ORIGINAL RESEARCH

Quantifying the prognostic significance of microRNA-17/17-5P in cancers: a meta-analysis based on published studies

Fujiao Duan[1]
Yang Yang[2]
Weigang Liu[3]
Jie Zhao[4]
Xiaoqin Song[4]
Lifeng Li[4]
Fuqin Li[2]

[1]Medical Research Office, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, Henan, China; [2]Department of Nosocomial Infection Management, First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, China; [3]Medical Record Statistics Office, Affiliated Hospital of Hebei University of Engineering, Handan, Hebei 056002, China; [4]Center of Telemedicine, First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450008, China

Objective: The aim of this study was to investigate the prognostic value of mircoRNA-17 and mircoRNA-17-5P (miR-17/17-5P) in patients with cancer.

Materials and methods: We conducted a comprehensive search on published literature following the guidelines of the meta-analysis of observational studies in epidemiology group for design, implementation, and reporting. The methodological qualities for included studies were assessed using the quality in prognosis studies. The pooled hazard ratios (HRs) with 95% CIs for overall survival (OS) and progression-free survival/recurrence-free survival/disease-free survival (PFS/RFS/DFS) were calculated to appraise the associations between miR-17/17-5P expression and cancer prognosis.

Results: A total of 21 studies involving 2099 subjects were analyzed in evidence synthesis. The results showed that high expression of miR-17 was associated with poor OS (HR=2.14; 95% CI: 1.69–2.71, $P<0.001$) in patients with cancer, especially in Caucasian (HR=2.23; 95% CI: 1.58–3.14, $P<0.001$) and digestive tract cancer (HR=1.29, 95% CI: 1.03–1.63, $P=0.03$), and miR-17 expression was significantly correlated with PFS/RFS in cancer patients (HR=1.69, 95% CI: 1.29–2.22, $P<0.001$). miR-17-5P overexpression was significantly linked with poor OS in cancer patients (HR=1.66; 95% CI: 1.31–2.09, $P=0.00$), especially in Asian (HR=1.81; 95% CI: 1.37–2.40, $P<0.001$), digestive tract cancer (HR=1.80; 95% CI: 1.29–2.50, $P<0.001$), and serum sample (HR=1.76; 95% CI: 1.29–2.41, $P<0.001$). miR-17-5P expression was significantly associated with DFS in cancer patients (HR=1.58, 95% CI: 1.07–2.35, $P=0.02$).

Conclusion: High expression of miR-17 and miR-17-5P are significantly associated with poor survival in patients with cancer. This indicated that miR-17/17-5P may be a novel prognostic indicator in cancer.

Keywords: miR-17/17-5P, prognosis, cancer, meta-analysis

Introduction

Cancer is one of the major disease burdens worldwide.[1] In 2016, cancer was the second leading cause of death in the United States.[2] Cancer has been the leading cause of death with about one-fourth of all deaths in China.[3] The burden of disease attributable to the occurrence of cancers was rising.

MicroRNA (miRNA) is a kind of small, non-protein-coding RNA (containing about 22 nucleotides) molecules involving in RNA silencing and post-transcriptional regulation of gene expression through mRNA degradation and translational repression,[4,5] which regulate gene expression by binding to the 3'-untranslated region (UTR) of target mRNAs.[6]

Correspondence: Fujiao Duan
Medical Research Office, Affiliated Cancer Hospital of Zhengzhou University, No. 127, Dongming Road, Zhengzhou, 450008, China (PRC)
Email fjduan@126.com

More and more studies had proved that aberrantly expressed miRNAs were involved in different types of cancers, which acted as tumor oncogenes or suppressors and played critical roles in many aspects of cancer carcinogenesis, including cell proliferation, differentiation, angiogenesis, and metastasis.[7–10] miRNAs are regarded as biomarkers for cancer prognosis and prediction of treatment response beacuse of the high stability of miRNAs in circulation and formalin-fixed, paraffin-embedded (FFPE) tissue.[11–13]

MicroRNA-17 (miR-17) family is the major common studied oncogenic miRNA (onco-miRNA) groups.[14] miR-17 and miR-17-5P (miR-17/17-5P) belong to miR-17 family, which has been shown to play a key role in the pathogenesis of diverse cancers.[15] miR-17 overexpression significantly improve the ability of migration and motility of melanoma cells by suppression of translation of *ETV1*.[16] The miR-17-5p was overexpressed in ovarian cancer cells. It activated AKT by lowering phosphatase and tensin homolog (PTEN) in ovarian cancer cells.[17]

High levels of the oncogenic miRNA (onco-miR) guide strand were called miR-17-5p. In triple-negative breast cancer, the overexpressed miR-17-5p can inhibit ribosomal translation of cancer suppressor gene mRNAs, such as PTEN or programmed cell death 4 (PDCD4).[18] However, expression of miR-17/17-5P in the circulation or tissue have not been predicted or experimentally confirmed, and the overall survival (OS) and progression-free survival/recurrence-free survival/disease-free survival (PFS/RFS/DFS) of the patterns and expression levels of miR-17/17-5P have not been well established.

In this study, a systematic evaluation with the prognostic data of miR-17/17-5P from published studies was first performed. We focused on correlations between the expression level of miR-17/17-5P and prognostic indicator, which can guide clinical decisions.

Materials and methods

The present study was executed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[19] group and criteria of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[20] The protocol of this meta-analysis has not been published or registered to any databases.

Search strategy

Studies related to miR-17/17-5P and cancers were retrieved from multiple databases: PubMed, EMBASE, Web of Science, Google Scholar, Wanfang (China), and the Chinese National Knowledge Infrastructure (CNKI) database through July 2017. The search items were combinations of "microRNA-17" or "miR-17", "microRNA-17-5P" or "miR-17-5P" and "neoplasms" or "cancer". We additionally manually retrieved bibliography of the selected articles to identify further potentially relevant studies that may be missed by online information retrieval.

Study selection and exclusion criteria

Studies were eligible for inclusion if they were: 1) cohort studies that investigated the relationship between miR-17/17-5P and patients with cancer prognosis; 2) provided available data to extrapolate the hazard ratio for survival and corresponding 95% CI; 3) the expression of miR-17/17-5P was measured in cancer tissue or serum; and 4) available in Chinese or English.

Exclusion criteria were: 1) reviews, experimental cell research, non-human research, letters; 2) neither Chinese nor English studies; 3) experiments not conducted on cancer patients; and 4) insufficient data to calculate the HRs and their 95% CIs, or the Kaplan–Meier curve unable to calculate HRs and 95% CI parameters. If a study had overlapping data with other published literature, we selected the study with a larger sample size or the latest published article. Two independent reviewers (FJD and WGL) screened all initially identified articles according to the eligibility for inclusion criteria.

Data extraction

Two reviewers (YY and JZ) independently identified eligibility studies and performed data extraction and quality assessment. Discrepancies were resolved by consensus and by referencing the original reports.

