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MicroRNA-17 and the prognosis of human carcinomas: a systematic review and meta-analysis

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ABSTRACT

Objective Although the role of microRNA-17 (miR-17) has been identified as a tumour biomarker in various studies, its prognostic value in cancers remains unclear. Therefore, we performed a systematic review and meta-analysis to analyse and summarise the relationship between the miR-17 status and clinical outcome in a variety of human cancers.

Design Systematic review and meta-analysis.

Data sources PubMed, Web of Science and Embase from the first year of records to 15 May 2017.

Outcomes The patients' survival results were pooled, and pooled HRs with 95% CIs were calculated and used for measuring the strength of association between miR-17 and the prognosis of cancers, including hepatocellular carcinoma, lung cancer, osteosarcoma, glioma, T-cell lymphoblastic lymphoma and colon cancer. Heterogeneity, publication bias and subgroup analysis were also conducted.

Results A total of 1096 patients were included in this meta-analysis from 12 articles. The results indicated that the increased expression of miR-17 played an unfavourable role in overall survival in various human carcinomas with the HR of 1.342 taking into account the publication bias. In subgroup analysis, HR of ethnicity (Caucasian HR=1.48 and Asian HR=1.40), disease (digestive system HR=1.36 and blood system cancer (HR=2.38), detection method (quantitative real-time PCR HR=1.40 and in situ hybridisation, HR=2.59) and detection sample (tissue HR=1.45 and serum HR=1.32) were significant with $p<0.05$. For the analysis of disease-free survival and recurrence-free survival, the increased expression of miR-17 was associated with unfavourable prognosis (HR=1.40).

Conclusions miR-17 may be a useful biomarker in predicting the clinical outcome of human cancers, but due to the limitations of the current studies, further verification of the role of miR-17 in human malignancies is urgently needed.

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Strengths and limitations of this study

- This is the first meta-analysis that summarised and reported the microRNA-17 as a novel potential cancer prognostic biomarker in the clinical field.
- We used strict, broad search strategy of the internet databases to minimise any potential publication bias.
- We conducted the subgroup analysis and found that the upregulated expression of microRNA-17 may imply poor clinical outcome in digestive system cancers.
- The major limitation of our meta-analysis is the inclusion of a limited number of studies carried out on Western populations decreasing the applicability of our results among other ethnicities. MicroRNA-17 detection is not routine clinical practice, and the prognostic value of microRNA-17 remains controversial. In the future, additional clinical trials are needed to verify the prognostic significance of microRNA-17.

INTRODUCTION

Despite significant advances in clinical research over the past few decades, cancer is still a key health burden and a leading cause of death worldwide. In the year 2017, it is estimated that 1 688 780 patients were diagnosed with cancers with 600 920 cancer deaths in the USA.[1] Due to the advanced screening methods and adjuvant systemic therapies for newly diagnosed cases, the mortality rate for cancers is declining in the developed countries,[2] whereas the clinical outcome of cancers in the low/middle-income countries is still poor.[3 4]

There are several independent factors for identifying and evaluating the clinical outcome of human cancers, including tumour size, histological grade, age of the patients and metastasis to lymph nodes.[5–8] Tissue-based and serum-based tumour biomarkers are widely used to predict the prognosis of neoplasms. However, these techniques are far from satisfactory due to the low specificity and sensitivity.[9–11] Thus, a less-invasive and more accurate biomarker would be of great value for the prognosis of human tumours.

The discovery of microRNAs (miRNAs) provided an innovative method for the prognosis of cancers by a less-invasive detection method.[12] miRNAs, a class of endogenous non-coding single-stranded RNAs with the

length of 18–25 nucleotides, act as regulators of gene expression by pairing with the complementary nucleotides in the 3'-untranslated regions (3'-UTR) of their target mRNAs. miRNAs may act as regulators of cell growth, proliferation, differentiation and apoptosis.[13] Because of these fundamental activities, numerous studies have shown that miRNAs function as tumour suppressors or oncogenes. It has also been reported that some miRNAs are differentially expressed between tumour and non-tumour tissues, and the abnormal expression of tumour-associated miRNAs can be detected in patient's blood, cancerous tissue and faecal samples.[14 15] Recent studies have demonstrated that aberrantly expressed miRNAs, especially those acting as tumour suppressors or oncogenes, are related to cancer development, progression and patients' response to therapy.[16–18] Therefore, miRNAs can be considered as useful prognostic biomarkers for various human cancers.

