ORIGINAL RESEARCH

Prognostic significance of miR-126 in various cancers: a meta-analysis

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Objective: Recent studies have demonstrated that microRNA-126 (miR-126) might be a promising prognostic factor for cancer patients. This meta-analysis was conducted to assess the effectiveness of miR-126 as a prognostic biomarker for various cancers.

Methods: The search of studies was performed by using PubMed and Embase until January 22, 2016. Pooled hazard ratio (HR) with 95% confidence interval (CI) for patients' survival was calculated. A fixed-effect or random-effects model was applied according to heterogeneity. The trim and fill method was used to adjust pooled HR.

Results: In all 17 articles comprising of 2,437 participants were included in this meta-analysis. The results indicated that a high level of miR-126 played a favorable role in the overall survival (HR 0.70, 95% CI: 0.62–0.79, random-effects model), with a heterogeneity measure index of I^2=63.2% ($P<0.01$). Subgroup analyses showed that pooled HR was more significant in patients with digestive system cancers (HR 0.70, 95% CI: 0.59–0.83, fixed-effects model) and respiratory system cancers (HR 0.71, 95% CI: 0.59–0.85, random-effects model). Owing to publication bias, HR was adjusted to 0.59 (0.463–0.752, $P<0.01$) by the trim and fill method.

Conclusion: miR-126 could be a promising biomarker for cancer prognosis prediction, especially in patients with digestive or respiratory system cancers.

Keywords: cancer, miR-126, prognosis

Introduction

MicroRNAs (miRNAs) are a class of highly conserved noncoding RNAs with a length of ~22 nucleotides that participate in a wide range of biological processes, such as proliferation, differentiation, and apoptosis.[1] Depending on the complementarity between miRNA and mRNA, they inhibit gene expression mostly by binding to 3′-untranslated region of target mRNAs, which leads to degradation or inhibition of the target mRNA translation. Notably, the research by Calin et al was the first to associate miRNAs with cancers. They reported that miRNA-15 and miRNA-16 were downregulated in 68% of chronic lymphocytic leukemias.[2] Since then, an increasing number of investigations across the globe began to focus on miRNA's role in different types of cancers. To date, hundreds of miRNAs were discovered. It was further demonstrated that certain types of cancers featured distinct miRNA expression profiles.[3,4]

Located within the seventh intron of epidermal growth factor-like protein 7 gene (*EGFL7*) on human chromosome 9, microRNA-126 (miR-126) is often expressed in endothelial cells, behaving to mediate angiogenesis and inflammation.[5] In most cases, miR-126 functions as a tumor suppressor.[6–9] Nonetheless, in other instances, it is more complicated or even helps to promote carcinogenesis and cancer progression.[10,11] Recent years have seen many studies concentrating on the association of miR-126 and cancer prognosis,[12–28] which may not only provide a promising target for future cancer

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treatment in the long term but also give some insights into whether miR-126 could be used as a prognostic biomarker in related scientific research or clinical trials in the short term. Generally, loss of miR-126 was a negative prognostic factor,[19,20] but similar to the results of in vitro study, their relationship is not consistent.[23,28] Thus, the present study was conducted to evaluate whether miR-126 could serve as prognostic classifiers in a variety of cancers.

Materials and methods
Search strategy
The search of studies was performed by using PubMed and Embase (updated by January 22, 2016). The following keywords were applied simultaneously: "(microRNA-126 or miR-126 or mir126) and (tumor or neoplasm or cancer or cancer or malignancy)". Potentially related studies were also collected from the reference lists. The comprehensive database search was carried out independently by two authors (Dong and Fu).

Inclusion and exclusion criteria
Studies were considered eligible if they met the following criteria: 1) investigated any cancer; 2) measured dichotomous miR-126 expression levels in tissue or blood, namely, survival data were presented as high-level expression group versus low-level expression group; and 3) analyzed association between miR-126 expression levels and overall survival (OS). Review articles or letters, non-English articles, editorials, laboratory studies, studies with nondichotomous miR-126 expression levels (eg, survival data divided by tertiles), and studies investigating a set of miRNAs were all excluded. If hazard ratio (HR) and 95% confidence interval (CI) could not be extracted from the articles due to the absence of key information, then these studies were not included in the analysis (Figure 1).

