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Original Article

The diagnostic value of circulating miRNA-499 in acute myocardial infarction: a systematic review and meta-analysis

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Abstract: Background: Acute myocardial infarction (AMI) is a common cardiovascular disease with high morbidity and mortality. Many recent studies have demonstrated that serum miRNA-499 levels are increased in the early stages of AMI. However, studies documenting the levels of miRNA-499 in AMI have had inconsistent results. Therefore, this study aimed to systematically evaluate the role of circulating miRNA-499 as a biomarker for AMI. Methods: According to the inclusion and exclusion criteria, a preliminary literature search was performed in the PubMed, Embase, and Cochrane databases up through October 2018. The meta-analysis was conducted used Review Manager 5.3 and Stata 12.0 software. The overall sensitivity, the overall specificity, the positive likelihood ratio (PLR), the negative likelihood ratio (NLR), the diagnostic odds ratio (OR), the receiver operating characteristic curve (AUROC), and the 95% confidence interval were presented to assess the diagnostic value of miRNA-499 in patients with AMI. Results: 16 articles that met the criteria were included in the qualitative synthesis. The studies included 1991 patients with AMI and 1950 healthy controls. The overall sensitivity of miRNA-499 for diagnosing AMI was 0.878 [95% CI: 0.827-0.915] and the specificity was 0.904 [95% CI: 0.831-0.947]. The PLR was 9.151 [95% CI: 4.993-16.770], and the NLR was 0.135 [95% CI: 0.092-0.199]. The overall diagnostic OR and 95% confidence interval were 67.776 and 27.994-164.092, respectively. The area under the AUROC was 0.95, and the 95% confidence interval was 0.920-0.960. Conclusions: In summary, miRNA-499 has a high diagnostic value in the diagnosis of AMI, and miRNA-499 may still be a valuable diagnostic marker for AMI. Furthermore, additional rigorously designed experiments with large sample sizes are needed to demonstrate the diagnostic value of miRNA-499 for AMI.

Keywords: MiRNA-499, myocardial infarction, biomarkers, meta-analysis

Introduction

Today, cardiovascular disease remains one of the most important diseases that threaten human health. Acute myocardial infarction (AMI) has become the most common cardiovascular disease and has a high morbidity and mortality [1]. According to a recent survey, there are approximately three to four million people who suffer from AMI each year [2]. Therefore, timely and accurate diagnoses are essential for clinicians to stratify patients according to risk and also to guarantee the immediate initiation of reperfusion therapy [3]. At present, cardiac troponin (cTn), which is considered to be the most reliable biomarker, has been widely used in clinical diagnosis [4, 5]. However, previous studies have shown that high levels of cTn are also detected in other acute and chronic diseases, such as congestive heart failure, myocarditis, coronary revascularization, renal failure, and skeletal muscle tissue damage [6]. These lead to a relatively low diagnostic accuracy of cTn [7], making its detection potentially limited. Thus, it is necessary to explore novel biomarkers with higher specificity and sensitivity for the early diagnosis of AMI [8-10].

MicroRNAs (miRNAs), constituting a large family of endogenous small non-coding RNA molecules of 21-25 nucleotides in length [11], can regulate gene expression and play important

roles in a variety of physiological and pathologic processes [12, 13]. The first confirmed miRNAs were lin-4 and let-7, which were discovered by Lee et al. [14] in C. elegans. Several research groups subsequently identified hundreds of miRNAs in a variety of biological species, including humans, fruit flies, and plants. According to the latest miRBase database 22.0, there are 1917 annotated hairpin precursors in the human genome [15]. MiRNAs can regulate translational inhibition or promote the degradation of certain messenger RNAs (mRNAs) by binding to the 3'-untranslated region (UTR) of the target genes. In addition, the circulating miRNAs, stored in microvesicles or combined with protein complexes before release, can be detected in serum or plasma in a stable form [16]. MiRNAs participate in a series of essential biological processes, such as cell growth, differentiation, proliferation, migration, apoptosis, necrosis, inflammation and immunity [17-19]. Recent studies have found that miRNAs are involved in the regulation of various pathological processes, such as cardiovascular diseases, various tumors, diabetes, and immune system and kidney diseases [20, 21]. Previous studies have shown that some miRNAs can be released from infarcted cardiomyocytes during AMI, leading to elevated circulating miRNA levels [22, 23]. Therefore, these miRNAs are expected to reflect cardiac damage associated with AMI, suggesting that cardiac-specific or cardiac-enriched miRNA-499 may be useful biomarkers for screening AMI. Among these miRNAs as potential biomarkers, miRNA-499 is the most notable miRNA.

