

BMJ Open Prognostic role of microRNA-205 in multiple human malignant neoplasms: a meta-analysis of 17 studies

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ABSTRACT

Objective: MicroRNA-205 (miRNA-205) was revealed as an attractive prognostic tumour biomarker in recent studies. However, the results of different studies have been inconsistent. We conducted a meta-analysis to elucidate the precise predictive value of miRNA-205 in various human malignant neoplasms.

Design: Meta-analysis.

Data sources: Qualified studies were identified up to 5 June 2014 by performing online searches in PubMed, EMBASE and Web of Science, and additional quality evaluations.

Participants: Seventeen eligible studies with 4827 patients were ultimately enrolled in this meta-analysis.

Outcome measures: The heterogeneity between studies was assessed using I² statistics. Pooled HRs with 95% CIs for patient survival and disease recurrence were calculated to investigate the correlation between miRNA-205 expression and cancer prognosis.

Results: Our results indicate that elevated miRNA-205 was significantly associated with enhanced overall survival in the breast cancer subgroup (HR=0.78, 95% CI 0.67 to 0.91) and superior disease-free survival/recurrence-free survival in the adenocarcinoma subgroup (HR=0.68, 95% CI 0.49 to 0.94).

Conclusions: miRNA-205 is a promising biomarker for predicting the recurrence and progression of patients with adenocarcinomas or breast cancer. Owing to its complex roles, further relevant studies are warranted.

INTRODUCTION

MicroRNAs (miRNAs), which belong to a class of highly conserved and small non-coding RNAs, are approximately 22–25 nucleotides in length and abundant in animals, plants and even in viruses.^{1 2} Mature miRNAs negatively regulate target gene expression at the post-transcriptional level by binding to the 3'-untranslated complementary sequence of target mRNA. Thus, miRNAs play vital roles in various biological processes, such as the cell cycle, apoptosis, proliferation and differentiation.^{3–6} A newly identified

Strengths and limitations of this study

- This is the first meta-analysis reporting the prognostic value of microRNA-205 (miRNA-205) for cancers in the medical literature.
- A broad search strategy was used with few restrictions to minimise any potential publication bias.
- The retrospective nature of the data collection process increased the risk of selection bias in the studies.
- For subgroup analysis, elevated miRNA-205 was significantly associated with enhanced overall survival in the breast cancer subgroup and superior disease-free survival/recurrence-free survival in the adenocarcinoma subgroup.
- The major limitation of our analysis involves the inclusion of a relatively small number of studies on Asians, which might have decreased the applicability of our results across different ethnicities.

function for miRNAs has also been reported, namely, the regulation of gene expression at the transcriptional level.⁷ Therefore, miRNAs are considered to be diagnostic or prognostic biomarkers of carcinomas.^{8–10}

miRNA-205 is one of the most frequently studied miRNAs, exhibiting aberrant expression in multiple human malignancies compared with their normal counterparts. The majority of studies have demonstrated that miRNA-205 is a tumour suppressor.^{5 6 8 11–17} For instance, Markou *et al* reported that breast cancer cell lines express reduced miRNA-205 levels compared with non-malignant cells. The ectopic expression of miRNA-205 significantly inhibits cell proliferation, growth and invasion, whereas downregulated miRNA-205 expression is associated with reductions in disease-free survival (DFS) and overall survival (OS) during the early stages of breast cancer.⁶ miRNA-205 expression is also significantly reduced in glioma tissues compared with non-neoplastic brain tissues. In addition, multivariate analyses have demonstrated that miRNA-205 expression is

an independent prognostic indicator of OS in patients with glioma.⁸ However, certain studies have presented contradictory results, suggesting that miRNA-205 may function as an oncogene.^{18–23} Karaayvaz *et al* have confirmed that the expression of miRNA-205 is significantly increased in endometrial tumours compared with normal tissues. Kaplan-Meier survival curve analysis revealed the association of increased miRNA-205 expression with poor OS.²¹ Moreover, a dynamic change in the prognostic value of miRNA-205 expression was observed between preoperative and postoperative patients with lung carcinoma.²⁴

Although various studies have reported contradictory results, miRNA-205 is undeniably an attractive mediator of specific target genes that play important roles in tumour initiation and progression. However, given its complex roles, it remains unclear whether miRNA-205 acts as a tumour suppressor or an oncogene. Therefore, we conducted this systematic review using meta-analysis to shed light on the relationship between miRNA-205 expression and the prognosis of patients with carcinoma. We also discussed the possibility of utilising miRNA-205 as a prognostic marker in clinical applications.

METHODS

Search strategy

We searched online databases, including PubMed, EMBASE and Web of Science, to identify relevant literature published until 5 June 2014. For the literature retrieval, combinations of the keywords ‘microRNA-205’, ‘microna-205’, ‘miRNA-205’, ‘miRNA-205’, ‘cancer’, ‘carcinoma’, ‘neoplasm’, ‘tumour’, ‘tumor’, ‘overall survival’, ‘recurrence’ and ‘prognosis’ were utilised. The following criteria were used to select the published studies: (1) English publications; (2) a focus on patients with malignancies and (3) the association of miRNA-205 expression with cancer prognosis. In addition, we searched for studies published in Chinese to comprehensively understand the role of miRNA-205 in cancer.

However, no Chinese studies were available regarding the association of miRNA-205 expression with cancer prognosis.

