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# Prognostic and clinicopathological significance of miR-638 in cancer patients
## A meta-analysis

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## Abstract

**Introduction:** MiR-638 is believed to be involved in human cancers. However, the prognostic value of miR-638 in human carcinomas is controversial and inconclusive. Therefore, we conducted this meta-analysis to investigate the association between miR-638 expression and clinical outcomes in the patients with various cancers.

**Methods:** We searched Pubmed, Embase, Wanfang, and the China National Knowledge Infrastructure (CNKI) up to September 1, 2020 to identify relevant studies. Hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were used to correlate expression of miR-638 with prognosis and clinicopathological features.

**Results:** A total of 18 studies involving 1886 patients were included in the meta-analysis. The results revealed that low miR-638 expression was significantly correlated with poor overall survival (OS) (HR = 2.09, 95% CI: 1.46–2.98, $P < .001$), but not with disease-free survival (DFS) (HR = 1.71, 95% CI: 0.31–9.56, $P = .540$). Subgroup analysis found that low miR-638 expression was associated with worse OS in patients with digestive system cancer (HR = 2.47, 95% CI: 1.85–3.30, $P < .001$), the reported directly from articles group (HR = 2.12, 95% CI: 1.34–3.33, $P < .001$), survival curves group (HR = 2.02, 95% CI: 1.07–3.80, $P = .029$), in studies with sample size ≥100 (HR = 2.12, 95% CI: 1.34–3.35, $P = .001$), and in studies with sample size <100 (HR = 2.02, 95%CI: 1.09–3.75, $P = .025$). Moreover, cancer patients with low miR-638 expression were prone to tumor size (OR = 1.47, 95% CI: 1.03–2.09, $P = .035$), earlier lymph node metastasis (present vs absent, OR = 2.26, 95% CI: 1.63–3.14, $P < .001$), earlier distant metastasis (present vs absent, OR = 2.60, 95% CI: 1.45–4.67, $P < .001$), TNM stage (III-IV vs I-II, OR = 2.01, 95% CI: 1.35–2.99, $P = .001$), and portal vein invasion (present vs absent, OR = 4.39, 95% CI: 2.23–8.64, $P < .001$), but not associated with age, gender, tumor differentiation, and vascular invasion.

**Conclusions:** MiR-638 may serve as a promising indicator in the prediction of prognosis and clinicopathological features in patients with different kinds of cancers.

**Abbreviations:** CI = confidence interval, CNKI = China National Knowledge Infrastructure, DFS = disease-free survival, EMT = epithelial-to-mesenchymal transition, ESCC = esophageal squamous cell carcinoma, HR = hazard ratio, miRNAs = microRNAs, NOS = Newcastle-Ottawa Scale, OR = odds ratio, OS = overall survival, OSCC = oral squamous cell carcinoma, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, qRT-PCR = quantitative reverse transcription-polymerase chain reaction, SOX2 = SRY (sex determining region Y)-box 2, VEGF = vascular endothelial growth factor.

**Keywords:** cancer, clinicopathology, meta-analysis, miR-638, prognosis

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## 1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide.[1] Due to the lack of specific symptoms of early cancer, cancer is often diagnosed at an advanced stage.[2] Despite continuously improving new treatment approaches including surgery, chemotherapy, radiotherapy and biological therapy, the prognosis of patients with cancer is still poor. Rising evidence demonstrated that the prognosis could be improved by using some molecular biomarkers. Therefore, identification of novel precise biomarkers is important and needed for the development of prognosis in cancer patients.

MicroRNAs (miRNAs), as a new type of biomarker, are small noncoding molecules of with a length of approximately 18 to 24 nucleotides, and can negatively regulate their target genes expression.[3,4] Many miRNAs have been confirmed to express abnormally in human cancers and can play an important role in different biological processes, such as cell cycle control,[5] proliferation,[6] differentiation,[7] metastasis,[8] and carcinogenesis.[9] Furthermore, a large number of miRNAs have been

identified to function as oncogenes or tumor suppressor genes in the tumorigenesis process.[10,11]

The human miR-638 is located in the 19p13.2 region. Previous studies have indicated that miR-638 plays an important role in several tumors.[12,13] Tang et al found that the expression of miR-638 was significantly decreased in oral squamous cell carcinoma (OSCC) tissues and cells and miR-638 could suppress the wnt/ b-catenin signaling pathway through PLD1, thus inhibiting OSCC progression.[14] Low expression of miR-638 is associated with a worse survival in patients with different cancers, such as breast cancer, colorectal carcinoma, hepatocellular carcinoma, cervical cancer, and lung cancer.[15–19] On the other hand, Zhang et al did not observe a significant association between miR-638 expression and overall survival (OS) of gastric cancer patients.[20] Because of the controversy involving the association between miR-638 and survival among patients with different carcinomas, we constructed this meta-analysis to explore the correlation between miR-638 expression and prognosis in various cancers.