At present, although many studies have shown that miRNA-499 has a certain value for the diagnosis of AMI, the results of these studies have been inconsistent [24, 25]. For example, Agiannitopoulos et al. [26] reported a higher specificity (100%) and a lower sensitivity (98%) of miRNA-499 for AMI diagnosis, but Velu et al. [27] confirmed a higher sensitivity of miRNA-499 (93.33%) and a lower specificity (86.67%). In addition, the robustness and reliability of these studies were largely influenced by the sample sizes. This study used a meta-analysis to expand the sample size and enhance the reliability of the results, thus establishing evidence-based medical findings for miRNA-499 of AMI.

Materials and methods

Literature retrieval

A preliminary literature search was performed using the PubMed, Embase, and Cochrane databases. The search period was from the databases' inceptions to October 2018, with the search terms "myocardial infarction" and "miRNA-499". In addition, manual searches of the references included were conducted to prevent the omission of high quality articles. The search strategy was to search the databases by combining the subject words with natural language terms.

Criteria for the inclusion and exclusion of published studies

The included studies had to meet these inclusion criteria: (1) The study subjects were clinically diagnosed as patients with AMI through clinical manifestations, electrocardiogram, coronary angiography, etc.; (2) Randomized control studies; (3) The study types were diagnostic or prognostic studies of miRNA-499 for AMI; (4) The experimental data were authentic and reliable, and could provide enough experimental data, including sample size, sensitivity, specificity and so on. Additionally, the major exclusion criteria were as follows: (1) The literature did not provide sufficient data results; (2) Patients with congenital heart disease; (3) Reviews, lectures, conference papers, academic dissertations, etc.; (4) The application of animal models in the experimental design; (5) The sample types were tissues, secretion or excreta; (6) Duplicate publication.

Quality evaluation

The quality of the registered literature was assessed by two independent researchers based on the QUADAS-2 scoring system prepared by the Cochrane Collaboration [28]. The results of the 11 evaluation items were answered using "yes", "no" and "not clear". 1 point was given for each "yes" indicating that the condition was satisfied, otherwise "no" was marked as -1 point. In addition, "not clear" was scored as 0 points, indicating partial satisfaction or no mention of relevant information in the article. Finally, studies with score above 7 were considered high-quality literature with a low risk of bias.

