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ORIGINAL ARTICLE

Diagnostic accuracy of anti-keratin antibody for rheumatoid arthritis: a meta-analysis

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Abstract

Objectives Anti-keratin antibody (AKA) is a serum antibody for patients with rheumatoid arthritis (RA), and it has a high specificity. Diagnostic role of AKA in RA was evaluated in this study.

Methods PubMed, EMBASE, and Web of Science were searched to acquire eligible studies. Articles published before 15 March 2018 were considered to be included. Quality Assessment of Diagnostic Accuracy Studies 2 was used to evaluate the risk of bias and application concern of the included articles. Pooled analysis of diagnostic indicators of AKA for RA was conducted by using a random effects model. Subgroup analysis was employed to explore the potential influencing factors. RevMan 5.3, Stata 11.0, and Meta-DiSc 1.4 software were used in this study.

Results A total of 15 studies (2350 positive and 2067 negative participants) were included. The pooled sensitivity was 0.46 (95% *CI* 0.44–0.48), pooled specificity was 0.94 (95% *CI* 0.93–0.95), and pooled diagnostic odds ratio was 15.86 (95% *CI* 9.48–26.52). In addition, the area under the curve was 0.7194.

Conclusions The current evidence indicated that AKA has high diagnostic specificity in RA and may be useful for RA diagnostic application in clinic.

Keywords Anti-keratin antibody (AKA) · Diagnostic · Meta-analysis · Rheumatoid arthritis (RA)

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which causes cartilage and bone damage as well as disability and loss of function [1, 2]. RA is one of the most prevalent diseases with an incidence of 0.5 to 1% [3]. It mainly causes joint damage, as well as the external clinical manifestation such as rheumatoid nodules and systemic comorbidities [1]. The prevalence of depression, anxiety disorder, and bipolar disorder of RA patients was on the rise, as compared with those of healthy population [4]. In addition, interstitial lung disease [5] and cardiovascular disease are also common complications in RA patients. The incidence of functional disability is rising along with the progress of the disease [6]. RA has caused a great burden on individuals and society because of long-term medical costs, functional disability, decreased ability to work, and social participation [7, 8]. In the early-stage disease, patients with RA who were treated with early remission induction therapy retain normal function, and they almost had no clinically relevant joint injuries. And the sooner the patient relieved, the better the clinical outcome will be turned out [9]. In order to reduce the burden of disease in RA patients and obtain a better prognosis, early diagnosis of RA is crucial. Nowadays, rheumatic factors (RF) [10] and anti-cyclopanine antibody (anti-CCP) [11] have been used as markers for early diagnosis of RA. In the 1987 American College of Rheumatology (ACR)

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diagnostic criteria [12] and 2010 American College of rheumatology/European League Against rheumatism (ACR/EULAR) classification criteria, RF is recommended as a good marker for the diagnosis of RA [13]. However, RF is not a specific antibody unique to RA. In lupus [14], Sjogren's syndrome [15], systemic sclerosis [16], and hepatitis C virus get–related arthropathy (HCVrA) [17], these disease positive rates are not low as expected. A systematic review showed that the sensitivity of RF for early diagnosis was from 77 to 80%, and the specificity was between 33 and 77% in 1987 diagnostic ACR criteria [18]. Anti-CCP antibody is an early diagnostic indicator not only for RA, but also for severe joint bone destruction [19, 20]. RF and anti-CCP are inadequate in the early diagnosis of RA, because these two antibodies are not sensitive enough to detect in a large proportion of early RA patients [10, 21]. Therefore, a higher unique laboratory test is needed in the early diagnosis of RA. In 1979, Young et al. found that there was an antibody in RA serum, which could react with rat esophageal cuticle. And this antibody was specific to RA. They finally named it anti-keratin antibody (AKA) [22]. In previous studies, it was found that a specificity of AKA was from 79 to 100% in the diagnosis of RA [23, 24], whereas its sensitivity ranged from 20 to 80% [25, 26]. Therefore, in order to determine whether AKA can be used as an auxiliary diagnostic serum marker for RA, we carried out this meta-analysis.

