Value of Blood-Based microRNAs in the Diagnosis of Acute Myocardial Infarction: A Systematic Review and Meta-Analysis

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Background: Recent studies have shown that blood-based miRNAs are dysregulated in patients with acute myocardial infarction (AMI) and are therefore a potential tool for the diagnosis of AMI. Therefore, this study summarized and evaluated studies focused on microRNAs as novel biomarkers for the diagnosis of AMI from the last ten years.

Methods: MEDLINE, the Cochrane Central database, and EMBASE were searched between January 2010 and December 2019. Studies that assessed the diagnostic accuracy of circulating microRNAs in AMI were chosen. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and area under the curve (AUC) were used to assess the test performance of miRNAs.

Results: A total of 58 studies that included 8,206 participants assessed the diagnostic accuracy of circulating miRNAs in AMI. The main results of the meta-analyses are as follows: (1) Total miRNAs: the overall pooled sensitivity and specificity were 0.82 (95% CI: 0.79–0.85) and 0.87 (95% CI: 0.84–0.90), respectively. The AUC value was 0.91 (95% CI: 0.88–0.93) in the overall summary receiver operator characteristic (SROC) curve. (2) The panel of two miRNAs: sensitivity: 0.88 (95% CI: 0.77–0.94), specificity: 0.84 (95% CI: 0.72–0.91), AUC: 0.92 (95% CI: 0.90–0.94). (3) The panel of three miRNAs: sensitivity: 0.91 (95% CI: 0.85–0.94), specificity: 0.87 (95% CI: 0.77–0.92), AUC: 0.92 (95% CI: 0.89–0.94). (4) Results by types of miRNAs: miRNA-1: sensitivity: 0.78 (95% CI: 0.71–0.84), specificity: 0.86 (95% CI: 0.77–0.91), AUC: 0.88 (95% CI: 0.85–0.90); miRNA-133a: sensitivity: 0.85 (95% CI: 0.69–0.94), specificity: 0.92 (95% CI: 0.61–0.99), AUC: 0.93 (95% CI: 0.91–0.95); miRNA-208b: sensitivity: 0.80 (95% CI: 0.69–0.88), specificity: 0.96 (95% CI: 0.77–0.99), AUC: 0.91 (95% CI: 0.88–0.93); miRNA-499: sensitivity: 0.85 (95% CI: 0.77–0.91), specificity: 0.95 (95% CI: 0.89–0.98), AUC: 0.96 (95% CI: 0.94–0.97).

Conclusion: miRNAs may be used as potential biomarkers for the detection of AMI. For single, stand-alone miRNAs, miRNA-499 may have better diagnostic accuracy compared to other miRNAs. We propose that a panel of multiple miRNAs with high sensitivity and specificity should be tested.

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

Although advanced clinical medications have recently been developed for the diagnosis and prevention of coronary heart disease (CAD), acute myocardial infarction (AMI), which includes ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), is still considered a primary public health threat, with high morbidity and mortality worldwide (Moss et al., 1996; GBD 2013 Mortality and Causes of Death Collaborators, 2015). Acute-phase reaction during ischemic damage is a crucial pathogenesis of ischemia myocardial issue (Hoffmeister et al., 2003). Dependent on accurate recognition and diagnosis, early effective revascularization treatment is an important strategy to repair ischemic myocardium and can significantly reduce the mortality of AMI patients (Hung et al., 2013). Currently, the most widely used biomarkers of myocardial injury during clinical practice are cardiac troponin and creatine kinase-MB (CK-MB), which may provide effective benefits for patients with revascularization therapy (Dohi et al., 2015; Anand et al., 2019). However, the elevation of cardiac troponin may be involved in serious, non-cardiac disease such as neuromuscular disorders, severe sepsis, and chronic renal insufficiency (Lamb et al., 2006; Finsterer et al., 2007; Vallabhajosyula et al., 2017). High levels of cardiac troponin have also been detected in patients with heart failure (Myhre et al., 2018). Therefore, early diagnostic biomarkers and improvement of the accuracy of approaches for the early prediction of AMI are still warranted.

Potential novel genetic and molecular biomarkers are currently being explored (Lorenzano et al., 2019). MicroRNAs (miRNAs/miRs) are endogenous, non-coding RNAs ∼19–25nt that play crucial post-regulatory roles in animals and plants by targeting mRNAs for translational or cleavage repression (Bartel, 2004). MiRNAs can inhibit or reduce target gene expression, subsequently affecting protein expression (Saxena et al., 2018). Thus, miRNAs play important regulatory roles in cell growth, development, and differentiation (Gabisonia et al., 2019). Further, miRNAs have been identified in extracellular fluid and can be extremely stable despite the presence of endogenous RNase (Chevillet et al., 2014). In recent years, a number of studies have reported that miRNAs are dysregulated in CAD, and that specific circulating miRNA signatures might be useful as biomarkers for the diagnosis of AMI and as therapeutic targets (Jakob et al., 2017). However, the results of previous studies were significantly different, potentially due to sample size, specimen types, and different detection technologies. Therefore, the purpose of this systematic review and meta-analysis was to summarize the diagnostic values of blood-based miRNA levels from published articles from the last 10 years and to appraise the accuracy of results to determine whether miRNAs may be used as novel biomarkers for the diagnosis of AMI.

MATERIALS AND METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (Hutton et al., 2015; Moher et al., 2015). Two reviewers (CN Zhai, R Li) were independently involved with study selection, data extraction, and quality assessment.

Study Selection

An electronic search of MEDLINE (including PubMed), the Cochrane Central database, and EMBASE was performed to identify relevant articles published between January 2010 and December 2019. The following medical subject heading terms were used: (“plasma” OR “serum” OR “circuiting”) AND (“microRNA” OR “miRNAs” OR “miR”) AND (“myocardial infarction” OR “AMI” OR “coronary heart disease” OR “coronary artery disease” OR “coronary syndrome” OR “ischemic heart disease”). No language restrictions were imposed. All relevant review articles were retrieved, and duplicates were removed by manually searching. Based on the title and abstract, manuscripts of interest were obtained for full-text review. Only full-text references were included.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were developed by the investigative team. The inclusion criteria were: (1) human studies, (2) studies related to circulating miRNAs levels and AMI, and (3) studies that contained enough data to evaluate the diagnostic value of miRNAs in AMI. Exclusion criteria were based on the following: (1) studies evaluating tissue miRNA or miRNA in other body fluids; (2) case reports, conference abstracts, and reviews; and (3) non-human studies.

Data Extraction, Meta-Analysis, and Quality Assessment

Each manuscript was assessed independently by two researchers (CN Zhai and K Hou). Disagreements among reviewers were resolved by consensus. Data extracted included the following: authors, publication year, country, type of blood-based fluid (serum or plasma), characteristics of the study population (both case and control), study design (qRT-PCR detection method), whether miRNA screening was performed, number of miRNAs assessed, listing of the specific dysregulated miRNAs in AMI patients compared with controls, and outcome of statistical analyses including details of miRNA analysis, such as type of reference miRNA utilized. Studies reporting on single miRNA were included in the meta-analysis and were evaluated according to the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist (Whiting et al., 2011), which is designed to assess the risk of bias and the applicability of studies of diagnostic accuracy. The following four key domains were included: patient selection, the index test, the reference standard, and flow and timing. Each was assessed with respect to the risk of bias, and the first three domains were assessed with respect to applicability.

Statistical Analysis

Analysis was based on the accuracy of the identified miRNAs for diagnosing the presence of AMI, as determined using Receiver Operator Characteristic (ROC) curves via the Area Under the Curve (AUC) value, and sensitivity and specificity where available (Carter et al., 2016). We calculated the pooled sensitivity,
specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and 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. Forest plots were constructed using STATA (15.0 StataCorp LP, College, Station, TX, USA). Due to the presumed heterogeneity of studies, a random-effects model (DerSimonian–Laird method) was used (Mahid et al., 2006). The heterogeneity of included studies was assessed using $I^2$, and the $P$-value was considered significant if $I^2$ was >50% or $P < 0.05$. Subgroup analyses were performed to explore the potential source of heterogeneity as follows: (1) based on the type of blood sample (plasma or serum), (2) the method of qRT-PCR detection (SYBR Green or TaqMan), (3) the type of reference control used for normalization (RNU or Cel-miRNA), (4) sample size (Sample size ≥ 100 or Sample size < 100), and (5) different populations (Caucasian or East Asian). To assess the publication bias of the included studies, we performed Deeks’ test of funnel plot asymmetry (Deeks et al., 2005).

