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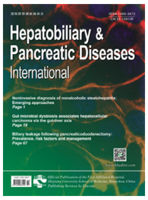

Meta-analysis

Low microRNA-139 expression associates with poor prognosis in patients with tumors: A meta-analysis

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ABSTRACT

Background: microRNA-139 (miR-139) is dysregulated in various types of tumors and plays a key role in carcinogenesis. miR-139 may be used as a diagnostic and prognostic biomarker of cancers. However, the data from the literature are not consistent. The present study aimed to verify the prognostic and diagnostic values of miR-139 in solid tumors.

Data sources: PubMed, Web of Science and Embase databases were searched and publications from January 2011 to August 2017 were included. We used Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) database to further validate this meta-analysis.

Results: Eight individual studies from seven articles were included. Pooled analyses showed that low miR-139 expression was related to worse overall survival (OS) [hazard ratio (HR) = 2.27; 95% confidence intervals (CI): 1.74–2.95; $P < 0.001$] in solid tumors, including hepatocellular carcinoma (HCC) and glioblastoma multiforme (GBM), consisting with the results of TCGA. However, our results of CRC showed that low miR-139 expression was associated with poor OS which was contradictory with the results in TCGA database and need larger samples to validate the phenomenon; whereas for CRC patients, high miR-139 expression predicted poor RFS, which was in good accordance with TCGA results. The results of 27 microarrays from GEO database showed that miR-139 expression levels were lower in tumor tissues compared to adjacent non-tumor tissues or healthy tissues. Decreased miR-139 expression was also significantly correlated with poor differentiation grade (OR = 3.57; 95% CI: 1.44–8.85; $P = 0.006$). However, the combined data indicated that no associations between miR-139 expression and the following parameters such as age (pooled OR = 1.50; 95% CI: 0.69–3.24; $P = 0.304$), gender (pooled OR = 0.92; 95% CI: 0.56–1.51; $P = 0.738$), tumor size (pooled OR = 1.51; 95% CI: 0.69–3.31; $P = 0.298$), late tumor-node-metastasis stage (pooled OR = 1.63; 95% CI: 0.99–2.68; $P = 0.057$) and lymph-node-metastasis (pooled OR = 0.66; 95% CI: 0.34–1.28; $P = 0.222$).

Conclusions: Low miR-139 expression was related to poor prognosis in HCC and GBM, which could be regarded as a potential prognostic biomarker. However, its precise functional role in CRC still need to be further investigated through larger samples and multicenter studies.

Introduction

Cancer is the leading cause of death in China and second leading cause of death in developed countries [1,2]. Statistics showed that in 2015 there were around 4 292 000 new cancer cases and 2 814 000 cancer-related deaths in China [3]. The carcinogenesis remains unclear and the complicated process of carcinogenesis makes the diagnosis very difficult. As early diagnosis plays a crucial role in the management, identifying novel diagnostic markers which help diagnose tumor in early stage is of great significance.

microRNAs (miRNAs), approximately 21-nucleotide in length, are involved in various biological processes, such as cellular growth, differentiation, proliferation, metastasis and migration [4,5]. Recently, there is a growing body of literature that recognizes the importance of miRNAs in the initiation and progression of human cancers. Some of them, such as let-7 [6],

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miR-143 [7,8], and miR-200 [9], are tumor suppressors, others, such as miR-21 [10], miR-155 [11], and miR-95 [12], are oncogenic.

Emerging evidence has shown that miR-139 is markedly downregulated in a variety of tumors and foreboded an unfavorable prognosis, such as hepatocellular carcinoma (HCC) [13], gastric and metastatic breast cancers [14,15], colorectal cancer (CRC) [16,17] or glioma [18] and so on. Nevertheless, the clinical and prognostic value of miR-139 is still inconclusive in human tumors [19]. The present meta-analysis is to investigate the prognostic value of miR-139 expression in various tumors. Our sources are from all relevant publications, the Gene Expression Omnibus (GEO) and the Cancer Genome Atlas (TCGA) databases.

Methods

The collection of data from the TCGA and GEO database

Thirty human solid cancers accompanying available miR-139 expression level and clinicopathological parameters were extracted from the Univeristy of California Santa Cruz (UCSC) Cancer Genomics Browser of TCGA (https://genome-cancer.soe.ucsc.edu/) and were used to evaluate the correlation of miR-139 expression with overall survival (OS) and/or recurrence-free survival (RFS). The 30 types of cancers are adrenocortical carcinoma, bladder carcinoma, breast cancer, cervical carcinoma, cholangiocarcinoma, colorectal carcinoma, lymphoid neoplasma, esophageal carcinoma, head and neck cancer, kidney chromophobe, renal clear cell carcinoma, lung adenocarcinoma, hepatocellular carcinoma, lower grade glioma, renal papillary cell carcinoma, lung squamous carcinoma, mesothelioma, ovarian carcinoma, pancreatic adenocarcinoma, pheochromocytoma, glioblastoma multiforme, rectum adenocarcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, testicular germ cell tumor, thyroid carcinoma, thymoma, uterine carcinosarcoma, and uveal melanoma.

In total, 27 miRNA datasets (6 for HCC, 5 for GBM and 16 for CRC) that have accompanying scientific publications were assembled via GEO of the National Center for Biotechnology Information (NCBI). The BRB-array tools were used to directly determine the miR-139 expression between healthy or adjacent tissue control samples and tumor samples in each dataset.

Search strategy for meta-analysis

For obtaining potentially eligible studies, the PubMed, Web of Science and Embase databases were used to acquire relevant literatures from January 2011 to August 2017. The searching key words were: “miR-139, human”, “hsa-miR-139”, “microRNA-139, human”, “miR-139-5p, human”, “microRNA-139-3p, human”, “neoplasia or malignancy”, “tumor or cancer or carcinoma”, and “prognosis or prognostic or survival”. Studies reporting hazard ratio (HR) for OS, RFS and/or disease free survival (DFS) were included.

Criteria of inclusion and exclusion

Inclusion criteria: (1) studies containing patients with one of the 30 types of tumor; (2) studies measured the expression of miR-139 in cancer tissues; (3) studies evaluated the relationship between miR-139 expression and survival outcomes; (4) studies provided sufficient data to extract or estimate the HR and 95% confidence intervals (CI); (5) full-text articles in English.

Exclusion criteria: (1) studies on animal experiments, case reports, reviews, conference abstracts, or letters without original data; (2) studies with duplicate or overlapping data; (3) the sample size of studies less than or equal to 30; (4) studies without adequate data for HRs and 95% CIs.

