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Diagnostic significance of circulating miRNAs in Kawasaki disease in China
Current evidence based on a meta-analysis

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Abstract

Background: There is no golden standard for the diagnosis of Kawasaki disease (KD), the most common cause of acquired heart disease in children in many countries. In recent years, many studies have focused on the relationship between microRNAs (miRNAs) and KD. Thus, we perform this meta-analysis to understand the role of circulating miRNAs as a biomarker to detect KD.

Methods: We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure through March 10, 2019. Meta-disc 1.4 and STATA 15.1 (Stata Corporation, College Station, TX) were used to conduct the meta-analysis.

Results: Six eligible articles were included in this meta-analysis. The overall performance of total mixed miRNAs detection was: pooled sensitivity, 0.7 (95% confidence interval, 0.66–0.74); pooled specificity, 0.87 (95% confidence interval, 0.83–0.90); and area under the summary receiver operating characteristic curves value (SROC), 0.8302. The meta-regression analysis indicated that the specimen types, the composition of the control group, and types of the reference miRNA were not responsible for the existing heterogeneities. The subgroup analysis showed that SROC of the plasma group (0.8890) was more significant than the serum group (0.7204), and SROC of the non-healthy control group (0.9622) was more significant than the healthy control group (0.8096).

Conclusions: This is the first meta-analysis show that miRNAs may be used as novel biomarkers for detecting KD, especially for distinguishing KD from other febrile diseases. More studies are needed in the future to clarify the association between KD and miRNAs.

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Abbreviations: AUC = area under the curve, DOR = diagnostic odds ratio, HC = healthy controls, KD = Kawasaki disease, miRNAs = microRNAs, NT-proBNP = nitrogen-terminal B-type natriuretic peptide, SROC = summary receiver operating characteristic curves value, TmiRs = total mixed miRNAs.

Keywords: biomarker, diagnosis, Kawasaki disease, meta-analysis, microRNA

1. Introduction

Kawasaki disease (KD) is an unknown cause of self-limited febrile vasculitis, which mainly affects children under 5 years old.[1] KD is the most common cause of acquired heart disease in children in many countries.[2–4] The major etiology of KD is unknown. Timely initial treatment with intravenous immunoglobulin reduced the incidence of coronary artery lesions from 25% to less than 5%.[5] Delayed diagnosis is associated with increased coronary artery lesions.[6] In clinical practice, the diagnosis of KD is mainly based on the American Heart Association[1] or Japanese Cardiology Society Joint Working Group criteria[7]; both made according to the clinical manifestations and laboratory tests. Laboratory tests, such as C reactive protein, erythrocyte sedimentation rate, and nitrogen-terminal B-type natriuretic peptide (NT-proBNP) have although been proved to be important in the diagnosis of KD, but none of them can accurately diagnose KD.[8,9] There is still a lack of specific laboratory indicators for the diagnosis of KD. Therefore, the search for new and reliable circulating biomarkers is of great significance for the early diagnosis of KD.

MicroRNAs (miRNAs) are a subset of intra hereditarily initiated single-stranded noncoding RNAs that participate in inhibiting protein translation or degradation of polypeptides by binding to the untranslated regions of mRNA.[10] Previous

studies have demonstrated that circulating miRNAs can be considered as potential biomarkers for detecting various diseases, including cancer, cardiovascular disease, and autoimmune diseases.[11–14] Besides, many studies have focused on the association between the miRNAs and the risk of KD, indicating that miRNAs might be potential and reliable biomarkers for diagnosing KD.[15,16] However, the results were inconsistent. Therefore, we performed this meta-analysis to assess the diagnostic accuracy of miRNAs for KD.

2. Materials and methods

2.1. Study protocol

This analysis was performed following a predetermined protocol by the recommendations of Deeks.[17] Data collection and reporting were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[18] As it is systematic literature research, there is no need for ethical approval. The protocol for this analysis was registered with PROSPERO (CRD42019129976).

2.2. Search strategy

We searched multiple databases, including PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure through March 10, 2019 to identify the relevant studies. Keyword search terms were ("mucocutaneous lymph node syndrome" or "Kawasaki disease" or "Kawasaki syndrome") and ("MicroRNAs" or "MicroRNA" or "miRNAs" OR "miRNA").

