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Prognostic Value of MicroRNAs in Coronary Artery Diseases: A Meta-Analysis

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Purpose: Coronary artery diseases (CADs) are the leading causes of death in the world. Recent studies have reported that differentially expressed microRNAs (miRNAs) are associated with prognosis or major adverse cardiac events (MACEs) in CAD patients. In a previous meta-analysis, the authors made serious mistakes that we aimed to correct through an updated systematic review and meta-analysis of the prognostic value of altered miRNAs in patients with CADs.

Materials and Methods: We performed a systematic search of MEDLINE (from inception to May 2017) and EMBASE (from inception to May 2017) for English-language publications. Studies of CADs with results on miRNAs that reported survival data or MACEs were included. Data were extracted from each publication independently by two reviewers.

Results: After reviewing 515 articles, a total eight studies were included in this study. We measured pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of miRNA 133a with a fixed-effect model (pooled HR, 2.35; 95% CI, 1.56–3.55). High expression of miRNA 133a, 208b, 126, 197, 223, and 122-5p were associated with high mortality. Additionally, high levels of miRNA 208b, 499-5p, 134, 328, and 34a were related with MACEs.

Conclusion: The present study confirmed that miRNA 133a, which was associated with high mortality in CAD patients, holds prognostic value in CAD. More importantly, this study corrected issues raised against a prior meta-analysis and provides accurate information.

Key Words: Coronary artery disease, microRNA, prognosis, meta-analysis

INTRODUCTION

Cardiovascular disease, including coronary artery diseases (CADs) is the one of the leading causes of death and illness in the developed world.[1-6] Although tremendous investment has revealed the pathogenesis of cardiovascular diseases, deaths from cardiovascular diseases are still increasing.[1-7] Hence, to predict the survival rate from cardiovascular diseases, identifying novel prognostic markers is required, it would contribute to selecting better treatment options and reducing mortality.

MicroRNAs (miRNAs) are small (approximately 20 nucleotide) noncoding RNAs, that can dysregulate protein translation by targeting messenger RNA.[8,9] MiRNAs are involved in various biological and physiological processes.[8,10] Furthermore, recent studies have suggested that levels of circulating miRNAs from vessel walls and inflammatory cells might be potential biomarkers of cardiovascular diseases.[11,12]

Recent research has reported that some miRNAs are associated with various diseases, including cancers, diabetes, and heart diseases.[13-17] As the importance of miRNAs increases more

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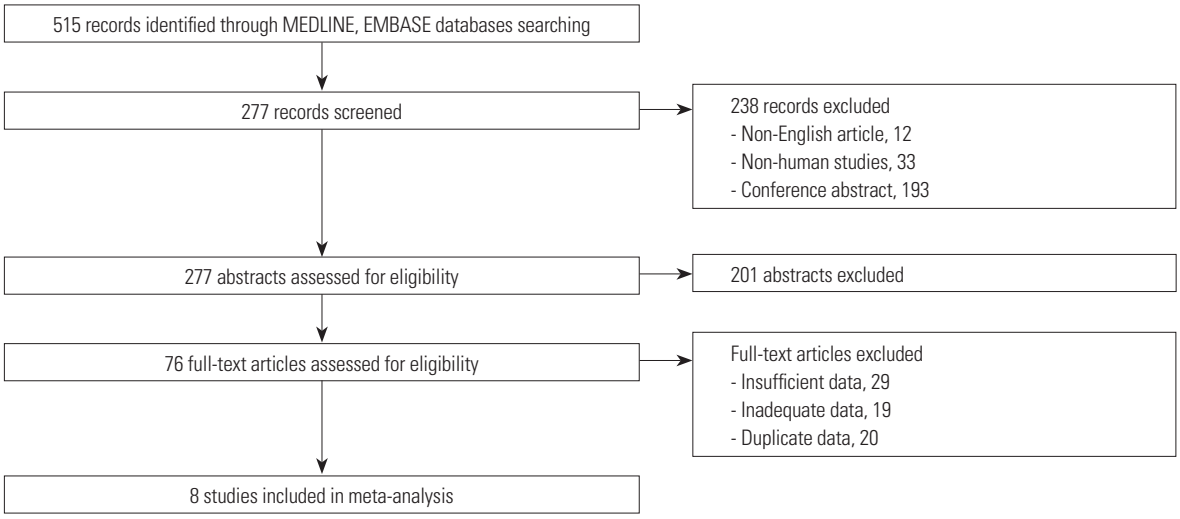