Data extraction
Data extraction was first performed carefully by Guan and Fu and subsequently checked by Zhou. Moreover, search was performed again in the excluded articles by Dong and Li in order to not miss any potentially related study. The extracted data elements of this review included the following: 1) publication details: first author's last name and publication year; 2) characteristics of the studied population: sample size, disease, and stage of disease; 3) miR-126 assessment and cutoff definition; and 4) HR of elevated miR-126 for OS, as well as
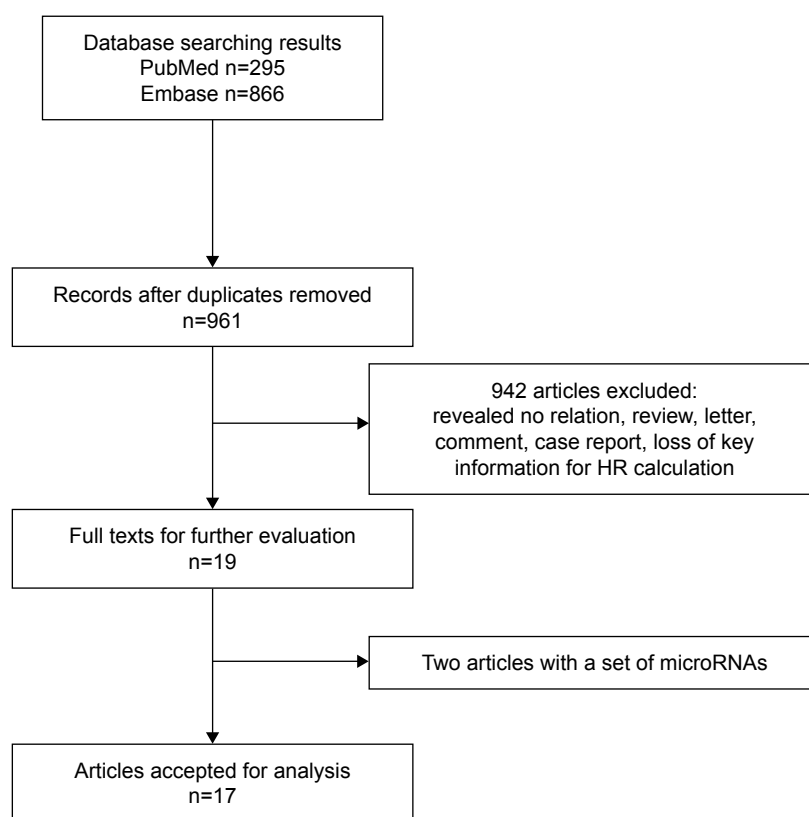
Database searching results
PubMed n=295
Embase n=866

↓

Records after duplicates removed
n=961

→ 942 articles excluded:
revealed no relation, review, letter,
comment, case report, loss of key
information for HR calculation

↓

Full texts for further evaluation
n=19

→ Two articles with a set of microRNAs

↓

Articles accepted for analysis
n=17

Figure 1 Flow diagram depicting the selection process of eligible studies.
Abbreviation: HR, hazard ratio.

their 95% CI and *P*-value. The simplest method consisted of direct collection of HR and their 95% CI from the original article or from authors, with an HR of >1 being associated with a poor outcome. If only Kaplan–Meier curves were available, data were extracted from the graphical survival plots and estimation of the HR was then performed using the described method.[29]

Qualitative assessment

Newcastle–Ottawa scale was used to assess the method-ological quality of studies incorporated in this meta-analysis, which was judged on three aspects: the selection of the study groups, the comparability of the groups, and the outcome of interest, respectively.[30–32] The lowest score was 0 and the highest was 9. Studies with a score <5 in the present study were not included in the final analysis.

Statistical analysis

Cochran's *Q* test and Higgin's *I²* statistic was used to mea-sure between-study heterogeneity. If heterogeneity did exist (*P*<0.05), random-effects model (DerSimonian and Laird method) was applied to calculate pooled HR. If not, fixed-effects model was used. Subgroup analysis, sensitive analy-sis, and meta-regression were further applied to investigate sources of heterogeneity. Publication bias was assessed by Begg's test and Egger's test.[33,34] If a publication bias did exist, the Duval and Tweedie's trim and fill method was used to adjust the results.[35] Stata Version 12.0 (StataCorp LP, Col-lege Station, TX, USA) was used in all analyses. A *P*-value of <0.05 was considered to be statistically significant.