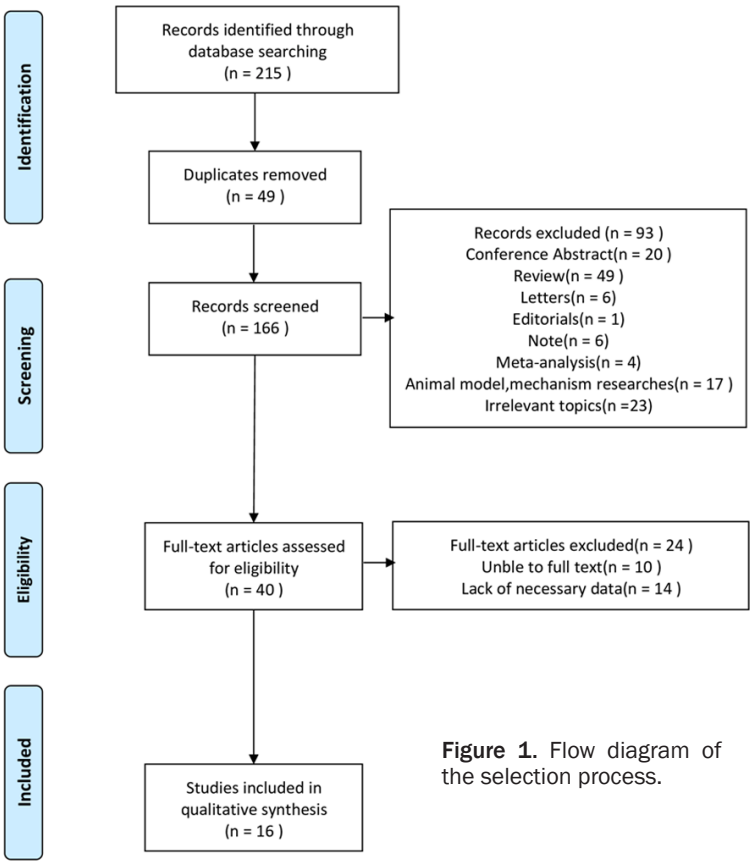

Figure 1. Flow diagram of the selection process.

Data extraction

Data necessary for the research objective were extracted from the selected literature by two staff members. The final decision was made by a third researcher when to the two staff members had different opinions, in order to ensure the reliability of the results. The main research data extracted included: name of first author, publication year, study country, ethnicity, the numbers in the case group and control groups, specimen type, sensitivity, specificity, AUC, cut-off value, and the method of quantifying miRNA-499.

Statistical method

The overall sensitivity, the overall specificity, the positive likelihood ratio (PLR), the negative likelihood ratio (NLR), the diagnostic odds ratio (OR), the receiver operating characteristic curve (AUROC), and the 95% confidence interval were presented to assess the diagnostic value of miRNA-499 in patients with AMI. We used I squared (I^2) to assess the magnitude of heterogeneity among the studies. When the I^2 was large, the random effects meta-analysis was used to incorporate heterogeneity among the studies. All statistical analyses were conducted used Review Manager 5.3 and Stata 12.0 software (StataCorp LP, College Station, TX).

Results

Literature selection and studies characteristics

The screening process for the included studies is shown in **Figure 1**. A preliminary literature search was performed on the databases based on the inclusion and exclusion criteria, and a 215 articles related to the topic were retrieved. After the first preliminary screening based on the abstracts, headlines, and article types, 93 articles were excluded and the remaining 40 articles were used for a further full-text review. After carefully reading the full-text articles, there were 10 articles for which we could not find the full text, and 14 articles lacked the necessary data. As a result, only 16 articles that met the criteria were included in the qualitative synthesis [26, 27, 29-42].

The basic information included in the studies is contained in **Table 1**. The 16 studies included 1991 patients with AMI and 1950 healthy controls. The study sample sizes ranged from 66 to 1155. The research countries included Greece, India, Egypt, Italy, Switzerland, Egypt, and China, and the ethnicities included Europeans, Indians, Egyptians, and Asians. The methods for detecting miRNA-499 expression were the TaqMan detection and the SYBR detection.

Heterogeneity test and publication bias

The sensitivity and specificity of the included studies are shown in **Figure 2**. The size of the heterogeneity was determined to be I^2 = 93.86% and $P < 0.05$. The results showed that there was a high degree of heterogeneity between the results ($I^2 > 50\%$; **Figure 2**).

The result of the funnel plot detection publication bias was P=0.276 (P>0.10) (**Figure 3**). This

Table 1. Characteristics and methodology assessment of the individual studies included in the meta-analysis

