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Research Paper

The Significance Role of microRNA-200c as a Prognostic Factor in Various Human Solid Malignant Neoplasms: A Meta-Analysis

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Abstract

Objective: The aim of this study was to conduct a meta-analysis of 49 relevant studies to evaluate the prognostic value of miRNA-200c in various human malignant neoplasms.

Methods: All relevant studies were identified by searching PubMed, Embase and Web of Science until August 15st, 2018. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) of miRNA-200c for overall survival (OS) and progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS) were calculated to investigate such associations.

Results: Overall, 49 eligible studies were included in this meta-analysis. Our results showed that high expression of miRNA-200c was significantly correlated with a poor OS in cancer (pooled HR = 1.32, 95% CI: 1.06-1.65), but was not significantly correlated with PFS/RFS/DFS in cancer (pooled HR=1.05, 95% CI: 0.84-1.23). In our subgroup analysis, high miRNA-200c expression predicted a significantly worse OS (pooled HR = 1.50, 95% CI: 1.12-2.01) only in Caucasians. Moreover, high miRNA-200c expression even showed significantly poor OS (pooled HR = 1.88, 95% CI: 1.39-2.54) in blood samples. In addition, a significantly unfavorable OS (pooled HR = 2.69, 95% CI: 1.49-4.85) and (pooled HR = 2.66, 95% CI: 1.07-6.59) associated with up-regulated miRNA-200c expression were observed in breast cancer and endometrial cancer, respectively. Besides, high miRNA-200c expression also showed significantly poor PFS/RFS/DFS (pooled HR=1.66, 95% CI: 1.03-2.67) in breast cancer.

Conclusions: Our findings indicated that high miRNA-200c expression was a promising biomarker for patient survival and disease progression in malignant tumors, especially in breast cancer and endometrial cancer. Considering the insufficient evidence, further large-scale researches and clinical studies were needed to verify these results.

Key words: malignant neoplasms, miRNA-200c, prognosis, overall survival, progression-free survival

Introduction

MicroRNAs (miRNAs) are a class of single stranded, highly conserved, endogenous, small non-coding RNAs (18-25 nucleotides in length) [1, 2]. Mature miRNAs negatively regulate target genes expression at the post-transcriptional level by binding to the 3′ untranslated region (3′UTR) of messenger

RNA (mRNA), resulting in suppression of translation or degradation of mRNAs. Therefore, miRNAs play vital roles in diverse biological processes, including cell cycle, apoptosis, differentiation and growth [3-6]. Due to the aberrant expression discrepancy between tumor tissues and normal tissues, emerging studies have demonstrated that miRNAs were willing to considered as diagnostic or prognostic biomarkers for multiple human cancers [7-9]. In addition, miRNAs can be classified into two categories, including protective miRNAs which are associated with favorable prognosis, and hazardous miRNAs which are known as poor survival predictors [10, 11]. As a member of miRNAs, miRNA-200c has been studied relatively intensively and thoroughly for the prognosis of cancer.

The miRNA-200 family consists of five members: miRNA-200a, miRNA-200b, miRNA-200c, miRNA-429, and miRNA-141, is closely associated with human health and disease [12, 13]. Recent studies have shown that the miRNA-200 family members, especially miRNA-200c, played a vital role in the process of epithelial-mesenchymal transition (EMT), which was important for embryonic development, cancer, and other diseases [12-15]. MiRNA-200c is highly enriched in epithelial tissues, and is deemed to repress the expression of E-cadherin transcription inhibitors ZEB1 and ZEB2, and has a direct influence on EMT. In recent times, increasing evidences have demonstrated that miRNA-200c was associated with patient prognosis and clinicopathology significance, such as ovarian cancer, gastric cancer, pancreatic cancer, colorectal cancer, esophageal cancer, and so on [16-22]. What's more, miRNA-200c expression was also related to tumor drug resistance [23, 24]. In addition, some studies have reported that miRNA-200c could be detectable in blood samples and had the potential to be new biomarkers in patients with cancer [25, 26]. Therefore, it is necessary and timely to perform a meta-analysis to evaluate the prognostic value and clinicopathology significance of miRNA-200c expression in patients with cancer.

To investigate whether the miRNA-200c expression could serve as a prognostic or clinical biomarker for cancer, we performed a systematic review and meta-analysis by extracting summary statistics of the published literature for survival endpoints.

Materials and Methods

Search Strategy

We systematically and carefully searched online databases, including PubMed, Embase and Web of Science for original articles analyzing the prognostic value of miRNA-200c in various cancers until August 15st, 2018. The relevant studies were selected according to varying combinations of the following keywords: 'cancer', 'carcinoma', 'neoplasm', 'tumour', 'tumor', 'microRNA-200c', 'microrna-200c', 'miRNA-200c', 'miR-200c', 'overall survival', 'recurrence', and 'prognosis'. Besides, the following criteria should be considered to select the literatures: (1) the studies exploring various human malignancies; (2) the relationship between miRNA200c and cancer prognosis. In order to supplement our literature search, the bibliographies of all eligible studies were reviewed for additional relevant publications. When more than one study had been published using the same series of study subjects, only the most recent and the most complete study was chosen in this meta-analysis.