One such example is of miR-17 that is aberrantly expressed in patients with cancer.[19–21] The miR-17 family, which includes six members, is one of the most extensively studied miRNA clusters.[22] These miRNAs are located within an 800 base-pair region of human chromosome 13, play an essential role in the development of the heart, lung and human immune system.[23] Recent studies have found that miR-17 may play a critical role in the development of human cancers.[24 25] Increased expression of miR-17 promotes the metastasis of lung and pancreatic cancers, suggesting its role as an oncogene.[26 27] However, other studies have reported that miR-17 inhibits tumour cell invasion and metastasis in breast cancer.[28] In all, the role of miR-17 in cancer development and the exact mechanism are not yet clearly described. According to the miRBase (http://www.mirbase.org), miR-17 includes two members, miR-17–5p and miR-17–3p which are located in the sequence of miR-17 with a stem-loop structure. As a result, the detection of miR-17–5p, miR-17–3p has the same effect as detecting miR-17.[29–33]

Several published results indicate that the higher expression of the miR-17 is indicative of poor prognosis in patients with cancer.[26 27 34–43] However, several confounding factors, including race, detection method and tumour site, may affect the observations making the relationship between aberrant expression of miR-17 and the clinical outcome of patients with cancer inconsistent. We, therefore, conducted a meta-analysis of available studies to evaluate the clinical utility of miR-17 as a novel cancer prognostic indicator.

MATERIAL AND METHODS

Data source and search strategy

The following online electronic databases were used for the literature search: PubMed, Web of Science and Embase. The search period was up to 15 May 2017. Key search words used were: (1) prognosis OR prognostic OR survival OR outcome OR mortality; (2) cancer OR tumur OR tumour OR carcinoma OR neoplasm; (3) miR-17 OR microRNA-17 OR hsa-mir-17. Details are listed in the online supplementary table 1. Additionally, we also searched the references and relevant published articles via Google Scholar.

Inclusion and exclusion criteria

The inclusion criteria of the articles were: (1) the cancers were diagnosed by the histological examination or any other accepted standard, (2) miR-17 was studied in human cancers, (3) the expression of miR-17 and the clinical outcome of patients were included in the research and (4) reports with survival outcome and the data analysed HR with 95% CI and HR with a p value.

The exclusion criteria were: (1) duplicate publications; (2) articles focused on other genes; (3) case reports, reviews, letters and animal trails; (4) unqualified or insufficient data; (5) HR, 95% CI and p value were not provided or could not be calculated and (6) articles concentrated on the polymorphisms or methylation patterns of miRNAs.

Questions of suitability of articles to be included were examined and discussed by the authors after reviewing the abstract and full-text manuscript. The final decision was made by the academic committee.

Data extraction and quality assessment

All included studies were decided by the two investigators (CH and XY) independently based on titles and abstracts. Full text of the articles was required if the articles were potentially suitable for the meta-analysis. Furthermore, the literature search was performed again in the excluded articles to avoid missing any article potentially relevant for the study. The original authors of the articles were contacted if any supplementary data were needed. Any disagreement was resolved by the two authors (CH and XY). The extracted details of the articles were as follows: (1) publication information: the name of the authors, publication area and publication year; (2) patient's characteristics: diseases, stage of the disease, RNA detection method, type of tissue sample and follow-up years; (3) the measurement of miR-17 measurement and its cut-off value and (4) HR of miR-17 for overall survival (OS), disease-free survival (DFS) and recurrence-free survival (RFS), as well as their 95% CI and p values. The HRs and their 95% CI were extracted from the original articles or via emails from the authors. If not, we calculated HR and 95% CI using the data of observed deaths, cancer recurrences or the original data provided by the authors. All calculations mentioned above were based on the methods provided by Parmar *et al*.[44] The quality of the included articles was assessed based on a systematic review checklist of the Dutch Cochrane Centre proposed by Meta-analysis Of Observational Studies in Epidemiology .[45]

Statistical analysis

The test of heterogeneity of pooled HRs was carried out by using Cochran's Q test and Higgins I^2 statistic. A p value of <0.05 or I^2 >50% was considered as statistically significant.