Methods

Search strategy

A systematic literature search on PubMed, EMBASE, and Web of Science was conducted to obtain the relevant articles. All articles published before 15 March 2018 should be considered to be included in this meta-analysis. The following search terms were used: anti-keratin antibody, AKA, rheumatoid arthritis, and RA. At the same time, all the references in the retrieved literatures were manually reviewed to identify other potential relevant articles.

Inclusion criteria

(1) Diagnosis of RA conforms to 1987 ACR criteria was regarded as the diagnostic gold standard.
(2) Diagnosis of RA and serum AKA concentration were collected as outcomes. Contents of the article include AKA and a diagnosis of RA.
(3) All articles reporting either sensitivity or specificity of AKA test in RA or reporting data allowing calculation of sensitivity or specificity against the "gold standard" were included.
(4) Samples in articles were restricted to human participants.
(5) Only sample size more than 50 was included.

Exclusion criteria

(1) Animal experiments.
(2) Sample size less than 50.
(3) 1958 ACR criteria, 1982 ACR criteria, or 2010 ACR/EULAR criteria as diagnostic gold standard.
(4) Beside the point.

Date extraction and quality assessment

The data were extracted by two investigators (Xue-Ping Wang and Qian-Yao Cheng) independently. When a disagreement arising, the third investigator (Ming-Ming Gu) was consulted to confirm the extracted data. First author, year of publication, ethnic, serum dilution state, sample size, sex ratio, mean age, and control participants' information were collected from each included study. Also, true-positive (TP) results, true-negative (TN) results, false-positive (FP) results, and false-negative (FN) results were extracted from each study.

Quality of each study was assessed by two investigators (Rui-Xue Leng and Yin-Guang Fan) independently using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, which is specially developed to evaluate the quality of diagnostic test. When disagreement happening, the third investigator (Bao-Zhu Li) solved it. Four main domains indicated a set of signal questions were contained in QUADAS-2. It helps researchers reach the judgments regarding bias and applicability. Answering to each question should be "yes," "no," or "unclear."

Statistical analysis

RevMan 5.3 was used to evaluate the relevant studies' quality, and Stata 11.0 was applied to evaluate the publication bias. Summary receiver operating characteristic (SROC) curve was drawn out via Meta-DiSc 1.4 software. 0.5 was added to each number for the value of 0 in Table 1 in this meta-analysis. TP, FP, FN, and TN were used to calculate the sensitivity and specificity. A random effects model was produced to obtain combine sensitivity, specificity, diagnostic odds ratio (DOR), and positive/negative likelihood (LR+/LR−). Besides, SROC was constructed to testify the summarized diagnostic rate. Cochran's Q test and inconsistency index (I^2) were used to evaluate statistical heterogeneity between eligible studies. I^2 greater than 75% suggest that there is substantial heterogeneity between studies [40]. Subgroup analysis was carried out to assess the source of potential heterogeneity. Deeks' funnel plot asymmetry test was used to evaluate the potential publication bias. The P value less than 0.05 can be considered significant difference.

Table 1 Characteristics of included studies in this meta-analysis

First author	Time	Ethnic	Detection method	Patient (control)	Sex ratio	Mean age	Age range	Disease duration (years)	Control participants
Cordonnier [24]	1996	European	IFF (1:10)	49 (20)	3.06	50.0	18–82	0.50	Other rheumatic diseases (20)
Vincent [27]	1999	European	IFF (1:10)	279 (213)	3.00	68.0	25–94	NA	Other rheumatic diseases (213)
Goldbach-Mansky [28]	2000	European	IFF (NA)	106 (132)	1.86	46.0	NA	NA	Other rheumatic diseases (132)
Vasiliauskiene [29]	2001	European	IFF (1:20)	96 (127)	6.38	55.0	18–76	7.80	Other rheumatic diseases (90), healthy control (37)
Bas [30]	2002	European	IFF (NA)	179 (50)	3.00	62.0	NA	NA	Other rheumatic diseases (50)
Saraux [31]	2002	European	IFF (1:10)	98 (172)	2.14	49.5	NA	< 1.00	Other rheumatic diseases (172)
Saraux [32]	2003	European	IFF (1:10)	86 (157)	2.00	49.4	19–86	< 1.00	Other rheumatic diseases (157)
Dubucquoi [33]	2004	European	IFF (1:5)	140 (131)	NA	NA	NA	< 2.00	Other rheumatic diseases (98), healthy control (33)
Grootenboer-Mignot [34]	2004	European	IFF (NA)	265(91)	NA	NA	NA	NA	Other rheumatic diseases (91)
Vittecoq [35]	2004	European	IFF (1:10)	176 (138)	2.17	51.7	19–84	0.35	Other rheumatic diseases (138)
Kamali [36]	2005	Asian	IFF (NA)	46 (94)	4.30	53.0	27–83	13.42	Other rheumatic diseases (54), healthy control (40)
Lutteri [37]	2007	European	IFF (1:5)	120 (170)	2.43	56.0	20–79	NA	Other rheumatic diseases (71)
Zhao [38]	2010	Asian	IFF (NA)	304 (247)	3.54	57.2	NA	8.90	Other rheumatic diseases (247)
Zhu [39]	2013	Asian	IFF (1:10)	56 (62)	2.29	45.0	19–71	5.50	Other rheumatic diseases (42), healthy control (20)
Sun [23]	2016	Asian	IFF (1:10)	350 (198)	3.28	49.2	NA	9.34	Other rheumatic diseases (98) healthy control (100)

