MicroRNA-200 families and prognostic value in various carcinomas: A systematic review and meta-analysis

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Abstract

Background: Recently, some studies have showed that miR-200 families act as novel biomarkers for the prediction of cancer outcomes.

Aims: This meta-analysis was designed to investigate the associations between miR-200 families and the prognosis of patients with various cancers.

Materials & Methods: Eligible published databases including PubMed, Embase and Chinese National Knowledge Infrastructure (CNKI) databases were searched for articles until October 18, 2016. We performed a meta-analysis by calculating pooled hazard ratios (HR) and 95% confidence intervals (CI). Data were extracted from studies comparing overall survival (OS), progression-free survival (PFS) or recurrence-free survival (RFS).

Results: For OS, the pooled HR was 1.54 (95% CI: 1.01-2.33), showing that high miR-200 family was clearly related to poor survival in various carcinomas, but no significantly association was found in PFS or RFS. Subgroup analysis indicated that upregulated miR-200 family was linked to poor OS in Asians (HR = 2.19, 95% CI: 1.27-3.78) but not in Caucasians (HR = 0.94, 95% CI: 0.46-1.91). Similarly, high miR-200 expression could not clearly predict the relationship with PFS and RFS. For cancer type, high miR-200 also predicted poor OS among lung cancer patients (HR = 3.09, 95% CI: 1.75-5.46). Besides, only elevated miR-200c of the miR-200 family indicated a significantly poor OS (HR = 2.25, 95% CI: 1.39-3.64).

Discussion: Aberrant expression of miRNAs played a crucial role in the area of human carcinomas. Many studies have indicated that miRNAs are considered promising tumor biomarkers for prognosis and potential targets for clinical treatment. We have testified that high levels of miR-200 family expression (predominantly miR-200c) are significantly associated with poor survival and prognostic outcomes of patients with cancers, especially in lung cancer. However, no statistically significant results were calculated for miR-200a/b and miR-429, and this might result from a relatively small number of articles about them. In other tumor models except lung cancer, our results indicated that high miR-200 family was not obviously associated with OS (Gastric or Colorectal cancer; Ovarian cancer; Others). In addition, some other records showed the opposite results, for they exhibited that upregulated miR-200 family level was linked to longer survival. For ethnic group, our stratified
analyses showed that the Asian population predicted poor OS. While the Caucasian population did not exhibit an significant association with OS. This discrepancy might result from different hereditary backgrounds and environment exposure. Although these results have indicated that miR-200 families were promising biomarkers to predict prognosis for patients with cancers, there were several limitations in this analysis that would impact its quality. Generally, further studies should be warranted to clarify this question and to provide a new novel idea for routine clinical application.

**Conclusion:** Our findings suggest that miR-200 family might be a potentially useful biomarker for predicting cancer prognosis, especially for lung cancer in Asians.

**KEYWORDS**
biomarker, carcinoma, miR-200 family, prognosis

1 | INTRODUCTION

MicroRNAs (miRNAs) are a new class of small non-coding, single-stranded RNA molecules with approximately 23 nucleotides in length, and they could pair to complementary sequences in the 3' untranslated region (3' UTR) of target mRNAs.1 Functionally, the miRNAs can not only regulate gene expression but also involve in diverse cellular biological processing, including differentiation, proliferation, growth, apoptosis, migration, and survival.1 Each miRNA can affect a variety of mRNAs, depending on its targets, and can play different roles in biological or pathological processes.2 The miR-200 family of miRNAs is composed of miR-200a, miR-200b, miR-200c, miR-141, and miR-429, which are located in two different clusters: miR-200a, miR-200b, and miR-429 on chromosome 1, miR-200c and miR-141 on chromosome 12.3 Recent studies have demonstrated that miR-200 families play significant roles in human various cancers, such as lung cancer, gastric cancer, colorectal cancer, ovarian cancer, breast cancer, and glioma.4-13

To date, some studies have investigated that downregulation of miR-200 family correlated with progressive pathological feature and poor prognosis in cancer patients.2,4-6 However, some others showed insignificant or opposite results.1,7-13 According to this, it remains unclear whether miRNA-200 families act as tumor suppressors or oncogenes in human malignancies and the prognostic significance.14 Thus, the prognostic value of miR-200 family in patients with various carcinomas remains controversial. In terms of the limits of the single study, we performed this meta-analysis of all eligible studies to discuss the relationship between miR-200 family and prognosis in human malignant neoplasms.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We searched online in PubMed, EMBASE, and CNKI databases up to October 18, 2016, to identify relevant studies, with a combination of the following keywords used simultaneously, namely "cancer," "carcinoma," "tumor," "micro-RNA-200 family," "miRNA-200," "miR-200," "hazard ratio (HR)," "follow-up," "survival," and "prognosis." We evaluated potentially relevant studies by examining their titles, abstracts, and full texts matching the eligible criteria retrieved.

