

# Prognostic value of miR-17-5 p in gastrointestinal cancers: a systematic review and meta-analysis

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**Background:** There are accumulating studies investigating the aberrant expression of microRNAs in tumor patients. As an important member of miR-17/92 cluster, miR-17-5 p has been identified as a potential prognostic factor for survival in tumor patients. We conducted this meta-analysis aimed to assess the effect of miR-17-5 p as a prognostic biomarker for gastrointestinal tumor patients.

**Materials and methods:** Eligible studies were enrolled by searching the online databases of PubMed, Embase, Web of Science, China National Knowledge Infrastructure, and WanFang Data until September 2017. We calculated pooled hazard ratios (HRs) and 95% CI of miR-17-5 p for overall survival and disease-free survival.

**Results:** In the categorical variable analysis, we identified 11 studies with 1,279 patients. The pooled analyses suggested that overexpression of miR-17-5 p may predict poor overall survival (HR = 1.86, 95% CI: 1.55–2.25,  $P < 0.001$ ) and disease-free survival (HR = 1.43, 95% CI: 1.01–2.03,  $P = 0.046$ ) in patients with gastrointestinal tumors. Subgroup analysis showed the pooled HR of overall survival was more significant in tissue specimen, Asian patients, and digestive tract tumors. But there was no correlation between the outcomes and European patients.

**Conclusions:** This meta-analysis suggested that miR-17-5 p has predictive effects on overall survival and disease-free survival of patients with gastrointestinal tumors.

**Keywords:** miR-17-5 p, microRNA-17-5p, prognosis, survival, meta-analysis

## Introduction

MicroRNAs (miRNAs) are a class of single-stranded noncoding RNAs 21–22 nucleotides in length processed from much longer primary transcripts. They may regulate up to 60% of human protein-coding genes.<sup>1</sup> MiRNAs participate in crucial biological processes such as cell proliferation, differentiation, apoptosis, and tumorigenesis.<sup>2–4</sup> MiR-17/92 cluster is one of the most popularly researched gene clusters and miR-17-5 p is an important member of the miR-17 family belonging to the miR-17/92 cluster. The human genome miR-17/92 cluster has two paralogues of the main cluster: the miR-106b/25 and the miR-106a/363 clusters. MiR-17/92 and miR-106b/25 are expressed abundantly in a wide spectrum of tissues but miR-106a/363 is expressed at lower levels. Together, these three miRNA clusters represent a combined total of 15 miRNAs that form four “seed” families: the miR-17 family, the miR-18 family, the miR-19 family, and the miR-92 family.<sup>5</sup> The miR-17/92 cluster encodes six miRNAs including miR-17, miR-18a, miR19a, miR19b, miR-20a, and miR-92a.<sup>6</sup> The recent studies showed that miRNAs are associated with prognosis in various cancers, suggesting that they could be used as prognostic classifiers to predict prognosis and guide therapeutic decisions.<sup>7–9</sup> MiR-17-5 p was identified to have oncogenic or suppressive ability in several cancers. Many researchers have identified that the members

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of miR-17/92 cluster are closely connected with diagnosis and prognosis of many kinds of tumors.<sup>10-13</sup> As the important member of miR-17/92 cluster, the influence of miR-17-5 p on the prognosis of glioblastoma, gastric carcinoma, hepatocellular carcinoma, lung cancer, pancreatic cancer, and malignant mesothelioma have been reported.<sup>14-22</sup>

However, there were still insignificant or opposite results. Therefore, we performed this meta-analysis to get a better understanding of the prognostic effect of miR-17-5 p on gastrointestinal cancer patients.

## Materials and methods

### Search strategy

The systematic literature search was carried out through the online databases of PubMed, Embase, Web of science, China National Knowledge Infrastructure (CNKI), and Wan Fang to retrieve eligible studies till September 2017. The keywords of “miR-17-5 p”, “miR17-5p”, “microRNA17-5p”, and “microRNA-17-5 p” were used to select the essays. Additionally, a manual search was conducted using all review articles on this topic. The researching of database was implemented by the authors QL and LB. The diagram of the study selection process is presented in Figure 1.