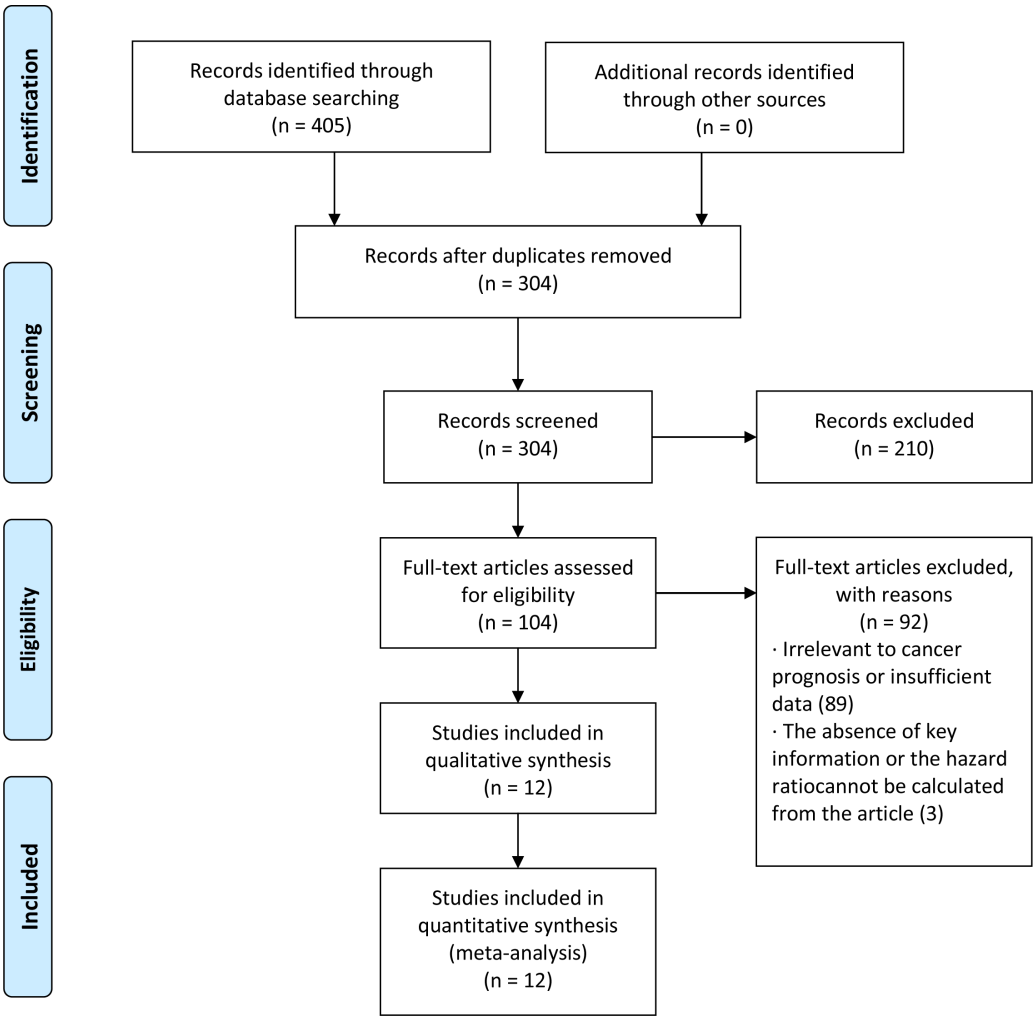

Figure 1 Flow diagram of the studies selection phase.

The 95% CI of I^2 was calculated by the method introduced by Hedges *et al*.[46] If heterogeneity existed, the random-effects model was performed among the included studies; otherwise, the fixed-effects model was selected. I^2 value ranged from 0% to 100%. All p values were two sided.

HR >1 presents of upregulated expression of miR-17 indicated poor prognosis in patients, and HR <1 suggested a better prognosis. Publication bias was evaluated by the Begg's test and Egger's test.[47 48] If the publication bias did exist, the trim and fill method introduced by Duval and the Tweedit's was used to adjust the results.[49] The STATA software V.14.0 (StataCorp) was used in all of the statistical analyses.

Patients and public involvement statement

The patients or public were not involved in the study.

RESULTS

Literature selection

We started with 405 articles associated with miR-17 and cancer prognosis was identified from online database searches. After removing the replicate records, 304 miR-17-related articles were left. The first screening based on the species, article type and language eliminated 210 citations from the analysis. Subsequently, the remaining 104 studies were carefully assessed by reviewing the abstract and full text of each article. After that, 89 articles were excluded from the study because they were unrelated to miR-17 expression levels or because of the lack of survival statistics such as HRs, 95% CI or p value. Finally, 15 studies, which investigated the potential relationship between miR-17 expression and prognosis of human cancers, remained for further detailed screening and data extraction. Three of the studies that explained the relationship between miR-17 expression and the clinical outcome of cancer had to be removed because the authors did not provide the exact HR value, or the value cannot be calculated from the data. Thus, 12 articles (12 studies)[26 27 34–43] were included in this meta-analysis (figure 1).

