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Prognostic potential of miR-144 in various cancers
A meta-analysis

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Abstract

Background: MicrorNA-144 (MiR-144) has been shown to be an attractive prognostic tumor biomarker and play a fundamental role in various cancers, However, the conclusion was inconsistency. The aim of this study was to identify the prognostic role of miR-144 in cancers.

Methods: Relevant studies were searched in PubMed, EMBASE and Web of Science up to April 20, 2022. Hazard ratios (HR), odds ratio (OR) and 95% confidence intervals were pooled from the selected studies.

Results: A total of 15 articles involving 1846 participants fulfilled the inclusion criteria. The results revealed that low miR-144 expression was significantly associated with favorable overall survival (HR: 0.68, 95% confidence interval [CI]: 0.53–0.88) in various cancers. Low miR-144 expression had better predictive value in patients with urinary system cancer (HR: 0.48, 95% CI: 0.35–0.64). In addition, low miR-144 expression was associated with tumor diameter (big vs small) (OR: 1.69, 95% CI: 1.08–2.75), tumor stage (III–IV vs I–II) (OR: 2.52, 95% CI: 3.76–8.14) and invasion depth ($T3 + T4$ vs $T2 + T1$) (OR: 3.24, 95% CI: 1.72–4.89).

Conclusion: miR-144 may serve as a prognostic biomarker in cancers.

Abbreviations: CI = confidence interval, 95% CIs = 95% confidence intervals, DFS = disease-free survival, HRs = hazard ratios, MiR-144 = microrNA-144, NOS = Newcastle–Ottawa Quality Assessment Scale, OR = odds ratio, OS = overall survival.

Keywords: cancer, meta-analysis, microrNA-144, prognosis

1. Introduction

As the primary public health hazard, cancer is an incurable and multi-factorial disease and is the premier cause of death throughout the world.[1] There will be an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths last year.[2] Most patients with cancers are diagnosed at an advanced stage and have a poor prognosis. Early detection or diagnosis plays a vital role in the treatment. Thus, it is urgent for us to find effective biomarkers to identify high-risk cancer patients so that clinicians can provide individualized treatment. MicroRNA (miRNA) is a highly conserved endogenous non-coding single-stranded RNA with a length of 18 to 22 nucleotides.[3] They negatively regulate target gene expression by base pairing with the 3′ untranslated region (3′ UTR) of target messenger RNA (mRNA), resulting in degradation or translation that inhibits the target gene expression at the post-transcriptional level.[4] Accumulated evidence have shown that miRNA is involved in

many aspects of tumor progression, including cell growth, apoptosis, proliferation, differentiation and migration.[5] MicroRNA has been widely recognized as an effective prognostic biomarker for cancers.

As one of the most attractive miRNAs, the miR-144 is located on chromosome 17q11.2 and plays a vital role in cancer biology.[6] A growing numbers of studies have suggested that miR-144 is involved in tumor biological processes, such as invasion, migration, angiogenesis and cell cycle.[7] MicrorNA-144 (MiR-144) is abnormally expressed in tumors. Some studies found that high miR-144 expression in cancer patients indicated a poor prognosis, while others displayed the different view.[8–10] So far, studies on miR-144 have confirmed that it participated in different metabolic processes of organisms, including promoting apoptosis and anti-apoptosis, and its specific function depended on the physiological status of organisms to a certain extent. However, the purpose of this study is to explore the potential impact of tumor

differentiation and malignant degree on the overall survival rate of tumor patients.

Currently, the prognostic values of miR-144 in cancers have still not been fully clear. Therefore, we summarized the available data from published studies and performed a meta-analysis to evaluate the prognostic significance of miR-144 in diverse cancers.

2. Methods

2.1. Search strategy

Eligible studies were identified through searching in PubMed, EMBASE, and Web of Science until April 20, 2022. Using the following words: (microRNA-144 odds ratio (OR) miR-144 OR miRNA-144) AND (tumor OR neoplasm OR cancer OR carcinoma) AND (prognosis OR prognostic OR survival OR outcome). Pooled hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated to assess the correlation between miR-144 expression and patient prognosis. In order to avoid omitting the potentially related studies, the reference lists were also screened. Two authors independently conducted this procedure. This study was a meta-analysis that does not require the approval of the ethics committee and the patient consent.

2.2. Selection criteria

The inclusion criteria were: English publications; miR-144 expression was evaluated in the human tissues; association of miR-144 expression with cancer prognosis; studies provided sufficient data. The exclusion criteria: non-English papers; cases, reports, meeting abstracts, reviews, letters or meta-analysis; the prognosis data originated from The Cancer Genome Atlas

(TCGA) database; or studies did not provide adequate data to calculate the HRs and 95% CI.