Quality assessment

This meta-analysis was strictly performed according to a critical review checklist of the Dutch Cochrane Centre proposed by MOOSE. The key points of the quality assessment included clear definitions of the following: (1) clear origin of country and description of study population; (2) clear definition of type of carcinoma; (3) clear explanation of study design; (4) clear detection of samples; (5) clear description of outcome assessment; (6) sufficient follow-up period. Studies without meeting all of the above criteria were excluded to maintain the quality of the meta-analysis. In addition, sensitivity analyses and published bias were also performed to promote the quality of this meta-analysis.

Data extraction

Two investigators (Feng Wang and Lei Zhang) independently identified all eligible studies, and uncertain data were reassessed by Haoxiang Xu. The extracted data elements included the following: (1) first author's name and year of publication; (2) study population, ethnicity and nationality; (3) study design, malignant types and detected samples; (4) HRs along with their 95% CIs associated with high miRNA-200c for overall survival (OS) and progression-free survival (PFS)/recurrence-free survival (RFS)/disease-free survival (DFS) were collected. In addition, only Kaplan-Meier curves was provided in some studies, the HRs and their 95% CIs were extracted from graphical survival plots using Engauge Digitizer version 4.1 [27, 28].

Statistical analysis

Heterogeneity test for pooled HRs was calculated by Cochran Q-test and Higgins I-squared statistic (I^2). $P < 0.05$ was considered statistically significance. According to the heterogeneity among the pooled investigations, the fixed-effects model (Mantel-

Haenszel method) or the random-effects model (DerSimonianLaird method) were chosen in this meta-analysis. If the heterogeneity was observed ($P < 0.05$ or $I^2 > 50\%$), a random-effects model was utilized; Otherwise, a fixed-effects model was conducted [29]. What's more, subgroup analysis upon similar characteristics were performed to minimize the influence of heterogeneity. To examine the stability and reliability of the overall meta-analysis results, sensitivity analysis was performed by excluding one single study one by one and recalculating their HRs. Publication bias was assessed by Begg's funnel plot and Egger linear regression test [30, 31]. All statistical analyses were conducted by using Stata version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Summary of enrolled studies

According to the study selection process, a total of 1,139 studies from PubMed, Embase, and the Web of Science were collected to focus on the relationship between miRNA-200c and the prognosis of cancer. After a primary evaluation of titles and abstracts, 955 studies were excluded if they were letters or review articles, were not human studies, were not related to prognosis or outcomes, and did not have relationship between miRNA-200c and malignancies. For further quality evaluation of remaining studies, 184 studies were excluded because of insufficient survival data, indirectly concern with specific outcomes, unrelated to tumor tissues and blood samples, incomplete or repeated data. Finally, 49 studies were considered applicable to this meta-analysis [16-22, 25, 26, 32-71]. The flowchart of literature search and selection procedure is shown in **Figure 1**.

Of the 49 eligible studies, 45 studies focused on OS, and 27 studies reported PFS/RFS/DFS. During these studies, 26 studies related to Asian population while 26 studies reported Caucasians. Meanwhile, 36 studies focused on tissues and other 17 studies investigated blood samples. What's more, the malignant neoplasms consisted of pancreatic cancer, ovarian cancer, bladder cancer, gastric cancer, endometrial cancer, lung cancer, breast cancer, colorectal cancer. All the analyses were retrospective studies with a maximum follow-up of 13-192 months. In this meta-analysis, all of the baseline characteristics of the studies associated with the prognosis of cancer are comprehensively listed in **Table 1**.

OS associated with miRNA-200c expression

A total of 41 studies were included in OS analysis with significant heterogeneity ($P < 0.001$, $I^2 = 80.5\%$). Thus, a random model was used to calculate a pooled HRs and 95% CIs. Our results found that high miRNA-200c expression was a significant predictor of poor OS (pooled HR = 1.32, 95% CI: 1.06-1.65) (**Figure 2A**). We conducted three subtotal analyses stratified to avoid the influence of heterogeneity, including dominant ethnicity, categories of detected samples, and malignant diseases. First of all, 22 studies in Caucasians demonstrated that patients with elevated miRNA-200c expression had a significantly poorer OS (pooled HR = 1.50, 95% CI: 1.12-2.01) by a random-effects model, because of significant heterogeneity among pooled studies. However, high miRNA-200c expression was not significantly associated with enhancing OS (pooled HR = 1.17, 95% CI: 0.81-1.69) by a random model in Asian populations (**Figure 3A**). Secondly, in subtotal analysis stratified by the category of detected samples, high miRNA-200c expression showed a significant relationship with poor OS by a random-effects model, mainly in blood samples (pooled HR = 1.88, 95% CI: 1.39-2.54) but not in tissue (**Figure 3B**). Thirdly, when stratified by malignant types, pooled analysis in the breast cancer subgroup with the fixed-effects model (pooled HR = 2.69, 95% CI: 1.49-4.85) and endometrial cancer subgroup with the random-effects model (pooled HR = 2.66, 95% CI: 1.07-6.59), exhibited a significant association between up-regulated expression of miR-200c. However, no other subgroups, including ovarian cancer, gastric cancer, lung cancer and colorectal cancer discovered any significant results, as shown by stratified analyses (**Figure 3C**).

