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Research Article

The Role of Micro RNAs (miRNAs) in Early Detection of Acute Myocardial Infarction: A Meta-Analysis

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Abstract

Background: Acute myocardial infarction (AMI) is the leading cause of mortality and morbidity worldwide. Early diagnosis is very important for emergency physician and patients.

Objective: To explore and analyze the role of miRNAs in early detection of AMI by meta-analysis.

Methods: We searched through domestic and foreign literatures that were published between January 2010 to February 2016 with the purpose of finding studies using miRNAs in the diagnosis of acute myocardial infarction. The quality of inclusive literatures was assessed by methods from Cochrane Handbook. Valid data were analyzed by Meta-Disc 1.4 Software.

Results: A total of 21 studies were included in our analysis. The pooled sensitivity, specificity and AUC for total miRNAs were: 0.74 (95%CI: 0.72-0.76), 0.80 (95%CI: 0.79-0.82) and 0.8800. In further subgroup analyses, we found that the the pooled sensitivity, specificity and AUC for Chinese ethnicity were: 0.74 (95%CI: 0.72-0.76), 0.88 (95%CI: 0.84-0.87) and 0.8883. Whereas for foreign ethnic were: 0.74 (95%CI: 0.70-0.77), 0.73 (95%CI: 0.71-0.76) and 0.8470. And we also analyzed the four most popular miRNAs: miRNA-208: sensitivity, specificity and AUC were: 0.73 (95%CI: 0.68-0.78), 0.81 (95%CI: 0.78-0.84) and 0.8660; miRNA-499: sensitivity, specificity and AUC were: 0.80 (95%CI: 0.77-0.83), 0.80 (95%CI: 0.77-0.83) and 0.9163; miRNA-133: sensitivity, specificity and AUC were: 0.77 (95%CI: 0.71-0.90), 0.91 (95%CI: 0.86-0.95) and 0.9460; miRNA-1: sensitivity, specificity and AUC were: 0.66 (95%CI: 0.62-0.71), 0.76 (95%CI: 0.73-0.80) and 0.9111.

Conclusion: miRNAs is a new biochemical marker for the diagnosis of Acute Myocardial Infarction, especially miRNA-133 has the better diagnostic performance. But these conclusions still need further studies and greater improvements to validate.

Keywords: Acute Myocardial Infarction; miRNAs; Meta-analysis

Introduction

Acute Coronary Syndrome (ACS), especially for Acute Myocardial Infarction (AMI), is one of the most serious cardiovascular events and a major cause of mortality and morbidity worldwide [1]. Therefore, an early and accurate diagnostic method is a necessity for timely therapy [2]. Even though Cardiac troponins, are a gold standard for diagnosing AMI, yet they do have certain limitations in early detection [3]. Hence, novel potential biomarkers are needed to improve the diagnosis of patients with AMI.

MicroRNAs (miRNAs) acts as a post-transcriptional regulator and has a variety of roles in cardiac and vascular injury [4]. Recently, increasing evidence indicates that miRNAs are useful markers for diagnosing AMI [5-7]. These findings suggested that circulating miRNAs may be early indicators of myocardial damage, although the outcomes of reports differ from each other Hence we designed this meta-analysis to determine and confirm whether miRNAs could serve as a diagnostic marker for early detection of AMI.

Materials and Methods

Search Methodology and Study Selection

We searched MEDLINE, EMBASE and Cochrane for articles between January 2010 to February 2016, which is reported on the diagnostic accuracy of miRNAs for AMI. The search terms used were ("microRNA OR miRNA") AND ("diagnoses OR ROC cure OR sensitivity OR specificity") AND ("acute myocardial infarction" OR "AMI" OR "acute myocardial infarction"). Also, manual retrieval was conducted to reduce selection bias.

Eligible studies should be strictly in accordance with the following criteria:

1. Focus on the use of miRNAs for AMI
2. AMI patients should be confirmed by a gold standard test
3. Sufficient data is available to derive the diagnostic two-by-two tables (true/false positive, true/false negative).

The following exclusion criteria were considered:

1. Studies not conducted on humans
2. Reviews articles, conference reports, editorials, letters
3. Studies without complete data

Data Extraction and Quality Assessment

The final included studies were independently assessed by two reviewers by using a standardized form. The following data were extracted from each study: first author, publication year, number of patients and controls, types of miRNAs, and relevant data for mata-analysis (sensitivity, specificity, data of two-by-two tables). The methodological quality of included studies were assessed by Standards for the Reporting of Diagnostic Studies (STARD), which is a tool for diagnostic accuracy studies [8].

Statistical Analysis

We performed all statistical analyses using Meta-Disc 1.4 Software. The true positives (TP), false positives (FP), true negatives (TN), and false negative (FN) were calculated with obtained data after constructing two-by-two tables. The following indices were computed: pooled sensitivity, pooled specificity, diagnostic odds ratio (DOR), and their corresponding 95% confidence intervals (CI). Cochran-Q value and I2 test were used to assess heterogeneity across studies. All statistical tests were two sided, and the significance level was set at $p < 0.05$.

Results

Search results and Characteristics of included Studies

Figure.1 illustrates the process of article retrieval and study selection. Initially, 829 studies were identified from various databases and 301 of them were excluded due to duplication. After titles and abstracts were reviewed, 427 of the remaining 528 articles were excluded as they were reviews, meta-analysis or unrelated to the topic. As a result, 101 studies were suitable for full-text review. However, 80 of the 101 studies were further excluded due to insufficient data or unrelated to the diagnosis.

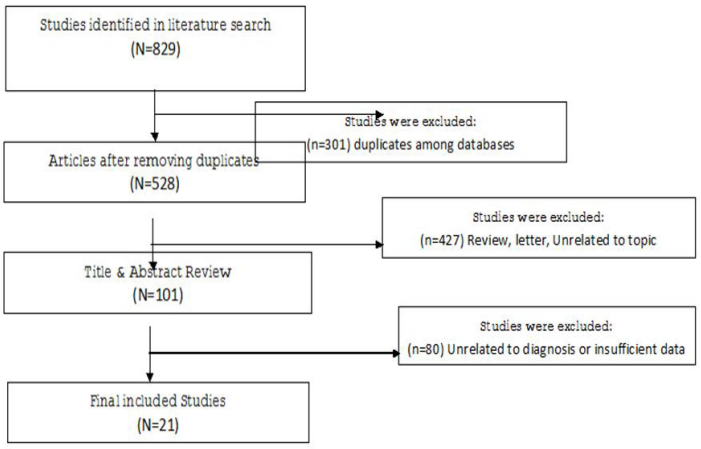


Figure 1: The flowchart of literature selection.