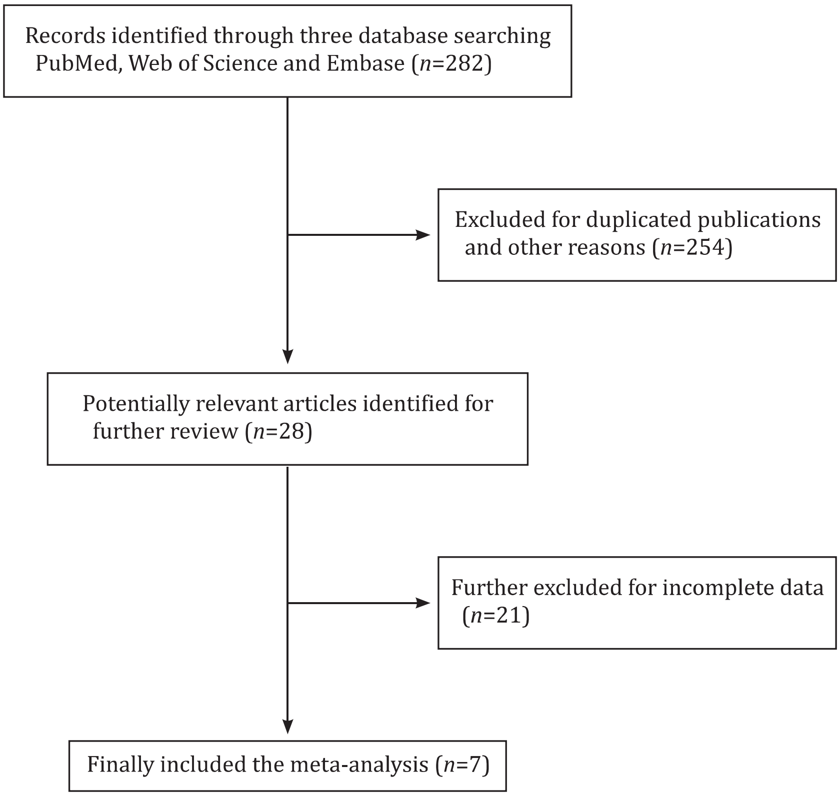

Fig. 1. Flow diagram of study selection in the meta-analysis.

Table 1
Characteristics of the eligible studies in meta-analysis.

Studies	Year	Country	Age (yr, mean)	No of patients	Sex (M/F)	Tumor type	Tumor stage	Detection method	Survival analysis	Outcomes	Follow-up (mon, median)
Wong et al. [15]	2011	China	NR	63	51/12	HCC	I-IV	qRT-PCR	Kaplan-Meier	OS	60
Song et al. [16]	2014	China	58	158	NR	CRC	I-IV	qRT-PCR, IHC	Kaplan-Meier	OS	100
Liu et al. [17]	2014	China	65	63	33/30	CRC	I-IV	qRT-PCR	Kaplan-Meier	OS	80
Wang et al. [28]	2016	China	55	79	52/27	HCC	NR	qRT-PCR	Kaplan-Meier	OS	60
Miyoshi et al. [29]	2017	USA	67 66	250	43/68 56/83	CRC	I-III	qRT-PCR	Kaplan-Meier	RFS	120
Guo et al. [30]	2012	China	NR	64	NR	CRC	NR	qRT-PCR	Kaplan-Meier	OS	100
Yue et al. [31]	2015	China	NR	92	NR	GBM	NR	qRT-PCR	Kaplan-Meier	OS	50

qRT-PCR: quantitative real time PCR; OS: overall survival; RFS: recurrence-free survival; NR: not report; HCC: hepatocellular carcinoma; CRC: colorectal cancer; GBM: glioblastoma multiforme.

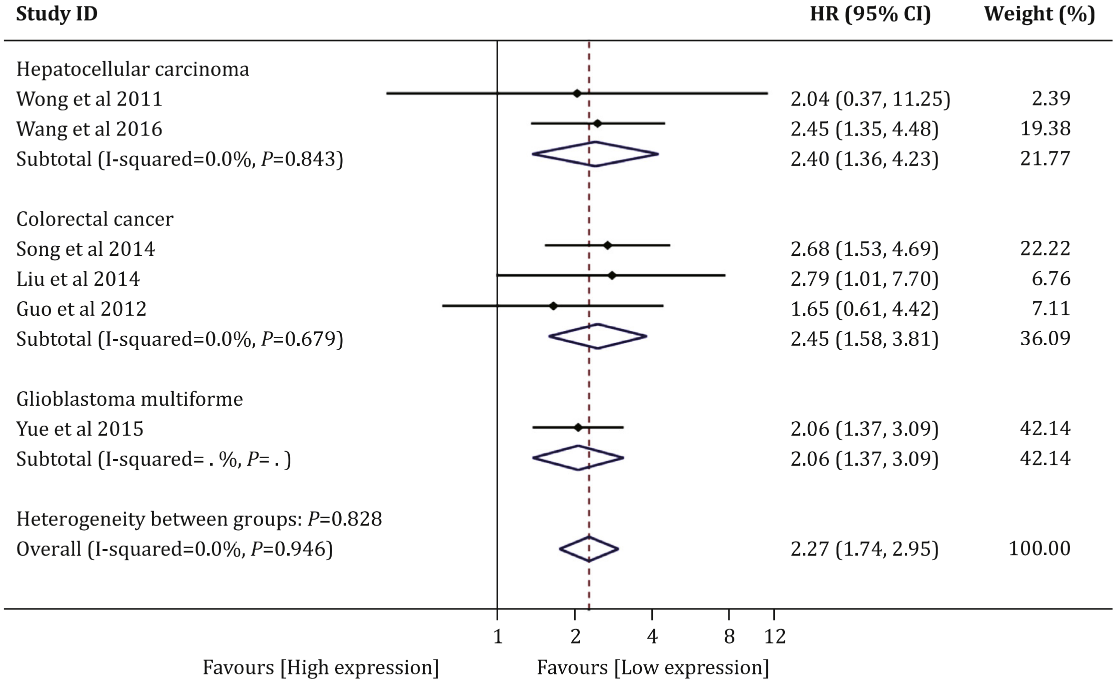

Fig. 2. Forest plot for the relationship between miR-139 expression and overall survival. HR: harzard ratio; CI: confidence interval.

Data extraction

The following information from the reports were extracted: first author's name, publication year, country, tumor type, sample size, follow-up time, miR-139 assessment methods, TNM stage, HRs and corresponding 95% CI of OS or RFS.

Statistical analysis

Patients were classified into two groups of higher and lower miR-139 expression by using X-tile, a novel tool for (a) the evaluation of biological relationships between a biomarker and outcome; and (b) the discovery of population cut-points based on marker expression [20]. The survival curves were examined using the Kaplan-Meier method and log-rank test.