2.3. Data extraction and quality assessment

Two reviewers independently extracted the following information from the included studies: first author's last name, year of publication, country, study type, tumor type, sample size, detected sample, detected method, analysis type, survival analysis, source of HR, and Newcastle–Ottawa Quality Assessment Scale (NOS) score. If both univariate and multivariate analysis results were offered for survival outcome, we preferred to select the latter ones. If the study provided no HRs and 95% CIs, survival data was extracted from the Kaplan–Meier curves by the software Engauge Digitizer version 4.1.[10] The NOS was used to evaluate the quality of the selected studies.[11]

2.4. Statistical analysis

HRs with 95% CIs were combined to assess the effect of miR-144 expression on prognosis in patients with a variety of cancers. A forest plot was used to estimate the effect of miR-144 expression on survival outcome. Heterogeneity was tested by the Cochran's Q test and the Higgins I^2 statistical method. If the P value of the Q test was < 0.05 and the I^2 statistic was > 50% (heterogeneity existed), the random effects model was adopted to calculate pooled HR; otherwise, the fixed effects model was used.[12] The heterogeneity was further explored through subgroup analyses. Sensitivity analysis was performed to test the stabilization of the results. Finally, we assessed the potential publication bias through Begg's test and Egger's test.[13,14] All analyses were performed using the STATA 12.0 software (Stata Corporation, College Station, TX). $P < .05$ was considered statistically significant.
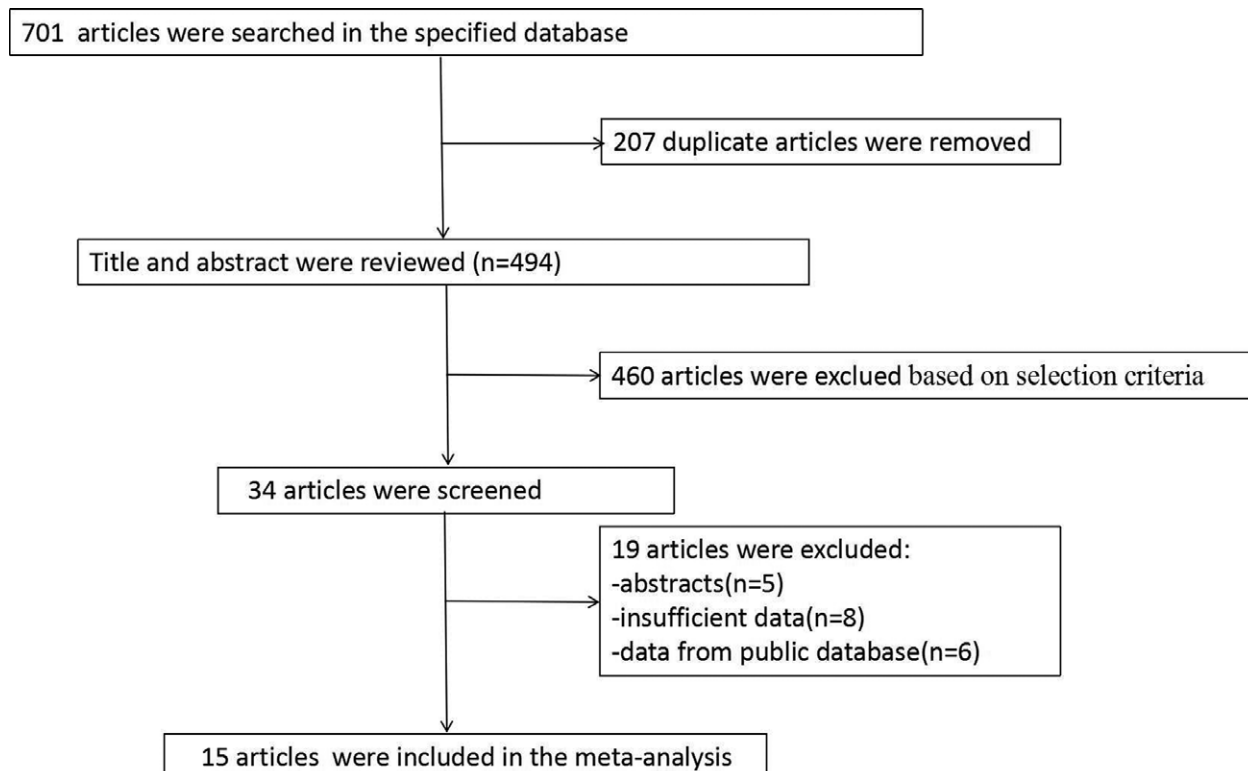

Figure 1. The flow chart of studies selecting process.

