Prognostic value of miR-17-5p in cancers: a meta-analysis

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Background: Studies have shown that miR-17-5p plays an important role in the development of cancer. The aim of this meta-analysis was to quantitatively analyze the association of miR-17-5p with prognosis in various cancers.

Materials and methods: We searched the PubMed, EMBASE, Web of Science, and Cochrane library databases for relevant studies through August 2017. The prognostic data and clinico-pathological features of overall survival (OS) and disease-free survival (DFS) were extracted to investigate the association between miR-17-5p expression and tumor prognosis. In addition, odds ratios (ORs) were used to assess the correlations between miR-17-5p expression and clinico-pathological characteristics.

Results: A total of ten studies were incorporated into this systematic review, and we found that high miR-17-5p expression can predict poor OS for malignancies (combined hazard ratio [HR]=1.87; 95% confidence interval [CI], 1.37–2.55; \( P=0.000 \)) as well as poor DFS (combined HR=1.60; 95% CI, 1.05–2.44; \( P=0.027 \)). Further subgroup analyses suggested that high miR-17-5p expression was related to poor OS in Asian patients (combined HR=1.92; 95% CI, 1.37–2.71; \( P=0.000 \)) and the serum/plasma sample source subgroup (combined HR=2.13; 95% CI, 1.36–3.31; \( P=0.001 \)). The combined OR indicated that the expression of miR-17-5p was associated with lymph node invasion (OR=1.28; 95% CI, 1.05–1.56; \( P=0.016 \)) and venous invasion (OR=1.92; 95% CI, 1.40–2.63; \( P=0.000 \)).

Conclusion: Elevated expression of miR-17-5p suggested a poor prognosis in cancer patients and may serve as a new tumor marker to monitor cancer development and progression.

Keywords: miR-17-5p, cancer, prognosis, meta-analysis

Introduction

Cancer has become a global public health problem, seriously endangering human life in recent decades.1 Early diagnosis of cancer greatly improves the survival of patients and their quality of life; however, there is no effective way to assess the prognosis of cancer patients based on clinical parameters. microRNAs (miRNAs), as a new type of biomarker, have gradually attracted the attention of many researchers.2 miRNAs are non-coding RNAs of approximately 18–25 nucleotides that facilitate messenger RNA (mRNA) degradation and inhibit translation by binding to the 3′-untranslated region of the mRNA.3

Recently, a growing amount of evidence has shown that miRNAs are engaged in diverse biological processes, including cellular growth, differentiation, proliferation, metastasis, invasion, migration, and apoptosis.4–8

The miR-17-92 cluster (which is situated at the human 13q31 and includes miR-17-3p, miR-17-5p, miR-19a, miR-18a, miR-19b, miR-20a, and miR-92-1) first attracted the attention of researchers after a series of reports linked these miRNAs to
tumor formation and progression. Specifically, researchers have found that miR-17-5p is a crucial member of the miR-17 cluster family that is highly expressed in various cancers such as hepatocellular carcinoma (HCC), lung cancer (LC), colorectal cancer (CRC), and other cancers.

Furthermore, researchers have found that high expression of miR-17-5p is negatively correlated with overall survival (OS) and disease-free survival (DFS) in different kinds of cancers. However, some studies have reported contradictory results; for example, Liu et al observed that high expression of miR-17-5p could negatively regulate the invasion and migration of HCC cell lines. Until now, a systematic review of the prognostic value of miR-17-5p in human tumors has not been reported. Therefore, we performed this meta-analysis to explore the prognostic role of elevated miR-17-5p expression in various cancers.

Materials and methods

Literature search

To identify relevant studies, we searched the online PubMed, EMBASE, Web of Science, and the Cochrane library database through July 2017. The keywords for the search were as follows: “miR-17-5p”, “microRNA-17-5p”, “miRNA-17-5p”, “cancer”, “carcinoma”, “neoplasm”, and “tumor” in combination with “prognosis”. In addition, the references of identified articles were also explored for additional relevant articles. All of the articles were reviewed by three investigators independently, and any disagreements were settled by discussion.