Characteristics of selected studies

All 12 studies included in the meta-analysis were retrospective studies published between 2010 and 2016.[26 27 34–43] Patient's OS was reported in all 12 studies, and 3 studies also examined the DFS or RFS. The type of the cancers

Table 1 A summary table of the meta-analysis

Study	Year	Country	Diseases	Case no	Stage	Sample	Assay	Cut-off value	HR	Follow-up (months)	Type of miR-17 detection
Chen *et al*[37]	2012	China	HCC	120	I–IV	Tissue	qRT-PCR	Median	RR	46	miR-17–5p
Qun *et al*[27]	2013	China	Lung cancer	221	I–IV	Tissue	qRT-PCR	Median	Given	50	miR-17
Li *et al*[41]	2014	China	Osteosarcoma	117	I–III	Tissue	qRT-PCR	Median	Given	44	miR-17
Lu *et al*[35]	2012	China	Glioma	108	I–IV	Tissue	qRT-PCR	Mean	RR	60	miR-17
Xi *et al*[42]	2015	China	T-cell lymphoblastic lymphoma	57	III, IV	Tissue	qRT-PCR	Median	Given	Up to 13 years	miR-17
Yu *et al*[40]	2012	China	Colon cancer	48	I–IV	Tissue	qRT-PCR	Median	Given	5–66	miR-17
Manuel *et al*[39]	2011	Spain	Gastrointestinal cancer	38	I–IV	Tissue	qRT-PCR	Mean	Given	38	miR-17
Robaina *et al*[38]	2016	Brazil	Burkitt lymphoma	41	I–IV	Tissue	ISH	Median	Given	69	miR-17
Xu *et al*[36]	2014	China	Oesophageal squamous cell carcinoma	105	I–IV	Tissue	qRT-PCR	Mean	Given	52	miR-17
Jun *et al*[26]	2010	Japan	Pancreatic cancer	80	I–IV	Tissue	qRT-PCR	Median	Given	60	miR-17–5p
Wang *et al*[43]	2011	China	Gastric cancer	65	I–IV	Serum	qRT-PCR	Median	Given	36	miR-17–5p
Zheng *et al*[34]	2013	China	HCC	96	I–IV	Serum	qRT-PCR	Median	Given	NG	miR-17–5p

HCC, hepatocellular carcinoma; ISH, in situ hybridisation; miR-17, microRNA-17; NG, not given; OS, overall survival; qRT-PCR, quantitative real-time PCR; RR, risk ratio.

included gastrointestinal cancers (colorectal cancer, gastric cancer), lung cancer, pancreatic cancer, hepatocellular cancer, osteosarcoma, glioma, T-cell lymphoblastic lymphoma and oesophageal squamous cell carcinoma. A total of 1096 patients with various types of cancers were from People's Republic of China, Japan, Spain and Brazil. Quantitative real-time PCR (qRT-PCR) was used to assess the expression of miR-17 in 12 studies, and 1 study used the in situ hybridisation (ISH). All studies used tissue and serum samples as the source of the miR-17. The majority (10 of 12) of the HRs reported in the present analysis were included in the multivariate analysis. The remaining two HRs could be estimated by Kaplan-Meier analysis and relative risk values. Most of the studies have the follow-up research for at least 38 months. The clinical characteristics of the studies included in this article are summarised in table 1.

Association between miR-17 and OS

Due to low heterogeneity, fixed-effects model was used to calculate and analyse the pooled HR value. High expression level of miR-17 was associated with the poor OS in patients with diverse cancers. The statistical power of Q test is low when there are limited studies included in the meta-analysis. We, therefore, conducted random-effect analysis on the OS (HR 1.45, 95% CI 1.29 to 1.63, p<0.001), which was not significantly different compared with the analysis of fixed-effect model. Details of the meta-analysis are systematically summarised in the figure 2.

To demonstrate the predictive role of miR-17, subgroups analysis was conducted based on patients' ethnicity, cancer type, methods identifying miRNAs and type of tissue samples. Clinical association between miR-17 and OS was found in the Asian and Caucasian patients (figure 3A). The association was also significant in other subgroups, including digestive system cancers and blood cancers (figure 3B), qRT-PCR detection method (figure 3C), and tissue and serum samples (figure 3D). miR-17 includes two members, miR-17–5p and miR-17–3p which are located in the sequence of miR-17 with a stem-loop structure. Therefore, analysis of miR-17–5p or miR-17–3p afforded the same effect (or result) as miR-17. To clarify the heterogeneity, we conducted a subgroup analysis concerning the detection method of miR-17 and found that the clinical value was also significant in miR-17 group and miR-17–5p group. There was no significant difference between the two groups (figure 3E), implying that same effect existed when detecting miR-17 and miR-17–5p. Details of the subgroup analysis are listed in the table 2.

Correlation between miR-17 and DFS and RFS

A total of three studies[37 38 41] were included in the analysis of DFS and RFS. The analyses revealed a predictive role of increased expression of miR-17 for the prognosis of patients with cancer (pooled HR 1.40, 95% CI 1.23 to 1.60, p<0.001) as determined by the fixed-effect model (I^2=15.8%, p=0.305) (figure 4).