## 2. Methods

### 2.1. Search strategies

The present systematic review and meta-analysis was conducted and reported according to the standards of quality detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[21] We searched Pubmed, Embase, Wanfang, and the China National Knowledge Infra-structure (CNKI) up to September 1, 2020 to identify relevant studies. The following keywords were adopted according to the retrieval strategy: "miR-638" OR "microRNA-638"; "cancer" OR "tumor" OR "carcinoma" OR "malignancy." Further manual inspection was performed to improve the integrity of the eligible papers by going through the title and abstract. Moreover, references in relevant publications were also browsed. The present study was meta-analysis and did not involve the collection of samples. Therefore, ethical approval was not required.

### 2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows:

1. research evaluated the association between miR-638 and cancer prognosis;
2. tumors were confirmed by histological or pathological examinations;
3. sufficient data was available for calculating the hazard ratio (HR) or odds ratio (OR) with their 95% confidence interval (CI).

The exclusion criteria were as follows:

1. letters, case reports, reviews, and conference abstracts without original data;
2. duplicate publications;
3. articles from which the relevant data could not be extracted.

### 2.3. Data extraction and quality assessment

Data extraction was conducted independently by 2 investigators from identified research in agreement with prescribed standards, during which disagreements were resolved by reaching a consensus on all contents. The extracted data elements mainly included the following information: author, publication year, country, cancer type, sample size, recruitment time, detection method, endpoints, HR obtain method, and NOS score. Additionally, clinical-pathological parameters, including age, gender, tumor size, tumor differentiation, lymph node metastasis, TNM stage, distant metastasis, portal vein invasion, and vascular invasion, were also extracted. When HRs and their 95% CIs were given in the articles, these data were extracted directly. If the prognosis was plotted as Kaplan–Meier survival curve, the data were digitized by the software Engauge Digitizer version 4.1 and calculated as described.[22,23] The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies.[24] This method comprised 3 parameters of quality: selection (score: 0–4), comparability (score: 0–2), and outcome assessment (score: 0–3), with total scores ranging from 0 to 9. The study with total scores greater than 6 was considered high quality in the present meta-analysis.

### 2.4. Statistical analysis

HRs with 95% CIs were calculated the association between miR-638 expression and the OS and disease-free survival (DFS) of cancer patients. ORs with 95% CIs were used to assess the association of miR-638 expression with clinicopathological characteristics. The evaluation of statistical heterogeneity was finished by using the Cochran $Q$ statistic and $I^2$ tests.[25] If the heterogeneity was significant between studies ($I^2 > 50\%$ or $P < .10$), the random-effects model was used; otherwise, the fixed-effects model was used.[26] Both Begg test and Egger test were used to evaluate the potential publication bias.[27] The statistical analysis was performed using STATA version 12.0 software (Stata Corporation, Collage Station, Texas). All $P$ values were two-sided and $P < .05$ was considered statistically significant.

## 3. Results

### 3.1. Literature search and study characteristics

The literature screening process is illustrated in Figure 1. Finally, 18 studies comprising 1886 patients were identified as eligible for the present quantitative analysis.[14–18,20,28,19,29–38] Thirteen of the 18 articles focused on the association of miR-638 with OS, and 3 articles investigated DFS. Moreover, 15 studies reported data on the relation between miR-638 expression and clinico-pathological features. The expression of miR-638 in tissue samples was measured by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). All of the included studies were performed in China and were published from 2014 to 2020. NOS used for evaluating quality of included studies varied from 6 to 8. The basic characteristics of the involved studies are presented in Table 1.