Inclusion and exclusion criteria

Researchers first screened the title and abstract and then screened out articles by skimming the full text. An eligible study was selected if it was consistent with the following inclusion criteria: 1) the study was based on human research; 2) hazard ratios (HRs) and their 95% confidence intervals (CIs) could be extracted from the article; 3) all patients could be separated into high and low expression level groups based on miR-17-5p quantity; and 4) the study was written in English and its full text was available.

Exclusion criteria for the articles were as follows: 1) the study was conducted using animals and/or cell lines; 2) the study was a systematic review or case report; 3) the study was not written in English; 4) the study lacked significant data; and 5) the study was a repeat study.

Data extraction

Three investigators (Kong WH, Cheng YS, and Liang H) extracted the data and information from the selected studies. Any disagreements were resolved through a panel discussion.

Results

Literature search and study characteristics

According to the inclusion and exclusion criteria, we selected a total of ten articles with data from approximately 1,135 people for meta-analysis, and the detailed selection steps are shown in Figure 1.

We summarize the major features of the selected studies in Table 1. Among these ten studies, nine measured miR-17-5p expression using polymerase chain reaction (PCR), while one study performed PCR and in situ hybridization (ISH).
Across these the ten studies, patients were diagnosed with CRC, HCC, colon cancer (CC), gastric cancer (GC), childhood infratentorial ependymoma (CIE), pancreatic cancer (PC), osteosarcoma (OSA), nasopharyngeal carcinoma (NPC), and LC. Eight studies directly provided HRs and 95% CIs, one study provided only a survival curve, and one study provided only the risk ratios (RRs); thus, we merged RRs and HRs.

**miR-17-5p expression and OS**

We included ten studies of OS in our analysis. Considering that potential heterogeneity may have been introduced in this study, we used a random effect model to conservatively estimate the effect of combined HRs and 95% CIs. We found that patients with high expression of miR-17-5p had a worse prognosis than those with low expression of miR-17-5p (HR=1.87; 95% CI, 1.37–2.55; \(P=0.000\)) (Figure 2).

To lessen the impact of heterogeneity, subgroup analyses were performed for sample size, ethnicity, sources of detected sample source, definition method, tumor types, and statistical mode (Table 2). First, we found that the expression level of miR-17-5p had a statistically significant effect on OS in subgroups with a sample size greater than or equal to 100 (HR=2.15; 95% CI, 1.37–3.37; \(P=0.001\)) as well as subgroups with a sample size of less than 100 (HR=1.72; 95% CI, 1.11–2.68; \(P=0.016\)). Second, we observed that miR-17-5p had a statistically significant effect on OS in the Asians patient subgroup (HR=1.92; 95% CI, 1.37–2.71; \(P=0.000\)), but no statistical significance was found in the European patient subgroup. Third, when we conducted a subgroup analysis for the sample source, we found that miR-17-5p was more strongly associated with the plasma/serum subgroup (HR=2.13; 95% CI, 1.36–3.31; \(P=0.001\)) than the tissue subgroup (HR=1.69; 95% CI, 1.05–2.71; \(P=0.031\)) using a random effects model. Fourth, miR-17-5p has a stronger correlation with median definition than other definition methods (HR=2.08; 95% CI, 1.54–2.81; \(P=0.000\)). Fifth, in a subgroup analysis stratified by the cancer type, all three of the subgroups showed a strong correlation between miR-17-5p and OS with a random effects model, indicating that miR-17-5p has a predictive effect for different kinds of tumors. Finally, considering that the combination of univariate analysis and multivariate analysis is unreasonable, we performed a subgroup analysis for statistical mode, and the results were consistent with the overall combined effect. Therefore, the conclusion is stable and credible.

**miR-17-5p expression and DFS**

Two studies focused on DFS analysis. Heterogeneity results showed a small amount of heterogeneity (\(I^2=0\); \(P=0.360\)), so we use a fixed effect model to compute the
combined HRs and 95% CIs for DFS. The results showed that the DFS of patients with elevated miR-17-5p expression was more affected than that of patients with decreased miR-17-5p expression (HR = 1.60; 95% CI, 1.05–2.44; P = 0.027) (Figure 3). Because only two studies reported DFS, the data are too limited to perform subgroup analysis for DFS.