RESULTS

Literature Search Results and Characteristics of the Included Studies

The PRISMA flow diagram of the literature search and inclusion of relevant studies are shown in Figure 1. Overall, 79 full-text articles were deemed relevant for a more detailed evaluation. Of these articles, 21 were excluded for the following reasons: review
| References                | Country       | Specimen | Diseases                  | Case (n) | Control (n) | Age [mean ± s.d. /range] | Gender (male:female) |
|---------------------------|---------------|----------|---------------------------|----------|-------------|--------------------------|----------------------|
| **Corsten et al. (2010)** | Netherlands   | Plasma   | STEMI vs. NC              | 32       | 36          | 62 ± 13                  | 24/12                |
| **Adachi et al. (2010)**  | Japan         | Plasma   | AMI vs. NC                | 9        | 10          | 66.8 ± 9.28              | 6/3                  |
| **Ai et al. (2010)**      | China         | Plasma   | AMI vs. NC                | 93       | 66          | 58.2 ± 10.2              | 67/26                |
| **Wang et al. (2010)**    | China         | Plasma   | AMI vs. non-AMI           | 33       | 33          | 63.5 ± 10.1              | 23/10                |
| **Cheng et al. (2010)**   | China         | Serum    | AMI vs. NC                | 31       | 20          | NA (45-71)               | NA                   |
| **D’Alessandra et al. (2010)** | Italy       | Plasma   | STEMI vs. NC              | 33       | 17          | 57.9 ± 8.6               | 31/2                 |
| **Gidlöf et al. (2011)**  | Sweden        | Plasma   | STEMI vs. NC              | 25       | 11          | 64.56 ± 2.7              | 20/5                 |
| **Meder et al. (2011)**   | Germany       | Blood    | AMI vs. NC                | 20       | 20          | 59.3 ± 14                | 16/4                 |
| **Wang et al. (2011)**    | China         | Plasma   | AMI vs. NC                | 51       | 28          | 60.06 ± 11.53            | 43/8                 |
| **Zile et al. (2011)**    | USA           | Plasma   | AMI vs. NC                | 12       | 12          | 58 ± 3                   | 9/3                  |
| **Devaux et al. (2012)**  | Netherlands   | Plasma   | STEMI & NSTEMI vs. NC     | 510      | 87          | 62 (0.32-91)             | 303/94               |
| **Long et al. (2012a)**   | China         | Plasma   | AMI vs. NC                | 17       | 25          | 53 ± 12.5                | 13/4                 |
| **Long et al. (2012b)**   | China         | Plasma   | AMI vs. NC                | 18       | 30          | 55 ± 11.4                | 13/5                 |
| **Li Y. Q. et al. (2013)**| China         | Plasma   | AMI vs. NC                | 67       | 32          | 63.84 ± 11.17            | 52/15                |
| **Li C. et al. (2013)**   | China         | Serum    | AMI vs. NC                | 117      | 100         | 62.7 ± 11.4              | 20/97                |
| **Lu et al. (2013)**      | China         | Plasma   | AMI vs. non-AMI           | 40       | 15          | 66.8 ± 11.1              | 30/10                |
| **Gidlöf et al. (2013)**  | Sweden        | Plasma   | AMI vs. non-AMI           | 319      | 88          | NA                       | NA                   |
| **Oliveri et al. (2013)** | Italy         | Plasma   | NSTEMI vs. NC             | 92       | 99          | 82.6 ± 6.9               | 39/53                |
| **Wang et al. (2013)**    | China         | Plasma   | AMI vs. NC                | 13       | 27          | NA                       | NA                   |
| **Li L. M. et al. (2014)**| China         | Plasma   | AMI vs. NC                | 56       | 28          | 63.95 ± 11.34            | 44/12                |
| **Li Z. et al. (2014)**   | China         | Plasma   | AMI vs. NC                | 27       | 31          | 54.15 ± 11.34            | 20/7                 |
| **Huang et al. (2014)**   | China         | Plasma   | AMI vs. NC                | 150      | 150         | 60.93 ± 12.86            | 122/28               |
| **Hsu et al. (2014)**     | China         | Serum    | STEMI vs. NC              | 31       | 31          | 59.0 ± 11.5              | 29/2                 |
| **He et al. (2014)**      | China         | Plasma   | AMI vs. non-AMI           | 359      | 30          | 58 ± 14                  | 301/58               |
| **Peng et al. (2014)**    | China         | Plasma   | AMI vs. non-AMI           | 76       | 110         | 64.6 (46-88)             | 43/33                |
| **Wang et al. (2014)**    | China         | Plasma   | AMI vs. NC                | 17       | 28          | 52 ± 11                  | 12/5                 |
| **Xiao et al. (2014)**    | China         | Serum    | AMI vs. NC                | NA       | NA          | NA                       | NA                   |
| **Biłek et al. (2015)**   | Poland        | Plasma   | STEMI vs. non-AMI         | 19       | 20          | 58 (55-65)               | 15/4                 |
| **Chen et al. (2015)**    | China         | Blood    | AMI vs. non-AMI           | 53       | 50          | 68.8 ± 7.3               | 44/9                 |
| **Devaux et al. (2015)**  | Luxembourg    | Plasma   | AMI vs. non-AMI           | 224      | 931         | 72 (61-80)               | 158/66               |
| **Gao et al. (2015)**     | China         | Plasma   | STEMI vs. non-AMI         | 35       | 160         | NA                       | NA                   |
| **Ji et al. (2015)**      | China         | Serum    | AMI vs. NC                | 98       | 23          | 64 ± 13.8                | 82/16                |
| **Han et al. (2015)**     | China         | Plasma   | AMI vs. non-AMI           | 42       | 42          | 69.2 ± 7.4               | 34/8                 |
| **Li et al. (2015)**      | China         | Plasma   | STEMI & NSTEMI Vs. NC     | 87       | 87          | 56.93 ± 9.17             | 62/25                |
| **Liu et al. (2015)**     | China         | Plasma   | AMI vs. NC                | 70       | 72          | 64.2 ± 11.2              | 34/36                |
| **Yao et al. (2015)**     | China         | Plasma   | AMI vs. NC                | 50       | 39          | 63.2 ± 11.4              | 33/17                |
| **Zhang L. et al. (2015)**| China         | Plasma   | AMI vs. non-AMI           | 142      | 85          | 64.86 ± 12.84            | 102/40               |
| **Zhang R. et al. (2015)**| China         | Plasma   | STEMI & NSTEMI            | 110      | 110         | 57.74 ± 12.03            | 87/23                |
| **Zhao et al. (2015)**    | China         | Serum    | AMI vs. NC                | 59       | 60          | 60.1 ± 11.3              | 34/25                |
| **Ke-Gang et al. (2016)** | China         | Plasma   | AMI vs. non-AMI           | 233      | 79          | 63 (20-91)               | 163/70               |
| **Wang et al. (2016)**    | China         | Plasma   | AMI vs. NC                | 32       | 36          | 55.62 ± 9.17             | 18/14                |
| **Yang et al. (2016)**    | China         | Plasma   | AMI vs. NC                | 54       | 30          | NA                       | NA                   |
| **Zhang et al. (2016)**   | China         | Plasma   | AMI vs. NC                | 17       | 10          | 59.7 ± 8.4               | 12/5                 |
| **Zhu et al. (2016)**     | China         | Plasma   | STEMI vs. NC              | 60       | 60          | 64.1 ± 10.3              | 46/14                |
| **Shalaby et al. (2016)** | Egypt         | Serum    | NSTEMI vs. NC             | 48       | 25          | 54.3 ± 8.3               | 32/16                |
| **Fawzy et al. (2018)**   | Egypt         | Serum    | STEMI vs. NC              | 110      | 121         | NA                       | 61/49                |
| **Guo et al. (2017)**     | China         | Plasma   | AMI vs. NC                | 90       | 45          | 35.2 ± 5.6               | 48/42                |
| **Yang et al. (2017)**    | China         | Serum    | AMI vs. NC                | 76       | 30          | 63.6 ± 11.7              | 48/28                |
| **Agianntopulos et al. (2018)** | Greece    | Plasma   | AMI vs. NC                | 50       | 50          | 62.12 ± 10.99            | 38/12                |

(Continued)
article \((n = 4)\), not about AMI \((n = 14)\), and not a diagnostic study \((n = 3)\). Finally, 58 studies investigating plasma, serum, or peripheral venous blood miRNAs in the diagnosis of AMI were identified as eligible for inclusion in this systematic review (Adachi et al., 2010; Ai et al., 2010; Cheng et al., 2010; Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010, 2011, 2013, 2014, 2016, 2019; Gidlöf et al., 2011, 2013; Meder et al., 2011; Zile et al., 2011; Devaux et al., 2012, 2015; Long et al., 2012a,b; Li Y. Q. et al., 2013; Lu et al., 2013; Olivieri et al., 2013; He et al., 2014; Li L. M. et al., 2014; Li Z. et al., 2014; Peng et al., 2014; Xiao et al., 2014; Białek et al., 2015; Chen et al., 2015; Gao et al., 2015; Han et al., 2015; Ji et al., 2015; Li et al., 2015; Liu et al., 2015; Liu et al., 2015, 2018; Yao et al., 2015; Zhao et al., 2015; Hsu et al., 2014; Huang et al., 2014; Hu et al., 2015). Fifty-one articles identified miRNAs based on their own previous studies or based on the literature (Ai et al., 2010; Cheng et al., 2010; Corsten et al., 2010; Wang et al., 2010, 2011, 2013, 2014, 2016, 2019; Gidlöf et al., 2011, 2013; Zile et al., 2011; Devaux et al., 2012, 2015; Long et al., 2012a,b; Li Y. Q. et al., 2013; Lu et al., 2013; Olivieri et al., 2013; He et al., 2014; Li L. M. et al., 2014; Li Z. et al., 2014; Peng et al., 2014; Xiao et al., 2014; Białek et al., 2015; Chen et al., 2015; Gao et al., 2015; Han et al., 2015; Ji et al., 2015; Liu et al., 2015, 2018; Yao et al., 2015; Zhang L. et al., 2015; Zhang R. et al., 2015, 2016, 2017; Zhang et al., 2016, 2018; Zhu et al., 2016; Guo et al., 2017; Agiannitopoulos et al., 2018; Fawzy et al., 2018; Yi and An, 2018; Bukauskas et al., 2019; Li H. et al., 2019; Li P. et al., 2019; Xue et al., 2019a,b). The expression of 50 miRNAs were identified as either significantly higher or lower expression in AMI cases; specific details were shown in Table 3. Thirty-three miRNAs were upregulated (miRNA-1, miRNA-17-5p, miRNA-19b-3p, miRNA-21, miRNA-23b, miRNA-26a-1, miRNA-30a, miRNA-122-5p, miRNA-124, miRNA-126, miRNA-133a/b, miRNA-134, miRNA-145-3p, miRNA-146a, miRNA-150, miRNA-181a, miRNA-186, miRNA-195, miRNA-199a-1, miRNA-208a/b, miRNA-210, miRNA-223, miRNA-302b, miRNA-328, miRNA-361-5p, miRNA-423-5p, miRNA-486, miRNA-494, miRNA-497, miRNA-499, miRNA-663b, miRNA-1291, and miRNA-1303) (Adachi et al., 2010; Ai et al., 2010; Cheng et al., 2010; Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010, 2011, 2013, 2014, 2016, 2019; Gidlöf et al., 2011, 2013; Meder et al., 2011; Zile et al., 2011; Devaux et al., 2012, 2015; Long et al., 2012a,b; Li C. et al., 2013; Hsu et al., 2014; Huang et al., 2014; Li et al., 2015). Identification of Dysregulated miRNAs in the Included Studies