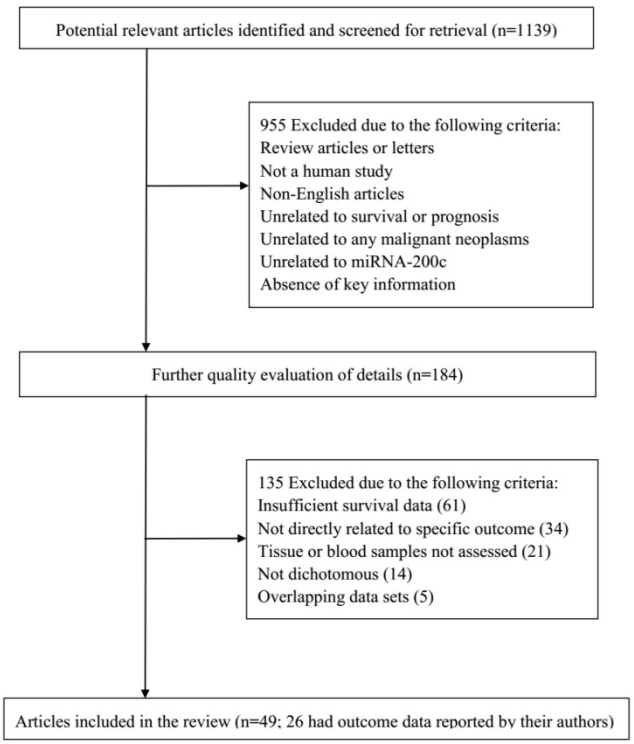

Figure 1. Flowchart of literature search and selection process.

Table 1. Main characteristics of studies included in the meta-analysis.

First author	Publication year	Case nationality	Dominant ethnicity	Study design	Number of cases	Malignant disease	Detected sample	Survival analysis	Source of HR	Maximum months of follow-up
Yu	2010	Japan	Asian	R	99	Pancreatic cancer	Tissue	OS	Reported	101
Marchini a	2011	Italy	Caucasian	R	89	Ovarian cancer	Tissue	OS,PFS	Reported	139.2
Marchini b	2011	Italy	Caucasian	R	55	Ovarian cancer	Tissue	OS,PFS	Reported	139.2
Hamano	2011	Japan	Asian	R	98	Esophageal cancer	Tissue	OS	Estimated	96.7
Leskelä	2011	Spain	Caucasian	R	72	Ovarian cancer	Tissue	PFS	Reported	125
Wiklund	2011	Denmark	Caucasian	R	100	Bladder cancer	Tissue	OS	Estimated	>40
Valladares-Ayerbes	2012	Spain	Caucasian	R	52	Gastric cancer	Blood	OS,PFS	Estimated	60
Karaayvaz	2012	America	Caucasian	R	34	Endometrial cancer	Tissue	OS	Reported	125
Liu	2012	China	Asian	R	70	Lung cancer	Tissue	OS	Reported	30
Madhavan	2012	Germany	Caucasian	R	164	Breast cancer	Blood	PFS	Estimated	24
Torres	2012	Poland	Caucasian	R	73	Endometrioid endometrial cancer	Blood	OS	Estimated	150
Yu	2013	China	Asian	R	157	Esophageal cancer	Blood	OS	Reported	50
Tanaka	2013	Japan	Asian	R	64	Esophageal cancer	Blood	PFS	Reported	42
Tang	2013	China	Asian	R	126	Gastric cancer	Tissue	OS,DFS	Estimated	60
Wotschofsky	2013	Germany	Caucasian	R	89	Renal cell carcinoma	Tissue	PFS	Reported	80
Berghmans	2013	Belgium	Caucasian	R	38	Lung cancer	Tissue	OS	Reported	60
Berglund	2013	Sweden	Caucasian	R	61	Diffuse large B-cell lymphoma	Tissue	OS	Estimated	192
Cao	2014	China	Asian	R	100	Ovarian cancer	Tissue	OS	Reported	56
Lin	2014	Australia	Caucasian	R	97	Prostate cancer	Blood	OS	Reported	62
Diaz	2014	Spain	Caucasian	R	127	Colorectal cancer	Tissue	OS,DFS	Estimated	120
Toiyama a	2014	Japan	Asian	R	156	Colorectal cancer	Blood	OS	Reported	70
Toiyama b	2014	Japan	Asian	R	182	Colorectal cancer	Tissue	OS	Reported	70
Tejero	2014	Spain	Caucasian	R	155	Lung cancer	Tissue	OS	Estimated	
Kim	2014	South Korea	Asian	R	72	Lung cancer	Tissue	OS	Reported	135
Li	2014	China	Asian	R	150	Lung cancer	Tissue	OS,PFS	Reported	20.6
Song	2014	china	Asian	R	385	Gastric cancer	Tissue	OS,PFS	Estimated	112
Elgaaen	2014	Norway	Caucasian	R	35	Ovarian cancer	Tissue	OS	Estimated	>100
Zhou	2014	China	Asian	R	64	Gastric cancer	Tissue	DFS	Estimated	>30
Martínez-Fernández	2015	Spain	Caucasian	R	87	Bladder cancer	Tissue	OS	Estimated	133.3
Meng	2015	Germany	Caucasian	R	163	Ovarian cancer	Blood	OS,PFS	Estimated	136
Song	2015	China	Asian	R	134	Breast cancer	Tissue	OS,PFS	Estimated	100
Gao	2015	China	Asian	R	93	Ovarian cancer	Blood	OS	Reported	>100
Antolín	2015	Spain	Caucasian	R	57	Breast cancer	Blood	OS,PFS	Reported	310.8
Ge	2015	China	Asian	R	163	Renal cell carcinoma	Tissue	OS	Reported	24.3
Yamagishi	2015	Japan	Asian	R	83	Malignant lymphoma	Tissue	OS	Estimated	>70
Zhang	2015	China	Asian	R	98	Gastric cancer	Blood	OS	Reported	60
Madhavan	2016	Germany	Caucasian	R	225	Breast cancer	Blood	OS,PFS	Estimated	>30
Urbas	2016	Austria	Caucasian	R	78	Biliary tract cancer	Tissue	OS	Reported	140
Bhardwaj	2017	india	Asian	R	42	Eyelid sebaceous gland carcinoma	Tissue	DFS	Estimated	44
Maierthaler a	2017	Germany	Caucasian	R	308	Colorectal cancer	Blood	OS,RFS	Reported	72
Maierthaler b	2017	Germany	Caucasian	R	219	Colorectal cancer	Blood	OS,RFS	Reported	72
Damiano	2017	Italy	Caucasian	R	51	Breast cancer	Tissue	DFS	Estimated	92
Li	2017	China	Asian	R	48	Colorectal cancer	Tissue	OS	Estimated	>60
Li a	2017	China	Asian	R	51	Gastric cancer	Tissue	OS,PFS	Reported	13
Li b	2017	China	Asian	R	51	Gastric cancer	Blood	OS,PFS	Reported	13
Lin	2017	Australia	Caucasian	R	89	Prostate cancer	Blood	OS	Reported	>40
Raychaudhuri	2017	Germany	Caucasian	R	42	Breast cancer	Tissue	OS	Estimated	120
Zhang	2017	China	Asian	R	169	Gastric cancer	Tissue	DFS	Reported	65.4
Wei	2018	China	Asian	R	60	Lung cancer	Tissue	OS	Estimated	60
Wilczynski	2018	Polish	Caucasian	R	119	Endometrioid endometrial cancer	Tissue	OS,DFS	Reported	119
Roh	2018	Korea	Asian	R	93	Colorectal cancer	Tissue	OS,RFS	Reported	93
Tayel	2018	Egypt	African	R	25	Colorectal cancer	Blood	OS	Estimated	25
Zhou	2018	China	Asian	R	108	Colorectal cancer	Tissue	OS,RFS	Reported	108

