**VIA MEDICA**

ORIGINAL ARTICLE

# Diagnostic performance of microRNA-133a in acute myocardial infarction: A meta-analysis

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**Abstract**

**Background:** *The aim of this study was to evaluate the diagnostic performance of microRNA-133a in the diagnosis of acute myocardial infarction (AMI).*

**Methods:** *Major databases including PubMed, Embase and the Cochrane Library were searched for case-controlled studies comparing AMI and non-AMI patients. The outcome was evaluated by the relative expression of microRNA-133a in plasma or serum. The Mantel-Haenszel odds ratio (OR) was calculated using a fixed-effects model meta-analysis for the outcome. The primary outcomes of interest were pooled sensitivity, specificity and diagnostic accuracy of microRNA-133a for AMI.*

**Results:** *Out of 137 identified related articles, 10 were found to conform with the inclusion and exclusion criteria of the study. The 10 case-controlled studies contained complete data for 1,074 patients (with no restrictions of race, age or sex), and a database containing 137 patients from the registry of each study. In addition to low heterogeneity, a statistically significant increase was found in overall microRNA-133a expression between AMI vs. non-AMI; the pooled OR was 22.84 (95% confidence interval [CI] 13.87–37.63), sensitivity was 0.84 (95% CI 0.75–0.90), specificity was 0.82 (95% CI 0.74–0.89) and area under curve (AUC) was 0.90 (95% CI 0.87–0.92).*

**Conclusions:** *Based on the meta-analysis of ten case-controlled studies including 1,074 patients, it was found that the level of microRNA-133a in blood serum or plasma maybe used as a diagnostic biomarker of AMI.* (Cardiol J 2018; 25, 2: 260–267)

**Key words: diagnostic accuracy/value/performance, acute myocardial infarction, microRNA-133a/miR-133a, meta-analysis**

## Introduction

Myocardial injury resulting from acute myocardial infarction (AMI) can cause blood circulation disorder and chest discomfort similar to heartburn symptoms, and can even lead to heart failure or cessation of blood flow [1]. AMI is a common coronary artery disease, with risk factors including smoking and hypertension present in nearly 90% of patients [2]. Environmental pollution, including noise and air pollution, can also have adverse effects on myocardial infarction (MI) [3]. The pathogenesis of AMI involves the accumulation of collagen fibers, resulting in myocardial fibrosis. Usually, healthy people have low expression levels of collagen, but in patients with MI the affected tissue and surrounding area have an increased expression [4]. Although diagnostic, assessment and therapeutic techniques such as ultrasound, biomarkers such as the C3G protein and stem cell transplantation, respectively, have been used successfully in detection, diagnosis and treatment of myocardial injury [5–7], there is still a need to further explore novel approaches for the diagnosis and treatment of AMI and to understand the pathophysiology of AMI.

MicroRNA (miRNA) is a short chain gene-editing, noncoding single-stranded ribonucleotide that can bind to messenger RNA (mRNA) on its poly-adenylated tail end (3'-UTR) in the noncoding region to inhibit or promote its degradation

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[8]. One kind of miRNA can interact with a variety of mRNAs, and one mRNA may interact with a variety of miRNAs together forming a sophisticated regulatory system. Recently, many studies have shown that after MI, the detection of blood miRNA expression can be used as a diagnostic and prognostic tool for AMI. For example, miRNA-21 expression can be increased to reduce the size of the infarct injury [9], miRNA-1 can be used as a potential molecular biomarker for AMI [10], and miRNA-133a can be used as a long-term prognostic indicator for patients after MI [11].

Studies have shown that the miRNA-133a expression level in blood and is related to AMI [12], and this interplay suggests that miRNA-133a could be used as a diagnostic molecular biomarker of AMI [13, 14]. MicroRNA-133a is a member of the miRNA-133 family. The aim of the present study is to determine the diagnostic value of the miRNA-133a expression level for AMI using a statistical method of meta-analysis.

## Methods

### Document retrieval

Keywords were searched in PubMed, Medline and Embase databases using the following medical subject headings (MeSH): "microRNA-133a", "miR-133a", and "myocardial infarction" The data was obtained by retrieving relevant literature references based on information about the studies included.