Fig. 1. Flow chart of study selection. We excluded 201 abstracts that are laboratory studies, review articles, letters, and comments. We excluded full-text articles that have insufficient data for calculating hazard ratio or odds ratio using Engauge Digitizer. If reported values were much different from calculated values by using Engauge Digitizer, we defined the paper as an inadequate article.

and more, new strategies based on miRNAs such as diagnostic and therapeutic targets have been developed.[8,12,13,16-18] Of these, many researchers have suggested that miRNA or miRNA signatures may be diagnostic and prognostic biomarkers for human diseases.[16,17] During a study of the relationship between CADs and miRNAs, we found severe errors in a previous meta-analysis.[19] Therefore, we conducted a systematic review and meta-analysis in the present study to better define the prognostic value of various miRNAs in patients with CADs.

MATERIALS AND METHODS

Eligibility and search strategy

We performed a systematic search of MEDLINE (from inception to May 2017) and EMBASE (from inception to May 2017) for English-language publications using the keywords "coronary artery disease," "NSTEMI," "STEMI," "cardiovascular disease," "microRNA," "death," "prognosis," and "major adverse cardiovascular events (MACEs)." All searches were limited to human studies. The inclusion criteria were studies of coronary artery diseases that reported the results of miRNA expressions, survival data, and MACEs. Laboratory studies, reviews, letters, comments, and editorial materials were excluded. We also excluded full-text articles that lacked sufficient data for calculating hazard ratios (HRs) or odds ratios (ORs) using Engauge Digitizer (http://digitizer.sourceforge.net). If reported values were much different from calculated values by using Engauge Digitizer, we defined the paper as an inadequate article. Two authors performed the searches and screening independently, and discrepancies were resolved by consensus. A flowchart of the study selection process is shown in Fig. 1.

Table 1. Quality Assessment Based on the Newcastle-Ottawa Scale

Study	Selection	Comparability	Outcome	Total score
Widera, et al.[28]	4	1	2	7
Eitel, et al.[25]	4	1	2	7
Ke-Gang, et al.[26]	4	1	3	8
Schulte, et al.[27]	4	1	3	8
Cortez-Dias, et al.[24]	4	1	2	7
Gidlöf, et al.[29]	4	1	1	6
He, et al.[30]	4	1	1	6
Lv, et al.[31]	4	1	1	6

Selection: representativeness of studies (maximum score-4), comparability: comparability of studies (maximum score-2), outcome: assessment of outcome and follow-up (maximum score-3).

Quality assessment

The Newcastle-Ottawa scale was used to evaluate the quality of studies incorporated in this meta-analysis, which was done based on the following three aspects: selection of the study groups, comparability of the groups, and the outcome of interest. The lowest score was 0 and the highest was 9. Studies with a score ≥6 were considered as high quality.[20-22] We set 12 months as an adequate follow-up length (Table 1).

Data extraction and statistical analysis

Data were extracted from the publications independently by two reviewers, and the following information was recorded: first author, year of publication, country, miRNA expression analyzed, number of patients, and end points. The primary outcome was mortality defined as the time from the initiation of therapy until death from any causes. The secondary endpoint was MACEs defined as cardiac death, heart failure, decreased ejection fraction, or cardiogenic shock.

The effects of miRNA expressions on mortality were assessed using HRs and on MACEs were assessed using ORs. In cases

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of mortality, a univariate HR estimate and 95% confidence intervals (CIs) were extracted directly from each study, if provided by the authors. Otherwise, *p* values of the log-rank tests, 95% CIs, number of events, and numbers of patients at risk were extracted to estimate the HR indirectly. Survival rates calculated from Kaplan-Meier curves were read using Engauge Digitizer, version 3.0 (http://digitizer.sourceforge.net) to reconstruct the HR estimate and its variance, assuming that patients were censored at a constant rate during follow-up. In case of MACEs, a multivariate OR estimate was extracted directly from each study. However, we could not perform meta-analysis because the variables were different in each of the studies. The HRs and ORs were calculated on the basis of high expression of miRNA, which means HR >1 and OR >1 implied poor prognosis and high MACEs for patients. Heterogeneity among studies was assessed using χ^2 tests and I^2 statistics. Heterogeneity was considered to be low if I^2 <25%, medium if between 25% and 75%, and high if I^2 >75%. If there was obvious heterogeneity (I^2>50%), the random-effects model was used, otherwise the fixed-model was used.[9] Funnel plots were used to assess publication bias.[23] Begg's test and Egger's test were also used to identify publication bias, and these tests were performed by using the 'metafor' package in R. The forest and funnel plots were depicted using Review Manager (RevMan, version 5.3: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark). *p* values <0.05 were considered to be statistically significant. The pooled HR and heterogeneity of miRNA 133a was calculated using Review Manager.