The following data/necessary information was extracted from the eligible studies if they were available: first author, year of publication, original country, histopathological classification and stage, sample size and type, detection method, cutoff value and follow-up, HRs of miR-17/17-5P for OS and/or PFS/RFS/DFS and their 95% CIs. If the study only provided survival data in a Kaplan–Meier curve, the HR and 95% CI were digitized and extracted using the methods designed by Parmar et al[21] and Tierney et al.[22]

Quality assessment

The quality of included studies was assessed according to the Newcastle–Ottawa Scale (NOS).[23] The method rates observational studies on a nine-point scale, and a study with a score ≥6 was considered a high-quality study.

The Quality In Prognosis Studies (QUIPS) for specific biases of prognosis was appraised based on the method of Hayden et al.[24] Estimation of the potential bias of the items included study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis, and reporting.

The quality evaluation was processed independently by two authors (FQL and WGL), and in case of any inconsistency, the final decision was reached with consensus.

Data synthesis and statistical analysis

Data were analyzed by using RRevMan (Version 5.3 for Windows, Cochrane Collaboration, Oxford, UK) and STATA (Version 13.1MP, StataCorp, College Station, TX, USA). HRs and corresponding 95% CIs were utilized to assess the relationship strength between miR-17/17-5P expression and prognosis. Inter-study heterogeneity was evaluated using the Cochran's Q test and Higgin's I^2. $P_{heterogeneity}<0.1$ and $I^2> 50\%$ represents high heterogeneity. The random-effects model (DerSimonian and Laird method)[25] was used in a

pooled analysis. Afterward, meta-regression was utilized to explore sources of heterogeneity.[26] Otherwise, a fixed-effects model (Mantel–Haenszel method)[27] was used. The subgroup analyses were performed by ethnicity (Asian, Caucasian) and cancer subtypes (pathological type), if a cancer type was studied in less than 2 individual studies, it was classified as the "other cancers" group. Assessing the impact of included studies on the pooled results, one-way sensitivity analyses were performed to compensate for statistical heterogeneity.

Begg's test (rank correlation test)[28] and Egger's test (weighted linear regression test)[29] are used to assess the extent of publication bias. A two-tailed value of $P<0.05$ was considered statistically significant.

Results
Study identification

The search process returned 1127 relevant citations and the titles were screened based on the search strategy (Figure 1). According to the exclusion criteria, the abstracts of 197 studies were reviewed. The titles and abstracts were screened
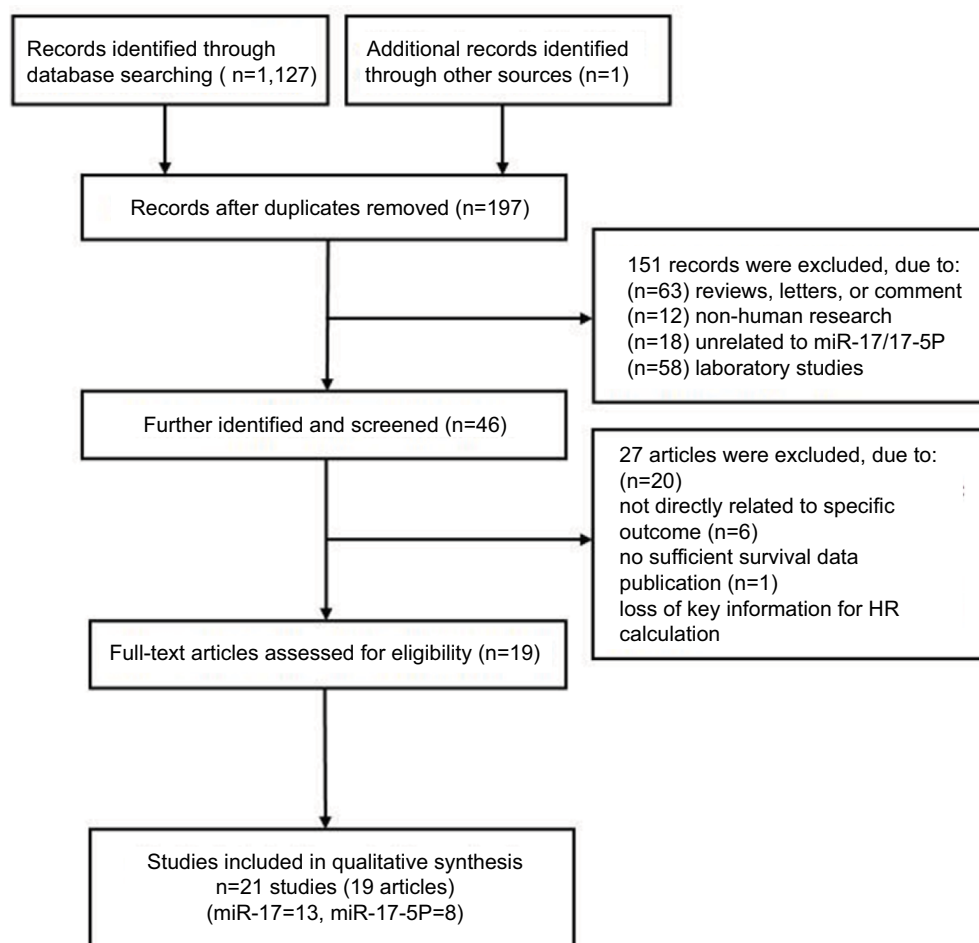
Figure 1 Flow chart of literature search and study selection.
Abbreviations: HR, hazard ratio; miR, microRNA.

by 2 of the authors. Full texts of potentially eligible articles were retrieved for further identification, 19 eligible articles were screened out. The reference lists of eligible articles were screened for potential publications. Finally, a total of 19 articles (21 studies)[30–48] including 11 articles (13 studies)[30–40] for miR-17 and 8[41-48] for miR-17-5P were considered in a pooled analysis. One of the articles[39] performed three cohort studies in different populations.

Baseline characteristics of included studies

The main characteristics of eligible studies are presented in Table 1. The studies were published from 2008 to 2017 and included 2099 patients from China, Brazil, America, Norway, Japan, Spain, and Italy. The patients were classified as Asian or Caucasian based on ethnic background. The types of cancer included breast cancer, osteosarcoma, lymphoma, esophageal squamous cell carcinoma (ESCC), oral cancer, glioma, myeloma, colon cancer, non-small cell lung cancer (NSCLC), gastric cancer, colorectal cancer, hepatocellular carcinoma (HCC), endometrial serous adenocarcinoma (ESC) and malignant mesothelioma (MM). The method of miR-17/17-5P detection was quantitative real-time polymerase chain reaction (qRT-PCR) in 21 studies. miR-17/17-5P expression levels were measured in tissue or serum. The cutoff values of miR-17/17-5P were mostly normal or median.