**miR-17-5p expression and clinicopathological characteristics**

Meta-analysis indicated that elevated miR-17-5p expression was associated with lymph node invasion (OR = 1.28; 95% CI, 1.05–1.56; P = 0.016) and venous invasion (OR = 1.92; 95% CI, 1.40–2.63; P = 0.000) (Table 3). No significant correlations were found for age (P = 0.24), gender (P = 0.212), tumor invasion depth (P = 0.400), distant metastasis (P = 0.499), tumor stage (P = 0.804), differentiation grade (P = 0.077), tumor size (P = 0.291), or hepatitis history (P = 0.550). Due to insufficient data, we failed to detect any correlations between elevated miR-17-5p expression and other clinicopathological characteristics.

**Sensitivity analysis**

Sensitivity analysis was implemented to assess the influence of each individual study on the integrated results of OS. We excluded each study, re-merged the meta-analysis results and then compared the results of the unexcluded meta-analysis to investigate the stability of the results. This analysis showed that the combined HR for the effect of miR-17-5p expression on OS was not remarkably influenced after eliminating any of the individual studies (Figure 4).

**Publication bias**

We use Egger’s tests and funnel plots to detect the publication bias. The results of the funnel plot for OS are shown in Figure 5. Since the Egger’s test has a P-value greater than 0.05, no publication bias was found. Due to the small number of studies that reported DFS, we were not able to determine the publication bias for DFS.

**Discussion**

In recent years, miRNAs have been considered to be closely related to carcinogenic processes such as angiogenesis, proliferation, differentiation, invasion, apoptosis, and metastasis. It is presumed that more than one third of human genes are regulated by miRNAs, which serve as negative regulatory molecules of gene expression at the posttranscriptional translation phase and are widely involved in the development...
and progression of human diseases, particularly human cancer. Since the publication of reviews about miRNA-17-5p in multiple journals, miR-17-5p has gradually attracted the attention of many researchers as a molecule of interest. miR-17-5p has also been found to be closely associated with the development of tumors. However, as no quantitative systematic reviews about miR-17-5p have been published so far, we conducted this meta-analysis.

### Table 2: The pooled HRs, 95% CIs, heterogeneity, and P-values of overall survival stratified by sample size, ethnicity, sample sources, definition method, tumor type, and statistical mode

| Stratified analysis                  | Number of studies | Number of patients | Pooled HR (95% CI) | P-value | Heterogeneity | Test of interaction |
|-------------------------------------|-------------------|--------------------|--------------------|---------|---------------|---------------------|
|                                    |                   |                    |                    |         | P (%)         | Model               | P-value |
|                                    |                   |                    |                    |         |               |                     |         |
| Sample size                        |                   |                    |                    |         |               |                     |         |
| ≥ 100                              | 3                 | 636                | 2.15 (1.37–3.37)   | 0.001   | 38.6          | 0.196               | Random  |
| < 100                              | 7                 | 499                | 1.72 (1.11–2.68)   | 0.016   | 48.6          | 0.070               | Random  |
| Dominant ethnicity                 |                   |                    |                    |         |               |                     |         |
| Asian                              | 8                 | 1,020              | 1.92 (1.37–2.71)   | 0.000   | 47.2          | 0.066               | Random  |
| European                           | 2                 | 115                | 1.69 (0.57–5.00)   | 0.344   | 55.6          | 0.133               | Random  |
| Source                             |                   |                    |                    |         |               |                     |         |
| Tissue                             | 6                 | 691                | 1.69 (1.05–2.71)   | 0.031   | 50.7          | 0.071               | Random  |
| Serum/plasma                       | 4                 | 444                | 2.13 (1.36–3.31)   | 0.001   | 40.5          | 0.169               | Random  |
| Definition                          |                   |                    |                    |         |               |                     |         |
| Median                             | 5                 | 555                | 2.08 (1.54–2.81)   | 0.000   | 1.5           | 0.398               | Random  |
| Stain score                        | 2                 | 376                | 1.77 (0.57–5.50)   | 0.327   | 76.4          | 0.015               | Random  |
| Others                             | 3                 | 204                | 1.76 (1.15–2.67)   | 0.008   | 0             | 0.438               | Random  |
| Tumor types                        |                   |                    |                    |         |               |                     |         |
| Digestive system                   | 6                 | 718                | 1.73 (1.20–2.49)   | 0.003   | 45.2          | 0.104               | Random  |
| Respiratory system                 | 2                 | 302                | 1.63 (1.02–2.60)   | 0.040   | 0             | 0.531               | Random  |
| Others                             | 2                 | 115                | 5.33 (1.72–16.50)  | 0.004   | 27.3          | 0.241               | Random  |
| Statistical mode                   |                   |                    |                    |         |               |                     |         |
| Univariate analysis                | 4                 | 429                | 1.59 (1.17–2.17)   | 0.003   | 0             | 0.663               | Random  |
| Multivariate analysis              | 6                 | 706                | 2.43 (1.39–4.26)   | 0.002   | 61.4          | 0.024               | Random  |