Author	Year	Country	Ethnicity	AMI/non-AMI	Specimen	Sensitivity	Specificity	AUC	cut-off value	Methods	QUADAS-2
Agiannitopoulos K [26]	2018	Greece	Caucasian	80/50	plasma	98.00%	100.00%	0.9992	18.56	TaqMan	8
Velu K [27]	2018	India	Indian	60/60	Serum	93.33%	86.67%	0.974	7	TaqMan	8
Fawzy MS [29]	2017	Egypt	Egyptian	110/121	Serum	97.20%	75.00%	0.953	4.8	TaqMan	8
Shalaby SM [30]	2016	Egypt	Egyptian	48/25	plasma	93.40%	100.00%	0.97	2.23	SYBR	10
Liu X [31]	2015	China	Asian	70/72	plasma	82.10%	94.00%	0.88	-	TaqMan	8
Zhang L [32]	2015	China	Asian	142/85	plasma	80.00%	80.00%	0.86	-	TaqMan	10
Zhao CH [33]	2015	China	Asian	59/60	plasma	86.37%	93.47%	0.915	1.5	SYBR	9
Yao Y [34]	2014	China	Asian	28/89	plasma	93.30%	85.70%	0.939	18.7477	TaqMan	11
Devaux Y [35]	2013	Luxembourg	Caucasian	224/931	plasma	78.00%	75.00%	0.65	10.9	SYBR	9
Gidlöf O [36]	2013	Switzerland	Caucasian	319/88	plasma	75.00%	72.00%	0.79	-	SYBR	8
Li C [37]	2013	China	Asian	117/100	Serum	80.00%	93.00%	0.755	-	TaqMan	9
Li YQ [38]	2013	China	Asian	67/32	plasma	90.00%	70.00%	0.884	-	SYBR	8
Devaux Y [39]	2012	Belgium	Caucasian	510/87	plasma	95.00%	100.00%	0.98	-	TaqMan	9
Olivieri F [40]	2012	Italy	Caucasian	92/81	plasma	88.00%	75.00%	0.88	-	TaqMan	8
Corsten MF [41]	2010	Belgium	Caucasian	32/36	plasma	84.00%	89.00%	0.918	-	SYBR	8
Wang GK [42]	2010	China	Asian	33/33	plasma	6.000%	90.30%	0.822	-	TaqMan	10

