Systematic Review and Meta-Analysis

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Identification of microRNAs as diagnostic biomarkers for acute myocardial infarction in Asian populations

A systematic review and meta-analysis

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Abstract

Background: Acute myocardial infarction (AMI) is one of the leading causes of mortality and morbidity worldwide. Recently, several studies have revealed the diagnostic value of circulating microRNAs (miRNAs) for AMI detection. However, the diagnostic capacity of miRNAs for AMI is still controversial due to the inconsistent results among studies.

Methods: A systematic literature search was conducted to retrieve relevant articles in PubMed and other databases up to February 2017. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) were used to assess the overall test performance of miRNAs. Subgroup analysis was conducted to explore the potential sources of heterogeneity. We evaluated the publication bias by the Deeks' funnel plot asymmetry test and all statistical analyses were performed using Meta-disc 1.4 and Stata software.

Results: A total of 26 articles comprising 1973 AMI patients and 1236 healthy controls were included in this meta-analysis. The overall pooled diagnostic data was as follows: the pooled sensitivity of 0.76 (95% confidence interval [CI]: 0.75–0.78), the pooled specificity of 0.82 (95% CI: 0.81–0.84), the pooled PLR of 4.68 (95% CI: 3.92–5.59), the pooled NLR of 0.28 (95% CI: 0.25–0.32), and the pooled DOR of 18.66 (95% CI: 14.11–24.68). The AUC value was 0.8661 in the overall summary receiver operator characteristic curve. Subgroup analysis indicated that miRNA-499 had better diagnostic accuracy over other miRNAs.

Conclusion: MiRNAs may serve as promising diagnostic biomarkers in the early diagnosis of AMI. Further studies were needed to evaluate the diagnostic value of miRNAs for AMI before clinical application.

Abbreviations: AMI = acute myocardial infarction, AUC = area under the curve, CI = confidence interval, cTn = troponin, DOR = diagnostic odds ratio, ECG = electrocardiogram, miRNA = microRNA, NLR = negative likelihood ratio, NSTEMI = non-ST elevated myocardial infarction, PLR = positive likelihood ratio, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2, SROC = summary receiver operator characteristic, STEMI = ST-elevation myocardial infarction.

Keywords: acute myocardial infarction, diagnosis, meta-analysis, miRNAs

1. Introduction

Acute myocardial infarction (AMI), which includes ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), is one of the leading causes of morbidity and mortality worldwide. A rapid diagnosis of AMI is essential for proper management of patients with clinical symptoms. Within 3 hours after the onset of chest pain, a timely revascularization treatment is recommended to repair the ischemic myocardium, which would ultimately reduce the mortality and improve prognosis of AMI.[1] Thus, an early and accurate diagnosis of AMI is warranted.

To date, clinical symptoms, electrocardiogram (ECG), and specific cardiac biomarkers are the main methods for the clinical diagnosis of AMI. In clinical practice, biomarkers, preferably troponin (cTn) I and T, are very critical in the diagnosis of AMI as patients with NSTEMI cannot be diagnosed on the basis of clinical symptoms and ECG alone. The cTn is considered the "gold standard" for the early diagnosis of AMI. Yet, the level of cTn not only increases in some cases of ischemic heart injury, but also in other serious diseases, such as heart failure, chronic kidney disease, neuromuscular disorders, severe sepsis, and septic shock.[2–4] Another weakness of cTn is its time restrain, because cTn can only be detected 3 to 6 hours after the onset of clinical symptoms of cardiac ischemia.[5] Therefore, in order to improve the determination of AMI, it is urgent to seek novel potential biomarkers for early diagnosis of AMI.

In recent years, the discovery of microRNAs (miRNAs) has provided a new method for the diagnosis of cardiovascular

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diseases. Since miRNAs were discovered in the 1990s, more than 2000 human miRNAs have been cloned and sequenced. Circulating miRNAs are short, endogenous, and noncoding ribonucleic Acids (19–25 nucleotides) that regulate genes expression posttranscriptionally.[6] MiRNAs have been shown to participate in various physiological and pathological processes, such as cell death, stress response, metabolism, cell differentiation, and proliferation.[6–8] And they have been demonstrated to be stable in the extracellular fluid and recommended as biomarkers for various diseases. Compared to cTn, miRNAs could be detected in the circulation at an earlier time point after AMI, appearing to be highly promising biomarkers for early diagnosis of AMI.[9] Several studies have reported the diagnostic value of miRNAs in AMI patients. However, the results among studies were inconsistent, which may be caused by specimen types, region, age, sample size, sampling time, severity of AMI, and so on. Considering the different regions may affect the results and most of the studies about miRNAs for AMI diagnosis were carried out in Asian populations up to now, the aim of this study is to summarize the existed insights into the potential use of miRNAs as biomarkers in AMI detection among Asian populations and evaluate the specificity and sensitivity of miRNAs so as to assess the feasibility of diagnosing AMI.

2. Methods

2.1. Publication search

A systematic literature search was conducted to obtain relevant studies for this meta-analysis. We searched the following databases for studies published up to February 2017 without language restriction: PubMed, Cochrane Library, Medline, Embase, CNKI, and Wanfang. The search keywords were "acute myocardial infarction," "AMI," "acute coronary syndrome," "ACS" or "heart infarction" combined with "microRNA," or "miRNA". Meanwhile, we searched the reference lists in order to avoid omitting relevant studies that had not been obtained from the databases. As this is a systematic review and meta-analysis, the ethical approval and patient written informed consent are not required.

2.2. Inclusion and exclusion criteria

All eligible studies in this meta-analysis were required to satisfy the following criteria: researches were related with miRNAs and AMI; studies were human and case–control studies; studies contained sufficient data to assess the diagnosis value of miRNAs in AMI detection. Exclusion criteria were based on the following: studies without usable or sufficient data; case reports, reviews, letters, editorials, and conference abstracts.

2.3. Data extraction and quality assessment

Two reviewers independently extracted data and information from the eligible studies, including first author, the year of publication, the country of origin, the number of cases and controls, AMI definition, time of blood sampling for diagnosis, and data needed for meta-analysis (sensitivity, specificity, true positives, false positives, true negatives, and false negatives). The quality of eligible studies was assessed by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) score system, which has been demonstrated to be an effective tool for evaluating the quality of diagnostic accuracy studies.[10] The QUADAS-2 tool, including 4 key domains (patient selection, the index test, the reference standard, and flow and timing), evaluates risk of bias and concerns about applicability as "yes (low risk/high concern)," "no (high risk/low concern)," or "unclear (unclear risk/unclear concern)" with a maximum score of 7.