Sex ratio, female/male; *IFF*, indirect immunofluorescence assay

Results

A total of 445 records were identified on PubMed, EMBASE, and Web of Science database, of which 240 were excluded on account of duplicate records. Following thorough examination, we excluded 140 of those 205 studies due to no relevant to topic or animal experiments. Only 65 articles were remained for assessing full-length paper. Of these articles, 16 were failed to obtain full articles, 22 were lack of complete basic data, 2 were letter, 1 was system review, and 9 did not meet the 1987 ACR criteria. Finally, 15 studies (2350 positive and 2067 negative units) met the inclusion criteria and were included in this meta-analysis. The study selection is shown on a flow diagram (Fig. 1).

Studies' characteristics

The main features of the 15 included articles were summed up in Table 1. The year of publication ranged from 1996 to 2016. Among the 15 studies, only 4 were Asian population, and others were European population. The number of participants varied from 69 to 551. The mean age ranged from 45.0 to 68.0 years, and the female-to-male ratio in the included articles was from 1.86 to 6.38. In all studies, indirect immunofluorescence (IIF) methods were used to detect AKA, and the serum dilution ratio varied from 1:5 to 1:20, of which about 46.7% was 1:10. Additionally, the control groups were divided into three subgroups according to their different characteristics. Among these studies, other non-RA rheumatic diseases were used as controls in the ten studies, while both healthy people and other non-RA rheumatic diseases were used as controls in another five studies (Table 1).

Study quality

The risks of bias and application concerns about reference standard in all included studies were low. The index test had almost 50% unclear risk of bias and application, while the rest was low. About the domain of flow and timing in QUADAS-2, only a small fraction had unclear risk of bias. Patient's selection in our meta-analysis had high, unclear, and low risk of bias and application concerns, respectively (Supplementary 1).

Diagnostic accuracy of AKA

First, sensitivity, specificity, LR+, LR−, and DOR were counted to assess the diagnostic value for AKA of RA. Since the I^2 of sensitivity and specificity was 90.2% and 85.9%, random effects model was applied to conclude the effective size. Then, the relevant pooled diagnostic values of AKA were calculated. The pooled sensitivity and specificity were 0.46 (95% *CI* 0.44–0.48) and 0.94 (95% *CI* 0.93–0.95), respectively. The

