

# A meta-analysis of the relations between blood microRNA-208b detection and acute myocardial infarction

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**Abstract. – OBJECTIVE:** To investigate the relationship between the expression levels of microRNA-208b and early diagnosis of the acute myocardial infarction.

**MATERIALS AND METHODS:** Literature search were performed within PubMed, Medline, Embase, and CNKI databases, according to inclusion and exclusion criteria, and other relevant literatures about included studies were searched to get more information about this study. Two staff members extracted data from the included studies for meta-analysis.

**RESULTS:** This study included 6 documents, involving a total of 826 patients with acute myocardial infarction and 429 controls. Meta-analysis results: sensitivity 82%, specificity 83%, positive likelihood ratio of 5.0, negative likelihood ratio 0.21, diagnostic odds ratio area was 23, area under operating characteristic curve was 0.88 (95% CI: 0.85-0.91).

**CONCLUSIONS:** microRNA-208b expression was increased in the blood of patients with acute myocardial infarction, and may be used for the early diagnosis of acute myocardial infarction molecular biomarkers.

Key Words:

microRNA, Acute myocardial infarction, Early diagnoses, Meta-analysis.

## Introduction

The myocardial injury caused by myocardial infarction can lead to the blood circulatory dysfunction, thoracic discomfort (like the symptoms of heartburn) or even the heart failure or blood circulation suspension<sup>1</sup>. Myocardial infarction is a common form of coronary artery disease, and for nearly 90% of patients with myocardial infarction, smoking and hypertension are

two risk factors<sup>2</sup>. Also, environmental pollution, including noise and air pollution, can generate the adverse impact on the onset of myocardial infarction<sup>3</sup>. The pathogenesis of myocardial infarction is that the aggregation of collagen fibers in the site of myocardial infarction can cause fibrosis of the injured myocardium, and the expressions of collagen in the area and surrounding areas of myocardial infarction are elevated; for a healthy person, these expressions are manipulated at a low level<sup>4</sup>. Excellent outcomes have been achieved in the diagnosis and treatment of myocardial injuries, such as ultrasonic diagnosis and evaluation<sup>5,6</sup>, stem cell transplantation and detection of C3G protein<sup>7</sup>. Nevertheless, we still need to carry out further investigations into the diagnosis and prognosis of myocardial infarction to lay a pathophysiological foundation for its diagnosis and prognosis.

Micro-RNAs, also known as miRNAs, are a kind of small, noncoding, single-strand RNAs that can bind with the noncoding region in the poly tail of mRNA to inhibit the activity or promote the degradation of mRNA<sup>8</sup>. The micro-RNA can identify multiple mRNA, and bind with multiple micro-RNA. Thus, mRNA and micro-RNA jointly consist of a precise regulation system. Many studies<sup>9</sup> have revealed that detection of the microRNA expression in the blood can be served for assaying the biological substances and evaluating the prognosis of myocardial infarction. For example, the elevated expression of microRNA-21 reduces the injury area after myocardial infarction; microRNA-1 can be served as a potential indicator in molecular biology for myocardial infarction<sup>10</sup>; microRNA-208b can be served as a long-term indicator for prognosis of patients after myocardial infarction<sup>11</sup>.

Research has shown that there is a certain relation between the concentration of microRNA-208 in the heart as well as blood and the injury of the myocardium<sup>12</sup>. This makes microRNA-208 an indicator in molecular biology for diagnosis and evaluation of myocardial infarction<sup>13,14</sup>. In this work, we aimed to reveal the application value of the microRNA-208b, as a member of microRNA-208 family, in the diagnosis of myocardial infarction through meta-analysis.

## Materials and Methods

### Literature Retrieval

Retrieval was carried out in the databases of PubMed, Medline, and Embase with the following key words: “microRNA-208”, “miR-208” and “myocardial infarction”. Also, we obtained the literature meeting the objective of this study through retrieving the relevant reference literature of the enrolled literature.

### Literature Inclusion and Exclusion Criteria

Inclusion criteria: a) patients were clinically diagnosed with acute myocardial infarction; b) the case-control method was applied in the design of experiment; c) literature was the original English work that had been published in public in recent years; d) data were true and intact; e) that was evaluated as high-quality according to the quality evaluation. Exclusion criteria: a) patients with congenital heart disease; b) reviews, conference papers and correspondences; c) animal models were applied in the design of experiment; d) specimens were collected from the tissues, secretion or excreta.