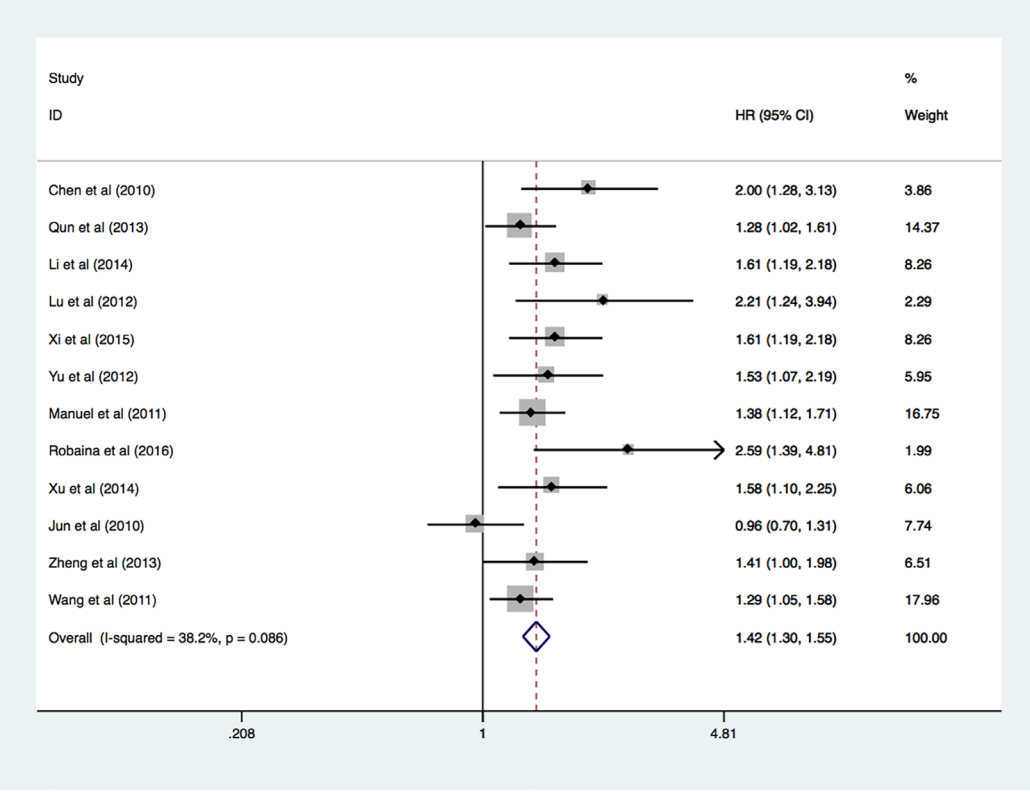

Figure 2 Forest plot of meta-analysis of overall survival in association with miR-17 expression.

Publication bias

We used Begg's funnel plot and Egger's test to assess the possible publication bias of the included studies.[47 48] In the analysis of relationship between miR-17 and the OS, the p values of Egger's test and Begg's test were 0.014 and 0.011, respectively. The funnel plot and Egger's plot are displayed in figure 5A,B. Both Begg's test and Egger's test implied a publication bias, thus, the trim and fill method was performed to make pooled HR more reliable.[49] The altered HR was 1.34, 95% CI 1.24 to 1.46, p<0.001, which was not significantly different from the pooled HR (online supplementary figure 1).

DISCUSSION

Previous studies have shown that miRNAs have a distinct expression profile in cancerous tissues which can be detected by qRT-PCR in frozen, formalin-fixed and paraffin-embedded tissues and in serum samples. Recently, miRNAs, serving as tumour suppressors or oncogenes, have been shown to play important roles in the evolution and progression of cancers. miRNAs are involved in a variety of crucial cellular pathways such as angiogenesis, innate and adaptive immune responses, cellular proliferation, invasion and metastasis.[12 16] Several studies have reported the potential use of miRNAs as tumour biomarkers for detecting tumour occurrence, development and prognosis. Unfortunately, effective diagnosis techniques and prognosis indicators of cancer have not been found. Developing a novel less-invasive detection method with higher accuracy for cancer prognosis is of great significance in evaluating cancer progression as well as monitoring patients' therapeutic response.

Over the last couple of decades, numerous studies have uncovered the involvement of miRNAs in the pathogenesis of cancer. Since miRNAs can be obtained non-invasively from the serum, urine and faecal samples, their utility as diagnostic and prognostic biomarkers in cancer and other diseases has been extensively explored. It has been reported that miRNA could be detected with higher accuracy than traditional cancer biomarkers in predicting the clinical outcome of the human colon cancers.[50] However, adequate evidence is still lacking for the utility of miRNAs as cancer biomarkers in clinical practice.