This meta-analysis comprises of 21 studies [6,9-28], including patients with AMI and healthy controls. Summarized main characteristics of the included studies are shown in Table.1. Using the modified 23-point Standards for the Reporting of Diagnostic Studies (STARD) for quality assessment, we modified this scoring system from 25 to 23 [8]. Then, we segregated studies into low and

high quality depending on whether they met < or > 50% of the study quality pro forma (Low < 12/23, High > 12/23).

Author Year	Patients(control)	Types	TP	FP	FN	TN	
An Hsu 2014[9]	39/39	mi-26a	23	16	16	23	9
		mi-126	25	14	14	25	
		mi-150	28	11	11	28	
		mi-191	24	12	15	27	
			24	15	15	24	
Benjamin Meder 2011[10]	20/20	mi-1291	17	3	3	17	8
C.H.Zhao 2015[11]	59/60	mi-663b	19	2	1	18	6
		mi-499	51	4	8	56	
Chencheng Li 2015[12]	87/87	mi-26a	64	24	23	63	10
		mi-191	54	27	33	60	
		mi-208b	52	23	35	64	
Fabiola Olivieri 2013[13]	92/99	mi-499	83	31	9	68	14
Guangwen Long 2012[14]	17/25	mi-1	14	1	3	24	10
		mi-126	13	5	4	21	
Guangwen Long 2012[15]	18/30	mi-30a	16	5	2	25	12
		mi-195	15	4	3	26	
Guo-Kun mi-499 Wang 2010[16]	33/33	mi-208a	30	0	3	33	13
		mi-499	12	0	21	33	
		mi-1	11	0	22	33	
		mi-133a	5	0	28	33	
Jianfeng Zhong 2014[17]	156/145	mi-19a	151	0	5	145	13
Jing Ai.2010[6]	93/66	mi-1	66	17	27	50	12
Li-ming Li 2014[18]	56/28	mi-1	51	1	5	27	6
Liu Peng 2014[19]	76/110	mi-133	62	10	14	100	9
		mi-1291	60	12	16	98	
		mi-663b	55	26	21	84	
Lizhu Zhang 2015[20]	142/85	mi-499	114	17	28	68	11
Maarten F. Corsten 2010[21]	32/36	mi-208	29	2	3	34	12
		mi-499	27	1	5	35	
Olof Gidlöf 2011[22]	25/11	mi-1	25	2	0	9	10
		mi-133	19	2	6	9	
		mi-208	25	11	0	0	
		mi-499	25	1	0	10	
Olof Gidlöf 2013[23]	74/333	mi-1	30	113	44	220	13
		mi-208	53	70	21	263	
		mi-499	56	90	19	243	
Rongrong Wang 2011[24]	51/28	mi-133	50	5	1	23	8
		mi-328	36	1	15	27	
Rui Zhang 2015[25]	110/110	mi-486	65	19	45	91	9
			70	31	40	79	

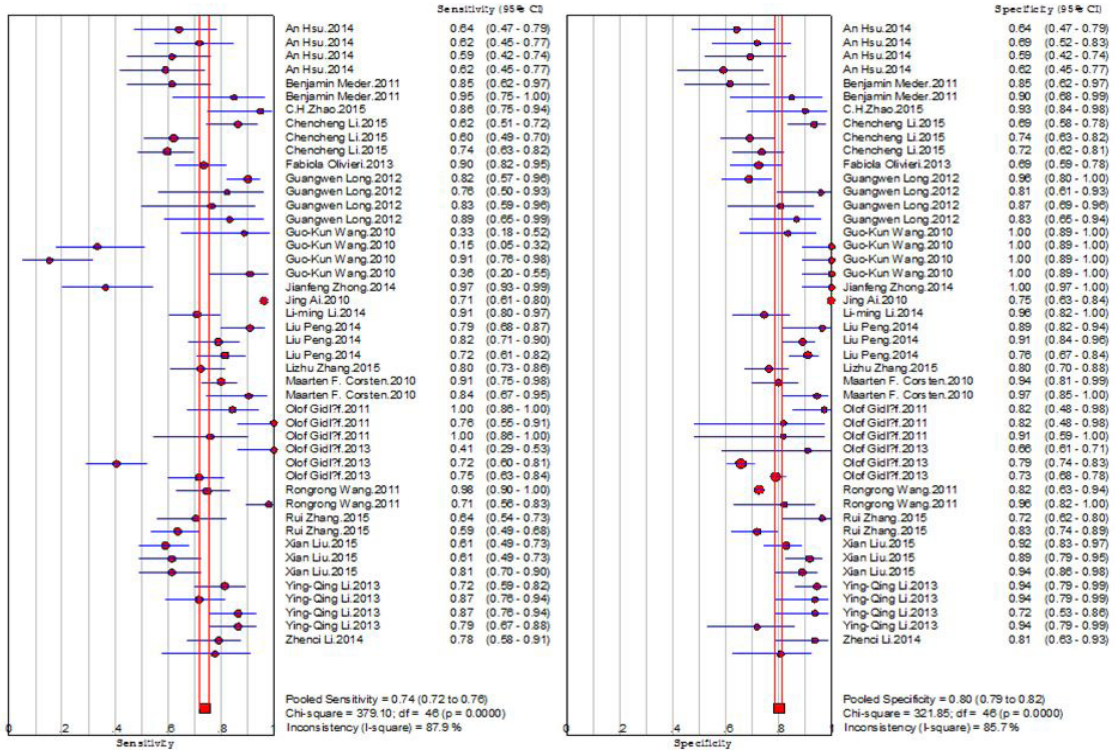
Xian Liu.2015[26]	70/72	mi-1	43	6	27	66	14
		mi-208	43	8	27	64	
		mi-499	57	4	13	68	
Ying-Qing Li.2013[27]	67/32	mi-1	48	2	19	30	10
		mi-133a	58	2	9	30	
		mi-208b	58	9	9	23	
		mi-499	53	2	14	30	
Zhenci Li.2014[28]	27/31	mi-497	21	6	6	25	6

TP = true positive, FP = false positive, TN = true negative, FN = false negative

Table.1: Main Characteristic of Included Studies in this Meta-Analysis.