RESULTS

Study characteristics

The electronic search identified 515 articles. Non-human studies (n=33), non-English articles (n=12), conference abstracts (n=193), and 201 studies that did not meet the inclusion criteria based on their title and abstract were excluded. After reviewing the full text of 76 articles, eight studies were eligible for inclusion in the study (5 articles; prognosis in 1987 patients, 3 articles; MACEs in 792 patients) (Fig. 1). All of the included studies had a prospective design, and reported the prognostic value of six different miRNAs (122-5p, 126, 133a, 197, 208b, 223) in HRs[24-28] and five different miRNAs (34a, 134, 208b, 328, 499-5p) in OR.[29-31] Included studies were performed recently (2011–2016), and the study characteristics are summarized in Table 2.

Quality assessment

The Newcastle-Ottawa scale indicated that the methodological quality of the included studies varied from 6 to 8. Three articles received a score of 6, three articles received a score of 7, and two articles received a score of 8 (Table 1).

Higher miRNA expression associated with worse prognosis of coronary artery diseases

To analyze the prognostic value of high expression of miRNAs in CADs, forest plots with mortality and MACEs are depicted in Figs. 2 and 3. High expression of miRNA 133a, 208b, 126, 197, 223, and 122-5p were associated with high mortality (Fig. 2A). The overall HR of all miRNAs for mortality was 1.76 (95% CI 1.40–2.23, *p*<0.00001) (Fig. 2A). High level of miRNA 208b, 499-

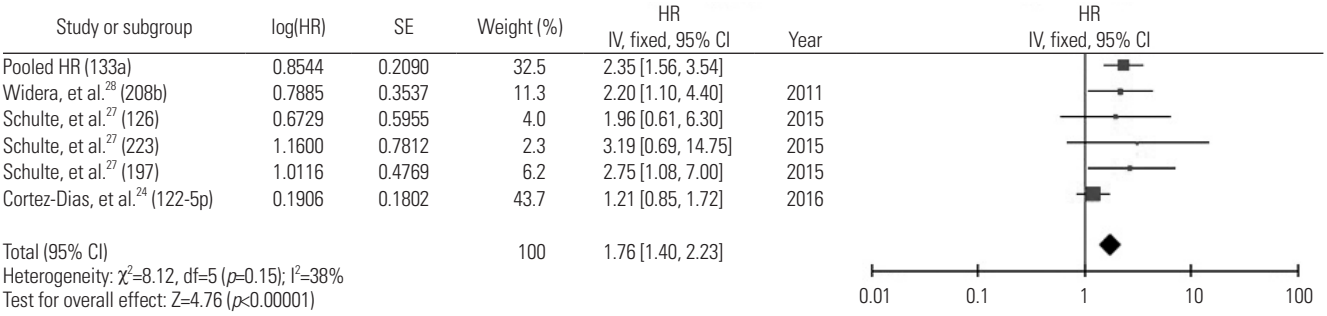
Table 2. Studies Included in This Meta-Analysis

Study	Year of publication	Country	miRNA	No. of patients	Follow up (month)	Study design	HR	Assay method	Sample
Mortality									
Widera, et al.[28]	2011	Germany	208b* 133a†	444	6	P	HR	RT-PCR	Plasma
Etel, et al.[25]	2012	Germany	133a*	216	6	P	HR	RT-PCR	Serum
Ke-Gang, et al.[26]	2016	China	133a* 126‡	312	24	P	HR	RT-PCR	Plasma
Schulte, et al.[27]	2015	Germany	197‡ 223‡	873	48	P	HR	RT-PCR	Serum
Cortez-Dias, et al.[24]	2016	Portugal	122-5p*	142	208	P	HR	RT-PCR	Serum
Major adverse cardiac events									
Gidlöf, et al.[29]	2013	Sweden	208b 499-5p	407	1	P	OR	RT-PCR	Plasma
He, et al.[30]	2014	China	134 328	359	6	P	OR	RT-PCR	Plasma
Lv, et al.[31]	2014	China	208b 34a	359	6	P	OR	RT-PCR	Serum