### Inclusion and exclusion criteria

Two reviewers independently screened all related titles and abstracts using the following inclusion and exclusion criteria. Inclusion criteria: 1) patients with clinical diagnosis of AMI; 2) the published study was a case-control design study; 3) the study was originally published in English within the past 10 years (range from 2006.11 to 2016.11); 4) the study provides accurate and complete information about AMI patients; 5) the study was assessed as a high-quality study; 6) the target miRNA of samples was normalized to an endogenous miRNA with the calculation formula $2^{-\Delta\Delta Ct}$: 2exp (mean Ct endogenous controls – Ct target miRNA). Exclusion criteria: 1) patients with congenital heart disease; 2) a review of the literature, meetings and correspondence letters; 3) experimental design involved an animal model; 4) specimen source from tissue, secretions or excretions.

### Evaluation of the quality of included studies

Two investigators systematically assessed the quality of each article included in the meta-analysis according to the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) with 11 entries for the answer "yes", "no" or "unclear". The "yes" answer is given a plus one-point score, the "no" answer is given a minus one-point score, and the "unclear" answer contributed to zero-point. A score of 7 points or more was considered high quality. Discrepancies were resolved by discussion to reach a consensus.

### Data extraction

Two reviewers independently extracted relevant data required for research purposes from the studies included. When discrepancies were encountered, either they were discussed until differences were settled or the two reviewers were assisted by a third staff member until a consensus was reached. Data extracted from the literature included: first author, year of publication, source documents, case or control group of patients who participated in the study, the method of detection of miRNA and type of specimen.

### Statistical analysis

After successful extraction of data, Stata 14.0 software was used for the meta-analysis. The pooled odds ratios (OR) were calculated and the associated 95% confidential intervals (CIs) using a fixed or random effects model with the statistical method of Mantel-Haenszel (M-H) or DerSimonian-Laird (D-L). Thevariability issue was addressed in results across studies by using the $I^2$ statistic and p-value obtained following the meta-analysis instructions of Stata. The analysis results include 1) publication bias and heterogeneity of included studies; 2) combined effect of the size of included studies; 3) being included in the study sensitivity, specificity, and diagnostic OR; and 4) subgroup analysis based on type of AMI: ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI).

Publication bias analysis was conducted with a comprehensive program of statistical and graphical routines for undertaking meta-analysis of diagnostic performance in Stata. Primary data combination is performed within the bivariate mixed-effects binary regression modeling framework. The model specification, estimation and prediction are carried out following the instructions in Stata release 14.0 (StataCorp LP, College Station, TX, USA).
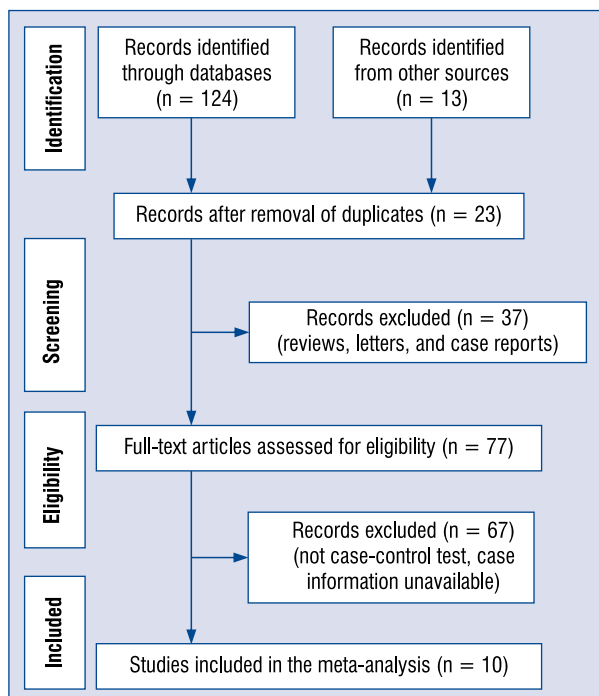
**Figure 1.** Flowchart of the study selection process.