Study design is described as prospective (P) or retrospective (R).

OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, relapse-free survival; NM, not mentioned.

Recurrence associated with miRNA-200c expression

A total of 24 studies focused on the PFS/RFS/DFS analysis revealed a protective role of high miRNA-200c expression (pooled HR=1.05, 95% CI: 0.84-1.32) by a random-effects model (**Figure 2B**). In the stratified analyses, increased miRNA-200c

expression correlated with favorable PFS/RFS/DFS in the Asian subgroup (pooled HR=0.84, 95% CI: 0.60-1.17; **Figure 4A**). In detected samples subgroup, the results suggested that high miRNA-200c expression was not a significant association with enhanced PFS/RFS/DFS in blood sample (pooled HR=1.35, 95% CI: 0.99-1.86; **Figure 4B**), and in tissue samples (pooled HR=0.88, 95% CI: 0.63-1.23; **Figure 4B**). What's more, up-regulated miRNA-200c expression was found to be significantly associated with worse PFS/RFS/DFS, only in breast cancer (pooled HR=1.66, 95% CI: 1.03-2.67; **Figure 4C**), but no significant relevance was observed in other subgroup of ovarian cancer (pooled HR=0.62, 95% CI: 0.26-1.49; **Figure 4C**), gastric cancer (pooled HR=0.79, 95% CI: 0.50-1.24; **Figure 4C**), and colorectal cancer (pooled HR=1.13, 95% CI: 0.84-1.50; **Figure 4C**).

Sensitivity analyses

In the OS and PFS/DFS/DSS studies, sensitivity analyses did not indicate alterations in the results if any individual study was excluded (**Figure 5**), which suggested that no single study significantly influenced the pooled HRs or the 95% CIs.

Publication bias

In this meta-analysis, publication bias was performed by Begg's tests and funnel plots (OS: P = 0.469, PFS/DFS/DSS: P = 0.917, respectively). As expected, the funnel plots were symmetrical, and the P values of Begg's tests were 0.897 for OS and 0.615 for PFS/DFS/DSS, suggesting that no significant publication bias was observed in the meta-analysis (**Figure 6**).