All included studies used Quantitative reverse transcription polymerase chain reaction (qRT-PCR) to detect the expression levels of miRNAs. A summary of all study methods is provided in Table 2. Seven studies performed miRNA screening to compare blood-based miRNAs between AMI patients and control groups (Adachi et al., 2010; D’Alessandra et al., 2010; Meder et al., 2011; Li C. et al., 2013; Hsu et al., 2014; Huang et al., 2014; Li et al., 2015).
### Study methods and corresponding dysregulated miRNAs identified.

| References                        | qRT-PCR detection method | Reference control | miRNA screening performed | Dysregulated miRNAs (n) | Significantly dysregulated miRNAs on validation (n) | AMI definition                                                                 | Time of blood sampling |
|-----------------------------------|--------------------------|-------------------|---------------------------|-------------------------|--------------------------------------------------|---------------------------------------------------------------------------------|------------------------|
| Corsten et al. (2010)             | SYBR                     | n/a               | N                         | 6                       | 2                                                | ST segment elevation; increase CK and TnI                                       | within 12h of chest pain onset |
| Adachi et al. (2010)              | TaqMan                   | n/a               | Y                         | 3                       | 1                                                | NA                                                                              | Within 48h after onset of chest pain |
| Ai et al. (2010)                  | SYBR                     | RNU6              | N                         | 2                       | 1                                                | Ischemic symptoms; increase cTnI and CK-MB; ST segment elevation or depression; pathological Q wave | NA |
| Wang et al. (2010)                | TaqMan                   | Cel-miR-39        | N                         | 40                      | 4                                                | Ischemia symptom; increase cTnI; ST segment change; coronary angiography         | Within 12h after admission |
| Cheng et al. (2010)               | n/a                      | n/a               | N                         | 1                       | 1                                                | Ischemic chest pain; increase CK-MB; ST segment elevation                         | Within 24h after AMI |
| D’Alessandra et al. (2010)        | TaqMan                   | n/a               | Y                         | 48                      | 6                                                | NA                                                                              | Within 12h after the onset of symptoms |
| Gidlöf et al. (2011)              | SYBR                     | miR-16            | N                         | 5                       | 4                                                | ST-segment elevation; coronary angiography                                        | Within 24h of the onset of ischemic symptoms |
| Meder et al. (2011)               | n/a                      | RNU6              | Y                         | 40                      | 20                                               | ESC/AHA guidelines                                                               | NA |
| Wang et al. (2011)                | SYBR                     | RNU6              | N                         | 2                       | 2                                                | Chest pain lasting >20 min; increase CK-MB and cTnI; ST segment and T- wave changes; pathological Q wave | Within 24h after the onset of syndromes |
| Zile et al. (2011)                | TaqMan                   | RNU6              | N                         | 6                       | 5                                                | AHA/ACC guidelines                                                               | Within 24h after admission |
| Devaux et al. (2012)              | TaqMan                   | n/a               | N                         | 2                       | 2                                                | ST segment elevation or depression; increase cTnI and coronary angiography        | Within acute and ongoing chest pain for 12 h |
| Long et al. (2012a)               | SYBR                     | RNU6              | N                         | 2                       | 2                                                | Ischemic symptom; increase cTnI and CK-MB; ST segment elevation or depression; pathological Q wave | Within 4h after onset of symptom |
| Long et al. (2012b)               | SYBR                     | RNU6              | N                         | 3                       | 3                                                | Ischemic symptom; increase cTnI and CK-MB; ST segment elevation or depression; pathological Q wave | Within 4h after onset of symptom |
| Li Y. Q. et al. (2013)            | SYBR                     | Cel-miR-39        | N                         | 4                       | 4                                                | Chest pain lasting >30 min; increase CK-MB and cTnI; ST segment elevation or depression; pathological Q wave | Within 12h of the onset of symptoms |
| Li C. et al. (2013)               | TaqMan                   | n/a               | Y                         | 21                      | 6                                                | Chest pain; ST segment elevation or depression; increase cTnI and CK-MB; pathological Q wave | Within 2h after hospitalization |
| Lu et al. (2013)                  | TaqMan                   | RNU6              | N                         | 1                       | 1                                                | Typical chest pain; increase cTnI; coronary angiography                           | The next morning after admission |
| Gidlöf et al. (2013)              | SYBR                     | miR-17            | N                         | 3                       | 2                                                | STEMI: ECG criteria; NSTEMI: increase troponin and clinical symptoms              | 71% were taken within 24h, 82% within 48h and 93% within 72h after onset of chest pain |
| Oliveri et al. (2013)             | TaqMan                   | miR-17, cel-miR-39| N                         | 6                       | 5                                                | Ischemic symptom; ST segment elevation or depression >1 mm/negative T wave/new onset LVBB; increase cTnT | Immediately after hospitalization |
| Wang et al. (2013)                | SYBR                     | RNU6              | N                         | 1                       | 1                                                | Acute ischemic chest pain within 24h; ECG changes; increase cTnT                  | Immediately after admission |

(Continued)
| References                          | qRT-PCR detection method | Reference control | miRNA screening performed | Dysregulated miRNAs\(^a\) (n) | Significantly dysregulated miRNAs on validation (n) | AMI definition                                                                 | Time of blood sampling                                      |
|------------------------------------|--------------------------|-------------------|--------------------------|--------------------------------|---------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------|
| Li L. M. et al. (2014)             | SYBR                     | Cel-miR-39        | N                        | 1                              | 1                                           | Increased cTnT or CK-MB; chest pain lasting for >30 min; pathological Q waves/ST-segment changes | Within 12h after onset of chest pain                             |
| Li Z. et al. (2014)                | SYBR                     | RNU6              | N                        | 1                              | 1                                           | Ischemic symptoms; increase cTnl and CK-MB; ST segment elevation or depression; pathological Q wave | Within 4h after onset of symptom                                      |
| Huang et al. (2014)                | n/a                      | Cel-miR-39        | Y                        | 77                             | 2                                           | Chest pain lasting >20 min; ST segment changes; pathological Q wave; increase cardiac biomarkers | NA                                                           |
| Hsu et al. (2014)                  | SYBR                     | n/a               | Y                        | 25                             | 5                                           | ACC/AHA guideline                                                               | NA                                                           |
| He et al. (2014)                   | SYBR                     | n/a               | N                        | 2                              | 2                                           | Ischemic symptoms; increase cTnl and CK; ST segment change; pathological Q wave | 6h after the onset of symptoms                                         |
| Peng et al. (2014)                 | TaqMan                   | miR-16            | N                        | 3                              | 3                                           | STEMI: ST segment elevation; NSTEMI: ischemic symptom and increase cTnl          | Within 3h after admission                                         |
| Wang et al. (2014)                 | SYBR                     | RNU6              | N                        | 3                              | 3                                           | Acute ischemic-type chest pain; ECG changes; increase cTnl                      | Immediately after admission                                      |
| Xiao et al. (2014)                 | TaqMan                   | Cel-miR-39        | N                        | 2                              | 2                                           | NA                                                                           | NA                                                           |
| Białek et al. (2015)               | TaqMan                   | HY3               | N                        | 1                              | 1                                           | Chest pain; ST segment elevation; coronary angiography                          | NA                                                           |
| Chen et al. (2015)                 | TaqMan                   | RNU6              | N                        | 1                              | 1                                           | Biochemical markers; acute ischemic-type chest pain; ECG changes; coronary angiography | Immediately after admission                                      |
| Devaux et al. (2015)               | SYBR                     | n/a               | N                        | 6                              | 3                                           | ACC/AHA guideline                                                               | With acute chest pain for 12 h                                    |
| Gao et al. (2015)                  | SYBR                     | Cel-miR-39        | N                        | 1                              | 1                                           | ACC/AHA guidelines                                                               | Immediately after hospitalization                                  |
| Ji et al. (2015)                   | SYBR                     | miR-16            | N                        | 3                              | 3                                           | Ischemia symptoms; ST segment elevation; increase cTnl and CK-MB                 | Immediately after hospitalization                                  |
| Han et al. (2015)                  | TaqMan                   | RNU6              | N                        | 1                              | 1                                           | ESC/AHA/ACC guidelines                                                            | Within 12h after the symptom onset                               |
| Li et al. (2015)                   | TaqMan                   | RNU6              | Y                        | 28                             | 3                                           | Ischemia symptoms; ST segment abnormality; pathological Q wave; increase cTnl and CK-MB | Within 4h after onset of symptoms                                      |
| Liu et al. (2015)                  | TaqMan                   | Cel-miR-39        | N                        | 3                              | 3                                           | Increased cTnT or CK-MB; chest pain lasting for >30 min; pathological Q waves/ST-segment changes | Within 2h after the onset of symptom                                 |
| Yao et al. (2015)                  | SYBR                     | RNU6              | N                        | 1                              | 1                                           | Ischemic symptoms; increase cTnl and CK-MB; ST segment changes and pathological Q wave | Within 4h after the onset of symptoms                                 |
| Zhang L. et al. (2015)             | TaqMan                   | RNU6              | N                        | 1                              | 1                                           | Ischemic-type chest pain; increase cTnl; ECG change; coronary angiography       | Within 12h after the onset of acute chest pain                      |
| Zhang R. et al. (2015)             | TaqMan                   | RNU6              | N                        | 2                              | 2                                           | Acute ischemic chest pain; abnormal ECG; increase cTnl and CK                    | Within 24h after admission                                       |
| Zhao et al. (2015)                 | SYBR                     | Cel-miR-39        | N                        | 1                              | 1                                           | ESC/ACC guidelines                                                               | Within 24h after hospitalization                                  |
| Ke-Gang et al. (2016)              | TaqMan                   | Cel-miR-39        | N                        | 1                              | 1                                           | ESC Guidelines                                                                  | Immediately after hospitalation                                   |