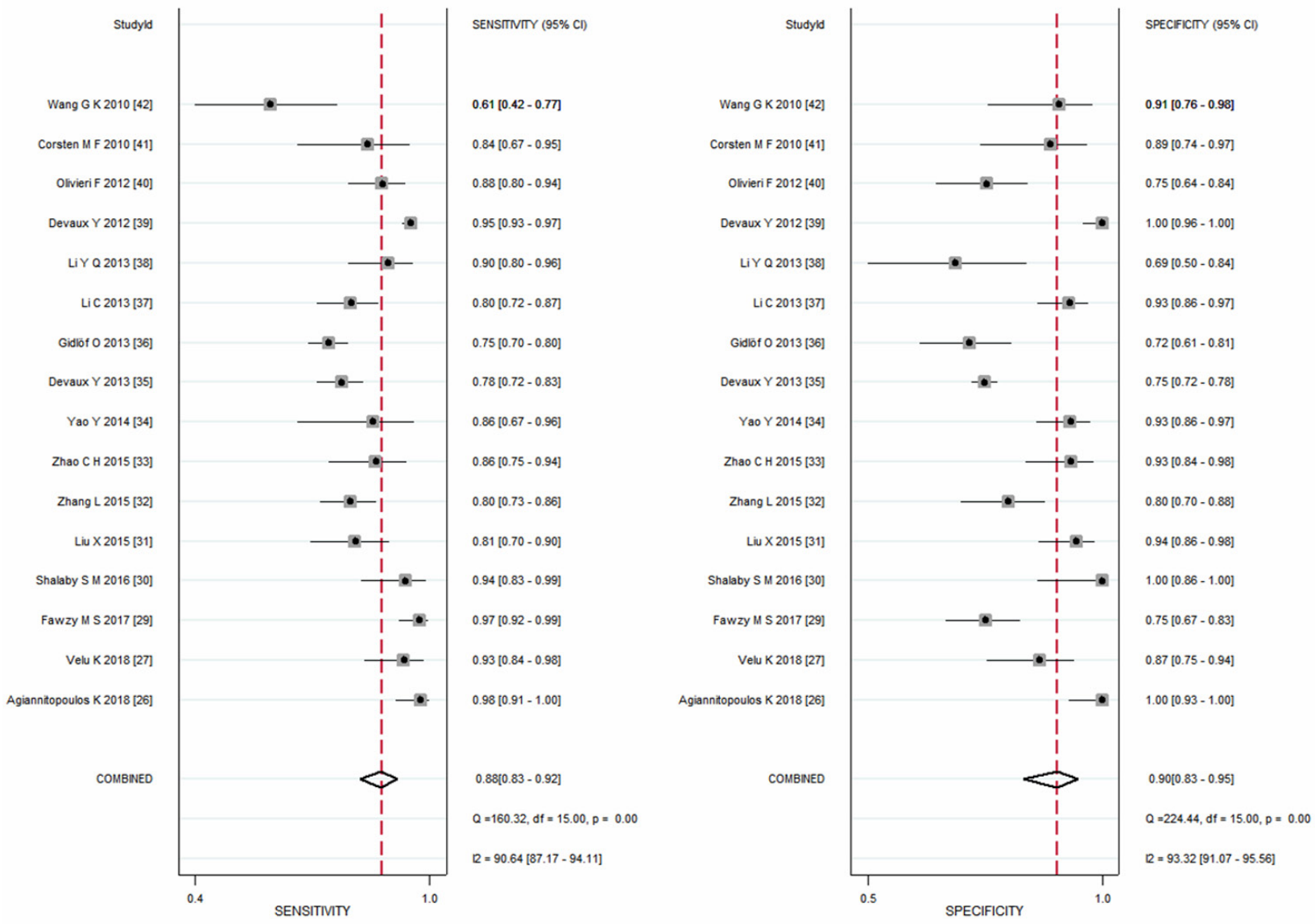

Figure 2. A forest plot of the sensitivity and specificity of miRNA-499 as a diagnostic marker for AMI.

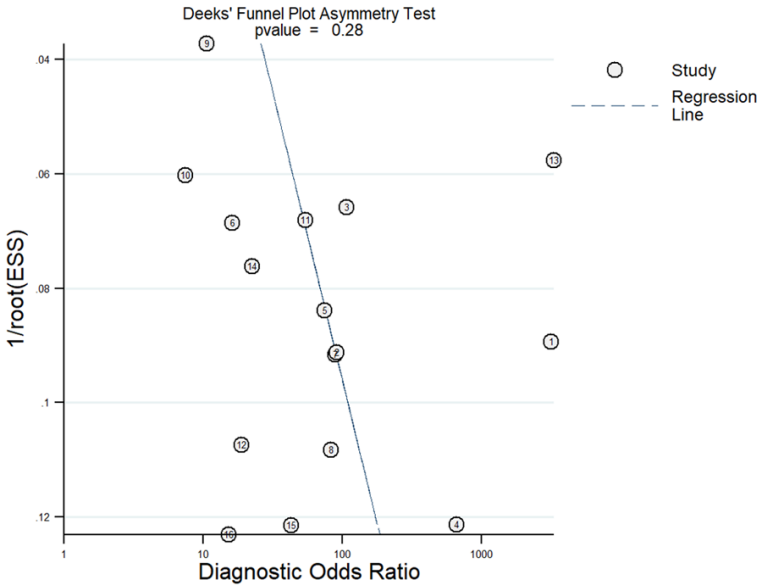

Figure 3. Publication bias of the included studies.

indicated that there was no significant asymmetry in the funnel plot and no significant publication bias in the study. A further analysis of heterogeneity sources showed that the Spearman correlation coefficient between the logic of sensitivity and the logic of 1-specificity was -0.303, and the *P* value was 0.254. These results suggest that there was no threshold effect between the results of each study. It suggested that heterogeneity may be derived from non-threshold effects, including ethnic differences in the population, the size of the study, and the reagents for detecting data. According to the different detection methods for miRNA-499, we further carried out a subgroup analysis. In the end, we found that the heterogeneity among the TaqMan detection results was 79.2%, and the heterogeneity among the SYBR detection results was 95.8% (**Figure 4**).