Quality assessment

This meta-analysis was strictly performed according to the preferred reporting items of the systematic reviews and meta-analysis (PRISMA) statement.²⁵ The key points of the quality assessment included clear definitions of the following: (1) the study population and country of origin, (2) the type of carcinoma, (3) the study design, (4) the outcome assessment, (5) the detection of miRNA-205, (5) the miRNA-205 cut-off value and (6) a sufficient follow-up period. Studies were excluded when they did not meet all of the above criteria, to maintain the quality of the meta-analysis. Sensitivity analyses were also performed to avoid biases in the results due to certain low-quality studies (figures 1A, B). Moreover, we used the Cochrane Risk of Bias tool and graded each potential source of bias as a low, high or unclear risk (<http://www.cochrane-handbook.org>; figures 2 and 3). A flow diagram with details of the study selection process is presented in figure 4.

Data extraction

All eligible studies were identified by J-yZ and M-yS, and uncertain data were reassessed by JY. The extracted data elements included the following: (1) the first author’s name and year of publication; (2) the study population, nationality, ethnicity, type of disease, pathology and detected sample; (3) the detection method, cut-off definition and follow-up time; (4) HR associated with down-regulated miRNA-205 expression for OS, recurrence-free survival (RFS), and DFS along with their 95% CI and p values and (5) the median or mean age of the patients. If only Kaplan-Meier curves were available, data were extracted from graphical survival plots to extrapolate HRs with 95% CIs using previously described methods.^{26 27} All of the aforementioned data are comprehensively detailed in tables 1 and 2.

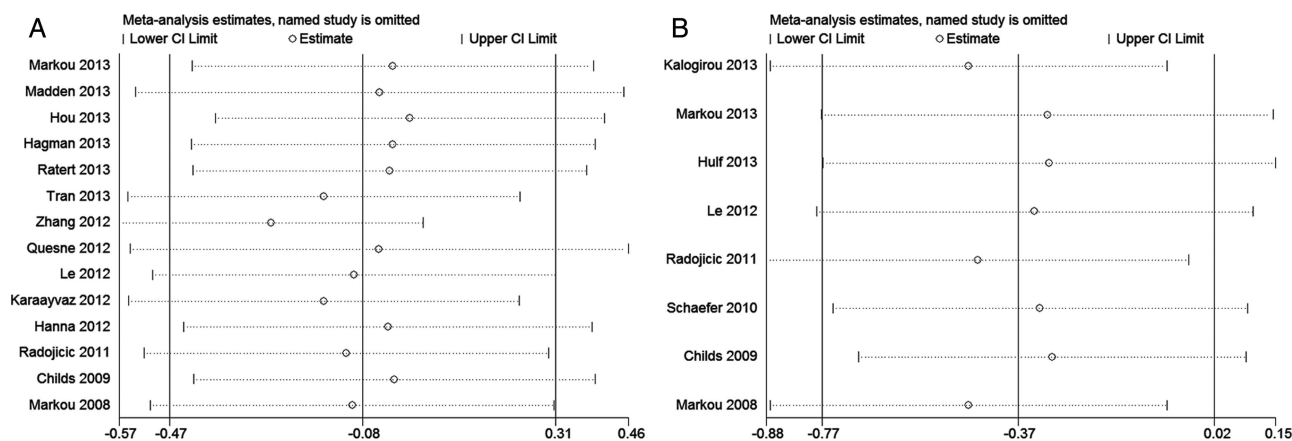


Figure 1 Sensitivity analysis of each included study. (A) Sensitivity analysis of overall survival for individual studies. (B) Sensitivity analysis of disease-free survival/relapse-free survival for individual studies.

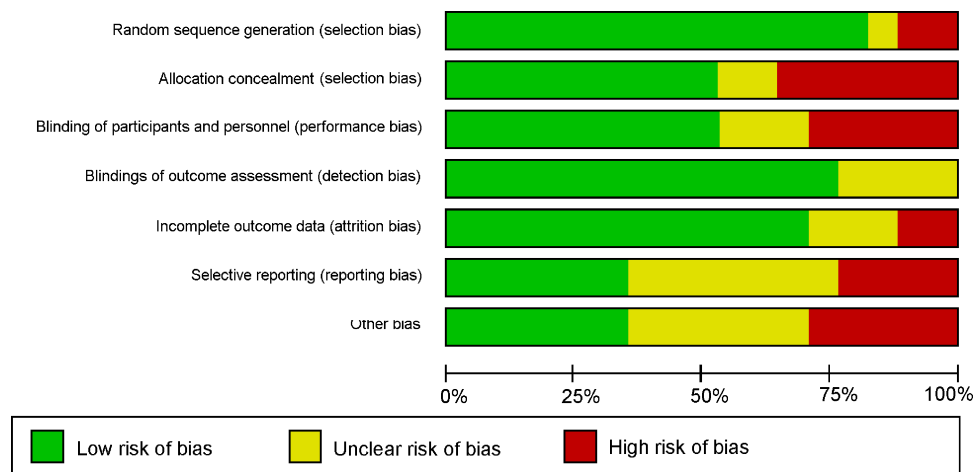


Figure 2 Risk of bias graph. Review authors' judgements for each risk of bias item are presented as percentages across all included studies.