Results

Summary of analyzed studies

By searching PubMed and Embase, a total of 1,161 records for miR-126 were collected. Then, 200 duplicate records were removed. In all, 941 studies did not meet the eligibility criteria. Two studies investigated a set of miRs but not miR-126 alone.[36,37] At last, 17 studies were included in the final meta-analysis that had a total of 2,437 patients from the USA, Denmark, the Netherlands, Serbia, Canada, South Korea, Japan, and the People's Republic of China. The types of carcinomas included non-small cell lung cancer (NSCLC), esophageal cancer, colorectal cancer (CRC), hepatocellular carcinoma, clear-cell renal cell carcinoma, adult T-cell leukemia, acute myeloid leukemia, and cervical cancer, osteosarcoma, melanoma, and laryngeal squamous cell carcinoma. Ten studies (n=842) included Asian patients. Four studies (n=602) concentrated on respiratory system

disease. Seven articles (n=1,088) focused on digestive system diseases. Tissue specimens were used in 14 studies. In situ hybridization (ISH) was applied in three studies. Quantitative real-time polymerase chain reaction (qRT-PCR) was used in 14 studies. Details of the key information in the final meta-analysis are listed in Table 1.

Qualitative assessment

Newcastle–Ottawa scale revealed that the study quality varied from 5 to 8, with a mean of 6.5 (Table 2). All the 17 studies were included in the final analysis.

OS associated with miR-126 expression

Because of the significant heterogeneity (*I²*=63.2%, *P*<0.01), random-effects model was performed, indicating that higher level of miR-126 significantly predicted better OS (HR 0.70, 95% CI: 0.62–0.79, random-effects model; Figure 2). Sub-group analysis was further conducted according to the main characteristics, which demonstrated that the predictive role of miR-126 was especially significant in digestive system cancers (HR 0.70, 95% CI: 0.59–0.83, fixed-effects model) and respiratory system cancers (HR 0.71, 95% CI: 0.59–0.85, random-effects model). In addition, the association was also significant in other subgroups, including Asian patients (HR 0.67, 95% CI: 0.58–0.77, fixed-effects model), white patients (HR 0.76, 95% CI: 0.63–0.92, random-effects model), studies testing tissue specimen (HR 0.68, 95% CI: 0.60–0.76, random-effects model), miR-126 assay by qRT-PCR (HR 0.70, 95% CI: 0.61–0.79, random-effects model), and HR obtained by report (HR 0.69, 95% CI: 0.61–0.79, random-effects model). Details are listed in Table 3.

Heterogeneity analysis

The subgroup analysis showed different prognostic powers in miR-126 (tissue or blood), miR-126 assay method (ISH or qRT-PCR), and data source (reported or extracted from the survival curve). The sensitivity analysis demonstrated that there was no significant change in heterogeneity, no matter which article was excluded (Figure 3). Moreover, meta-regression analysis was performed to further identify the source of heterogeneity, showing that heterogeneity may be induced by disease types (*I²*=59.74%, adjusted *R²*=17.4%) and data source (*I²*=60.35%, adjusted *R²*=15.75%), although neither reached statistical significance (*P*>0.05).

Publication bias

We performed Begg's and Egger's tests to assess potential publication bias.[33,34] The value was 0.064 for Begg's test and