### Quality Evaluation Criteria for Literature

Quality evaluation was conducted for the enrolled literature using the QUADAS-2 scoring system prepared by Cochrane Collaboration. 11 items were answered using yes, no and not clear, in which a “yes” was for 1 point, a “no” for -1 point and a “not clear” for 0 points. Finally, literature with a score not less than 7 points was considered as high-quality literature.

### Data Retrieval

Data necessary for the research objective were extracted from the enrolled literature by two staffs. When it came to different opinions, they should work out the problem through negotiation or the assistance of a third staff. Extracted litera-

ture mainly included the following information: first author, publication year, source of literature or cases, and the number of cases in case group and control group, detection method of microRNA and the source of specimens.

### Statistical Analysis

The meta-analysis was performed for the data that were successfully extracted using Stata 14.0 in the following procedures: a) test of publication bias and heterogeneity for enrolled literature; b) effect size of incorporated literature that was enrolled; c) acquiring the sensitivity (SENS), specificity (SPEC) and diagnostic odds ratio (DOR) of the enrolled literature; d) sensitivity analysis.

## Results

### Result of Literature Retrieval

The procedure of retrieval is shown in Figure 1. A total of 154 English works of literature relating to microRNA-208b were searched in the preliminary literature retrieval. After the screen, only 6 works of literature met the inclusion criteria<sup>15-20</sup>. Table I shows the basic information of the included literature.

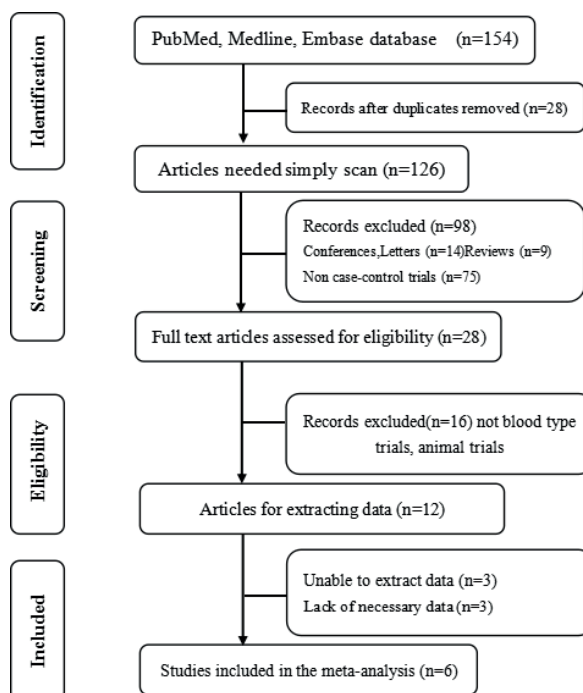


Figure 1. Literature screening process.

**Table 1.** Characteristics of included studies.

ID	Author	Year	Country	Specimen	Patients	Control	SENS	SPEC	AUC	Method
1	Devaux, Y	2015	Luxembourg	blood	45	179	0.61	0.839	0.78	SYBR
2	Li, C	2015	China	plasma	87	87	0.78	0.836	0.67	TaqMan
3	Li, Y Q	2013	China	plasma	67	18	0.824	0.998	0.89	SYBR
4	Devaux, Y	2012	Luxembourg	plasma	510	174	0.83	0.78	0.87	TaqMan
5	Gidlof, O	2011	Sweden	plasma	9	11	0.89	0.86	0.92	SYBR
6	Corsten, M F	2010	Netherlands	plasma	32	36	0.909	0.947	0.94	SYBR

### Test of Publication Bias and Heterogeneity for Enrolled Literature

The results of Begger rank correlation test were  $z = 0.94$  and  $p = 0.348$ , the results of Egger linear regression analysis were  $t = 1.29$  and  $p = 0.267$  (Figure 2B), and the heterogeneity of effect size test was  $I^2 = 43.3\%$  and  $p = 0.116$  (Figure 2A). The results revealed that there was no significant publication bias but a low heterogeneity in enrolled literature ( $I^2 < 50\%$ ). The random effect model was selected for integrating the effect size of enrolled literature.