Statistical analysis

The fixed-effects model (Mantel-Haenszel method) or the random-effects model (DerSimonian-Laird method) was

used for meta-analysis according to the heterogeneity among the pooled studies.²⁸ The heterogeneity test for pooled HRs was verified using the Cochran Q test and quantified using the Higgins I² statistic. If significant heterogeneity was observed ($p < 0.10$ or $I^2 > 50\%$), a random-effects model was applied; otherwise, the fixed-effects model was utilised. Moreover, we minimised the influence of heterogeneity by classifying the enrolled studies into subgroups based on similar characteristics. The publication bias was estimated using Egger's linear regression test with a funnel plot.²⁹ All p values were calculated using a two-sided test, and a p value of less than 0.05 was considered statistically significant. All statistical analyses were conducted with Stata12 (StataCorp LP, College Station, Texas, USA), Review Manager (RevMan) V.5.3 (Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and Microsoft Excel (V.2007, Microsoft Corporation, Redmond, Washington, USA).

RESULTS

Summary of enrolled studies

A total of 415 studies were collected from a primary literature survey using PubMed, EMBASE and Web of Science, and 346 records were excluded because they were review articles, letters, non-English articles, did not use human subjects, or were not relevant to the current analysis. Of the remaining studies under evaluation, 27 did not contain sufficient survival data (HRs and survival curves), 13 were not directly related to the specific outcomes, 7 did not use tumour tissues or blood samples, 4 did not report dichotomous outcomes for miRNA-205 expression and 1 had overlapping data sets. Finally, 17 studies were considered eligible for this meta-analysis^{5 6 8 11-24} (figure 4).

The main features of the 17 enrolled studies are systematically summarised in tables 1 and 2. Nine studies reported patient OS, three focused on RFS and five investigated OS as well as DFS. We collected data from these 17 studies, which included 4892 participants. Of these studies, 14 focused on Caucasians and 3 evaluated

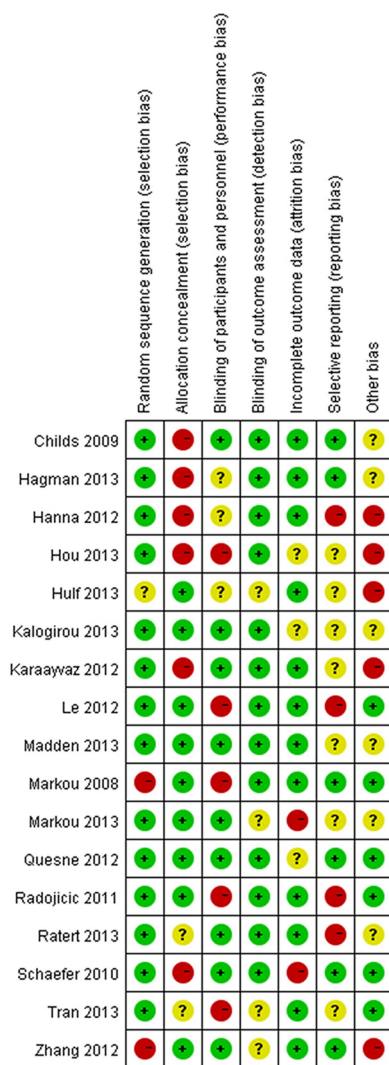


Figure 3 Risk of bias summary. Review authors' judgements for each risk of bias item for each included study.

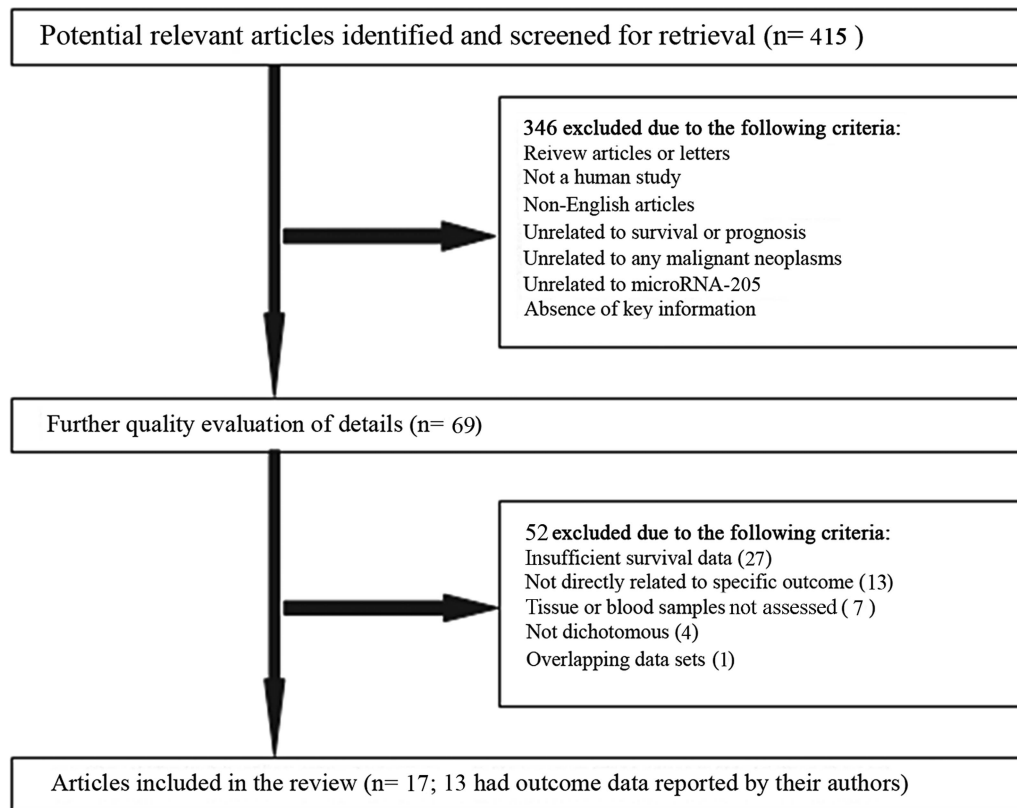


Figure 4 Flow diagram of the study selection process.