(Continued)
## TABLE 2 | Continued

| References                  | qRT-PCR detection method | Reference control | miRNA screening performed | Dysregulated miRNAs* (n) | Significantly dysregulated miRNAs on validation (n) | AMI definition                                                                 | Time of blood sampling                  |
|-----------------------------|--------------------------|-------------------|---------------------------|--------------------------|---------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------|
| Wang et al. (2016)          | SYBR                     | Cel-miR-39        | N                         | 3                        | 3                                                 | ESC/AHA/ACC guidelines                                                            | Within 12 h after the onset of chest pain |
| Yang et al. (2016)          | SYBR                     | RNU6              | N                         | 1                        | 1                                                 | Coronary angiography                                                             | NA                                      |
| Zhang et al. (2016)         | TaqMan                   | Cel-miR-39        | N                         | 1                        | 1                                                 | ESC/AACC guidelines                                                              | Immediately after admission            |
| Zhu et al. (2016)           | TaqMan                   | RNU6              | N                         | 1                        | 1                                                 | Ischemic chest pain lasting>30 min; increase cTnI; new ST segment elevation        | Immediately after admission            |
| Shalaby et al. (2016)       | SYBR                     | RNU6              | N                         | 2                        | 2                                                 | Ischemic symptom; no ST segment elevation; increase cTnI; coronary angiography    | Within 24 h of onset of chest pain                                               |
| Fawzy et al. (2018)         | TaqMan                   | RNU6              | N                         | 1                        | 1                                                 | Ischemic symptoms; ECG changes; coronary angiography                              | Within the first 12 h of the chest pain                                         |
| Guo et al. (2017)           | n/a                      | GAPDH             | N                         | 1                        | 1                                                 | Guideline for AMI by Chinese Medicine Academy                                      | Within 12 h of chest pain onset                                                  |
| Yang et al. (2017)          | SYBR                     | RNU6              | N                         | 1                        | 1                                                 | Clinical symptoms; ECG changes; increase cTnI; CK and CK-MB                        | Within 24 h of symptoms onset                                                     |
| Agiannitopoulos et al. (2018) | TaqMan     | RNU24             | N                         | 2                        | 2                                                 | Ischemic chest pain; ST segment elevation or depression; pathological Q wave; rise of cardiac biomarkers | Within 24 h of onset of chest pain                                               |
| Liu et al. (2018)           | SYBR                     | n/a               | N                         | 4                        | 4                                                 | ACC guideline                                                                     | Within 2-4 h after admission                                                      |
| Wang et al. (2019)          | n/a                      | Cel-miR-39        | N                         | 6                        | 2                                                 | Ischemic symptoms; ST segment-T wave changes or new LBBB; pathological Q wave; rise of cardiac biomarkers | Within 4 h of onset of chest pain/dyspnea                                         |
| Yi and An (2018)            | SYBR                     | RNU6              | N                         | 1                        | 1                                                 | Coronary angiography; increase cTnI and CK-MB                                      | NA                                      |
| Zhang et al. (2018)         | SYBR                     | n/a               | N                         | 1                        | 1                                                 | ST segment elevation; coronary angiography                                          | Within 6 h after the onset of symptoms                                           |
| Bukauskas et al. (2019)     | SYBR                     | Cel-miR-39        | N                         | 3                        | 3                                                 | 2015 ESC Guidelines for the management of ACS                                       | Within the first 24 h of admission                                               |
| Li H. et al. (2019)         | SYBR                     | Cel-miR-39        | N                         | 3                        | 3                                                 | ACC/AHA guideline                                                                  | With chest pain for 10 h                                                          |
| Li P. et al. (2019)         | SYBR                     | RNU6              | N                         | 4                        | 4                                                 | Ischemic symptoms; ST segment elevation or pathological Q wave; increase cTnI     | With chest pain for 3 h                                                          |
| Xue et al. (2019a)          | SYBR                     | Cel-miR-39        | N                         | 3                        | 3                                                 | 2012 ESC/AHA/ACC guidelines                                                        | Within 4 h of onset of chest pain                                               |
| Xue et al. (2019b)          | SYBR                     | Cel-miR-39        | N                         | 6                        | 3                                                 | 2012 ESC/AHA/ACC guidelines                                                        | With chest pain onset < 4 h duration                                               |

SYBR, SYBR Green; RNU6, small nuclear RNA U6; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase-MB. Cardiac troponin I/T, cTnI/T; ECG, electrocardiogram.

*Based upon miRNA screening, or based upon literature review or prior work (see text).

Y or N: Yes or No; NA: not available.
| miRNAs          | References                        | Expression | Area under the curve (AUC) | Sensitivity | Specificity |
|-----------------|-----------------------------------|------------|-----------------------------|-------------|-------------|
| **Single miRNA**|                                   |            |                             |             |             |
| miRNA-1         | Ai et al., 2010                    | Upregulated| 0.774                       | 70.0%       | 75.0%       |
|                 | Corsten et al., 2010              |            |                             | 90.0%       | 95.0%       |
|                 | Cheng et al., 2010                |            |                             |             |             |
|                 | D’Alessandra et al., 2010         |            |                             |             |             |
|                 | Wang et al., 2010                 |            | 0.847                       | 78.0%       | 80.0%       |
|                 | Gidlöf et al., 2011               |            | 0.979                       | 88.9%       | 100%        |
|                 | Li Y. Q. et al., 2013             |            | 0.827                       | 80.0%       | 90.0%       |
|                 | Long et al., 2012a                |            | 0.92                        | 93.0%       | 90.0%       |
|                 | Oliveri et al., 2013              |            |                             |             |             |
|                 | Li C. et al., 2013                |            |                             |             |             |
|                 | Gidlöf et al., 2013               |            |                             | 80.0%       | 86.0%       |
|                 | Li. L. M. et al., 2014            |            | 0.854                       | 80.0%       | 90.0%       |
|                 | Liu et al., 2015                  |            | 0.81                        | 70.0%       | 90.0%       |
|                 | Liu et al., 2018                  |            | 0.773                       | 75.7%       | 53.5%       |
| miRNA-17-5p     | Xue et al., 2019a                 | Upregulated| 0.857                       | 85.2%       | 85.7%       |
| miRNA-19b-3p    | Wang et al., 2016                 | Upregulated| 0.821                       | 72.2%       | 66.7%       |
|                 | Wang et al., 2019                 |            | 0.667                       | 61.1%       |             |
| miRNA-21        | Zile et al., 2011                 | Upregulated|                             |             |             |
| miRNA-21-5p     | Oliveri et al., 2013              |            |                             |             |             |
|                 | Zhang et al., 2016                |            | 0.892                       | 78.6%       | 100%        |
|                 | Wang et al., 2014                 |            | 0.949                       |             |             |
| miRNA-23b       | Zhang et al., 2018                | Upregulated| 0.809                       | 88.1%       | 60.3%       |
| miRNA-26a-1     | Xue et al., 2019b                 | Upregulated| 0.965                       | 100%        | 85.2%       |
| miRNA-30a       | Long et al., 2012b                | Upregulated| 0.88                        | 88.3%       | 82.5%       |
| miRNA-122-5p    | Yao et al., 2015                  | Upregulated| 0.865                       | 100%        | 60.2%       |
|                 | Wang et al., 2019                 |            | 0.626                       | 63.8%       | 73.9%       |
| miRNA-124       | Guo et al., 2017                  | Upregulated| 0.86                        | 52.0%       | 91.0%       |
| miRNA-126       | Long et al., 2012a                | Upregulated| 0.86                        | 75.1%       | 83.1%       |
| miRNA-126-5p    | Xue et al., 2019a                 | Upregulated| 0.802                       | 100%        | 61.9%       |
| miRNA-133       | Xue et al., 2011                  | Upregulated| 0.89                        | 98.0%       | 73.0%       |
| miRNA-133a      | Peng et al., 2014                 | Upregulated| 0.912                       | 81.1%       | 91.2%       |
|                 | Liu et al., 2016                  |            | 0.928                       | 71.0%       | 96.5%       |
| miRNA-133b      | Corsten et al., 2010              |            |                             |             |             |
|                 | D’Alessandra et al., 2010         |            |                             |             |             |
|                 | Wang et al., 2010                 |            | 0.867                       | 87.3%       | 84.9%       |
|                 | Gidlöf et al., 2011               |            | 0.859                       | 99.6%       | 63.6%       |
|                 | Li Y. Q. et al., 2013             |            | 0.947                       | 82.7%       | 100%        |
|                 | Oliveri et al., 2013              |            |                             |             |             |
|                 | Wang et al., 2013                 |            |                             |             |             |
|                 | Ji et al., 2015                   |            | 0.787                       | 85.4%       | 99.8%       |
|                 | Ke-Gang et al., 2016              |            | 0.867                       | 61%         | 68%         |
|                 | D’Alessandra et al., 2010         |            |                             |             |             |
| miRNA-134       | He et al., 2014                   | Upregulated| 0.818                       | 79.4%       | 77.1%       |
| miRNA-134-5p    | Li C. et al., 2013                |            | 0.657                       | 53.6%       | 78.1%       |
| miRNA-145-3p    | Wang et al., 2016                 |            | 0.827                       | 77.8%       | 77.8%       |
| miRNA-146a      | Xue et al., 2019b                 | Upregulated| 0.720                       | 81.8%       | 61.9%       |
| miRNA-146a      | Xue et al., 2019b                 | Upregulated| 0.911                       | 100%        | 66.7%       |
| miRNA-150-3p    | Hsu et al., 2014                  | Upregulated| 0.715                       | 71.3%       | 70.1%       |
| miRNA-150       | Li H. et al., 2019                |            | 0.904                       | 88.2%       | 75.9%       |
| miRNA-181a      | Zhu et al., 2016                  | Upregulated| 0.834                       | 81.5%       | 81.8%       |
| miRNA-186       | Li C. et al., 2013                | Upregulated| 0.715                       | 77.8%       | 60.9%       |
| miRNA-186-5p    | Wang et al., 2016                 | Upregulated| 0.824                       | 77.8%       | 77.8%       |
|                 | Wang et al., 2019                 |            | 0.692                       | 56.9%       | 84.3%       |