Qualitative assessment

The results based on QUIPS are summarized in Table 2. The estimated items include the participation, attrition, measurement of prognostic factor, confounding measurement and account, outcome measurement, and analysis and reporting 6 bias domains and the risk of bias shown in Figures 2 and 3. According to the NOS (Table S1), 84% (16/19) of these articles were high-quality (quality score ≥ 6).

Test of heterogeneity

The results of heterogeneity tests are shown in Table 3. There was no significant heterogeneity among studies for the miR-17(I^2=23%, P=0.21) and miR-17-5P (I^2 =0%, P=0.53) in association between miR-17/17-5P expression and the risk of tumorigenesis. Therefore, the fixed effects were applied to calculate the pooled HR for miR-17/17-5P.

Meta-analysis findings

We applied a fixed-effects model to evaluate the pooled HR value (95% CI).

As for the miR-17, HRs of OS were provided by 11 studies, and a significant relation was observed between high miR-17 expression levels and poor OS (HR=2.14; 95% CI: 1.69–2.71, P<0.001). HRs of disease progression were provided by 3 studies and the miR-17 expression level was significantly correlated with PRS/RFS in cancers (HR=1.69; 95% CI: 1.29–2.22, P<0.001) (Figure 2, Table 3). Subgroup analysis was conducted by ethnicity and miR-17 expression was significantly associated with OS in Asian (HR=2.06; 95% CI: 1.49–2.87, P<0.001) and Caucasian (HR=2.23; 95% CI: 1.58–3.14, P<0.001) (Table 3). Additionally, subgroup analysis was carried out according to cancer subtype and the results indicated that a high expression level of miR-17 significantly predicted poor OS in digestive tract cancer (DTC) (HR=2.10; 95% CI: 1.54–2.87, P<0.001) and other cancer types (HR=2.20; 95% CI: 1.53–3.16, P<0.001) (Table 3).

As for the miR-17-5P, HRs of OS were provided by 8 studies, and a significant association was observed between high miR-17-5P expression level and poor OS (HR=1.66; 95% CI: 1.31–2.09, P<0.001) (Figure 3, Table 3). HRs for disease progression were provided by 2 studies, and miR-17-5P expression was significantly correlated with DFS in cancers (HR=1.58; 95% CI: 1.07–2.35, P=0.02) (Figure 3, Table 3). Subgroups analyses were carried out by ethnicity and miR-17-5P expression level was significantly correlated with OS in Asian (HR=1.81; 95% CI: 1.37–2.40, P<0.001), but not in Caucasian (HR=1.36; 95% CI: 1.89–2.07, P=0.15). Subgroups analyses were also carried out based on cancer subtypes and miR-17-5P expression was significantly correlated with OS in DTC (HR=1.80; 95% CI: 1.29–2.50, P<0.001) and other cancer types (HR=1.53; 95% CI: 1.10–2.13, P<0.001). Furthermore, subgroups analyses were performed according to sample types and the result indicated that a high expression level of miR-17 significantly predicted poor OS in tissue sample (HR=1.53; 95% CI: 1.08–2.18, P=0.02) and serum sample (HR=1.76; 95% CI: 1.29–2.41, P<0.001) (Table 3).

Sensitivity analyses

Sensitivity analysis was performed to assess the contribution of each study to the pooled estimate by omitting individual data sets and recalculating the pooled HR estimates for the remaining studies. The stable pooled HR was found not to be dominantly influenced by any individual study (Figure 4).

Publication bias

Begg's and Egger's tests were used to assess the publication bias. No significant publication bias was found in the included

**Table 1** Clinicopathological characteristics of eligible studies

Author	Year	Country	Ethnicity	Locus	Number of samples OS	Number of samples DFS/PFS/RFS	Histology	TNM stage	Sample	Assay	Follow-up (months)	Cutoff	Hazard ratios
Yang et al[30]	2017	China	Asian	miR-17	132		Breast cancer	NA	Frozen tissue	qRT-PCR	84	Normal	SC
Li et al[31]	2016	China	Asian	miR-17	46		Osteosarcoma	NA	Frozen tissue	qRT-PCR	43	Normal	SC
Robaina et al[32]	2016	Brazil	Caucasian	miR-17	41		Lymphoma	I–IV	Frozen tissue	qRT-PCR	69	Median	HR/SC
Xi et al[33]	2015	China	Asian	miR-17	57		Lymphoma	I–IV	Frozen tissue	qRT-PCR	156	Median	HR/SC
Xu et al[34]	2013	China	Asian	miR-17	105		ESCC	I–IV	Frozen tissue	qRT-PCR	52	Median	HR/SC
Chang et al[35]	2013	China	Asian	miR-17	98		Oral cancer	I–IV	Frozen tissue	qRT-PCR	84	Normal	SC
Lu et al[36]	2012	China	Asian	miR-17	108	PFS, 138	Glioma	I–IV	Frozen tissue	qRT-PCR	120	Median	HR/SC
Gao et al[37]	2012	China	Asian	miR-17			Myeloma	NA	Serum	qRT-PCR	35	Median	SC
Yu et al[38]	2012	China	Asian	miR-17	96		Colon cancer	I–IV	Frozen tissue	qRT-PCR	66	Normal	HR/SC
Saito et al[39]	2012	America	Caucasian	miR-17	89		NSCLC	I–III	Frozen tissue	qRT-PCR	80	Median	HR
	2012	Norway	Caucasian	miR-17	37		NSCLC	I–III	Frozen tissue	qRT-PCR	80	Median	HR
	2012	Japan	Asian	miR-17		RFS, 191	NSCLC	I–III	Frozen tissue	qRT-PCR	80	Normal	HR
Valladares-Ayerbes et al[40]	2011	Spain	Caucasian	miR-17	38	PFS, 38	Gastric cancer	I–IV	Serum	qRT-PCR	97	Mean	HR/SC
Komatsu et al[41]	2013	Japan	Asian	miR-17-5P	69		Gastric cancer	I–IV	Serum	qRT-PCR	40	Median	SC
Chen et al[42]	2013	China	Asian	miR-17-5P	221		Lung cancer	I–IV	Serum	qRT-PCR	48	Median	HR/SC
Zheng et al[43]	2013	China	Asian	miR-17-5P	96		HCC	I–IV	Serum	qRT-PCR	76	Median	HR
Chen et al[44]	2012	China	Asian	miR-17-5P	120	DFS, 120	HCC	I–IV	Frozen tissue	qRT-PCR	46	Median	HR/SC
Wang et al[45]	2012	China	Asian	miR-17-5P	65		Gastric cancer	I–IV	Serum	qRT-PCR	34	Normal	HR/SC
Yu et al[46]	2010	Japan	Asian	miR-17-5P	80		Pancreatic cancer	I–IV	Frozen tissue	qRT-PCR	100	Normal	HR/SC
Busacca et al[47]	2010	Italy	Caucasian	miR-17-5P	24		MM	NA	Frozen tissue	qRT-PCR	20	Median	SC
Díaz et al[48]	2008	Spain	Caucasian	miR-17-5P	110	DFS, 100	Colon cancer	I–IV	Frozen tissue	qRT-PCR	99	Median	HR/SC

Abbreviations: OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; SC, survival curve; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; MM, malignant mesothelioma; NA, not applicable.