Asians. All of these studies were retrospective in design except for one, which was prospective. The malignant neoplasms assessed in these studies included breast cancer, bladder cancer, endometrial cancer, head and neck cancer, glioma, melanoma, non-small cell lung cancer and prostate cancer. Twelve studies focused on the pathological type of adenocarcinoma (adenoCA), two assessed squamous carcinoma (SqCa), two evaluated combined carcinomas (adenoCA and SqCa) and one focused on glioblastomas. Tissue samples were used to determine miRNA-205 expression in all studies except one, which detected expression in serum samples. Quantitative real-time PCR (qRT-PCR) was widely used in 14 studies to assess miRNA-205 expression, in situ hybridisation was performed in 2 studies and microarray analysis was conducted in 1 study.

OS associated with miRNA-205 expression

A total of 14 studies were used for OS analysis (table 3 and figure 5) with a random-effects model due to significant heterogeneity ($p < 0.001$, $I^2 = 76.8\%$). Our results failed to demonstrate any significant association between miRNA-205 expression and OS. Moreover, stratified analyses were performed using studies with the same characteristics (table 3, figures 5 and 6). However, only a pooled analysis of four studies in the breast cancer subgroup indicated that increased miRNA-205 expression was significantly correlated with enhanced OS (pooled HR=0.78, 95% CI 0.67 to 0.91), which was determined

using a fixed-effects model given the low heterogeneity among the studies ($p = 0.199$, $I^2 = 35.5\%$). No other subgroups exhibited any significant results as shown by stratified analyses.

Recurrence associated with miRNA-205 expression

A total of eight studies included in the DFS/RFS analysis revealed a protective role of increased miRNA-205 expression (pooled HR=0.69, 95% CI 0.46 to 1.03), as determined by a random-effects model ($p = 0.079$, $I^2 = 45.1\%$; table 3 and figure 5). In the stratified analyses, increased miRNA-205 expression was significantly associated with enhanced DFS/RFS in the adenoCA subgroup (pooled HR=0.68, 95% CI 0.49 to 0.94), as determined by a fixed-effects model ($p = 0.116$, $I^2 = 45.9\%$). However, no significant association was observed for any other subgroup (table 3, figures 5 and 6).

Sensitivity analyses

In the OS and DFS/RFS studies, our sensitivity analyses did not indicate alterations in the results due to the inclusion of any individual study (figure 1A,B), suggesting that no single study significantly influenced the pooled HR or the 95% CI.

Publication bias

The funnel plots of the publication bias are presented in figure 5C, D. In the pooled analyses of OS and DFS/RFS, the Egger's test p values were 0.720 and 0.581,

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

First author, publication year	Case nationality	Median or mean age	Dominant ethnicity	Study design	Malignant disease	Main type of pathology	Detected sample	Survival analysis	Source of HR	Maximum months of follow-up
Markou, 2013	Greece	60 ^{Median}	Caucasian	R	Breast cancer	AdenoCA	Tissue	OS/ DFS	Reported	140
Madden, 2013	Ireland	NM	Caucasian	R	Breast cancer	AdenoCA	Tissue	OS	Reported	175
Kalogirou, 2013	Germany	63 ^{Median}	Caucasian	R	Prostate cancer	AdenoCA	Tissue	bRFS	Reported	154
Hulf, 2013	Australia	61 ^{Median}	Caucasian	R	Prostate cancer	AdenoCA	Tissue	RFS	Reported	150
Hou, 2013	China	45 ^{Mean}	Asian	R	Human glioma	Glioblastomas	Tissue	OS	Reported	60
Hagman, 2013	Sweden	NM	Caucasian	R	Prostate cancer	AdenoCA	Tissue	OS	Reported	204
Ratert, 2013	Germany	NM	Caucasian	R	Bladder cancer	AdenoCA	Tissue	OS	SC	161
Tran, 2013	USA	NM	Caucasian	R	Bladder cancer	AdenoCA	Tissue	OS	SC	150
Zhang, 2012	China	60 ^{Mean}	Asian	R	NSCLC	SqCa	Tissue	OS	Reported	16.25
Quesne, 2012	UK	NM	Caucasian	R	Breast cancer	AdenoCA	Tissue	OS	Reported	120
Le, 2012	China	60 ^{Mean}	Asian	R	NSCLC	AdenoCA/SqCa	Serum	OS/DFS	Reported	30
Karaayvaz, 2012	USA	NM	Caucasian	R	Endometrial cancer	AdenoCA	Tissue	OS	Reported	150
Hanna, 2012	USA	63.43 ^{Mean}	Caucasian	R	Melanoma	AdenoCA	Tissue	OS	Reported	120
Radojicic, 2011	Greece	NM	Caucasian	R	Breast cancer	AdenoCA	Tissue	OS/DFS	SC	120
Schaefer, 2010	Germany	63 ^{Median}	Caucasian	R	Prostate cancer	AdenoCA	Tissue	RFS	Reported	93
Childs, 2009	USA	60 ^{Mean}	Caucasian	P	HNC	SqCa	Tissue	OS/DFS	Reported	60
Markou, 2008	Greece	60 ^{Median}	Caucasian	R	NSCLC	AdenoCA/SqCa	Tissue	OS/DFS	SC	50

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

AdenoCA, adenocarcinoma; bRFS, biochemical recurrence-free survival; DFS, disease-free survival; HNC, head and neck cancer; NM, not mentioned; NSCLC, non-small cell lung cancer; OS, overall survival; RFS, relapse-free survival; SC, survival curve; SqCa, squamous carcinoma.