Pooled Diagnostic Performance

A forest plot of the total miRNAs is shown in Figure 2.1 and 2.2. The pooled specificity, specificity, DOR and the area under the curve (AUC) were 0.74 (95%CI: 0.72-0.76), 0.80 (95%CI: 0.79-0.82), 18.55 (95%CI: 12.66-27.18) and 0.8800, significantly indicating that miRNAs have a high diagnostic accuracy in differentiating AMI patients from healthy controls. However, the I2 value of sensitivity and specificity were 87.9% and 85.7%, indicating significant heterogeneity in our study. Hence, the random effects model was used to evaluate the pool estimates.



SROC=Summary Receiver Operating Characteristic; AUC=Area Under The Curve

Figure 2.1: The sensitivity and specificity, for total miRNAs levels in the diagnosis of myocardial infarction.

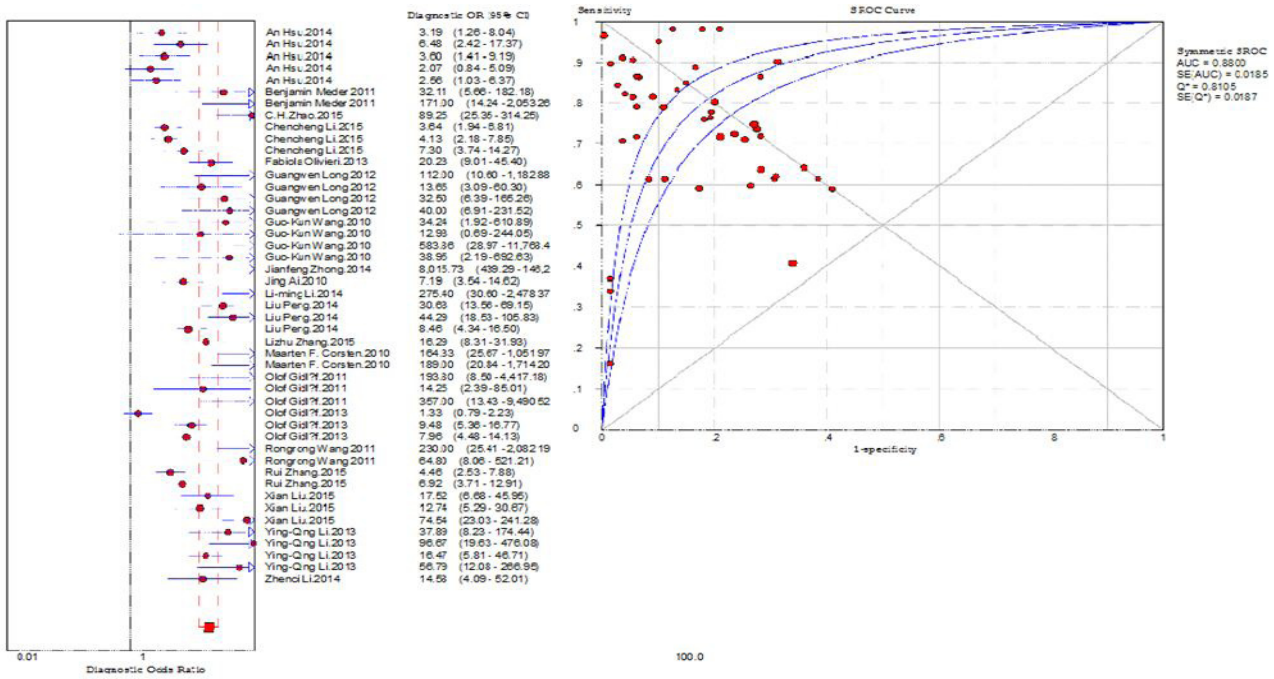


Figure 2.2: Diagnostic OR, SROC curve with AUC for total miRNAs levels in the diagnosis of myocardial infarction.