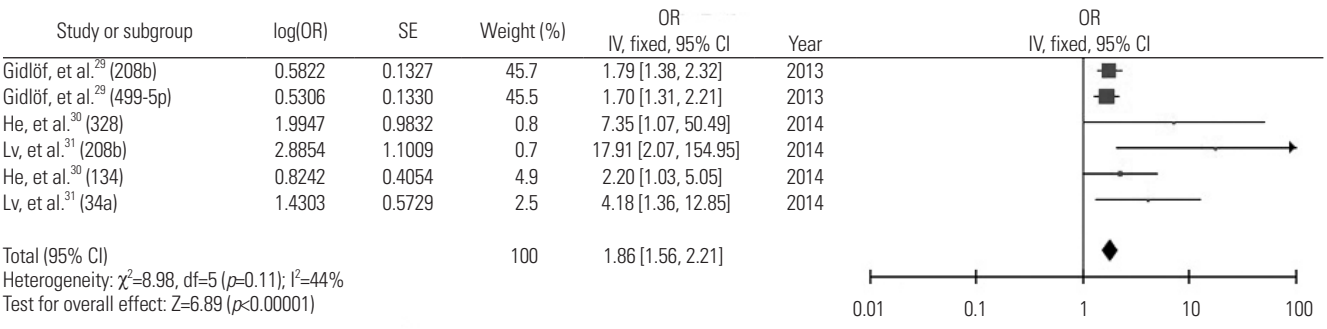
HR, hazard ratio; OR, odds ratio; P, prospective.
Follow up; *Median, †Upper 25%, ‡Second tertile.

5p, 134, 328, and 34a showed significance with MACEs (overall OR 1.86, 95% CI 1.56–2.21, $p<0.00001$) (Fig. 2B).

We analyzed prognostic significance between mortality and expression of miRNA 133a that were studied by three independent articles. We applied the fixed-effect model on miRNA 133a because we determined that heterogeneity was low through various statistical values ($\chi^2=0.69$, $p=0.71$, $I^2=0\%$) (Fig. 3A). As shown in Fig. 3A, the pooled HR of miRNA 133a for

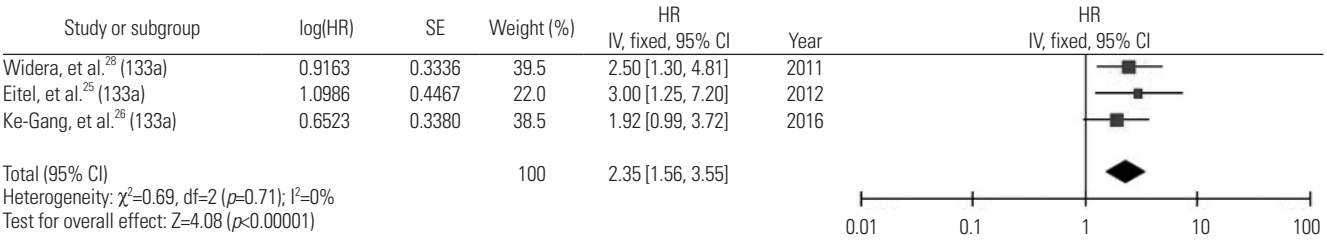


A



B

Fig. 2. Systematic summary for prognostic values of miRNAs with CADs. (A) Forest plots for mortality of miRNA expression in patients with CADs. (B) Forest plots for major adverse cardiac events of miRNA expression in patients with CADs. HR, hazard ratio; OR, odds ratio; SE, standard error; CI, confidence interval; miRNA, microRNA; CAD, coronary artery disease.