### Data extraction

The investigators (QL and LB) performed data extraction using a standard data extraction form to determine eligibility

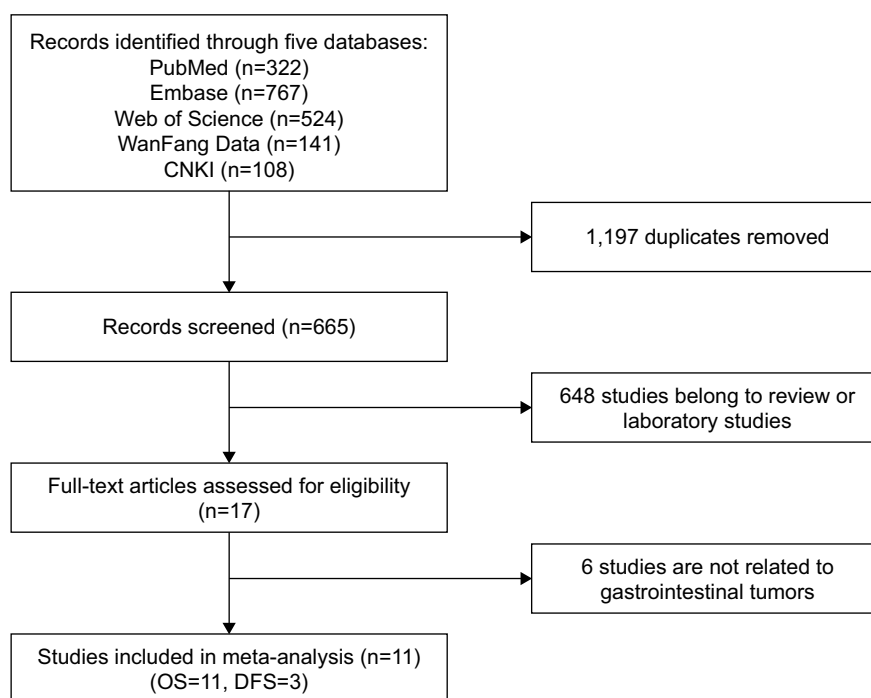
for inclusion and extract data. Discrepancies were adjudged by the third investigator (ML) until consensus was achieved. The following inclusion criteria were used to select eligible studies in our meta-analysis: 1) patients with gastrointestinal cancers are included; 2) publication details: the name of tumors, first author’s last name, and publication year; 3) characteristics of the studied population: follow-up time and stage of disease; 4) materials and methods of experiments; 5) miR-17-5 p assessment and cutoff definition; and 6) hazard ratios (HRs) of elevated miR-17-5 p for overall survival (OS) and disease-free survival (DFS) as well as their 95% CI and *P*-values. The HRs and their 95% CIs were performed in the original articles; if the HRs were not available, data were calculated following Tierney et al’s method.

### Quality assessment

We used Newcastle–Ottawa scale to assess the quality of enrolled studies. There are three aspects in Newcastle–Ottawa scale: the selection of the study groups, the comparability of the groups, and measuring of outcomes. The score of this scale is ranged from 0 to 9.

### Statistical analysis

To avoid calculating error, we pooled only HRs with their corresponding 95% CIs given explicitly in the publications in the analyses. Cochran’s *Q* test and Higgin’s *I*<sup>2</sup> statistic were



**Figure 1** Flow diagram of the study selection process.

**Abbreviations:** OS, overall survival; DFS, disease-free survival.

used to measure the heterogeneity between studies. If  $P > 0.1$  or  $I^2 < 50\%$ , fixed-effects model (Mantel–Haenszel test) was used; otherwise, random-effects model (DerSimonian and Laird method) was chosen. Sensitivity analysis was conducted by omitting one single research at a time and recounting HRs and 95% CIs to assess the stability of the meta-analysis results. Publication bias among the included studies was evaluated by Egger’s and Begg’s statistical tests. All  $P$ -values were two-sided. All statistical tests were analyzed by STATA 11.0 (STATA Corporation, College Station, TX, USA).

## Results

### Description of included studies

The flowchart of detailed searching process is illustrated in Figure 1. We used the searching strategy described above to search the online databases of PubMed, Embase, Web of Science, CNKI, and Wan Fang. A total of 1,862 records were initially collected by our literature search strategy. After manually screening the titles and abstracts, our investigators excluded duplicates and articles that failed to meet the aim of our study. Then 17 records were assessed for full-text review. Finally, eleven<sup>15–19,23–28</sup> studies that evaluated the prognostic effect of miR-17-5 p for OS and three<sup>16,25,26</sup> studies for DFS were included.

### Characteristics of eligible studies

A total of 1,279 cases from China, Japan, Spain, and Hungary were included to evaluate the relationship between miR-17-5 p expression and tumor prognosis. The patients were diagnosed with gastrointestinal cancers, including colorectal carcinoma, hepatocellular carcinoma, pancreatic carcinoma, gastric carcinoma, esophageal squamous cell carcinoma, and cholangiocarcinoma. Tissue and blood samples were used to determine expression levels of miR-17-5 p while quantitative real-time polymerase chain reaction had been used in all studies. The most frequently applied cutoff value was the median which was used in seven studies and others were different. Other basic characteristics are all listed in Table 1. All the HRs and their 95% CIs in the collected articles are shown in Table 2.