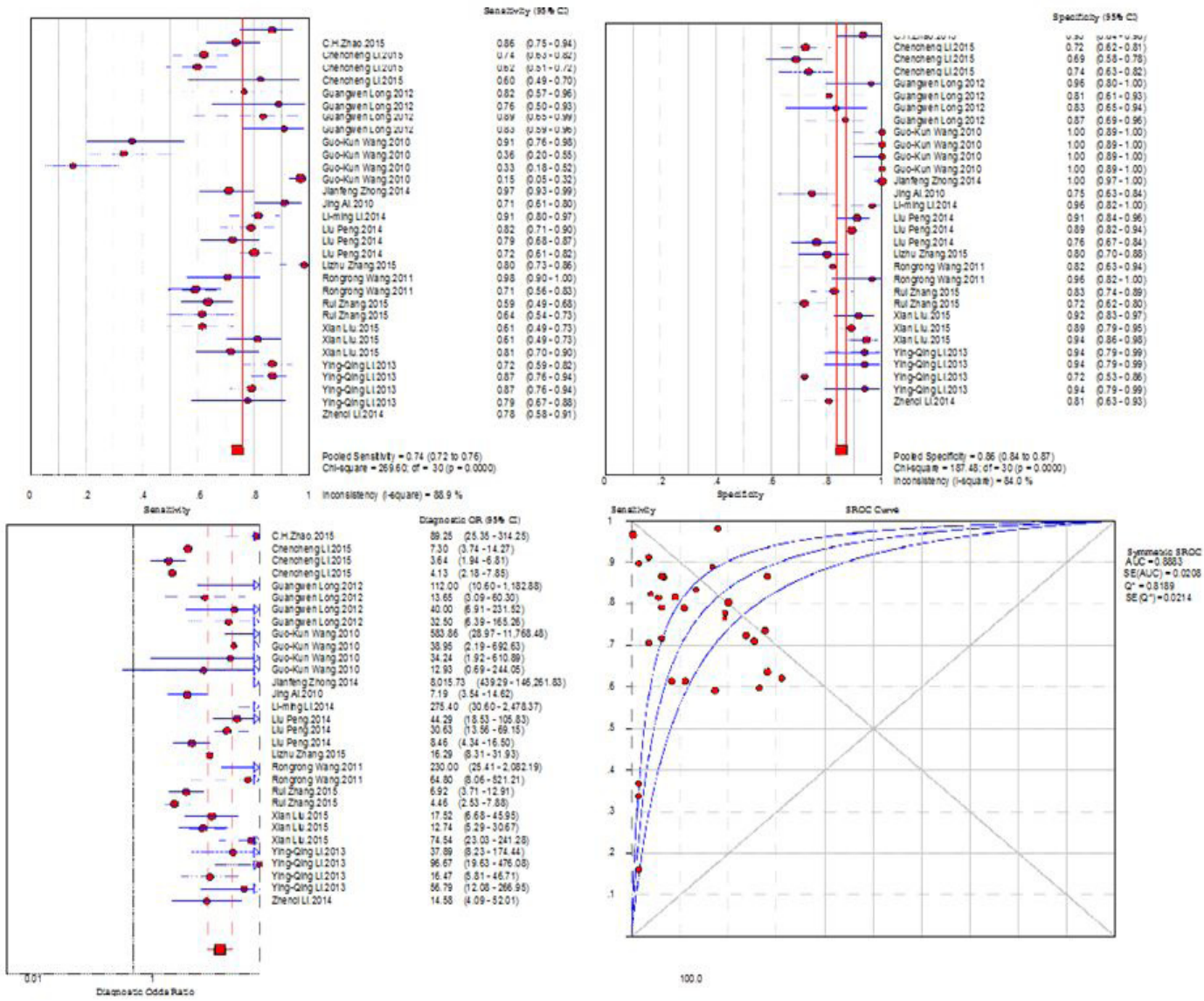
Subgroup Analyses

Heterogeneity analysis & different ethnics

Subgroup analysis was performed to assess the differences in heterogeneity and diagnostic accuracy between the specified groups (Table 2). The heterogeneity of the DOR was lower in the high-quality studies (I2, 58% vs 82.7%). We also found that there was less heterogeneity in prior years (2010-2012), in comparison with the recent 3 years (2013-2015) (55.5% vs 86.5%).

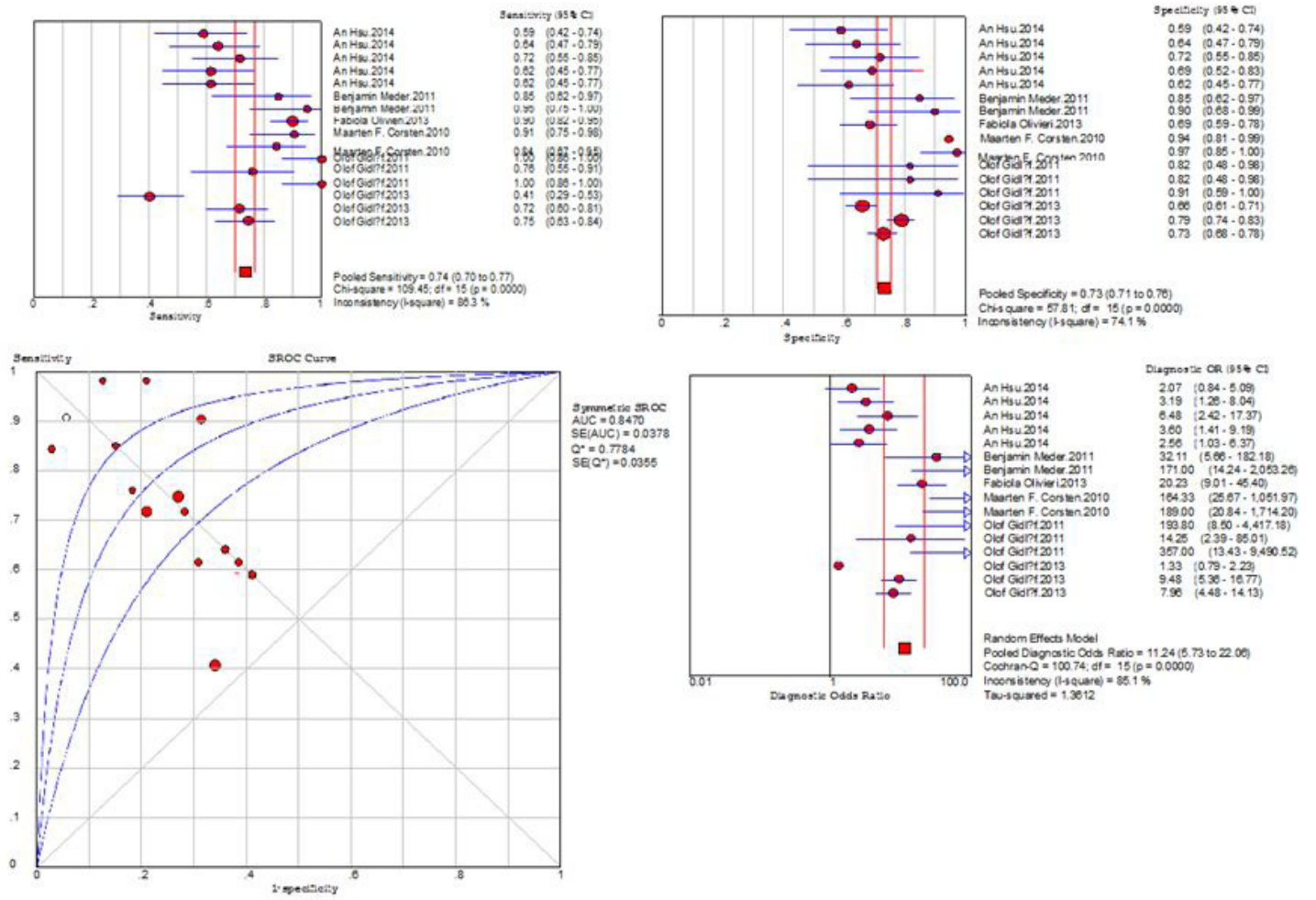
Sub groups	No. of studies	Pooled Sen (95%CI)%	Pooled Spe (95%CI)%	Pooled DOR(95%CI)	I2(%)DOR
ALL studies	21	74(72-76)	80(79-82)	18.55(12.66-27.18)	83.3
Era					
Early(2010-2012)	7	74(71-78)	90(87-92)	50.75(25.07-102.73)	55.3
Late(2013-2015)	14	74(72-76)	78(77-80)	12.34(8.04-18.93)	86.5
Quality assessment					
Low	13	73(71-75)	83(81-85)	18.94(11.76-30.50)	82.7
High	8	80(77-83)	80(78-82)	19.81(12.49-31.42)	58
Location					
Chinese	15	74(72-76)	86(84-87)	23.53(15.16-36.57)	79.7
Foreign	6	74(71-78)	74(71-76)	13.02(6.40-26.47)	85.4
No.of patients					
« 50	8	70(66-74)	83(80-86)	21.58(10.64-43.78)	75.2
» 50 13	13	75(73-77)	79(78-81)	17.65(11.05-28.19)	87.2