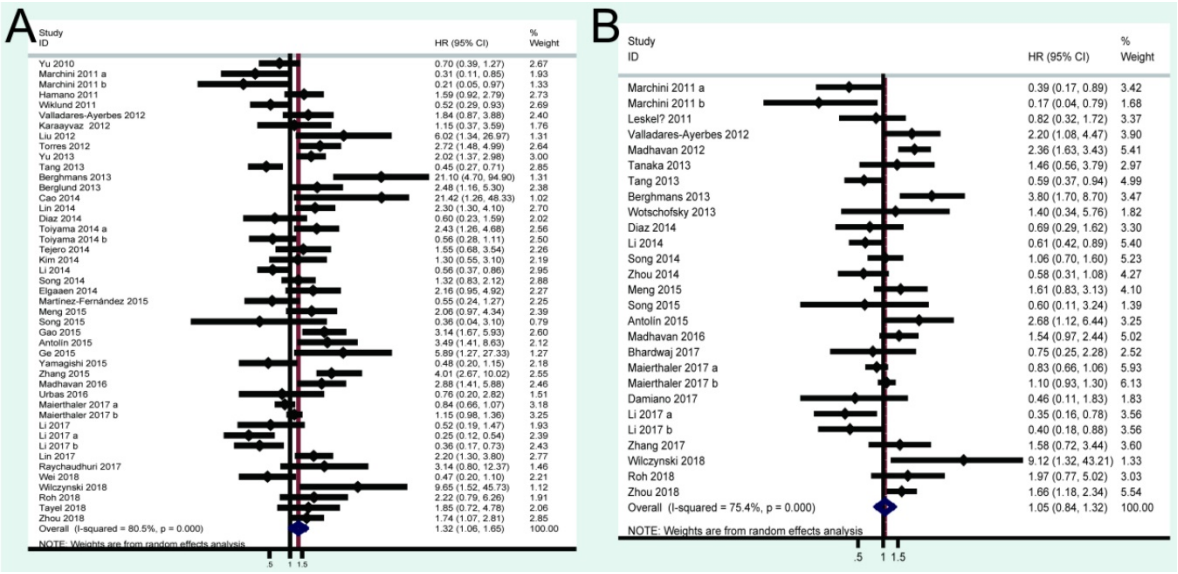

Figure 2. Forest plots of merged analyses of OS and PFS/RFS/DFS in association with miRNA-200c expression.

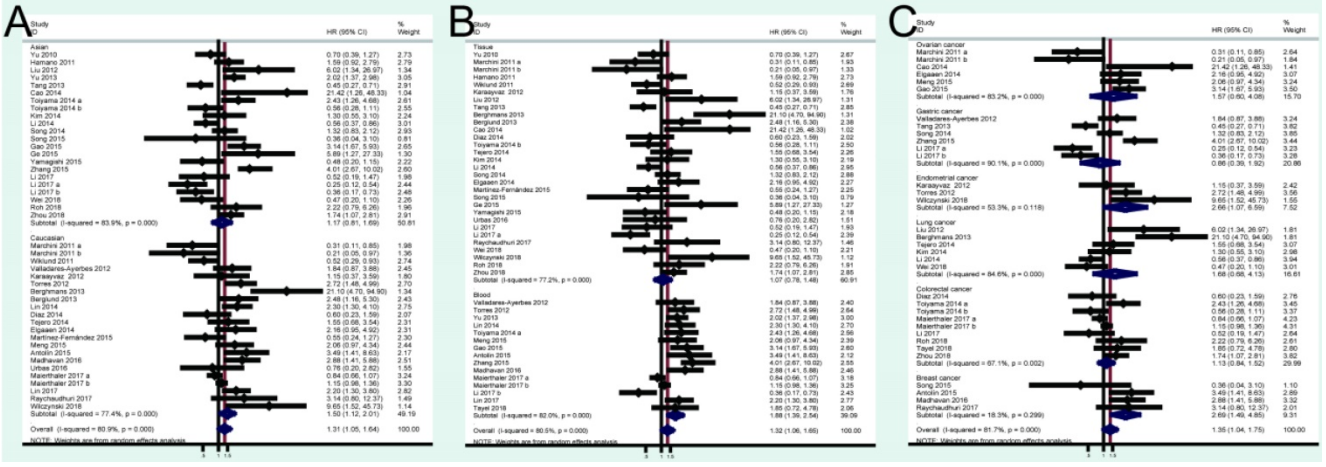

Figure 3. Forest plots of merged analyses of OS in association with miRNA-200c expression for the different subgroups. A: stratified by dominant ethnicities; B: stratified by detected sample; C: stratified by malignant diseases.