miR-17, a widely studied miRNA, is aberrantly expressed in different kinds of cancers, such as glioma,[35] oesophageal and oral squamous cell carcinomas,[36 51] pancreatic cancer,[26] gastrointestinal cancers,[39] osteosarcoma[52] and Burkitt lymphoma,[38] and is significantly related to the clinical outcome of cancers. Our meta-analysis indicated that the elevated miR-17 expression is significantly associated with poor OS (HR=1.42) in patients with various types of carcinomas. The analysis using the Cochran's Q test and Higgins I^2 test implied low heterogeneity. As limited number of studies were included in the meta-analysis, the Q test had inadequate statistical power. We, therefore, applied the fixed-effects model to calculate and analyse the pooled HR value. We also conducted random-effect analysis on the OS, which was not significantly different when compared with analysis of fixed-effect model (figure 2). In the subgroup analysis, we found that the

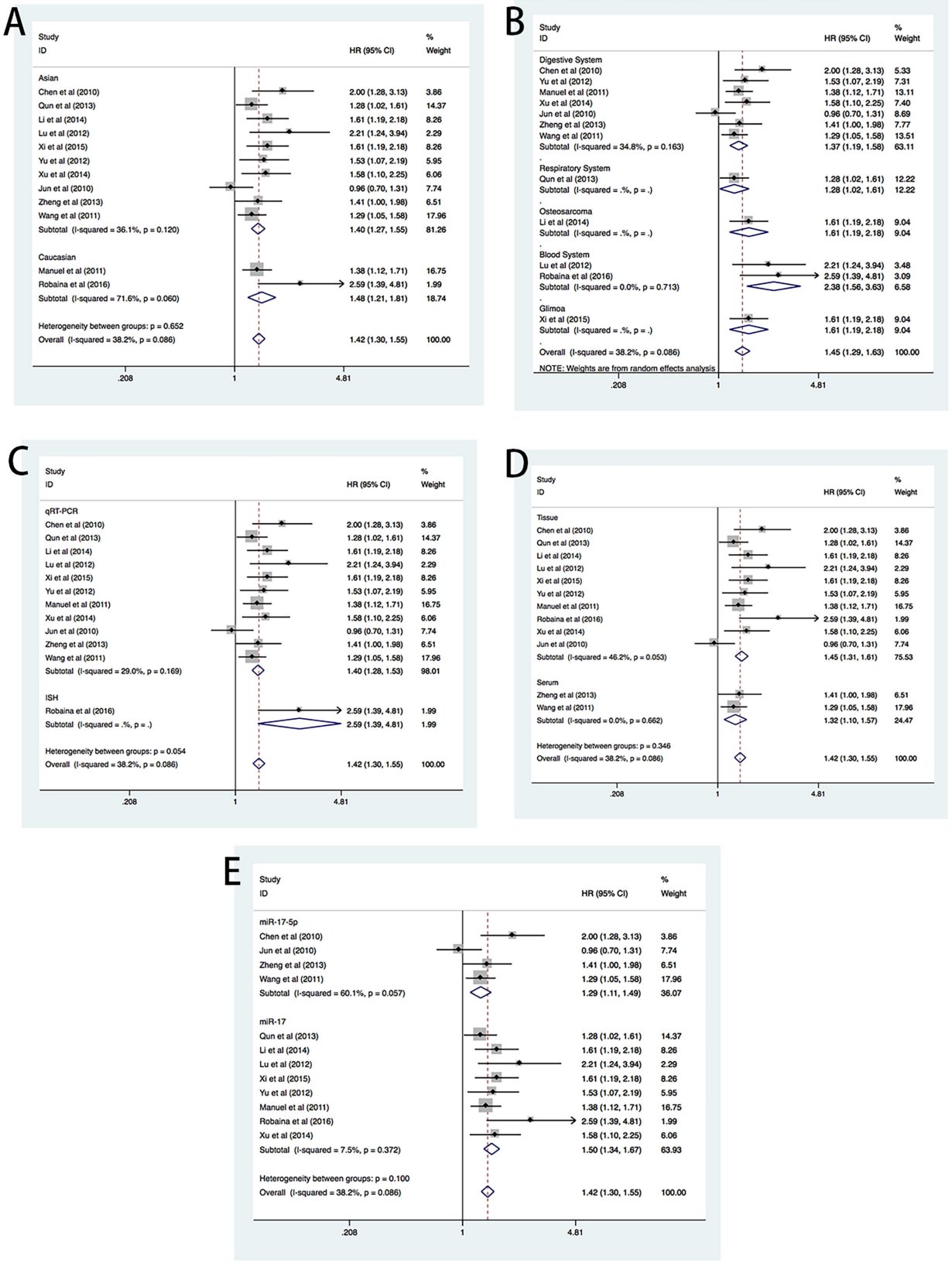

Figure 3 Forest plots of subgroup meta-analysis of OS in association with miR-17 expression. (A) Forest plots of the merged analyses of OS in different ethnic groups. Squares and lines correspond to the study-specific HRs and 95% CIs, respectively. The area of the squares represents the weight, and the diamonds represent the summary of HRs and 95% CIs. (B) Forest plots of the merged analyses of OS in different diseases groups. (C) Forest plots of the merged analyses of OS in different RNA detection methods groups. (D) Forest plots of the merged analyses of OS in different sample groups. (E) Forest plots of the merged analyses of OS in the detection method of miR-17. ISH, in situ hybridisation; miR-17, microRNA-17; OS, overall survival; qRT-PCR, quantitative real-time PCR.

