Original Article

Circulating miRNA-21 as a diagnostic biomarker for acute coronary syndrome: a systematic review and meta-analysis of diagnostic test accuracy study

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Background: Both early detection and treatment for acute coronary syndrome (ACS) have positively affected prognosis. A microRNA, miRNA-21 (miR-21), may have additional diagnostic potential for ACS among the others. This systematic review and meta-analysis aimed to evaluate the potential role of miR-21 in identifying ACS.

Methods: PubMed, EMBASE and CENTRAL databases were searched up to March 17, 2024, for case-control and cohort studies assessing the diagnostic value of circulating miR-21 in patients with ACS. The search was limited to studies published in either English or Chinese. The primary outcome was the discriminative ability to circulate miR-21 for ACS, represented by the area under the standard receiver operating characteristic curve (AUC) analysis. Meta-analyses combined the AUCs using a random-effects model. Heterogeneity among the studies was detected by the I^2 and Q statistics. The quality of the studies included was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2. Publication bias analysis was assessed constructing by the Egger's test (PROSPERO: CRD42020209424).

Results: Eleven case-control studies containing a total of 2,413 subjects with 1,236 ACS cases and 1,177 controls were included. The mean age of participants in these studies ranges between 51.0 and 69.0 years. The meta-analysis showed an overall pooled AUC of 0.779 [95% confidence interval (CI): 0.715–0.843], with high heterogeneity noted between the studies (Q statistic =190.64, I^2=94.23%, P<0.001). In subgroup analyses according to the subtypes of ACS, a pooled AUC of 0.767 (95% CI: 0.648–0.887) was derived from the studies focused on acute myocardial infarction cases only. The pooled AUC for unstable angina was 0.770 (95% CI: 0.718–0.822). In subgroup analyses according to the types of control groups, pooled AUC for ACS versus healthy controls was 0.779 (95% CI: 0.715–0.843), whereas the pooled AUC for ACS versus unhealthy controls was 0.740 (95% CI: 0.645–0.836). The quality assessment showed that the studies' overall quality was moderate. No evidence of publication bias was noted (P=0.49).

Conclusions: Circulating miR-21 shows abilities to differentiate between ACS and non-ACS, suggesting its potential as a novel diagnostic biomarker for ACS. However, the evidence is weakened by high heterogeneity observed among the studies. Further research is essential before it can be applied in clinical practice.

Keywords: Acute coronary syndrome (ACS); acute myocardial infarction (AMI); biomarkers; circulating microRNAs; unstable angina (UA)

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Introduction

Acute coronary syndrome (ACS) is a group of ischemic conditions associated with decreased blood flow in the coronary arteries, including, ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), which occurs most commonly as a result of a thrombus forming within the lumen of a coronary artery and lead to acute myocardial infarction (AMI) (1,2). Globally around 110 million men and 80 million women have coronary heart disease (CHD) (3). The overall mortality for those patients was estimated to be 52% (4). Early diagnosis of ACS is critical since timely intervention may improve patients' prognosis (5).

In the context of clinical and electrocardiography (ECG) findings, the diagnosis of ACS primarily relies on elevated high-sensitivity cardiac troponin I or T levels (hs-cTnI or hs-cTnT). However, their predictive accuracy within the first 2 hours after ACS onset is below 65%, driving the search for more accurate biomarkers for improved diagnosis at the critical early stages of ACS (1,6).

The microRNAs (miRNAs) are endogenous, small, noncoding RNAs that help to regulate gene expression of target mRNA in post-transcription processing (7). Last decade, miRNAs have been shown to be involved in various physiological and pathological processes, including cardiac hypertrophy, fibrosis, and apoptosis (8), stroke (9); and cellular differentiation, proliferation, apoptosis and stress response (8,10). Otherwise, circulating miRNAs are suggested in several studies to be potential biomarkers for the diagnosis of cardiovascular diseases (2,11-13), such as improving the diagnostic accuracy of AMI and predicting cardiovascular events.

Recently, miR-21, has been shown to participate in metabolic and inflammatory processes, and may have diagnostic potential as a biomarker for ACS, including myocardial infarction and UA, among others (13-17), although the studies cited are with relatively small sample sizes and had inconsistent outcomes. While a list of meta-analyses have been conducted on the diagnostic roles of various miRNAs such as miR-133 in CHD and AMI (18-21), no prior literature has systemically reviewed the evidence regarding the roles of miR-21 in AMI or ACS. Therefore, this systematic review and meta-analysis aimed to comprehensively evaluate the diagnostic potential of miR-21 for ACS based on the up-to-date evidence. We present this article in accordance with the PRISMA-DTA reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-385/rc) (22).