### Results of Meta-analysis

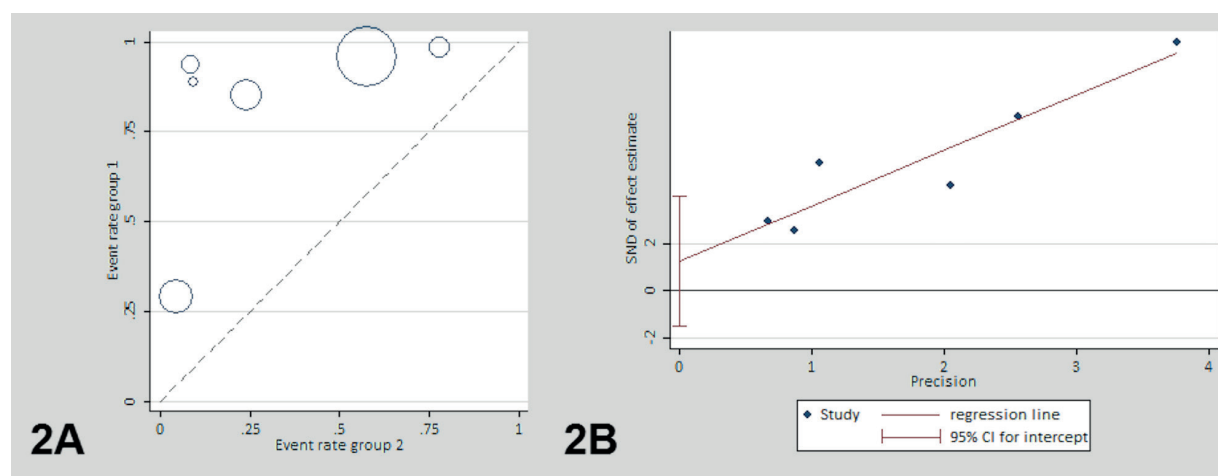
The analysis of integrated literature that was enrolled in this study revealed that the SENS was 0.82 (95% CI: 0.78-0.85), SPEC was 0.83 (95% CI: 0.79-0.87), positive likelihood ratio (PLR) was 5.0 (95% CI: 3.9-6.2), negative likelihood ratio (NLR) was 0.21 (95% CI: 0.18-0.26), diagnostic odds ratio (DOR) was 23 (95% CI: 16-33), and the area under the receiver operating characteristic (AUROC) curves was 0.88 (95% CI: 0.85-0.91). The integrated effect size was 19.27 (95% CI: 10.45-35.51) (Figure 3).

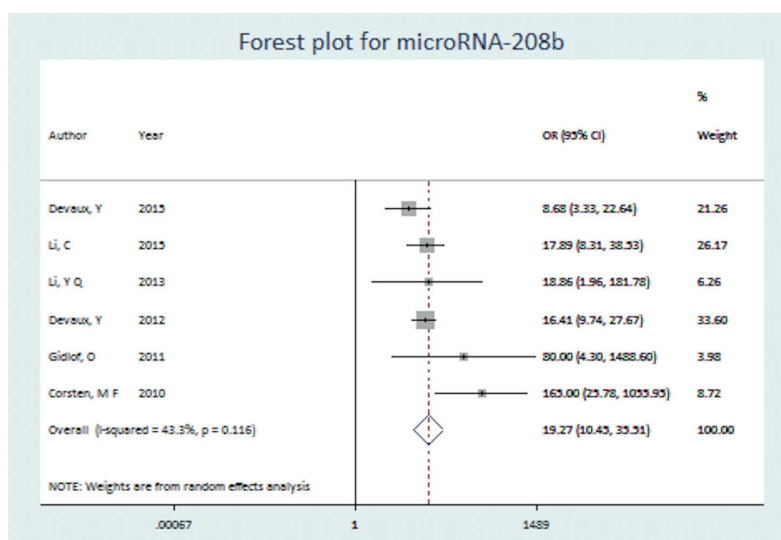
According to the subgroup analysis of detection for microRNA, we found that the heterogeneity among the TaqMan detection results was 0% ( $p = 0.856$ ) and the integrated effect size was 16.87 (95% CI: 10.95-25.98); the heterogeneity among the SYBR detection results was 66.3% ( $p = 0.031$ ) and the integrated effect size was 32.36 (95% CI: 6.51-160.98) (Figure 4).

Analysis of enrolled literature using Trim-and-Fill approach showed that there remained missing studies in this study. Thus, the quantity of relevant studies should be expanded to reduce the bias (Figure 5). Sensitivity analysis of the results indicated no result with a high sensitivity.