Table 1 A summary table of the meta-analysis

Study	Year	Origin of population	Tumor type	Sample number	Stage	Follow-up (months)[a]	Source of RNA	miR-126 assay	Cutoff	Hazard ratio	Multivariate analysis
Hu et al[12]	2011	USA	EC	99	NR	256.43	Tissue	ISH	Staining intensity (+, ++, +++)	Report	Yes
Hansen et al[13]	2011	Denmark	CRC	81	I–IV	NR	Tissue	ISH	Median	Report	No
Hansen et al[14]	2012	Denmark	CRC	83	IV	NR	Tissue	ISH	Median	DE	No
Ishihara et al[15]	2012	Japan	ATL	35	NR	NR	Blood	qRT-PCR	Median	DE	No
Yang et al[16]	2012	People's Republic of China	NSCLC	442	I–IV	60*	Tissue	qRT-PCR	Median	Report	Yes
Jusufović et al[17]	2012	Serbia	NSCLC	50	II–IV	NR	Tissue	qRT-PCR	Median	Report	No
Han et al[18]	2012	People's Republic of China	HCC	105	I–IV	42.89	Tissue	qRT-PCR	Fold change =2	Report	No
Chen et al[19]	2013	People's Republic of China	HCC	68	I–III	49	Tissue	qRT-PCR	0.7 (ROC curve)	DE	No
Liu et al[20]	2014	People's Republic of China	CRC	92	I–IV	65	Tissue	qRT-PCR	Median	Report	Yes
Kim et al[21]	2014	South Korea	NSCLC	72	I–IV	31	Tissue	qRT-PCR	Median	Report	Yes
Hansen et al[22]	2014	Denmark	CRC	560	II	84	Tissue	qRT-PCR	Median	Report	Yes
de Leeuw et al[23]	2014	the Netherlands	AML	92	NR	NR	Blood	qRT-PCR	Median	DE	No
Yang et al[24]	2014	People's Republic of China	CC	133	I–IV	NR	Tissue	qRT-PCR	Median	Report	Yes
Sun et al[25]	2014	People's Republic of China	LSCC	38		NR	Blood	qRT-PCR	Median	DE	No
Liu et al[26]	2015	People's Republic of China	Osteosarcoma	122	I–IV	NR	Tissue	qRT-PCR	Median	Report	Yes
Lin et al[27]	2015	People's Republic of China	Melanoma	108	I–IV	NR	Tissue	qRT-PCR	Median	Report	Yes
Khella et al[28]	2015	Canada	RCC	257	I–IV	NR	Tissue	qRT-PCR	20th percentile	Report	Yes

Notes: The "*" denotes maximal survival. Cutoff is the standard used to define the expression level. [a]Data presented as median.
Abbreviations: miR-126, microRNA-126; EC, esophageal cancer; NR, not reported; ISH, in situ hybridization; CRC, colorectal cancer; DE, data extrapolated; ATL, adult T-cell leukemia; qRT-PCR, quantitative real-time polymerase chain reaction; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; ROC, receiver operating characteristic; AML, acute myeloid leukemia; CC, cervical cancer; LSCC, laryngeal squamous cell carcinoma; RCC, clear-cell renal cell carcinoma.

0.042 for Egger's test (Figure 4). Although no publication bias was revealed in Begg's test, Egger's test revealed publication bias. Thus, trim and fill method was performed to make pooled HR more reliable. The adjusted HR was 0.59 (0.432–0.752, $P<0.01$).