Highlight box

Key findings

- The systematic review and meta-analysis of 11 case-control studies involving 2,413 subjects found that circulating miR-21 has a pooled area under the standard receiver operating characteristic curve of 0.779 for discriminating between acute coronary syndrome (ACS) and non-ACS individuals.

What is known and what is new?

- ACS is a significant cause of morbidity and mortality, and early detection is crucial for improving prognosis.
- This study suggests that miR-21 in circulation could serve as a candidate diagnostic biomarker for ACS.

What is the implication, and what should change now?

- The findings implicate miR-21 as a potential ACS diagnostic tool. More research is needed to validate miR-21's diagnostic value with larger prospective studies and to investigate its post-ACS prognostic role.

Methods

Search strategy

The protocol was registered on the PROSPERO registry (CRD42020209424). The search included: PubMed, EMBASE, and CENTRAL databases until March 17, 2024. The search used combinations of the keywords "acute coronary syndrome", "ACS", "myocardial infarction", "AMI", "angina", "microRNA-21", and "miR-21" properly combined with Boolean operators and using Medical Subject-Headings (MeSH) terms where appropriate. As an example, the specific search formula applied to PubMed was: (((“acute coronary syndrome” OR ACS) OR (“myocardial infarction” OR AMI)) OR (angina)) AND (microRNA-21 OR miR-21).

The reference lists of eligible articles were also searched manually for additional eligible studies. A comprehensive search strategy, which includes both the keywords and Boolean operators across all queried databases, along with the applied filters and limits, is detailed in the Table S1 for further reference (Table S1).

Selection criteria and data extraction

Inclusion criteria for eligible studies were: (I) case-control or cohort studies assessing the diagnostic value of circulating microR-21 in patients with ACS (including AMI, UA, or patients with ACS not specified as AMI or UA) compared to non-ACS; ACS was diagnosed by clinical symptoms and tests based on American College of Cardiology (ACC)/American Heart Association (AHA) guidelines; (II) miR-21 was quantified from plasma or serum using quantitative reverse transcription polymerase chain reaction (qRT-PCR); (III) sample size and area under the standard receiver operating characteristic curve (area under ROC curve; AUC) was reported with standard error (SE) or contained sufficient information for calculating SE. Non-human studies; reports written in languages other than English or Chinese; and letters, comment, reviews, editorials, case reports, proceedings, conference abstracts, personal communications and protocols were excluded. Eligibility of the studies were determined by two independent reviewers (J.G.H. and X.H.C.) using the above inclusion/exclusion criteria. When there was uncertainty regarding eligibility, a third reviewer (Z.W.D.) was consulted.

The following data were extracted from the included studies: name of first author, year of publication, study country, study design, characteristics of case and control groups, number of patients in each group, participants' age, gender, specimen type, detection method for miR-21, maximum time from symptom onset to sample acquisition, relative fold increases in miR-21 and AUC values.

Quality assessment

The quality of each article included in this diagnostic meta-analysis was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) score system, which has been demonstrated to be an effective tool for evaluating the quality of diagnostic accuracy studies (23). The QUADAS-2 tool, including four key domains (patient selection, index test, reference standard, flow and timing). Each is evaluated based on their risk of bias, and the first three are also examined for potential concerns related to applicability. Discrepancies were resolved by discussion to reach a consensus. Specifically, risk of bias and concerns were rated as either a high, low, or unclear risk/concern.

Statistical analysis

The primary outcome for this meta-analysis is the pooled discriminative ability of circulating miR-21 for the presence of ACS, which was assessed by the AUC. A χ^2-based test of heterogeneity was performed and the inconsistency index (I^2) and Q statistics were determined. If I^2 was >50% or >75%, the trials were considered to be heterogeneous or highly heterogeneous, respectively. If I^2 was <25%, the studies were considered to be homogeneous. The meta-analysis was conducted based on a random-effects model (DerSimonian-Laird method) because the pooled ROC curve only represents the relationship between sensitivity and specificity values across studies with different thresholds for each method. Pooled effects were calculated and a two-sided P value of <0.05 was regarded as statistical significance. In addition, subgroup analyses were performed according to types of ACS (AMI and UA) and types of control group (healthy and unhealthy) as well. Publication bias analysis was assessed by constructing funnel plots. The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution (24). All analyses were performed using MedCalc version 19.4 (MedCalc Software Ltd., Belgium).

Results

Literature search and study selection

A flowchart of the search and study selection process is shown in *Figure 1*. The electronic search identified a total of 455 citations. Amongst, 204 duplicate records were excluded, leaving 251 records. After screening titles and abstracts, 86 studies were retrieved for further full-text assessment for eligibility. Amongst, 11 studies (2,14,15,17,25-31) were included for the qualitative review and quantitative synthesis. The most common reasons for exclusion were: study had different objectives, studies investigated mRNAs other than miR-21, as well as no quantitative outcomes of interest were reported.