### 3.2. The correlation between miR-638 expression and the prognosis of cancers

Thirteen studies with 1502 patients were included in the meta-analysis of OS. The main results of this meta-analysis are listed in Table 2. The results indicated that low expression of miR-638 was highly correlated with poor prognosis of OS (HR = 2.09, 95% CI: 1.46–2.98, $P < .001$) (Fig. 2). Three studies with 501 patients were included in the meta-analysis of DFS. The results indicated that no connection was identified between miR-638
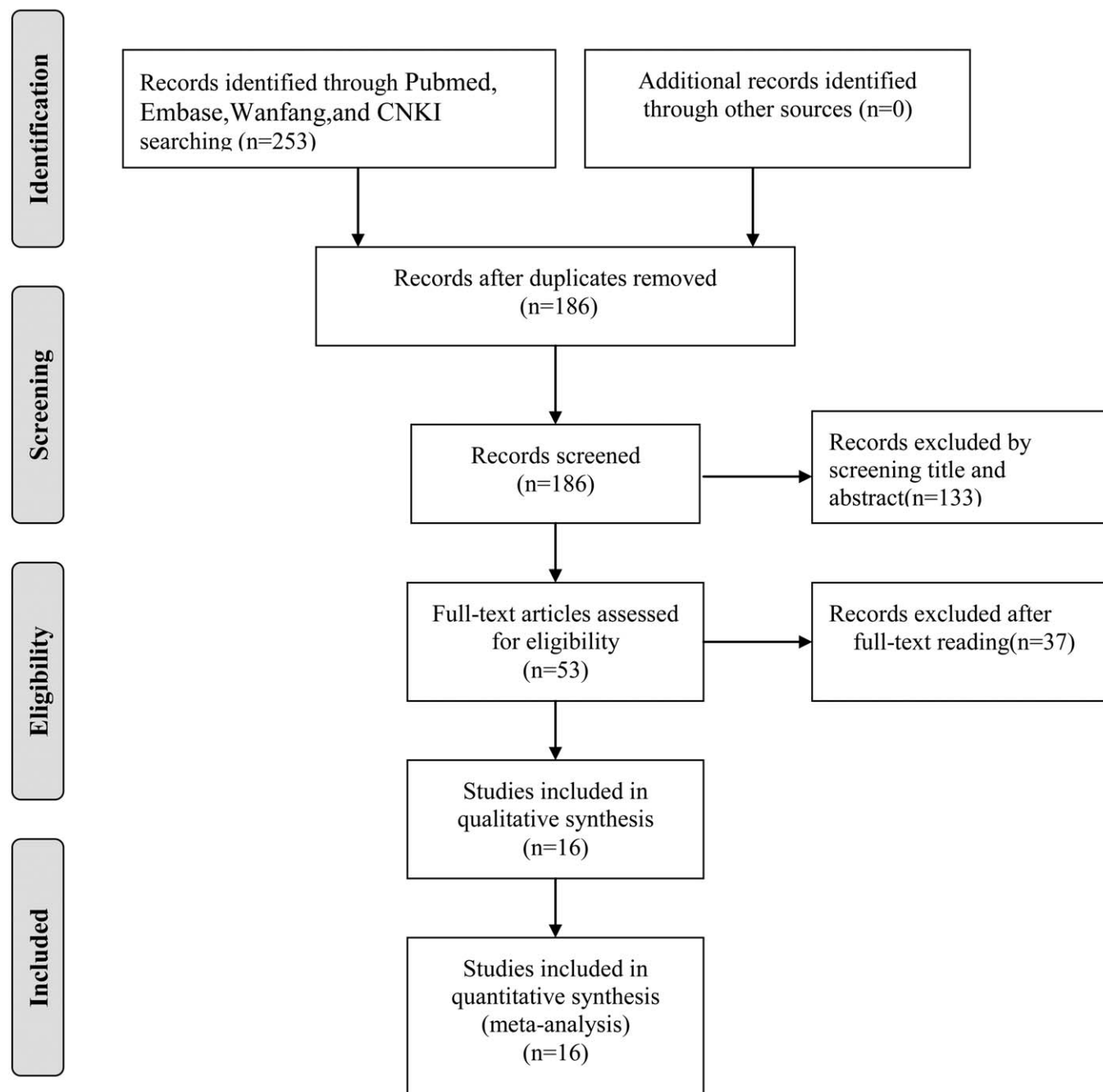
**Figure 1.** Flow diagram of the literature selection process.

expression and DFS (HR = 1.71, 95% CI: 0.31–9.56, $P$ = .540) (Fig. 3).

### 3.3. Subgroup analysis

Next, we proceeded with subgroup analyses stratified by cancer type, HR obtain method and sample size for OS. We found that low miR-638 expression was a powerful prognostic marker for shorter OS in patients with digestive system cancer (HR = 2.47, 95% CI: 1.85–3.30, $P$ < .001), but not with other cancers (HR = 1.78, 95% CI: 0.90–3.50, $P$ < .001) (Fig. 4). Subgroup analysis

based on the HR obtain method suggested that low expression of miR-638 predicted poor OS for both the reported directly from articles group (HR = 2.12, 95% CI: 1.34–3.33, $P$ < .001) and, survival curves group (HR = 2.02, 95% CI: 1.07–3.80, $P$ = .029) (Fig. 5). Furthermore, the subgroup analyses classified by sample size validated that low expression of miR-638 was a unfavorable prognostic factor in studies with sample size ≥100 (HR = 2.12, 95% CI: 1.34–3.35, $P$ = .001), and in studies with sample size <100 (HR = 2.02, 95% CI: 1.09–3.75, $P$ = .025) (Fig. 6).

Nevertheless, there was no significant association between miR-638 expression and DFS in patients with digestive system