(Continued)
## TABLE 3 | Continued

| miRNAs | References | Expression | Area under the curve (AUC) | Sensitivity | Specificity |
|--------|------------|------------|-----------------------------|-------------|-------------|
| miRNA-195 | Long et al., 2012b | Upregulated | 0.89 | 100% | 44.7% |
| miRNA-199a-1 | Xue et al., 2019b | Upregulated | 0.855 | 96.8% | 66.7% |
| miRNA-208b | Corsten et al., 2010 | Upregulated | 0.944 | 90.6% | 94.1% |
|           | Gidlöf et al., 2011 | 1.0 | 100% | 100% |
|           | Devaux et al., 2012 | 0.90 | 79.5% | 99.8% |
|           | Li Y. Q. et al., 2013 | 0.89 | 82.4% | 99.8% |
|           | Gidlöf et al., 2013 | 0.82 | 79.0% | 70.0% |
|           | Devaux et al., 2015 | 0.76 | 64.7% | 80.2% |
|           | Li et al., 2015 | 0.674 | 59.8% | 73.6% |
| miRNA-208a | Agiannitopoulos et al., 2018 | Upregulated | 0.999 | 98% | 100% |
|           | Wang et al., 2010 | 0.965 | 90.9% | 100% |
|           | Xiao et al., 2014 | — | — | — |
| miRNA-208 | Białek et al. (2015) | 0.778 | 75.8% | 73.1% |
|           | Li C. et al., 2013 | — | — | — |
|           | Han et al., 2015 | — | — | — |
|           | Liu et al., 2015 | 0.72 | 65.0% | 90.0% |
|           | Liu et al., 2016 | 0.9940 | 90.0% | 100% |
|           | Li P. et al., 2019 | 0.868 | 70.0% | 97.5% |
| miRNA-210 | Shalaby et al., 2016 | Upregulated | 0.90 | 83.3% | 100% |
| miRNA-223 | Li C. et al., 2013 | Upregulated | 0.741 | 77.8% | 68.3% |
| miRNA-302b | Yang et al., 2017 | Upregulated | 0.95 | 88.2% | 93.3% |
| miRNA-328 | He et al., 2014 | Upregulated | 0.887 | 86.3% | 74.6% |
| miRNA-361-5p | Wang et al., 2014 | Upregulated | 0.881 | — | — |
| miRNA-423-5p | Oliveri et al., 2013 | Upregulated | — | — | — |
| miRNA-486-3p | Hsu et al., 2014 | Upregulated | 0.629 | 38.8% | 84.1% |
| miRNA-486 | Zhang R. et al., 2015 | Upregulated | 0.731 | 56.5% | 86.5% |
| miRNA-494 | Li P. et al., 2019 | Upregulated | 0.839 | 79.6% | 82.1% |
| miRNA-497 | Li Z. et al., 2014 | Upregulated | 0.88 | 82% | 94% |
| miRNA-499 | Corsten et al., 2010 | Upregulated | 0.918 | 84.5% | 93.9% |
|           | Adachi et al., 2010 | — | — | — |
|           | Wang et al., 2010 | 0.822 | 60.0% | 90.3% |
|           | Devaux et al., 2012 | 0.98 | 95.0% | 100% |
|           | Li Y. Q. et al., 2013 | 0.884 | 80.0% | 94.0% |
|           | Li C. et al., 2013 | 0.755 | 80.0% | 93.0% |
|           | Xiao et al., 2014 | — | — | — |
|           | Chen et al., 2015 | 0.65 | 35.7% | 90.3% |
|           | Devaux et al., 2015 | 0.88 | 82.0% | 94.0% |
|           | Li et al., 2015 | 0.86 | 80% | 80.28% |
|           | Zhang L. et al., 2015 | 0.915 | 86.37% | 93.47% |
|           | Zhao et al., 2015 | 0.97 | 93.4% | 100% |
|           | Shalaby et al., 2016 | — | — | — |
|           | Agiannitopoulos et al., 2018 | — | — | — |
|           | Liu et al., 2018 | 0.999 | 98% | 100% |
|           | Li P. et al., 2019 | 0.995 | 98.4% | 100% |
|           | Li P. et al., 2019 | 0.852 | 71.5% | 89.3% |
|           | D’Alessandro et al., 2010 | — | — | — |
| miRNA-499-5p | Gidlöf et al., 2011 | Upregulated | 0.989 | 87.7% | 100% |
|           | Oliveri et al., 2013 | 0.88 | 88.0% | 75.0% |
|           | Gidlöf et al., 2013 | 0.79 | 64.0% | 90.0% |
| miRNA-499a | Fawzy et al., 2018 | 0.953 | 97.2% | 75% |
| miRNA-663b | Meder et al., 2011 | Upregulated | 0.94 | 90% | 95% |
| miRNA-1291 | Peng et al., 2014 | 0.811 | 72.4% | 76.5% |
| miRNA-1303 | Peng et al., 2014 | 0.695 | 78.4% | 89.5% |
| miRNA-22-5p | Li H. et al., 2019 | Upregulated | 0.884 | 81.2% | 89.3% |
|           | Wang et al., 2019 | Downregulated | 0.975 | 96.7% | 96.7% |
| miRNA-23a-3p | Bukauskas et al., 2019 | Downregulated | 0.806 | 73.3% | 79.6% |
| miRNA-26a-5p | Hsu et al., 2014 | Downregulated | 0.675 | 57.8% | 90.2% |
| miRNA-26a | Li et al., 2015 | 0.745 | 73.6% | 72.4% |
| miRNAs                  | References                  | Expression                  | Area under the curve (AUC) | Sensitivity | Specificity |
|------------------------|-----------------------------|-----------------------------|-----------------------------|-------------|-------------|
| miRNA-30d-5p           | Bukauskas et al., 2019      | Downregulated               | 0.745                       | 80.9%       | 64.9%       |
| miRNA-99a              | Yang et al., 2016           | Downregulated               | —                           | —           | —           |
| miRNA-125b             | Huang et al., 2014          | Downregulated               | 0.858                       | —           | —           |
| miRNA-126-3p           | Hsu et al., 2014            | Downregulated               | 0.694                       | 64.1%       | 80.0%       |
| miRNA-132-5p           | Li H. et al., 2019          | Downregulated               | 0.886                       | 85.3%       | 74.1%       |
| miRNA-145              | Gao et al., 2015            | Downregulated               | —                           | —           | —           |
| miRNA-146a-5p          | Bukauskas et al., 2019      | Downregulated               | 0.800                       | 84.5%       | 70.4%       |
| miRNA-191-5p           | Hsu et al., 2014            | Downregulated               | 0.652                       | 48.6%       | 93.8%       |
| miRNA-191              | Li et al., 2015             | Downregulated               | 0.669                       | 62.1%       | 69.0%       |
| miRNA-214              | Lu et al., 2013             | Downregulated               | —                           | —           | —           |
| miRNA-320b             | Huang et al., 2014          | Downregulated               | 0.866                       | —           | —           |
| miRNA-375              | D’Alessandra et al., 2010   | Downregulated               | —                           | —           | —           |
|                       | Wang et al., 2019           |                             | 0.510                       | 92.6%       | 33.1%       |
| miRNA-379              | Yi and An, 2018             | Downregulated               | 0.751                       | —           | —           |
| miRNA-519-5p           | Wang et al., 2014           | Downregulated               | 0.798                       | —           | —           |
| miRNA-let-7d           | Long et al., 2012b          | Downregulated               | 0.86                        | 64.7%       | 100%        |