2.4. Statistical analysis

All statistical analyses were performed using Meta-disc 1.4 (XI Cochrane Colloquium, Barcelona, Spain) and Stata (12.0 Stata Corp, College Station, TX) software. We calculated the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), generated the bivariate summary receiver operator characteristic (SROC) curve, and calculated the area under the curve (AUC) to assess the overall diagnostic accuracy of miRNAs in distinguishing AMI patients from controls. In this meta-analysis, Spearman correlation coefficient was used to assess the heterogeneity caused by threshold effect. If P value of Spearman correlation coefficient was less than .05, it indicated the existence of heterogeneity from threshold effect. In addition, chi-square and I^2 test were performed to analyze the heterogeneity from nonthreshold effect. If $P < .1$ or $I^2 > 50\%$, it indicated that heterogeneity existed from nonthreshold effect and a random effects model would be used, otherwise a fixed effects model would be applied ($P > .1$ or $I^2 < 50\%$). Subgroup analysis was performed to explore the potential source of heterogeneity. In addition, we evaluated the publication bias of the selected studies using the Deeks' funnel plot asymmetry test.

3. Results

3.1. Data selection and study characteristics

In the initial search, totally 408 articles were retrieved from databases and other sources, of which 292 duplicates were excluded. After reading the titles and abstracts, 55 were removed, including 18 reviews or letters and 37 irrelevant articles. After carefully reviewing full texts, 35 were excluded from analysis due to the lack of sufficient data. Eventually, 26 eligible publications were included in our meta-analysis. The flow diagram of the selected studies is summarized in Fig. 1.

The characteristics of the studies included in our meta-analysis were shown in Table 1. The 26 articles comprised 1973 AMI patients and 1236 healthy controls. Among the included studies, 10 focused on miRNA-499,[11,13,18–20,22,26,30,31,36] 9 on miRNA-1,[12–14,16,19–22,26] 5 on miRNA-133,[14,15,20,22,23] 3 on miRNA-208a,[13,19,26] 3 on miRNA-208b,[20,22,32] 3 on miRNA-134,[19,24,33] and 20 on other 17 types of miRNAs. A total of 23 types of miRNAs were involved. A total of 5 studies used serum samples, whereas the rest used plasma. Quantitative reverse transcription polymerase chain reaction was used to detect the expression levels of miRNAs in all studies. The quality of included studies was assessed by QUADAS-2 and most studies had moderately high scores. The risk of bias and applicability concerns graph for included studies were presented in Fig. 2.

3.2. Pooled diagnostic accuracy of miRNAs in AMI

The pooled diagnostic accuracy of miRNAs in AMI diagnosis was conducted. The P value of Spearman correlation coefficient in the pooled analysis was less than 0.05. I^2 value was 77.9% for sensitivity and 77.3% for specificity, and P values of chi-square

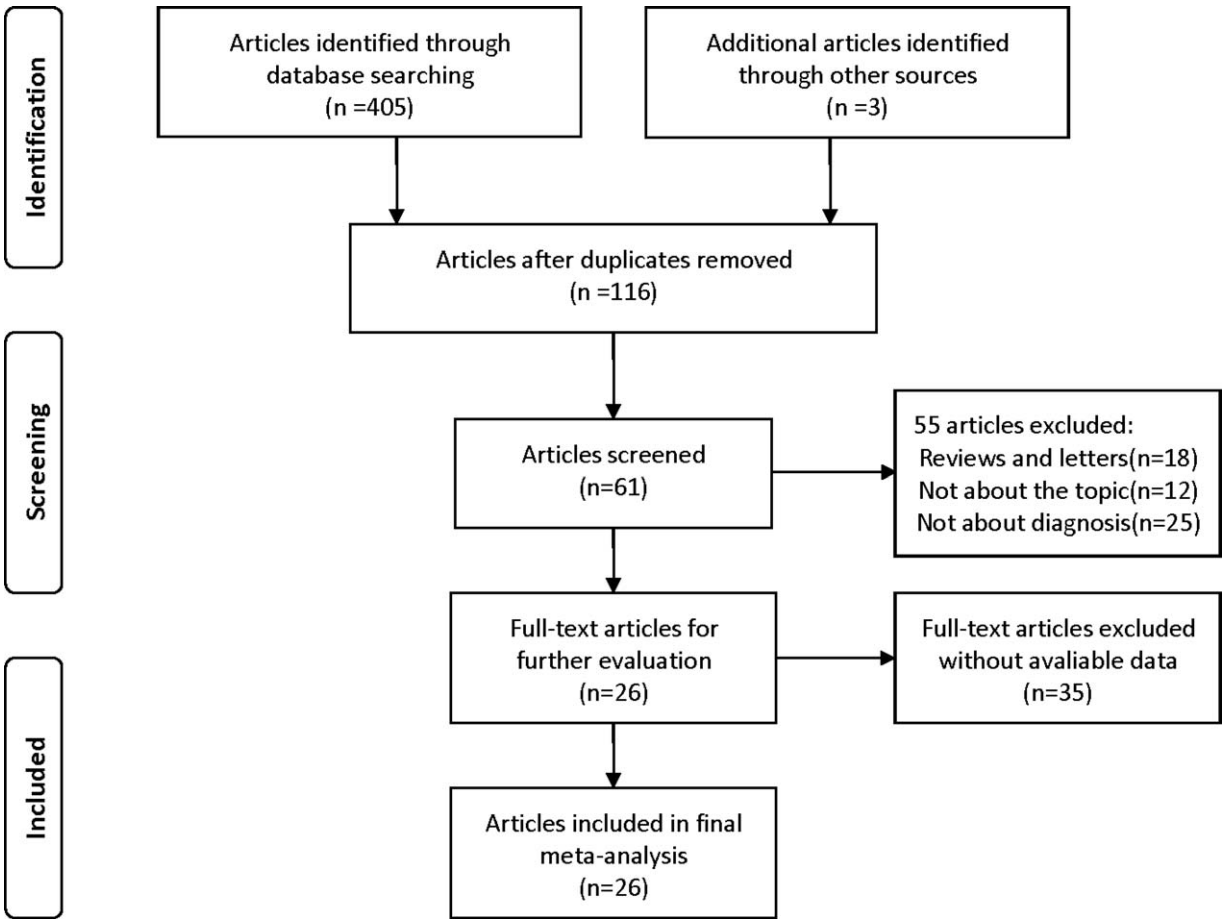

Figure 1. Flowchart of the selection process of studies included in this meta-analysis.

test were all less than 0.1, which suggested significant heterogeneity between studies. Thus, a random-effects model was applied to calculate the pooled diagnostic parameters for this study.