Table 2 HRs and 95% CIs for patient survival or disease progression in association with miRNA-205 expression in enrolled studies

First author, publication year	Main assay method	Cut-off value	Case number		OS		DFS/RFS/bRFS	
			High expression	Low expression	HR (95% CI)	p Value	HR (95% CI)	p Value
Markou, 2013	qRT-PCR	Mean	47	57	0.41 (0.18 to 0.94) ^M	0.036	0.50 (0.26 to 0.93) ^M	0.030
Madden, 2013	Microarray	NM	291	290	0.77 (0.61 to 0.97) ^U	0.025	NM	NM
Kalogirou, 2013	qRT-PCR	Median	59	19	NM	NM	1.32 (0.62 to 2.86) ^M	0.472
Hulf, 2013	qRT-PCR	Median	106	43	NM	NM	0.50 (0.28 to 0.90) ^M	0.020
Hou, 2013	qRT-PCR	Median	41	61	0.24 (0.11 to 0.56) ^M	0.001	NM	NM
Hagman, 2013	qRT-PCR	Median	NM	NM	0.43 (0.20 to 0.90) ^U	0.030	NM	NM
Ratert, 2013	qRT-PCR	Median	25	15	0.28 (0.07 to 1.11) ^{U*}	0.070	NM	NM
Tran, 2013	qRT-PCR	Mean	49	49	2.08 (1.25 to 3.57) ^{U*}	0.005	NM	NM
Zhang, 2012	qRT-PCR	Mean	NM	NM	42.33 (1.51 to 148.52) ^U	<0.001	NM	NM
Quesne, 2012	LNA-ISH	NM	NM	NM	0.79 (0.64 to 0.97) ^U	0.020	NM	NM
Le, 2012	qRT-PCR	Mean	21	21	1.23 (0.45 to 3.37) ^U	0.689	0.50 (0.18 to 1.35) ^U	0.169
Karaayvaz, 2012	qRT-PCR	Mean	24	15	2.65 (1.11 to 6.25) ^M	0.028	NM	NM
Hanna, 2012	qISH	Mean	113	93	0.51 (0.26 to 0.997) ^M	0.049	NM	NM
Radojicic, 2011	qRT-PCR	Median	38	49	1.45 (0.65 to 3.23) ^{U*}	0.361	1.16 (0.52 to 2.56) ^{U*}	0.721
Schaefer, 2010	qRT-PCR	Median	NM	NM	NM	NM	0.37 (0.10 to 1.40) ^M	0.457
Childs, 2009	RT-PCR	Mean	NM	NM	0.40 (0.18 to 0.88) ^M	0.025	0.24 (0.06 to 0.99) ^M	0.049
Markou, 2008	qRT-PCR	2.00	31	17	1.27 (0.52 to 3.13) ^{U*}	0.610	1.32 (0.62 to 2.86) ^{U*}	0.476

The source of HR and 95% CI is described as derived from univariate analysis (U) or multivariate analysis (M).

*HR and 95% CI calculated from survival curves.

bRFS, biochemical recurrence-free survival; DFS, disease-free survival; HR, HR (high vs low); LNA-ISH, locked nucleic acid probe in situ hybridisation; NM, not mentioned; OS, overall survival; qISH, quantitative in situ hybridisation; qRT-PCR, quantitative real-time PCR; RFS, relapse-free survival.

Table 3 Pooled HRs, 95% CIs, and p values for OS or DFS/RFS stratified by ethnicity and main pathological type for overall and subgroup analyses

Subgroup	OS			DFS/RFS		
	N	pHR (95% CI)	p Value	N	pHR (95% CI)	p Value
Total	14	0.82 (0.59 to 1.15)*	0.255	8	0.69 (0.46 to 1.03)*	0.067
Ethnic subtotal						
Caucasian	11	0.82 (0.60 to 1.12)*	0.214	7	0.71 (0.46 to 1.11)*	0.133
Asian	3	1.76 (0.20 to 15.74)*	0.611	1	–	–
Disease subtotal						
Breast cancer	4	0.78 (0.67 to 0.91)†	0.001	2	0.74 (0.32 to 1.67)*	0.463
Bladder cancer	2	0.85 (0.12 to 5.99)*	0.869	–	–	–
NSCLC	3	2.70 (0.62 to 11.79)*	0.186	2	0.86 (0.34 to 2.21)*	0.756
Prostate cancer	1	–	–	3	0.67 (0.32 to 1.41)*	0.287
Pathological type subtotal						
AdenoCA	9	0.85 (0.60 to 1.19)*	0.333	5	0.68 (0.49 to 0.94)†	0.020
SqCa	2	3.62 (0.04 to 346.07)*	0.581	1	–	–
Detected sample subtotal						
Tissue	13	0.80 (0.56 to 1.14)*	0.221	7	0.71 (0.46 to 1.11)*	0.133
Serum	1	–	–	1	–	–

*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 0.1 or I^2 was greater than 50%.

†The HRs and 95% CIs of the enrolled studies were pooled using the fixed-effects model.

AdenoCA, adenocarcinoma; DFS, disease-free survival; N, number of studies; NSCLC, non-small cell lung cancer; OS, overall survival; pHR, pooled HR; RFS, relapse-free survival; SqCa, squamous carcinoma.