**Table 1**

**Characteristics of the included studies.**

| Author (year) | Country | Cancer type | Sample size | Recruitment time | Detection method | Endpoints | HR obtain method | NOS score |
|---|---|---|---|---|---|---|---|---|
| Xia et al (2014) | China | NSCLC | 107 | 2010.3–2013.6 | qRT-PCR | NR | NR | 6 |
| Zhang et al (2014) | China | CRC | 113 | 2005–2008 | qRT-PCR | OS | reported directly | 8 |
| Zhang et al (2015) | China | Gastric cancer | 64 | 2008–2012 | qRT-PCR | OS | survival curves | 7 |
| Wang et al (2015) | China | NSCLC | 189 | 2009.7–2013.3 | qRT-PCR | OS | reported directly | 7 |
| Cheng et al (2016) | China | HCC | 100 | 2008.01–2014.06 | qRT-PCR | OS | survival curves | 7 |
| Zhang et al (2017) | China | HCC | 113 | 2007.3–2009.6 | qRT-PCR | OS, DFS | reported directly | 8 |
| Wei et al (2017) | China | Cervical cancer | 196 | 2008.7–2012.1 | qRT-PCR | OS, DFS | reported directly | 6 |
| Wang et al (2017) | China | Osteosarcoma | 64 | 2008–2012 | qRT-PCR | OS | survival curves | 7 |
| Yan et al (2017) | China | Colon cancer | 192 | 2008–2014 | qRT-PCR | OS, DFS | OS:reported directly DFS: survival curves | 8 |
| Ye et al (2018) | China | HCC | 78 | 2011.1–2012.7 | qRT-PCR | OS | reported directly | 7 |
| Shi et al (2018) | China | HCC | 126 | 2008–2011 | qRT-PCR | OS | reported directly | 7 |
| Zheng et al (2018) | China | Glioma | 24 | 2011.9–2013.12 | qRT-PCR | OS | survival curves | 8 |
| Li et al (2018) | China | Breast cancer | 125 | 2007.1–2012.12 | qRT-PCR | OS | reported directly | 7 |
| Pan et al (2020) | China | RCC | 118 | 2013-2015 | qRT-PCR | OS | reported directly | 7 |
| Tang et al (2019) | China | OSCC | 107 | NR | qRT-PCR | NR | NR | 6 |
| Cheng et al (2017) | China | HCC | 60 | 2008–2010 | qRT-PCR | NR | NR | 6 |
| Shen et al (2017) | China | Gastric cancer | 68 | 2010–2014 | qRT-PCR | NR | NR | 6 |
| Yang et al (2020) | China | HCC | 42 | NR | qRT-PCR | NR | NR | 6 |

CRC = colorectal cancer, DFS = disease-free survival, HCC = hepatocellular carcinoma, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, NR = not reported, NSCLC = non-small-cell lung cancer, OS = overall survival, OSCC = oral squamous cell carcinoma, qRT-PCR = quantitative real-time reverse transcription polymerase chain reaction, RCC = renal cell carcinoma.

cancer (HR=1.18, 95% CI: 0.05–26.74, $P$=.916), or the reported directly from articles group (HR=0.92, 95% CI: 0.07–12.26, $P$=.951).

### 3.4. Association between miR-638 expression and clinicopathological characteristics

Meta-analysis of the relationship between miR-638 expression and clinicopathological characteristics failed to show a significant association of low miR-638 expression with age (OR=0.85, 95% CI: 0.63–1.15, $P$=.293), gender (OR=1.06, 95% CI: 0.83–1.34, $P$=.656), tumor differentiation (poor vs well +moderate, OR=1.42, 95% CI: 0.97–2.06, $P$=.068), or vascular invasion (present vs absent, OR=2.35, 95% CI: 0.81–6.83, $P$=.117) (Table 3).

In contrast, low miR-638 expression was significantly related to tumor size (OR=1.47, 95% CI: 1.03–2.09, $P$=.035), earlier lymph node metastasis (present vs absent, OR=2.26, 95% CI: 1.63–3.14, $P<$.001), earlier distant metastasis (present vs absent, OR=2.60, 95% CI: 1.45–4.67, $P<$.001), TNM stage (III-IV vs I-II, OR=2.01, 95% CI:1.35–2.99, $P$=.001), and portal vein invasion (present vs absent, OR=4.39, 95% CI: 2.23–8.64, $P<$.001) (Table 3).

### 3.5. Sensitivity analysis

For the purpose of assessing the reliability and stability of our results, sensitivity analysis was contacted by sequentially omitting any individual cohort analysis. Fortunately, the pooled HR for OS was not influenced, which meant increased credibility (Fig. 7).

**Table 2**

**Main meta-analysis results of miR-638 expression in cancer patients.**

| Analysis | Numbers of studies | HR (95%CI) | $P$ value | $\chi^2$ | Heterogeneity $I^2$ (%) | $P$ value |
|---|---|---|---|---|---|---|
| Overall survival (OS) | 13 | 2.09 (1.46–2.98) | <.001 | 33.77 | 64.5 | .001 |
| Cancer type | | | | | | |
|   digestive system cancer | 7 | 2.47 (1.85–3.30) | <.001 | 3.62 | 0.0 | .728 |
|   other cancer | 6 | 1.78 (0.90–3.50) | .096 | 25.68 | 80.5 | <.001 |
| HR obtain method | | | | | | |
|   survival curves | 4 | 2.02 (1.07–3.80) | .029 | 6.32 | 52.5 | .097 |
|   reported directly | 9 | 2.12 (1.34–3.33) | .001 | 26.89 | 70.2 | .001 |
| Sample size | | | | | | |
|   ≥100 | 9 | 2.12 (1.34–3.35) | .001 | 26.86 | 70.2 | .001 |
|   <100 | 4 | 2.02 (1.09–3.75) | .025 | 6.46 | 53.6 | .091 |
| Disease-free survival (DFS) | 3 | 1.71 (0.31–9.56) | .540 | 20.38 | 90.2 | <.001 |
| Cancer type | | | | | | |
|   digestive system cancer | 2 | 1.18 (0.05–26.74) | .916 | 18.10 | 94.5 | <.001 |
| HR obtain method | | | | | | |
|   reported directly | 2 | 0.92 (0.07–12.26) | .951 | 14.78 | 93.2 | <.001 |