Table 2 Quality assessment of included studies based on the Quality in Prognosis Studies (QUIPS)

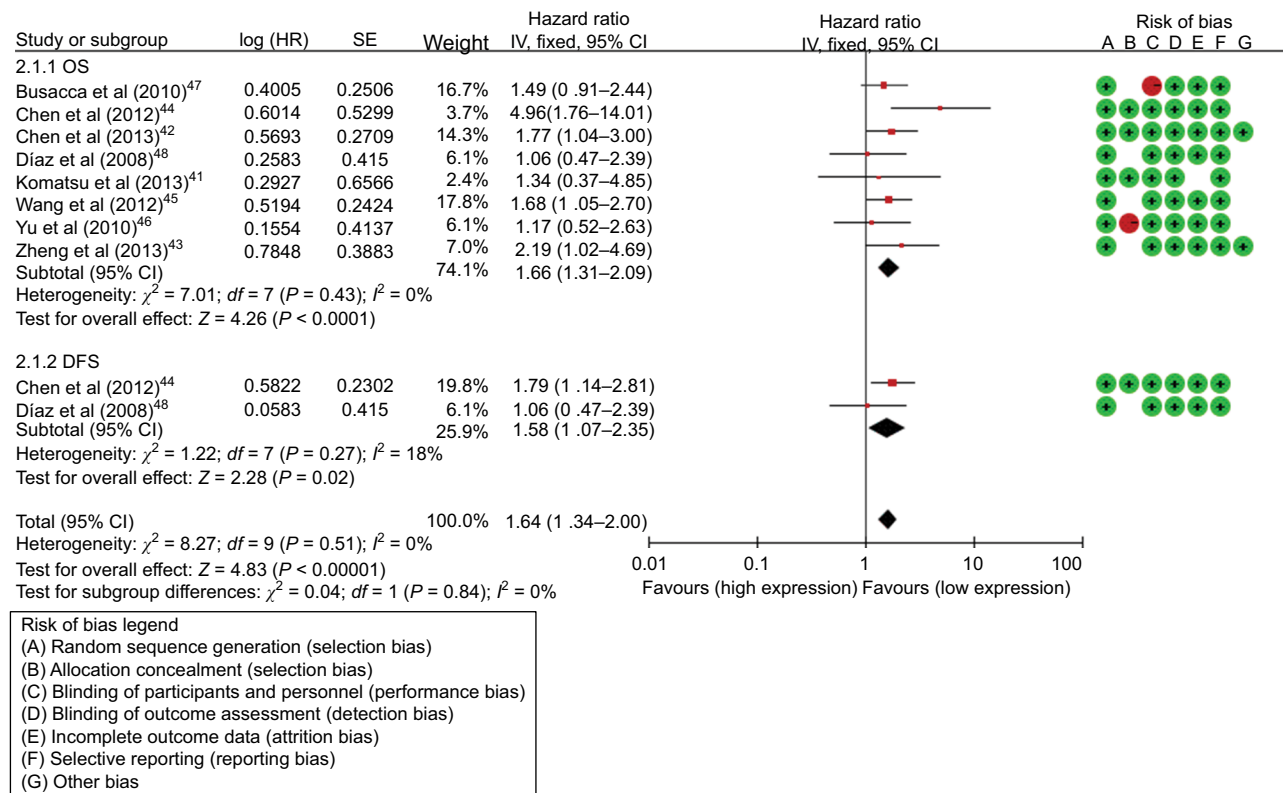| Study	Quality evaluation of prognosis study						Total score[a]	Level of evidence[b]
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting		
Yang et al (2017)[30]	Partly	Partly	Yes	Partly	Partly	Partly	7	2b
Li et al (2016)[31]	Yes	Partly	Yes	Partly	Partly	Partly	7	1b
Robaina et al (2016)[32]	Partly	Yes	Yes	Yes	Partly	Yes	8	2b
Xi et al (2015)[33]	Partly	Partly	Yes	Yes	Partly	Yes	7	2b
Xu et al (2013)[34]	Yes	Partly	Yes	Yes	Partly	Yes	8	2b
Chang et al (2013)[35]	Partly	Partly	Partly	Yes	Partly	Yes	5	2b
Lu et al (2012)[36]	Yes	Partly	Yes	Yes	Partly	Yes	7	2b
Gao et al (2012)[37]	Partly	Partly	Yes	Partly	Partly	Partly	5	2b
Yu et al (2012)[38]	Yes	Yes	Yes	Yes	Partly	Yes	8	2b
Saito et al (2012)[39]	Yes	Yes	Yes	Yes	Partly	Yes	8	1b
Valladares-Ayerbes et al (2011)[40]	Yes	Yes	Yes	Yes	Partly	Yes	8	2b
Komatsu et al (2013)[41]	Partly	Yes	Yes	Yes	Partly	Partly	8	2b
Chen et al (2013)[42]	Yes	Yes	Yes	Yes	Partly	Yes	9	1b
Zheng et al (2013)[43]	Yes	Partly	Yes	Yes	Partly	Yes	8	2b
Chen et al (2012)[44]	Yes	Yes	Yes	Yes	Partly	Yes	7	2b
Wang et al (2012)[45]	Yes	Partly	Yes	Yes	Partly	Yes	6	2b
Yu et al (2010)[46]	Partly	Partly	Yes	Partly	Partly	Yes	6	2b
Busacca et al (2010)[47]	Yes	Partly	Partly	Yes	Partly	Partly	8	2b
Díaz et al (2008)[48]	Yes	Partly	Yes	Yes	Partly	Yes	4	2b