Discussion

To date, miRNA expression profiling studies reported aberrant expression of miR-126 in a variety of cancers, including CRC, esophageal cancer, hepatocellular carcinoma, acute myeloid leukemia, gastric cancer, thyroid cancer, breast cancer, oral cancer, and prostate cancer.[38] Studies in vitro revealed complexity of miR-126 in the biological regulation. On one hand, it serves as a tumor suppressor.[39–42] In
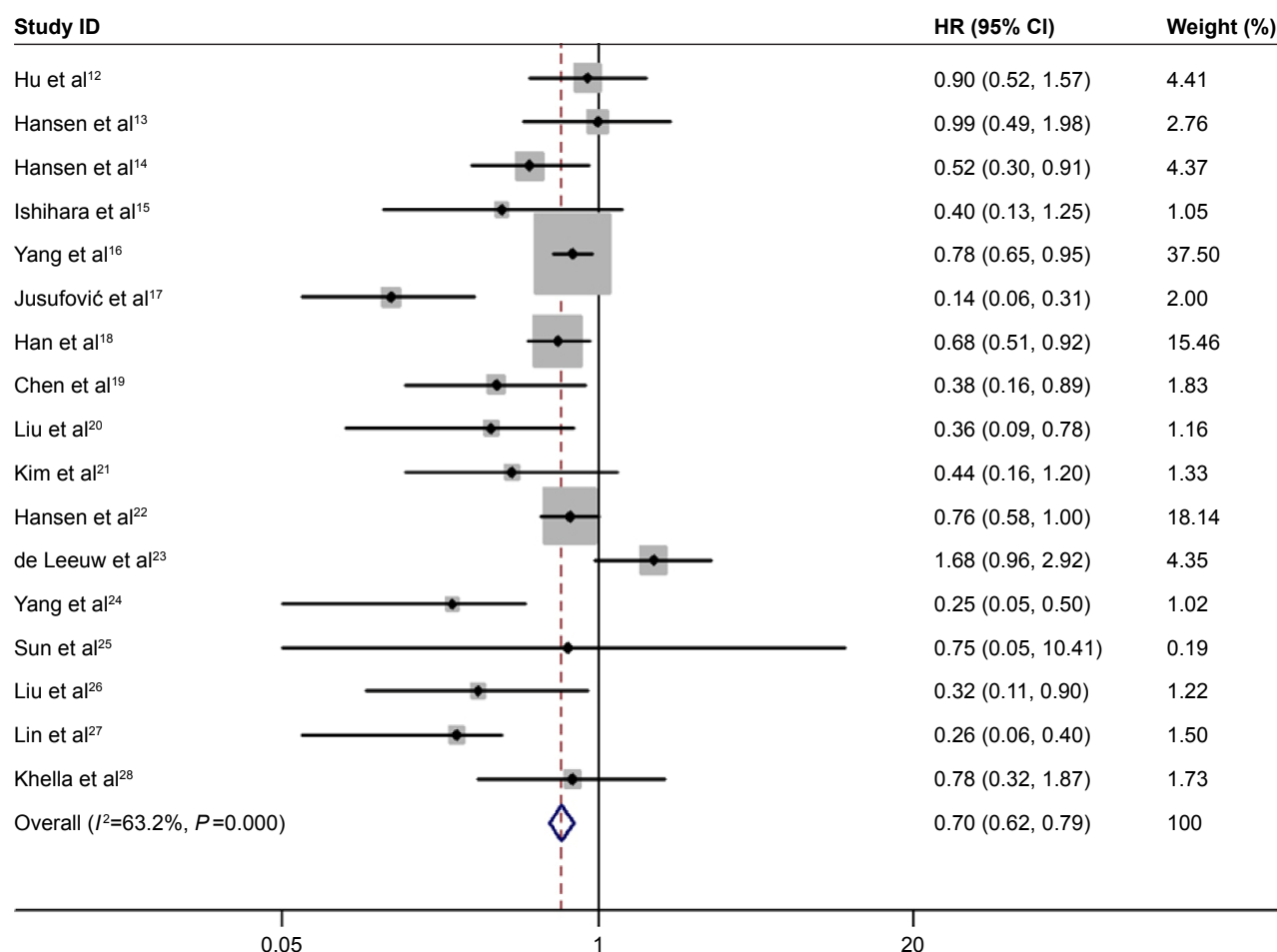
terms of cell cycles, Miko et al discovered that small cell lung cancer cells were delayed in the G1 phase by miR-126 overexpression.[39] Consistently, cell cycle progression from the G1/G0 phase to S phase was also inhibited by miR-126 in the breast cancer cell MCF-7.[40] Targeting EGFL7, miR-126 decreased angiogenesis factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor in oral squamous cell carcinoma cells. By contrast, transfection with miR-126 dramatically decreased cell proliferation, cell cycle progression, and cell invasion.[41] In colon cancer, Li et al transfected miR-126 into CRC SW480 and HT-29, in which inhibited growth was observed.[42] In addition, as is well known, epithelial–mesenchymal transition is generally regarded as the initial step toward distant metastasis.

Table 2 Quality assessment based on the Newcastle–Ottawa scale

Study ID	Selection	Comparability	Outcome	Total score
Hu et al[12]	4	0	2	6
Hansen et al[13]	4	2	1	7
Hansen et al[14]	4	1	1	6
Ishihara et al[15]	4	0	1	5
Yang et al[16]	4	2	2	8
Jusufović et al[17]	4	0	1	5
Han et al[18]	4	0	2	6
Chen et al[19]	4	2	2	8
Liu et al[20]	4	1	2	7
Kim et al[21]	4	1	2	7
Hansen et al[22]	4	1	2	7
de Leeuw et al[23]	4	0	1	5
Yang et al[24]	4	1	2	7
Sun et al[25]	4	2	1	7
Liu et al[26]	4	1	1	6
Lin et al[27]	4	1	1	6
Khella et al[28]	4	1	1	6

Note: Selection: representativeness of studies (maximum score of 4). Comparability: comparability of studies based on the the design or analysis (maximum score of 2). Outcome: assessment of outcome and follow-up (maximum score of 3). For futher details see Wells et al.[30]