3. Results

3.1. Literature search

A total of 701 studies were initially retrieved from PubMed, Web of Science and EMBASE. The detailed searching process of literature selection was illustrated in Figure 1. After removing literatures, 34 articles remained. Through further browsing, 19 articles were further excluded. Finally, 15 articles were included in this meta-analysis.[9,10,15–25] Characteristics of the included studies was presented in Table 1.

3.2. Study characteristics

The studies were published from 2012 to 2021. Types of tumors included: gastric cancer, lung adenocarcinoma, Lung squamous cell carcinoma, colorectal cancer, non-small-cell lung cancer, glioblastoma, acute myeloid leukemia, retinoblastoma, osteosarcoma, renal cell carcinomas, prostate cancer and breast cancer. The detected sample was different, most with serum or tissue, and 1 study in bone marrow. Most studies were from China, and 5 studies came from Japan, Netherlands, Romania and Germany, respectively. All studies assessed miR-144 expression by quantitative real-time polymerase chain reaction (qRT-PCR). The enrolled studies of the NOS score ranged from 6 to 7.

3.3. Association between miR-144 expression and overall survival

18 studies evaluated the correlation between low miR-144 expression and overall survival (OS). Due to the heterogeneity was significant among these studies ($I^2 = 73.4\%$), the random effect model was utilized to calculate the HR and 95% CI. We found that low miR-144 expression was significantly associated with good OS (HR: 0.68, 95% CI: 0.53–0.88) (Fig. 2).

In order to explore the source of the heterogeneity, we conducted the subgroup analysis based on cancer type, analysis type, race, sample type, source of HR and sample size (Table 2). In the stratified analysis of cancer type, low miR-144 expression had better predictive value in patients with urinary system cancer (HR: 0.48, 95% CI: 0.35–0.64). In addition, there was a significant association between low miR-144 expression and analysis type (univariate analysis), race (Asian), sample type, source of HR (SC) and sample size.

3.4. Association between miR-144 expression and disease-free survival

As shown in Figure 3, 6 studies reported the relationship between miR-144 expression and disease-free survival (DFS). The random-effect model was performed because of significant obvious heterogeneity in these studies ($I^2 = 84.5\%$). The pooled results indicated that low miR-144 expression was no association with DFS (HR: 0.87, 95% CI: 0.59–1.59) (Fig. 3).

3.5. Association between miR-144 expression and clinicopathological features

The results were shown in Table 3. Low miR-144 expression showed significant association with tumor diameter (big vs small) (OR: 1.69, 95% CI: 1.08–2.75,), tumor stage (III–IV vs I–II) (OR: 2.52, 95% CI: 3.76–8.14) and invasion depth ($T3 + T4$ vs $T2 + T1$) (OR: 3.24, 95% CI: 1.72–4.89). In addition, there was no significance correlation between gender (male vs female) (OR: 1.02, CI: 0.54–1.47), age (old vs young) (OR: 2.21, CI: 0.85–1.63), tumor differentiation (poor vs moderate/well) (OR: 2.43, CI: 0.66–3.2), lymph node status (yes vs no) (OR: 5.68, CI: 0.75–4.84) and distant metastasis (yes vs no) (OR: 2.93, CI: 0.91–5.83) and the low miR-144 expression.

3.6. Sensitivity analyses

In order to examine the stability of the overall results, sensitivity analysis was implemented. Sensitivity analysis showed that the result was not obviously influenced, suggesting the outcomes were stable (Figs. 4 and 5).

3.7. Publication bias

Begg's funnel plot and Egger's test were used to evaluate the potential publication bias. The p values of Begg's test and Egger's test for OS were 0.820 and 0.917, respectively (Fig. 6). The P values of Begg test and Egger test for DFS were 1 and 0.651, respectively (Fig. 7). P values were more than 0.05, indicating no significant publication bias.

Table 1										
Basic information of eligible studies for miR-144.										
Study	Year	Country	Cancer type	Sample size	Detected sample	Detected method	Analysis type	Survival analysis	Source of HR	NOS score
Akiyoshi	2012	Japan	GC	93	Bone marrow	qRT-PCR	Multivariate	OS	Reported	6
Wu	2016a	China	LUAD	129	Serum	qRT-PCR	Multivariate	OS	Reported	6
Wu	2016b	China	LUSC	54	Serum	qRT-PCR	Univariate	OS	Reported	7
Iwaya	2012	Japan	CRC	137	Tissue	qRT-PCR	Multivariate	OS	Reported	6
Wouter	2020	Netherlands	LC	26	Tissue	qRT-PCR	Univariate	OS	Reported	6
Cheng	2017	China	glioblastoma	111	Tissue	qRT-PCR	Multivariate	OS	Reported	7
Brinzan	2019	Romania	CRC	82	Tissue	qRT-PCR	Multivariate	OS	Reported	7
Zhao	2017	China	AML	120	Serum	qRT-PCR	Univariate	OS	SC	7
Zheng	2020	China	retinoblastoma	50	Tissue	qRT-PCR	Univariate	OS、DFS	SC	6
Wang	2015	China	osteosarcoma	67	Tissue	qRT-PCR	Univariate	OS	SC	7
Liu	2016	China	RCC	120	Tissue	qRT-PCR	Univariate	OS	SC	7
Liu	2017a	China	GC	96	Tissue	qRT-PCR	Univariate	OS、DFS	SC	7
Liu	2017b	China	GC	96	Serum	qRT-PCR	Univariate	OS、DFS	SC	6
Liu	2015	China	PC	40	Tissue	qRT-PCR	Univariate	OS	SC	7
Madhavan	2016	Germany	BC	265	Tissue	qRT-PCR	Multivariate	OS	Reported	6
Li	2021	China	CRC	300	Tissue	qRT-PCR	Multivariate	OS, DFS	Reported	7
Meng	2021	China	RCC	60	Tissue	qRT-PCR	Multivariate	OS, DFS	Reported	6