Study characteristics

Characteristics of the studies included are summarized in

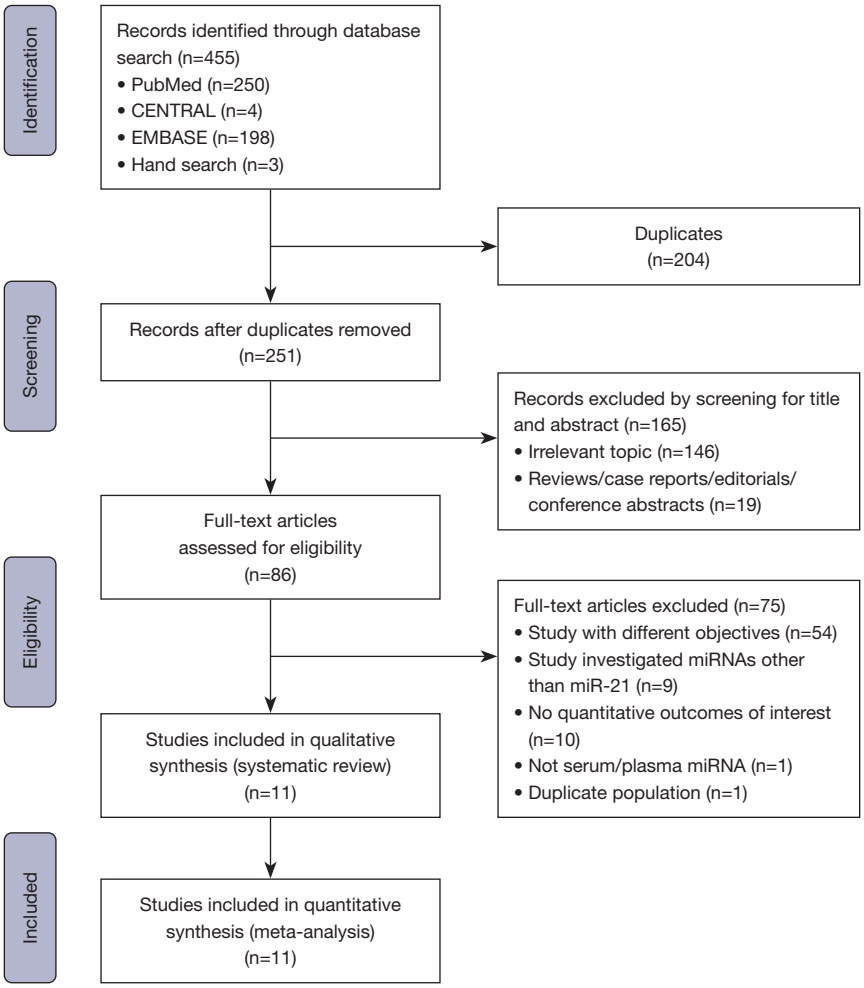

Figure 1 PRISMA flow diagram of study selection. miRNAs, microRNAs; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Table 1. The 11 included studies were published between 2012 and 2023. Six studies were conducted in China, one in Iran, one in China/Sweden, one in India, one in Germany and one in the Netherlands. Study sample sizes ranged from 27 to 1,042 subjects. Overall, the included studies reported on a total of 2,413 subjects, with 1,236 ACS cases and 1,177 controls. Participants' mean age ranged from 51.0 to 69.0 years and the proportion of males ranged from 38.5% to 79.6% across the studies.

Meta-analysis

The forest plot in *Figure 2* shows the results of the meta-analysis. Eleven studies (2,14,15,17,25-31) provided AUCs, from which a pooled AUC of 0.779 [SE =0.033; 95% confidence interval (CI): 0.715–0.843] was derived. High heterogeneity was noted among the studies (Q statistic =190.64, I^2=94.23%, P<0.001) (*Figure 2*).