Results of the meta-analysis

A comprehensive literature analysis undertaken in this study revealed that the overall sensitivity (SENS) of miRNA-499 for diagnosing AMI was 0.878 [95% CI: 0.827-0.915] and the specificity (SPEC) was 0.904 [95% CI: 0.831-0.947]. The positive likelihood ratio (PLR) was 9.151 [95% CI: 4.993-16.770], and the negative likelihood ratio (NLR) was 0.135 [95% CI: 0.092-0.199]. The overall diagnostic OR and 95% confidence interval (CI) were 67.776 and 27.994-164.092, respectively. In addition, we further analyzed the overall diagnostic performance of miRNA-499 for AMI using the SROC curve, as shown in **Figure 5**. The area under the receiver operating characteristic (AUROC) curves was 0.950, and the 95% confidence interval was 0.920-0.960.

Discussion

Acute myocardial infarction (AMI) is a major disease that threatens human health in our society. AMI, arising from myocardial ischemia, is the world's leading cause of morbidity and mortality [43]. The early discovery and diagnosis of the disease have an extremely important clinical significance for patients with AMI. The main pathological changes in AMI are myocardial ischemic injury and myocardial apoptosis, which ultimately lead to heart failure [44]. With the development of AMI, many biomarkers can be detected in the peripheral blood, such as the isoenzyme of creatine kinase-MB (CK-MB), cTn and myoglobin. Many studies have shown that an abnormal expression of miRNAs may be involved in the pathogenesis of AMI [45, 46], and miRNAs can be released into the blood from dying cardiomyocytes during AMI, leading to elevated circulating miRNAs levels [47, 48]. MiRNAs have significant advantages as markers of AMI because their expected half-life in vivo is very short [49] and may be able to show transient changes during disease progression. Levels of the circulating miRNAs have been reported to turn higher with the progression of AMI, suggesting a promising role of miRNAs in early AMI diagnosis. Therefore, circulating miRNAs may serve as additional specific biomarkers for the diagnosis and treatment of AMI.

MiRNA-499 is located in the intron of the cardiac β-myosin heavy chain 7B (MYH7B) gene on chromosome [50]. Huang Y et al. [51] pointed out that miRNA-499 is highly expressed in the myocardium and is rarely expressed in other skeletal muscle tissues. Under normal physiological conditions, miRNA-499 has a low expre-