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, OS = overall survival.
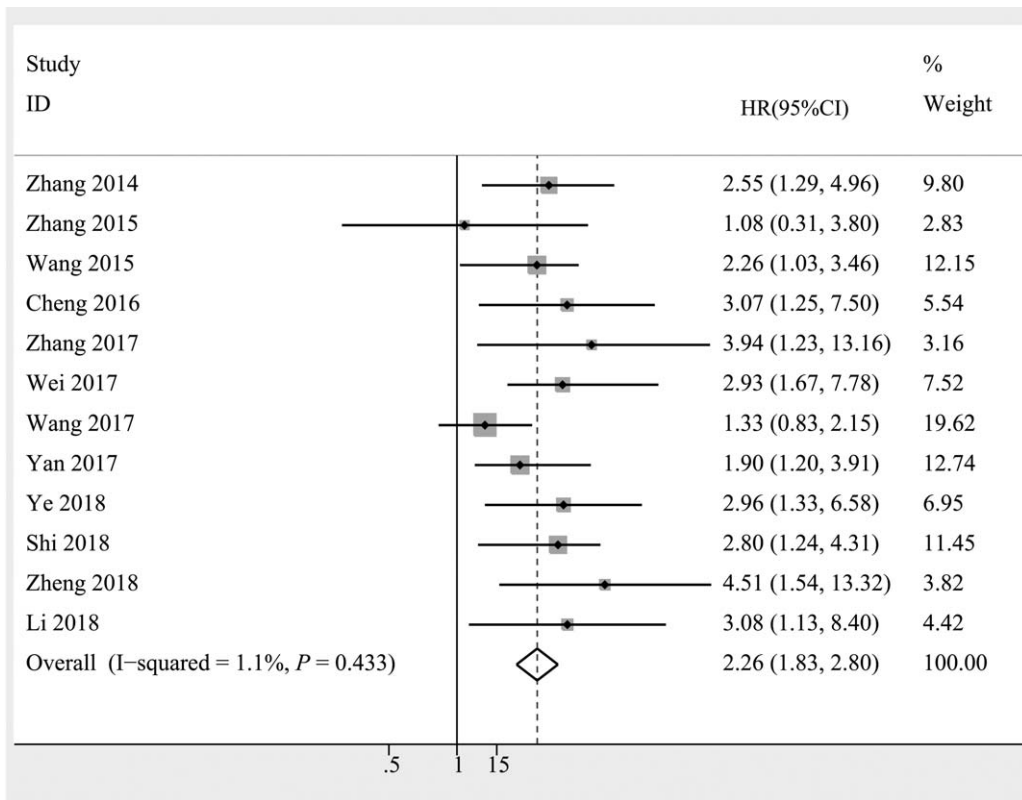
**Figure 2.** Forest plot of HRs for correlation between miR-638 expression and overall survival (OS).
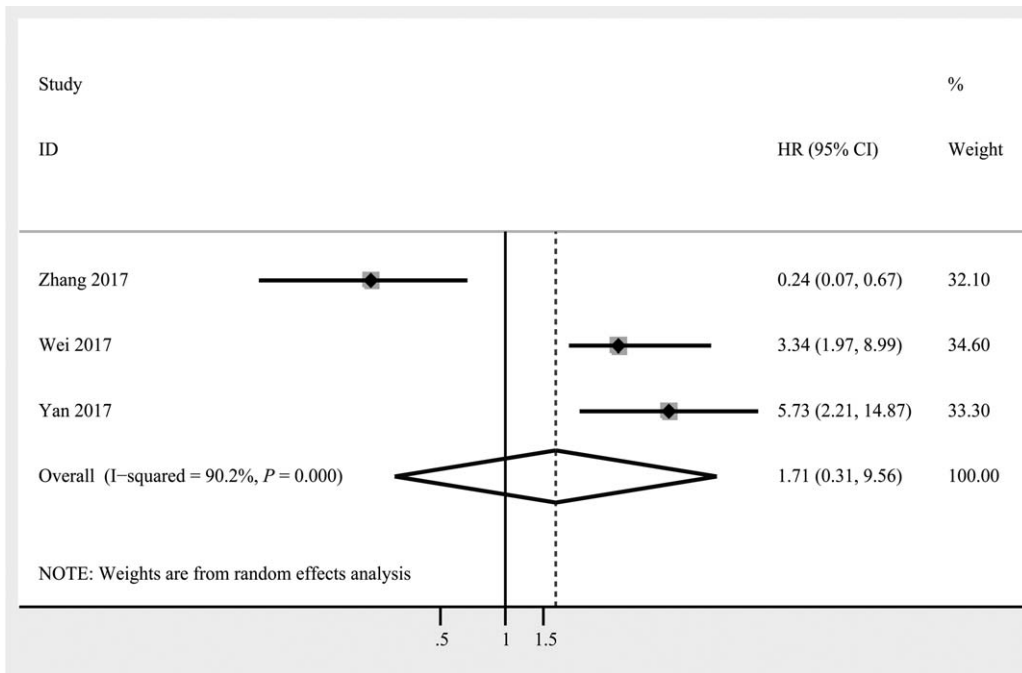