Six studies (14,17,26,28,30,31) reported AUCs in discriminating AMI from control group, and three studies (15,28,29) reported AUCs for UA from control. Subgroup analyses were performed in order to determine whether circulating miR-21 has different discriminative performance by which to distinguish AMI and UA from controls. A pooled AUC of 0.767 (SE =0.061; 95% CI: 0.648–0.887) was derived for discriminating AMI from non-ACS control, with high heterogeneity detected (Q statistic =182.76, I^2=97.26%) (*Figure 3A*). Pooled AUC for discriminating UA from non-ACS control was 0.770 (SE 0.027; 95% CI:0.718–0.822), with no heterogeneity detected (Q statistic =1.297,

Table 1 Study characteristics: an overview of studies

First author [year]	Country	Case/control	No. of patients	Mean age (years)	Male (%)	Specimen	Detection method	Maximum time from symptom onset to sample acquisition	Relative fold increase
Xu [2023] (31)	China	AMI	40	55.7	75.0	Plasma	SYBR	6 h	NA
		UA	22	56.9	54.5				
		Healthy (clinically unsuspected of CAD)	22						
Biener [2021] (26)	Germany	AMI	137	69.0	79.6	Plasma	TransTaq	NA	NA
		With symptoms suggestive of ACS including chest pain, dyspnea, or atypical chest pain	905	64.0	64.0				
Kumar [2020] (27)	India	AMI and UA	32	58.7	62.8	Plasma	TransTaq	NA	2.46
		Healthy (clinically unsuspected of CAD)	50	53.1	64.8				
Ling [2020] (28)	China	AMI	34	57.8	70.6	Serum	SYBR	Within 2 h after AMI	NA
		UA	31	60.1	61.3				
		Healthy (clinically unsuspected of CAD)	22	58.5	50.0				
Gao [2019] (14)	China	AMI	184	59.0	67.4	Serum	TransTaq	NA	NA
		Healthy (clinically unsuspected of CAD)	150	60.4	68.0				
Darabi [2017] (25)	Iran	AMI and UA	53	63.1	62.3	Serum	ROX	NA	2.39
		Stable CAD	52	62.3	61.5				
Liu [2017] (15)	China	UA	98	68.1	51.0	Plasma	TaqMan	12 h	2.02
		Non-cardiac chest pain	95	51.0	50.5				
Zhang [2016] (17)	China	AMI	17	62.8	70.6	Plasma	TaqMan	NA	4.7
		Non-cardiac chest pain	10	56.2	50.0				
Wang [2014] (30)	China	AMI	17	52.0	70.6	Plasma	SYBR	24 h	NA
		Healthy volunteer	28	58.0	42.9				
Ren [2013] (29)	China, Sweden	UA	45	61.0	53.8	Plasma	TaqMan	NA	NA
		Non-cardiac chest pain	37	56.0	38.5				
Oerlemans [2012] (2)	Netherland	AMI and UA	106	68.7	66.0	Serum	TaqMan	NA	NA
		Stable angina, rhythm disorders, heart failure, pericarditis, other cardiac diagnosis and non-cardiac chest pain	226	60.2	53.1				

AMI, acute myocardial infarction; UA, unstable angina; CAD, coronary artery disease; NA, not applicable.

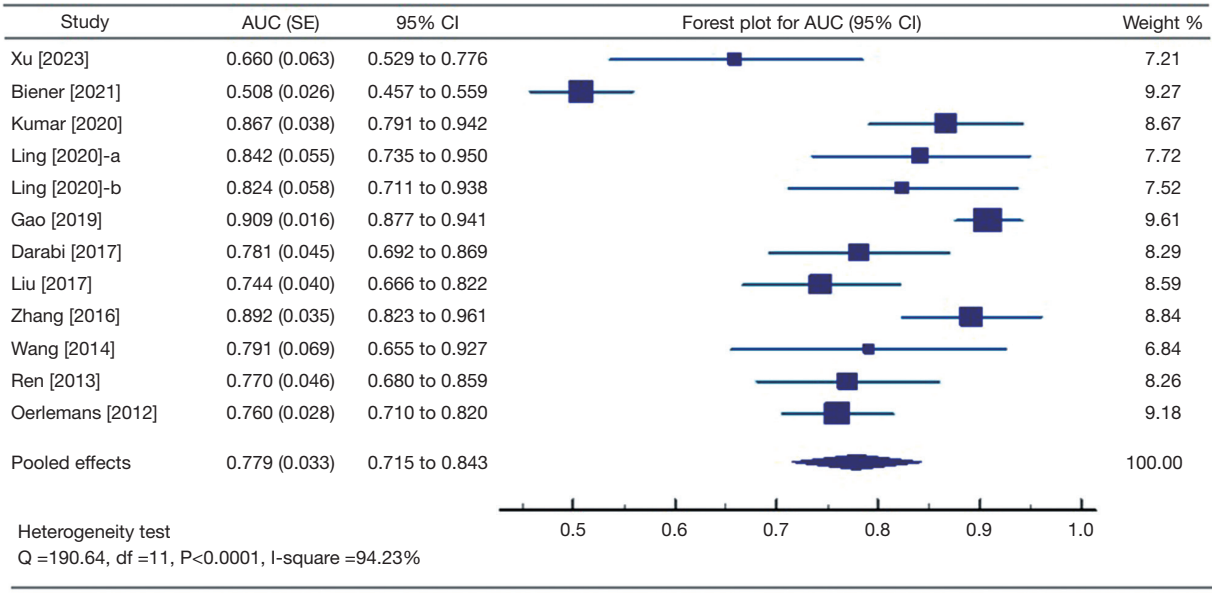

Figure 2 Forest plot of circulating miR-21 AUC values for discriminating ACS from non-ACS control. AUC, area under the standard ROC curve; ROC, receiver operating characteristic; SE, standard error; CI, confidence interval; ACS, acute coronary syndrome.