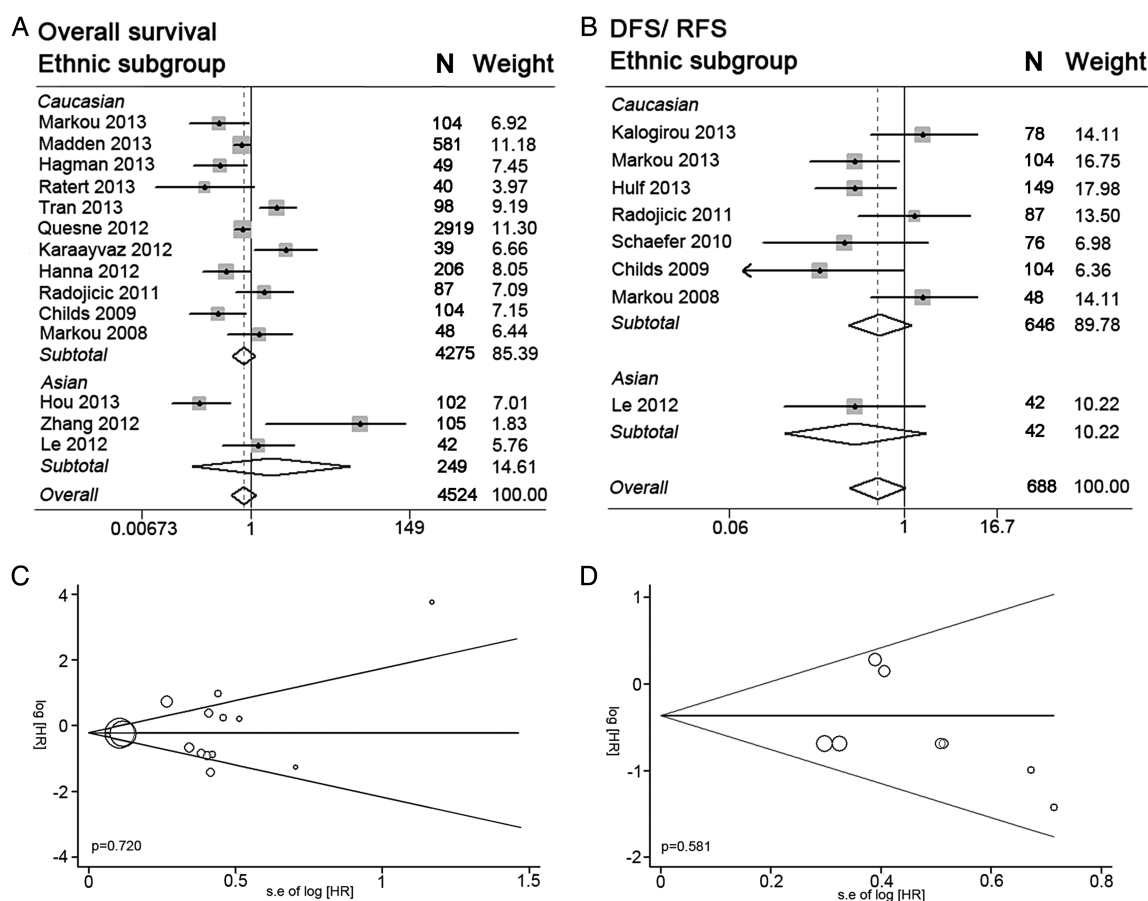


Figure 5 Forest plots of merged analyses of overall survival (OS) or DFS, disease-free survival (DFS)/relapse-free survival (RFS) in association with microRNA-205 expression and Begg's funnel plots of the publication bias. (A) Forest plots of overall and ethnic subgroup analyses of OS. Squares and horizontal lines represent study-specific HRs and 95% CIs, respectively. The areas of the squares correspond to weights, and the diamonds represent the overall HRs and 95% CIs. (B) Forest plots of overall and ethnic subgroup analyses of DFS/RFS. (C) Begg's funnel plots of the publication bias for overall merged analysis of OS. Each point represents a separate study. (D) Begg's funnel plots of the publication bias for the overall merged analysis of DFS/RFS.