**Figure 3.** Forest plot of HRs for correlation between miR-638 expression and disease-free survival (DFS).
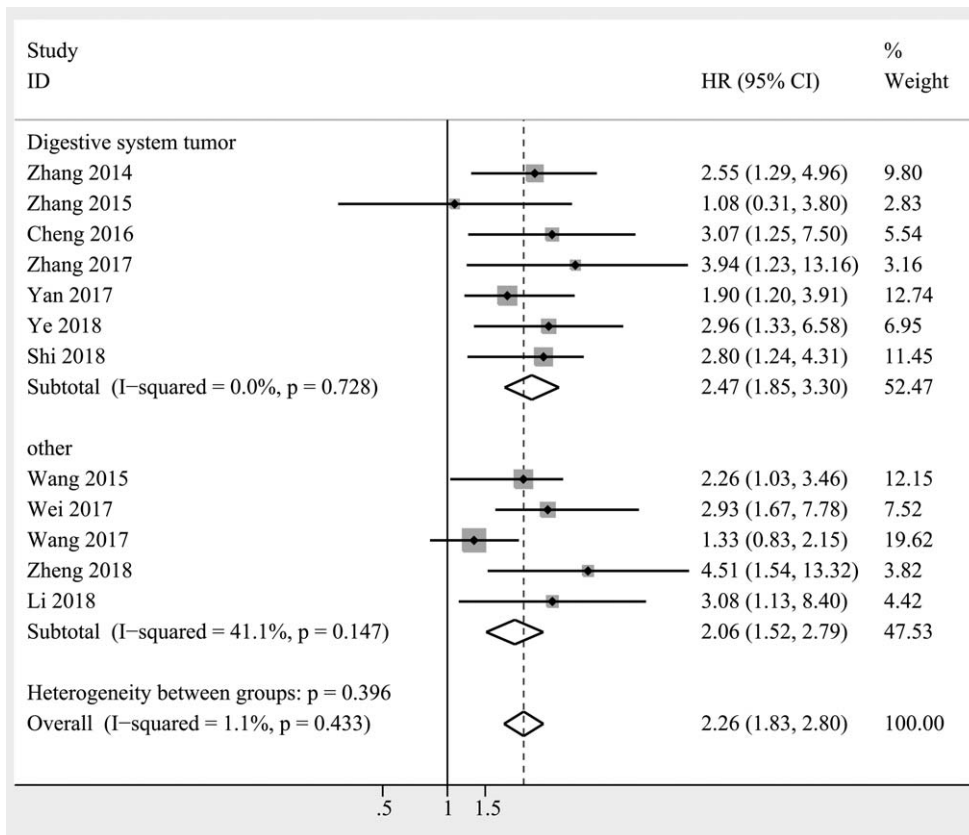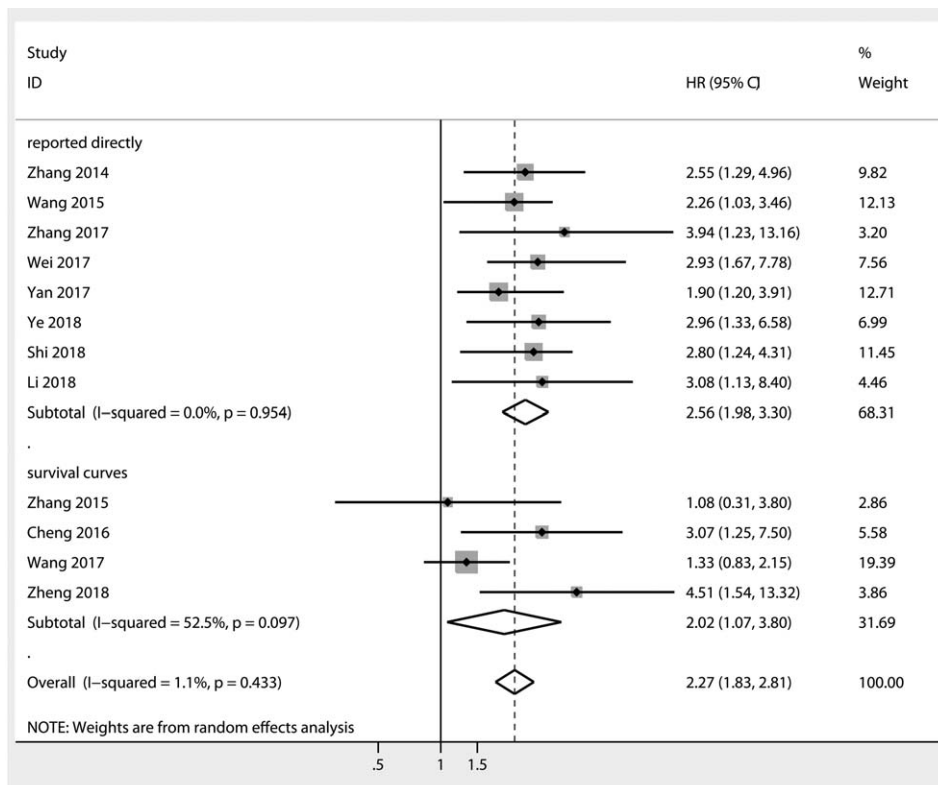
**Figure 4.** Subgroup analysis of the HR of overall survival (OS) by cancer type.