Forest plots of the sensitivity, specificity, DOR, and SROC curve with AUC for miRNAs in AMI detection in this meta-analysis were plotted. The overall pooled diagnostic data were as follows: the pooled sensitivity (Fig. 3A) of 0.76 (95% confidence interval [CI]: 0.75–0.78), the pooled specificity (Fig. 3B) of 0.82 (95% CI: 0.81–0.84), the pooled PLR of 4.68 (95% CI: 3.92–5.59), the pooled NLR of 0.28 (95% CI: 0.25–0.32), and the pooled DOR (Fig. 3C) of 18.66 (95% CI: 14.11–24.68). The corresponding SROC curve was shown in Fig. 3D and the AUC value was 0.8661 in the overall SROC curve, which suggested a relatively high accuracy for diagnosing AMI based on miRNAs assays. In addition, the Deeks' test (Fig. 3E) was performed for DOR to evaluate the potential of publication bias in this meta-analysis. The *P* value was 0.07 for Deeks' test on publications of multiple miRNAs, which suggested a low possibility of publication bias.

3.3. Subgroup analysis

In order to explore the potential sources of heterogeneity, we conducted subgroup analysis based on miRNA profiling. The comparison of diagnostic value of miRNAs was shown in Table 2.

3.3.1. miRNA-499. Ten studies discussed the diagnostic value of miRNA-499 in AMI detection, and forest plots of the sensitivity, specificity, DOR, and SROC curve with AUC for miRNA-499 in the diagnosis of AMI in this meta-analysis were plotted. Due to the heterogeneity (all $I^2 > 50\%$), a random effects model was used for the meta-analysis. The pooled sensitivity (Fig. 4A), specificity (Fig. 4B), and DOR (Fig. 4C) with their 95% CI and the AUC value (Fig. 4D) of miRNA-499 in the 10 studies were 0.80 (95% CI: 0.77–0.83; $P = .0037$), 0.89 (95% CI: 0.86–0.92; $P = .0018$), 38.15 (95% CI: 19.20–75.81; $P = .0007$), and 0.8961, respectively. In addition, the Deeks' test (Fig. 4E) was performed to evaluate publication bias of miRNA-499, which suggested a low possible publication bias.

3.3.2. miRNA-1. Nine studies focused on the diagnostic value of miRNA-1 for AMI. Forest plots of the sensitivity, specificity, DOR, and SROC curve with AUC for miRNA-1 in the diagnosis of AMI in this meta-analysis were plotted. Due to the heterogeneity (all $I^2 > 50\%$), a random effects model was applied for the meta-analysis. The pooled sensitivity (Fig. 5A), specificity (Fig. 5B), and DOR (Fig. 5C) with their 95% CI and the AUC value (Fig. 5D) of the miRNA-1 in the 9 studies were 0.70 (95% CI: 0.66–0.74; $P = .0130$), 0.81 (95% CI: 0.78–0.85; $P = .0001$), 15.20 (95% CI: 7.48–30.89; $P = .0000$), and 0.8409, respectively. In addition, the Deeks' test (Fig. 5E) was performed to evaluate publication bias of miRNA-1, which suggested a low possible publication bias.

Table 1

Characteristics of the 26 studies included in our meta-analysis.

Reference	Year	Country	AMI patients	Healthy controls	MiRNAs profiled	Specimen	AMI definition	Detection	Time of blood sampling	Sensitivity (%)	Specificity (%)	AUC	QUADAS-2 score
Adachi et al[11]	2010	Japan	9	10	miR-499	Plasma	NR	RT-qPCR	Within 48 h after onset of chest pain	100	100	1.000	4
Ai et al[12]	2010	China	93	66	miR-1	Plasma	Ischemic symptoms; increased cTnI and CK-MB; pathological Q wave; ST-segment elevation or depression	RT-qPCR	NR	73	88	0.744	6
Wang et al[13]	2010	China	33	33	miR-208a	Plasma	Biochemical markers (cTnI > 0.1 ng/mL); acute ischemic-type chest pain; electrocardiogram change; coronary angiography	RT-qPCR	Within 12 h after onset of chest pain	91	100	0.970	5
					miR-1					78	80	0.847	
					miR-499					60	90	0.822	
Kuwabara et al[14]	2011	Japan	29	42	miR-1	Serum	CK-MB; cTnI; pathological Q wave; ST-segment elevation or depression; chest pain	RT-qPCR	<3 h of onset of chest pain	60	96	0.777	6
					miR-133a					87	91	0.932	
Wang et al[15]	2011	China	51	28	miR-133	Plasma	Chest pain lasting >20 min or diagnostic serial ECG changes consisting of new pathological Q waves or ST-segment and T-wave changes	RT-qPCR	Within 24 h after onset of chest pain	98	73	0.890	7
Long et al[16]	2012	China	17	25	miR-1	Plasma	CK-MB; cTnI; pathological Q wave; ST-segment elevation or depression; ischemic symptoms	RT-qPCR	4 h after onset of symptoms	93	90	0.920	5
					miR-126					81	78	0.860	
Long et al[17]	2012	China	18	30	miR-30a	Plasma	CK-MB; cTnI; pathological Q wave; ST-segment elevation or depression; ischemic symptoms	RT-qPCR	4 h after onset of symptoms	88	83	0.880	7
					miR-195					82	88	0.890	
Li et al[18]	2012	China	67	32	miR-499	Plasma	Chest pain lasting >30 min; increased CK-MB, cTnI; new pathological Q wave and ST-segment elevation or depression	RT-qPCR	Within 12 h after symptoms	81	91	0.884	7
Li et al[19]	2013	China	117	100	miR-1	Serum	CK-MB; cTnI; pathological Q wave; ST-segment elevation or depression; chest pain	RT-qPCR	Within 2 h after hospitalization	60	70	0.696	7
					miR-134					55	75	0.657	
					miR-186					78	58	0.715	
					miR-208					78	76	0.778	
					miR-233					78	68	0.741	
					miR-499					80	93	0.755	
Li et al[20]	2013	China	67	32	miR-1	Plasma	Chest pain lasting >30 min; increased CK-MB, cTnI; new pathological Q wave and ST-segment elevation or depression	RT-qPCR	Within 12 h of the onset of symptoms	78	85	0.827	6
					miR-133a					88	96	0.947	
					miR-208b					82	100	0.890	
					miR-499					80	94	0.884	

(*continued*)

Table 1
(continued).