Table 2 Subgroup analysis

Subgroup	No of studies	Heterogeneity I^2 (95% CI)	P values	Pooled HR (95% CI)	P values
Total	12	38.2% (0% to 68.7%)	0.086	1.42 (1.30 to 1.55)	<0.001
Ethnic subtotal					
Caucasian	2	71.6% (0% to 93.6%)	0.06	1.48 (1.21 to 1.81)	<0.001
Asian	10	36.1% (0% to 69.5%)	0.12	1.40 (1.27 to 1.55)	<0.001
Disease subtotal					
Digestive system	7	34.8% (0% to 72.4%)	0.163	1.36 (1.22 to 1.51)	<0.001
Respiratory system	1	NA	NA	1.28 (1.02 to 1.61)	0.036
Blood system	2	0	0.713	2.38 (1.56 to 3.63)	<0.001
Glioma	1	NA	NA	1.61 (1.19 to 2.18)	0.002
Osteosarcoma	1	NA	NA	1.61 (1.19 to 2.18)	<0.001
Detected method subtotal					
qRT-PCR	11	29.0% (0% to 65.0%)	0.169	1.40 (1.28 to 1.53)	<0.001
ISH	1	NA	NA	2.59 (1.39 to 4.81)	0.003
Detected sample subtotal					
Tissue	10	46.2% (0% to 74.1%)	0.053	1.45 (1.31 to 1.61)	<0.001
Serum	2	0	0.662	1.32 (1.10 to 1.57)	0.002
Detection of miR-17 subtotal					
miR-17	8	60.1% (13.2% to 81.7%)	0.057	1.29 (1.11 to 1.49)	<0.001
miR-17–5p	4	7.5% (0% to 43.4%)	0.372	1.50 (1.34 to 1.67)	0.001

ISH, in situ hybridisation; miR-17, microRNA-17; miR-17-5p, microRNA-17-5p; NA, not available; qRT-PCR, quantitative real-time PCR.

potential heterogeneity may have originated from the Caucasian group in the study conducted by Robaina *et al*.[38] Unlike the commonly used RT-PCR, ISH technique was used to detect miR-17. Other factors contributing to the heterogeneity may include the limited number of patients (n=41) recruited in the study. However, both studies from Spain and Brazil recruited population of Caucasians decreasing the heterogeneity.

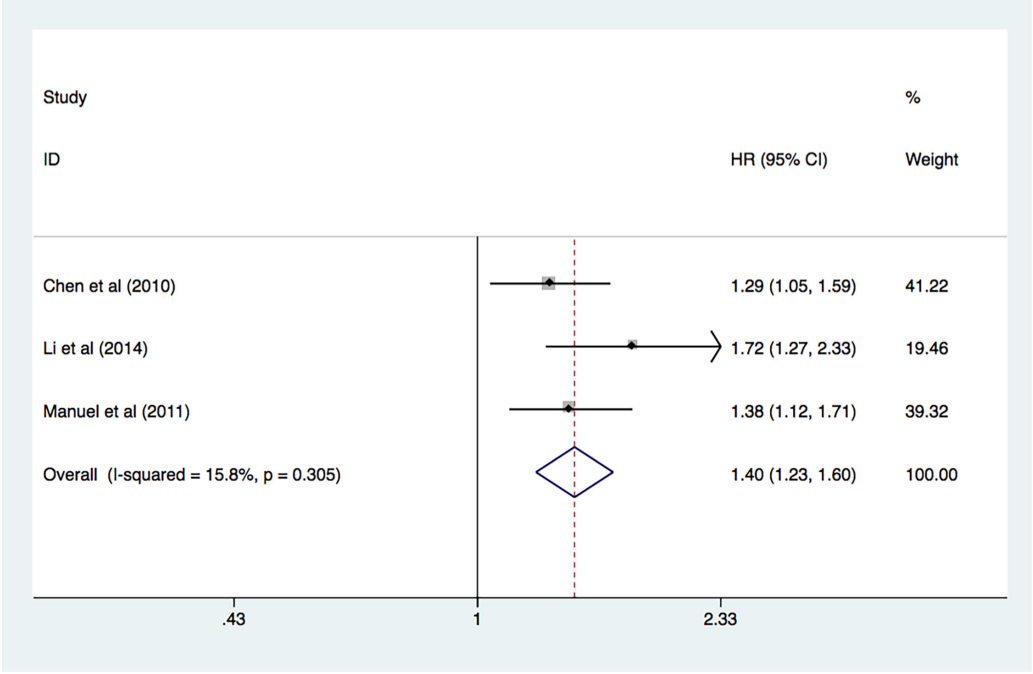

Figure 4 Forest plot of disease-free survival and recurrence-free survival in association with miR-17 expression. miR-17, microRNA-17.