### Qualitative assessment

After using Newcastle–Ottawa scale to assess the quality of studies, the study quality varied from 5 to 9; the studies that achieved a score  $>6$  were included. The clinicopathological characteristics of the eligible studies are summarized in Table 3.

**Table 1** Characteristics of studies included

Study	Origin of population	Year	miR-17-5 p assay	Stage	Follow-up months	Cutoff	Source of RNA	Sample number	Risk evaluation method	Study design	Survival analysis	Hazard ratios	Tumor type
Zheng et al <sup>18</sup>	China	2012	qRT-PCR	I–IV	–	Median	Serum	96	Univariate	Retrospective	OS	R	Hepatocellular carcinoma
Chen et al <sup>16</sup>	China	2012	qRT-PCR	I–IV	20 (2–46)	Median	Tissue	120	Univariate	Retrospective	OS, DFS	R	Hepatocellular carcinoma
Gyöngyösi et al <sup>15</sup>	Hungary	2014	qRT-PCR	–	Median 33.6	Median	Tissue	20	Univariate	Retrospective	OS	R	Hepatocellular carcinoma
Yu et al <sup>17</sup>	Japan	2010	qRT-PCR	IA–IV	Up to 110	–	Tissue	80	Multivariate	Retrospective	OS	R	Pancreatic cancer
Wang et al <sup>19</sup>	China	2012	qRT-PCR	I–IV	Up to 40	Median	Plasma	65	Univariate	Retrospective	OS	R	Gastric cancer
Díaz et al <sup>26</sup>	Spain	2008	qRT-PCR	I–IV	Up to 96	Median	Tissue	110	–	Retrospective	OS, DFS	R	Colorectal cancer
Fang et al <sup>27</sup>	China	2014	qRT-PCR	I–IV	Up to 96	Median	Tissue	295	Multivariate	Retrospective	OS	R	Colorectal cancer
Komatsu et al <sup>23</sup>	Japan	2013	qRT-PCR	I–IV	Up to 40	Median	Plasma	69	–	Retrospective	OS	SC	Gastric carcinoma
Ma et al <sup>24</sup>	China	2012	qRT-PCR	I–IV	Up to 100	–	Tissues	240	Multivariate	Retrospective	OS	SC	Colorectal cancer
Guo et al <sup>25</sup>	China	2016	qRT-PCR	I–IV	Up to 60	–	Plasma	79	–	Retrospective	OS, DFS	SC	Cholangiocarcinoma
Xu et al <sup>28</sup>	China	2014	qRT-PCR	I–IV	Up to 60	–	Tissue	105	Multivariate	Retrospective	OS	R	Esophageal squamous cell carcinoma

**Abbreviations:** DFS, disease-free survival; OS, overall survival; qRT-PCR, quantitative real-time polymerase chain reaction; R, reported; SC, survival curve.

**Table 2** Summary of HRs and their 95% CI

Study	Origin of population	Year	Disease	HR	OS 95% CI	P-value	HR	DFS 95% CI	P-value
Komatsu et al <sup>23</sup>	Japan	2013	Gastric carcinoma	1.33	0.15–11.79	0.7978	NR	NR	NR
Ma et al <sup>24</sup>	China	2012	Colorectal cancer	2.24	1.58–3.18	<0.001	NR	NR	NR
Guo et al <sup>25</sup>	China	2016	Cholangiocarcinoma	1.55	0.83–2.89	0.169	1.09	0.57–2.06	0.7
Zheng et al <sup>18</sup>	China	2012	Hepatocellular carcinoma	2.192	1.024–4.691	0.043	NR	NR	NR
Chen et al <sup>16</sup>	China	2012	Hepatocellular carcinoma	4.96	1.78–13.82	0.002	1.79	1.14–2.98	0.0
Gyöngyösi et al <sup>15</sup>	Hungary	2014	Hepatocellular carcinoma	1.09	0.37–3.26	0.88	NR	NR	NR
Yu et al <sup>17</sup>	Japan	2016	Pancreatic cancer	0.9	0.4–1.7	0.13	NR	NR	NR
Wang et al <sup>19</sup>	China	2012	Gastric cancer	1.785	1.110–2.870	0.017	NR	NR	NR
Díaz et al <sup>26</sup>	Spain	2008	Colorectal cancer	1.06	0.47–2.39	0.9	1.13	0.48–2.68	0.7
Fang et al <sup>27</sup>	China	2014	Colorectal cancer	1.9	1.195–3.022	0.007	NR	NR	NR
Xu et al <sup>28</sup>	China	2014	Esophageal squamous cell carcinoma	2.849	1.258–6.455	0.012	NR	NR	NR