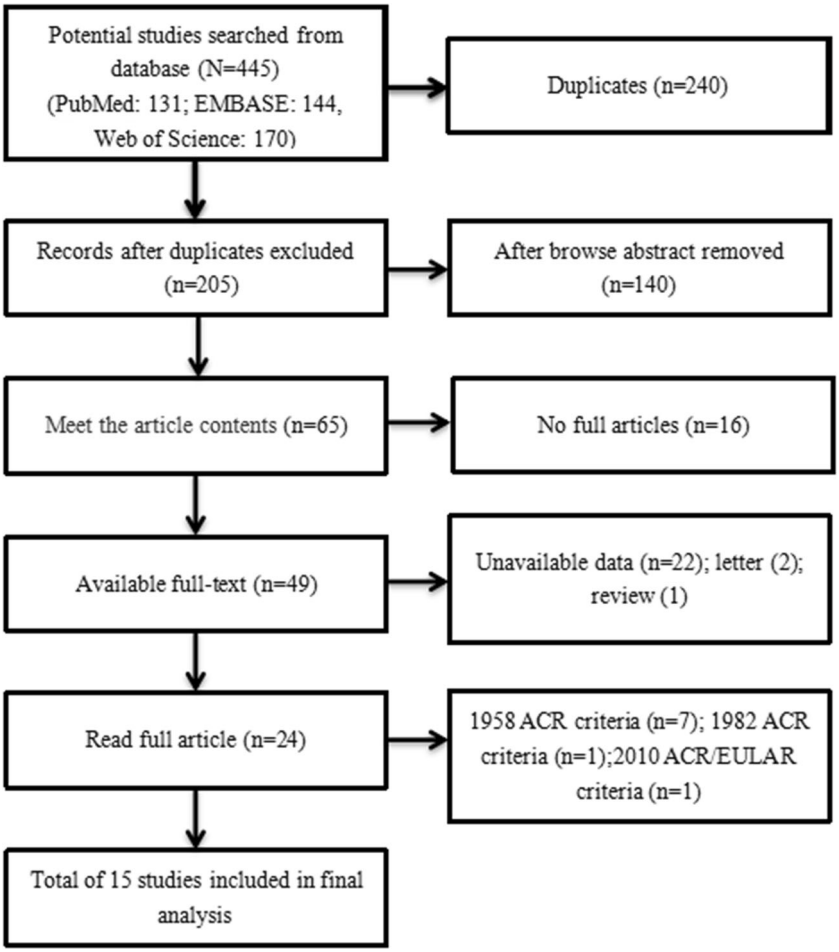

Fig. 1 Flow diagram for studies retrieved

pooled LR+ and LR− were 9.13 (95% *CI* 5.52–15.11) and 0.58 (95% *CI* 0.52–0.65) (Tables 2 and 3). In this study, the pooled DOR was 15.86 (95% *CI* 9.48–26.52), area under the curve (AUC) was 0.7194, and the *Q* value was 0.6684 (Fig. 2).

Heterogeneity test

The heterogeneity of diagnostic test included threshold effect and non-threshold effect. The most important source of heterogeneity due to different sensitivities and specificities of included studies caused by different cutoffs and threshold effect [41]. This analysis of diagnostic threshold showed that logarithmic Spearman's correlation coefficient value of sensitivity (1-specificity) was 0.147, with a *P* value of 0.602. This result indicated that this meta-analysis did not exist a threshold effect.

Sensitivity analysis

We conducted sensitivity analysis by deleting the included study one by one to detect the consistency of the remaining study effect. The same statistic values were recalculated after removing studies. In this meta-analysis, only when the study wrote by Sun et al. removed [23], I^2 value of sensitivity goes down from 90.2 to 79.9%, and I^2 value of specificity goes down from 85.9 to 70.4% (Supplementary 2).

Subgroup analysis

Subgroup analysis was conducted to explore the heterogeneity caused by the non-threshold effect in this meta-analysis. We carried out subgroup analysis based on the quality of the literature, ethnic, disease duration, serum dilution ratio, and the type of controlling factors. Among subgroup analyses, studies were excluded because relevant data were not available. We removed Sun's study in subgroup analysis to avoid its influence on total effect (Supplementary 3). These results implied that ethnic and the quality of studies may be the causes of high heterogeneity.

Publication bias

A linear regression method was used to test the inadequacy of funnel plot and evaluate publication bias. If the value of regression coefficient was not equal to 0, we concluded that no

Table 2 Characteristics of included studies about the AKA antibody in this meta-analysis

