

Original Article

Plasma levels of microRNA-499 in patients with acute myocardial infarction: a meta-analysis

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Abstract: The purpose of this meta-analysis was to investigate whether plasma miR-499 levels was an accurate biomarker for acute myocardial infarction (AMI) by comparing plasma miR-499 levels of AMI patients and normal controls. Pubmed, Embase and Medline databases (up to June 2015) were used to search all related articles. The weighted mean differences (WMDs) with 95% confidence interval (CI) were calculated using random-effect model analysis. The Cochrane Q test and I^2 statistic were used to test heterogeneity. To assess publication bias, the Egger's test and Beeg's test were used. A total of four studies including 149 patients and 189 healthy controls were finally included in the meta-analysis. The results revealed that the plasma miR-499 level was no significant difference between AMI patients and normal control (WMD=6.202, 95% CI=-0.158~12.562, $P=0.056$). In conclusion, this meta-analysis indicates that plasma miR-499 level has no association with the risk of AMI and was not an accurate biomarker for AMI.

Keywords: Acute myocardial infarction, MicroRNA-499, meta-analysis

Introduction

Acute myocardial infarction (AMI) is the leading cause of acute chest pain and represents a most common cardiovascular disease with high morbidity and mortality worldwide [1, 2]. A quickly diagnosis of AMI is the critical for clinical treatment. Generally speaking, the diagnosis of AMI is mainly based on electrocardiography (ECG). However, the diagnosis of the ECG is quite subjective and some AMI patients have no typical ECG manifestations. In contrast, laboratory marker are more and more favorable by clinicians, such as troponin (cTnI/T), creatine kinase-MB (CK-MB) [3] and microRNAs (miRNAs) [4].

MiRNAs are 20-25 nucleotide long non-coding RNAs that are negative regulators of gene expression by binding to 3'UTR of mRNA [5]. Accumulating evidences have demonstrated that the expression of miRNAs in tissues contributes to diseases, such as cancer, aging, and cardiovascular disease [6-8]. In addition, recent studies discovered that miRNAs are stably present in human serum/plasma [9]. Most

importantly, these circulating miRNAs can serve as a potential biomarker in many disease, including cancer [10] and autoimmune diseases [11].

In the past few years, several studies have detected plasma miR-499 level in many AMI patients. In addition, miRNA array analysis showed that plasma miR-499 concentrations increased in AMI patients [12-15]. However, there was no comprehensive review and meta-analysis to conclusive the association between miR-499 levels and AMI and investigate possible roles of miR-499 in physiopathology of AMI. Therefore, we perfume a meta-analysis to derive a more precise estimation of the relationship between plasma miR-499 level and AMI.

Materials and methods

Publication search

We obtained literature search through Pubmed, Embase and Medline databases to identify studies published in English up to June 2015.

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

Author	Publish year	County	Case			Control			Reference
			N	Mean	SD	N	Mean	SD	
Zhao et al.	2015	China	59	22.10	3.71	60	0.70	0.15	[18]
Chen et al.	2015	China	53	5.12	2.29	30	0.50	0.35	[13]
Yao et al.	2014	China	28	17.18	1.12	89	20.14	1.65	[19]
Adachi et al.	2010	Japan	9	4.19	0.24	10	2.38	0.13	[12]

N: number, SD: standard deviation.

Table 2. The results of random effects and heterogeneity test in AMI

Disease	N	Random effect			Heterogeneity test		Egger's test		Begg's test
		WMD	95% CI	P	Q	P	I ² %	P	P
AMI	4	6.202	-0.158 to 12.562	0.056	2005.66	<0.001	99.90%	0.511	0.174

WMD: weighted mean difference, 95% CI: 95% confidence interval.

The search terms and key words were used as follows: "Acute myocardial infarction" or "AMI" combined with "microRNA-499" or "miR-499" in the title or abstract, and was limited by "clinical trials, randomized controlled trial, review" published in English. Studies contained available data were considered eligible in this meta-analysis: (1) case-control study and clinical study design, (2) article provided the mean and the standard deviation (mean ± SD) of the miR-499 level in AMI patients and healthy controls. Among the studies with overlapping data published by the same author, only the complete study was included in this meta-analysis.

Data extraction and classification

The extracted information for each study included first author's last name, publication year, country, case/control number, and the mean and standard deviation (mean ± SD) of the plasma miR-499 of case and control.

Statistical analysis

The measure of the association between plasma miR-499 level and the AMI by the weighted mean difference (WMD), which is a standard statistic to measure the absolute difference between the mean value in the two groups. WMD also used as a summary statistic in meta-analysis when results in all studies are made on a similar scale. In our analysis, the methods used for detecting the level of plasma of all studies were similar (4 studies were real-time PCR), so WMD with 95% confidence interval (CI)

was used to evaluate the association between plasma miR-499 level and AMI. The mean and standard deviation (mean ± SD) were extracted from each study. The Cochrane Q test (chi-square test, χ^2) was used to test heterogeneity, and the I² statistic was used to quantify the inconsistency [16]. Publication bias was assessed by a Begg-adjusted rank correlation test (funnel plot method) and Egger's linear regression asymmetry test [17]. For all analysis, the statistical analysis method is logistic regression analysis and P-value of <0.05 was considered statistically significant. All meta-analysis were performed using Stata/SE software (version 9.0; Stata Corporation, College Station, TX).