Notes: [a]Quality assessment of included studies based on the Newcastle–Ottawa Scale. [b]The levels of evidence were estimated for all included studies with the Oxford Centre for Evidence-based Medicine criteria.
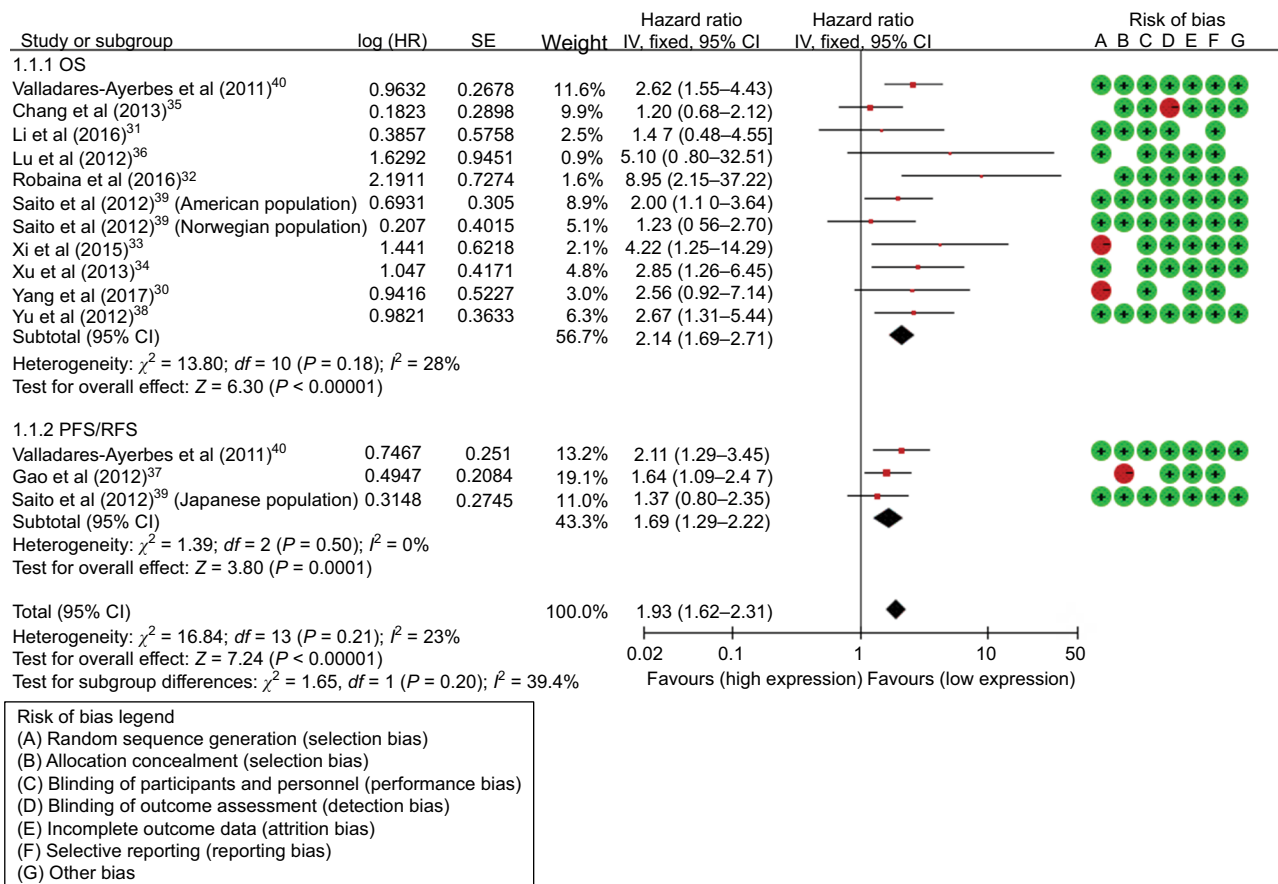
Figure 2 Forest plots of studies evaluating the HRs of high and low miR-17 expression with respect to OS and PFS/RFS.
Abbreviations: OS, overall survival; PFS; progression-free survival; RFS, recurrence-free survival; SE, standard error; *df*, degrees of freedom; HRs, hazard ratios; miR, microRNA.
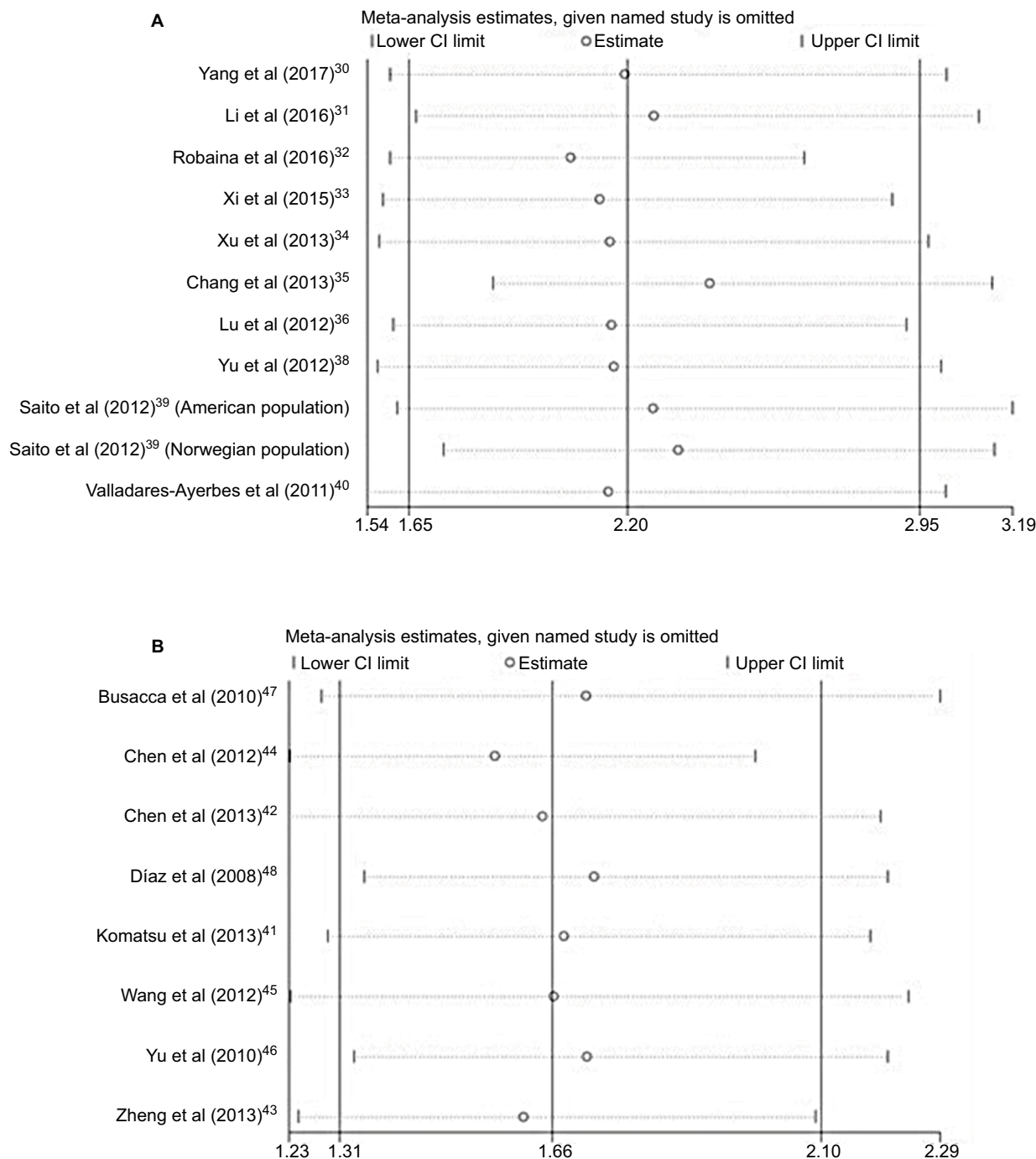
Study or subgroup	log (HR)	SE	Weight	Hazard ratio IV, fixed, 95% CI	Hazard ratio IV, fixed, 95% CI	Risk of bias A B C D E F G
2.1.1 OS						
Busacca et al (2010)[47]	0.4005	0.2506	16.7%	1.49 (0 .91–2.44)		
Chen et al (2012)[44]	0.6014	0.5299	3.7%	4.96(1.76–14.01)		
Chen et al (2013)[42]	0.5693	0.2709	14.3%	1.77 (1.04–3.00)		
Díaz et al (2008)[48]	0.2583	0.415	6.1%	1.06 (0.47–2.39)		
Komatsu et al (2013)[41]	0.2927	0.6566	2.4%	1.34 (0.37–4.85)		
Wang et al (2012)[45]	0.5194	0.2424	17.8%	1.68 (1 .05–2.70)		
Yu et al (2010)[46]	0.1554	0.4137	6.1%	1.17 (0.52–2.63)		
Zheng et al (2013)[43]	0.7848	0.3883	7.0%	2.19 (1.02–4.69)		
Subtotal (95% CI)			74.1%	1.66 (1.31–2.09)		