In pancreatic cancer cells, miR-126 was involved in this process by regulating disintegrin and metalloproteinase domain-containing protein 9 (ADAM9). Reexpression of miR-126 led to reduced cellular migration, invasion, and induction of epithelial marker E-cadherin.[43] On the other hand, it was suggested that overexpression of exogenous miR-126 favored growth of gastric cancer cell lines by regulating its downstream target genes. These results suggested the complex behavior of miR-126, which may function either as an oncogene or as a tumor suppressor in biological activities.[10] Numerous pathways participated in the function of miR-126. In breast cancer, miR-126 inhibited endothelial cell recruitment and angiogenesis by negatively regulating insulin-like growth factor-binding protein 2/insulin-like growth factor 1/insulin-like growth factor 1 receptor and growth arrest-specific 6/MERTK signaling pathways.[44] Zhu et al revealed that miR-126 facilitated tumor genesis and growth by regulating the VEGF/phosphoinositide

Study ID	HR (95% CI)	Weight (%)
Hu et al[12]	0.90 (0.52, 1.57)	4.41
Hansen et al[13]	0.99 (0.49, 1.98)	2.76
Hansen et al[14]	0.52 (0.30, 0.91)	4.37
Ishihara et al[15]	0.40 (0.13, 1.25)	1.05
Yang et al[16]	0.78 (0.65, 0.95)	37.50
Jusufović et al[17]	0.14 (0.06, 0.31)	2.00
Han et al[18]	0.68 (0.51, 0.92)	15.46
Chen et al[19]	0.38 (0.16, 0.89)	1.83
Liu et al[20]	0.36 (0.09, 0.78)	1.16
Kim et al[21]	0.44 (0.16, 1.20)	1.33
Hansen et al[22]	0.76 (0.58, 1.00)	18.14
de Leeuw et al[23]	1.68 (0.96, 2.92)	4.35
Yang et al[24]	0.25 (0.05, 0.50)	1.02
Sun et al[25]	0.75 (0.05, 10.41)	0.19
Liu et al[26]	0.32 (0.11, 0.90)	1.22
Lin et al[27]	0.26 (0.06, 0.40)	1.50
Khella et al[28]	0.78 (0.32, 1.87)	1.73
Overall (I^2=63.2%, P=0.000)	0.70 (0.62, 0.79)	100

Figure 2 Forest plot of the relationship between miR-126 expression and OS.
Abbreviations: miR-126, microRNA-126; OS, overall survival; CI, confidence interval; HR, hazard ratio.

Table 3 Subgroup analysis

Subgroup	I^2 (%)	P-value	HR (95% CI)	P-value
Origin of population				
White patients	77.6	<0.01	0.76 (0.63–0.92)[a]	0.04
Asian patients	42.1	0.08	0.67 (0.58–0.77)[b]	<0.01
Tumor type				
Digestive system cancers	9.9	0.35	0.70 (0.59–0.83)[b]	<0.01
Respiratory system cancers	82.2	<0.01	0.71 (0.59–0.85)[a]	<0.01
Source of RNA				
Tissue	60.3	0.02	0.68 (0.60–0.76)[a]	<0.01
Blood	60.9	0.08	1.25 (0.76–2.04)[b]	0.38
miR-126 assay				
ISH	25.9	0.26	0.75 (0.53–1.05)[b]	0.10
qRT-PCR	68.0	<0.01	0.7 (0.61–0.79)[a]	<0.01
HR				
Report	63.2	0.02	0.69 (0.61–0.79)[a]	<0.01
DE	70.0	0.01	0.75 (0.54–1.05)[a]	0.10
Cutoff				
Median	70.4	<0.01	0.70 (0.62–0.80)[a]	<0.01
Others	0	0.42	0.69 (0.54–0.88)[b]	<0.01
Multivariate analysis				
Yes	42.9	0.08	0.72 (0.63–0.83)[b]	<0.01
No	75.8	<0.01	0.66 (0.54–0.81)[a]	<0.01

Notes: [a]Random-effects model. [b]Fixed-effects model. P-value <0.05 was considered to be statistically significant.
Abbreviations: HR, hazard ratio; miR-126, microRNA-126; ISH, in situ hybridization; qRT-PCR, quantitative real-time polymerase chain reaction; DE, data extrapolated; CI, confidence interval.

3-kinase/AKT signaling pathway.[45] Li et al demonstrated that miR-126 inhibited colon cancer cell proliferation and invasion via RhoA/ROCK signaling.[46] A better understanding of miR-126 biological features is important to understand its role as a prognostic factor and its possible role as a treatment target.