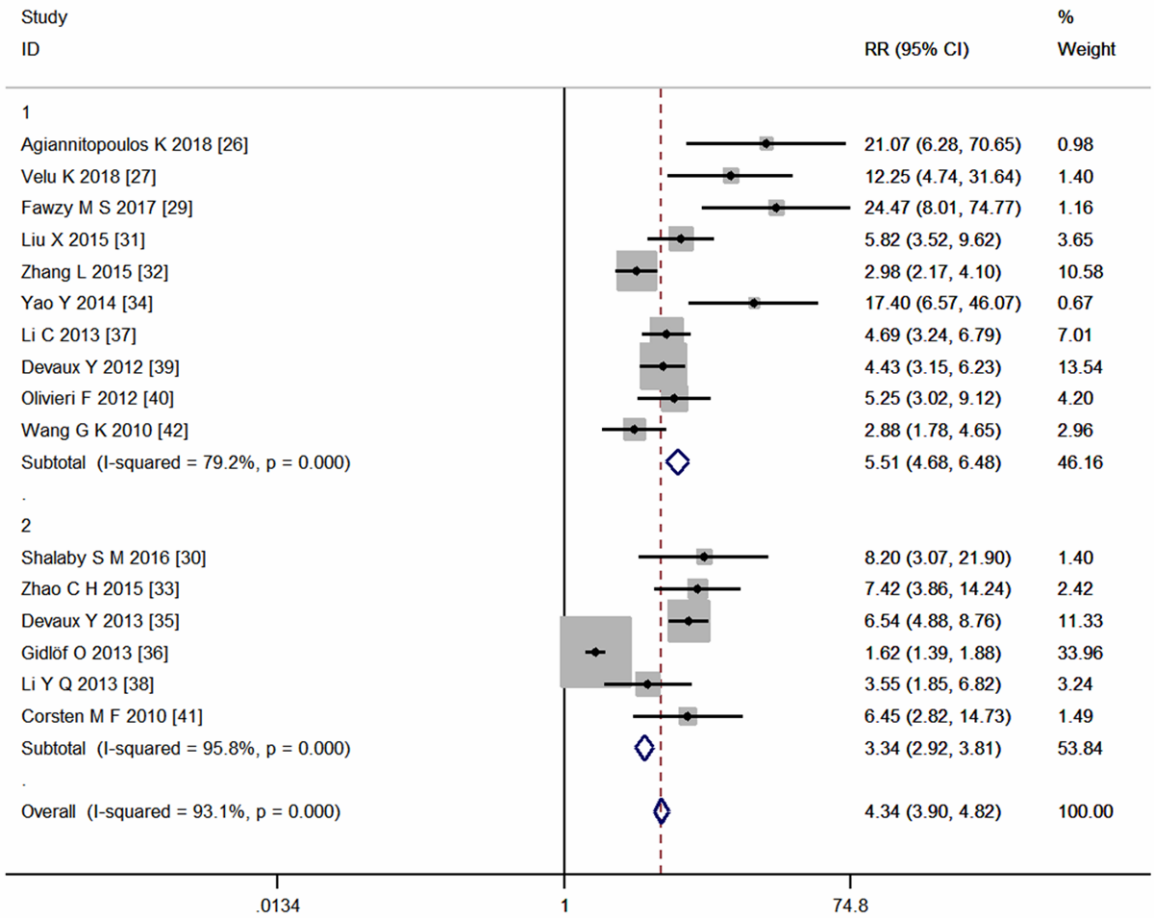

Figure 4. Subgroup analysis-forest plot for the serum levels of miRNA-499 tested using the TaqMan or SYBR method.

ssion level, which regulates the expression of the β-myosin heavy chain, leading to an increase in myocardial oxygen metabolism and tolerance [33], and playing an important regulatory role in the differentiation of myocardial and skeletal muscle cells [52]. In the pathological process of myocardial infarction, miRNA-499 may regulate the apoptosis pathway mainly by regulating calcineurin and dynamin-related protein-1 (Drp1). Tan et al. [53] pointed out that miRNA-499 binds directly to calcineurin and causes cell apoptosis. However, in recent years, some scholars have suggested that miRNA-499 inhibits apoptotic activity in cardiomyocytes by inhibiting the calcineurin-mediated dephosphorylation of dynamin-related protein-1 (Drp1) [54].

We all know that, if AMI is not treated promptly, it is fatal. Although the existing myocardial markers can diagnose most cases of AMI, some AMIs cannot be treated in time due to the detection time limit or for other reasons. In addition, high levels of cTn are also detected in other acute and chronic diseases, which poses a challenge to the early diagnosis of AMI. Since the discovery of the relationship between miRNAs and AMI in 2010, many studies on miRNA-499 and AMI have been published. These studies suggested that miRNA-499 could improve the diagnostic efficiency of AMI. Although there have been many studies showing that circulating miRNA-499 had a certain diagnostic value for AMI, the results of these studies were inconsistent. And the results of these studies were largely affected by the sample size in terms of accuracy and robustness. Therefore, our study used a meta-analysis as a powerful and useful tool to expand the sample size and enhance the stability. As a result, we suggested that there existed a much better way to prove the association between the level of serum miRNA-499 and the diagnosis of AMI patients. Compared to other meta-analyses, our meta-analysis incorporates more updated studies. Our current findings are consistent with reports