## Discussion

In this study, the results revealed that the expression of microRNA-208b in blood was elevated after myocardial infarction, and confirmed the regulatory effect of microRNA-208b in the process of myocardial infarction, concluding

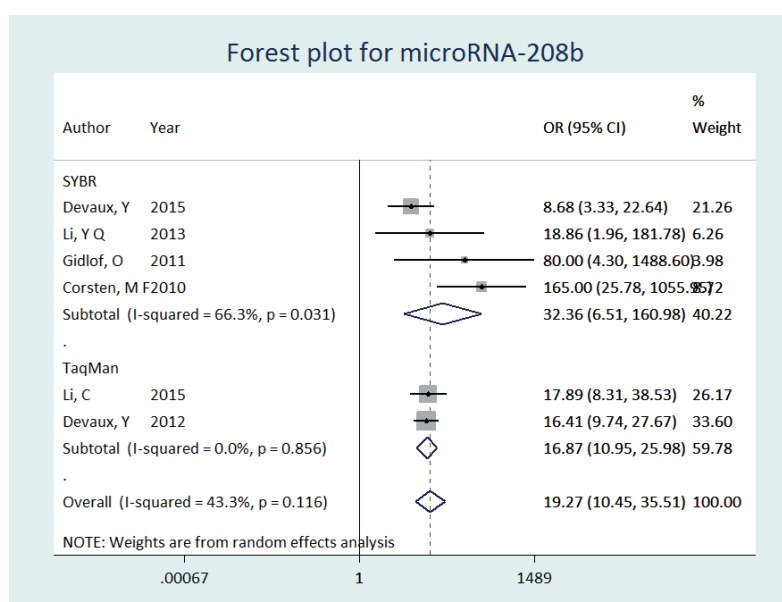
**Figure 2.** The heterogeneity test and publication bias of included literature.



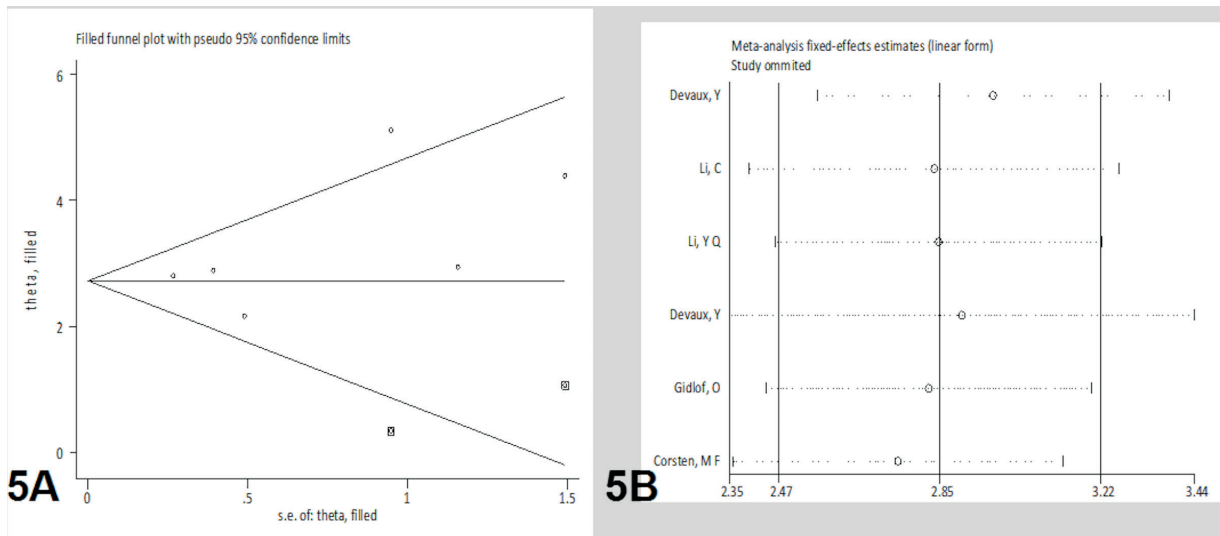
**Figure 3.** Forest plot for relative expression of microRNA-208b in blood and publication bias of included literature (acute myocardial infarction patients vs. control group, OR: Odds Ratio).

that micro-RNA was of great significance for the diagnosis and treatment of acute myocardial infarction in an early stage. MicroRNA, a kind of endogenous small RNA fragment, do not encode any protein. Instead, it is involved in the signal transduction of various biological processes. Thus, it has been applied in the diagnosis of heart failure or hypertension<sup>21,22</sup>. Also, some literature has confirmed that microRNA may also be used as a molecular biology indicator

for the diagnosis and prognosis of myocardial infarction<sup>23,24</sup>. Through the analysis of multiple case-control studies, we comprehensively analyzed the expressions of microRNA-208b in the blood of patients with acute myocardial infarction and patients with non-acute myocardial infarction. The results revealed that the increases in expressions of microRNA-208b in the blood of patients were consistent. The accumulated meta-analysis on variation trend and the results



**Figure 4.** Subgroup analysis-forest plot for relative expression of microRNA-208b in blood tested with TaqMan or SYBR method (acute myocardial infarction patients vs. control group, OR: Odds Ratio).