Heterogeneity: χ^2 = 7.01; df = 7 (P = 0.43); I^2 = 0%
Test for overall effect: Z = 4.26 (P < 0.0001)

2.1.2 DFS						
Chen et al (2012)[44]	0.5822	0.2302	19.8%	1.79 (1 .14–2.81)		
Díaz et al (2008)[48]	0.0583	0.415	6.1%	1.06 (0 .47–2.39)		
Subtotal (95% CI)			25.9%	1.58 (1 .07–2.35)		

Heterogeneity: χ^2 = 1.22; df = 7 (P = 0.27); I^2 = 18%
Test for overall effect: Z = 2.28 (P = 0.02)

Total (95% CI)   100.0%   1.64 (1 .34–2.00)
Heterogeneity: χ^2 = 8.27; df = 9 (P = 0.51); I^2 = 0%
Test for overall effect: Z = 4.83 (P < 0.00001)
Test for subgroup differences: χ^2 = 0.04; df = 1 (P = 0.84); I^2 = 0%

0.01   0.1   1   10   100
Favours (high expression) Favours (low expression)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 3 Forest plots of studies evaluating the HRs of high and low miR-17-5P expression with respect to OS and DFS.
Abbreviations: OS, overall survival; SE, standard error; df, degrees of freedom; DFS, disease-free survival; HR, hazard ratio; miR, microRNA.

Table 3 Main results of pooled HRs in the meta-analysis

Comparisons	Heterogeneity test			Summary HR (95% CI)	Hypothesis test		Studies
	Q	P	I^2(%)		Z	P	
MircroRNA-17							
OS							
Total	13.80	0.18	28	2.14 (1.69–2.71)	6.30	<0.001	11
Ethnicity							
Asian	7.36	0.29	19	2.06 (1.49–2.87)	4.32	<0.001	7
Caucasian	6.33	0.10	53	2.23 (1.58–3.14)	4.54	<0.001	4
Cancer subtypes							
OS							
DTC	5.38	0.15	44	2.10 (1.54–2.87)	4.64	<0.001	4
Other cancers	8.38	0.21	28	2.20 (1.53–3.16)	4.26	<0.001	7
PFS/RFS							
Total	1.39	0.50	0	1.69 (1.29–2.22)	3.80	<0.001	3
MircroRNA-17-5P							
OS							
Total	7.01	0.43	0	1.66 (1.31–2.09)	4.26	<0.001	8
Ethnicity							
Asian	5.29	0.38	6	1.81 (1.37–2.40)	4.16	<0.001	6
Caucasian	0.50	0.48	0	1.36 (0.89–2.07)	1.44	0.15	0
Cancer subtypes							
DTC	5.83	0.21	31	1.80 (1.29–2.50)	3.49	<0.001	5
Other cancers	0.72	0.70	0	1.53 (1.10–2.13)	2.53	0.01	3
Sample							
Tissue	6.14	0.10	51	1.53 (1.08–2.18)	2.39	0.02	4
Serum	0.53	0.91	0	1.76 (1.29–2.41)	3.57	<0.001	4
DFS							
Total	1.22	0.27	18	1.58 (1.07–2.35)	2.28	0.02	2

Abbreviations: OS, overall survival; DTC, digestive tract cancer, including colorectal cancer, esophageal squamous cell carcinoma, pancreatic cancer and hepatocellular carcinoma, oral cancer; PFS, progression-free survival; RFS, recurrence-free survival; DFS, disease-free survival.

A Meta-analysis estimates, given named study is omitted

B Meta-analysis estimates, given named study is omitted

Figure 4 (**A**) Sensitivity analysis for OS of miR-17. (**B**) Sensitivity analysis for OS of miR-17-5P.
Abbreviations: OS, overall survival; miR, microRNA.

studies (Table 4). Meanwhile, the shape of the funnel plots indicated no obvious publication bias (Figures S1 and S2).

Discussion

Emerging studies have demonstrated that miRNAs can act as oncogenes and tumor suppressor genes and play a crucial role in several processes, including cell proliferation, apoptosis, differentiation and metastasis.[49,50] Therefore, explor-ing the profiles of miRNAs and corresponding target genes involved in tumorigenesis may promote the understanding of underlying mechanisms of tumor formation and provide valuable insights for the treatment and early diagnosis of such diseases.[51,52] Results from published studies have continually indicated that the miRNAs which are present in the circula-tion can be promising diagnostic and prognostic biomarkers for tumors.[53,54]

Table 4 Publication bias of miR-17/17-5P for Begg's[28] test and Egger's[29] test

Comparisons	Begg's test		Egger's test		
	z	P	t	P	95% CI
MircroRNA-17					
OS	1.56	0.119	1.73	0.118	−0.506–3.774
PFS/RFS	−0.52	0.602	−0.14	0.909	−7.383–7.221
MircroRNA-17-5P					
OS	0.30	0.764	0.42	0.686	−2.459–3.494
DFS[a]	−	−	−	−	−

Note: [a]Insufficient observations.
Abbreviations: OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; DFS, disease-free survival; miR, microRNA.