Reference	Year	Country	AMI patients	Healthy controls	MiRNAs profiled	Specimen	AMI definition	Detection	Time of blood sampling	Sensitivity (%)	Specificity (%)	AUC	QUADAS-2 score
Li et al[21]	2014	China	56	28	miR-1	Plasma	Increased cTnT or CK-MB levels; chest pain lasting for >30 min; new pathological Q waves or ST-segment elevation or depression	RT-qPCR	Within 12 h after onset of chest pain	80	90	0.854	6
Xu et al[22]	2014	China	68	100	miR-499	Serum	Ischemic symptoms; pathological Q wave; ST-segment elevation or depression; coronary angiography	RT-qPCR	Immediately after hospitalization	68	81	0.730	6
					miR-1					65	71	0.680	
					miR-133a					68	82	0.750	
					miR-208b					71	88	0.800	
Peng et al[23]	2014	China	76	110	miR-133	Plasma	ECG criteria; cTnI and clinical symptoms of ischemia	RT-qPCR	71% were taken within 24 h, 82% within 48 h and 93% within 72 h after onset of chest pain	81	91	0.912	5
					miR-1291					78	90	0.695	
					miR-663b					72	77	0.611	
He et al[24]	2014	China	359	30	miR-328	Plasma	Ischemic symptoms; increased cTnI and CK-MB; pathological Q waves; ST segment elevation or depression	RT-qPCR	6 h after the onset of symptoms	86	75	0.877	5
					miR-134					79	77	0.818	
Li et al[25]	2014	China	27	31	miR-497	Plasma	Ischemic symptoms; increased cardiac cTnI, CK-MB; pathological Q wave; ST-segment elevation or depression	RT-qPCR	4 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±60 min), 48 h (±60 min), and 72 h (±60 min) after the onset of symptom	81	90	0.870	7
Liu et al[26]	2015	China	70	72	miR-1	Plasma	Ischemic symptoms plus increased cTnI or CK-MB; chest pain lasting for >30 min; pathological Q waves or ST-segment elevation or depression	RT-qPCR	Within 2 h after the onset of symptoms	70	90	0.810	7
					miR-208					65	90	0.720	
					miR-499					82	94	0.880	
Yang et al[27]	2015	China	17	10	miR-21	Plasma	Ischemic symptoms; increased CK-MB and cTnI; ST-segment abnormality; pathological Q wave	RT-qPCR	NR	74	78	0.689	6
Luo et al[28]	2015	China	49	31	miR-222	Plasma	Criteria of diagnosis and treatment of acute myocardial infarction of cardiovascular branch of Chinese Medical Association	RT-qPCR	Within 24 h after onset of chest pain	65	94	0.808	6

(*continued*)

Table 1
(continued).

Reference	Year	Country	AMI patients	Healthy controls	MiRNAs profiled	Specimen	AMI definition	Detection	Time of blood sampling	Sensitivity (%)	Specificity (%)	AUC	QUADAS-2 score
Wang et al[29]	2015	China	175	24	miR-126	Plasma	ACCF/AHA guideline	RT-qPCR	Within 2 h after hospitalization	54	88	0.735	6
Zhao et al[30]	2015	China	59	60	miR-499	Serum	World Health Organization clinical diagnosis criteria for AMI	RT-qPCR	Within 3 h after onset of chest pain	86	94	0.915	6
Zhang et al[31]	2015	China	142	85	miR-499	Plasma	Biochemical markers; acute ischemic-type chest pain; ECG change; coronary angiography	RT-qPCR	Within 2 h after hospitalization	80	80	0.860	5
Li et al[32]	2015	China	87	87	miR-26a	Plasma	Ischemic symptoms; increased CK-MB and cTnI; ST-segment abnormality; pathological Q wave	RT-qPCR	Within 4 h after onset of symptoms	74	72	0.745	6
					miR-191					62	69	0.669	
					miR-208b					60	74	0.674	
Wang et al[33]	2016	China	50	56	miR-19b	Plasma	Lasting ischemic symptoms (>30 min); increased CK-MB and cTnI; pathological Q waves; ST-T segment and T wave changes; coronary angiography	RT-qPCR	10.40±3.52 h after the onset of chest pain symptoms	83	78	0.849	7
					miR-134					83	83	0.883	
					miR-186					78	72	0.796	
Zhang et al[34]	2016	China	17	10	miR-21	Plasma	Increased cTnI and CK-MB; pathological Q waves; ST segment elevation or depression	RT-qPCR	NR	78	100	0.892	5
Jia et al[35]	2016	China	172	79	miR-125b	Plasma	International standards	RT-qPCR	0–3, 3–6, 6–9, 9–12, and 12–24 h following admission	81	85	0.879	6
					miR-30d	plasma				86	81	0.915	
Shalaby et al[36]	2016	Egypt	48	25	miR-499	Serum	NSTEMI: chest pain; no ST segment elevation, elevated cardiac cTnI; coronary angiography	RT-qPCR	Within 24 h of onset of chest pain	93	100	0.970	6
					miR-210					83	100	0.900	

AMI = acute myocardial infarction, AUC = area under the curve, CK-MB = creatine kinase isoenzyme, cTn = troponin, ECG = electrocardiogram, miRNA/miR = microRNA, NR = not reported, NSTEMI = non-ST-elevation myocardial infarction, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2, RT-qPCR = quantitative reverse transcription polymerase chain reaction.

