] (see Supplementary material, Figure 4). With regard to RF, among the 33 originally included studies, 17 [10–12, 14, 16, 22, 24, 27, 29, 31, 34–40] of which lacked information of RF tests from the disease controls, only about half of the studies could be used to perform the following analysis. The result demonstrated a combined sensitivity of 0.77 [0.68–0.84], a specificity of 0.73 [0.63–0.82] for RF and an AUC of 0.82 [0.78–0.85] according to SROC curve (see Supplementary material, Figures 5 and 6). However, the results revealed substantial heterogeneity among the studies for each diagnostic marker. The I^2 of sensitivity for CCP was 92.70 [90.67–94.74], and that of specificity was 79.93 [72.44–87.42]. A lower heterogeneity of 89.94 [86.13–93.75] was observed in sensitivity for RF, with I^2 of specificity being 93.37 [91.55–95.59]. The p-value for the Q test was 0.00 for all the four heterogeneity results mentioned here.

Figure 5: Forest plot of coupled sensitivity and specificity for anti-CCP in the diagnosis of RA vs. DC.

Forest plots (for sensitivity and specificity) and pooled estimates (95%CI) by using the I^2 test (quantified by p-value <0.01) were yielded to show heterogeneity between studies.

Combinations of markers in series and in parallel

Ten studies [13–15, 22–25, 37–40] were included to calculate the combined sensitivity of anti-MCV and anti-CCP when performed in parallel. The result suggested a sensitivity of 0.77 [0.72–0.82], with $I^2=80.1\%$ [64.1%–88.9%]. Eleven studies [13, 15, 22, 24, 25, 30, 35, 37–40] contained information on the performance of anti-MCV and anti-CCP in series and their combined sensitivity was 0.60 [0.54–0.67], with $I^2=84.7\%$ [74.8%–90.7%]. Nevertheless, no information on the control groups can be abstracted from almost all the studies, so the combined specificity was not available. Three studies [32, 36, 37] were incorporated to evaluate the serial tests for anti-MCV and RF, with the combined sensitivity of 0.64 [0.40–0.83], with $I^2=95.7\%$ [90.7%–98.0%]. All these calculations regarding the diagnostic values of combinations of the markers were done using random effects models, and all Q tests suggested $p<0.0001$.

Discussion

ACPAs play a crucial role in the differential diagnosis of patients with joint swelling and arthralgia, as well as prognosis evaluation and tailored therapy for RA [43]. As one of the members of the ACPA family, anti-Sa antibodies were first described in the serum of RA patients in 1994. Citrullinated forms of vimentin were recognized as the major antigen of Sa in 2004. MCV was discovered in 2007 to determine the existence of additional vimentin modifications or different isoforms of vimentin in order to improve the diagnostic efficiency of RA [4, 5, 44]. Recently, anti-MCV IgG isotype autoantibodies have been quantitatively measured by ELISA assay mostly for the diagnosis of RA, showing high sensitivity and specificity [44, 45]. It is known that the citrulline-driven immunological response is specifically associated with RA. The formation of autoantibodies against citrullinated vimentin interacts with the osteoclast lineage, thus promoting bone loss and leading to joint destruction [46, 47]. Here, we perform a meta-analysis to identify the diagnostic value of anti-MCV for RA again, in order to compensate for unsolved limitations.

According to the already published reviews, the sensitivity of anti-MCV was reported as 0.69–0.77 with the specificity against either healthy controls or disease controls to be from 0.89 to 0.94, and an AUC of 0.88 was observed against healthy controls in one meta-analysis, which was consistent with our meta-analysis. In consideration that healthy controls may not be the comparator group

in a clinic setting, in the present review we restricted the studies by RA diagnosis vs. disease control group only, and according to the AUCs, we revealed that anti-CCP performed the best diagnostic value, followed by anti-MCV and RF.

Individual markers were combined in parallel and in series to improve sensitivities and specificities in this review, and it is the common practice in clinical diagnosis. In total, there were four different kinds of combinations in parallel and four in series in the combinations of anti-MCV, anti-CCP and RF. Unfortunately, due to the lack of studies containing information about combined test characteristics, no AUCs can be used to infer a best combination of markers for RA diagnosis.