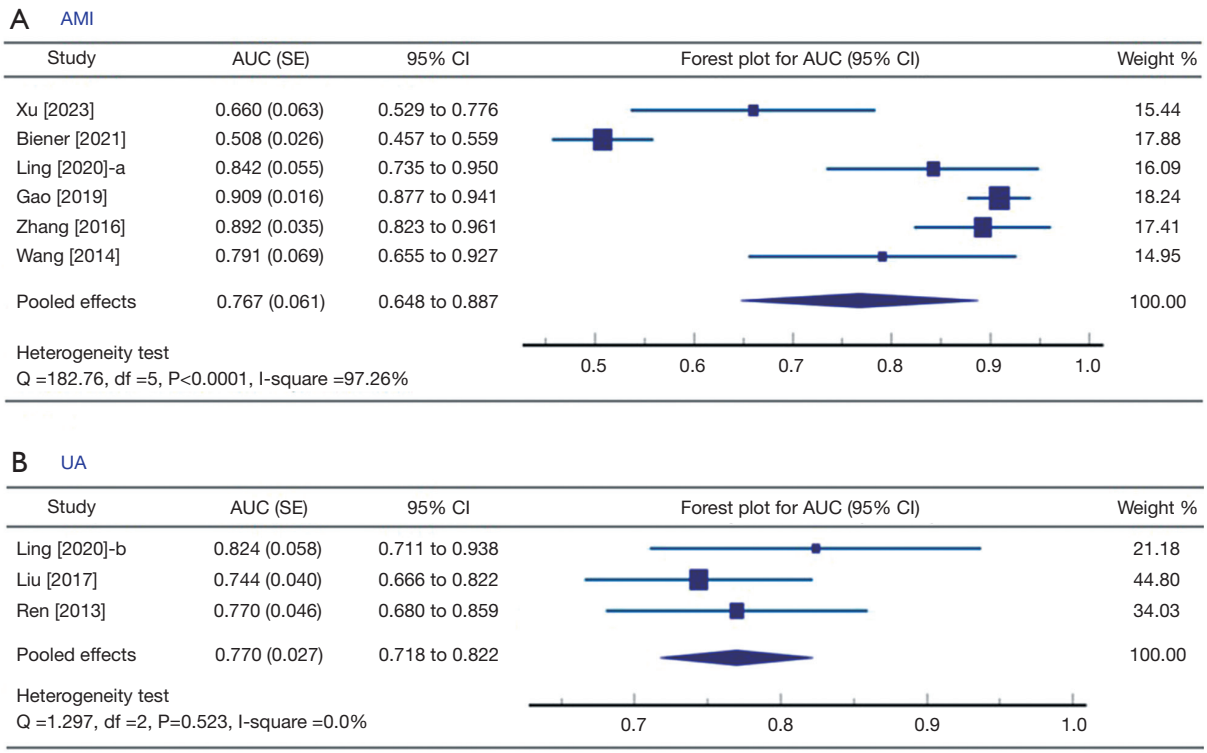

Figure 3 Subgroup analysis of circulating miR-21 AUC values for discriminating (A) AMI and (B) UA from non-ACS control. AMI, acute myocardial infarction; AUC, area under the standard ROC curve; ROC, receiver operating characteristic; SE, standard error; CI, confidence interval; UA, unstable angina; ACS, acute coronary syndrome.