>**Figure 5.** Subgroup analysis of the HR of overall survival (OS) by HR obtain method.
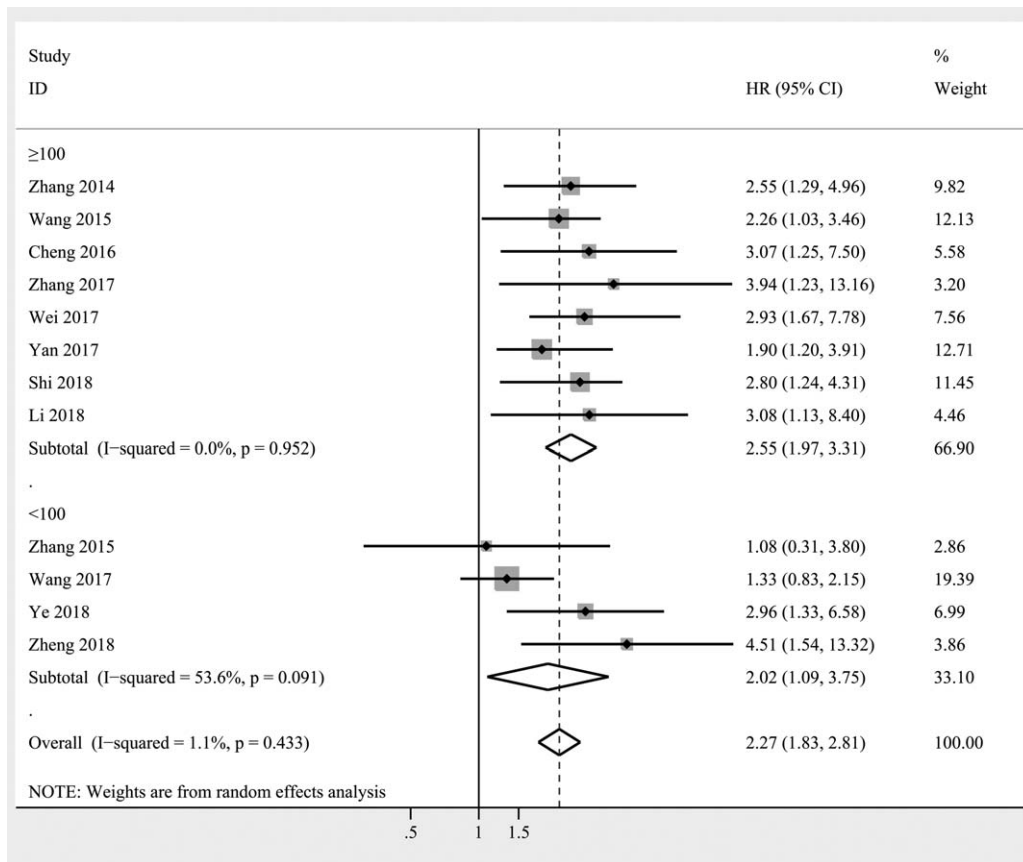
**Figure 6.** Subgroup analysis of the HR of overall survival (OS) by sample size.

### 3.6. Publication bias

Begg test was performed to evaluate the publication bias of the meta-analysis. The results indicated that there was no significant publication bias in this meta-analysis for OS ($P = .381$) and DFS ($P = .058$) (Fig. 8).

## 4. Discussion

Accumulated evidences exerted that miR-638 acted critical roles in physiological and pathological processes via their regulation of a wide variety of genes. For example, Cheng et al[29] showed that miR-638 was downregulated in hepatocellular carcinoma and could repress tumor growth and inhibit angiogenesis by down-regulating vascular endothelial growth factor (VEGF). Moreover, downregulated miR-638 has been shown to induce cell invasion and proliferation by regulating SRY (sex determining region Y)-box 2 (SOX2), which is related to epithelial-to-mesenchymal transition (EMT) in the development of non-small cell lung cancer.[28] Similarly, another study found that loss of miR-638 repressed cell proliferation and colony formation in patients with osteosarcoma by targeting suppress proviral integration site for Moloney murine leukemia virus 1 expression.[32] Those results suggested that miR-638 may serve as a tumor suppressor. However, miR-638 has also been reported to promote melanoma