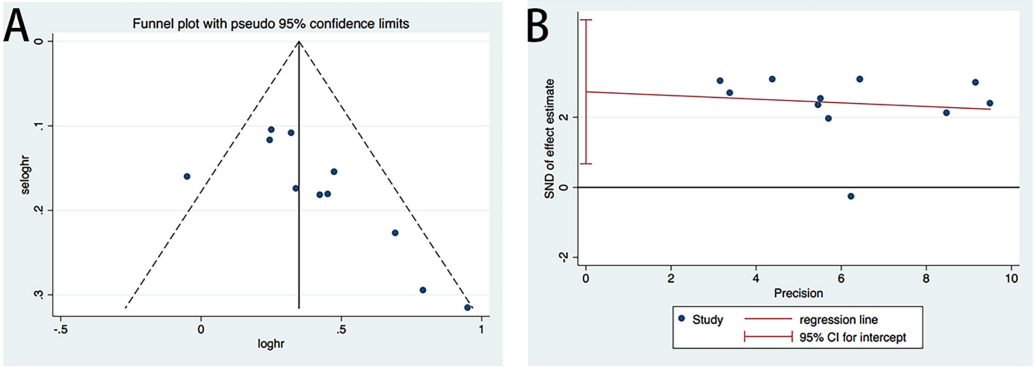

Figure 5 (A) Funnel plot of merged analysis of OS comparing high or low expression of miR-17. (B) Egger's test plot of merged analysis of OS comparing high or low expression of miR-17. miR-17, microRNA-17; OS, overall survival; SND, standard normal deviate.

As the Begg's test and the Egger's test implied publication bias, we used the trim and fill method to obtain a more reliable pooled HR. We found that the adjusted HR was not significantly different from the pooled HR. In subgroup analysis, based on the characteristics of the individual studies, significant HR was found in the Caucasian and Asian groups, the qRT-PCR group and the tissue and serum sample groups. Furthermore, the increased expression of miR-17 indicated poor DFS and RFS in hepatocellular carcinoma (HCC) and gastrointestinal cancers. Several investigators have explored the functional roles of miR-17 and its involvement in human cancers. Yang *et al* found that the miRNA-17 was overexpressed in the HCC tissue, and promoted the phosphorylation of heat shock protein 27 (HSP27). The phosphorylated HSP27 then enhanced the migration of the HCC cells implying a significant role of miRNA-17 in the progression of HCC.[53] Wang *et al* reported that the upregulated expression of miRNA-17–5p promoted cancer cells proliferation and inhibited apoptosis by post-transcriptional modulation of mRNA-p21 and tumour protein p53-induced nuclear protein 1.[54] In the study by Ma *et al*, overexpression of miRNA-17 promoted cancer cells progression by targeting P130.[55] Yan *et al* found overexpression of the miR-17–5p in pancreatic cancer. The miR-17–5p inhibitor promoted the expression of Bim protein by targeting the 3'-UTR of its mRNA and negatively regulating at the post-transcriptional level. Therefore, the authors suggested that the miR-17–5p inhibitor may be a novel therapeutic approach for pancreatic cancer.[56] Together with our meta-analysis, these findings suggest that the detection of tissue or serum miR-17 expression may be a useful prognostic biomarker in patients with HCC, pancreatic cancer and gastrointestinal cancers.

There are potential limitations of this study. The literature searches using authentic and widely used data bases found studies performed predominantly on Asian populations not encompassing sufficient numbers of other populations such as Caucasians. Our results of miR-17 as a potential biomarker may, therefore, not be applicable to other populations. The pooled HR values were also not sufficiently strong. Furthermore, the relatively limited sample size of 1031 patients weakened the statistical significance of the prognostic potential of miR-17 expression levels.

CONCLUSIONS

In summary, our meta-analysis suggested that miR-17 is a potential biomarker in various types of cancers. However, further multicentre clinical trials with larger sample size and prospective studies including Caucasians and patients representing other ethnicities are needed to confirm the prognostic value of miR-17 and its subsequent application as a prognostic biomarker in the routine clinical guidance of cancers.

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Contributors CH and MY conceived the study. CH and XY performed the data extraction and analysed the data. CH and MY wrote the paper. All authors had full access to all of the data and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The study does not include human participants or animals.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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