Table.2: Assessment of diagnostic accuracy and heterogeneity in subgroup analysis.



SROC=Summary Receiver Operating Characteristic; AUC=Area Under the Curve

Figure 3.1: The sensitivity, specificity, diagnostic of OR, SROC curve with AUC of miRNAs for Chinese ethnic in the diagnosis of myocardial infarction.



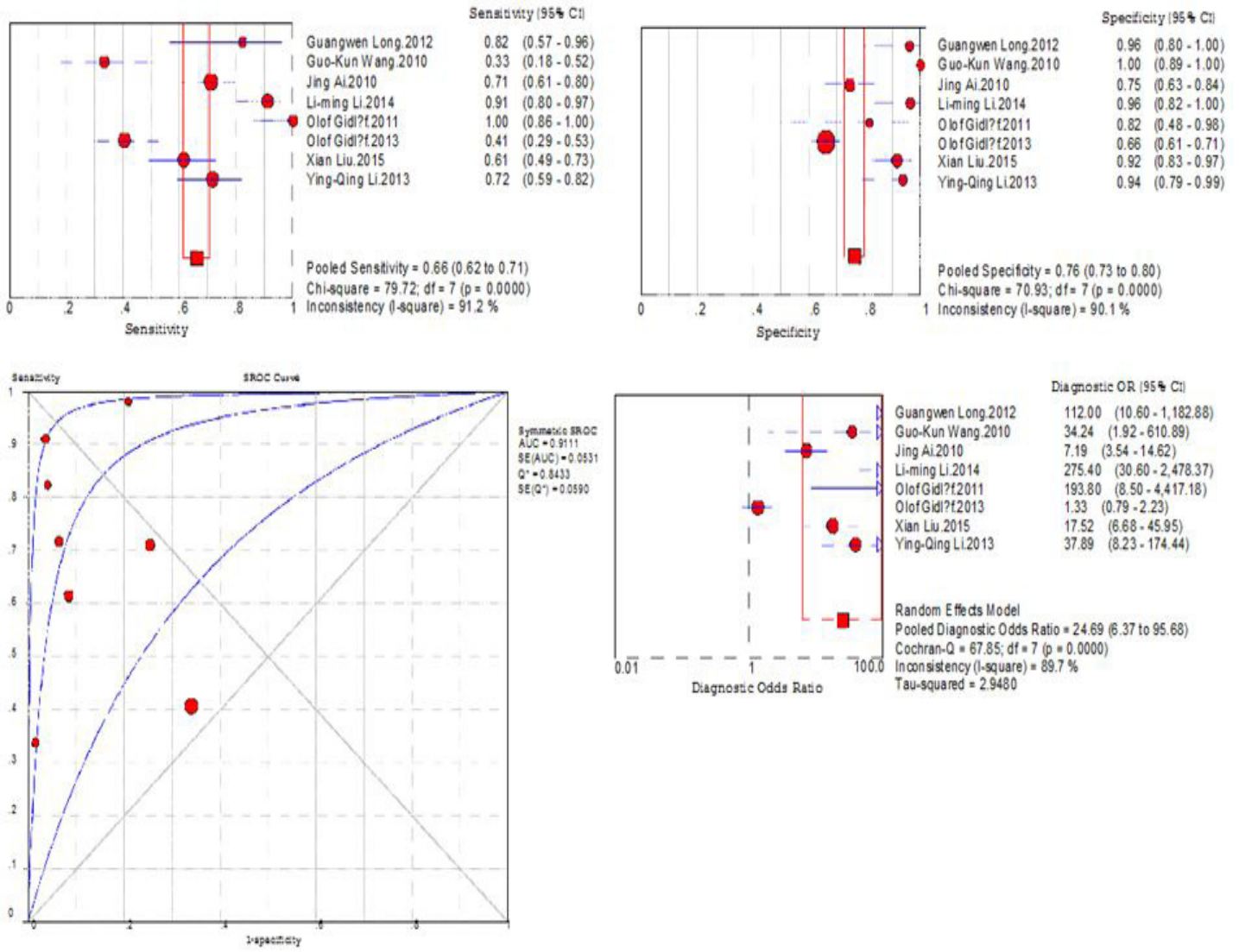
SROC=Summary Receiver Operating Characteristic; AUC=Area Under The Curve

Figure 3.2: The sensitivity, specificity, diagnostic of OR, SROC curve with AUC of miRNAs for foreign ethnic in the diagnosis of myocardial infarction.