In this study, increased expression of miR-17 and miR-17-5P were found to be good predictors of poor survival in patients with a variety of cancers. The combined HRs of OS were 2.14 (95% CI: 1.69–2.71) for miR-17 and 1.69 (95% CI: 1.31–2.09) for miR-17-5P, indicating that elevated miR-17/17-5P levels are closely linked with the prognosis of patients with different types of malignant tumors. This is particularly true for miR-17 in the Caucasian, whose pooled HR of OS was 2.23 (95% CI: 1.58–3.14), and this result further demonstrated the predictive value of miR-17. Subgroup analyses also indicated a closer relationship between rising miR-17 levels and poor survival in the Caucasian subgroup. Among 19 studies reporting on OS in 12 cancer types, 10 were DTC. Due to the limited number of included studies for each cancer type, we carried out a stratified analysis of DTC. The result also revealed that elevated miR-17/17-5P yielded worse OS in DTC (HR=2.10; 95% CI: 1.54–2.87 for miR-17; HR=1.80; 95% CI: 1.29–2.50 for miR-17-5P). Meanwhile, further research is needed to explore whether pathological types of specific cancers affect the prognostic role of miR-17/17-5P.

Because the eligible studies used various indices to assess cancer progression, such as DFS, PRS, and RFS, we combined these prognostic indicators to evaluate the prognostic value of miR-17/17-5P. The results indicated an intimate association between high miR-17 expression levels and PFS/RFS (pooled HR=1.69; 95% CI: 1.29–2.22) and high miR-17-5P expression levels and DFS (pooled HR=1.58; 95% CI: 1.07–2.35). Therefore, high miR-17/17-5P expression levels may be a promising negative prognostic factor in DTC. In addition, subgroup analyses were performed according to sample types. However, further study is needed to confirm the role of miR-17/17-5P in predicting the prognosis of different types of cancer.

Evidence has suggested a controversial role of the miR-17 in tumorigenesis, tumor suppressive,[55,56] or oncogenic,[57,58]

which suggested a tumor/tissue-specific role of miR-17. The miR-17-5p functionally modulates sensitivity to radiation in vitro in esophageal adenocarcinoma cells and alters expression of predicted miR-17-5p target genes, such as C6orf120.[59] In vivo, miR-17-5p is decreased significantly, while target gene expression is increased significantly in pretreatment tumor biopsies from patients who have a poor response to neoadjuvant chemoradiation therapy.[60] It indicates that miR-17-5p can be regarded as a predictive marker of response to neoadjuvant chemoradiation therapy and novel therapeutic target to enhance efficacy of esophageal adenocarcinoma in chemoradiation therapy.[61] Meanwhile, compared to normal tissue, miR-17/17-5P have been found at higher levels in colorectal cancerous tissue, although with varied expression of each individual component.[38,62] A similar result was observed by Wang et al,[45] who demonstrated that the circulating miR-17-5p expression level might be a molecular marker for gastric cancer.

As a comprehensive review of prognostic studies, one limitation is the heterogeneous nature of the identified studies. The reviewed studies varied in study quality, study populations, and statistical analyses. The influencing factors of heterogeneity included in analysis model, definitions of measurement, pathologic classification, laboratory techniques, and treatments received.[63] In some situations, inadequate data from some types of cancer and subgroup analyses in HRs may be the origin of heterogeneity.[64] The miRNAs can induce widely variable effects depending on tumor biology, microenvironment, and a multitude of other interconnected factors. If the number of studies is very small, it may be impossible to estimate the between-studies variance (τ^2) with any precision.[65]

To our knowledge, there is no evidence-based meta-analysis to evaluate the prognostic values of miR-17/17-5P. Therefore, we pooled the available evidence from all relevant studies to assess the prognostic values of miR-17/17-5P. Although our meta-analysis is robust, several limitations deserved focus as follows. First, not all the included studies provide multivariate adjusted HRs and corresponding 95CI%. In this case, the data was extracted from Kaplan–Meier survival curves, which can result in several tiny errors on calculated HRs with the 95% CIs. Second, although we find no evidence of publication bias, included studies were mostly in English, which may generate publication bias. Third, the cutoff values (median, mean, etc.) were applied to evaluate the different miR-17/17-5P expression, but the actual values may be discrepant due to different algorithms and result in some heterogeneity. Diversity of anatomical locations can be considered as another potential reason for heterogeneity.

Fourth, given the limited availability of included studies, for DFS/PFS/RFS, the included studies were not stratified. Finally, the influence of adjuvant therapies on the prognostic effect of malignant tumor was not assessed in our study due to scant data. In spite of these limitations, the study about the relationship between miR-17/17-5P and prognosis of cancers is certainly warranted. In summary, the high expression of miR-17/17-5P was significantly associated with poor survival in patients with cancer. In addition, overexpression of miR-17/17-5P was associated with ethnicity, cancer subtypes, and sample types. These findings suggested that miR-17/17-5P might be a novel prognostic indicator of cancer. Given its limitations, the results of the present analysis should be interpreted with caution. Further clinical investigations are needed to determine the association between miR-17/17-5P and cancer prognosis.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Quality assessment of included studies based on the Newcastle–Ottawa Scale for assessing the quality of cohort studies

Study	Selection (score)				Comparability (score)	Exposure (score)			Total score[b]
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Based on the design or analysis[a]	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Yang et al (2017)[1]	—	0	0	—	2	—	—	—	7
Li et al (2016)[2]	—	—	—	—	—	—	0	—	7
Robaina et al (2016)[3]	—	0	—	—	2	—	—	—	8
Xi et al (2015)[4]	—	0	—	—	—	—	—	—	7
Xu et al (2013)[5]	—	0	—	—	2	—	—	—	8
Chang et al (2013)[6]	—	0	0	—	0	—	—	—	5
Lu et al (2012)[7]	—	0	—	—	—	—	—	—	7
Gao et al (2012)[8]	—	0	—	—	0	—	0	—	5
Yu et al (2012)[9]	—	0	—	—	2	—	—	—	8
Saito et al (2012)[10]	—	—	—	—	2	—	—	—	9
Valladares-Ayerbes et al (2011)[11]	—	0	—	—	2	—	—	—	8
Komatsu et al (2013)[12]	—	0	—	—	2	—	—	—	8
Chen et al (2013)[13]	—	—	—	—	2	—	—	—	9
Zheng et al (2013)[14]	—	0	—	—	2	—	—	—	8
Chen et al (2012)[15]	—	0	0	—	2	—	—	—	7
Wang et al (2012)[16]	—	0	—	—	2	—	0	—	6
Yu et al (2010)[17]	—	0	0	—	0	—	—	—	6
Busacca et al (2010)[18]	—	0	—	—	2	—	—	—	8
Díaz et al (2008)[19]	—	0	0	—	0	0	0	—	4