During recent years, many efforts were made to explore the association between miRNAs and cancers in diagnosis,[47] prognosis,[48] and treatment response[49] in order to find potential biomarkers to be used in future clinical practice. Undoubtedly, miR-126 is a promising one. Yang et al revealed that downregulation of miR-126 in NSCLC patients is correlated with worse OS (HR 0.782, 95% CI: 0.647–0.945).[16] Similar results were reported by Jusufović et al who discovered that lower miR-126 expression was a negative prognostic factor for both progression free survival (HR 0.10, 95% CI: 0.04–0.21) and OS (HR 0.14, 95% CI: 0.06–0.31) in NSCLC patients, which may be attributed to elevated tumor angiogenesis.[17] Using qRT-PCR, Yang et al examined miR-126 expression level in human cervical cancer tissues and indicated that miR-126 was an independent prognostic factor (HR 3.97, 95% CI: 2.01–20.22).[24] The potential prognostic role
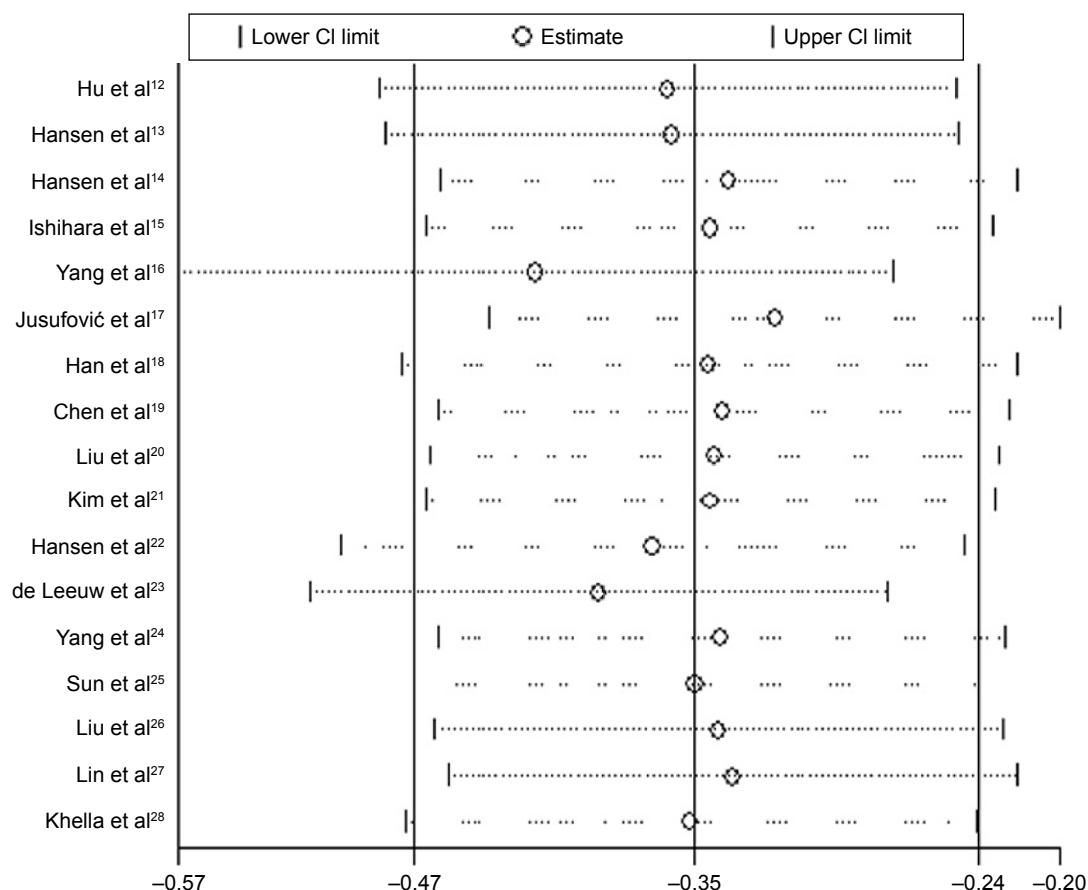
Figure 3 Sensitivity analysis for meta-analysis.
Abbreviation: CI, confidence interval.