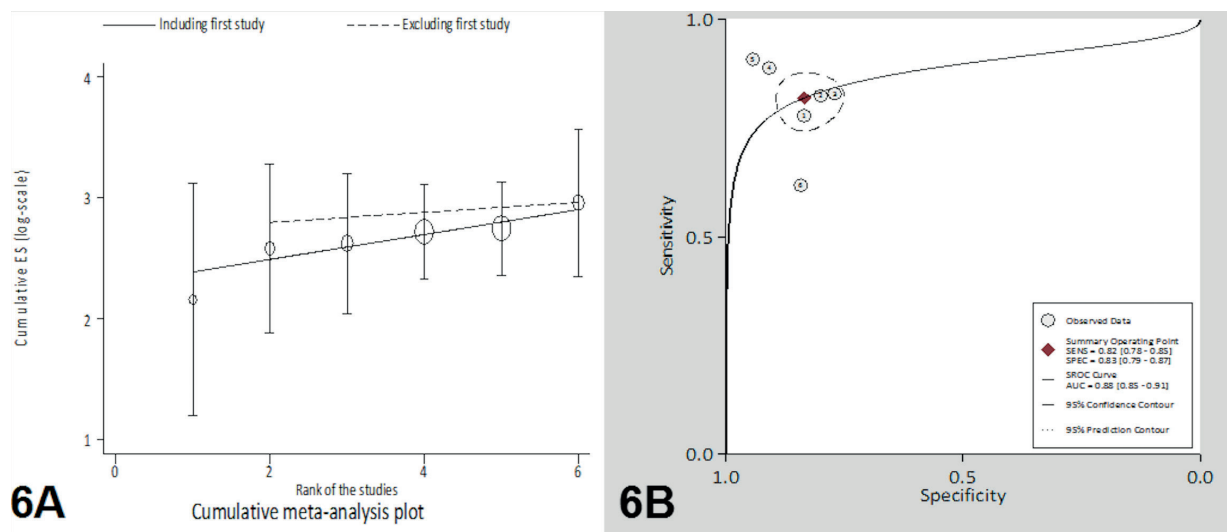
**Figure 5.** Duval and Tweedies Trim-and-Fill approach for heterogeneity test and publication bias of included literature.

of AUROC also implicated that microRNA-208b might be served as an indicator for diagnosis of acute myocardial infarction (Figure 6).

Recently, many reports<sup>25,26</sup> have shown that microRNAs in the blood circulation may affect the mortality rate of patients with acute myocardial infarction and that their concentrations may impact the one-year survival rate of a patient in the prognosis<sup>27,28</sup>. Besides, some studies<sup>29,30</sup> have found that microRNAs are correlated with the myocardial remodeling. The molecular mechanism of microRNA in the diagnosis remains unclear. Nevertheless, based on these results, it can

still be used as a molecular biology indicator for diagnosis of acute myocardial infarction. Besides, the scientific features of this meta-analysis are enhanced. In addition, analysis of hierarchical summary receiver operating characteristic (HSROC) curve also obtained the results like those in the meta-analysis, suggesting that this meta-analysis is reliable.

However, this study has some limitations. Firstly, the analysis was based on a relatively small research group, and there remained some individual or regional differences among the research groups. Thus, a trial with a larger



**Figure 6.** Cumulative meta-analysis of included literature and the receiver-operating characteristic curve.



group of cases is necessary for supporting the reliability of this result. Moreover, the results of microRNA detection were also only the expressions in a certain time point, and no consecutive detections were carried out, which decreased the reliability of this comprehensive analysis in this study.

## Conclusions

With this meta-analysis, we observed that after acute myocardial infarction, the expression of microRNA-208b in blood was elevated. microRNA-208b might be served as an indicator of diagnosis of acute myocardial infarction. Further exploration and analysis are still necessary to acquire a precise statistical analysis result.

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## Conflict of interest

The authors declare no conflicts of interest.

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