First author	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PLR	NLR	DOR
Cordonnier [24]	18	0	31	20	36.7	100.0	15.54	0.65	24.08
Vincent [27]	144	7	135	206	51.6	96.7	15.71	0.50	31.39
Goldbach-Mansky [28]	27	21	79	111	25.5	84.1	1.60	0.88	1.81
Vasiliauskiene [29]	42	4	54	123	43.8	96.9	13.89	0.58	23.92
Bas [30]	82	3	97	47	45.8	94.0	7.64	0.58	13.24
Saraux [31]	46	10	52	162	46.9	94.2	8.07	0.56	14.33
Saraux [32]	40	9	46	148	46.5	94.3	8.11	0.57	14.30
Dubucquoi [33]	68	8	72	123	48.6	93.9	7.95	0.55	14.52
Grootenboer-Mignot [34]	106	5	159	86	40.0	94.5	7.28	0.64	11.47
Vittecoq [35]	40	4	136	134	22.7	97.1	7.84	0.80	9.85
Kamali [36]	27	1	19	93	58.7	98.9	55.17	0.42	132.16
Lutteri [37]	54	4	66	166	45.0	97.6	19.13	0.56	33.96
Zhao [38]	132	4	172	243	43.4	98.4	26.81	0.58	46.62
Zhu [39]	27	1	29	41	48.2	97.6	20.25	0.53	38.17
Sun [23]	238	41	112	157	68.0	79.3	3.28	0.40	8.14

TP, true positive; *FP*, false positive; *FN*, false negative; *TN*, true negative; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio; *NA*, not available

publication bias existed. Besides, *P* value of Deeks' funnel plot asymmetry test of the included 15 studies was 0.93 indicating that no potential publication bias existed in this study (Fig. 3).

Discussion

RA is a chronic inflammatory autoimmune disease. Irreversible synovial joint damages, synovitis, acute phase synovial swelling and oozy, articular cartilage lesions, and joint deformity are characteristic of RA [6]. Early diagnosis of RA and appropriate intervention are critical to the prognosis of the disease [42]. The main purpose of this study is to summarize the published articles and to provide the latest data and comprehensive information for AKA on the diagnostic value of RA. Results of this meta-analysis showed that AKA was a considerable serum diagnostic marker of RA.

In this study, the pooled value of sensitivity was 0.46 (0.44–0.48), which indicated the antibody had a moderate sensitivity but less than anti-CCP antibody [11]. It has reported that AKA had a higher specificity in RA patients with negative anti-perinuclear factor [35]. A PLR of 9.13 implied that the positive rate of AKA in RA patients was 9.13 times than in non-RA patients, which demonstrated a potential role for AKA confirming RA. The current study showed that the summarized pooled DOR was 15.86, and this result indicated that AKA antibody has high diagnostic accuracy for RA. SROC and the AUC were two other ways to comprehensively evaluate the accuracy of screening test. To demonstrate

Table 3 Summary receiver operating characteristic (SROC) curve of all included studies for the diagnosis of RA through AKA antibody

Parameter	Result	95% *CI*	Heterogeneity chi-squared	*P* value
Pooled sensitivity	0.46	0.44–0.48	142.42	< 0.001
Pooled specificity	0.94	0.93–0.95	99.33	< 0.001
Pooled LR+	9.13	5.52–15.11	84.45	< 0.001
Pooled LR−	0.58	0.52–0.65	124.97	< 0.001
Pooled DOR	15.86	9.48–26.52	64.32	< 0.001
Spearman's correlation coefficient	0.147			0.602
SROC				
AUC	0.7194			
Q*	0.6684			

(LR+/LR-): positive/negative likelihood; DOR: diagnostic odds ratio; AUC: area under the SROC curve; Q*: Q index.