2.3. Study selection

The title and abstract of the article were preliminarily selected through system retrieval. Then, potentially relevant studies were searched by full text and evaluated for inclusion and exclusion criteria.

The criteria for inclusion were

(1) all KD subjects were confirmed by KD diagnosis criteria;
(2) randomized controlled or non-randomized controlled, clinical trials, cohort studies to evaluate miRNAs expression;
(3) data including true positive, false positive, false negative, and true negative can be calculated, such as data of the receiver operating characteristic (ROC) curve and essential sample size;
(4) all studies had non-KD subjects as the control group, either healthy or febrile controls;
(5) the expression of miRNAs detection methods must be conventional, such as miRNA sequence, real-time polymerase chain reaction (RT-PCR), and quantitative real-time polymerase chain reaction (qRT-PCR); and all specimens were obtained during the acute phase of KD before treatment.

The criteria for exclusion were

(1) conferences articles, reviews, letters, editorials, abstracts, expert opinions, or case reports without controls;
(2) no complete data to form a 2×2 table; and
(3) duplicated reports.

2.4. Data collection and assessment of research quality

Two researchers (Gang Wu, Peng Yue) independently assessed studies eligibility by title or abstract, and a third reviewer (Xiaolan Zheng) determining the divergences based on inclusion or exclusion criteria and reports quality. Quality assessment of all selected studies was conducted independently by 2 researchers (Fan Ma, Yi Zhang) following 14-item quality assessment of diagnostic accuracy studies list,[19] and any disagreement was resolved through discussion. All assessments were reported in descriptive forms, as a well-conducted study might score poorly once relevant parts of the methodology and results are missing.

2.5. Evaluation indicators

We measured the following indicators for different types of miRNAs: sensitivity, specificity, diagnostic odds ratio (DOR), area under the summary receiver operating characteristic curves value (SROC). The proportion of KD patients with positive miRNAs expression represented sensitivity. Besides, the proportion of non-KD cases correctly identified with negative miRNAs expression represented specificity. Furthermore, DOR more reliably defined a summary of test performance rather than combine sensitivity and specificity of individual studies. Meanwhile, DOR was an independent index in a range from 0 to infinity. The higher the DOR, the better the test discrimination ability.[20] SROC was plotted according to sensitivity and specificity. In addition, the area under the curve (AUC) value was a global measure of test performance, and the closer the AUC was to 1, the better the test performance.[21]

2.6. Publication bias

We used STATA version 15.1 (Stata Corporation, College Station, TX) statistical software to quantify all publication bias using Deeks' test. Asymmetric distribution of data points in Deeks' test plot, quantified $P < .05$, indicating potential publication bias.[22]

2.7. Heterogeneity and meta-regression

Heterogeneity of pooling sensitivity and specificity was examined by the X^2 test. We used the Cochran Q test to examine the heterogeneity of pool DOR. Heterogeneity was statistically significant when $P < .05$. We also performed the I^2 test to quantitatively estimate the proportion of total variation across reports in every summary analysis. I^2 value ranging from 0 to 100%, with values of 25, 50, and 75%, respectively, were considered as evidence of low, moderate, and high heterogeneity.[23] A curvilinear shape in the SROCs indicated a threshold effect. We conducted meta-regression analysis to identify potential factors that might contribute to heterogeneity. All the possible factors extracted from baseline measurements and original testing procedures were considered for the meta-regression. The meta-regression could determine the correlation between potential factors and existing heterogeneity. When significant differences were discovered, the factor should have a significant impact on the homogeneity of the included studies with a P value $< .05$.