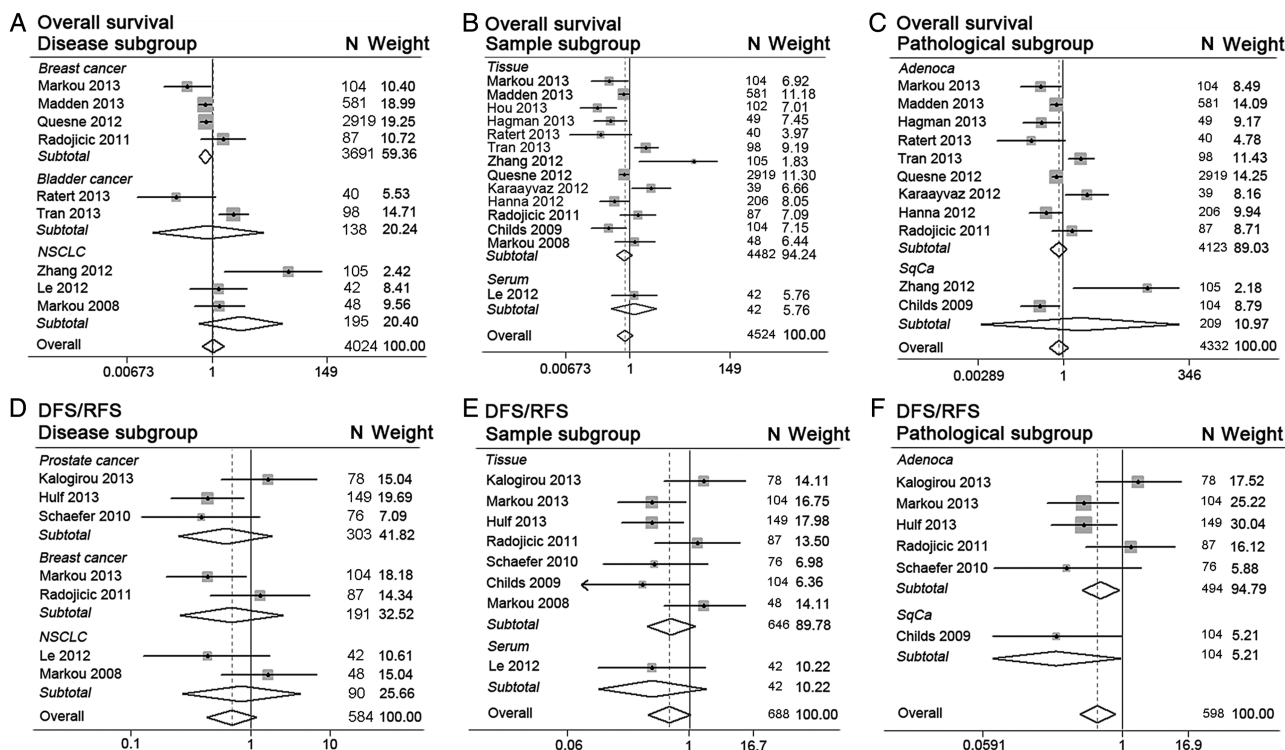


Figure 6 Forest plots of merged analyses of OS or DFS/RFS in association with miRNA-205 expression for the different subgroups. (A) Forest plots of the merged analyses of OS in the different disease subgroups. Squares and horizontal lines correspond to the study-specific HRs and 95% CIs, respectively. The areas of the squares represent the weight, whereas the diamonds represent the summary HRs and 95% CIs. (B) Forest plots of the merged analyses of OS for the different disease subgroups. (C) Forest plots of the merged analyses of OS for the different sample subgroups. (D) Forest plots of the merged analyses of DFS/RFS for the different disease subgroups. (E) Forest plots of the merged analyses of DFS/RFS for the different sample subgroups. (F) Forest plots of the merged analyses of DFS/RFS for the different pathological subgroups. Adenoca, adenocarcinoma; SqCa, squamous carcinoma; DFS, disease-free survival; RFS, relapse-free survival; NSCLC, non-small cell lung cancer; miRNA-205, microRNA-205; OS, overall survival.

respectively, as shown by symmetric funnel plots. Therefore, no evidence of publication bias was noted.

DISCUSSION

To identify prognostic biomarkers for patients with carcinoma, elaborate efforts have been invested in establishing reliable and convincing evidence. In the last decade, miRNAs have been considered to be potential biomarkers of cancer prognosis given their unique expression profiles in the tissues or serum of patients with cancer compared with normal individuals. MicroRNAs are more stably expressed than mRNAs and can be easily assessed by qRT-PCR.³⁰ Recently, a number of miRNAs, acting as tumour-suppressors or oncogenes, have been shown to play important roles in tumorigenesis and cancer progression.^{31–33} Among them, miRNA-205 is considered to be important given its significant difference in expression between cancer and normal tissues.

This meta-analysis is the first systematic evaluation of the association between elevated miRNA-205 expression and the prognosis of patients with various cancers. The association of miRNA-205 expression with tumour prognosis may be partially attributed to its biological function.

Recent studies have reported that miRNA-205 is frequently deregulated in multiple tumour entities and involved in various crucial pathways, such as cell proliferation, apoptosis and angiogenesis, by mediating the expression of multiple oncogenes (figure 7). Hanna *et al*¹⁵ confirmed that miRNA-205 overexpression suppresses cell growth in vivo, induces cell senescence and reduces cell proliferation by downregulating adenovirus E2 promoter-binding transcription factor 1 (E2F1) in patients with melanoma. MicroRNA-205 also specifically activates the tumour suppressor genes IL24 and IL32 by targeting specific sites in their promoters⁷ and participates in the epithelial-mesenchymal transition by regulating zinc finger E-box-binding proteins (ZEB1/ZEB2).²⁰

Our OS analysis revealed a pooled HR of 0.82, demonstrating that increased miRNA-205 expression is associated with a favourable outcome; however, this result was not significant ($p=0.225$). On the contrary, the pooled outcome in the DFS/RFS analysis indicated that increased miRNA-205 expression is predictive of a better prognosis, with an HR value of 0.69, but this association was also statistically insignificant ($P=0.067$). Insignificant pooled outcomes may imply that the role of miRNA-205 in human tumours is complex and controversial. The