**Two miRNA panels**

| miRNA-191-5p,-486-3p   | Hsu et al., 2014            | Upregulated and downregulated | 0.867 | 83.87% | 83.33% |
| miRNA-486-3p,-126-3p   | Hsu et al., 2014            | Upregulated                  | 0.849 | 61.29% | 93.55% |
| miRNA-126-3p,-150-3p   | Hsu et al., 2014            | Upregulated                  | 0.843 | 93.55% | 64.52% |
| miRNA-26a-5p,-26a-5p   | Hsu et al., 2014            | Upregulated and downregulated | 0.821 | 87.10% | 64.52% |
| miRNA-26a-5p,-150-3p   | Hsu et al., 2014            | Upregulated and downregulated | 0.821 | 83.87% | 70.97% |
| miRNA-191-5p,-150-3p   | Hsu et al., 2014            | Upregulated and downregulated | 0.789 | 77.42% | 77.42% |
| miRNA-150,-486         | Zhang R. et al., 2015       | Upregulated                  | 0.771 | 72.6%  | 72.1%  |
| miRNA-499,-210         | Shalaby et al., 2016        | Upregulated                  | 0.98  | 97.9%  | 100%   |
| miRNA-22-5p,-122-5p    | Wang et al., 2019           | Upregulated and downregulated | 0.976 | 98.4%  | 96.2%  |

**Three miRNA panels**

| miRNA-30a,-195, let-7d | Long et al., 2012b          | Upregulated and downregulated | 0.930 | 94%    | 90%    |
| miRNA-21-5p,-361-5p,-519-5p | Wang et al., 2014     | Upregulated and downregulated | 0.989 | 93.9%  | 100%   |
| miRNA-19b-3p,-134-5p,-186-5p | Wang et al., 2016   | Upregulated                   | 0.898 | 88.9%  | 77.8%  |
| miRNA-22-5p,-150-3p,-132-5p | Li H. et al., 2019   | Upregulated and downregulated | 0.942 | 91.2%  | 87.0%  |
| miRNA-17-5p,-126-5p,-145-3p | Xue et al., 2019a     | Upregulated                   | 0.857 | 84.0%  | 85.7%  |
| miRNA-26a-1,-146a-1,-199a-1 | Xue et al., 2019b    | Upregulated                  | 0.913 | 97.8%  | 71.6%  |

**Panels with ≥ 4 miRNAs**

| miRNA-1,-134,-186,-208,-223,-499 | Li C. et al., 2013 | Upregulated                  | 0.811 | 55.3%  | 90.1%  |

AMI, acute myocardial infarction; miRNA, microRNA.

*Not reported. **Upregulated and downregulated: where the individual miRNAs were either upregulated or downregulated in AMI compared with control groups.

2019; Gidlöf et al., 2011, 2013; Devaux et al., 2012, 2015; Li Y. Q. et al., 2013; Olivieri et al., 2013; He et al., 2014; Hsu et al., 2014; Peng et al., 2014; Xiao et al., 2014; Bialek et al., 2015; Chen et al., 2015; Han et al., 2015; Ji et al., 2015; Li et al., 2015; Liu et al., 2015, 2018; Zhang L. et al., 2015; Zhang R. et al., 2015; Ke-Gang et al., 2016; Shalaby et al., 2016; Agiannitopoulos et al., 2018; Fawzy et al., 2018; Li H. et al., 2019; Li P. et al., 2019 and three downregulated miRNAs (miRNA-26a, miRNA-191,
and miRNA-375) (D’Alessandra et al., 2010; Hsu et al., 2014; Li et al., 2015; Wang et al., 2019) were identified by more than one study. Among these articles, which included 22 original studies, miRNA-499 was the most frequently identified dysregulated miRNA in AMI patients (Adachi et al., 2010; Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Devaux et al., 2012, 2015; Li C. et al., 2013; Li Y. Q. et al., 2013; Olivieri et al., 2013; Xiao et al., 2014; Chen et al., 2015; Liu et al., 2015, 2018; Zhang L. et al., 2015; Zhang R. et al., 2015; Shalaby et al., 2016; Agiannitopoulos et al., 2018; Fawzy et al., 2018; Li P. et al., 2019). 16 studies focused on the miRNA-208 family (miRNA-208a/b) (Corsten et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Devaux et al., 2012, 2015; Li C. et al., 2013; Li Y. Q. et al., 2013; Xiao et al., 2014; Bialek et al., 2015; Han et al., 2015; Li et al., 2015, 2018; Agiannitopoulos et al., 2018; Li P. et al., 2019), 14 studies focused on miRNA-1 (Ai et al., 2010; Cheng et al., 2010; Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Long et al., 2012a; Li C. et al., 2013; Li Y. Q. et al., 2013; Olivieri et al., 2013; Li L. M. et al., 2014; Liu et al., 2015, 2018), and 14 studies focused on the miRNA-133 family (miRNA-133a/b) (Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010, 2011, 2013; Gidlöf et al., 2011; Li Y. Q. et al., 2013; Olivieri et al., 2013; Peng et al., 2014; Ji et al., 2015; Ke-Gang et al., 2016; Liu et al., 2018). Additionally, four studies identified a panel of two miRNAs (Hsu et al., 2014; Zhang R. et al., 2015; Shalaby et al., 2016; Wang et al., 2019), six studies identified a panel of three miRNAs (Long et al., 2012b; Wang et al., 2014, 2016; Li H. et al., 2019; Xue et al., 2019a,b), and one study identified a panel of more than four miRNAs that were elevated in AMI (Li C. et al., 2013).

Sensitivity, Specificity, and Area Under the Curve

Among the included studies, the most common methods of assessing the diagnostic accuracy of dysregulated miRNAs were AUC and sensitivity and specificity, as determined from ROC curves. In the identified dysregulated miRNAs, AUC values ranged from 0.510 to 1.0, sensitivity ranged from 48.6% to 100%, and specificity from 33.1% to 100%. In the single identified miRNAs, the highest AUC sensitivity and specificity combination was reported for miRNA-208b (AUC 1.0, sensitivity 100%, specificity 100%) (Gidlöf et al., 2011). In the panel of two miRNAs, the highest value combination was reported for miRNA-499 and miRNA-210 (AUC 0.98, sensitivity 97.9%, specificity 100%) (Shalaby et al., 2016). In the panel of three miRNAs, the highest value combination was reported for miRNA-21-5p, miRNA-361-5p, and miRNA-519-5p (AUC 0.989, sensitivity 93.9%, specificity 100%) (Wang et al., 2014). In the panel of ≥ 4 miRNAs, there was one study about AUC 0.811, which had sensitivity 55.3% and specificity 90.1% (Li C. et al., 2013).

Meta-Analysis Outcomes of Diagnostic Accuracy of miRNAs in AMI

The Quality Assessment of Included Studies

The pooled result of the meta-analysis for the diagnostic accuracy of blood-based miRNAs in AMI was pooled from 42 studies (Ai et al., 2010; Corsten et al., 2010; Wang et al., 2010, 2011, 2014, 2016, 2019; Gidlöf et al., 2011, 2013; Meder et al., 2011; Devaux et al., 2012, 2015; Long et al., 2012a,b; Li C. et al., 2013; Li Y. Q. et al., 2013; Olivieri et al., 2013; Li L. M. et al., 2014; Liu et al., 2015, 2018) and 16 studies focused on the miRNA-208 family (miRNA-208a/b) (Corsten et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Devaux et al., 2012, 2015; Li C. et al., 2013; Li Y. Q. et al., 2013; Xiao et al., 2014; Bialek et al., 2015; Han et al., 2015; Li et al., 2015, 2018; Agiannitopoulos et al., 2018; Li P. et al., 2019), 14 studies focused on miRNA-1 (Ai et al., 2010; Cheng et al., 2010; Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Long et al., 2012a; Li C. et al., 2013; Li Y. Q. et al., 2013; Olivieri et al., 2013; Li L. M. et al., 2014; Liu et al., 2015, 2018), and 14 studies focused on the miRNA-133 family (miRNA-133a/b) (Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010, 2011, 2013; Gidlöf et al., 2011; Li Y. Q. et al., 2013; Olivieri et al., 2013; Peng et al., 2014; Ji et al., 2015; Ke-Gang et al., 2016; Liu et al., 2018). Additionally, four studies identified a panel of two miRNAs (Hsu et al., 2014; Zhang R. et al., 2015; Shalaby et al., 2016; Wang et al., 2019), six studies identified a panel of three miRNAs (Long et al., 2012b; Wang et al., 2014, 2016; Li H. et al., 2019; Xue et al., 2019a,b), and one study identified a panel of more than four miRNAs that were elevated in AMI (Li C. et al., 2013).