**Abbreviations:** DFS, disease-free survival; HR, hazard ratio; NR, not reported; OS, overall survival.

## Meta-analysis results

All the studies were pooled into this meta-analysis, and the result is shown in Figure 2. As no heterogeneity was found in OS research ( $I^2=22.6\%$ ,  $P=0.228$ ) and DFS research ( $I^2=0\%$ ,  $P=0.40$ ), therefore, fixed model was applied. The result indicated that overexpression of miR-17-5 p significantly predicted poor OS (HR = 1.86, 95% CI: 1.55–2.25; Figure 2A), and the effect reached the level of statistical significance ( $P<0.001$ ). DFS was reported in three studies. The pooled HR of DFS was 1.43 (95% CI: 1.01–2.03,  $P=0.046$ ; Figure 2), indicating that the high level of miR-17-5 p expression was related to poor DFS. Detailed analyses were also carried out. We further researched the meta-analysis of miR-17-5 p expression and OS in different cancer types: three studies including colorectal carcinoma, three studies including hepatocellular carcinoma, two studies including gastric carcinoma, one study including pancreatic carcinoma,

**Table 3** Quality assessment based on the Newcastle–Ottawa scale

	Selection	Comparability	Outcome	Total score
Komatsu et al/2013 <sup>23</sup>	3	1	3	7
Zheng et al/2013 <sup>18</sup>	3	2	1	7
Chen et al/2012 <sup>16</sup>	4	2	3	9
Gyöngyösi et al/2014 <sup>15</sup>	4	1	2	7
Yu et al/2016 <sup>17</sup>	4	1	2	7
Ma et al/2012 <sup>24</sup>	4	2	3	9
Guo et al/2016 <sup>25</sup>	3	1	2	6
Díaz et al/2008 <sup>26</sup>	4	2	1	7
Xu et al/2014 <sup>28</sup>	4	1	2	7
Fang et al/2014 <sup>27</sup>	4	2	2	8
Wang et al/2012 <sup>19</sup>	4	2	2	8

**Notes:** Selection: representativeness of studies (maximum score of 4). Comparability: comparability of studies based on the design or analysis (maximum score of 2). Outcome: assessment of outcome and follow-up (maximum score of 3).

one study including esophageal squamous cell carcinoma, and one study including cholangiocarcinoma (Figure 2). No obvious heterogeneity was found in each subgroup. The results prompt that overexpression of miR-17-5 p was related to poor OS in colorectal carcinoma, hepatocellular carcinoma, and gastric carcinoma. But the difference was not significant in pancreatic carcinoma.

Subgroup analyses were conducted according to the main characteristics. The results showed that the predictive role of miR-17-5p was significant in blood specimen (HR = 1.70, 95% CI: 1.23–2.34, fixed-effects model), tissue specimen (HR = 1.90, 95% CI: 1.29–2.80, random-effects model), Asian patients (HR = 1.98, 95% CI: 1.61–2.38, fixed-effects model), digestive tract tumors (including gastric carcinoma, colorectal carcinoma, esophageal squamous cell carcinoma; HR = 1.97, 95% CI: 1.58–2.45, fixed-effects model), hepatobiliary system, and pancreas tumor (including hepatocellular carcinoma, pancreatic carcinoma, and cholangiocarcinoma; HR = 1.62, 95% CI: 1.14–2.31, fixed-effects model). The association between overexpressed miR-17-5 p and poor OS was not significant in the subgroup of European patients (Table 4).

## Sensitivity analysis

Considering the number of the OS studies was more than ten, a sensitivity analysis was performed to assess the stability of the meta-analysis results. After omitting one study each time, the pooled HRs were calculated again. The stability of the entire study was not influenced by one individual study (Figure 3).

## Publication bias assessment

The Begg's funnel plot and Egger's test were applied to detect publication bias in this OS and DFS meta-analysis among

included studies (Figure 4). In OS and DFS meta-analysis, the values of Begg's regression were 0.558 and 0.373. The result suggests that no obvious risk of publication bias was found in the meta-analysis.