2.8. Sensitivity analysis

Sensitivity analysis of included studies was performed using STATA version 15.1 to determine the impact of individual trials on the results. Meta-disc 1.4 (Ramón y Cajal Hospital, Madrid, Spain) was used to detect the threshold effects in the study.[24]
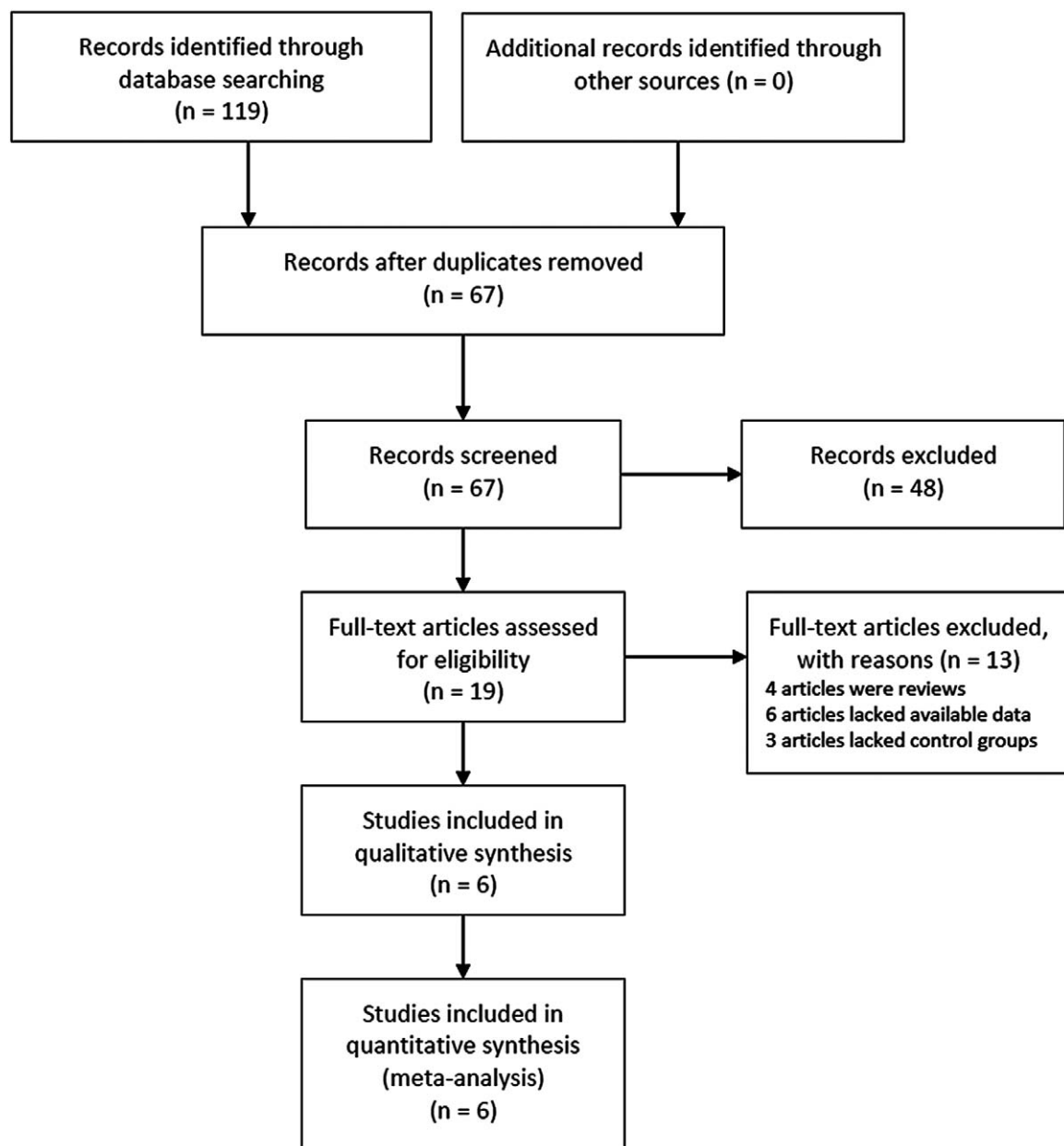
Figure 1. Flow chart of the study selection process.

2.9. Statistical analysis

Meta-disc 1.4 (Ramón y Cajal Hospital, Madrid, Spain) was utilized for data analysis. Besides, publication bias analysis was conducted by STATA Version 15.1. Homogeneous results were statistically analyzed by fixed effects model, while heterogeneous ($I^2 > 50\%$) results were statistically analyzed by random effects model, and the data were presented by forest map.