Using coefficients and variance-covariance matrices estimated by the optimal model, the summary operating sensitivity and specificity (with confidence and prediction contours in the summary receiver operating characteristic [ROC] curve space), the summary likelihood and ORs were also calculated. The global and relevant test performance metric-specific heterogeneity statistics are also provided. Studies of the meta-analytical integration of the diagnostic accuracy facilitate the extensive statistical and graphical data synthesis and exploratory analyses of the heterogeneity, covariate effects, publication bias and impact. The Bayes' nomograms and likelihood ratio matrices may be obtained and used to guide the clinical decision-making process.

## Results

### Literature search results

The initial literature search retrieval process is shown in Figure 1 total of 137 publications relevant to miRNA-133a in the English literature were searched, according to the inclusion and exclusion criteria. In summation, 10 articles met the inclusion criteria [12–20]. The documents included are contained in the basic information as shown in Tables 1 and 2.

**Table 1.** Information of the included studies.

| Author, year | Country | Specimen | Total | Sensitivity | Specificity | AUC | Methods | Case-control | QUADAS-2 |
|---|---|---|---|---|---|---|---|---|---|
| Gacon, 2016 | Poland | Serum | 43 | 0.675 | 0.652 | 0.582 | SYBR | STEMI vs. NSTEMI | 9 |
| Devaux, 2015 | Luxembourg | Blood | 224 | 0.651 | 0.808 | 0.530 | SYBR | STEMI vs. NSTEMI | 9 |
| Ji, 2015 | China | Blood | 98 | 0.854 | 0.998 | 0.787 | SYBR | STEMI vs. NSTEMI | 7 |
| Jaguszewski, 2014 | Switzerland | Plasma | 63 | 0.906 | 0.630 | 0.751 | TaqMan | STEMI vs. NSTEMI | 10 |
| Wang, 2013 | China | Plasma | 246 | 0.794 | 0.887 | 0.785 | SYBR | AMI vs. non-AMI | 7 |
| Li, 2013 | China | Plasma | 85 | 0.823 | 0.998 | 0.947 | SYBR | AMI vs. non-AMI | 8 |
| Gidlof, 2011 | Sweden | Blood | 20 | 0.807 | 0.638 | 0.859 | SYBR | STEMI vs. NSTEMI | 8 |
| Kuwabara, 2011 | Japan | Serum | 71 | 0.865 | 0.907 | 0.932 | TaqMan | AMI vs. non-AMI | 7 |
| Wang(a), 2011 | China | Plasma | 79 | 0.977 | 0.825 | 0.890 | SYBR | AMI vs. non-AMI | 8 |
| Wang(b), 2011 | China | Blood | 79 | 0.708 | 0.685 | 0.702 | SYBR | AMI vs. non-AMI | 7 |
| Wang, 2010 | China | Plasma | 66 | 0.843 | 0.878 | 0.867 | TaqMan | AMI vs. non-AMI | 10 |

AMI — acute myocardial infarction; AUC — area under curve; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction; QUADAS-2 — Quality Assessment of Diagnostic Accuracy Studies tool