R = retrospective, P = prospective, BC = breast cancer, GC = gastric cancer, RCC = renal cell carcinomas, CRC = colorectal cancer, AML = acute myeloid leukemia, CC = cervical cancer, NOS = Newcastle–Ottawa Quality Assessment Scale, PC = prostate cancer, OS = overall survival, DFS = disease-free survival, SC = survival curve.
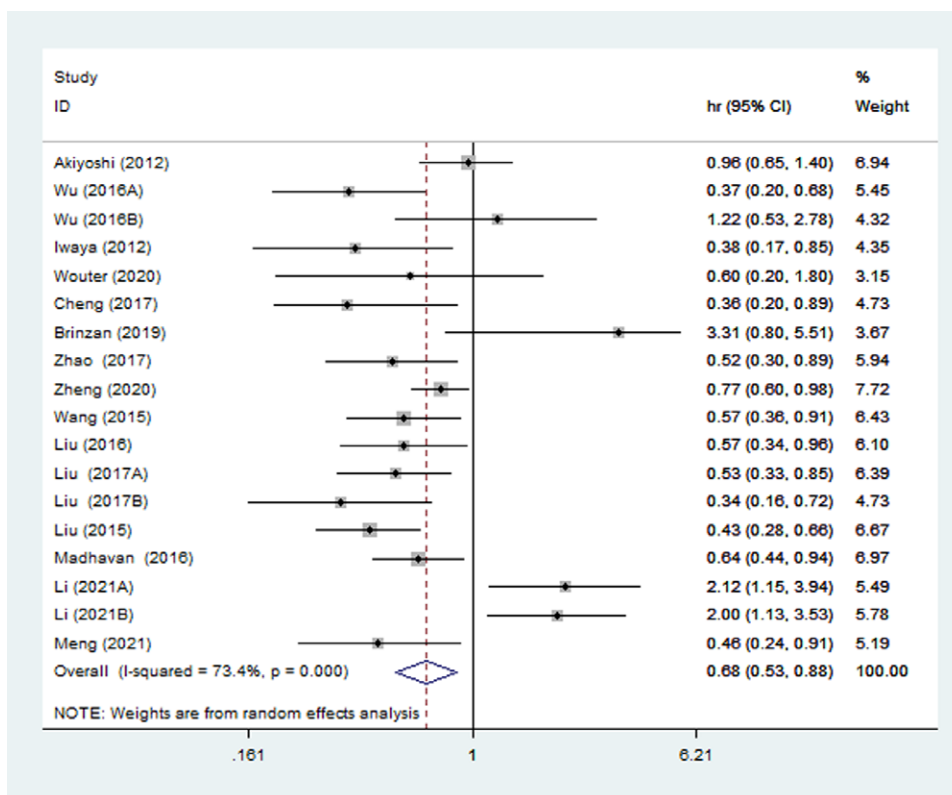
Figure 2. Forest plot for the association between miR-144 expression and OS. OS = overall survival.

Table 2

Subgroup analysis for OS.

Stratified analysis	No. of studies	Pooled HR (95% CI)	P value	Heterogeneity		
				I^2 (%)	P value	Model
Cancer type						
Digestive system	7	0.98 (0.54–1.73)	.939	83.9	.00	Random
Urinary system	3	0.48 (0.35–0.64)	.00	000	.709	Fixed
Respiratory system	3	0.62 (0.29–1.35)	.231	61.6	.074	Random
Others	5	0.66 (0.55–0.78)	0	24..2	.26	Fixed
Analysis type						
Univariate analysis	11	0.62 (0.54–0.71)	0	25	.213	Fixed
Multivariate analysis	6	0.67 (0.34–1.34)	.261	81.7	0	random
Race						
Caucasian	3	1.05 (0.37–2.92)	.932	79.8	.007	Random
Asian	14	0.68 (0.45–0.84)	.001	73.8	0	Random
Sample						
Tissue	13	0.70 (0.53–0.97)	.033	76.3	0	Random
Serum/bone marrow	5	0.60 (0.37–0.97)	.038	69.3	.01	Random
Source of HR						
Reported	9	0.72 (0.42–1.23)	.228	74.6	0	Random
SC	9	0.61 (0.52–0.70)	0	25	.23	fixed
Sample size						
≥100	8	0.61 (0.41–0.64)	0	0	.553	Fixed
<100	10	0.70 (0.52–0.96)	.027	68.7	.001	Random