Studies were considered eligible if they met the following criteria: (i) studies focused on patients with any type of cancers; (ii) studies measuring the expression of miR-200 family in tissue or serum/plasma; (iii) studies investigating the association between miR-200 family expression and prognosis outcomes. Articles were excluded if they were review articles or letters, not focusing on human carcinomas. Other exclusion criteria included studies lacking key information such as HR, 95% confidence intervals (CIs), and P value, without survival curves.

2.2 | Data extraction

We extracted relevant data from included studies and recorded these data based on a standardized form. Extracted data elements included: (i) the name of first author and publication year; (ii) characteristics of the studied population, including total number of patients, country, ethnicity, cancer type, and sample category; (iii) test method; (iv) study design; (v) cutoff value; (vi) follow-up time; (vii) HRs of elevated miR-200 family expression for OS, PFS, and RFS, along with their 95% CIs and P values. If HRs and 95% CIs were not directly reported, data would be extracted from Kaplan-Meier curves of graphical survival plots to calculate HRs and 95% CIs.15 The extracted information was summarized in a consistent manner to prevent bias.

2.3 | Statistical methods

The aggregation of HRs and 95% CIs was calculated in the following Tierney method.16 Forest plots were used to estimate the effect of miR-200 family expression on patients' survival. A test of heterogeneity among included studies was carried out using Cochran Q test and Higgins I-squared statistic. If P < .1 and the percentage of I^2 > 50%, then random-effects model (Der Simonian and Laird method) was adopted, otherwise, the fixed-effects model (Mantel-Haenszel test)
was used. Subgroup analysis was performed by the ethnicity, cancer type, and miRNA type method. Publication bias was assessed by Egger’s linear regression test with a funnel plot. For all analyses, a \( P \) value < .05 was considered to be statistically significant, and all the \( P \) values were two-sided. All analyses were performed with the STATA 11.0 software (Stata Corp LP, College Station, TX, USA).

3 | RESULTS

A total of 274 potentially relevant studies were identified from literature search in PubMed, EMBASE and CNKI databases; 257 papers were excluded after manual screening of titles, abstracts and key words, because they were not related to the current study. After reading the full texts of the remaining 17 studies, 12 eligible studies were included for the final analysis. A flow diagram of the study selection process is shown in Figure 1.

We collected data from enrolled 12 retrospective studies. Ten of these studies examined cancerous tissue, and only two did with serum or plasma. The expression level of miR-200 was widely detected by quantitative real-time polymerase chain reaction (qRT-PCR) assay. The cutoff values of miR-200 family were different in each study, such as median, mean, quintile, or twofold. The main characteristics of analyzed studies are systematically listed in Table 1. For prognosis, all the studies analyzed OS and significant heterogeneity between studies was shown \( (P < .001, I^2 = 79\%) \); hence, a random-effects model was applied to estimate a pooled HR \( (HR = 1.54) \) along with its 95% CI \( (1.01-2.33) \). We found that higher expression of miR-200 family significantly associated with poorer OS. Three studies evaluated PFS or RFS, and the results indicated that there was no statistical association (Table 2; Figure 2).

Furthermore, stratified analyses were performed, such as ethnicity, cancer type, and miRNA type. Firstly, for ethnicity, seven studies in Asian subgroup investigated that elevated miR-200 family significantly predicted poor survival \( (HR = 2.19, 95\% CI \ 1.27-3.78) \) by a random-effects model \( (P < .001, I^2 = 78\%) \), and the other five studies in Caucasian subgroup could not show a significant association between miR-200 family and Caucasian cases \( (HR = 0.94, 95\% CI \ 0.46-1.91) \). Secondly, for cancer type, two studies in lung carcinoma subgroup displayed a worse survival outcome linked to the elevated miR-200 family \( (HR = 3.09, 95\% CI \ 1.75-5.46) \) using a fixed-effects model \( (P = .60, I^2 < 0) \). And in other subgroups of gastric or colorectal cancer, ovarian cancer, breast cancer, and glioma, there was no obviously significant association with poor survival \( (HR = 1.00, 95\% CI \ 0.67-1.50; HR = 3.49, 95\% CI \ 0.47-25.62; HR = 1.63, 95\% CI \ 0.40-6.69, respectively) \). In addition, for miRNA type, eight studies also indicated that high miR-200c expression was a significant predictor for worse outcome \( (HR = 2.25, 95\% CI \ 1.39-3.64) \). No significant association was found in miR-200a, miR-200b, and miR-429 subgroups (Table 2).