**Table 2.** Characteristics of included patients in each study.

| Author, year | Male/Female | Mean age | Biochemical information | Characters of included samples | Characters of included patients |
|---|---|---|---|---|---|
| Gacon, 2016 | STEMI: 14/2, NSTEMI: 20/7 | STEMI: 57.5 ± 9.64, NSTEMI: 57.6 ± 10.42 | STEMI: TnT 2.04 ng/mL, Cr 78 ± 15.52 μmol/L; NSTEMI: TnT 0.38 ng/mL, Cr 77 ± 15.0 μmol/L | Blood were collected after heparin treatment in 30 min. | All patients underwent urgent coronary angiography according to ESC/AHA guidelines. Any signs of heart failure (in Killip classes II, III and IV) were excluded before catheterization, prior fibrinolysis, mechanical or electrical complications of ACS. |
| Devaux, 2015 | 158/66 | AMI: 61–80, Non-AMI: 49–74 | cTnT 1.04 ng/mL | Blood samples for determination of cTnT were collected at presentation. | AMI was diagnosed if there was evidence of myocardial necrosis was diagnosed by at least one cTn value above 99th percentile with a significant rise and/or fail. |
| Ji, 2015 | STEMI: 68/9, NSTEMI: 14/7 | STEMI: 61 ± 13.7, NSTEMI: 67 ± 13.9 | STEMI: Cr 83.36 μmol/L, NSTEMI: Cr 87.71 μmol/L | Venous blood was collected immediately after AMI diagnosed and kept at room temperature for 30 min. | Ischemic chest pain lasted for more than 30 min; at least two ECG branches showing 0.1 Mv ST segment elevation; serum cTnl and CK-MB levels were higher than normal at least two times. Patients with severe arrhythmia, heart failure and malignant tumor were excluded. |
| Gidlof, 2011 | 16/4 | 65.09 ± 3.51 | NA | Blood sample was obtained by venipuncture within 24 h of the onset of symptoms. | Patients eligible for inclusion were those undergoing primary percutaneous coronary intervention. |
| Kuwabara, 2011 | AMI: 23/6, Non-AMI: 24/18 | AMI: 69.7 ± 2.4, Non-AMI: 69.2 ± 2.2 | AMI: CK-MB 74.2 ± 31.1 IU/L, Cr 1.1 ± 0.2 μmol/L, AST 108.7 ± 34.0 IU/L; Non-AMI: CK-MB 13.4 ± 1.3 IU/L, Cr 1.2 ± 0.2 μmol/L, AST 24.1 ± 1.5 IU/L | Blood sample was obtained by venipuncture within 24 h of the onset of symptoms. | AMI was diagnosed 20 min with more of chest pain and (1) CK-MB and CPK were rised, or cTnT level ≥ 0.1 ng/mL, (2) new Q-wave formation during the initial 24 h; or (3) at least two contigous ECG ST-segment elevated more than 0.2 mV within 24 h of admission. |
| Jaguszewski, 2014 | STEMI: 3/33, NSTEMI: 4/23 | STEMI: 61 ± 13.7, NSTEMI: 67 ± 13.9 | STEMI: CK-MB 132 U/mL, cTnT 350 pg/mL; NSTEMI: CK-MB 14 U/L, cTnT 257 pg/mL | Plasma sample was collected within 24 h after the onset of symptoms. | Patients from multi-centres were included the present study based on the ESC/AHA/ACC guidelines. |
| Wang, 2013 | AMI: 120/34, Non-AMI: 45/47 | AMI: 59.6 ± 10.5, Non-AMI: 56.5 ± 10.4 | NA | Blood samples were collected immediately after the AMI patient was admitted, the subsequent blood samples were obtained at 4 h, 12 h, 24 h, 48 h. and 72 h | AMI patients inclusion criteria were based on (1) acute ischemic chest pain within 24 h; (2) ECG change of pathological Q-wave and/or ST-segment elevation; (3) plasma cTnl > 0.1 ng/mL. |
| Wang, 2010 | AMI: 23/10, Non-AMI: 22/11 | AMI: 63.5 ± 10.1, Non-AMI: 64.2 ± 7.6 | Cr 72.4 ± 15.6 μmol/L | Blood samples were collected from the patients in the emergency department or the cardiac catheterization laboratory. | AMI patients were clinically diagnosed by biochemical markers (cTnl > 0.1 ng/mL), acute ischemic-type chest pain, ECG change and coronary angiography. |
| Li, 2013 | AMI: 52/15, Non-AMI: 22/10 | AMI: 63.8 ± 11.8, Non-AMI: 61.8 ± 9.6 | NA | Venous blood samples were collected form AMI patients within 12 h of the onset of symptoms (4.6 ± 2.9 h). | Inclusion criteria for patients with AMI were based on the evidence with increased cTnT or CK-MB levels combined with chest pain lasting more than 30 min and ECG findings such as new pathological Q-waves ro ST-segment elevation or depression. |
| Wang (a,b), 2011 | AMI: 43/8, Non-AMI: 19/9 | AMI: 60.1 ± 11.5; non-AMI: 57.9 ± 10.4 | AMI: Cr 75.02 ± 15.7 μmol/L, CK-MB 254.6 ± 188.65 IU/L, Tnl 14.81 ± 13.85 ng/mL; Non-AMI: Cr 71.61 ± 12.14 μmol/L, CK-MB 9.89 ± 3.37 IU/L, Tnl 0.02 ± 0.02 ng/mL | Whole blood samples were collected from AMI patients within 24 h after onset of syndromes. | Patients were included with the evidence of plasma CK-MB levels increased to twice of the normal or Tnl levels were greater than 0.1 ng/mL. And at least one of the following criteria: chest pain lasting > 20 min or ECG changes consisting of new pathological Q waves or ST-segment. |