## Discussion

The function of miR-17-92 cluster had been reported in many different aspects. As an important member of miR-17-92 cluster, miR-17-5 p had been demonstrated playing an important role in aging of brain, heart, and bone. According to the recent researches, the review of Dellago summed up that miR-17-5 p is at the crossroads of aging, longevity, and cancer and can be used a biomarker or a therapeutic tool.<sup>29</sup>

Emerging evidence indicate that the miR-17-92 cluster may play an important role in tumorigenesis as a novel class

of oncogenes.<sup>30,31</sup> MiR-17-5 p is one of the main effectors of the miR-17-92 cluster components. MiR-17-5 p, as a novel biomarker of prognosis in many types of cancer, has generated much interest. Many studies suggest that overexpression of miR-17-5 p plays important roles in increasing cell proliferation, migration, and invasion. MiR-17-5 p functions as a tumor suppressor in biological activities. Cheng et al revealed that miR-17-5 p promotes tumor cell migration by upregulating a calcium-activated potassium channel subunit alpha 1 (KCa1.1) in malignant pleural mesothelioma.<sup>32</sup> Li et al discovered that overexpression of miR-17-5 p in MCF-7 cells promote the invasive and migratory abilities by targeting HBP1 through  $\beta$ -catenin pathway.<sup>33</sup>

In addition, the role of miR-17-5 p as an oncogene or tumor suppressor has also been reported in cervical cancer<sup>34</sup>