Meta-analysis was carried out adhering to the PRISMA statement [21]. HRs and corresponding 95% CIs were pooled in meta-analyses using Stata software [22]. Engauge Digitizer version 4.1 was used to collect data from Kaplan-Meier survival curves. Evidence of heterogeneity among studies was assessed using I^2 statistics. When $I^2 > 50\%$ or $P < 0.05$ was regarded as obvious heterogeneity and a random effect model would be performed for HRs and 95% CIs [23]. Otherwise, a fixed effect model would be used [24]. The value of pooled HRs was more than 1 with $P < 0.05$ representing poor prognosis of decreased miR-139 expression. The consistency of pooled outcomes was examined by sensitivity analysis [25]. The bias of publications was conducted via funnel plots with Egger's test and Begg's test [26,27]. A $P < 0.05$ was considered statistically significant.

Results

Characteristics of publications in this meta-analysis

A sum of 282 potentially relevant studies was collected from PubMed, Web of Science and Embase after an initial electronic search on the basis of title and abstract. The detailed process of literature selection was shown in Fig. 1. After animal experiments, case reports, reviews, conference abstracts, or letters and duplicate records were removed, 28 studies remained. Twenty-one of them were excluded due to incomplete data. Among the remaining 7 articles, one study analyzed two distinct cohorts. Ultimately, eight individual studies from 7 articles containing 769 patients were enrolled. The main characteristics of these studies are listed in Table 1. Of the 7 eligible articles, three types of cancers were included in our study including, HCC [3,28], CRC [16,17,29,30], and

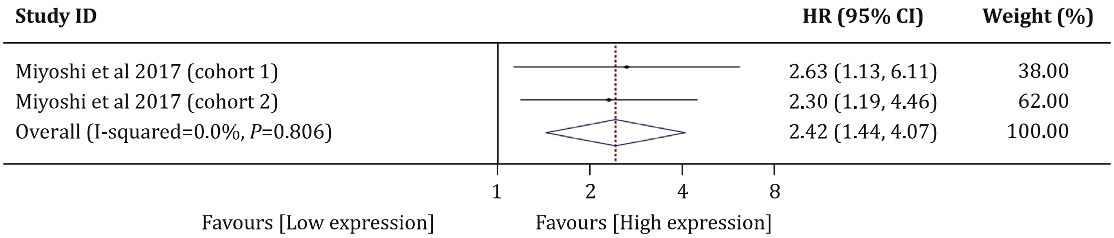

Fig. 3. Forest plot for the relationship between miR-139 expression and recurrence-free survival in CRC. HR: harzard ratio; CI: confidence interval; CRC: colorectal cancer.

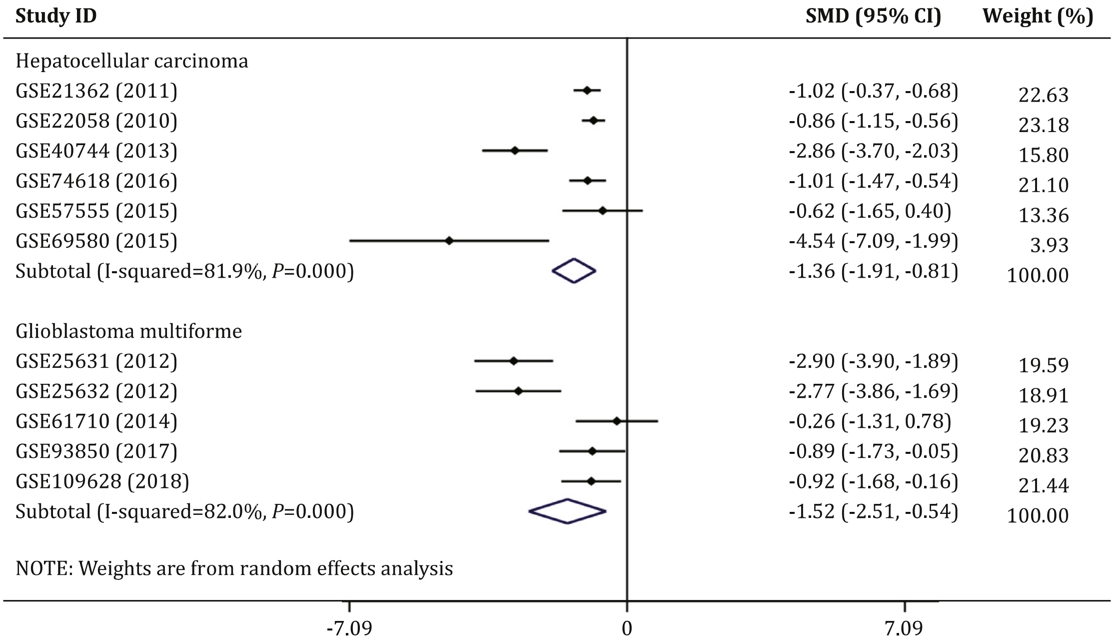

Fig. 4. Forest plot evaluating differences in miR-139 expression between HCC or GBM tissues and adjacent non-tumor samples or healthy tissues, respectively. HCC: hepatocellular carcinoma; GBM: glioblastoma multiforme; SMD: standard mean difference; CI: confidence interval.

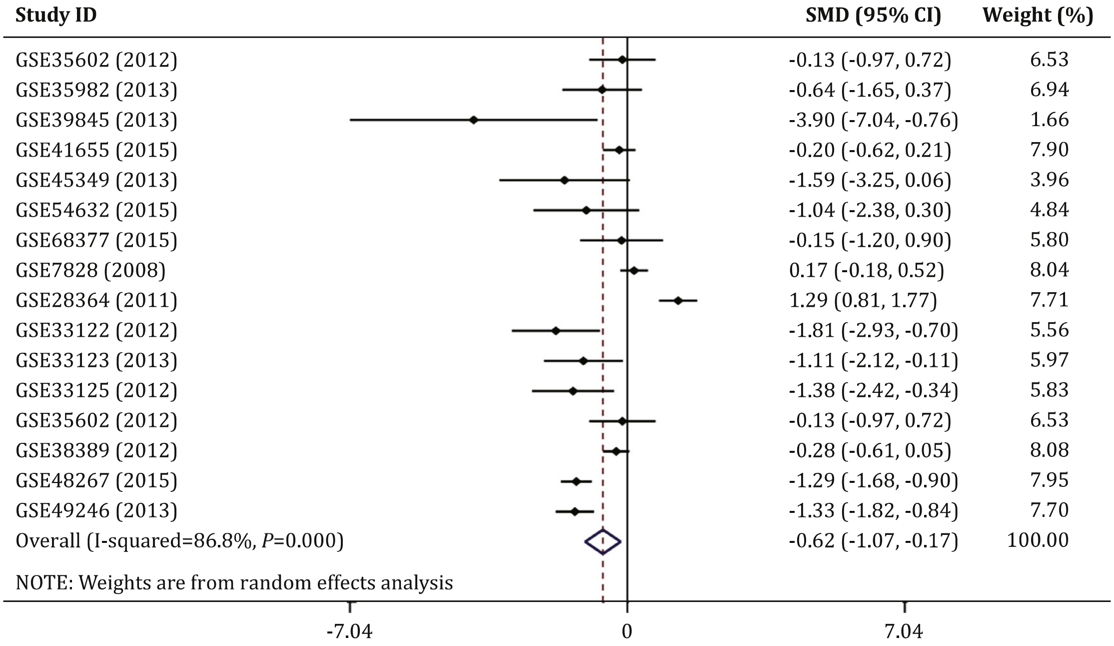

Fig. 5. Forest plot evaluating differences in miR-139 expression between CRC tissues and adjacent non-tumor samples or healthy tissues. CRC: colorectal cancer; SMD: standard mean difference; CI: confidence interval.