Finally, the funnel plot and Egger tests were used to detect publication bias of the included studies. As shown in Figure 3, the funnel plot was almost symmetric. In OS meta-analysis, the \( P \) value of the
Egger test was .120; therefore, there was no evidence for significant publication bias in the meta-analysis.

4 | DISCUSSION

Aberrant expression of miRNAs played a crucial role in the area of human carcinomas.\textsuperscript{19-21} Many studies have indicated that miRNAs are considered promising tumor biomarkers for prognosis and potential targets for clinical treatment.\textsuperscript{22} As described above, we have testified that high levels of miR-200 family expression (predominantly miR-200c, HR = 2.25, 95% CI 1.39-3.64) are significantly associated with poor survival and prognostic outcomes of patients with cancers, especially in lung cancer (HR = 3.09 95% CI 1.75-5.46). Liu et al\textsuperscript{11} reported that expression of miR-200c was upregulated in non-small cell lung cancer (NSCLC) tissues, and the patients with high miR-200c expression had a short survival time in a cohort of 70 NSCLC patients. This might indicate that high miR-200c plays a potential role in promoting progression of NSCLC. Some previous literatures have mentioned that miR-200c has a binding site in the 3\textsuperscript{\textprime} UTR of \(\beta\)-tubulin III and elevated miR-200c in cell lines decreased \(\beta\)-tubulin III protein. And high tumoral \(\beta\)-tubulin III was related to worse survival in NSCLC, breast and ovarian cancer.\textsuperscript{23} In addition, it was also shown to play a role in the regulation of mesenchymal-epithelial transition (MET), induction of MET is important at a later point in the metastasis process and MET enables primary tumor to colonize and produce metastases in distant organs.\textsuperscript{3} Tejero et al\textsuperscript{7} recommended that only miR-200c influenced MET/EMT in the H23, A-549, and HCC-44 cell lines, and Liu et al\textsuperscript{11} also found that overexpression of miR-200c was associated with advanced clinical