95% CIs = 95% confidence intervals, OS = overall survival.

4. Discussion

With the growth of population and aging, the incidence and mortality of cancer is growing rapidly, and it remains a serious threat to human health.[2] Accurate diagnosis and appropriate monitoring of cancer patients remains a major challenge.

Therefore, specific therapeutic and prognostic biomarkers are important.[16] MicroRNAs are small, non-coding RNA molecules that can be highly conserved between different organisms. Numerous studies have demonstrated that in peripheral circulation, miRNAs were more stably expressed compared with mRNAs and less easily degradable, and can be detected by
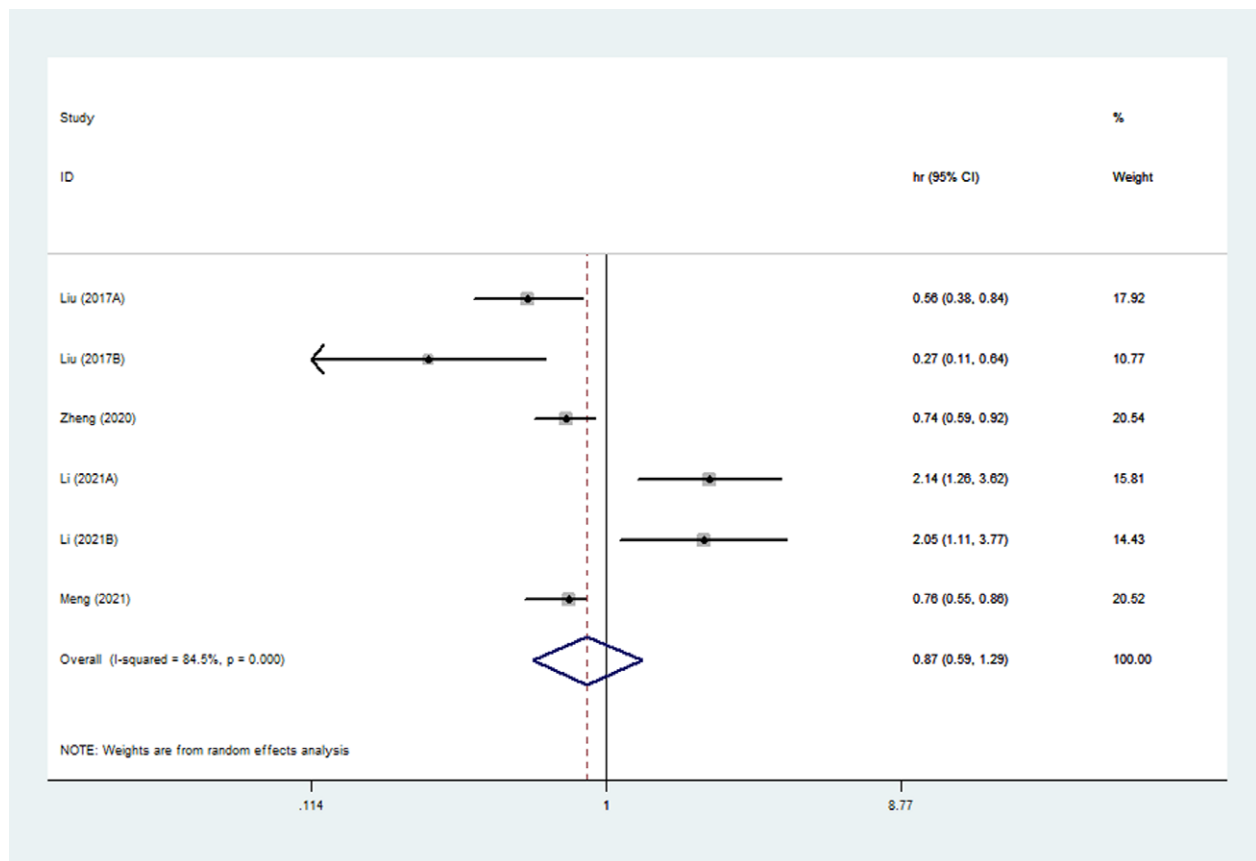
Figure 3. Forest plot for the association between miR-144 expression and DFS. DFS = disease-free survival.