GBM [31]. In all of studies, quantitative reverse transcription PCR (qRT-PCR) was used for miR-139 expression assay. Additionally, six studies reported data on OS and one provided data on RFS (Table 1). HRs and 95% CI were extracted from 3 studies immediately [16,17,29] and were calculated with survival curves from the others.

Relationship between miR-139 expression and OS/RFS

There are six studies reported the correlation between miR-139 and OS, including 519 patients. Owing to no significant heterogeneity in these studies ($I^2 = 0$, $P = 0.946$), meta-analysis of fixed-effect model was applied and the results of pooled HR and

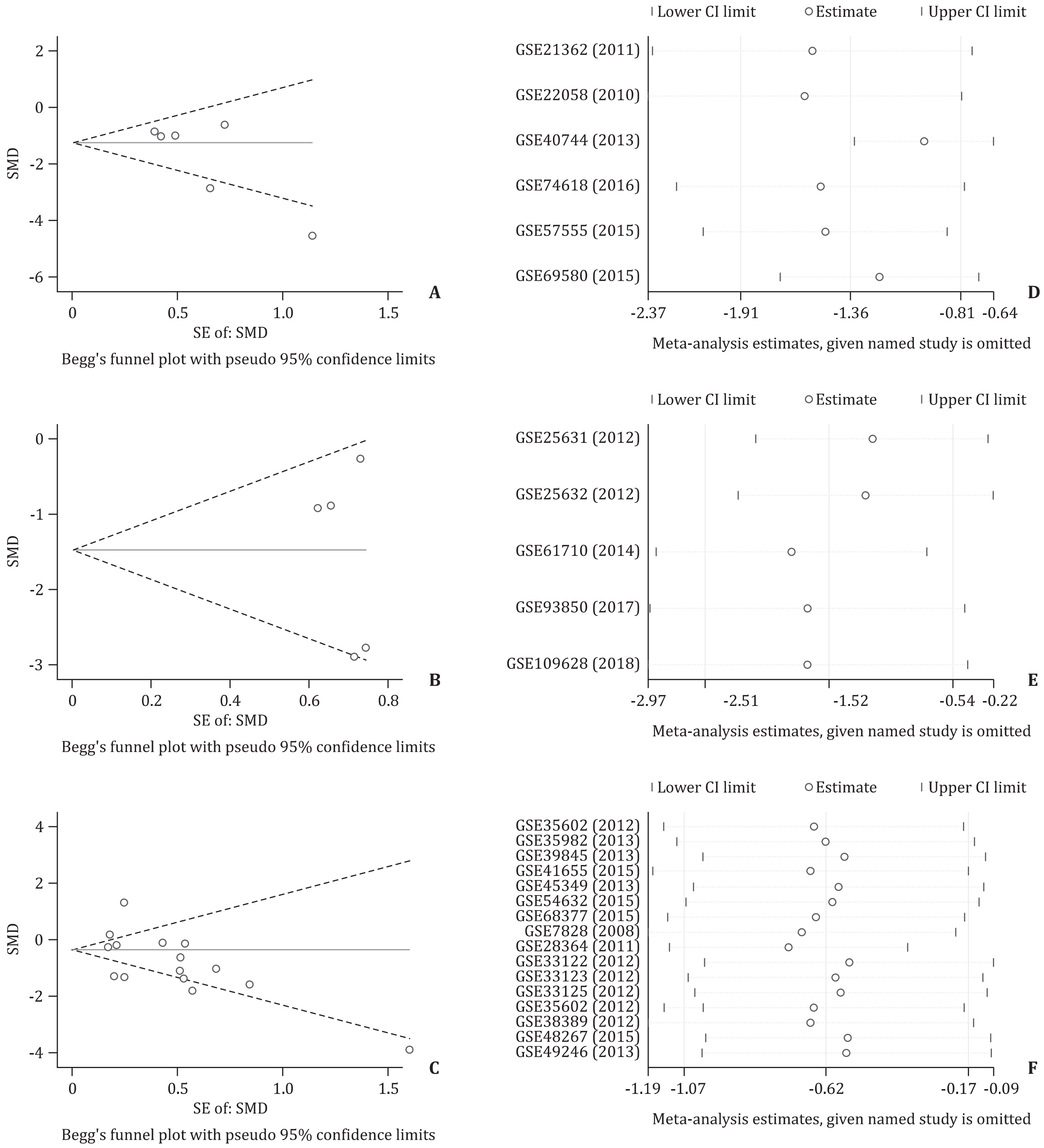

Fig. 6. Funnel plot for the publication bias test of GEO microarrays on HCC (**A**), GBM (**B**) and CRC (**C**). Each point represents a single microarray. Sensitivity analysis of HRs on HCC (**D**), GBM (**E**) and CRC (**F**). The results were calculated by omitting each microarray in turn. SMD: standard mean difference; GEO: Gene Expression Omnibus; HCC: hepatocellular carcinoma; GBM: glioblastoma multiforme; CRC: colorectal cancer; HR: hazard ratio; CI: confidence interval.

Table 2
Meta-analysis results on the association of decreased miR-139 expression with clinicopathological parameters.

Clinicopathological parameter	No. of patients	No. of studies	OR (95% CI)	*P* value	Heterogeneity		Effect model
					I^2	*P* value	
Age (> median vs. ≤ median)	392	4	1.50 (0.69–3.24)	0.304	97.2%	<**0.001**	Random
Sex (male vs. female)	455	5	0.92 (0.56–1.51)	0.738	79.4%	**0.001**	Random
Tumor size (> median vs. ≤ median)	126	2	1.51 (0.69–3.31)	0.298	0	0.948	Fixed
TNM stage (advanced vs. early)	376	4	1.63 (0.99–2.68)	0.057	68.9%	**0.022**	Random
Differentiation stage (poor vs. well/moderate)	126	2	3.57 (1.44–8.85)	**0.006**	42.6%	0.187	Fixed
Lymph node metastasis (yes vs. no)	313	3	0.66 (0.34–1.28)	0.222	50.8%	0.131	Random

TNM: tumor-node-metastasis; OR: odd ratio; CI: confidence interval.