| Author & Year | Country   | Ethnicity | N   | Study design | Cancer type | Cutoff | Method   | Sample | Follow-up (mo) | miR type | Survival |
|---------------|-----------|-----------|-----|--------------|-------------|--------|----------|--------|---------------|----------|----------|
| Tejero 2014   | Spain     | Caucasian | 155 | R            | Lung        | NG     | qRT-PCR  | Tissue | 43 (2-160)    | miR-200c | OS       |
| Cao 2014      | China     | Asian     | 100 | R            | Ovarian     | Median | qRT-PCR  | Tissue | 36.8 (6-56)   | miR-200a | OS       |
| Cao 2014      | China     | Asian     | 100 | R            | Ovarian     | Median | qRT-PCR  | Tissue | 36.8 (6-56)   | miR-200b | OS       |
| Cao 2014      | China     | Asian     | 100 | R            | Ovarian     | Median | qRT-PCR  | Tissue | 36.8 (6-56)   | miR-200c | OS       |
| Men 2014      | China     | Asian     | 168 | R            | Glioma      | Median | qRT-PCR  | Tissue | 60            | miR-200b | OS       |
| DIAZ 2014     | Spain     | Caucasian | 127 | R            | Colorectal  | NG     | qRT-PCR  | Tissue | 120           | miR-200a | OS       |
| DIAZ 2014     | Spain     | Caucasian | 127 | R            | Colorectal  | NG     | qRT-PCR  | Tissue | 120           | miR-200c | OS       |
| DIAZ 2014     | Spain     | Caucasian | 127 | R            | Colorectal  | NG     | qRT-PCR  | Tissue | 120           | miR-429  | OS       |
| Toiyama 2013  | Japan     | Asian     | 182 | R            | Colorectal  | NG     | qRT-PCR  | Serum  | 60            | miR-200c | OS       |
| Leskela 2011  | Spain     | Caucasian | 72  | R            | Ovarian     | NG     | qRT-PCR  | Tissue | 128           | miR-429  | OS       |
| Ayerbes 2012  | Spain     | Caucasian | 52  | R            | Gastric     | Mean   | qRT-PCR  | Serum  | 26.3 (6-53)   | miR-200c | OS       |
| Hu 2009       | China     | Asian     | 55  | R            | Ovarian     | NG     | qRT-PCR  | Tissue | 50            | miR-200a | OS       |
| Song 2013     | China     | Asian     | 180 | R            | Gastric     | Quintile| Microarray| Tissue | 35 (1-112)   | miR-200a | OS       |
| Song 2013     | China     | Asian     | 180 | R            | Gastric     | Quintile| Microarray| Tissue | 35 (1-112)   | miR-200b | OS       |
| Song 2013     | China     | Asian     | 180 | R            | Gastric     | Quintile| Microarray| Tissue | 35 (1-112)   | miR-200c | OS       |
| Liu 2012      | China     | Asian     | 70  | R            | Lung        | Twofold| qRT-PCR  | Tissue | 24            | miR-141  | OS       |
| Liu 2012      | China     | Asian     | 70  | R            | Lung        | Twofold| qRT-PCR  | Tissue | 24            | miR-200c | OS       |
| Tuomarila 2014| Finland   | Caucasian | 172 | R            | Breast      | Median | qRT-PCR  | Tissue | 240           | miR-200c | OS       |
| Li 2012       | China     | Asian     | 107 | R            | Colorectal  | NG     | qRT-PCR  | Tissue | 65 (11-82)    | miR-429  | OS       |
| Men 2014      | China     | Asian     | 168 | R            | Glioma      | Median | qRT-PCR  | Tissue | 60            | miR-200b | PFS      |
| Ayerbes 2012  | Spain     | Caucasian | 52  | R            | Gastric     | Mean   | qRT-PCR  | Serum  | 26.3 (6-53)   | miR-200c | PFS      |
| Song 2013     | China     | Asian     | 180 | R            | Gastric     | Quintile| Microarray| Tissue | 35 (1-112)   | miR-200a | PFS      |
| Song 2013     | China     | Asian     | 180 | R            | Gastric     | Quintile| Microarray| Tissue | 35 (1-112)   | miR-200b | PFS      |
| Song 2013     | China     | Asian     | 180 | R            | Gastric     | Quintile| Microarray| Tissue | 35 (1-112)   | miR-200c | PFS      |
| Leskela 2011  | Spain     | Caucasian | 72  | R            | Ovarian     | NG     | qRT-PCR  | Tissue | 128           | miR-429  | PFS      |
| Leskela 2011  | Spain     | Caucasian | 72  | R            | Ovarian     | NG     | qRT-PCR  | Tissue | 128           | miR-200c | PFS      |
| Leskela 2011  | Spain     | Caucasian | 72  | R            | Ovarian     | NG     | qRT-PCR  | Tissue | 128           | miR-141  | RFS      |
| Hu 2009       | China     | Asian     | 55  | R            | Ovarian     | NG     | qRT-PCR  | Tissue | 50            | miR-200a | RFS      |
| Tuomarila 2014| Finland   | Caucasian | 172 | R            | Breast      | Median | qRT-PCR  | Tissue | 240           | miR-200c | RFS      |

N, number of patients; R, retrospective; qRT-PCR, quantitative real-time PCR; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; CI, confidence interval; NG, not given.
stage and lymph node metastasis. Thus, miR-200c could be used as a potential biomarker in the prognosis of cancer patients, mainly in lung cancer. However, no statistically significant results were calculated for miR-200a/b and miR-429, and this might result from a relatively small number of articles about them.

In other tumor models except lung cancer, our results indicated that high miR-200 family was not obviously associated with OS (gastric or colorectal cancer: HR = 1.00, 95% CI 0.67-1.50; ovarian cancer: HR = 3.49, 95% CI 0.47-25.62; others: HR = 1.63, 95% CI 0.40-6.69). We speculated that the discordancy might result from different extent of tumor growth in cancer cells.24 Pacurari et al25 indicated that expression of miR-200 family was rather complex during tumorigenesis, which elevated in primary tumors and down-regulated in metastatic cells. Thus, it can be seen that the role of miR-200 may differ depending on cancer type and stage. In addition, some other records showed the opposite results,2,5,6 for they exhibited that upregulated miR-200 family level was linked to longer survival.1,4-7,13 MiR-200 family was previously showed to inhibit the epithelial-mesenchymal transition (EMT) and cell migration. EMT plays a key role in invasion and metastasis during carcinogenesis. Herein, these patients with high miR-200 family expression levels might have longer survival by inhibiting EMT.