ACS — acute coronary syndrome; AMI — acute myocardial infarction; Cr — creatine; CK-MB — MB isoenzyme of creatine kinase; CPK — creatine phosphokinase; cTnT — cardiac troponin T; ECG — electrocardiogram; NA — not applicable; TnI — troponin I; TnT — troponin T; AST — aspartate aminotransferase; STEMI — ST-segment elevated myocardial infarction
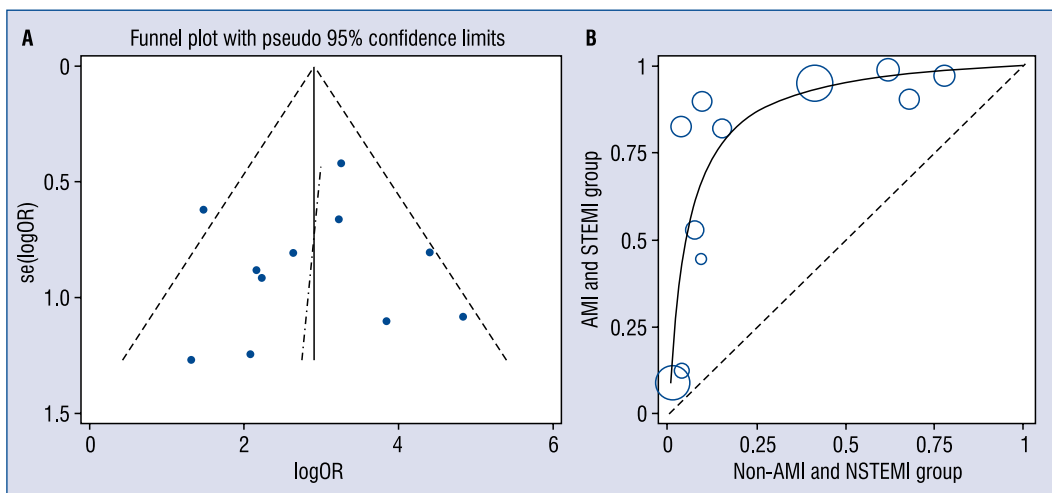
**Figure 2.** Publication bias test and heterogeneity of the included studies. **A.** Funnel plot of the included studies; **B.** Labbe plot for detecting heterogeneity; AMI — acute coronary syndrome; NSTEMI — non-ST-segment elevation myocardial infarction; OR — odds ratio.
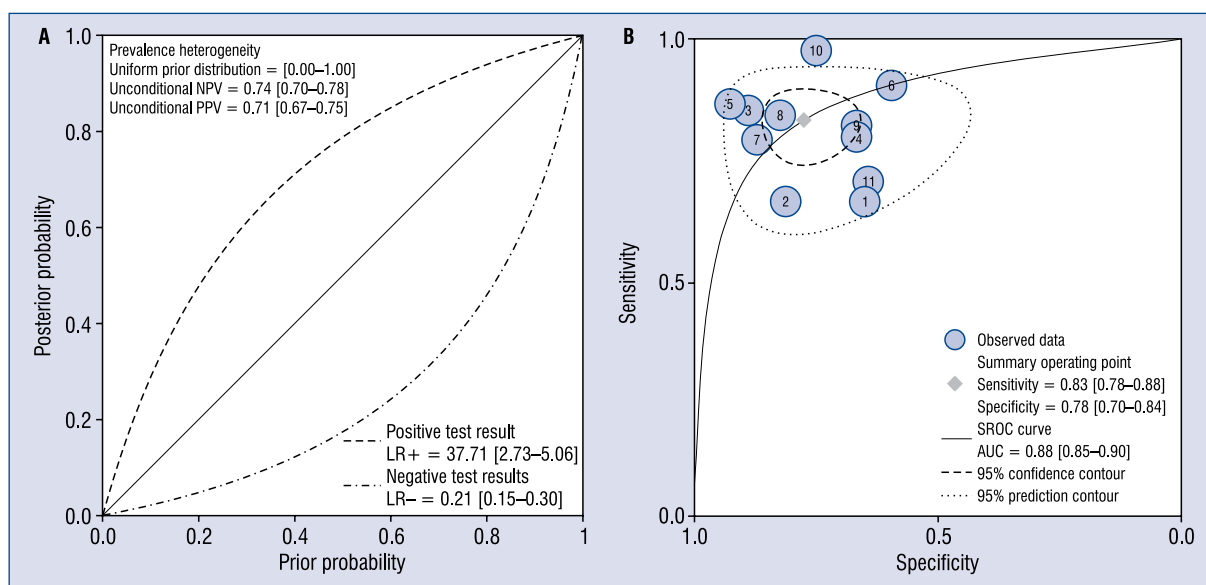