The heterogeneity of both sensitivity and specificity in studies of RA diagnosis against a disease control group remained high across all three diagnostic markers. Among the studies included in this review, ELISA, with the kit produced by Orgentec Diagnostika GmbH (Germany), recommended the cutoff value at 20 U/mL; while the POCT LFIA device and other immunological assays were also used, with cutoff set at different values. ELISAs were mainly used to detect anti-CCP2 IgG, however, either the second or the third generation anti-CCP ELISA was popularly used among the studies, causing variable cutoff values ranging between 5 and 25 U/mL. Nephelometry was a popular method to test RF, followed by ELISA which was less popular. Although sometimes the positivity of IgG, IgA and IgM RF were all available, IgM RF was chosen to represent the diagnostic value of RF because of its greater universality; cutoffs of which ranges from 6 to 30 U/mL. Therefore, the high heterogeneity can be partially explained by different kinds of specific testing methods and reagents, as well as the different cutoffs set by individual researchers, which varied in different laboratories or institutions and across time. In addition, certain baseline clinical characteristics of RA patients may probably contribute to the heterogeneity, such as baseline inflammation indicators, including the erythrocyte sedimentation rate and C-reactive protein, DAS28, the general assessment score of RA, current anti-rheumatic therapy, including the usage and dosage of DMARDs and corticosteroids, radiography evaluation, like the Larsen score, and so on. However, this information could only be extracted from a limited small number of studies.

One of the main prognostic factors for RA is bone erosion, which results in the severe outcome of destructive and deforming arthritis. However, only six [12, 15, 27, 30, 31, 37] of the included studies in the present review discussed the relation of anti-MCV with radiographic

progression, either quantitatively or qualitatively, so unfortunately we were unable to extract data to perform a meta-analysis. More severe radiographic progression, specified by the changes in the Larsen score compared to the baseline, was observed in anti-MCV positive patients than in anti-MCV negative patients in the subgroup of early RA patients [30, 37]. Although no significant correlation of anti-MCV with the Larsen score or the number of erosions of joints on ultrasonography in patients with established RA was observed in the studies included here, the anti-MCV titer was suggested as a marker of disease activity [12, 15, 27, 31]. Long-term prospective randomized controlled trials are needed to determine the predictive value of baseline anti-MCV for RA progression.

To date, there are two authoritative criteria for the diagnosis of RA: the 2010 ACR/EULAR criteria aimed at classifying early RA and demonstrating higher sensitivity but lower specificity, especially in patients aged over 60 years old compared to the 1987 ACR criteria, while the latter was considered to predict a more erosive disease [14]. However, existing data suggested that not fulfilling the 2010 ACR/EULAR criteria does not rule out RA diagnosis, for example, those seronegative for RF or anti-CCP RA patients with less than 10 involved joints [48]. RF is the only biomarker in the ACR 1987 criteria, while the ACR/EULAR 2010 criteria use both RF and ACPA, which is typically tested as anti-CCP antibodies [5, 49, 50]. Neither of these two criteria mentioned anti-MCV as a new valid diagnostic marker. Additionally, anti-carbamylated protein (anti-CarP) IgA antibodies were observed as another distinct autoantibody in the sera of RA patients in 2011, and is regarded as a promising biomarker for detecting early RA and very early RA [43, 51]. A sensitivity of 42% and an overall specificity of 89% of antiCarP antibodies for RA were reported, and the correlation between antiCarP antibodies and disease activity is still debated [43, 52, 53]. Nevertheless, no study included in this meta-analysis mentioned the performance of anti-CarP in the diagnosis for RA.

The early identification of RA is a great challenge, as the prognosis would be significantly improved with early diagnosis and intervention of RA. It is implied that anti-MCV may behave a bit differently in the diagnosis of early RA compared with established RA [4]. Meanwhile, interpreting diagnostic values of the combined markers might be the solution for detecting serum negative RA, but a tradeoff exists between sensitivity and specificity. Therefore, more diagnostic trials of the combined performance of anti-MCV and anti-CCP for RA diagnosis and prognosis, especially the combined specificity, as well as

its application in the diagnosis of early RA compared with established RA, are required.

In summary, anti-MCV demonstrates a comparable diagnostic value to anti-CCP and RF, therefore is suggested as an alternative biomarker for RA classification in clinical practice, and may be written into the next authoritative criteria.

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