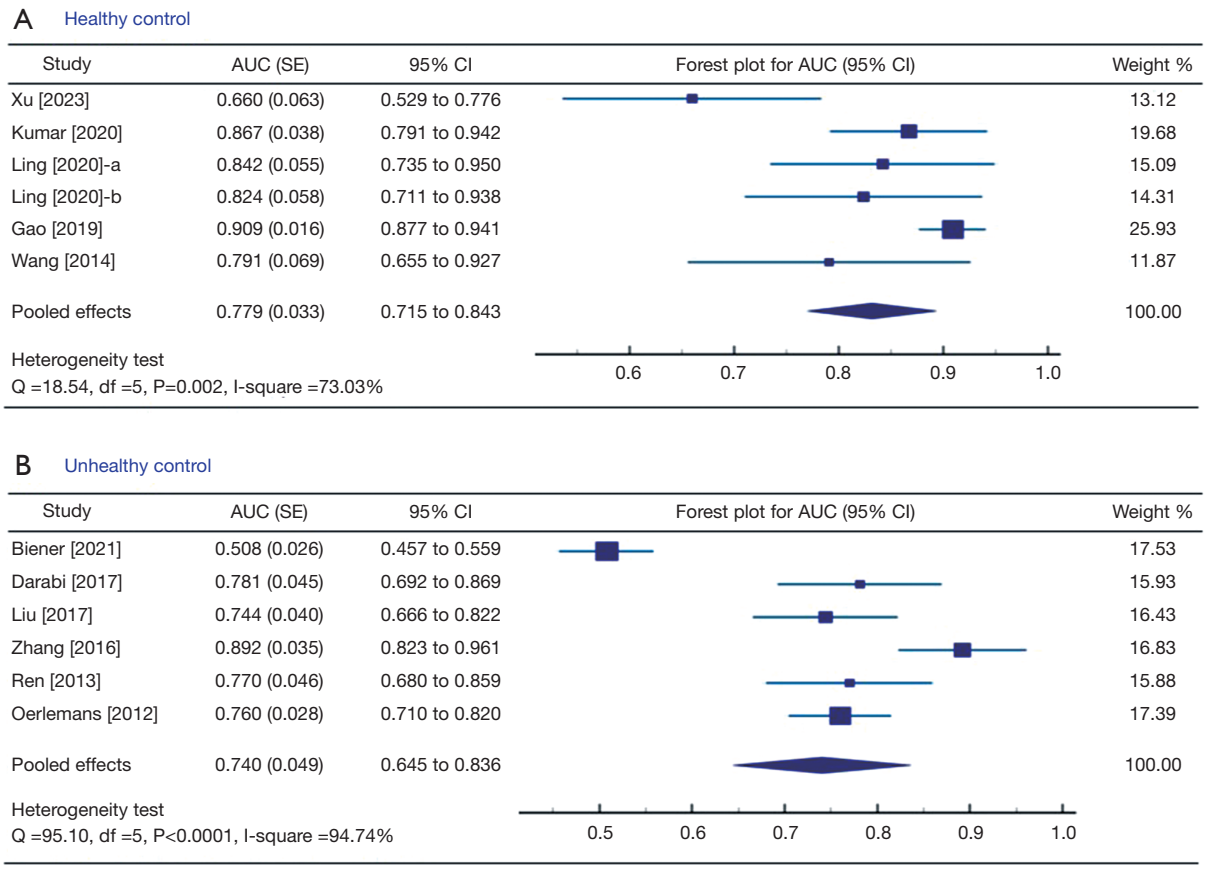

Figure 4 Subgroup analysis of circulating miR-21 AUC values for discriminating ACS from (A) healthy control and (B) unhealthy control. AUC, area under the standard ROC curve; ROC, receiver operating characteristic; SE, standard error; CI, confidence interval; ACS, acute coronary syndrome.

I^2=0.0%) (*Figure 3B*).

In subgroup analyses based on different types of control group, the pooled AUC for discriminating ACS versus healthy controls, derived from five studies (14,27,28,30,31), was 0.779 (SE =0.033; 95% CI: 0.715–0.843), with high heterogeneity detected (Q statistic =18.54, I^2=73.03%) (*Figure 4A*). The pooled AUC for discriminating ACS versus unhealthy controls, derived from six studies (2,15,17,25,26,29), was 0.740 (SE =0.049; 95% CI: 0.645–0.836), also with high heterogeneity detected (Q statistic =95.10, I^2=94.74%) (*Figure 4B*).

Publication bias

The results of funnel plot revealed there was no evidence of publication bias (P=0.49 by the Egger's test) (*Figure 5*).

Quality of the included studies

The result of QUADAS-2 quality assessment of the included studies is shown in Table S2. The overall quality of the included studies was considered moderate. All of the studies were of a case-control design, and thus had a high risk of bias in patient selection. Not all the studies mention a definite threshold of miR-21 for predicting ACS. The studies included also had raised high applicability concerns in the patient selection domain (Table S2).

Discussion

The present systematic review and meta-analysis combined the diagnostic performance of miR-21 for the detection of ACS based on 2,413 subjects and 11 studies from the most up-to-date literature. No publication bias was noted.