**Figure 3.** Diagnostic probabilities and summary receiver operating characteristic (SROC) curve; **A.** Line graph of post-test probabilities versus prior probabilities between 0 and 1 using summary likelihood ratios; CI — confidence interval; NPV — negative predictive value; PPV — positive predictive value; **B.** Summary receiver operating characteristic curve; AUC — area under curve.

## Document publication bias and heterogeneity test

The results of Begg's rank correlation test were as follows z = –0.7, p = 0.484; Egger regression analysis t = –0.23, p = 0.824; and the effect of size in detecting heterogeneity was $I^2 = 41.7\%$, p = 0.071. The results showed that studies included have moderate publication bias (Fig. 2A),

and low heterogeneity ($25\% < I^2 < 50\%$; Fig. 2B). Accordingly, a fixed effect model to merge the effect size of the studies included was selected.

## Meta-analysis and subgroup meta-analysis

The combined analysis of the included studies revealed that sensitivity was 0.83 (95% CI 0.78––0.88), the specificity was 0.78 (95% CI 0.70–0.84),
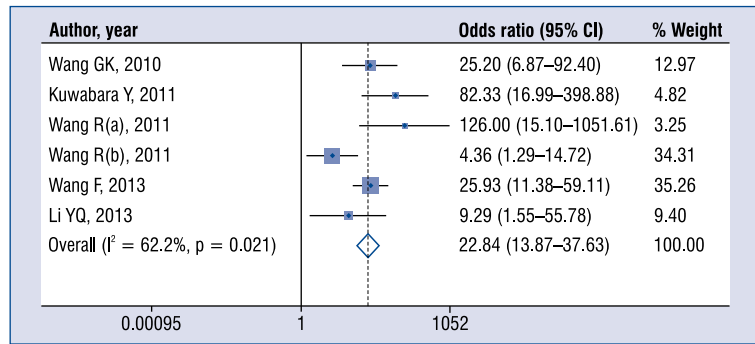
**Figure 4.** Forest plot comparing acute myocardial infarction (AMI) and non-AMI in relation to expression of miR-133a; CI — confidence interval.
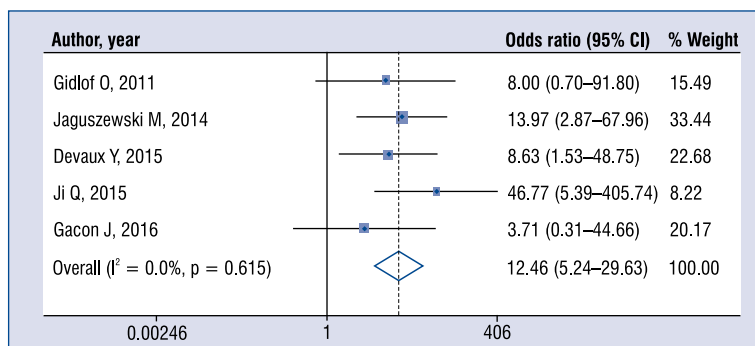


**Figure 5.** Forest plot comparing ST-segment elevation myocardial infarction (STEMI) and non-NSTEMI in relation to expression of miR-133a; CI — confidence interval.

positive likelihood ratio was 3.7 (95% CI 2.7–5.1), the negative likelihood ratio was 0.21 (95% CI 0.15–0.30), the diagnostic OR was 17 (95% CI 10–30), the area under the summary ROC curve was 0.88 (95% CI 0.85–0.90) (Fig. 3A, B).