Four Most Popular miRNAs

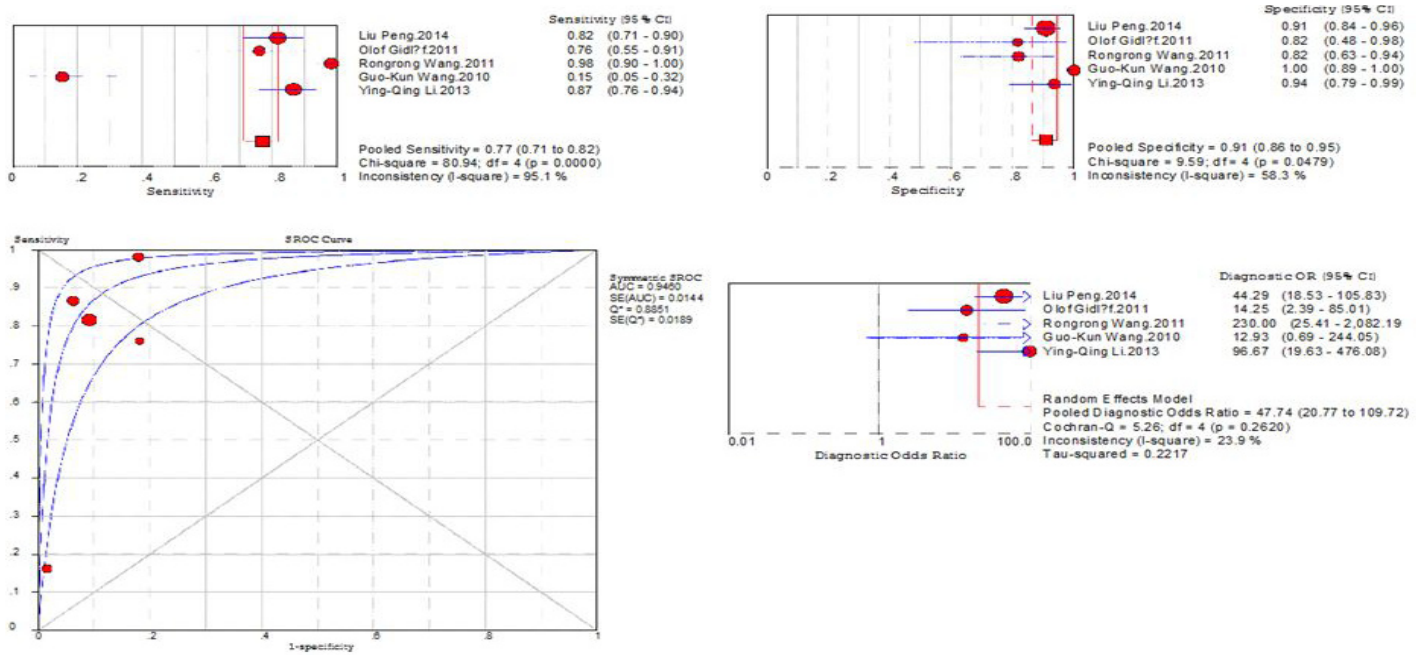
For further analysis, we found the top-four popular miRNAs: miRNA-1, miRNA-133, miRNA-208 and miRNA-499 (Figure 4-7). It is indicated that the miRNA-133 has the best diagnostic performance. The sensitivity, specificity and AUC for miRNA-133 were: 0.77 (95%CI: 0.71-0.90), 0.91 (95%CI: 0.86-0.95) and 0.9460. Among the four popular miRNAs, miRNA-499 has the best sensitivity. The sensitivity, specificity and AUC for miRNA-499 were: 0.80 (95%CI: 0.77-0.83), 0.80 (95%CI: 0.77-0.83) and 0.9163. The sensitivity, specificity and AUC for miRNA-1 were: 0.66 (95%CI: 0.62-0.71), 0.76 (95%CI: 0.73-0.80) and 0.9111. And the final one is miRNA-208, its sensitivity, specificity and AUC were: 0.73 (95%CI: 0.68-0.78), 0.81 (95%CI: 0.78-0.84) and 0.8660.

The I2 of the four popular miRNAs were: miRNA-133 (23.9%), miRNA-499 (73.0%), miRNA-208 (79.7%) and miRNA-1 (89.7%). As a result of this, other than miRNA-133, we all use the random effect model.



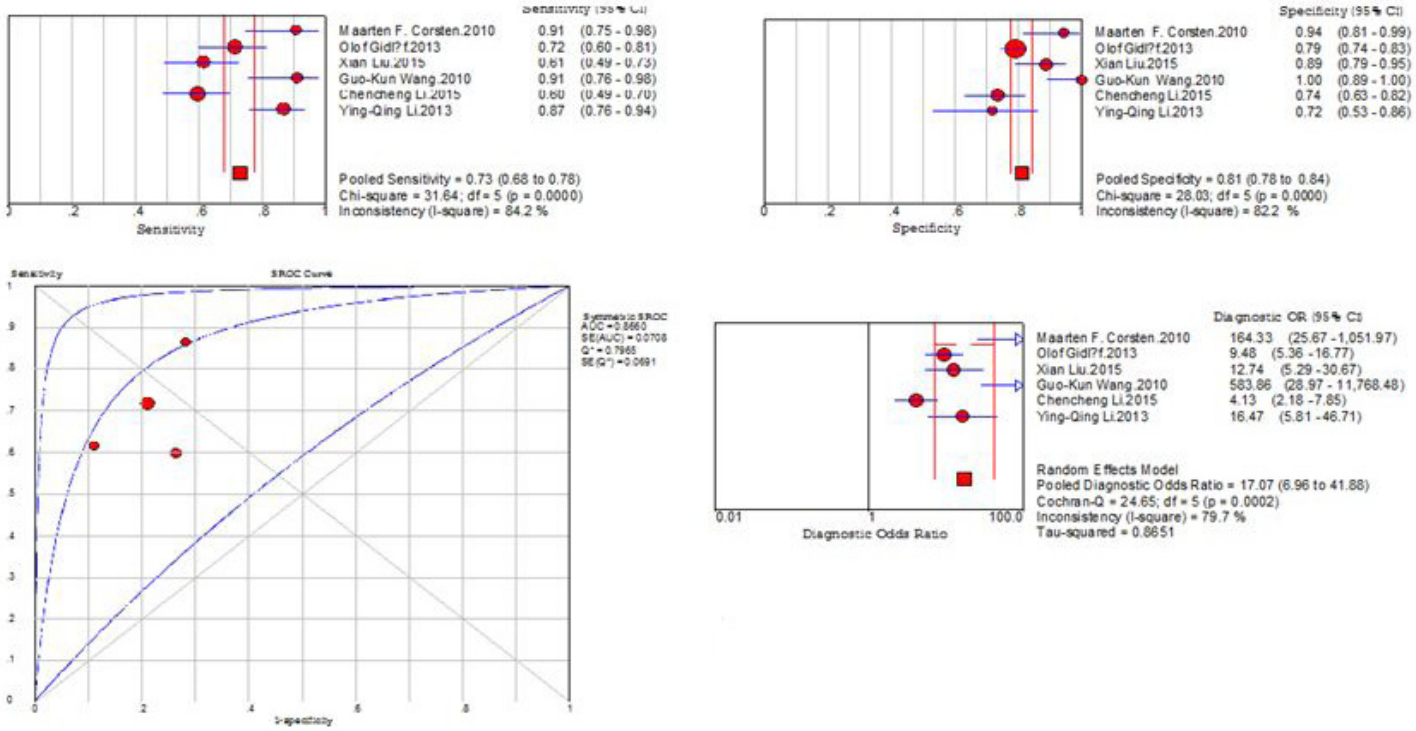
SROC=Summary Receiver Operating Characteristic; AUC=Area Under The Curve