3. Results

3.1. Search results

Initially, 119 potentially relevant papers were retrieved using the above search method, 19 of which were considered to be interested

by scanning titles and abstracts. However, due to article types, 4 reports were excluded by reading the full article, 6 studies lacked available data to construct a 2×2 table, and 3 articles lacked non-KD controls. Finally, 6 studies[25–30] were included in the meta-analysis. The process of study selection was illustrated in Figure 1. All included reports were prospective trials. In the included studies, the sample types of 3 studies were plasma,[25–27] and the remaining 3 studies were serum.[28–30] Besides, 3 studies defined healthy children as healthy controls (HCs),[26,27,29] 1 study defined juvenile systemic lupus erythematosus as the control,[25] 2 studies used both healthy and febrile children as controls.[28,30] Meanwhile, there were 2 types of reference miRNA, cel-miR-39,[25,27,28,30] and U6.[26,29] The basic characteristics of the included studies were shown in Table 1.

Table 1

Characteristics of studies in this meta-analysis.

No.	First author	Yr	Country	Design	Composition of control	Detection method	Reference	Reference miRNA	Specimen	Case (male/female)	Age of case	Control (male/female)	Age of control	Selected miRNAs	Expression	Sensitivity	Specificity
1	Sun J	2015	China	Prospective	JSLE	qRT-PCR	AHA	Cel-miR-39	Plasma	26 (N/R)	2.2	20 (N/R)	10.7	miR-1825	Up-regulated	1	1
2	Sheng WW	2016	China	Prospective	HC	qRT-PCR	AHA	U6	Plasma	45 (27/18)	0.3–7	30 (18/12)	0.3–7	miR-145	Up-regulated	0.6444	0.9
														miR-143	Up-regulated	0.6444	0.8667
3	Jia LH	2016	China	Prospective	HC	qRT-PCR	AHA	Cel-miR-39	Plasma	33 (25/8)	2.1	15 (11/4)	1.7	miR-21	Up-regulated	0.846	0.714
4	Rong X	2017	China	Prospective	HC FC	RT-PCR	JCS	Cel-miR-39	Serum	45 (34/11)	2.1	30 (21/9) 30 (23/7)	1.7 1.5	miR-92a-3p miR-92a-3p	Up-regulated Up-regulated	0.733 0.733	0.889 0.733
5	Zhang W	2017	China	Prospective	HC	qRT-PCR	AHA	U6	Serum	102 (60/42)	2.2	80 (45/35)	2.3	miR-200c miR-371–5p	Up-regulated Up-regulated	0.6 0.667	0.8 0.866
6	Rong X	2018	China	Prospective	HC FC	qRT-PCR	AHA	Cel-miR-39	Serum	34 (24/10)	2.7	42 (27/15) 15 (10/5)	3.6 4.1	miR-27b miR-27b	Up-regulated Up-regulated	0.853 0.676	1 0.933

AHA = American Heart Association, FC = febrile control, HC = healthy control, JCS = Japanese Cardiology Society, JSLE = juvenile systemic lupus erythematous, miR = mircoRNA, N/R = not report.

Table 2

Quality assessment of diagnostic accuracy studies criteria of included studies.

No.	Spectrum composition	Selection criteria	Reference standard	Disease progression bias	Partial verification	Differential verification	Incorporation bias	Index test execution	Reference standard execution	Test review bias	Reference standard review bias	Clinical review bias	Uninterruptible test results	Withdrawals
1	?	+	+	?	+	+	+	+	+	+	+	+	+	?
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	+	+	+	?	+	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+	+	+	+	+	?
5	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6	?	+	+	?	+	+	+	+	+	+	+	+	+	?

3.2. Study quality

The quality assessment of the included studies was done following the quality assessment of diagnostic accuracy studies list of questions, with the results shown in Table 2.