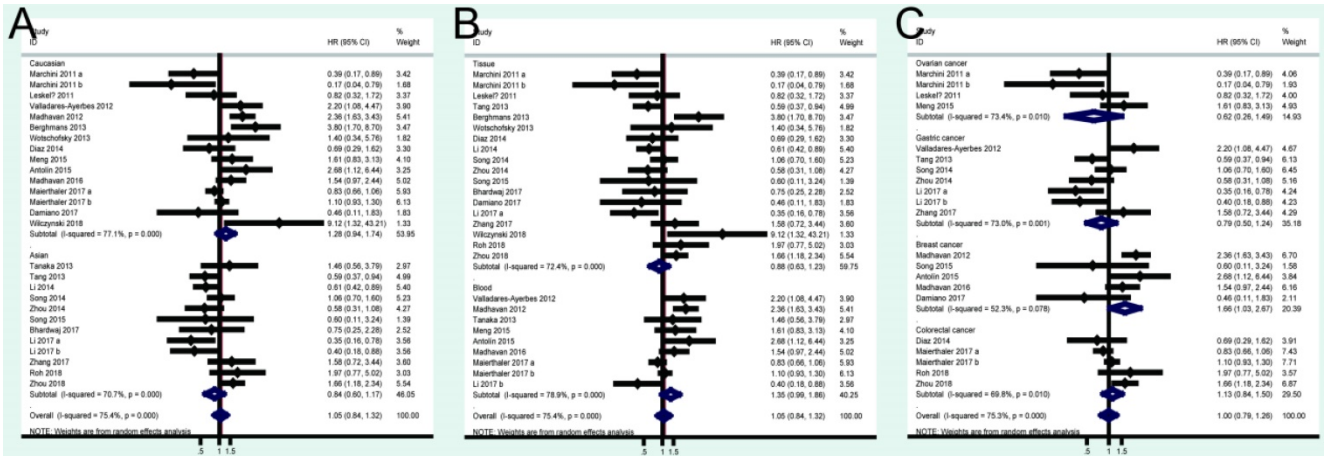

Figure 4. Forest plots of merged analyses of PFS/RFS/DFS in association with miRNA-200c expression for the different subgroups. A: stratified by dominant ethnicities; B: stratified by detected sample; C: stratified by malignant diseases.

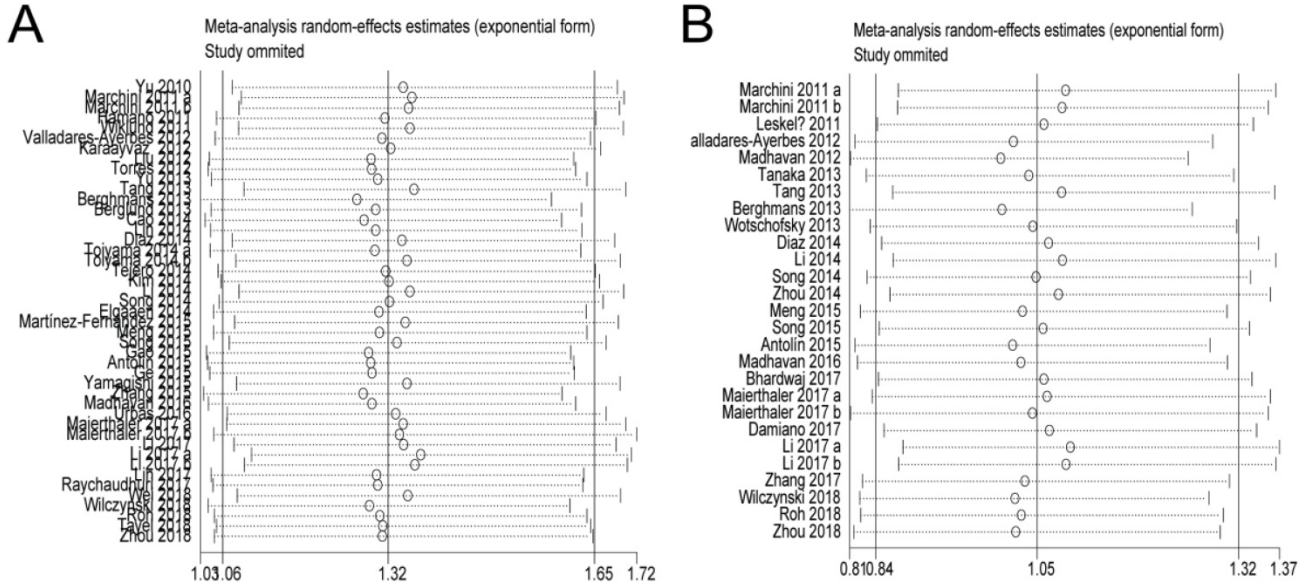

Figure 5. Sensitivity analysis. A: Pooled HR for OS under Random-effort model; B: Pooled HR for PFS/RFS/DFS under Random-effort model.