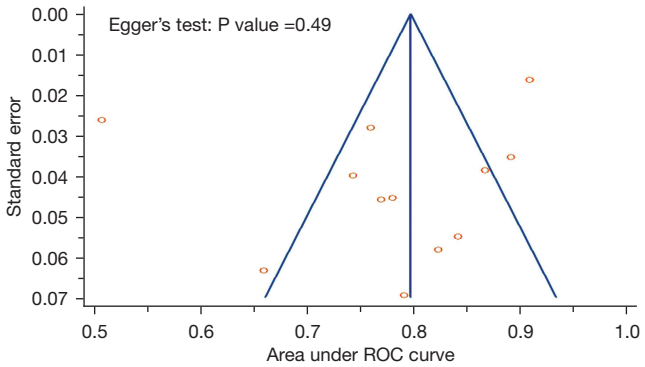

Figure 5 Funnel plot for publication bias. ROC, receiver operating characteristic.

The pooled AUC of 0.779 demonstrates a 'satisfactory' discriminatory ability (31), indicating that miR-21 may be useful for distinguishing between ACS and non-ACS individuals. Subgroup analyses were performed according to the subtypes of ACS and to the characteristics of the control groups. Although the results revealed that miR-21 also exhibited a satisfactory discriminating ability for AMI from non-ACS controls; however, high heterogeneity still existed. Nevertheless, the pooled AUC for UA demonstrated a satisfactory diagnostic accuracy (AUC =0.770) with no heterogeneity, indicating that such results can be considered reliable. In addition, analyses of miR-21's ability to distinguish ACS from both healthy and unhealthy controls also demonstrated AUCs over 0.7 but with notable heterogeneity among the studies in the subgroups detected.

As of the current date, the investigation into the role of miR-21 in ACS has been relatively limited, leading to a restricted pool of eligible studies for our analysis. Despite this limitation, the subgroup analyses focused on UA individually revealed no heterogeneity, suggesting that the initial heterogeneity might have been partly influenced by studies that included a combination of non-unified cases (mix of AMI and UA). Heterogeneity could also have come from the choice of controls, which could be a significant methodological issue in research on the diagnostic potential of miRNAs, as pointed out in other studies (32). Among the included studies, five studies were controlled using healthy participants (14,27,28,30,31), three using participants with non-cardiac chest pain (15,17,29), one using patients with pre-existing stable CAD (25), one with symptoms suggestive of ACS (26), and one with mixed controls (2). We also attempted to tackle heterogeneity by analyzing the value of miR-21 in distinguishing ACS from healthy and unhealthy controls separately. Despite these efforts, significant heterogeneity was still evident in the subgroup analyses. One of the included studies, Wang *et al.* [2014] (30), reported a higher diagnostic value for AMI *vs.* non-ischemic controls (AUC =0.981) than for AMI *vs.* ischemic controls (AUC =0.889), which indicates that miR-21 might be more effective in differentiating ACS from healthy individuals than from those with pre-existing CHD. Furthermore, the heterogeneity observed in the subgroup analyses may result from a combination of clinical, demographic, methodological, and procedural factors. For example, the heterogeneity found in the subgroup of studies on AMI might be sourced from the inability to analyze NSTEMI and STEMI separately. Grouping these conditions in reports may obscure the differences between them. As mentioned previously, varied characteristics of the control groups might reflect underlying differences in risk factors or comorbidities, thus leading to heterogeneity. Even in the studies using 'healthy controls', inconsistencies in participant demographics such as age and race, diverse miRNA detection and processing methods, and potential difference in time window of miRNA sample collection might all introduce variability and could influence the analytic outcomes. Nevertheless, the findings underscore the necessity for further research to fully understand miR-21's diagnostic potential and its role in ACS. Future meta-analyses are warranted to address the issue of heterogeneity by distinguishing NSTEMI and STEMI, or further adjusting for relevant confounders if possible.

In the clinical setting, the diagnostic methods for ACS include evaluating circulating biomarkers, which are suggested in the guidelines of the ACC and AHA (1,4) to be essential for confirming the diagnosis of ACS because of the limitations of clinical symptoms and ECG alone in diagnosing patients with NSTEMI or UA. Currently, in the context of clinical and ECG findings, the diagnosis of ACS is based on elevation of hs-cTnI or hs-cTnT (33,34), which the guidelines (1) and independent authors (16) also recommend. Although hs-cTn tests are recommended for ACS prediction, the sensitivity and specificity of accurate prediction are below 65% within a 2-hour window after the onset of ACS (6). This makes researchers continue their search for novel biomarkers with better accuracy in prediction, such as miRNAs, to gain additional diagnostic advantages, especially at the instance of ACS occurrence. Despite discovering the diagnostic value of miR-21 for ACS in the current meta-analysis, we acknowledge that certain gaps still exist before its routine application in diagnostic