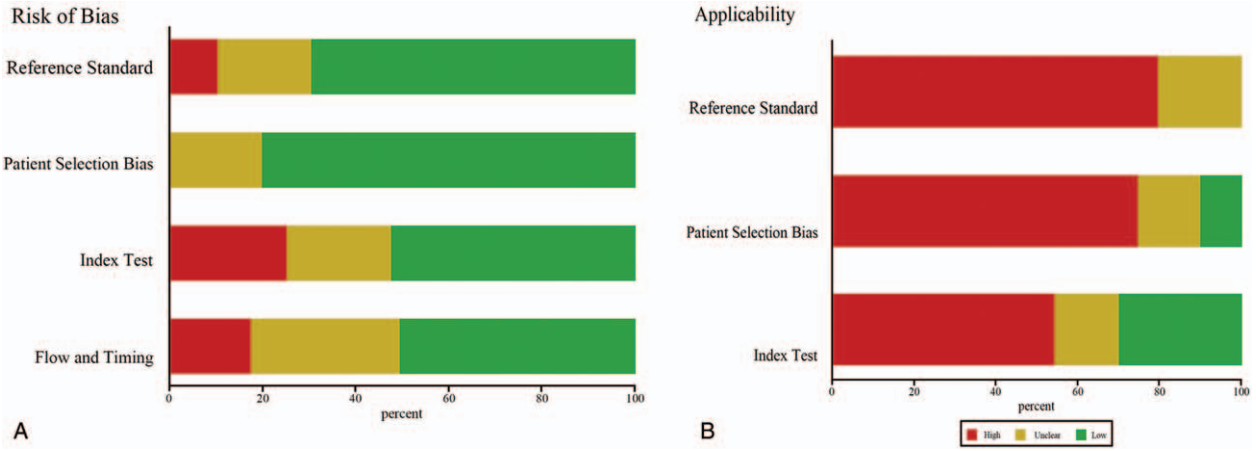

Figure 2. Bar graphs of the quality assessment of studies included using the Quality Assessment of Diagnostic Accuracy Studies 2 score system. (A) Risk of bias. (B) Applicability.

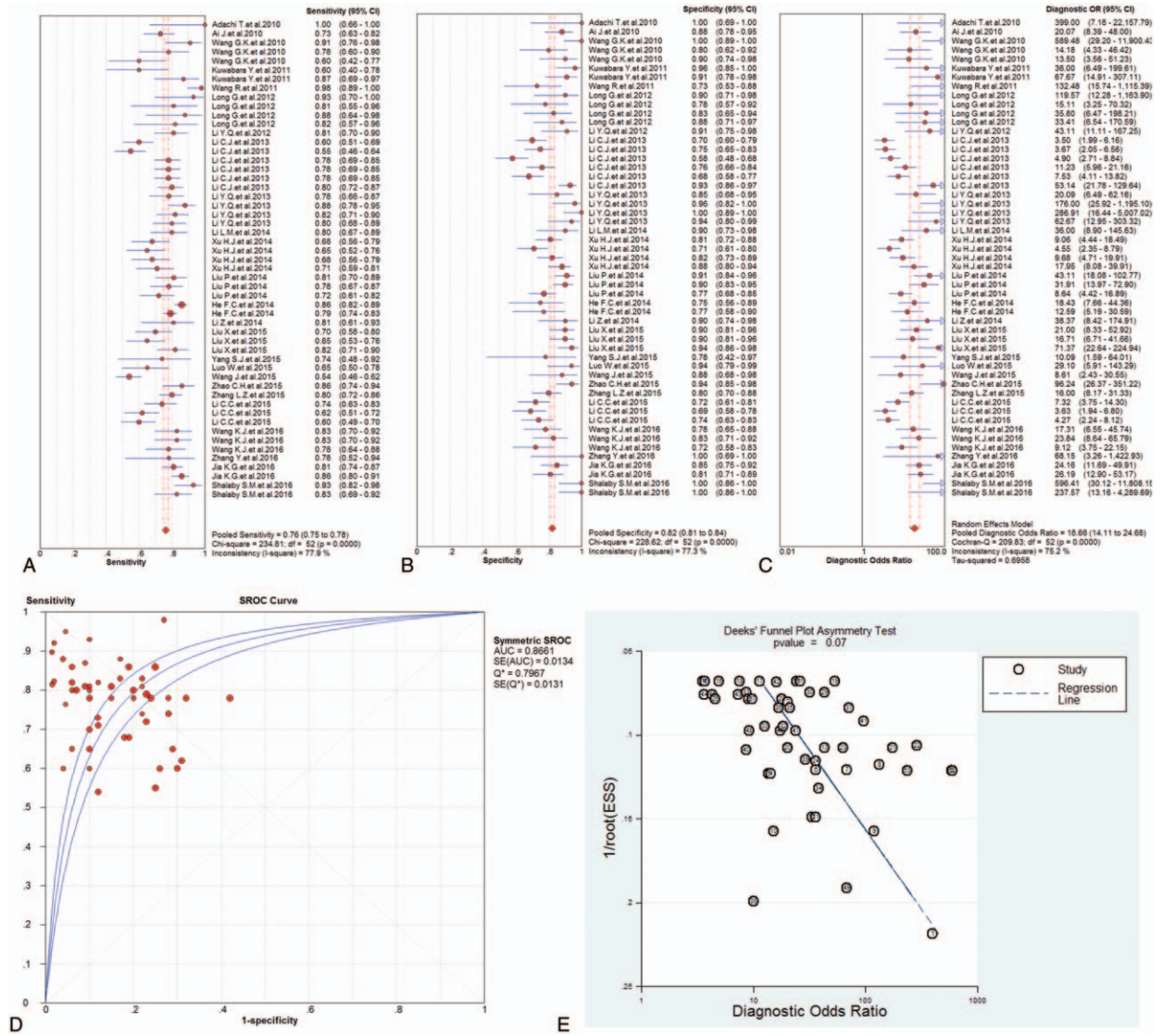

Figure 3. The sensitivity, specificity, diagnostic odds ratio (DOR), summary receiver operator characteristic (SROC) curve with area under the curve (AUC), and funnel graph of the total microRNAs in the diagnosis of acute myocardial infarction. (A) Sensitivity. (B) Specificity. (C) DOR. (D) SROC curve with AUC. (E) Funnel graph. AMI = acute myocardial infarction, AUC = area under the curve, DOR = diagnostic odds ratio, SROC = summary receiver operator characteristic.

Table 2

Comparison of diagnostic value of miRNAs.