Figure 4: The sensitivity, specificity, diagnostic of OR, SROC curve with AUC for miRNA-1 levels in the diagnosis of myocardial infarction.



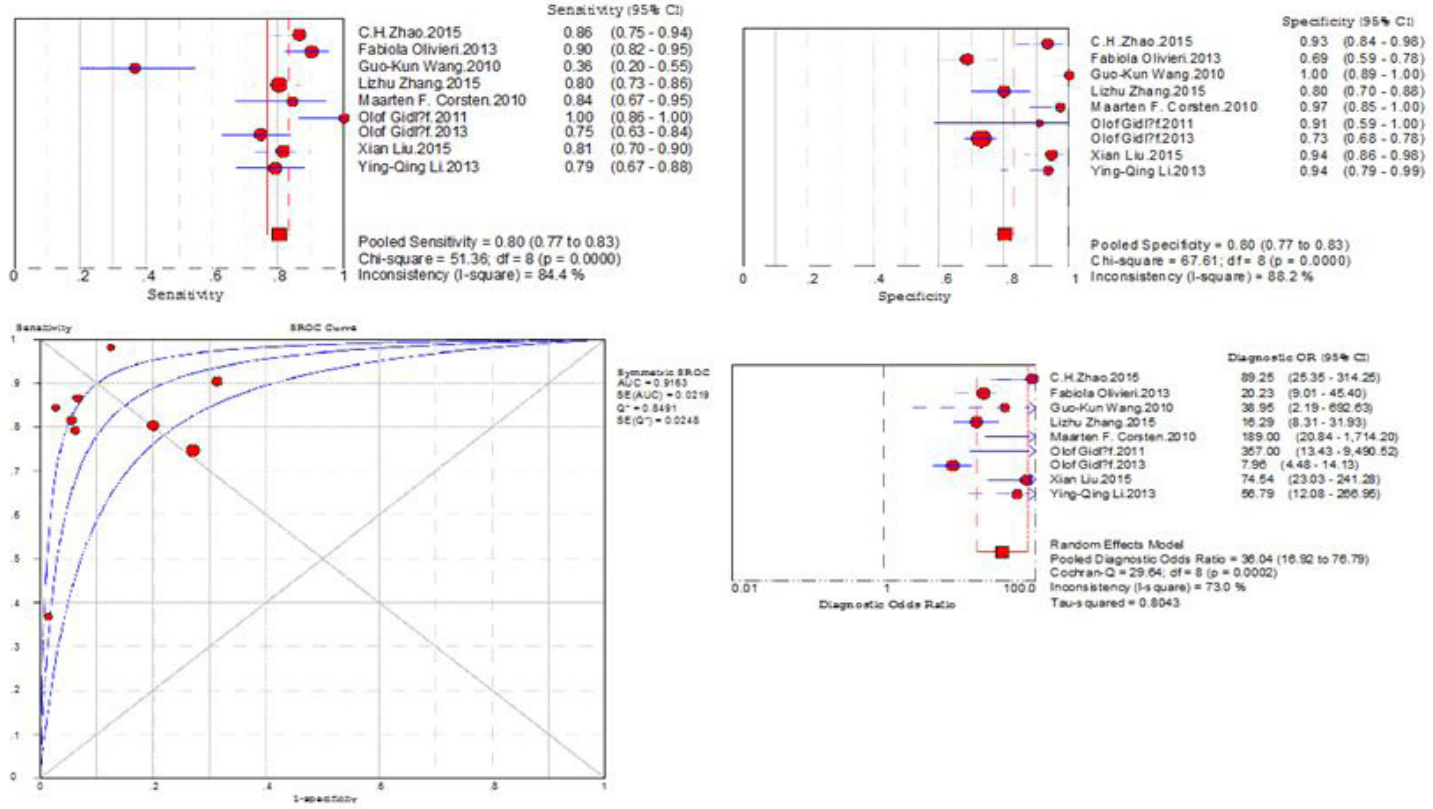
SROC=Summary Receiver Operating Characteristic; AUC=Area Under The Curve

Figure 5: The sensitivity, specificity, diagnostic of OR, SROC curve with AUC for miRNA-133 levels in the diagnosis of myocardial infarction.



SROC=Summary Receiver Operating Characteristic; AUC=Area Under The Curve

Figure 6: The sensitivity, specificity, diagnostic of OR, SROC curve with AUC for miRNA-208 levels in the diagnosis of myocardial infarction.



SROC=Summary Receiver Operating Characteristic; AUC=Area Under The Curve

Figure 7: The sensitivity, specificity, diagnostic of OR, SROC curve with AUC for miRNA-499 levels in the diagnosis of myocardial infarction.