Additionally, a meta-regression analysis was performed to determine the reason for the moderate heterogeneity. Results showed that moderate heterogeneity originated from the difference between the AMI and STEMI and the different methods of detecting miRNA-133a. Thus, a subgroup meta-analysis was performed based on results of the meta-regression analysis. Combined results of AMI vs. non-AMI are shown in the figures as follows (Fig. 4), pooled OR was 22.84 (95% CI 13.87–37.63), $I^2 = 62.2\%$, p = 0.021; STEMI vs. NSTEMI; (Fig. 5), pooled OR was 12.46 (95% CI 5.24–29.63), $I^2 = 0.0\%$, p = 0.615. The pooled OR of the TaqMan detection method was 28.29 (95% CI 12.00–66.68), $I^2 = 21.7\%$, p = 0.279; The pooled OR of the SYBR detection method was 17.01 (95% CI 10.30–28.09), $I^2 = 45.8\%$, p = 0.074 (Fig. 6).

## Discussion

This analysis showed that the expression level of miRNA-133a after AMI is increased in plasma and serum, and confirmed the diagnostic performance of miRNA-133a during the formation of AMI. This finding has important clinical significance for early diagnosis of AMI and its treatment. MicroRNAs are a class of endogenous short RNA fragments, that do not encode proteins, but are involved in many biological processes associated with signal transduction, and therefore they have been used to diagnose heart failure or hypertensive patients [21, 22]. In addition, some reports confirmed that miRNAs could perhaps be used as molecular biomarkers for diagnosis and prognosis of MI diagnosis and prognosis [23, 24]. Using a number of case-control studies, a comprehensive analysis was performed of the expression of miRNA-133a in patients with AMI and non-AMI in their blood, and results showed increased expression of miRNA-133a in blood of patients with AMI. Moreover, results of a summary ROC curve
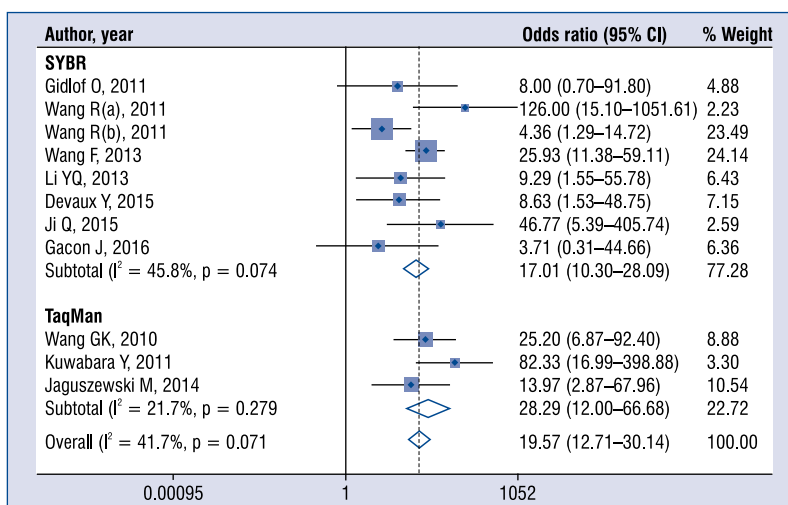
| Author, year | Odds ratio (95% CI) | % Weight |
|---|---|---|
| **SYBR** | | |
| Gidlof O, 2011 | 8.00 (0.70–91.80) | 4.88 |
| Wang R(a), 2011 | 126.00 (15.10–1051.61) | 2.23 |
| Wang R(b), 2011 | 4.36 (1.29–14.72) | 23.49 |
| Wang F, 2013 | 25.93 (11.38–59.11) | 24.14 |
| Li YQ, 2013 | 9.29 (1.55–55.78) | 6.43 |
| Devaux Y, 2015 | 8.63 (1.53–48.75) | 7.15 |
| Ji Q, 2015 | 46.77 (5.39–405.74) | 2.59 |
| Gacon J, 2016 | 3.71 (0.31–44.66) | 6.36 |
| Subtotal ($I^2$ = 45.8%, p = 0.074) | 17.01 (10.30–28.09) | 77.28 |
| | | |
| **TaqMan** | | |
| Wang GK, 2010 | 25.20 (6.87–92.40) | 8.88 |
| Kuwabara Y, 2011 | 82.33 (16.99–398.88) | 3.30 |
| Jaguszewski M, 2014 | 13.97 (2.87–67.96) | 10.54 |
| Subtotal ($I^2$ = 21.7%, p = 0.279) | 28.29 (12.00–66.68) | 22.72 |
| | | |
| Overall ($I^2$ = 41.7%, p = 0.071) | 19.57 (12.71–30.14) | 100.00 |