Total miRNAs

Dysregulated miRNAs in AMI patients compared with controls, the SROC curve with AUC, sensitivity, specificity, PLR, NLR, and DOR for miRNAs were included in our meta-analysis (Table 4). A random effect model was used for the meta-analysis due to significant heterogeneity (all $I^2 > 50%$). Forty-four individual
miRNAs were identified in 43 studies (Ai et al., 2010; Corsten et al., 2010; Wang et al., 2010, 2011, 2014, 2016, 2019; Gidlof et al., 2011, 2013; Meder et al., 2011; Devaux et al., 2012, 2015; Long et al., 2012a,b; Li C. et al., 2013; Li Y. Q. et al., 2013; Olivieri et al., 2013; He et al., 2014; Hsu et al., 2014; Li L. M. et al., 2014; Li Z. et al., 2014; Peng et al., 2014; Ji et al., 2015; Li et al., 2015; Liu et al., 2015, 2018; Yao et al., 2015; Zhang L. et al., 2015; Zhang R. et al., 2015; Ke-Gang et al., 2016; Shalaby et al., 2016; Wang et al., 2019) focused on miR-499 (miR-208b (niR-208 a/b (niR-1 (niR-133 a/b (niR-133a (niR-208 a/b (niR-208b (niR-499 (niR-133). The sensitivity, specificity, and the corresponding SROC value with 95% CIs (95% confidential intervals) of the total miRNAs in the diagnostic of AMI were 0.82 (95% CI: 0.79–0.85), 0.87 (95% CI: 0.84–0.90), and 0.91 (95% CI: 0.88–0.93), respectively (Supplementary Figures 2A,B, 3A). The Deeks’ funnel plot asymmetry test suggested a potential for publication bias in the total miRNAs (p-value = 0.00, Supplementary Figure 3B).

Panels of Multiple miRNAs
As shown in Table 3, four studies (Hsu et al., 2014; Zhang R. et al., 2015; Shalaby et al., 2016; Wang et al., 2019) focused on the diagnostic value of a panel of two types of miRNAs, and the pooled sensitivity (Figure 3A) and specificity (Figure 3B) estimates were 0.88 (95% CI: 0.77–0.94) and 0.84 (95% CI: 0.72–0.91), respectively. The area under the SROC curve (Figure 3C) was 0.92 (95% CI: 0.90–0.94). The Deeks’ test (Figure 3D) was performed to evaluate publication bias, and results suggested a low probability of publication bias.

From the analysis of a panel of three types of miRNAs in six studies (Long et al., 2012b; Wang et al., 2014, 2016; Ke-Gang et al., 2016; Li H. et al., 2019; Xue et al., 2019a,b) (Table 3), the pooled sensitivity (Figure 4A) and specificity (Figure 4B) estimates were 0.91 (95% CI: 0.85–0.94) and 0.87 (95% CI: 0.77–0.92), respectively. The area under the SROC curve (Figure 4C) was 0.92 (95% CI: 0.89–0.94). The Deeks’ test was performed and suggested that publication bias likely had a low effect on the summary estimates (Figure 4D).
Sensitivity Analyses

Sensitivity analyses were performed on the included studies according to the following factors: (1) Type of patient blood sample (plasma vs. serum): the SROC values were 0.92 vs. 0.89, the pooled sensitivity and specificity were 0.84 vs. 0.78 and 0.87 vs. 0.87, respectively; (2) Type of miRNA detection method (SYBR green vs TaqMan): the SROC values were 0.92 vs. 0.90, the pooled sensitivity and specificity were 0.84 vs. 0.80 and 0.87 vs. 0.88, respectively; (3) Type of miRNA reference used for normalization (RNU or Cel-miRNA): the SROC values were 0.93 vs. 0.90, the pooled sensitivity and specificity were 0.86 vs. 0.82 and 0.89 vs. 0.85, respectively; (4) different study
sizes (sample size ≥ 100 vs. sample size < 100): the SROC values were 0.89 vs 0.93, the pooled sensitivity and specificity were 0.79 vs. 0.85 and 0.86 vs. 0.87, respectively; (5) Different populations (Caucasian vs. East Asian): the SROC values were 0.95 vs. 0.89, the pooled sensitivity and specificity were 0.86 vs. 0.80 and 0.94 vs. 0.84, respectively. A summary of the sensitivity analysis results is shown in Table 4. According to compared diagnostic values from each of the above groups, no major improvement or differences were found in the diagnostic accuracy values.

Meta-Analysis by Types of miRNAs

miRNA-1

In total, 11 studies identifying the diagnostic value of miRNA-1 in AMI were included in the meta-analysis (Ai et al., 2010; Corsten et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Long et al., 2012a; Li C. et al., 2013; Li Y. Q. et al., 2013; Li L. M. et al., 2014; Liu et al., 2015, 2018) (Table 3). As shown in Figures 5A,B, the pooled sensitivity and specificity estimates were 0.78 (95% CI: 0.71–0.84) and 0.86 (95% CI: 0.77–0.91), respectively. The area under the SROC curve for miRNA-1 was
0.88 (95% CI: 0.85–0.90) (Figure 5C). The pooled PLR was 5.41 (95% CI: 3.18–9.19), and the pooled NLR was 0.26 (95% CI: 0.18–0.36). The DOR was 21.07 (95% CI: 9.17–48.38). Additionally, the Deeks’ test suggested that publication bias may have some effect on the summary estimates (p-value = 0.01) (Figure 5D). Representative results from the above analyses are shown in Table 4.

### miRNA-133

Nine studies that focused on the diagnostic accuracy of miRNA-133 (including miRNA-133a/b) in AMI were included in the meta-analysis (Corsten et al., 2010; D’Alessandra et al., 2010; Wang et al., 2010, 2011, 2013; Gidlöf et al., 2011; Li Y. Q. et al., 2013; Olivieri et al., 2013; Peng et al., 2014; Ji et al., 2015; Ke-Gang et al., 2016; Liu et al., 2018) (Table 3). As
shown in Figures 6A, B, the pooled sensitivity and specificity estimates with 95% CI were 0.85 (95% CI: 0.72–0.92) and 0.92 (95% CI: 0.78–0.98), respectively. The area under the SROC curve for miRNA-133 was 0.94 (95% CI: 0.92–0.96) (Figure 6C). The pooled PLR was 10.79 (95% CI: 3.63–32.09) and the pooled NLR was 0.17 (95% CI: 0.09–0.31). The DOR was 64.18 (95% CI: 19.03–216.49). The Deeks’ test suggested a potential publication bias (p-value = 0.01) (Figure 6D). Further subgroup analysis was conducted on miRNA-133a in the diagnosis of AMI and the SROC value, the pooled sensitivity, specificity, and DOR in the five studies (Wang et al., 2010; Gidlöf et al., 2011; Li Y. Q. et al., 2013; Ji et al., 2015; Ke-Gang et al., 2016) were 0.93 (95% CI: 0.91–0.95), 0.85 (95% CI: 0.69–0.94), 0.92 (95% CI: 0.61–0.99), and 66.15 (95% CI: 7.41–590.92). Representative results from the above analyses are shown in Table 4.
miRNA-208

Thirteen studies evaluated the diagnostic value of miRNA-208 (including miRNA-208a/b) in AMI and were included in the meta-analysis (Corsten et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Devaux et al., 2012, 2015; Li C. et al., 2013; Li Y. Q. et al., 2013; Li et al., 2015; Liu et al., 2015, 2018; Agiannitopoulos et al., 2018; Li P. et al., 2019) (Table 3). As shown in Figures 7A, B, the pooled sensitivity and specificity estimates with 95% CI were 0.83 (95% CI: 0.74–0.89) and 0.98 (95% CI: 0.88–0.99), respectively. The area under the SROC curve for miRNA-208 was 0.94 (95% CI: 0.91–0.95) (Figure 7C). The pooled PLR was 35.45 (95% CI: 5.90–212.88), and the pooled NLR was 0.18 (95% CI: 0.11–0.28). The DOR was 201.13 (95% CI: 24.36–1660.71). The Deeks' test suggested a possible publication bias (p-value = 0.04) (Figure 7D). In the subgroup analysis of miRNA-208b in the diagnosis of AMI, the SROC value, the pooled sensitivity,
miRNA-499
Seventeen studies involving 3,976 individuals investigated the diagnostic accuracy of miRNA-499 as a novel biomarker for AMI (Corsten et al., 2010; Wang et al., 2010; Gidlöf et al., 2011, 2013; Devaux et al., 2012, 2015; Li C. et al., 2013; Li Y. Q. et al., 2013; Olivieri et al., 2013; Liu et al., 2015, 2018; Zhang L. et al., 2015; Zhang R. et al., 2015; Shalaby et al., 2016; Agiannitopoulos et al., 2018; Fawzy et al., 2018; Li P. et al., 2019) (Table 3). As shown in Figures 8A, B, the pooled sensitivity and specificity estimates with 95%CI were 0.85 (95% CI: 0.77–0.91) and 0.95 (95% CI: 0.89–0.98), respectively. The area under the SROC curve for miRNA-499 was 0.96 (95% CI: 0.94–0.97) (Figure 8C). The pooled PLR was 16.27 (95% CI: 7.31–36.22), and the pooled NLR was 0.16 (95% CI: 0.10–0.26). The DOR was 103.54 (95% CI: 31.08–345.01). The Deeks’ test suggested a low possibility of publication bias (p-value = 0.12) (Figure 8D). Representative results from the above analyses are shown in Table 4.