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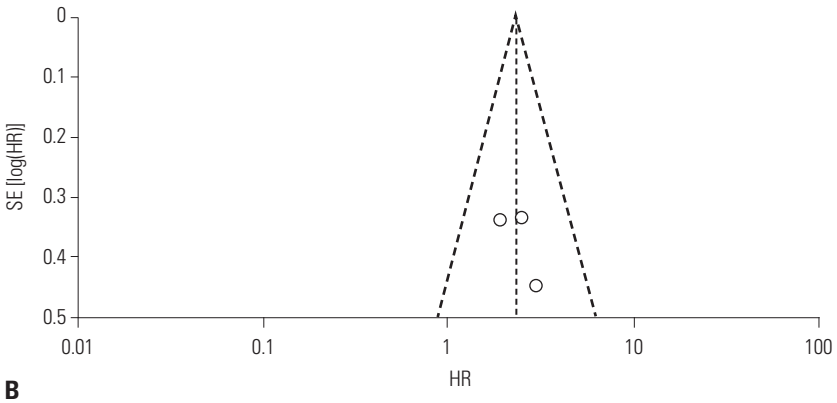

B

Fig. 3. Forest plot (A) and funnel plot (B) for mortality of microRNA 133a expression in patients with coronary artery diseases in this meta-analysis. SE, standard error; HR, hazard ratio; CI, confidence interval.

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Table 3. Begg's and Egger's Test for Evaluating Publication Bias

Hazard ratio	*p* value of Begg's test	*p* value of Egger's test
Overall	0.2493	0.3333

mortality was 2.35 (95% CI 1.56–3.55, $p<0.0001$), which means high expression of miRNA 133a showed a strong relationship with high mortality in CADs.

Publication bias

The funnel plot in this meta-analysis seemed symmetrical (Fig. 3B). The results of Begg's and Egger's test were not significant (Table 3). These results suggested no evidence for publication bias.

DISCUSSION

A systematic review and meta-analysis provides significant information to researchers, such that analysis performed incorrectly can cause serious problems. In a previous meta-analysis, the authors made severe mistakes when they extracted and merged various results. First, the authors changed some ORs in references to HRs, and then the changed HRs that were combined with other HRs from other researches.[29-32] Because OR is quite different from HR, they should not be combined in the meta-analysis. Second, they merged HRs from univariate analysis with other HRs from multivariate analysis.[19] Univariate analysis is the simplest statistical method because it only considers only one variable, whereas multivariate analysis involves analysis of more than one variable at a time. For that reason, HRs from univariate analysis are not that same as HRs from multivariate analysis, even though they can be calculated using same data.[29-31] Time-to-event outcomes are the most important factors in prognostic studies; however, the authors in the previous meta-analysis misused the mean follow-up months from reference.[33] For these reason, we corrected critical problems of the previous meta-analysis[19] and updated recent results on the prognostic value of miRNAs in CADs to help scientists interested in miRNA research.

Circulating miRNAs have emerged as potential diagnostic markers in various diseases, including CADs, due to their accessibility by drawing a patient's blood.[24-33] In this study, we found that high levels of circulating miRNA 133a, 208b, 126, 197, 223, and 122-5p in CAD patients were related with high mortality.[24-28] In addition, high expression of miRNA 208b, 499-5p, 134, 328, and 34a were associated with MACEs.[29-31] Although many miRNAs in this study were found to be associated with prognosis of CADs patients, most of them were identified only by a single report, except miRNA 133a.[24-31] Therefore, we have shown through meta-analysis of miRNA 133a that high expression of it is associated with a poor prognosis of CADs.

MiRNAs are known to be important regulators of all major cellular functions, including differentiation, proliferation, apoptosis, and angiogenesis.[25,34] Among them, miRNA 133a has been widely reported as a regulator of cardiomyocyte proliferation, and tumor-suppressor.[35-38] Moreover, recent studies found that increased levels of circulating miRNA 133a in CADs patients, which had correlation with troponin.[13,28,29,39,40] In this meta-analysis, three articles showed consistent results suggesting that high expression of miRNA 133a is strongly associated with poor prognosis in CAD patients (Fig. 3).[25,26,28]

Several limitations need to be considered when interpreting the results of the current study, although this study has an advantage because it corrects previous miscalculations.[19] Although included studies in this study addressed diverse miRNAs, we could not perform a systematic review of the relationship between miRNA expressions and MACEs because the data were analyzed by multivariate analyses using different variables. Thus, large prospective studies will be required to confirm our findings and would be helpful to developing prognostic markers of CADs.

In summary, despite the limitations, this comprehensive systematic review and meta-analysis reveals that circulating miRNAs, especially miRNA 133a, could be potential prognostic markers of CADs. The most important aspect of this study is that it can prevent problems caused by previously erroneous studies.

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