MiRNA	N	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC
miRNA-499	10	0.80 (0.77–0.83)	0.89 (0.86–0.92)	8.18 (5.00–13.38)	0.23 (0.18–0.30)	38.15 (19.20–75.81)	0.8981
miRNA-1	9	0.70 (0.66–0.74)	0.81 (0.78–0.85)	4.69 (2.94–7.50)	0.35 (0.27–0.45)	15.20 (7.48–30.89)	0.8409
miRNA-133	5	0.82 (0.77–0.86)	0.87 (0.82–0.90)	5.82 (3.62–9.34)	0.21 (0.12–0.35)	35.92 (13.96–92.47)	0.9292
Multiple miRNAs	26	0.76 (0.75–0.78)	0.82 (0.81–0.84)	4.68 (3.92–5.59)	0.28 (0.25–0.32)	18.66 (14.11–24.68)	0.8881

AUC = area under the curve, CI = confidence interval, DOR = diagnostic odds ratio, miRNAs = microRNAs, NLR = negative likelihood ratio, PLR = positive likelihood ratio.

3.3.3. miRNA-133. Five studies investigated the diagnostic value of miRNA-133 for AMI and forest plots of the sensitivity, specificity, DOR, and SROC curve with AUC for miRNA-133 in the diagnosis of AMI in this meta-analysis were plotted. Due to the heterogeneity (all $I^2 > 50\%$), a random effects model was applied for the meta-analysis. The pooled sensitivity (Fig. 6A), specificity (Fig. 6B), and DOR (Fig. 6C) with their 95% CI and the AUC value (Fig. 6D) of miRNA-133 in the 5 studies were 0.82 (95% CI: 0.77–0.86; $P = .0002$), 0.87 (95% CI: 0.82–0.90; $P = .0692$), 35.92 (95% CI: 13.96–92.47; $P = .0121$), and 0.9292, respectively. In addition, the Deeks' test (Fig. 6E) was performed to evaluate publication bias of miRNA-133, which suggested a low possible publication bias.

4. Discussion

In this meta-analysis, we evaluated the diagnostic value of miRNAs as biomarkers of AMI. The results described above showed that miRNAs are promising biomarkers for the diagnosis of AMI with good accuracy. In addition, we conducted subgroup analysis based on miRNA profiling in order to reduce the effects from heterogeneity. Three miRNAs that had been studied most frequently were chosen for subgroup analysis: miRNA-499, miRNA-1, and miRNA-133. The comparison of diagnostic value between each single miRNA and multiple miRNAs showed that miRNA-499 had better diagnostic accuracy over other miRNAs.

AMI is a common clinical cardiovascular disease. Early detection, diagnosis, and treatment are significant for the

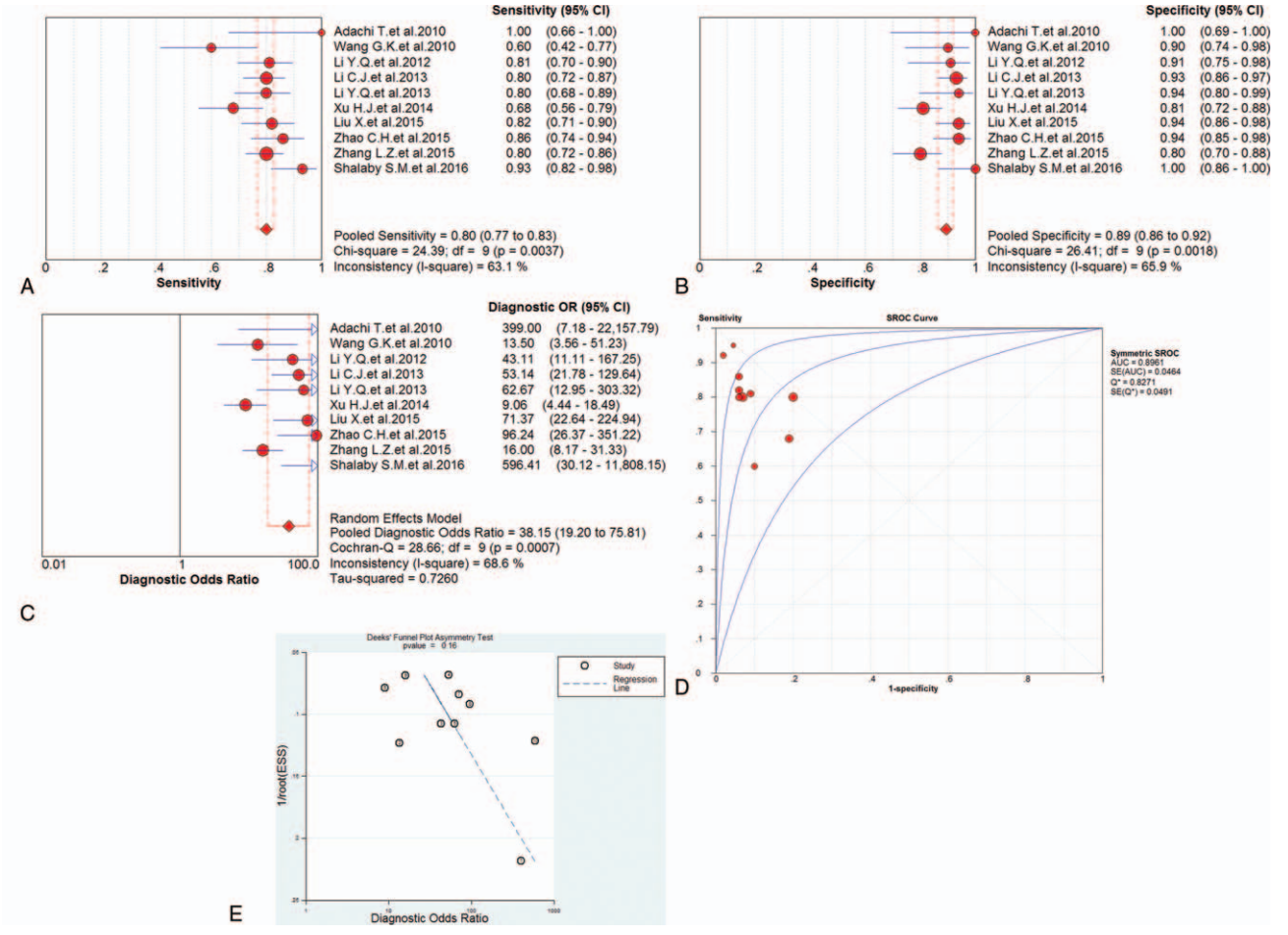

Figure 4. The sensitivity, specificity, diagnostic odds ratio (DOR), summary receiver operator characteristic (SROC) curve with area under the curve (AUC), and funnel graph of microRNA-499 in the diagnosis of acute myocardial infarction. (A) Sensitivity. (B) Specificity. (C) DOR. (D) SROC curve with AUC. (E) Funnel graph. AMI = acute myocardial infarction, AUC = area under the curve, DOR = diagnostic odds ratio, SROC = summary receiver operator characteristic.