Table 3

Association between low miR-144 expression and clinicopathological features.

Clinicopathologic features	No. of studies	Estimate OR (95% CI)	P value	Heterogeneity		
				I^2 (%)	P value	Model
Gender (male vs female)	8	1.02 (0.54–1.47)	.51	0	.38	Fixed
Age (old vs young)	9	2.21 (0.85–1.63)	.27	0	.15	Fixed
Tumor diameter (big vs small)	8	1.69 (1.08–2.75)	.031	48	.048	Random
Tumor stage (III–IV vs I–II)	7	2.52 (3.76–8.14)	0	79	0	Random
Tumor differentiation (poor vs Moderate/Well)	6	2.43 (0.66–3.2)	.299	56	.002	Random
Lymph node status (yes vs no)	5	5.68 (0.75–4.84)	.401	87	0	Random
Distant metastasis (yes vs no)	6	2.93 (0.91–5.83)	.084	75	.037	Random
Invasion depth (T3 + T4 vs T2 + T1)	3	3.24 (1.72–4.89)	0	0	.512	Fixed

OR = odds ratio.

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high-throughput techniques such as qRT-PCR, microarray and sequencing.[17] Through these ways, a growing number of miR-NAs have been found to be associated with diagnostic, prognostic and therapeutic value in a variety of tumors.[18]

Previous studies have been found that a significant relationship between miR-144 expression levels and the prognosis of various malignant tumor patients.[9,10,15–25] However, the results were inconsistent. Akiyoshi et al retrospectively collected the bone marrow of 93 primary gastric cancer patients who underwent surgical treatment, and performed microRNA microarray and gene expression microarray analysis of total RNA in the bone marrow. They found that low miR-144 expression in cancer cells metastasized to the bone marrow was associated with gastric cancer progression, and indicated a poor prognosis.[26] Luo et al reveled that low miR-144 expression in colorectal cancer tissues was associated with enhanced malignant potential,

such as venous infiltration, liver metastasis, and liver recurrence. Further multivariate analysis showed that low miR-144 expression was an independent prognostic factor for survival outcome.[19] However, Liu et al displayed that high miR-144 expression could serve as a useful prognostic and clinical target in thyroid cancer (TC).[20] The prognostic value of miR-144 in a variety of cancers was controversial. Thus, in order to determine the prognostic value of miR-144 in various cancers, we conducted the meta-analysis to clarify this question.

A total of 15 articles were eventually included in this meta-analysis. By the pooling strategy, we found that low miR-144 expression was significantly associated with good OS in patients with various cancers. Subsequently, we performed a subgroup analysis for OS. The results showed that cancer type, analysis type, race, sample, type, source of HR and sample size were the sources of heterogeneity. We also found that Low
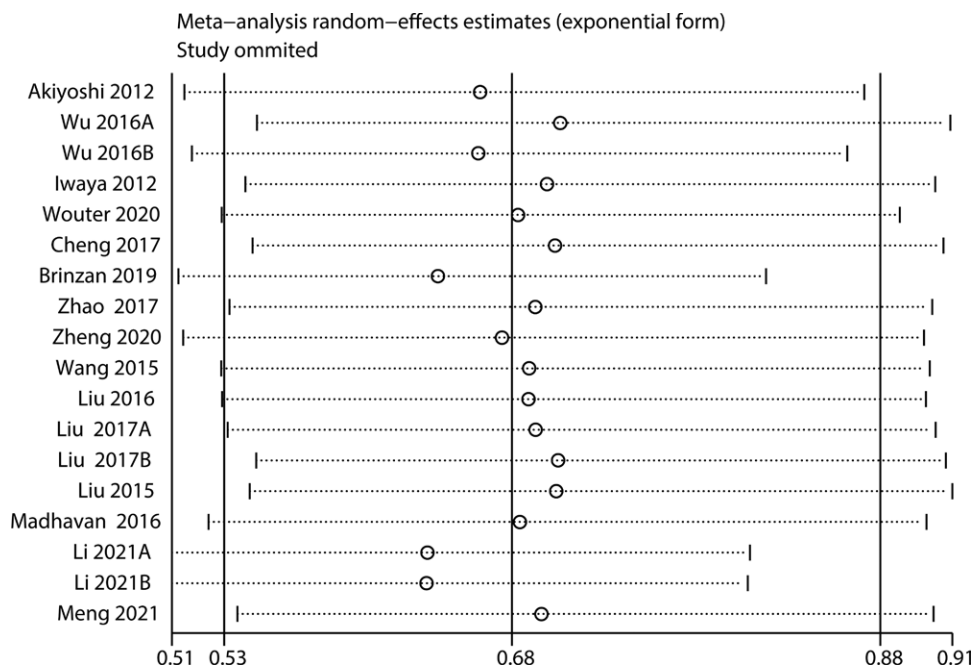
Meta−analysis random−effects estimates (exponential form)
Study ommited

Figure 4. Sensitivity analysis for OS. OS = overall survival.