**Note:** Data in bold P<0.05.

**Abbreviations:** CI, confidence interval; HR, hazard ratio.
In this study, we strictly adhered to the MOOSE guidelines to perform the meta-analysis and to assess the quality of the included studies using the scales recommended by the Cochrane Collaboration. The results indicated that high expression of miR-17-5p plays an unfavorable role in OS and DFS. Considering the potential heterogeneity of the included studies, we used a random effects model to combine the data and then performed subgroup analysis, sensitivity analysis, and publication bias detection; the findings of these analyses show that our results are stable and credible.

Furthermore, we carried out subgroup analyses to explore the prognostic significance of miR-17-5p in OS, and we have successfully drawn some valuable conclusions for clinical practice. To rule out the impact of different races on prognosis, we divided the ten studies into patient groups of Asian and European ethnicities. We observed that the elevated expression of miR-17-5p predicts significantly worse OS in Asian patients (pooled HR=1.92; 95% CI, 1.37–2.71; P=0.000), but no statistical significance was found in European patients (combined HR=1.69; 95% CI, 0.57–5.00, P=0.344) (Table 2). This difference may be due to the different genetic backgrounds, geographical locations, climates etc., of the different races. Therefore, we concluded that miR-17-5p might be a more valuable predictor of cancer prognosis in Asian populations. To illustrate the relationship between the expression level of miR-17-5p and prognosis using different sample sources, we divided the patients into two subgroups, serum/plasma and tissue, and we observed that the serum/plasma group had a worse prognosis (combined HR=2.13; 95% CI, 1.36–3.31; P=0.001) than tissue-derived specimens (combined HR=1.69; 95% CI, 1.05–2.71; P=0.031) (Table 2). Although the detection of miR-17-5p in tumor specimens has been widely used to study tumor prognosis, plasma/serum specimen detection is more convenient and effective, and it

Table 3 Meta-analysis results of the correlation between elevated miR-17-5p expression and multiple clinicopathological characteristics

| Stratified analysis | Number of studies | Number of patients | Pooled OR (95% CI) | P-value | Heterogeneity | Model |
|---------------------|-------------------|--------------------|--------------------|---------|---------------|-------|
| Age (old vs young)  | 6                 | 663                | 1.08 (0.95–1.24)   | 0.240   | 0             | 0.578 Fixed |
| Gender (male vs female) | 6               | 663                | 0.92 (0.80–1.05)   | 0.212   | 0             | 0.809 Fixed |
| Invasion depth (T3+T4 vs T1+T2)* | 2               | 160                | 1.45 (0.61–3.45)   | 0.400   | 87.7          | 0.004 Random |
| Lymph node invasion (≥2 vs <2) | 2               | 201                | **1.28 (1.05–1.56)** | 0.016   | 0             | 0.404 Fixed |
| Distant metastasis (yes vs no) | 3               | 242                | 1.24 (0.66–2.32)   | 0.499   | 83.4          | 0.002 Random |
| Tumor stage (III+IV vs I+II) | 4               | 463                | 1.09 (0.56–2.10)   | 0.804   | 88.8          | 0.000 Random |
| Venous invasion (yes vs no) | 2               | 200                | 1.92 (1.40–2.63)   | 0.000   | 0             | 0.776 Fixed |
| Differentiation grade (poorly vs well and moderately) | 2               | 161                | 1.33 (0.97–1.84)   | 0.077   | 0             | 0.361 Fixed |
| Tumor size (>5 vs ≤5) (cm) | 3                | 281                | 0.90 (0.62–1.30)   | 0.291   | 53.4          | 0.117 Random |
| Hepatitis history (yes vs no) | 3               | 216                | 1.20 (0.66–2.16)   | 0.550   | 58.9          | 0.119 Random |

Notes: *According to the size of the tumor and/or the extent of the primary tumor are defined as different T stages. Data in bold P<0.05.
Abbreviations: CI, confidence interval; OR, odds ratio.
Figure 4 Sensitivity analysis of overall survival in this meta-analysis.