Discussion

Acute myocardial infarction (AMI) is considered as the leading cause of death and disability worldwide. About 17.50 million people died in 2012, more than 82% of deaths take place in low- and middle-income countries due to cardiovascular disease. And even worse, it is estimated that approximately 23.3 million people will die annually from cardiovascular disease by 2030 [29]. Thus the requirement for early diagnosis is becoming increasingly important. The current standard for diagnosing AMI is based on serial troponin increase and the new-generation hs-Tn T and I had showed an excellent diagnostic performance in AMI patients. However, because of often delayed troponin increase and interference with other diseases (for example, heart failure, hypertension, renal failure and pulmonary embolism. et al), safe exclusion of AMI within 1-2 hours is still a major clinical challenge [30].

The implication of miRNAs in cardiovascular diseases have been recognized quite recently, and numerous studies have supported the promising role of miRNAs as biomarkers in AMI [4,31]. However, the estimation of miRNAs diagnostic performance in AMI remained inconsistent among various studies. In one of such studies, it reported the high accuracy of miRNA-208 for AMI diagnosis: a sensitivity of 0.91 and a specificity of 1.0, whereas miRNA-1 has shown a low sensitivity of 0.41 and a specificity of 0.66 [13,16]. In 2013, Lippi carried out a meta-analysis of nine studies involving 1295 patients to assess the diagnostic value of miRNAs in AMI. The pooled sensitivity, specificity and AUC were 0.92 (95% CI: 0.90-0.93), 0.87 (95% CI: 0.83-0.90) and 0.935 [32]. Another meta-analysis was also reported in 2014 [33], they included 19 studies in the final analysis and evaluated the 4 most frequently mentioned miRNAs. The authors emphasized that miRNA-133 and miRNA-499 may have an important role as biomarkers for MI. Due to the inconsistencies of the overall studies, we conducted the latest meta-analysis to determine whether miRNAs could be used as an effective method for early detection of AMI.

A total of 21 studies were included in our meta-analysis. The overall diagnostic accuracy of miRNAs was with a pooled specific-

ity, specificity, DOR and AUC: 0.74 (95%CI: 0.72-0.76), 0.80 (95%CI: 0.79-0.82), 18.55 (95%CI: 12.66-27.18) and 0.8800, indicating that miRNAs had high diagnostic accuracy in differentiating AMI patients. Further more, subgroup analyses by ethnicity, times, study quality, miRNAs types, and sample size were also included in our study. It suggests that the high quality studies have better diagnostic performance than the low quality studies. We also found that there was less heterogeneity among studies published in prior years (2010-2012), in comparison with those published in the recent 3 years (55.5% vs 86.5%). In the context of ethnicity, miRNAs has no obvious diagnostic value between the chinese and foreign ethnics.

To further analyze the four popular miRNAs: miRNA-1, miRNA-133, miRNA-208 and miRNA-499, we found miRNA-133 has the best diagnostic performance with a pooled sensitivity, specificity and AUC: 0.77(95%CI: 0.71-0.90), 0.91(95%CI: 0.86-0.95) and 0.9460. In terms of the diagnostic value of specificity: miRNA-133 has 0.91(95%CI: 0.86-0.95), miRNA-208 has 0.81(95%CI: 0.78-0.84), miRNA-499 has 0.80(95%CI: 0.77-0.83) and miRNA-1 has 0.76(95%CI: 0.73-0.80), miRNA-133 is also the best among them. Published research had confirmed the use of miRNA-133 expression as a biomarker for AMI [7,24]. Recently, some studies also reported good sensitivity and specificity, especially in the differential diagnosis of ST segment elevation myocardial infarction (AUC values range between 0.86 to 0.93) [22,34,35]. We also found miRNA-499 has the best diagnostic performance in terms of sensitivity: miRNA-499 (95%CI: 0.77-0.83), miRNA-133 (95%CI: 0.71-0.90), miRNA-208 (95%CI: 0.68-0.78) and miRNA-1 (95%CI: 0.62-0.71). Plasma miRNA-499 was below the detection limit in healthy individuals, but are elevated in AMI patients [16,36]. According to the studies reported during recent years, its diagnostic performance is good, as indicated by AUC values which range from 0.82 to 0.99 [16,21,22].

In addition, we have also done some research in our hospital to explore the plasma miRNAs expression profiles in AMI from 2011 to 2014. Through this analysis, we get to know that miRNA-155, miR-142-3p, miR-423-5p and miR-1 were significantly up-regulated, the areas under the receiver operating characteristic curve (ROC curve) range between 0.673~0.799. In the literature,. There are some studies with similar results published during the previous year's [37,39]. We conclude that these miRNAs could become potential biomarkers for the identification and diagnosis of AMI.

From the above analysis, we can see that miRNAs have been suggested as biomarkers for AMI diagnosis and prognosis. In addition to AMI, miRNAs also have diagnostic values for unstable angina pectoris (UAP), regulate cardiac regeneration and cardiac fibroblasts [40,41]. However, several critical issues should be taken into account before they can be applied into clinical practice. First, all the above-mentioned studies in our meta-analysis were done in a relatively small sample size. Therefore, global large-scale studies are required to confirm the correlation between miRNAs and AMI. Secondly, the values of miRNAs should be reevaluated in correlation with the traditional biomarkers, especially the previous gold standard troponin [42].

Limitations

There also seemed to be some limitations in our meta-analysis. First, a lot of confounding factors may result in biased statistical results, such as times, ethnics, sample size, miRNA types, quality of studies and so on. Second, although we tried our best to search all relevant studies, it is possible that we may have missed some qualified studies. Despite the above limitations, our study is the latest meta-analysis to evaluate the diagnostic value of miRNAs in the early detection of AMI patients.

Conclusion

In summary, miRNAs is a new biochemical marker for diagnosis of AMI, especially miRNA-133 has the better diagnostic performance. But these conclusions still need more large and high-quality clinical trials to validate.

Acknowledgments

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Conflicts of interest

No authors have any competing interests.

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