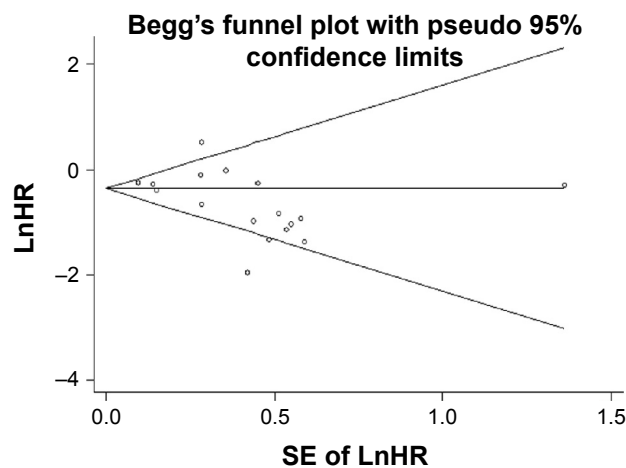## Begg's funnel plot with pseudo 95% confidence limits

Figure 4 Funnel plot of miR-126 and overall survival.
Abbreviations: miR-126, microRNA-126; HR, hazard ratio; SE, standard error.

of miR-126 was extensively explored in CRC. Focusing on stage II colon cancer patients, a study by Hansen et al showed that correlation between miR-126 and OS approached statistical significance (HR 0.76, 95% CI: 0.58–1.00).[22] Liu et al found that CXCR4 in CRC was the target of miR-126, which contributed to poor survival of patients with low miR-126.[20] However, the results of related investigations have not demonstrated concordance to the same extent. In 2008, Díaz et al divided miR-126 expression by tertiles in human colon cancer patients and did not find statistical significance in the comparison both in medium versus low expression group (HR 1.02, 95% CI: 0.43–2.41) and in high versus low expression group (HR 0.91, 95% CI; 0.39–2.15).[50]

According to our study, higher level of miR-126 predicted better OS (HR 0.70, 95% CI: 0.62–0.79, random-effects model), especially in digestive system cancers (HR 0.70, 95% CI: 0.59–0.83, fixed-effects model) and respiratory system cancers (HR 0.71, 95% CI: 0.59–0.85, random-effects model). However, we must interpret the conclusion with caution. We believe that miRNA alone is not the ideal biomarker for cancer prognosis. In the first place, miRNA regulates multiple target mRNAs, and each target mRNA is regulated by multiple miRNAs. Moreover, regulation of miR-126 mediated various signal pathways in different tissues. Its multiple functions seem to rely on the cell type and the cellular environment, which was suggested by the researches showing that not all validated miR-126 target mRNAs were affected by miR-126 in every cell type, for instance, *EGFL7*.[50,51] Thus, association between aberrant expression levels of miR-126 with prognosis needs further validation. In the second place, miR-126 combined with other biomarkers may be more reasonable to be used as a prognostic factor and they have already revealed an elevated prognostic power than

miR-126 alone, for instance, miR-126 combining let-7b[17] or miR151-3p.[36] We hypothesized in future clinical practice that a set of related miR may be a better option.[37] Moreover, by taking all participants with varied cancer types in this meta-analysis, the favorable trend of miR-126, outweighed the absolute value of pooled HR, because, even if miR-126 was established as a critical prognostic factor like Her-2, we believe that the prognosis of patients depends on many factors, including general condition, tumor differentiation, and TNM staging. Thus, in a short term, the aim to elucidate association of miR-126 with prognosis is not to apply miR-126 in guiding clinical practice immediately; instead, it may provide some insights into designs of clinical trials or scientific research.

There are limitations to consider. First, heterogeneity in the present study amounted to 63.2%. To find its source, sensitivity analysis as well as meta-regression showed no factors profoundly influencing heterogeneity. Nonetheless, according to subgroup analysis, sources of miR-126 (tissue or blood), miR-126 assay method (ISH or qRT-PCR), and data source (reported or extracted from the survival curve) may partly contribute to the heterogeneity. Therefore, we recommend future investigations to use qRT-PCR and tissue specimen in order to compare with other researches. Second, the value of Egger's test reveals a potential publication bias. To make our results more reliable, trim and fill method was subsequently performed. The HR after adjustment changed to 0.59 (0.463–0.752, $P<0.01$), almost consistent with the unadjusted result. Thus, our result was reliable. In addition, publication bias may also contribute to heterogeneity. To reduce it, further studies enrolling more patients are needed.

Conclusion

This meta-analysis indicated that a high level of miR-126 played a favorable role in predicting patients' OS, especially for patients with digestive or respiratory system cancers. However, given the limitations of the present study, further investigations are needed.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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