Meta−analysis random−effects estimates (exponential form)
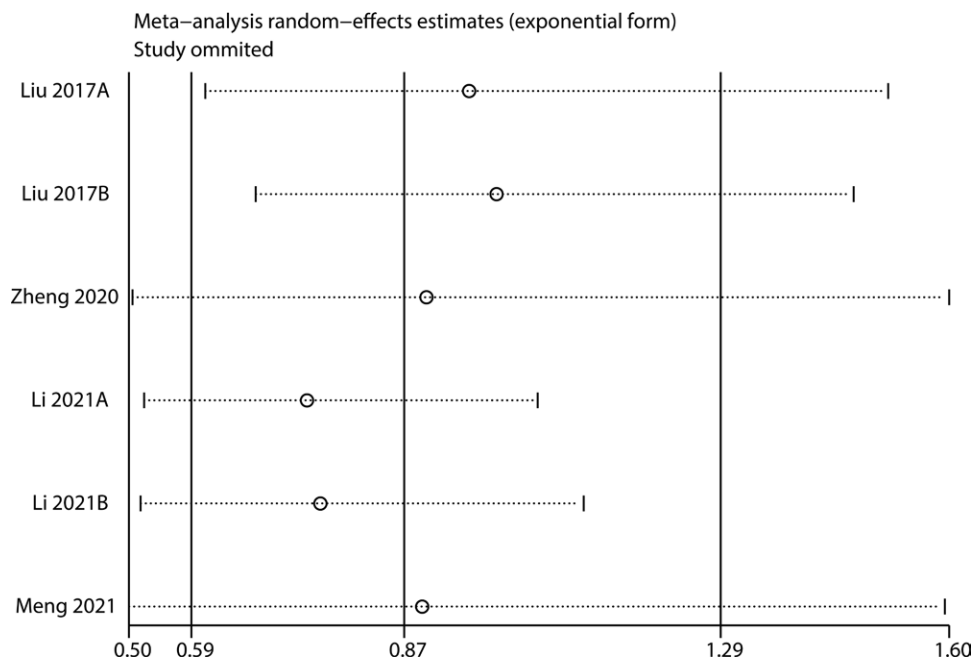Study ommited

Figure 5. Sensitivity analysis for DFS. DFS = disease-free survival.

miR-144 expression had better predictive value in patients with urinary system cancer. In addition, low miR-144 expression was associated with tumor diameters (Big vs Small), tumor stage (III–IV vs I–II) and invasion depth ($T3 + T4$ vs $T2 + T1$).

MiR-144 plays an important role in tumor growth, invasion and metastasis. For instance, Cao et al reported that miR-144 suppressed the proliferation and metastasis of hepatocellular carcinoma (HCC) cells partially by targeting E2F transcription factor 3 (E2F3). E2F3 is an oncogene located at 6P22 and has a strong proliferative potential.[21] G1 to S-phase transition 1 (GSPT1) protein may be an important factor involving in regulation of the cell cycle and proliferation and apoptosis. GSPT1 was regarded as a potential proto-oncogene involved in