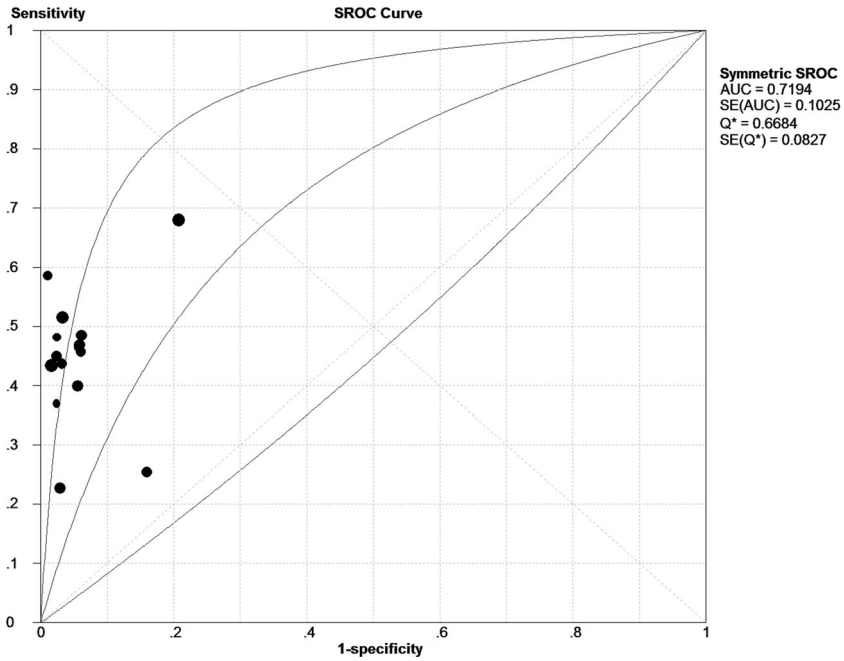

Fig. 2 Summary receiver operating characteristic (SROC) curve for the diagnostic for RA through AKA in the included studies

excellent accuracy, the value of AUC should be more than 0.97, and AUC of 0.75–0.92 is considered to be good [43]. AUC value was 0.7194 in this study implied that AKA had a moderate diagnostic accuracy, and it was higher than in previous study [25].

Our study further evaluated the potential sources of inconsistency among included studies in our meta-analysis. On the whole, the stability of the study was high. Only when the author excluded the literature of Sun, the sensitivity (43%) and specificity (96%) of the remaining literature changed significantly, and meantime, AUC decreased to 0.5337. The literature with higher sensitivity and lower specificity compared with other studies, so the overall sensitivity of the remaining studies decreased and the specificity increased after eliminating the study. This heterogeneity may result from different designs among the studies, such as the duration of RA. In

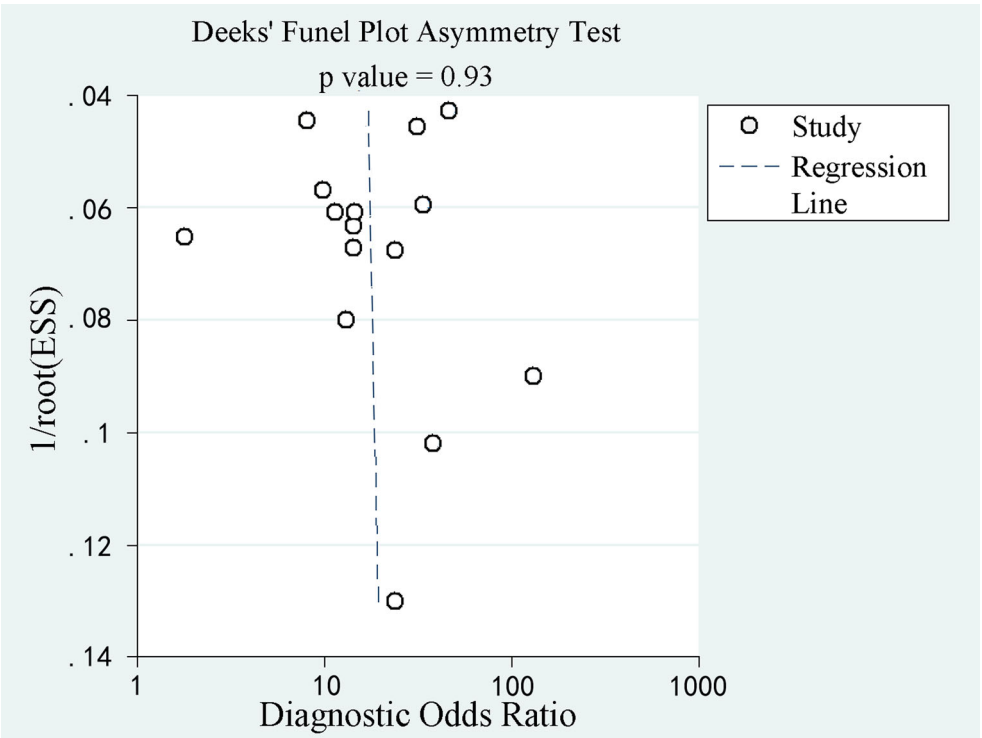

Fig. 3 Funnel plots for detecting publications in this meta-analysis

the study, the average disease in RA patients was 9.34 years, and this result was different from other studies. In RA patients with a disease duration longer than 2 years and shorter than 2 years, the positive rates of AKA were 33.8% and 61.3%, respectively [33]. However, a paradoxical result showed that the positive rate of AKA antibody in early RA (shorter than 1 year) was greater than that of the long-standing RA [34]. In this meta-analysis, when the duration was more than 2 years, the diagnostic accuracy was increased with DOR. Results of two subgroups indicated that there may be a link between the disease duration of RA and heterogeneity. Further studies are needed to expound the hypothesis. In addition, Sun's study recruited 548 subjects, and the larger study sample may be another factor affecting the stability of the summary results.