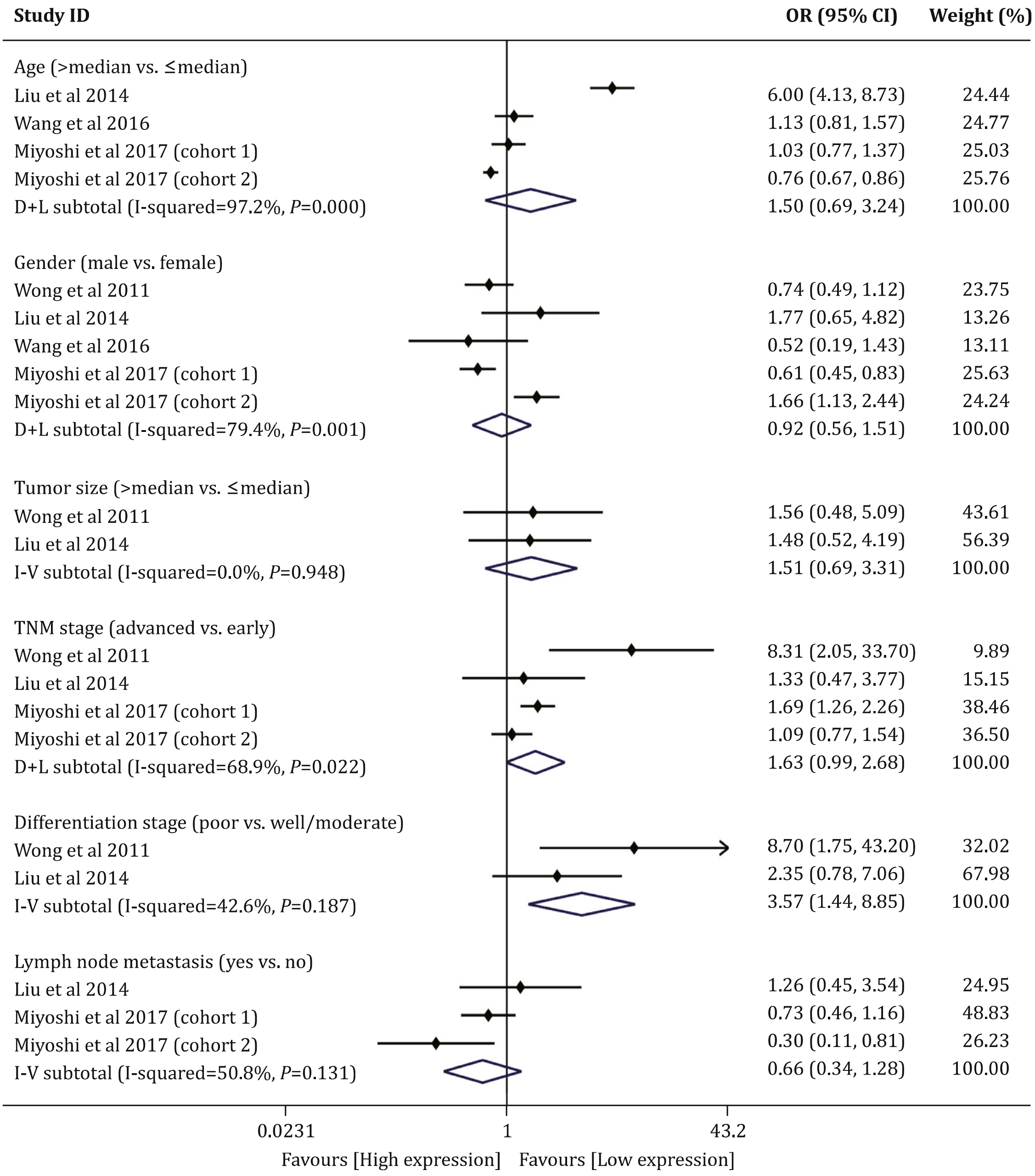

Fig. 7. Forest plot for the relationship between miR-139 expression and clinicopathological parameters. OR: odd ratio; CI: confidence interval; TNM: tumor-node-metastasis.

95% CI were 2.27 and 1.74–2.95 ($P < 0.001$), suggesting that low miR-139 was strongly associated with worse accumulative OS in cancerous tissues (Fig. 2). In the stratified analysis by tumor type, low levels of miR-139 were significantly correlated with a poorer OS for patients with HCC (HR = 2.40; 95% CI: 1.36–4.23; $P = 0.002$), CRC (HR = 2.45; 95%CI: 1.58–3.81; $P < 0.001$) and GBM (HR = 2.06; 95%CI: 1.37–3.09; $P < 0.001$) (Fig. 2). We evaluated the relationship between RFS and miR-139 expression through 2 clinical cohorts comprising of 250 patients from one article. Due to no heterogeneity in these clinical cohorts ($I^2 = 0$, $P = 0.806$), meta-analysis of

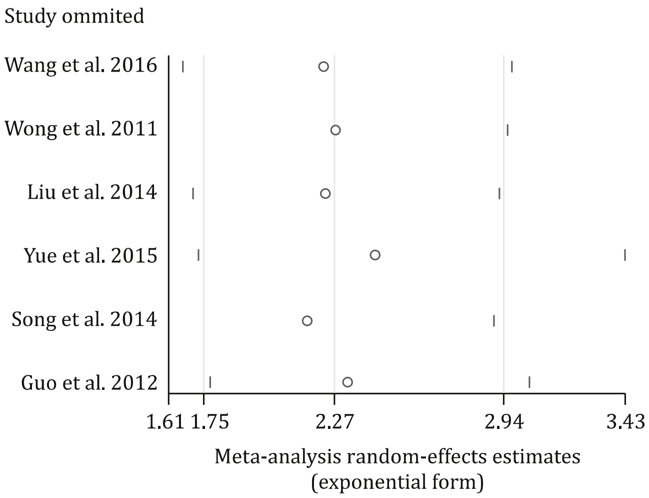

Fig. 8. Sensitivity analysis for the meta-analysis: overall survival based on miR-139 expression.

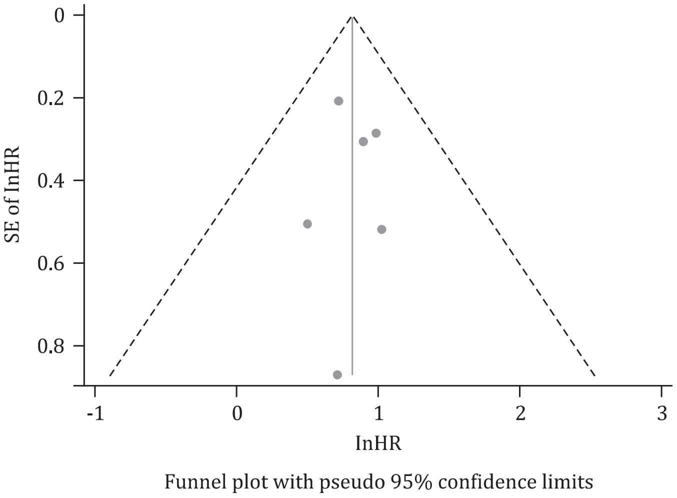

Fig. 9. Funnel plot analysis of potential publication bias in the meta-analysis: overall survival based on miR-139 expression. HR: hazard ratio.