3.3. Diagnostic accuracy of miRNAs

The overall diagnostic measurements for detecting KD of total mixed miRNAs (TmiRs) was summarized in Figure 2. The pooled sensitivity was 0.70 (95%CI, 0.66–0.74), and the pooled estimation showed significant heterogeneity ($P = .0001$, $X^2 = 33.98$, $I^2 = 73.5\%$) (Fig. 2A). Meanwhile, the summary specificity was 0.87 (95%CI, 0.83–0.90), and the pooled estimation also showed noticeable heterogeneity ($P = .0012$, $X^2 = 27.40$, $I^2 = 67.20\%$) (Fig. 2B). The pooled DOR was 15.53 (95% CI, 8.37–28.85), with significant heterogeneity ($P = .0171$, $X^2 = 20.13$, $I^2 = 55.3\%$) (Fig. 2C). The calculated AUC value was 0.8302 ± 0.0402 (Fig. 2D). There was no curvilinear shape in SROC,
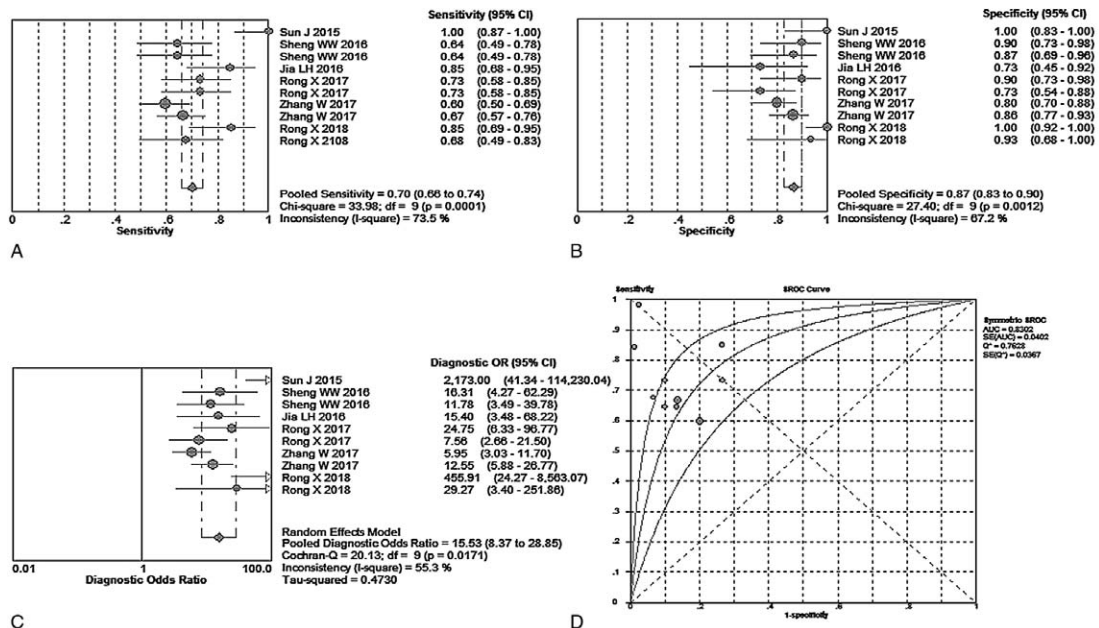

Figure 2. Performance of total mixed miRNAs detection for the diagnosis of Kawasaki disease. (A) Pooled sensitivity. (B) Pooled specificity. (C) Overall DOR. (D) The summary receiver operating characteristic curves value for all datasets.
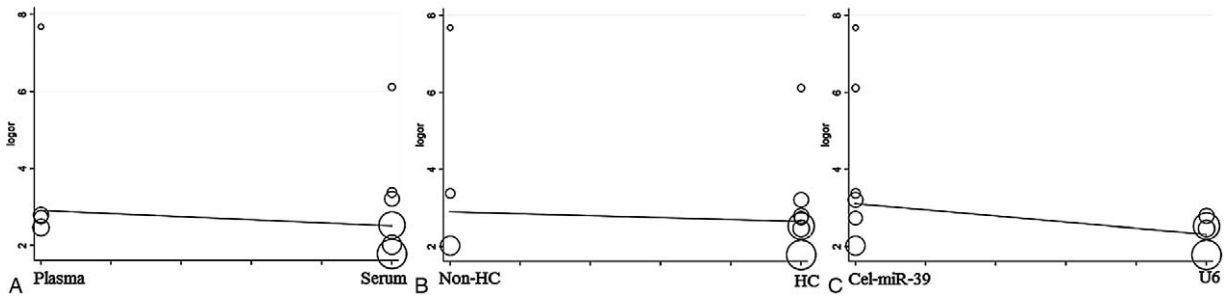
Figure 3. The meta-regression of the enrolled studies. (A) For the specimen types. (B) For the composition of the control group. (C) For the types of reference microRNA.