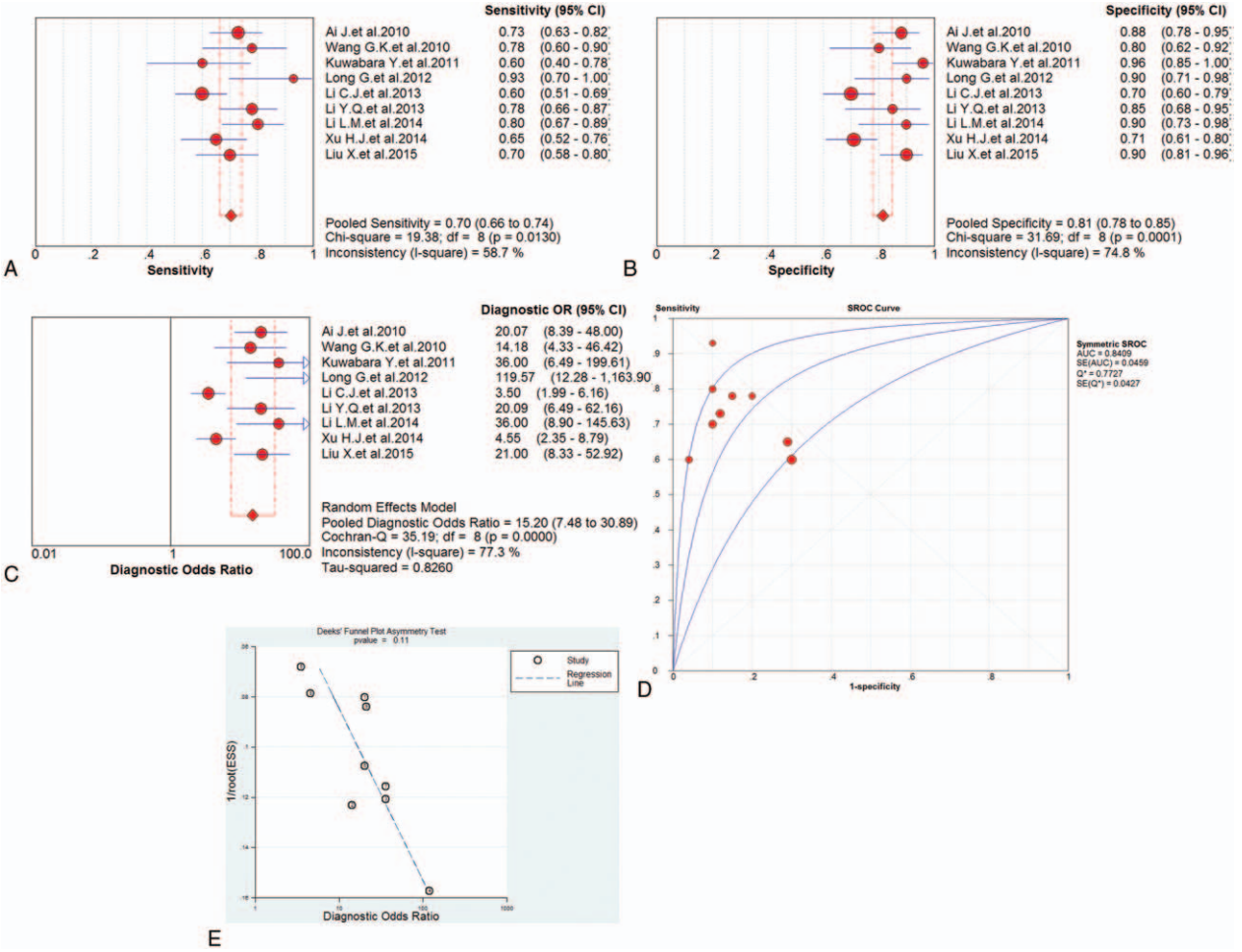

Figure 5. The sensitivity, specificity, diagnostic odds ratio (DOR), summary receiver operator characteristic (SROC) curve with area under the curve (AUC), and funnel graph of the microRNA-1 in the diagnosis of acute myocardial infarction. (A) Sensitivity. (B) Specificity. (C) DOR. (D) SROC curve with AUC. (E) Funnel graph. AMI = acute myocardial infarction, AUC = area under the curve, DOR = diagnostic odds ratio, SROC = summary receiver operator characteristic.

prognosis of AMI patients. There are plenty of biomarkers available for clinical diagnosis of AMI, including creatine kinase, creatine kinase isoenzyme, cTn, and myoglobin. The cTn is recognized as the most reliable biomarker, but it cannot rule in or rule out AMI at an early stage. Therefore, it is necessary to seek more sensitive and specific novel biomarkers for the diagnosis of AMI.

Preferably, a biomarker in the AMI detection should meet the following characteristics: First, the biomarkers should be easily accessible by the minimally invasive and painful methods, such as blood and urine. Second, it should be specifically present and abundantly expressed in the heart, which makes it specific to the disease. Third, its expression level in the circulatory system should be very low or undetectable under normal conditions and the expression level of biomarkers should closely correlate with the severity of AMI. Finally, if the AMI occurs, the biomarker should release from the damaged heart to the blood circulation in a very short time and has a relative long half-life in order to facilitate detection. Currently, miRNAs have been studied as a promising scientific tool for the early detection of AMI, which satisfy all the above characteristics. Some miRNAs are specific to heart or muscle tissue and considered to be the best candidates for the diagnosis of AMI. It has been demonstrated that circulating miRNAs can resist freeze–thaw cycles, boiling, high and low potential of hydrogen, and they can still remain stable in the extracellular fluid despite the presence of ribonucleases.[37] When necrosis occurs during AMI, cTn releases into the serum. However, the release of miRNAs can be affected by any form of cellular stress, such as hypoxia, lactic acidosis, or cell edema, which occurs earlier than necrosis in AMI. In summary, miRNAs may be potential biomarkers for the detection of AMI at an earlier time compared with cTn.