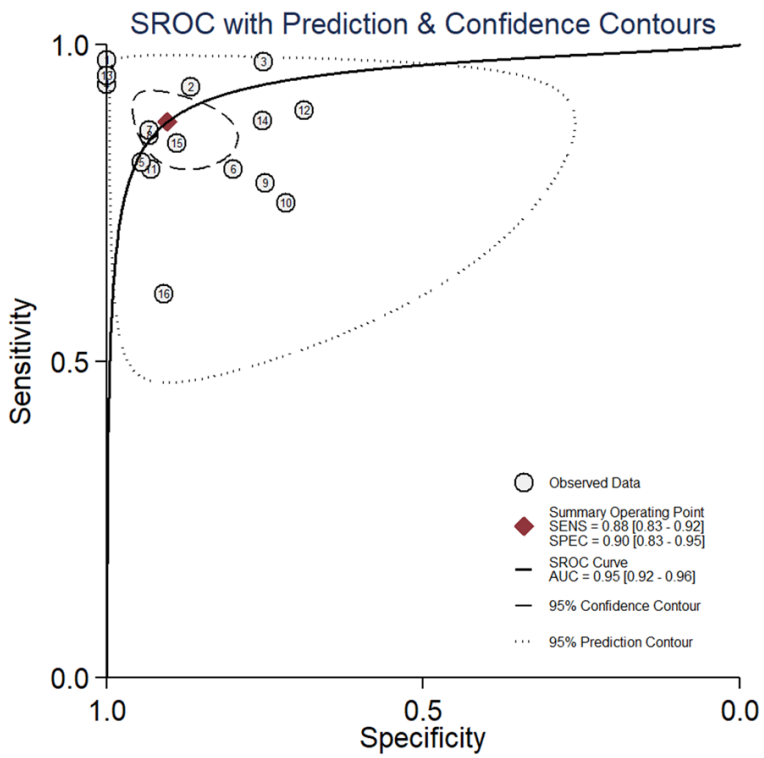

Figure 5. Summary receiver operating characteristic curve.

from Liu et al. [55] and Cheng et al. [56], indicating increased levels of circulating miRNA-499 during AMI and levels significantly higher than in healthy volunteers. The results of Lin Zhang et al. [57] showed that the plasma levels of miR-499 were slightly increased in AMI patients, but the differences were not statistically significant.

A total of 16 articles were included in our study. The meta-analysis showed that the overall sensitivity and specificity of miRNA-499 for diagnosing AMI were 0.878 and 0.904, which was slightly lower than the sensitivity and specificity of other meta-analysis such as those by Liu et al. [32] (0.83 and 0.90) and Cheng et al. [58] (0.88 and 0.87). The diagnostic odds ratio for our study was 67.776 [95% CI: 27.994-164.092], indicating that the probability of miRNA-499 positivity in AMI patients was 67.776 times higher than that in non-AMI patients. In our study, the AUC of the SROC curve was 0.95 [95% CI: 0.92-0.96], suggesting that miRNA-499 had a high diagnostic value for AMI. Overall, these results suggest that miRNA-499 has a high overall diagnostic performance for AMI and could be used as a potential biomarker for the diagnosis of AMI.

However, there are some limitations in this meta-analysis. First, the information retrieval was limited to English and studies written in other languages were not included, which may lead to the absence of some high-quality studies. Second, the countries covered by the included papers are mainly developed countries, leading to the existence of regional bias; Third, the detection time and the detection process of miRNA-499 have not been fully standardized. The relevant technology is not yet mature, which may lead to the creation of some bias. Therefore, subsequent improvements to the miRNA-499 detection methods are particularly important. Finally, due to the limited number of articles included, subgroup analyses were not performed for some causes such as miRNA-499 species, ethnicity, sample size, and so on.

Conclusion

In conclusion, despite some limitations, miRNA-499 may still be a new diagnostic marker for AMI. Moreover, with the quick development and continuous improvement of various analytical techniques and miRNAs detection technology, a more accurate, fast, and inexpensive method of detection methods may appear. Simultaneously, considering the limitations, such as the time limit for detection and the number of samples, further studies are still needed to confirm the results.

Disclosure of conflict of interest

None.

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