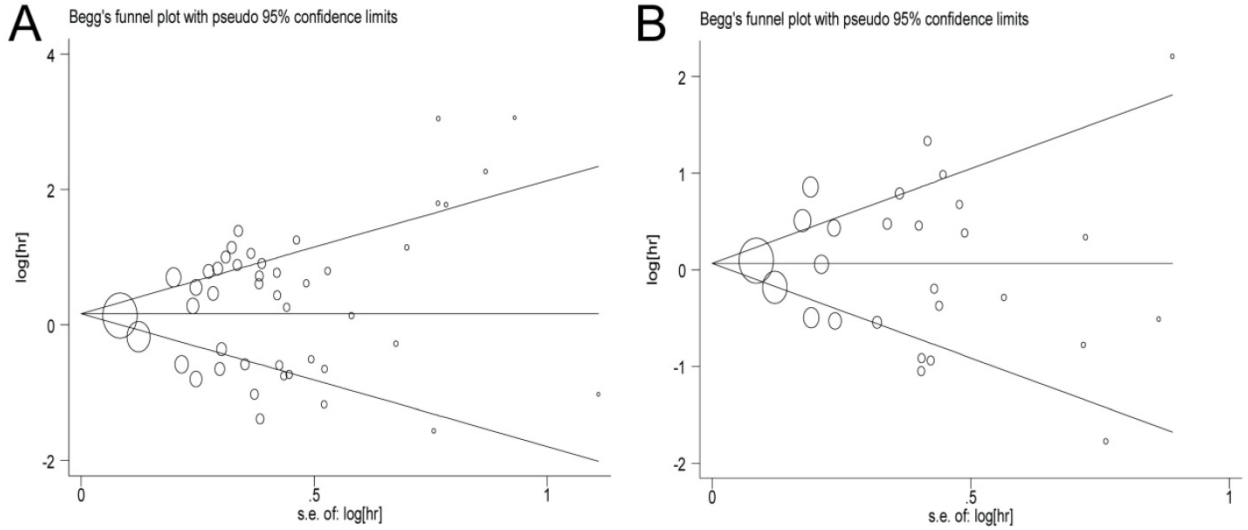

Figure 6. Begg's funnel plot of publication bias test. A: Pooled HR for OS under Random-effort model; B: Pooled HR for PFS/RFS/DFS under Random-effort model.

Table 2. The pooled HRs, 95% CIs, p values and I^2 of OS and PFS/DFS stratified by ethnicity, detected samples

	OS				PFS/DFS			
	N	pHR (95% CI)	p Value	I^2	N	pHR (95% CI)	p Value	I^2
All studies	40	1.29 (1.02,1.63)[a]	0.000	81.5%	24	0.97(0.77,1.23)[a]	0.000	74.7%
Race								
Caucasian	21	1.44(1.08,1.92)[a]	0.000	77.1%	14	1.22(0.90,1.65)[a]	0.000	76.7%
Asian	19	1.16(0.77,1.76)[a]	0.000	85.2%	10	0.71(0.53,0.94)[b]	0.056	45.7%
Detected sample								
Tissue	26	1.00(0.71,1.40)[a]	0.000	76.6%	15	0.74(0.54,1.01)[a]	0.001	60.3%
Blood	14	1.88(1.38,2.57)[a]	0.000	83.2%	9	1.19(0.99,1.86)[a]	0.000	78.9%
Disease type								
Ovarian cancer	6	1.57(0.60,4.08)[a]	0.000	83.2%	4	0.62(0.26,1.49)[a]	0.010	73.4%
Gastric cancer	6	0.86(0.39,1.92)[a]	0.000	90.1%	7	0.79(0.50,1.24)[a]	0.001	73.0%
Lung cancer	5	1.68(0.68,4.13)[a]	0.000	84.6%	-	-	-	-
Colorectal cancer	6	0.95(0.68,1.32)[a]	0.005	70.5%	3	0.95(0.75,1.21)[b]	0.124	52.1%
Breast cancer	4	2.69(1.49,4.85)[b]	0.299	18.3%	5	1.66(1.03,2.67)[b]	0.078	52.3%

a, The HRs and 95% CIs of the enrolled studies were pooled using the random-effects model if the p Value for the heterogeneity test was less than 0.05 or I^2 was greater than 50%. b, The HRs and 95% CIs of the enrolled studies were pooled using the fixed-effects model.

pHR, pooled HR; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; N, number of studies.

Discussion

MiRNA-200c is a member of the miRNA-200 family, which inhibits epithelialto-mesenchymal transition (EMT) by targeting the transcriptional repressor of cadherin 1 (CDH1), zinc fnger E-box binding homeobox 1 (ZEB1), and survival of motor neuron protein interacting protein 1 (SIP1), leading to prevent tumor progression and metastasis in various malignancies [13, 14, 72, 73]. Growing evidences have demonstrated that the dysregulation of miRNA-200c was involved in several malignancies. MiRNA-200c is up-regulated in several cancers, such as ovarian cancer, bile duct cancer, nasopharyngeal carcinoma, lung cancer, colorectal cancer, gastric cancer [18, 35, 74-79]; whereas miRNA-200c is down-regulated in bladder cancer, spinal cord injury, breast cancer and so on [52, 80, 81]. Meanwhile, the prognostic role of miRNA-200c in human malignancies was still controversial. Jurmeister S et al. [82] found that miRNA-200c repressed migration and invasion of breast cancer cells by targeting actin-regulatory proteins formin homology 2 domain containing 1 (FHOD1) and protein phosphatase, Mg2/Mn2 dependent, 1F (PPM1F). Song et al. [52] showed that miRNA-200c inhibited breast cancer proliferation by targeting KRAS. However, some studies found that miRNA-200c was considered as a driver of biological aggressiveness in ovarian cancer and colon cancer [83, 84]. What's more, miRNA-200c expression was related with tumor drug resistance. For instance, it has been reported that miRNA-200c was a marker of chemoresistance and aggressiveness in female reproductive cancers [23, 24]. Cochrane DR et al. [24] found that miRNA-200c suppressed invasiveness and restored sensitivity to microtubule-targeting chemo-therapeutic agents in breast and ovarian cancer cells. Shimono Y et al. [85] showed that down-regulation of miRNA-200c linked breast cancer stem cells with normal stem cells. Thus, miRNA-200c was undeniably an promising biomarker of human malignancies and played important roles in tumour initiation and progression. In this meta-analysis, we aimed to explore the association between miRNA-200c expression and the prognosis and clinicopathology of cancer.