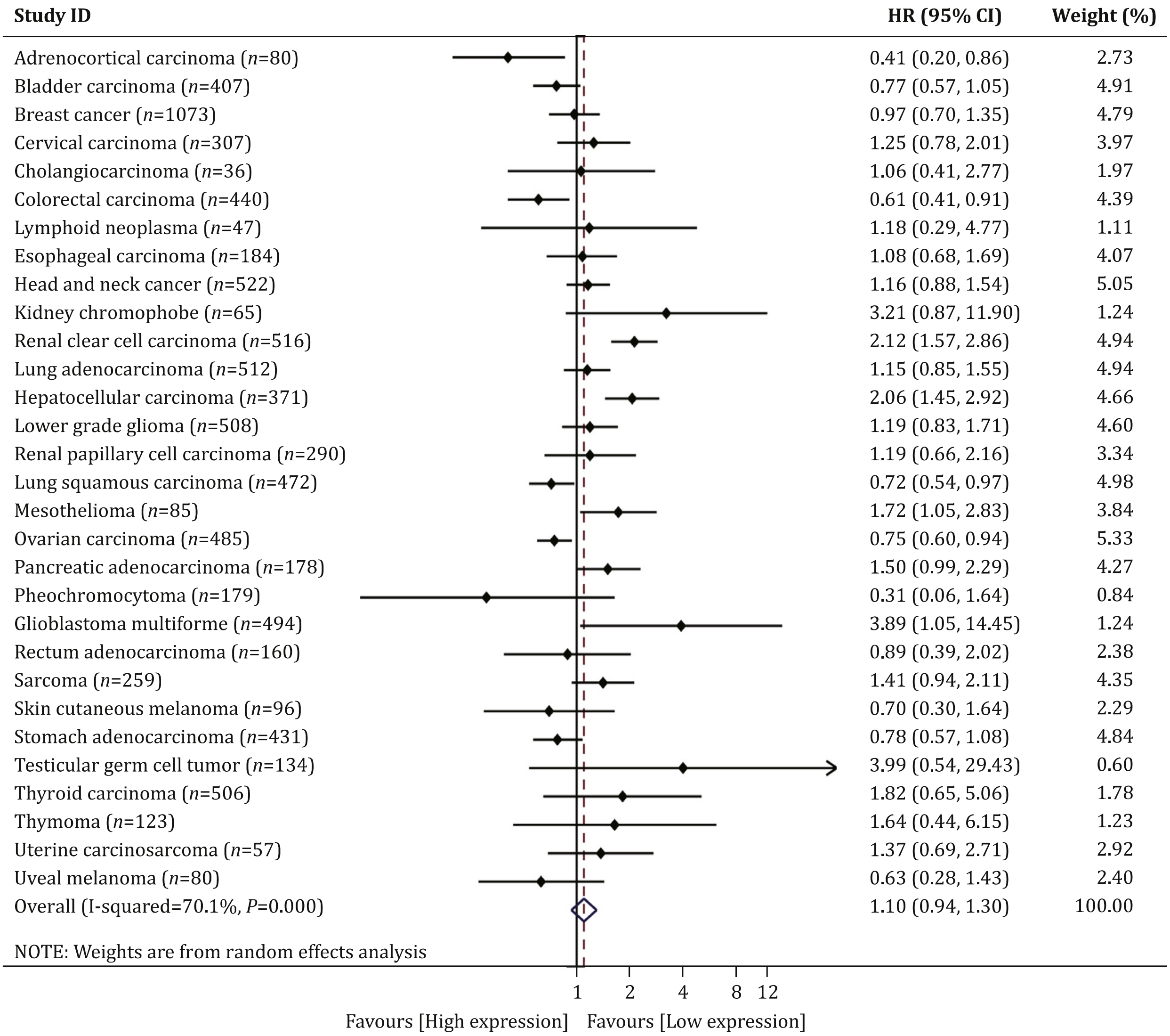

Fig. 10. Forest plot for the relationship between miR-139 expression and overall survival based on The Cancer Genome Atlas (TCGA) datasets. HR: hazard ratio; CI: confidence interval.

Table 3
HRs and corresponding 95% CIs of miR-139 down-expression in tumors based on The Cancer Genome Atlas (TCGA) datasets.

Tumor type	Sample size	OS		RFS	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
All tumors	9097	1.10 (0.94–1.30)	0.2470	1.07 (0.93–1.23)	0.3530
Adrenocortical carcinoma	80	0.41 (0.20–0.86)	**0.0180**	0.27 (0.14–0.52)	**0.0001**
Bladder carcinoma	407	0.77 (0.57–1.05)	0.0962	1.04 (0.80–1.35)	0.7744
Breast cancer	1073	0.97 (0.70–1.35)	0.8695	1.10 (0.83–1.48)	0.5064
Cervical carcinoma	307	1.25 (0.78–2.01)	0.3431	1.09 (0.71–1.67)	0.6864
Cholangiocarcinoma	36	1.06 (0.41–2.77)	0.9035	1.70 (0.72–4.00)	0.2242
Colorectal carcinoma	440	0.61 (0.41–0.91)	**0.0147**	0.68 (0.49–0.94)	**0.0208**
Lymphoid neoplasma	47	1.18 (0.29–4.77)	0.8132	2.10 (0.76–5.81)	0.1526
Esophageal carcinoma	184	1.08 (0.68–1.69)	0.7510	1.15 (0.80–1.67)	0.4507
Head and neck cancer	522	1.16 (0.88–1.54)	0.2934	1.04 (0.81–1.34)	0.7391
Kidney chromophobe	65	3.21 (0.87–11.90)	0.0808	1.06 (0.83–1.38)	0.9148
Renal clear cell carcinoma	516	2.12 (1.57–2.86)	**<0.0001**	1.90 (1.46–2.49)	**<0.0001**
Lung adenocarcinoma	512	1.15 (0.85–1.55)	0.3703	1.06 (0.83–1.36)	0.6355
Hepatocellular carcinoma	371	2.06 (1.45–2.92)	**<0.0001**	1.66 (1.26–2.19)	**0.0003**
Lower grade glioma	508	1.19 (0.83–1.71)	0.3315	1.14 (0.86–1.51)	0.3531
Renal papillary cell carcinoma	290	1.19 (0.66–2.16)	0.5595	0.98 (0.61–1.56)	0.9205
Lung squamous carcinoma	472	0.72 (0.54–0.97)	**0.0313**	0.58 (0.44–0.78)	**0.0002**
Mesothelioma	85	1.72 (1.05–2.83)	**0.0309**	1.96 (1.22–3.16)	**0.0058**
Ovarian carcinoma	485	0.75 (0.60–0.94)	**0.0128**	0.83 (0.68–1.01)	0.0675
Pancreatic adenocarcinoma	178	1.50 (0.99–2.29)	0.0553	1.45 (1.01–2.07)	**0.0437**
Pheochromocytoma	179	0.31 (0.06–1.64)	0.1702	0.42 (0.18–0.97)	**0.0424**
Glioblastoma multiforme	494	3.89 (1.05–14.45)	**0.0421**	1.51 (0.99–2.30)	0.0575
Rectum adenocarcinoma	160	0.89 (0.39–2.02)	0.7806	0.60 (0.33–1.10)	0.0987
Sarcoma	259	1.41 (0.94–2.11)	0.1006	1.45 (1.03–2.04)	**0.0354**
Skin cutaneous melanoma	96	0.70 (0.30–1.64)	0.4103	0.88 (0.45–1.71)	0.6999
Stomach adenocarcinoma	431	0.78 (0.57–1.08)	0.1343	0.80 (0.60–1.07)	0.1367
Testicular germ cell tumor	134	3.99 (0.54–29.43)	0.1744	1.76 (0.90–3.46)	0.1005
Thyroid carcinoma	506	1.82 (0.65–5.06)	0.2511	2.03 (1.22–3.37)	**0.0062**
Thymoma	123	1.64 (0.44–6.15)	0.4646	1.17 (0.53–2.60)	0.6905
Uterine carcinosarcoma	57	1.37 (0.69–2.71)	0.3699	1.13 (0.60–2.11)	0.7118
Uveal melanoma	80	0.63 (0.28–1.43)	0.2657	0.48 (0.23–1.24)	0.0606