0.00095      1      1052

**Figure 6.** Forest plot of different detection methods of the expression of miR-133a; CI — confidence interval.

analysis suggest that miRNA-133a may be used for diagnosis of AMI patients.

Additionally, an interesting idea was sparked by the subgroup analysis result: the TaqMan detection method for miRNA-133a may be more accurate than the SYBR Green detection method. Based on TaqMan had pooled OR value 28.29 vs. 17.01 of the SYBR Green, calculations for each group's AUC was done, also an un-paired test between the two groups ORs was performed. The results are positive and statistically significant according to these findings. That is to say, the TaqMan detection method is superior to the SYBR Green method just as the other authors have described in prior studies [25].

Numerous studies have investigated whether miRNA-133a could be an optimal biomarker for patients with AMI. The results showed inconsistency in the diagnostic value of miRNA-133a. The results of several study analyses support a role for miRNA-133a as a biomarker [16, 19, 23, 24, 26]. However, the number of AMI patients and healthy controls participating in these studies were relatively small. Widera et al. [27] reported that there was a large overlap between patients with unstable angina or MI in relation to the level of miRNA-133a. Kuwabara et al. [12] reported significantly increased serum levels of miRNA-133a in patients with AMI, as well as in patients with unstable angina pectoris. These studies had a larger sample size than the studies mentioned above and support a role for miRNA-133a as a diagnostic biomarker. Additionally, the present data adequately supports the suggestion that miRNA-133a could be used as a biomarker for AMI diagnosis, particularly considering that the pooled AUC of the ROC curve is 0.88 (95% CI 0.85–0.90) (Fig. 3B). Overall, the results of this meta-analysis indicate that miRNA-133a can be used as a diagnostic biomarker for AMI.

Recently, many studies have shown that miRNA circulating in the blood may affect mortality in patients with AMI [11, 27], and miRNA concentration may influence the prognosis of patient 1-year survival [28, 29]. In addition, a few studies have shown that miRNAs are involved in myocardial remodeling [30, 31]. Although, according to the results of these reports, the molecular mechanism of miRNA involvement in AMI remains largely unclear, the miRNA may still be used as molecular diagnosis biomarker of AMI. Moreover, the results of the hierarchical summary ROC curve analysis were also consistent with other results of this meta-analysis.

### Limitations of the study

This study has its own limitations. First, analysis is based on a relatively small study population. Additionally, there are individual and regional differences between research groups. Moreover, a larger group of patients should be included in this study to support more reliable results. In addition, the studies included miRNA expression levels were measured only at one point in time, with no continuous detection. which reduces the reliability of this study.

### Conclusions

In short, the present study confirmed the diagnostic role of miRNA-133a in AMI patients.

However, compared with the present gold standard biomarkers such as creatine troponin T, troponin I and MB isoenzyme of creatine kinase, miRNA is not the best candidate at the present time due to protocol and cost of these detection methods. So, before miRNA-133a becomes commonly used for AMI patients clinically. Further investigation should be conducted to obtain accurate statistical analyses, and results should be subjected to further inquiry and analysis.

**Conflict of interest:** None declared

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