indicating no potential threshold effect. After a review of the baseline data and original data generation, specimen types, control group composition, and reference miRNA type were considered in meta-regression to detect the origin of heterogeneity. According to the results (Fig. 3), the meta-regression did not find that specimen type was a dramatic impact factor on the homogeneity of the included studies, $P=.604$, $t=-0.54$, 95%CI (0.12, 3.71) (Fig. 3A). Besides, the composition of the control group was not a significant factor, $P=.791$, $t=-0.27$, 95%CI (0.09, 6.49) (Fig. 3B). Meanwhile, the meta-regression also did not detect types of the reference miRNA has a dramatic impact on the homogeneity of the enrolled studies, $P=0.263$, $t=-1.21$, 95%CI (0.10, 2.06) (Fig. 3C). Therefore, specimen type, control group composition, and reference miRNA type were not responsible for the heterogeneity.

3.4. Sensitivity analysis and subgroup analysis

We systematically and qualitatively analyzed the sensitivity of the included studies to determine the impact of individual trials on TmiRs results, using STATA 15.1 for meta-analysis random-effects estimates. Finally, we did not detect any significant impact

from every single research and confirmed the TmiRs results (Fig. 4). Meanwhile, Meta-disc 1.4 (Ramón y Cajal Hospital, Madrid, Spain) was used to detect whether there was a threshold effect in the report. Spearman correlation coefficient was −0.255 and $P=.478$, indicating there was no threshold effect related to heterogeneity. Then, we performed 2 subgroups analysis according to the specimen type, and the composition of the control group. The results were illustrated in Table 3. Subgroup analysis showed that the SROC of the plasma group (0.8890) was more significantly higher than that of the serum group (0.7204), and that of the non-HC group (0.9622) was significantly higher than that of the HC group (0.8096).

3.5. Publication bias

We used the Deeks' test plots to assess the publication bias of the included reports. Each of these dots represented a report. The distance between each point and the vertical line indicated bias in each report. Meanwhile, no asymmetric distribution suggested no publication bias existed. The Deeks' test plots in Figure 5A to E showed a degree of symmetry, suggested no potential publication bias existed in the studies included.
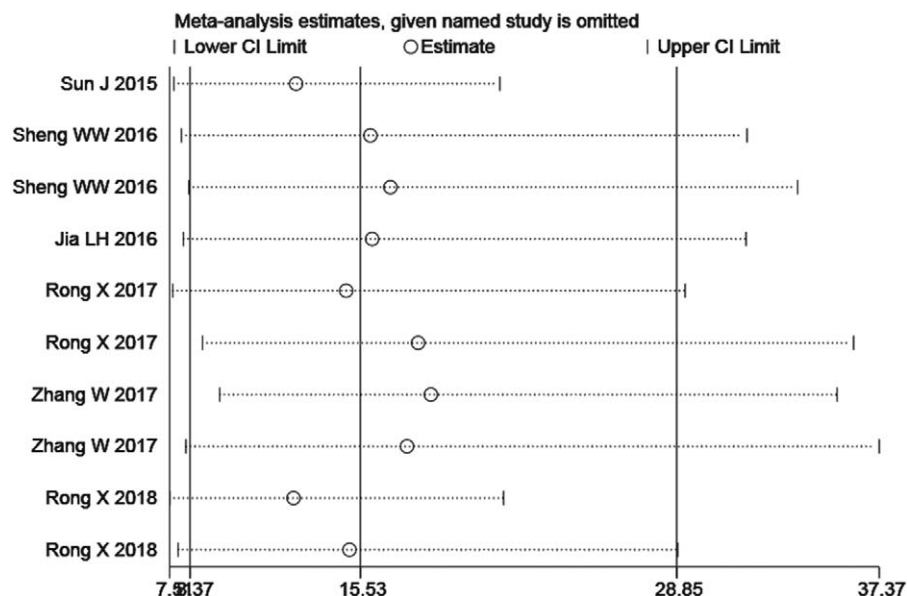

Figure 4. Sensitivity analysis of the individual trials on the results total mixed miRNAs.