OS: overall survival; RFS: recurrent-free survival; HR: hazard ratio; CI: confidence interval.

fixed-effect model was conducted. The pooled HR indicated that high miR-139 expression was associated with unfavorable RFS in CRC (HR = 2.42; 95% CI: 1.44–4.07; *P* = 0.001) (Fig. 3).

Meta-analysis to evaluate the diagnostic value of miR-139 of microarrays in the GEO dataset

In order to further validate the diagnostic values of miR-139 in HCC, GBM and CRC, we searched GEO database and 27 eligible microarrays were finally identified for analysis (6 for HCC, 5 for GBM and 16 for CRC). The standard mean difference (SMD) with 95% CI was used to evaluate continuous outcomes. Because of the significant heterogeneity among the microarrays, the random-effect model was conducted to evaluate the pooled SMD and 95% CI. The pooled SMD (95% CI) for HCC was −1.36 (−1.91 to −0.81; Fig. 4), for GBM −1.52 (−2.51 to −0.54; Fig. 4) and for CRC −0.62 (−1.07 to −0.17; Fig. 5), which suggested that the expression of miR-139 in these tumors was lower than that in the healthy tissue. We further generated funnel plots to access the publication bias (Fig. 6A–C). The funnel plots were basically symmetric. The Begg's test (for HCC *P* = 0.260, for GBM *P* = 0.806, for CRC *P* = 0.072) and Egger's test (for HCC *P* = 0.134, for GBM *P* = 0.392, for CRC *P* = 0.222) showed no statistical significance. Taken together, there was no significant publication bias among these studies. A sensitivity analysis was performed to evaluate differences among the included studies, revealing no significant differences (Fig. 6D-F).

Relationship between miR-139 expression and clinicopathologic features

The correlation of miR-139 expression with clinicopathological features are exhibited in Table 2 and Fig. 7. Decreased miR-139 level was significantly correlated with poor differentiation (OR = 3.57; 95% CI: 1.44–8.85; *P* = 0.006). These results indicated that low miR-139 expression is related to high tumor malignancy. However, the combined data indicated no associations between miR-139 expression and the following parameters such as age (pooled OR = 1.50; 95% CI: 0.69–3.24; *P* = 0.304), gender (pooled OR = 0.92; 95% CI: 0.56–1.51; *P* = 0.738), tumor size (pooled OR = 1.51; 95% CI: 0.69–3.31; *P* = 0.298), late tumor-node-metastasis stage (pooled OR = 1.63; 95% CI: 0.99–2.68; *P* = 0.057) and lymph-node-metastasis (pooled OR = 0.66; 95% CI: 0.34–1.28; *P* = 0.222). The insufficient data precluded us to investigate the association between miR-139 expression and other clinicopathological features.

Sensitivity analysis and publication bias

Sensitivity analysis was conducted by sequentially omitting individual studies using random-effect model and fixed-effect model (Fig. 8). When any individual study was discarded, the pooled HRs was not significantly altered, indicating that the results were stable and reliable.

A funnel plot was used to estimate the potential publication bias (Fig. 9). The results showed no obvious asymmetry for OS. Moreover, Egger's test (*P* = 0.979) and Begg's test (*P* = 0.851) strengthened that no significant publication bias existed among the included studies.

Prognostic analysis of decreased miR-139 level in cancer patients based on the TCGA cohorts

In order to validate the results of miR-139 value in this meta-analysis, we then extracted data from the TCGA datasets, including 30 types of human solid tumors to more precisely evaluate