DISCUSSION
This systematic review and meta-analysis of 58 manuscripts that utilize blood circulating miRNAs (including plasma- or serum-based) in the diagnosis of AMI identified 51 significantly dysregulated miRNAs between AMI cases and controls. Additionally, this review assessed the feasibility of using these miRNAs as novel biomarkers for the diagnosis of AMI patients. Sixteen of the abnormally expressed miRNAs were investigated by more than one study, including thirteen upregulated miRNAs: miRNA-1, miRNA-19b-3p, miRNA-21, miRNA-122-5p, miRNA-126, miRNA-133a/b, miRNA-134, miRNA-150, miRNA-186, miRNA-208a/b, miRNA-486, miRNA-499, and miRNA-663b, and three downregulated miRNAs: miRNA-26a, miRNA-191, and miRNA-375. A further 34 dysregulated miRNAs were only reported by one study. The overall pooled diagnostic data of total miRNAs expression were as follows: SROC curve with AUC: 0.91, sensitivity: 0.82, specificity: 0.87, showing that circulating miRNAs might be suitable for use as potential biomarkers of AMI. Furthermore, the present meta-analysis was conducted via subgroup analyses based on type of miRNAs, including miRNA-1, miRNA-133a/b, miRNA-208a/b, and miRNA-499. MiRNA-499 had the highest diagnostic value (sensitivity: 0.85, specificity: 0.95, SROC curve with AUC: 0.96), followed by miRNA-133a (sensitivity: 0.85, specificity: 0.92, SROC curve with AUC: 0.93), and miRNA-208b had better specificity (0.96) than sensitivity (0.80). These results indicate a relatively high diagnostic accuracy for AMI based on significantly dysregulated miRNAs.

It is well-known that an early, accurate diagnosis and effective revascularization therapy play vital roles in reducing morbidity and mortality in patients with AMI (Yeh et al., 2010). At present, cardiac troponin, creatine kinase-MB (CK-MB), and myoglobin are the most widely used biomarkers in the diagnosis of AMI (de Winter et al., 1995). A good standard for the early diagnosis of AMI is an increase of cTn level (Celik et al., 2011). However, these markers are also likely to be elevated in patients with other diseases, whether or not CAD is also present (French and White, 2004). The detection of cTn has time constraints, as significant levels are reached 4–8 h following the onset of ischemia symptoms. Thus, novel genetic and molecular biomarkers of myocardial damage that have high sensitivity and specificity are still urgently needed.

Significant advances have occurred in the field of cardiovascular disease and miRNAs since their first discovery in the blood (Karukas et al., 2017). A growing number of studies indicate that the abnormal expression of miRNAs plays a critical role due to their various pathological functions in the presence of myocardial infarction (Gurha, 2016; Moghaddam et al., 2019). MiRNAs are steadily present in bodily fluids (including plasma, serum, urine, and saliva) due to protection from RNase via binding to argonaute proteins and the ability to be released from cells via microvesicles, exosomes, or bound to proteins (Meister, 2013). Moreover, recent studies have shown that cTn is more difficult to detect than miRNAs in patients with MI during the earlier acute stage, as it is usually below the cut-off value (Gidlöf et al., 2013; Zhang L. et al., 2015). This suggests a difference between these two types of biomarkers in the physiological process of myocardial infarction. Cardiac troponin releases into the blood during necrosis and during the pathological process of myocardial hypoxia and ischemia (Wu and Ford, 1999). However, miRNAs can be released in response to several forms of cellular stress occurring earlier than cell necrosis such as anoxia, lactic acidosis, and cellular edema (Edeleva and Shcherbata, 2013). Thus, experts may consider the expression levels of dysregulated miRNAs at an earlier stage of AMI, as they might be reliable candidate biomarkers for the diagnosis of AMI (Li C. et al., 2013).

In this study, the summary of single miRNAs showed that miRNA-1, miRNA-133, miRNA-208, and miRNA-499 are potential candidates for the detection of AMI, as they were most frequently detected in the previous studies. Among these individual miRNAs, circulating miRNA-499 might be an effective candidate biomarker of AMI. Some studies have demonstrated that miRNA-499 was specifically expressed in the myocardium and skeletal muscle of mammals (Xue et al., 2019a) and played a critical role in the recovery process following cardiac injury (Hosoda et al., 2011). Based on the present study, miRNA-499 has a higher sensitivity and specificity in identifying patients with AMI, and these results were similar to or better than previous studies (Cheng et al., 2014; Zhao et al., 2019). Previous studies were based on relatively small sample sizes and did not include studies published in recent years. Thus, the results of the present study are more reliable and convincing. Furthermore, we strictly considered the precise setting of specific miRNAs in the diagnosis of AMI and that assessing their diagnostic performance in combination with other biomarkers, especially highly sensitive troponin immunosassays, may be warranted. A study by Olivieri et al. showed a significant correlation between miRNA-499 and cTnT, and that the diagnosis value of this combination was
superior to either one alone (Olivieri et al., 2013). However, another study reported that the diagnostic value of miRNA-499 and hs-cTnT combined was not better than either them alone (Devaux et al., 2012). Thus, due to the limited sample sizes of these studies, further research is required.

There are only a small number of high-quality studies with large sample sizes focused on the diagnostic value of miRNAs in AMI. To the best of our knowledge, this study has included the largest sample size of dysregulated miRNAs as novel biomarkers for AMI for summary and evaluation. Further high-quality studies should be performed to acquire more reliable data for use in formulating standard diagnostic criterion and to determine optimal cut-off values. Moreover, due to the different diagnostic values of miRNAs, our study demonstrated that a panel of 2
or 3 miRNAs might be superior for diagnostic accuracy. The combination of 3 miRNAs trended toward a higher sensitivity than others for use as biomarkers in the diagnosis of AMI. Therefore, to further improve the feasibility of clinical diagnosis, future research should explore the most effective combination of multiple miRNAs, especially those confirmed to have a higher utilization value in the single miRNA groups.

Aside from the many studies investigating miRNA profiles in the detection of AMI, researchers should pay closer attention to the search for the technology to detect miRNAs quickly and accurately. Methods of RNA detection tend to be time-consuming, expensive, require sophisticated techniques, and are difficult to implement for urgent testing, especially in some developing countries (Lippi et al., 2013). However, novel detection technologies developed in recent years may provide a solution to these issues, which would also support the clinical application of miRNAs in the future. Examples of new technologies include isothermal reactions based on cleavage with DNAzyme and signal amplification, which can simultaneously amplify and detect RNA (Zhao et al., 2013). This method is thought to be immune to genomic DNA pollution and has a relatively reliable sensitivity and specificity. We believed that new, precise methods of diagnosis that can detect miRNAs very rapidly and inexpensively need to be continuously improved.

In addition, the heterogeneity of the results of this study was substantial and could not be completely resolved. We found that the sources of heterogeneity included the following: quality of included studies, age, gender proportion, regional and environmental factors, and sampling criteria. Despite the heterogeneity, we believe the results of this study are worthwhile and valuable. Results of the overall and stratified analysis of different subgroups trended toward satisfactory values of miRNAs as novel biomarkers in the diagnosis of AMI. Furthermore, it was remarkable that some publication bias was found in the present study and might imply that the potential negative results were less likely to be published.

Although this study had a satisfactory result regarding the use of miRNAs for AMI detection, conclusions should be drawn cautiously due to several limitations: (1) there was a lack of standardization due to different normalization procedures across the included studies; (2) the exclusion of non-English articles may have caused important studies to be overlooked and publication bias due to significant results being more easily published; (3) the combined analysis of multiple miRNAs for a panel were insufficient, and we were unable to conduct a meta-analysis based on the data from limited studies; and (4) the results may have been affected by the impact of inevitable clinical heterogeneity, including the general condition of the included individuals, effects of medication, and medical history.

**CONCLUSION**

The current systematic review identifies numerous miRNAs associated with AMI and suggested that miRNAs may be used as a potential biomarker for the detection of AMI. For single, stand-alone miRNAs, miRNA-499 had better diagnostic accuracy than other miRNAs. A panel of two or three miRNAs might be superior for diagnostic accuracy. To develop a diagnostic test for AMI diagnosis, we suggest that a panel of miRNAs with high sensitivity and specificity should be tested. For this purpose, large scale, high-quality studies are still required to validate the clinical application of miRNAs for AMI diagnostics, as well as to identify the precise setting of dysregulated miRNAs in patients with AMI.

**DATA AVAILABILITY STATEMENT**

Publicly available datasets were analyzed in this study. Datasets are available through the corresponding author upon reasonable request.

**ETHICS STATEMENT**

All analyses were based on previous published studies; thus no ethical approval or patient consent were required. All previous published studies were approved by Ethics Committee, respectively.

**AUTHOR CONTRIBUTIONS**

HC and CZ designed the study. CZ carried out the statistical analysis and participated in most of the study steps. CZ, RL, JC, KH, and MA prepared the manuscript and assisted in the study processes. YH, JZ, YZ, LW, and RZ assisted in the data collection and helped in the interpretation of the study. All authors read and approved the final manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2020.00691/full#supplementary-material

**Supplementary Figure 1 | Methodological quality of studies in the meta-analysis using the Quality Assessment of Diagnostic Accuracy Studies 2 score system, including risk of bias and applicability concerns. The items were scored with “yes,” “no,” or “unsure”.

**Supplementary Figure 2 | Forest plots of the total miRNAs in the diagnosis of acute myocardial infarction among the studies included in the meta-analysis. (A) Sensitivity. (B) Specificity.

**Supplementary Figure 3 | Summary receiver operator characteristic (SROC) curve with area under the curve (AUC) and funnel graph of the total miRNAs in the diagnosis of acute myocardial infarction. (A) SROC curve with AUC. (B) Funnel graph.
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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