Subgroup analysis results of all included studies.

	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	SROC (AUC±SE)
TmiRs	0.70 (0.66–0.74)	0.87 (0.83–0.90)	15.53 (8.37–28.85)	0.8302±0.0402
P/I^2	.0001/73.5%	.0012/67.2%	.0171/55.3%	
Specimen type				
Plasma	0.75 (0.67–0.82)	0.88 (0.80–0.94)	20.94 (6.38–68.76)	0.8890±0.0361
P/I^2	.0001/86.2%	.0540/60.7%	.0976/52.4%	
Serum	0.68 (0.63–0.73)	0.86 (0.81–0.90)	13.75 (6.43–29.42)	0.7204±0.0828
P/I^2	.0846/48.4%	.0016/74.2%	.0285/60.0%	
Control group Composition				
HC	0.68 (0.63–0.73)	0.87 (0.82–0.90)	12.63 (8.76–18.20)	0.8096±0.0576
P/I^2	.0244/58.7%	.0084/65.2%	.0700/48.5%	–
Non-HC	0.78 (0.69–0.86)	0.86 (0.75–0.93)	42.43 (3.21–560.31)	0.9622±0.0719
P/I^2	.0005/87.0%	.0063/80.3%	.0142/76.5%	–

AUC = area under the curve, CI = confidence interval, DOR = diagnostic odds ratio, HC = healthy control, SE = standard error, SROC = summary receiver operating characteristic curves value, TmiRs = total mixed miRNAs.

4. Discussion

Since its discovery, the stability of circulating miRNAs has stimulated interest in their role as the biomarkers for the diagnosis and prognosis of various diseases, including cardiovascular diseases.[31] Meanwhile, some studies were carried out to assess whether miRNAs have sufficient capability as biomarkers of KD.[25–30,32] To our knowledge, this study is the first meta-analysis to focus on the accuracy of miRNAs in detecting KD. Since there are not enough researches to analyze specific individual miRNAs, it seems reasonable to use the results of mixed total miRNAs as the first look at miRNAs in detecting KD.

In this meta-analysis, we enrolled 6 studies[25–30] and finally found that the combined AUC of TmiRs was 0.8302 with a pooled sensitivity of 70% and a pooled specificity of 87%, indicating that miRNAs had a moderate diagnostic accuracy as a diagnostic biomarker in discriminating KD from other people.

Moreover, compared to NT-proBNP, which achieved a combined AUC of 0.87 with 84% pooled sensitivity and 79% pooled specificity in a recent meta-analysis,[33] the accuracy of miRNAs was similar and should be considered as a useful biomarker for KD.