After our subgroup analysis, the most significant correlation was found between miRNA-499 and AMI. MiRNA-499 not only has high sensitivity and specificity, but also shows superiority in other aspects. MiRNA-499 is a member of the miRNAs family encoded by myosin gene and located in an intron of the *Myh7b* gene discovered recently. It has been demonstrated to be specially expressed in myocardium and skeletal muscle in mammals.[38] In addition, miRNA-499 has been studied that it can induce structural and functional differentiation of cardiac stem cells into cardiomyocytes, thereby promoting the recovery of cardiac function after injury.[39] Several studies have demonstrated that miRNA-499 and cTn have certain correlation, indicating that miRNA-499 can be used as a diagnostic biomarker for AMI. Studies also have shown that the level of miRNA-499 could be

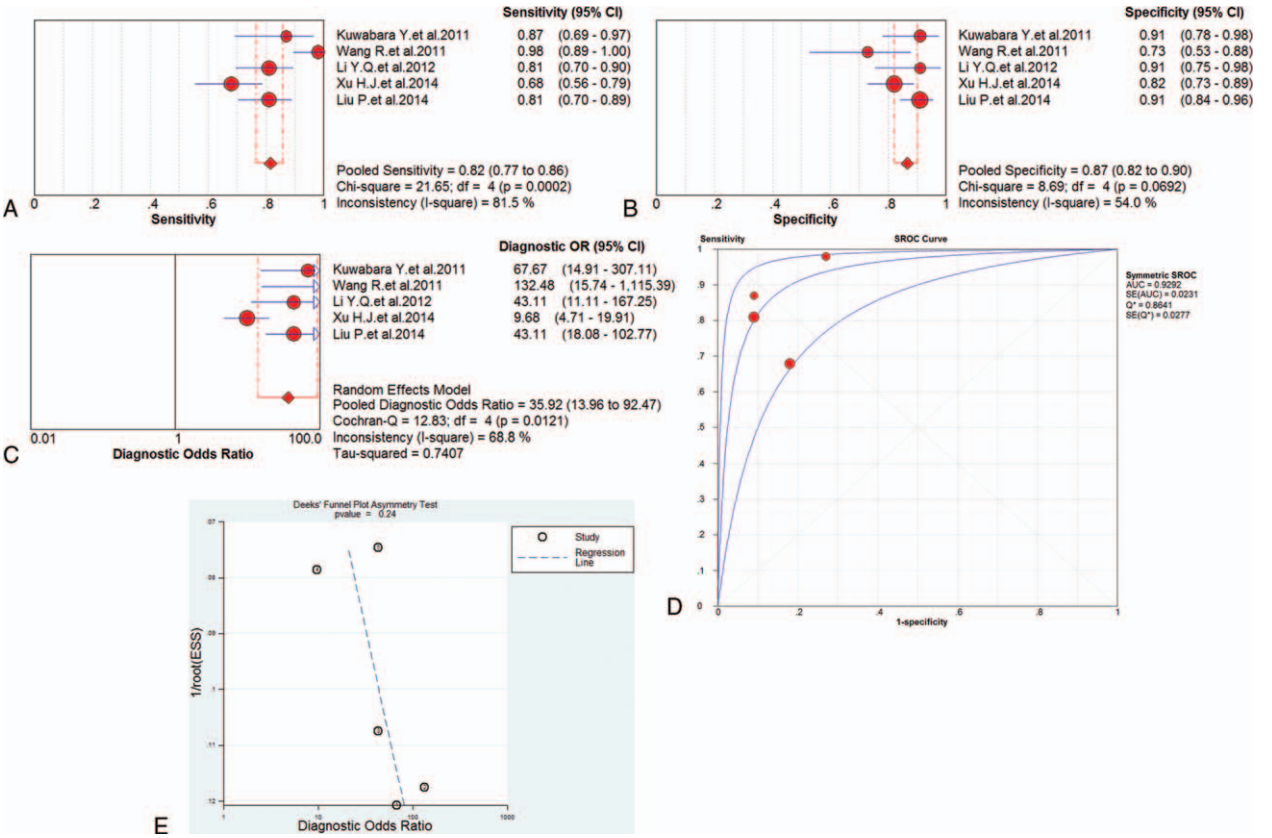

Figure 6. The sensitivity, specificity, diagnostic odds ratio (DOR), summary receiver operator characteristic (SROC) curve with area under the curve (AUC), and funnel graph of the microRNA-133 in the diagnosis of acute myocardial infarction. (A) Sensitivity. (B) Specificity. (C) DOR. (D) SROC curve with AUC. (E) Funnel graph. AMI = acute myocardial infarction, AUC = area under the curve, DOR = diagnostic odds ratio, SROC = summary receiver operator characteristic.

detected within a few hours of the onset of AMI symptoms and the peak fold change reached 3×10^5, which made detection of miRNA-499 relatively easy.[40] Therefore, evaluating the level of miRNA-499 would be helpful in the early diagnosis of AMI.

Despite this meta-analysis had an encouraging result of miRNAs for AMI detection, there were still some limitations that needed to be considered before making a clinical conclusion. First, most of the sample size is limited, so the clinical application of miRNAs for AMI detection still needs long-term and follow-up studies for further validation. Second, some studies may be missed during the selection process and some were excluded due to insufficient data. And the diagnostic superiority of miRNAs assessment was unclear due to the missing data of posterior probability analyses. So, more researches and analyses are needed. Third, the methods used in the study lack uniform standard, which certainly would affect the results.

5. Conclusion

The current meta-analysis suggested that miRNAs hold great potential in the early diagnosis of AMI in Asian populations. However, the clinical application of miRNAs for AMI early detection still needs large-scale studies for further validation. Due to the different diagnostic values of miRNAs, the combination of 2 or 3 miRNAs may be a better way to diagnose AMI more accurately. It is essential to explore the most effective combination of multiple miRNAs to improve the diagnostic accuracy.

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