Meta-analysis is a powerful tool and can provide more sufficient results compared to a single study especially in analyzing unexplained studies. As a result, we suggested that meta-analysis had some stronger advantages to prove the prognostic role of microRNA-200c expression in multiple human malignancies. In our meta-analysis, high expression of miRNA-200c was significantly correlated with a poor OS in cancer, but was not significantly correlated with PFS/RFS/DFS in cancer. These inconsistent pooled outcomes might imply that patient survival or tumor progression was influenced by dissimilar potential mechanisms. These inconsistent outcomes might hint at dissimilar potential mechanisms that affected patient survival or tumor progression.

Furthermore, in subgroup analyses based on dominant ethnicity, categories of detected samples, and malignant diseases, we successfully drew some valuable conclusions for clinical application. Our study found that increased miRNA-200c expression predicted a significantly worse OS in Caucasians, but there was no statistical significance in Asians. Besides, the high expression of miRNA-200c could predict a significantly favorable PFS/RFS/DFS in Asians. These discrepancies might result from different hereditary backgrounds and environmental exposure. Extensive researchers have discovered the predictive values of miRNAs and diverse expression levels in different ethnic groups [86-88]. Recent evidences have suggested that miRNAs were considered as potential biomarkers in various cancers by detected in blood, including hepatocellular carcinoma [89], esophageal

squamous cell cancer [90], non-small cell lung cancer [91] and breast cancer [92]. Valladares-Ayerbes M et al. reported that circulating miRNA-200c could be considered as a diagnostic and prognostic biomarker for gastric cancer [25]. In our subgroup analysis of detected samples, we found that high expression of miRNA-200c significantly related to a poor OS in blood samples, but not in tissue. Consistent with previous results, up-regulated miRNA-200c expression was found to be significantly associated with enhanced PFS/RFS/DFS in blood subgroup, but failed to find a significant consequence in tissue. These results might demonstrate that miRNA-200c might serve as a blood biomarker for cancer. Meanwhile, compared with tissue sample, detection by blood samples was faster and convenient, which could effectively evaluate survival prognosis and recurrence risk at any time point. Hence, it might be efficacious for dynamically monitoring the prognosis and therapeutic effects in cancer patients by detecting blood miRNA-200c during follow-up. What's more, in subgroup analyses based on different malignant diseases, we observed statistically significant outcomes in both the OS of the breast cancer subgroup and PFS/RFS/DFS of the breast cancer subgroup. Therefore, we suggested that high miRNA-200c expression might be a promising risk biomarker for poor prognosis in breast cancer.

These results suggested that miRNA-200c was a promising biomarker, to be used to predict cancer prognosis. However, there were still some limitations in our meta-analysis. Firstly, the number of studies included was not sufficient, which weakened the reliability of our results and led to the relative insufficiency of studies in subgroup analyses. The subgroups based on detected samples and tumor types were not fully elucidated due to the insufficient studies. Secondly, no independent study in Africans was included in the meta-analysis, which might hinder the comprehensive investigation of the relationship between miRNA-200c expression and cancer prognosis. What's more, only articles in English were included in our meta-analysis, which might lead to a possibility of language bias. Thirdly, cut-off values were different among these eligible studies; it was difficult for us to set up a baseline referring to high miRNA-200c expression. Thus, the pooled outcome could be higher or lower than the actual value, which might have caused a bias in the results. In addition, the heterogeneity existed in the total OS and PFS/RFS/DFS analyses. The source of heterogeneity was likely because of different characteristics of the patients, including race, age, pathological type, disease type, and cut-off value and so on. Moreover, as a cancer biomarker, detection of miR-200c in blood samples was faster, more convenient and more acceptable for patients to dynamically monitor their prognosis and therapeutic effects through their lifetime. Therefore, more studies were needed to evaluate further the prognostic role of miRNA-200c in various human malignant diseases.

Conclusions

In summary, this meta-analysis demonstrated that miRNA-200c over-expression could significantly predict poor prognostic outcomes in diverse human neoplasms, particularly in breast cancer and endometrial cancer. Moreover, further large-scale researches and clinical studies were needed to investigate the relationship between high miRNA-200c expression and the prognosis of cancer.

Competing Interests

The authors have declared that no competing interest exists.

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