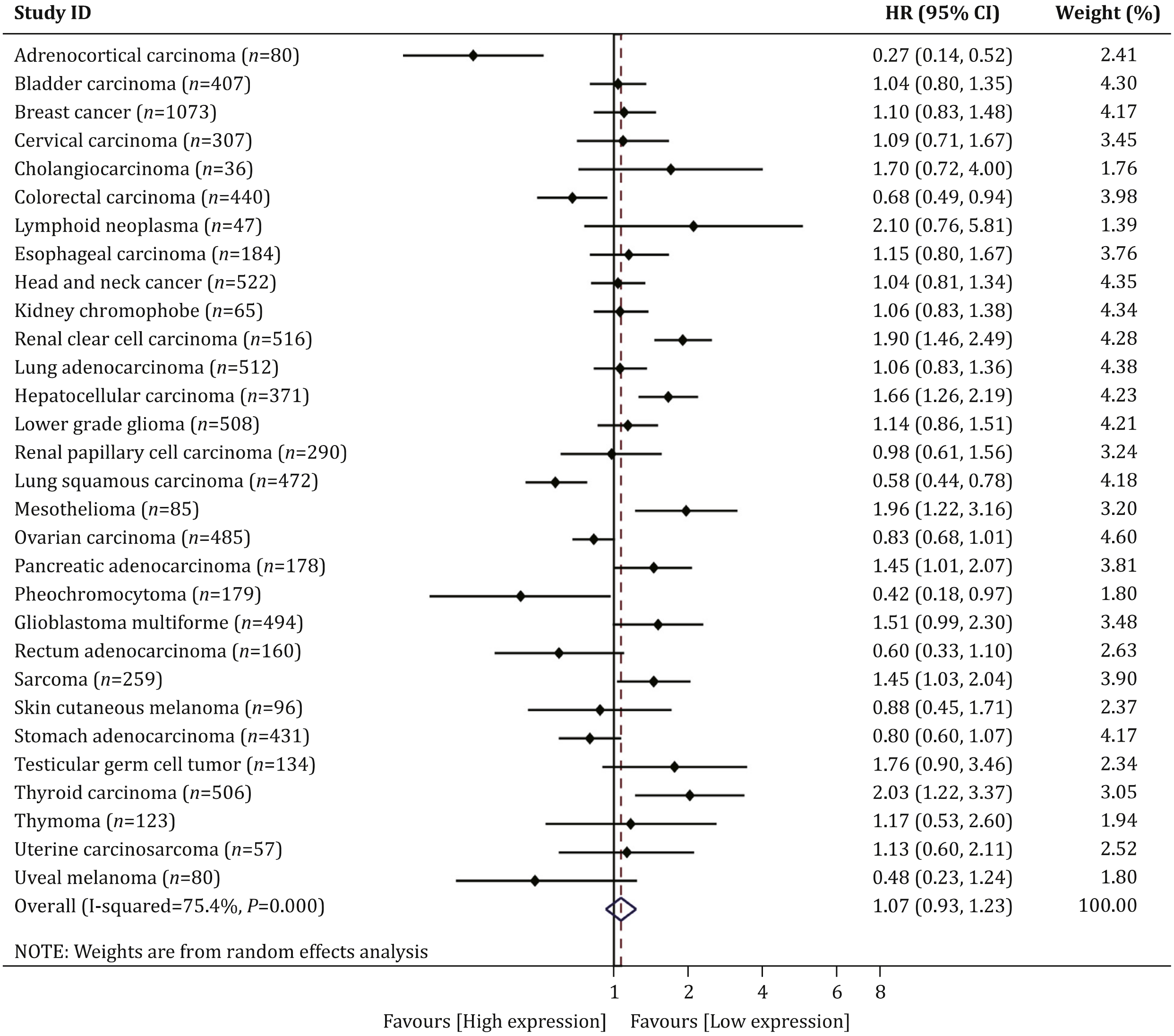

Fig. 11. Forest plot for the relationship between miR-139 expression and recurrence-free survival based on The Cancer Genome Atlas (TCGA) datasets. HR: hazard ratio; CI: confidence interval.

the prognostic value of miR-139. The results suggested that down-expressed miR-139 was not associated with shorter OS (HR = 1.10; 95% CI: 0.94–1.30; $P = 0.247$) (Table 3, Fig. 10) or RFS (HR = 1.07; 95% CI: 0.93–1.23; $P = 0.353$) (Table 3, Fig. 11). Nevertheless, we discovered that, in single tumor types, low miR-139 expression was significantly related with shorter OS in HCC, GBM, renal clear cell carcinoma, and mesothelioma while the association was opposite in adrenocortical carcinoma, lung adenocarcinoma, ovarian carcinoma and CRC or with worse RFS in HCC, renal clear cell carcinoma, mesothelioma, pancreatic adenocarcinoma, sarcoma, and thyroid carcinoma while opposite in CRC, adrenocortical carcinoma, lung squamous carcinoma, and pheochromocytoma (Table 3). Thus, these outcomes were almost consistent with our meta-analysis, except CRC on OS, indicating that miR-139 was able to predict the prognosis of human tumors.

Discussion

miRNAs exert biological functions via binding to the 3′-untranslated region (UTR) of their specific mRNAs [32]. It has previously been observed that miR-139 is down-regulated in diverse human tumors which is associated with poor prognosis for cancer patients. Wong et al. [13] first found that miR-139 suppresses metastasis and progression of HCC by downregulating rho-kinase 2. Bao et al. [33] reported that HER2 and CD44 inhibit miR-139 expression and increase expression of its target CXCR4 in gastric cancer. Subsequent studies showed that miR-139 inhibit CRC growth, and its level was inversely correlated with prognosis in CRC patients [34]. Collectively, miR-139 plays a vital role in tumor cell proliferation, differentiation and metastasis, and is considered as a tumor suppressor. However, up-regulation of miR-139 has been discovered in pancreatic cancer [19], which indicates that miR-139 might be oncogenic factor in some cancer types and tumor suppressor in other types of cancers. Thus, it is controversial whether miR-139 can be regarded as a prognostic and diagnostic biomarker in cancer.

In the present meta-analysis, 769 patients comprised 7 articles were enrolled to determine the relationship of miR-139 expression with clinical outcomes. We demonstrated that low expression of miR-139 was markedly associated with poor OS. During the analysis about diverse types of cancers, low miR-139 expression predicted a worse OS in individual with HCC, GBM or CRC. Additionally, we analyzed the data from the TCGA datasets to validate the role of miR-139 expression in the prognosis of cancer patients. The same results were found in HCC, GBM, but not in CRC. Additionally, our pooled data indicated that high miR-139 expression was correlated with worse RFS in CRC patients, which was inconsistent with OS according to the enrolled studies, but in good accordance with the results of TCGA database. MiR-139 is a tumor suppressor, tumors with low miR-139 supposed to be more aggressive and therefore, it is not logical that patients with high miR-139 had poorer RFS. The conflicts on RFS and OS of CRC patients need further investigation.

To further explore the prognostic value of miR-139 on various tumors, the correlation between its expression level and clinicopathological features were analyzed. The data was processed according to age, gender, TNM stage, tumor size, differentiation grade and LNM. According to the pooled results, negative relationships were observed between miR-139 expression and differentiation grade. Moreover, the results of 27 microarrays from GEO database showed that miR-139 expression was lower in HCC, GBM and CRC tissues, indicating it might be a diagnostic biomarker for these types of cancers. No obvious publication bias or heterogeneity was found about the pooled outcomes, and sensitivity analysis further confirmed the robustness of the meta-analysis results.

This meta-analysis has some limitations. One is the diversity of cancers which might possibly produce significant bias due to diverse baseline characteristics. Second is that the stage of cancers was different and the criteria for calculating miR-139 cut-off values were not consistent among studies. The third is that the HRs of some studies was calculated indirectly which were less reliable.

In conclusion, as far as we know, this was the first comprehensive meta-analysis on the prognostic value of miR-139 in various cancer types. The results showed that miR-139 could be an independent prognostic biomarker for clinical outcomes in HCC and GBM. However, its precise functional role in CRC still need to be further investigated by larger samples and multicenter studies. Additionally, owing to the limitations mentioned above, further clinical studies are required to confirm the utility of miR-139 on cancer diagnosis and prognosis and furthermore, therapeutics.

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Contributors

RZG and SRR design the research. CJA and YY wrote the paper and analyzed the data. XC, CXL and LJ collected the data. CGY and LKF revised the paper. All authors contributed to the design and interpretation of the study and to further drafts. CJA and YY contributed equally to the work. SRR is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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