Notes: [a]When there was no statistical significance in the response rate between case and control groups by using a chi-squared test ($P > 0.05$), one point was awarded. [b]Total score was calculated by adding up the points awarded in each item.
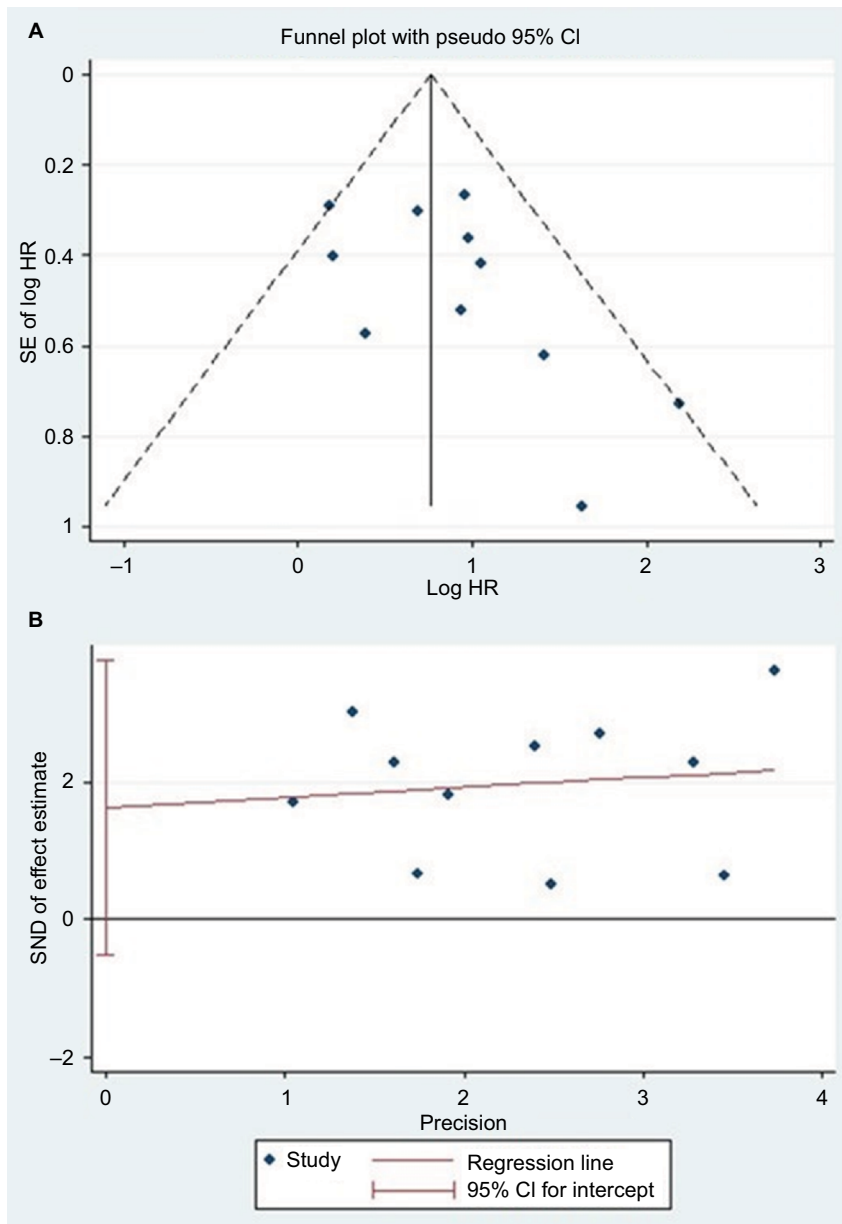
Figure S1 (**A**) Begg's funnel plot of publication bias on the relationship between miR-17 expression and OS.[20] (**B**) Egger's funnel plot of publication bias on the relationship between miR-17 expression and OS.[21]
Abbreviations: HR, hazard ratio; miR, microRNA; SND, standard normal deviate.
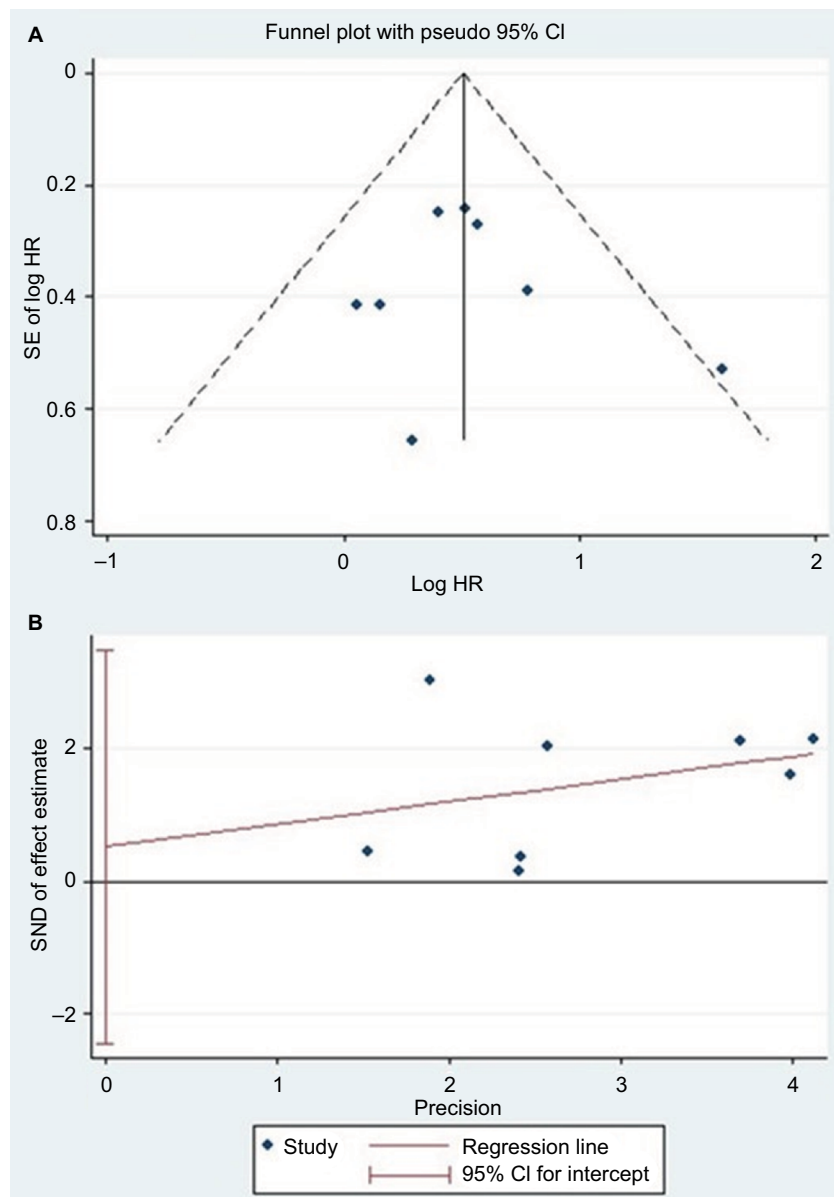
Figure S2 (**A**) Begg's funnel plot of publication bias on the relationship between miR-17-5P expression and OS.[20] (**B**) Egger's funnel plot of publication bias on the relationship between miR-17-5P expression and OS.[21]
Abbreviations: HR, hazard ratio; miR, microRNA; SND, standard normal deviate.

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