Results

Study characteristics

In all, four studies including 149 AMI patients and 189 normal control were included. The basic characteristics of the included four studies are shown in **Table 1**. The baseline date of plasma miR-499 levels in AMI patients and normal persons were collected in these studies. Measurement methods of plasma miR-499 level of 4 studies were real-time PCR.

Meta-analysis result

Significant heterogeneity was observed among the 4 studies ($P < 0.05$), so the random-effects model was selected. The results of this meta-analysis are shown in **Table 2**.

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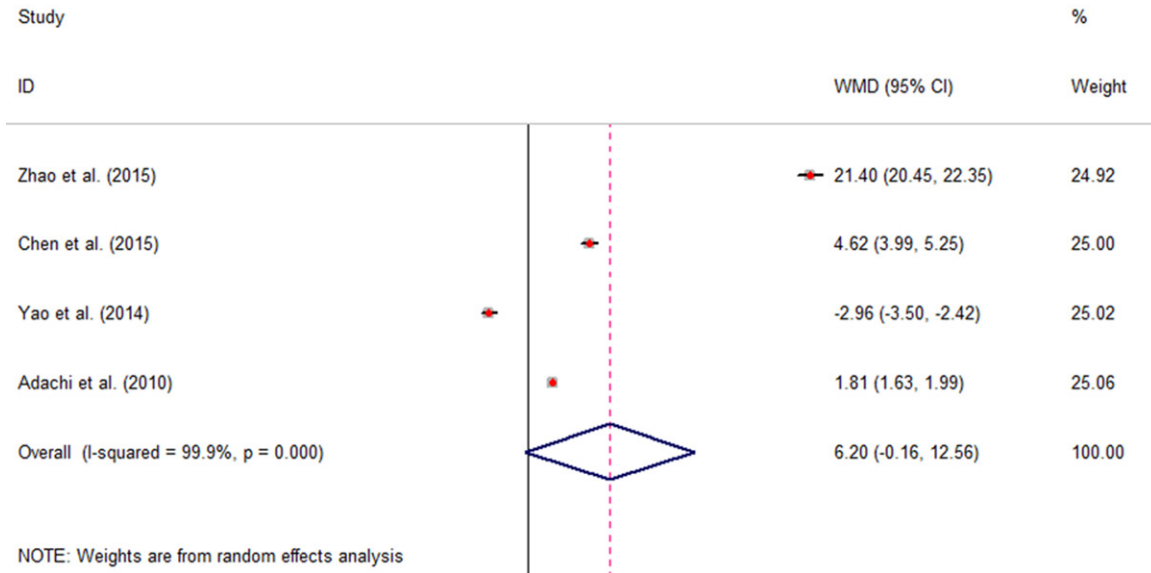


Figure 1. Forest plot of studies in plasma miR-499 level for patients with AMI versus healthy subjects.

Analysis in AMI

Significant heterogeneity was found among the four studies ($Q=2005.66$, $P<0.001$, $I^2=99.90\%$). The random-effects meta-analysis results suggested that the plasma miR-499 level in AMI patients was higher than that in healthy controls, but not statistically significant ($WMD=6.202$, $95\% CI=-0.158\sim 12.562$, $P=0.056$) (**Table 2** and **Figure 1**). Egger's tests and Begg's tests for publication bias showed no publication bias (Egger's $P=0.511$, Begg's $P=0.174$). This data suggests that plasma miR-499 level has no association with the risk of AMI.

Discussion

MiR-499 is discovered recently and highly conserved in mammals. It mainly exists in the myocardium and skeletal muscle. Accumulation studies reported that the plasma levels of miR-499 were significantly increased in patients with AMI [12, 13]. They considered that miR-499 may be a clinical marker for the diagnosis of AMI. However, results from these studies were limited. So we implemented a comprehensive meta-analysis to identify whether plasma miR-499 is a biomarker of AMI.

In our meta-analysis, we evaluated the association of plasma miR-499 levels with AMI. Our data suggested that the plasma levels of miR-499 was slight increase in AMI patients but not statistically significant. The meta-analysis results

showed that based on current clinical data, miR-499 plasma miR-499 levels were not an accurate biomarker for AMI.

This is the first meta-analysis to evaluate the relationship of plasma miR-499 levels with AMI. However, there are several limitations such as the limited sample sizes, unpublished studies, and significant heterogeneity. Thus, the results of meta-analysis should be interpreted with caution.

In conclusion, our meta-analysis shows that the plasma levels of miR-499 in AMI patients had no statistically significant compared with normal controls. The results indicate that plasma miR-499 levels were not an accurate biomarker for AMI. Nevertheless, given to the limitations mentioned above, further studies that contain large sample sizes are still needed.

Disclosure of conflict of interest

None.

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