In this meta-analysis, our stratified analyses showed that the combined HR of Asian population was 2.19 (95% CI 1.37-3.78) and predicted poor OS. While the HR of Caucasian population was 0.94 (95% CI 0.46-1.91), it did not exhibit an significant association with OS. This discrepancy might result from different hereditary backgrounds and environment exposure.26

Although these results have indicated that miR-200 families were promising biomarkers to predict prognosis for patients with cancers, there were several limitations in this analysis that would impact its quality. First, the number of records was only 12 with a small sample size. In particular, all studies were Asians or Caucasians, and no African population were included in the analysis. Therefore, we need more proper studies included in our meta-analysis. Second, the relatively large heterogeneity in the present study must make caution, although it signified that the variation was not due to chance. This may arises from many factors, including tumor types, different ethnicities, or selection of subjection. The expression of miR-200 family was detected in tumor tissues and blood samples such as plasma and serum may partly contribute to the heterogeneity. Therefore, we strongly recommend future investigations should be performed with matched cancer type, specimen, and ethnicity to confirm the conclusion. Third, the cutoff definition of miR-200 family appeared to be different in each study, while we could not provide a clear interpretation. And then, estimates derived from different tumors are not comparable, and then inconsistent cutoff value may be the reason that provided contradictory results. Finally, as a cancer biomarker, the prognostic role was proven, besides, it remained unknown whether miR-200 family should be used as an independent biomarker or used with several other biomarkers for predicting outcomes. Generally, further studies should be warranted to clarify this question and to provide a new novel idea for routine clinical application.

### TABLE 2 Patient survival by total and stratified analyses

| Subgroup          | OS       |       |       |       |       |       |       |       |       |       |       |       |
|-------------------|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                   | n        | HR (95% CI) | P     | n        | HR (95% CI) | P     | n        | HR (95% CI) | P     |
| Overall           | 19       | 1.54 (1.01-2.33) | .044  | 5        | 0.92 (0.67-1.26) | .582  | 5        | 0.65 (0.29-1.48) | .307  |
| Caucasian         | 7        | 0.94 (0.46-1.91) | .862  | 1        | – –        | – –   | 4        | 0.74 (0.28-2.01) | .559  |
| Asian             | 12       | 2.19 (1.27-3.78) | .005  | 4        | 0.82 (0.65-1.02) | .080  | 1        | – –        | – –   |
| Cancer type       |          |       |       |       |       |       |       |       |       |       |       |       |
| Lung              | 3        | 3.09 (1.75-5.46) | <.001 | – –        | – –   | – –   | – –   | – –   | – –   | – –   | – –   | – –   |
| Gastric or Colorectal | 9   | 1.00 (0.67-1.50) | .992  | 4        | 0.95 (0.67-1.33) | .745  | – –        | – –   | – –   | – –   | – –   | – –   |
| Ovarian           | 5        | 3.49 (0.47-25.62) | .220  | – –        | – –   | – –   | – –   | 4        | 0.43 (0.29-0.66) | <.001  |
| Others            | 2        | 1.63 (0.40-6.69) | .498  | 1        | – –        | – –   | – –   | – –   | – –   | – –   | – –   | – –   |
| miRType           |          |       |       |       |       |       |       |       |       |       |       |       |
| miR-200a          | 4        | 1.03 (0.32-3.82) | .961  | 1        | – –        | – –   | 1        | – –        | – –   |
| miR-200b          | 3        | 1.83 (0.44-7.65) | .406  | 2        | 0.79 (0.55-1.14) | .213  | – –        | – –   | – –   | – –   | – –   | – –   |
| miR-200c          | 8        | 2.25 (1.39-3.64) | .001  | 2        | 1.28 (0.79-2.09) | .314  | 2        | 1.20 (0.18-8.09) | .854  |
| miR-429           | 3        | 0.69 (0.22-2.17) | .522  | – –        | – –   | – –   | – –   | 1        | – –        | – –   | – –   | – –   |
| miR-141           | 1        | – –        | – –   | – –        | – –   | – –   | – –   | 1        | – –        | – –   | – –   | – –   |

OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

*The HRs and 95% CIs of analyzed studies were pooled by the random-effects model if the P value for heterogeneity was <.10 or I² was >50%.

**The HRs and 95% CIs of analyzed studies were pooled by the fixed-effects model if the P value for heterogeneity was more than .10 or I² was <50%.

In summary, our meta-analysis represents that high level of miR-200 family expression is significantly associated with poor survival in
patients with a variety of cancers. However, the evidence was not so convincing due to the limitations mentioned above, and further studies and more clinical investigations are required to predict the clinical outcome of patients with various carcinomas.

**CONFLICT OF INTEREST**

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