Furthermore, we intended to detect individual miRNAs in the entire miRNA library. Unfortunately, there were no single miRNAs have been used repeatedly in individual studies. Based on this, we took sensitivity analysis and subgroup analysis in the next step. Subgroup analysis indicated that compared with the healthy control group, circulating miRNAs could be considered as diagnostic biomarkers discriminating KD from other febrile diseases with relatively higher accuracy (SROC: 0.9622±0.0719, and 0.8096±0.0576, respectively). Also, our meta-analysis showed that plasma-based specimens had higher accuracy than serum-based samples (SROC: 0.8890±0.0361, and 0.7204±0.0828, respectively). Besides, human miRNAs isolated from
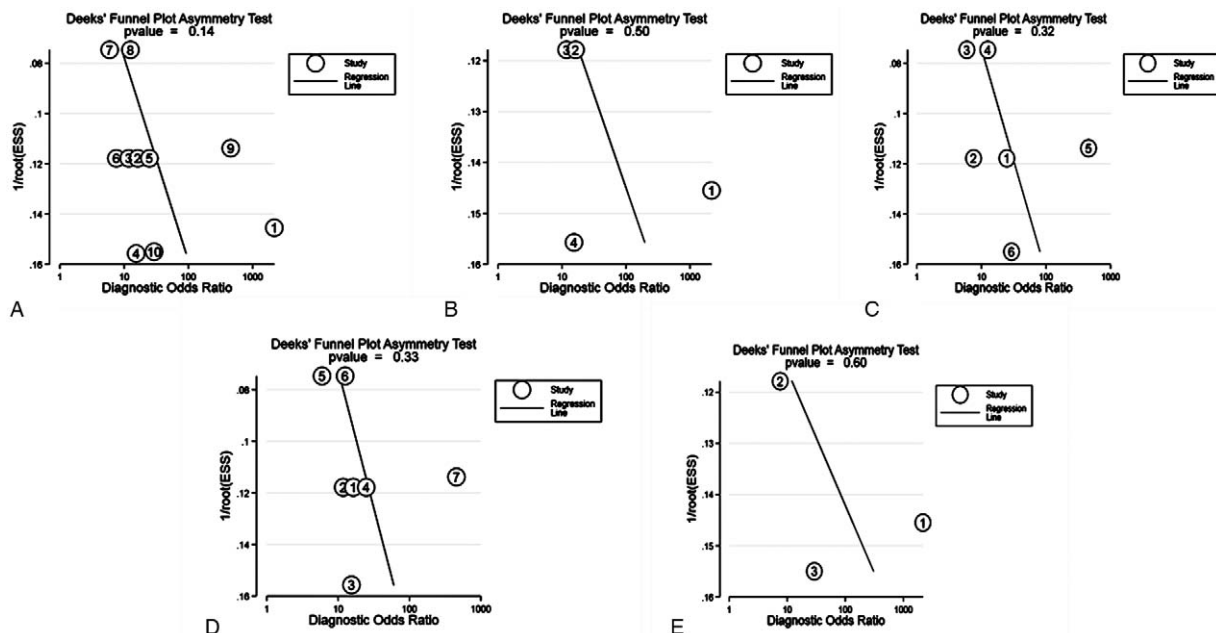

Figure 5. The Deeks' test plot for the assessment of potential publication bias. (A) total mixed miRNAs pooled result. (B) Plasma pooled result. (C) Serum pooled result. (D) healthy control pooled result. (E) Non- healthy control pooled result.

plasma are highly stable in boiling water, able to tolerate high or low pH, and able to resist repeated freeze-thaw or prolonged room temperature incubation.[34] These reasons make plasma seem to be the right candidate for clinical specimen collection, but more research is needed in the future to clarify.

However, it is worth to note that miRNAs may have many targets, so they may only play an auxiliary role in disease diagnosis.[35] Therefore, none of the miRNAs are disease-specific. We can combine them with other indicators to improve diagnostic accuracy. Meanwhile, further experimental studies are needed to explore the cause and mechanism of miRNAs expression in KD.

This meta-analysis has several limitations. First, our study included 8 miRNAs, and all miRNAs were not repeatedly used in individual publications, so we did not analyze the same miRNA across studies. Second, due to the lack of available data from other countries except for China, which limits the cross-comparison between reports conducted by different countries or ethnicities, might produce unconvincing results for the included studies. Third, no included articles combined miRNAs with other laboratory tests, such as C reactive protein, erythrocyte sedimentation rate, and NT-proBNP to identify the diagnostic accuracy of KD, which could provide a better method for the detection of KD.

In conclusion, this is the first meta-analysis to demonstrate that circulating miRNAs may be considered as potential novel biomarkers for the detection of KD, particularly to distinguish KD from other febrile diseases. Besides, more studies are needed in the future to clarify the association between KD and miRNAs. Furthermore, a combination of miRNAs and other laboratory tests needs to be done to launch the application of miRNAs as biomarkers for KD detection in the clinic.

Author contributions

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Visualization: Xiaolan Zheng, Yifei Li.
Writing – original draft: Xiaolan Zheng.
Writing – review & editing: Yifei Li.

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