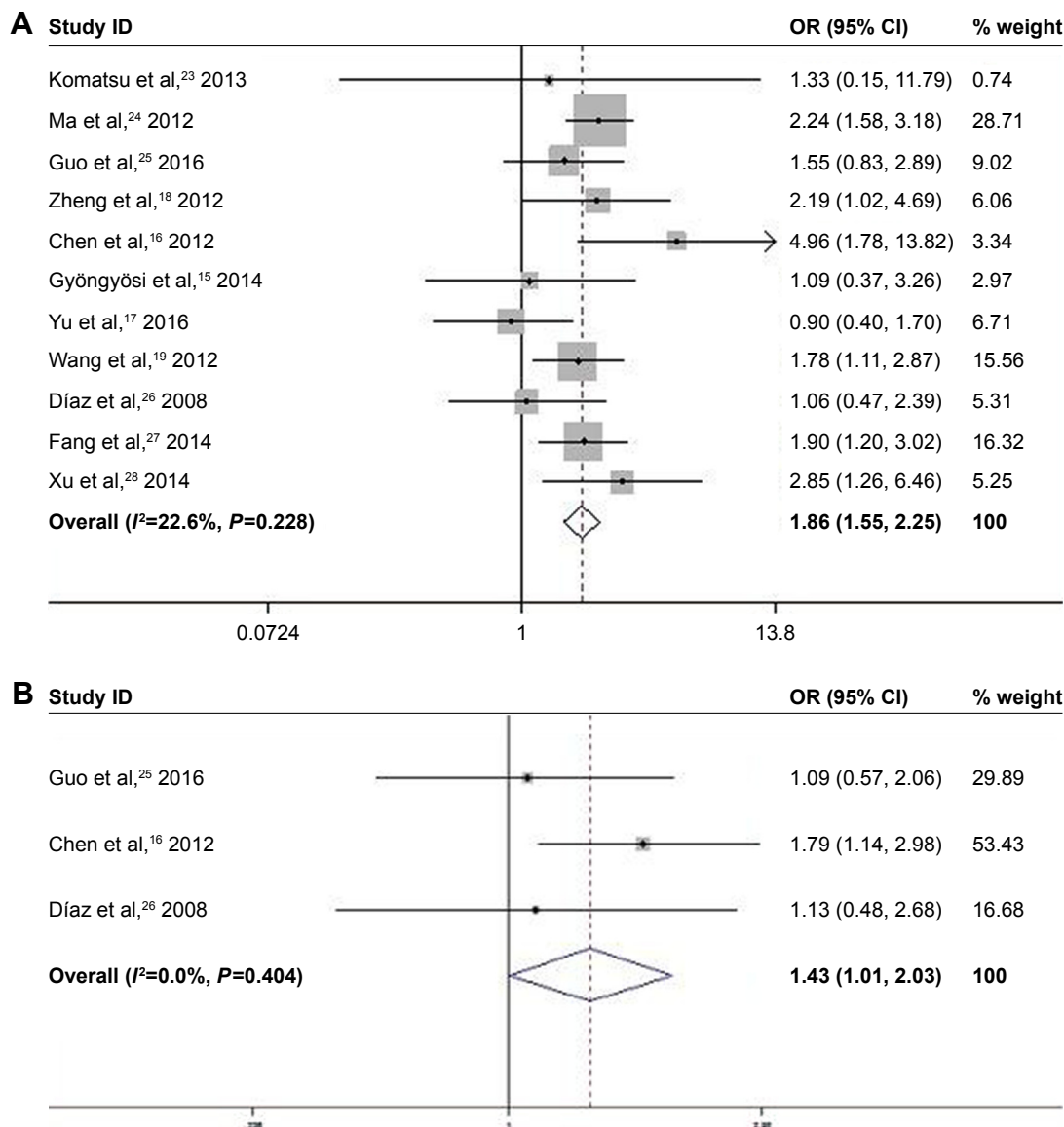
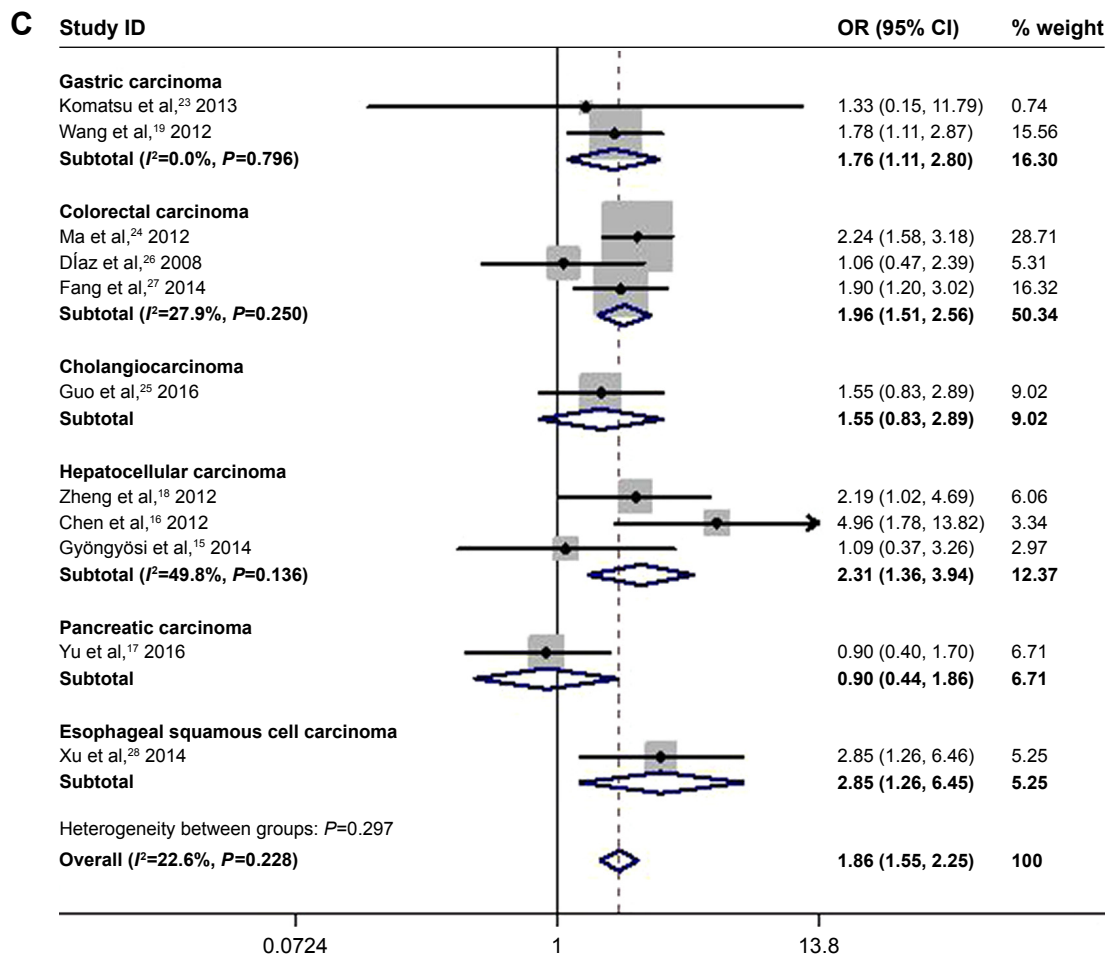


Figure 2 (Continued)



**Figure 2** Forest plot of overall survival analysis and disease-free survival analysis.

**Notes:** (A) Meta-analysis of miR-17-5 p expression and overall survival. (B) Meta-analysis of miR-17-5 p expression and disease-free survival. (C) Meta-analysis of miR-17-5 p expression and overall survival in different kinds of tumors.