Meta-analysis random-effects estimates (exponential form)
study omitted

| Study          | Inh            |
|----------------|---------------|
| Chen et al 10  | 1.29          |
| Zakrzewska et al 10 | 1.37          |
| Wang et al 17  | 1.87          |
| Diaz et al 18  | 1.87          |
| Zheng et al 19 |               |
| Yu et al 19    |               |
| Fang et al 19  |               |
| Chen et al 19  |               |
| Chen et al 12  |               |
| Zhu et al 14   |               |

Figure 5 Begg’s funnel plot with pseudo 95% CI of the publication bias for overall survival.

Abbreviations: Inh, logarithm of the hazard ratio; SE, standard error.

can efficiently assess the risk of hospital stay and postoperative recurrence. The expression of miR-17-5p in the blood is more predictive than in tissue, which can be applied in clinical research. Therefore, the detection of miR-17-5p in plasma/serum during postoperative follow-up periods might be an effective way to closely monitor disease-progression and treatment in cancer patients.

Moreover, we carried out meta-analyses with respect to pathological characteristics. We found that elevated miR-17-5p expression is predominantly correlated with lymph node invasion (combined OR=1.28; 95% CI, 1.05–1.56; P=0.016) and venous invasion (combined OR=1.92; 95% CI, 1.40–2.63; P=0.000). No statistically significant correlations were found for age, gender, tumor invasion depth, distant metastasis, tumor stage, differentiation grade, or hepatitis history. Therefore, we concluded that miR-17-5p may be involved in the progression of lymphatic metastasis and vein invasion in cancer.

To the best of our knowledge, miR-17-5p has been found to be closely associated with cancers through complicated regulatory mechanisms. For instance, Yang et al 27 observed that miR-17-5p can facilitate the migration and proliferation of human liver cancer cells through the p38-MAPK-HSP27 pathway. Li et al 28 discovered that miR-17-5p can boost the invasion and migration of human breast tumor cells by inhibiting HMG box-containing protein 1 (HBP1), a tumor suppressor. Qu et al 29 observed that miR-17-5p can negatively regulate transforming growth factor-beta receptor 2 (TGFBR2), which serves as an original regulator of the TGF-beta signaling pathway, and reduction or loss of its expression can lead to uncontrolled cell proliferation and invasion, thus promoting cell growth and migration. Wang et al 30 noticed that miR-17-5p can promote the proliferation of OSA in a breast cancer cell 2 (BRCC2)-dependent mechanism, which plays a key role in suppressing tumorigenesis.
To some extent, these mechanisms explain why patients with elevated miR-17-5p expression have multiple lymphatic metastases and venous violations, but the specific mechanism still requires further investigation.

These studies had several limitations. First, the definition of high miR-17-5p expression was not the same across studies; thus, it was difficult to define miR-17-5p overexpression in various cancers. Second, the study included a total of only ten articles; therefore, the data are not sufficient. Third, there was considerable heterogeneity among the different studies in terms of cancer type, specimen source, detection method and definition of high miR-17-5p expression. Fourth, eligible studies only included positive results, and there may be publication bias. Fifth, combining univariate and multivariate analysis is somewhat unreasonable. Finally, part of the HR value was calculated using a survival curve, which may lead to some error.

**Conclusion and recommendations**

Our meta-analysis has explored the predictive value of miR-17-5p in different types of carcinomas. miR-17-5p may serve as a new tumor marker for predicting prognosis and for evaluating the clinicopathological characteristics of different kinds of carcinomas. Ultimately, considering the limitations of this study, these conclusions require additional large-sample and high-quality research to further clarify the relationship between miRNA-17-5p and prognosis.

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**Disclosure**

The authors report no conflicts of interest in this work.

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