investigations. First, non-cardiac diseases and phenotypes (e.g., end-stage kidney disease, age, and sex) and intake of medicines (e.g., statins and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker) may influence circulating miRNA levels (11,13). The other key issue associated with applying miR-21 as a biomarker for ACS is its cardiac specificity (35). As reported previously, miR-21 has exhibited certain diagnostic capabilities in several types of cancer (36) and has been shown to be significantly involved in diabetes (35) and pulmonary hypertension. One of the studies included in this meta-analysis, Oerlemans *et al.* (2), reported that when miRNA-21 was combined with hs-cTn, it offered a greater diagnostic accuracy than did miRNA-21 or troponin alone, supporting proper integration of this novel and the traditional biomarkers may further benefit the diagnosis. The authors of that study concluded that miR-21 could be used at least complementarily with conventional biomarkers to improve early diagnosis.

Features of miRNAs and evidence supporting their use in diagnosing cardiovascular disease are found in fairly recent studies. Several miRNAs have been evaluated in previous meta-analyses, including miR-499, miR-1, miR-133a, miR-208b for AMI (2,19-21,37). The miRNAs appear to function in a regulated process to repress protein synthesis, although the precise molecular mechanisms are not fully understood; however, they are known to directly regulate the activity of up to 60% of protein-coding genes, which may help to explain their presence in miRNA-mediated events such as ACS (10). The current findings add to previous knowledge and are the first to examine the role of miR-21 in ACS. Other studies have reported that miR-21 is expressed in cardiomyocytes, fibroblasts, and endothelial cells where apoptosis is adequately regulated, as well as cardiac fibrosis, proliferation, and cellular migration (32,35,38-40). Dong *et al.* [2014] (38) suggested that elevated miR-21 expression may precipitate cardiac hypertrophy and fibrosis, but that silencing the miR-21 gene inhibited fibrosis and improved cardiac function. A systematic review and meta-analysis by Chen *et al.* [2017] (41) identified miRNAs as diagnostic biomarkers for AMI in Asian populations. The authors of that study suggested that 2–3 miRNAs may need to be combined to provide more accurate diagnostic ability. This notion was supported by several studies. Oerlemans *et al.* (2) found that three miRNAs produced a significantly higher AUC (0.94) than hs-troponin T (0.89), displaying the great potential of miRNAs in early diagnosis of AMI. Shalaby *et al.* (42) also reported that combining miRNA-499 and miRNA-210 significantly improved the AUC to 0.96 for ACS onset <3 hours. Besides these combinations, miR-361-5 and miR-145 also provide AUC at 0.870 (43) and 0.852 (44), respectively. Monitoring potential biomarkers might accelerate the diagnosis of ACS patients in the emergency unit. Clearly, more evidence is needed to confirm the results of studies conducted to date.

Strengths and limitations

This is the first meta-analysis to evaluate the diagnostic value of miR-21 for discriminating ACS patients from non-ACS individuals. The inclusion criteria were established rigorously and heterogeneity across studies was carefully managed using a random-effects model and subgroup analyses. In particular, AUC was used to explicitly demonstrate the diagnostic value, which is more informative than only showing associations of dysregulation of certain miRNA as done in many previous studies. Nevertheless, the present review had several limitations. First, it included only a small number of studies with relatively small sample sizes, especially in subgroup analyses, in which the effect size might have been overestimated. NSTEMI and STEMI were not reported individually in any of the included studies, hence they could not be analyzed separately in this meta-analysis. The control groups were not homogenous, and even the studies that included healthy controls might have included subjects with different risk factors or comorbidities that could influence the results. We also were unable to control the discrepancies of age, race/ethnicity, detection and processing techniques of miRNAs or other potential factors that could possibly bias the meta-analysis. The precise time points of miRNA sample collection were not stated clearly in all included studies, thus the impact that time has could not be investigated. We did not assess the prognostic role of miR-21 after ACS. Some authors suggested that miR-21 could be used as a predictor of prognosis and survival after AMI (13), which was not assessed in this review due to limited data.

Conclusions

This meta-analysis of the most updated literature indicates that circulating miR-21 has satisfactory discriminative performance in differentiating between ACS and non-ACS. Circulating miR-21 may be considered a potential candidate as a novel diagnostic biomarker for ACS, although some

limitations including the presence of study heterogeneity pose challenges to the interpretation and applicability of the findings. Future research involving larger, prospective studies is needed. As more studies become available, an updated meta-analysis will be crucial to corroborate the findings of this review and further validate the use of miRNAs in the clinical diagnosis of ACS.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-385/rc

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-385/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-385/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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