and breast cancer.<sup>35,36</sup> Furthermore, in gastrointestinal tumors, miR-17-5 p-induced phosphorylation of HSP27 enhances the migration of HCCs through the p38 MAPK pathway.<sup>37</sup> In gastric cancer, miR-17-5 p downregulated TGFBR2 expression, thereby promoting cell growth and migration.<sup>38</sup>

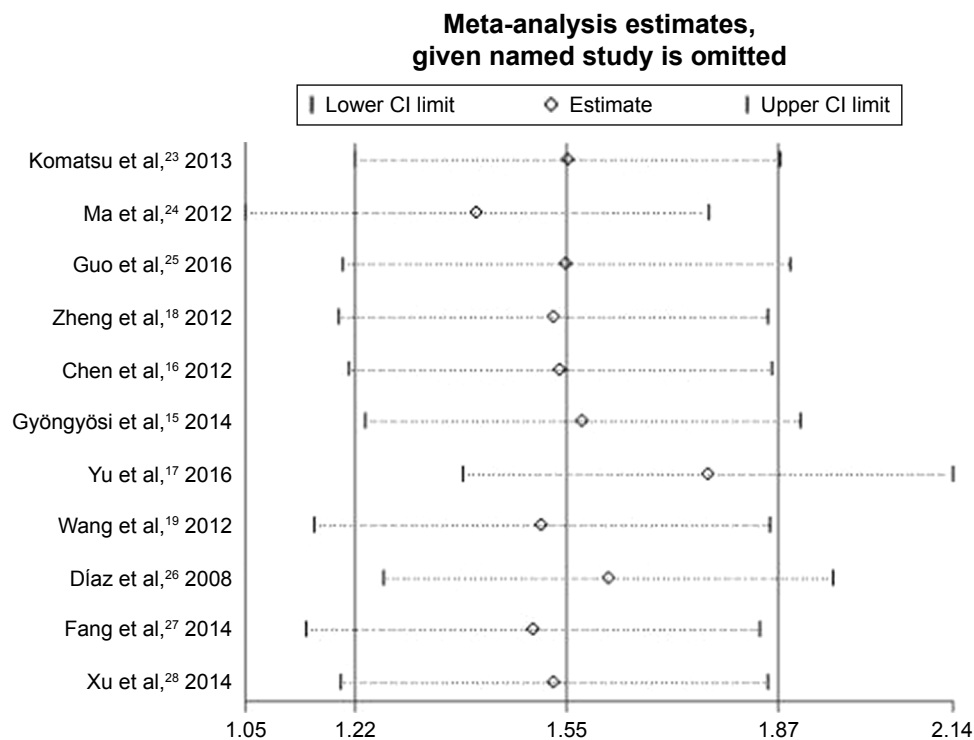
GFRalpha2 influences cell growth and apoptosis through regulating tumor gene PTEN via mir-17-5 p in pancreatic cancer.<sup>39</sup>

Up to now, many studies have reported that miR-17-5 p influences the effectiveness of the chemotherapy in some

**Table 4** Meta-analysis of overall survival and subgroup analysis

Stratified study	No of studies	HR (95% CI)	Model	P-value	Heterogeneity	
					$I^2$ (%)	P-value
<b>Year</b>						
>2012	6	2.05 (1.61–2.61)	Fixed	<0.001	18.5	0.293
≤2012	5	1.62 (1.21–2.18)	Fixed	0.001	25.2	0.253
<b>Race</b>						
Asian	9	1.98 (1.61–2.38)	Fixed	<0.001	19	0.274
European	2	1.07 (0.56–2.05)	Fixed	0.837	0	0.968
<b>Material</b>						
Blood	5	1.70 (1.23–2.34)	Fixed	0.001	0	0.871
Tissue	6	1.90 (1.29–2.80)	Random	<0.001	55.3	0.048
<b>Cancer type</b>						
Digestive tract tumors	6	1.97 (1.58–2.45)	Fixed	<0.001	0	0.572
Hepatobiliary system and pancreas tumors	5	1.62 (1.14–2.31)	Fixed	0.007	51.5	0.083