The diagnostic value of AKA in RA patients is different among ethnics. In European group, the pooled sensitivity decreased (0.42 (0.39–0.44)), while pooled specificity had no apparent change (0.95 (0.93–0.96)). However, in Asian population, both the sensitivity (0.46 (0.41–0.51)) and specificity increased (0.98 (0.97–0.99)). Study has reported that there was a relationship between AKA and disease activity [29]. The racial and ethnic disparities in RA patients showed not only the different disease activities, but also the clinical outcomes and joint function [44, 45]. These differences may be the reason for the different diagnostic accuracies of related antibodies in different races. In a meta-analysis, a difference of the diagnostic accuracy of anti-CCP antibody also existed among European and Asian population [11]. After grouping, heterogeneity of the two groups decreased, and the Asian group even dropped to 0 after grouping. Q statistic test performance was low, and in the case of fewer studies, false-negative situation is sometimes presented. In order to increase the test efficiency, we raised the inspection level to 0.1. Overall, these results suggested that different races may be a source of heterogeneity.

Literature quality assessment is an important method to investigate the heterogeneity of methodology. The differences of methodology (such as participants, research design type, and the selection of gold standard) will bring the heterogeneity. In the included studies, 11 were case-control studies, and another 4 were cohort studies. Most of the participants were clearly diagnosed, which may lead to higher diagnostic evaluation. According to the risk of bias and application concern, the included articles were split into three groups. In two red sign group, the pooled sensitivity and specificity were 0.51 (0.46–0.55) and 0.97 (0.96–0.99). DOR increased (36.46 (19.93–66.70)) compared to the whole study. The risk bias and application of patient selection increased diagnostic value. The heterogeneity reduced significantly in subgroups, even to 0. Above all, we can conclude that the quality of the studies may be another source of heterogeneity. All of the 15 studies were detected by IFF, and the serum dilution was 1:5, 1:10, and 1:20. Higher dilution ratio of serum indicated the higher specificity of screening test. Different threshold values of AKA antibodies may affect the diagnostic accuracy of RA. Correlation analysis suggested that no threshold effect existed in this current study ($r_s = 0.147$, $P = 0.602$). In other rheumatic disease group, the diagnostic value of sensitivity decreased to 0.41 (0.39–0.44), and AUC reduced to 0.5654. Compared with the total effect, the sensitivity of mixed groups increased to 0.49 (0.43–0.54), and AUC decreased to 0.4506. After grouping, the heterogeneity of the mixed groups was significantly decreased. This result indicated that the number of articles is reduced which may be the reason of heterogeneity change.

This article had some advantages. To our knowledge, this meta-analysis was the first comprehensive study to summarize the diagnostic accuracy of AKA in RA patients and obtained relatively stable and reliable results. The gold standard of the included studies was applicable, and the risk of bias about patient flow and time effect was low. Besides, no publication bias was presented in this article. Although we try our best to reduce bias, some limits still existed in this meta-analysis. First, we retrieved articles which meet our predetermined requirements from multiple databases, but some of the literature may still be missing. Second, the included studies were mostly case-control designs, and the results of AKA detection from the case group and the control group were not obtained through follow-up study. This may have a certain effect on the quality of the articles. Third, a large heterogeneity in this meta-analysis existed, so the random effects model and subgroup analysis were adopted to control the size of heterogeneity. Finally, the number of included studies in this meta-analysis did not meet meta-regression requirement, and no meta-regression was conducted to explore possible heterogeneity sources.

In conclusion, this meta-analysis showed that AKA had considerably high specificity when diagnosing RA. It can be applied to the clinical practice of early diagnosis of RA. Considering that the shortcomings of this literature, relevant prospective experiments still need to be carried out.

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Compliance with ethical standards

Disclosures None.

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