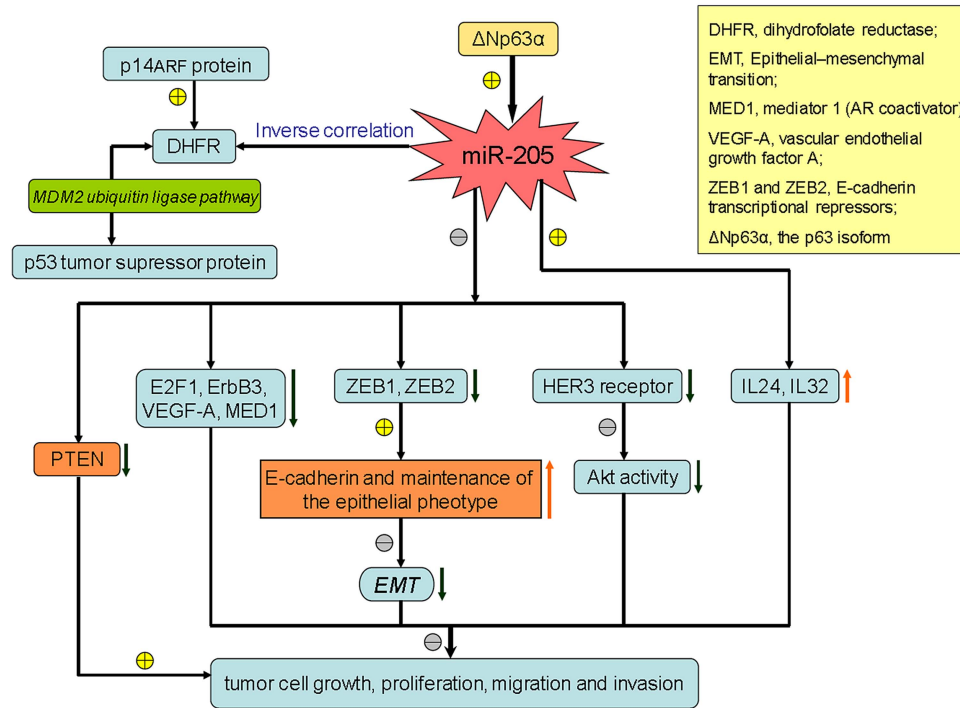


Figure 7 The complex roles of miRNA-205 in tumour growth, migration and invasion (miRNA-205, microRNA-205; PTEN, phosphatase and a tensin homolog on chromosome 10).

majority of studies have suggested that miRNA-205 is an important tumour suppressor. However, its oncogenic role has also been confirmed, which involves the inhibition of tumour suppressors, such as phosphatase and a tensin homolog on chromosome 10 (PTEN). Karaayvaz *et al*²¹ indicated that miRNA-205 and PTEN expression levels are inversely correlated in patients with endometrial cancer, implying a significant inhibitory mechanism of miRNA-205 in mediating PTEN expression.

Furthermore, in subgroup analyses based on the characteristics of the individual studies, we observed statistically significant outcomes in the OS of the breast cancer subgroup and the DFS/RFS of the adenoCA subgroup, with pooled HRs of 0.78 and 0.68, respectively. Iroio *et al* described miRNA-205 as a new oncosuppressive gene in breast cancer, which interferes with the proliferative pathway mediated by the human epidermal growth factor receptor (HER) family. This group also provided experimental evidence suggesting that miRNA-205 improves a patient's response to specific anticancer therapies.³³ These findings suggest that the detection of miRNA-205 expression in patients with breast cancer and adenoCA may be useful for prognosis prediction.

However, our conclusions should be considered with caution for the following five reasons. First, the power of the pooled HRs was not sufficiently strong even though our results indicate that miRNA-205 expression is significantly associated with the prognoses of breast cancer and adenoCA. Second, the statistical power of the association result of miRNA-205 with adenoCA was reduced as a result of five studies that were included in the DFS/RFS

meta-analysis with a relatively small sample size of 494 patients. Moreover, three studies in the adenoCA subgroup exhibited statistically insignificant outcomes. Third, the lack of global miRNA-205 expression data makes it difficult to define a standard cut-off. Most of the current studies have established a median or mean value as the expression cut-off, and these values have varied. Therefore, the pooled outcome may be higher or lower than the actual value, which may have caused a bias in the results of the effectiveness of miRNA-205 as a prognostic factor. Fourth, heterogeneity existed in the total OS and DFS/RFS analyses. The heterogeneity of the population was likely due to the different characteristics of the patients, such as age, race, disease type and pathological type, as well as the cut-off value of miRNA-205 expression. For instance, when we stratified the OS studies according to disease type, the heterogeneity disappeared in the breast cancer subgroup ($p=0.199$, $I^2=35.5\%$). The heterogeneity was also reduced in the adenoCA subgroup when the DFS/RFS studies were classified by pathological type ($p=0.116$, $I^2=45.9\%$). Fifth, although miRNA-205 is considered an independent risk factor for carcinomas,^{5 8 12} recent studies have used a linear combination of several miRNAs rather than a unique miRNA to increase predictive power. Shiyama *et al*³⁴ demonstrated that the combined assessment of miRNA-9, miRNA-145, miRNA-150, miRNA-155 and miRNA-205 was more sensitive than the assessment of any of these miRNAs individually for distinguishing patients with metastatic melanoma from patients with non-metastatic melanoma. Therefore, relevant studies are required to address the aforementioned problems before

miRNA-205 may be used as a prognostic biomarker in clinical applications.

CONCLUSIONS

In summary, our findings suggest that miRNA-205 is a potential biomarker and that the detection of its expression in patients with breast cancer may allow for accurate prognostic predictions. Moreover, further investigation of the relationship between miRNA-205 expression and cancer prognosis is required to enable its future clinical application.

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Contributors JY and J-yZ conceived and designed the study. M-yS and N-hS collected the data. J-yZ, Z-ID and C-yX performed statistical analyses. J-yZ, M-yS and JY drafted the manuscript. J-yZ and C-yX revised the manuscript. All authors have read and approved the final version.

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