**Abbreviation:** HR, hazard ratio.

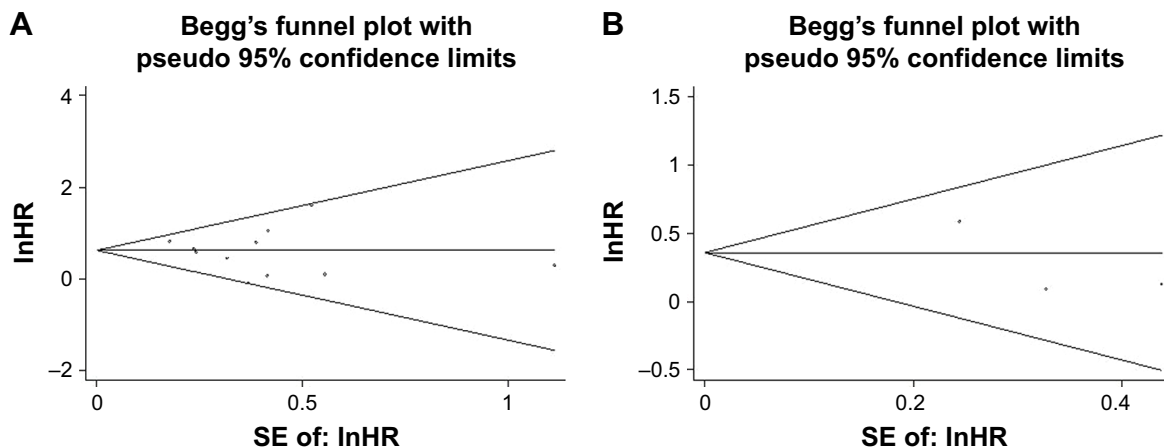


**Figure 3** Result of sensitivity analyses by omitting one study in each turn.

tumors in vivo. In Yan’s research, inhibiting miR-17-5 p expression increased chemosensitivity to gemcitabine in the Panc-1 and BxPC3 cells.<sup>40</sup> Fang et al found that miRNA-17-5 p promotes tumor metastasis and chemotherapeutic drug resistance of colorectal cancer by downregulating the expression of PTEN.<sup>27</sup> Chatterjee et al examined that miR-17-5 p downregulation contributes to paclitaxel resistance through altering Beclin1 expression in lung cancer.<sup>41</sup> By performing a similar study in radiotherapy, Wu et al identified that miRNA-17-5 p regulated radiosensitivity in oral squamous cell carcinoma.<sup>42</sup> The downregulated mir-17-5 p

in esophageal adenocarcinoma cancer stem-like cells may promote the radioresistant phenotype.<sup>43</sup>

Recently, many studies reported that miR-17-5 p is associated with poor OS in many types of tumor. However, the sample size of these studies is relatively small. In most researches,<sup>14,16,18,19</sup> miR-17-5 p indicates a poor prognosis in hepatocellular, lung, and gastric carcinomas. But there is still argument between the function of overexpression of miR-17-5 p and predicting the survival. In Yu et al’s multi-variate survival analyses of pancreatic cancer and Gyöngyösi et al’s research of hepatocellular carcinoma, there was no



**Figure 4 (A)** Funnel plot of miR-17-5 p and overall survival. **(B)** Funnel plot of miR-17-5 p and disease-free survival. **Abbreviations:** HR, hazard ratio; SE, standard error.

significant association between overexpression of miR-17-5 p level and the OS time.<sup>15,17</sup> In contrast, in Srinivasan et al's study of glioblastoma,<sup>20</sup> overexpression of miR-17-5 p was proved to contribute to increase the patients' survival time. With the increasing number of researches related to miR-17-5 p in gastrointestinal tumors, we noted that half of researches about the prognostic value of miR-17-5 p in gastrointestinal tumors were insignificant. So we conducted this meta-analysis aiming to better understand the association between miR-17-5 p expression and survival in gastrointestinal tumor patients. Our study included eleven researches and higher expression of miR-17-5 p predicted poor OS (HR = 1.86, 95% CI: 1.55–2.25; fixed-effects model) and poor DFS (HR = 1.43, 95% CI: 1.01–2.03; fixed-effects model). Nevertheless, the present study has some limitations that require consideration. First, our study analyzed only unvaried factors; we did not stratify and analyze factors such as gender, treatment, and environmental variables due to lack of data. Second, the types of tumor are still deficient. Third, the analysis of the expression of miR-17-5 p and DFS is based only on three studies, one from each of three different cancer types including one study looking at plasma expression. Fourth, although our research shows that miR-17-5 p is significantly correlated with the prognosis of gastrointestinal tumors, the clinical characteristics of different tumors may affect the combined results. The influence of different sample sources (tissue/serum) on the combined results should also be taken into consideration. Therefore, a more precise analysis needs to be performed.

## Conclusion

In conclusion, the results of our meta-analysis support a potential prognostic role for miR-17-5 p in some cancers. Further studies should be performed to analyze the association between prognosis and other clinic characteristics.

## Disclosure

The authors report no conflicts of interest in this work.

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