multiple tumorigenesis.[22] Xiao et al suggested that miR-144 inhibited cell proliferation and migration by GSPT1 in colorectal cancer. Therefore, miR-144 may be an essential element in colorectal cancer development.[23] MiR-144 inhibited tumor cell growth and metastasis via directly targeting VEGFA and VEGFC.[24] Moreover, miR-144 induced ell cycle arrest and cell apoptosis in pancreatic cancer cells through the mitogen-activated protein kinase signal pathway.[25] In laryngeal squamous cell carcinoma (LSCC), Wu et al observed that miR-144 functioned as a tumor suppressor via targeting IRS1.[27] In addition, related studies have further confirmed that the expression of miR-144 is positively correlated with the expression of apoptosis-related genes such as TP53, FASL, CASP3 and so on.[28]
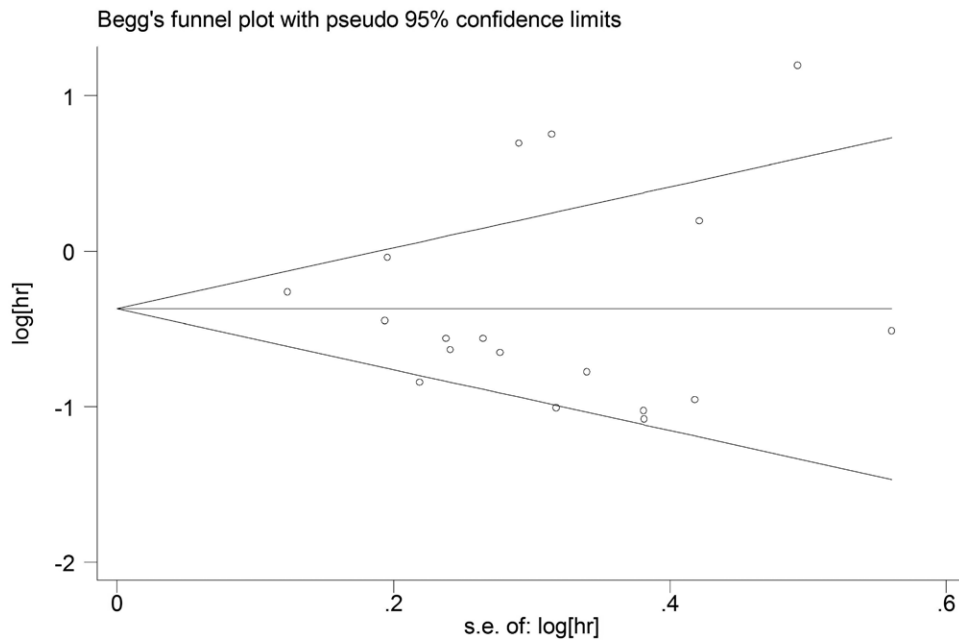
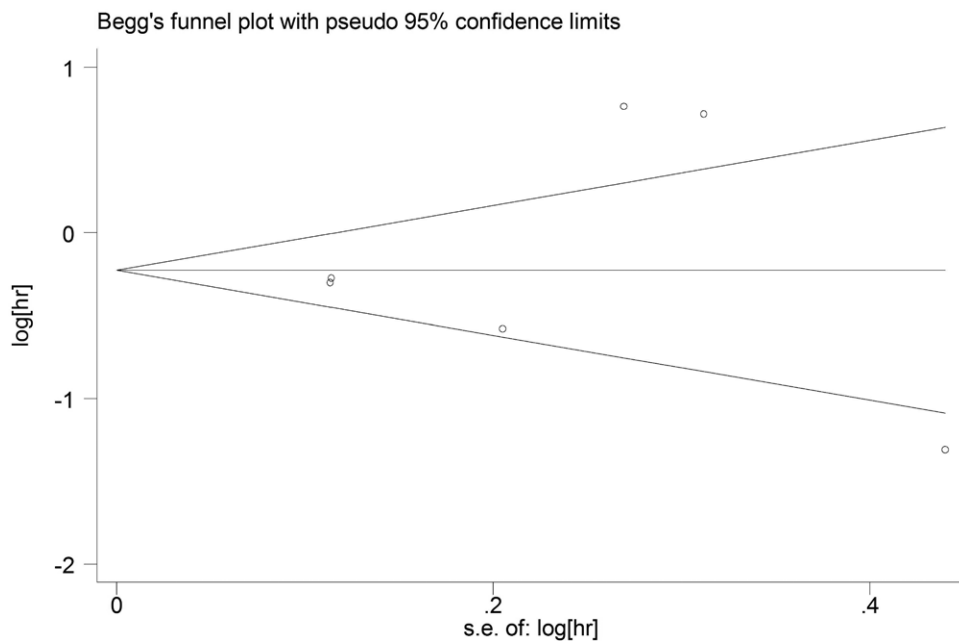**Figure 6.** Publication bias for OS. OS = overall survival.

Figure 7. Publication bias for DFS. DFS = disease-free survival.

Related studies have further confirmed that the overexpression of miR-144 is related to the mechanism of vascular endothelial injury caused by atherosclerosis, which involves the 7-KC-MiR-144-IDH2 signal pathway.[29] Therefore, the expression level of miR-144 gene is closely related to various metabolic processes, cell proliferation and differentiation, tumor invasiveness and metastatic ability.

There were several inevitable flaws in our study. Firstly, only 13 studies with 1390 patients were included in our study. Secondly, most eligible studies were from China, and the prognostic value of miR-144 needs to be verified by further studies in other countries and region. Thirdly, some HRs with 95% CIs were extracted from the survival curves, which could cause some bias. Finally, there was still significant heterogeneity.

5. Conclusion

Low miR-144 expression was significantly associated with good OS. MiR-144 could be used as a valid biomarker for tumor prognosis, especially in urinary system cancer. However, further larger sample and multi-center prospective studies are needed to confirm these findings before miR-144 can be used in clinical applications.

Author contributions

All authors approved the final version of the manuscript.
Conceptualization: Chong-Yang Jia, Shi-Nan Wu, Ying Wang.
Data curation: Ying Wang.

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