**Table 3**

**Results of the association of miR-638 expression with clinicopathological features.**

| Clinicopathological parameter | N | OR (95% CI) | P value | Heterogeneity test (Q, $I^2$, P-value) |
|---|---|---|---|---|
| Age (<60 vs ≥60 years ) | 7 | 0.85 (0.63-1.15) | .293 | 2.48, 0.0%, .871 |
| Gender (male vs female) | 13 | 1.06 (0.83-1.34) | .656 | 13.76, 12.8%, .316 |
| Tumor size (≥5 vs <5) | 7 | 1.47 (1.03-2.09) | .035 | 10.31, 41.8%, .112 |
| Tumor differentiation (poor vs well+moderate) | 4 | 1.42 (0.97-2.06) | .068 | 2.02, 0.0%, .732 |
| Lymph node metastasis (Present vs Absent) | 6 | 2.26 (1.63-3.14) | <.001 | 1.18, 0.0%, .947 |
| TNM stage (III-IV vs I-II) | 13 | 2.01 (1.35-2.99) | .001 | 31.57, 62.0%, .002 |
| Distant metastasis (Present vs Absent) | 4 | 2.60 (1.45-4.67) | <.001 | 4.78, 37.3%, .188 |
| Portal vein invasion (Present vs Absent) | 3 | 4.39 (2.23-8.64) | <.001 | 0.05, 0.0%, .975 |
| Vascular invasion (Present vs Absent) | 3 | 2.35 (0.81-6.83) | .117 | 7.29, 72.6%, .026 |

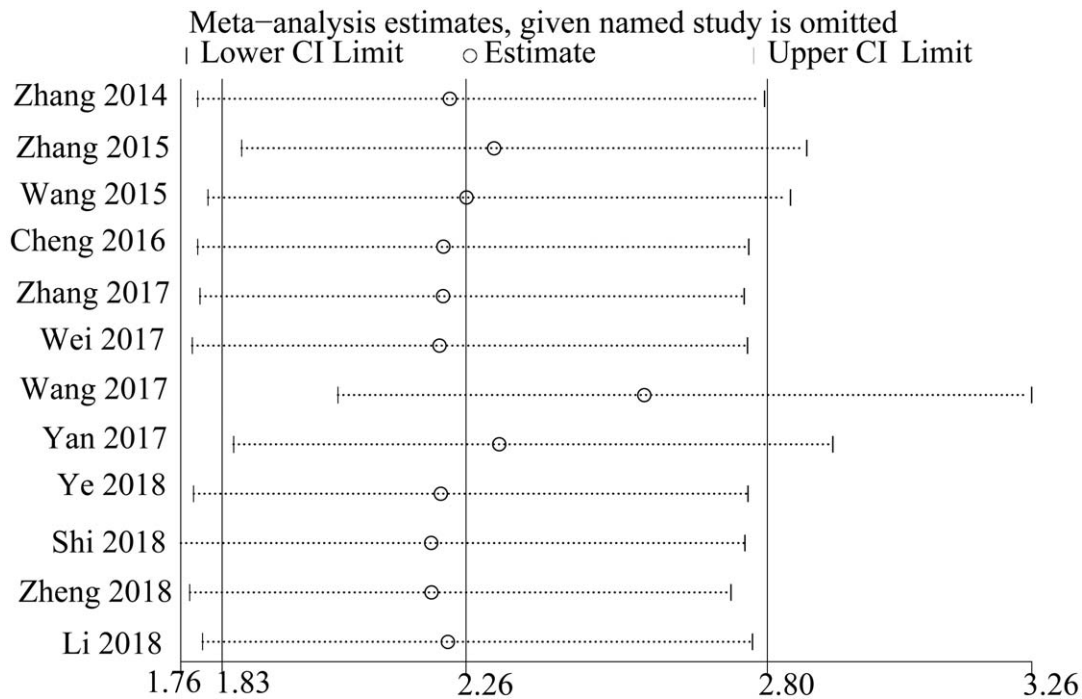CI = confidence interval, N = numbers of studies, OR = odds ratio.

**Figure 7.** Sensitivity analysis of miR-638 expression and overall survival (OS).

progression and metastasis by suppressing p53 pro-apoptotic signaling as an oncogene.[39] Furthermore, Ren et al also identified miR-638, as a potential oncogene, promoting tumorigenic properties, including cell proliferation, migration, and invasion in esophageal squamous cell carcinoma (ESCC) and breast cancer.[40] Thus, miR-638 may serve as an oncogene according to the kind of tumors.

The current study presented the first meta-analysis to comprehensively evaluate the relationship between miR-638 expression and prognosis and clinicopathological characteristics of tumors. In the present study, a total of 18 eligible studies containing 1886 patients were enrolled in this meta-analysis. The results provided strong evidence that low expression of miR-638 was significantly correlated with shorter OS. However, similar result was not seen in DFS. The negative outcome of correlation between miR-638 and DFS might result from the fewer number of the included study and smaller sample size. Subgroup analysis found that low miR-638 expression was associated with worse OS in patients with digestive system cancer (HR = 2.47, 95% CI: 1.85–3.30, $P < .001$), the reported directly from articles group (HR = 2.12, 95% CI: 1.34–3.33, $P < .001$), survival curves group (HR = 2.02, 95% CI: 1.07–3.80, $P = .029$), in studies with sample size ≥100 (HR = 2.12, 95% CI: 1.34–3.35, $P = .001$), and in studies with sample size <100 (HR = 2.02, 95% CI: 1.09–3.75, $P = .025$).

In this meta-analysis, the association between expression levels of miR-638 and clinicopathological characteristics was evaluated. Cancer patients with low miR-638 expression were prone to
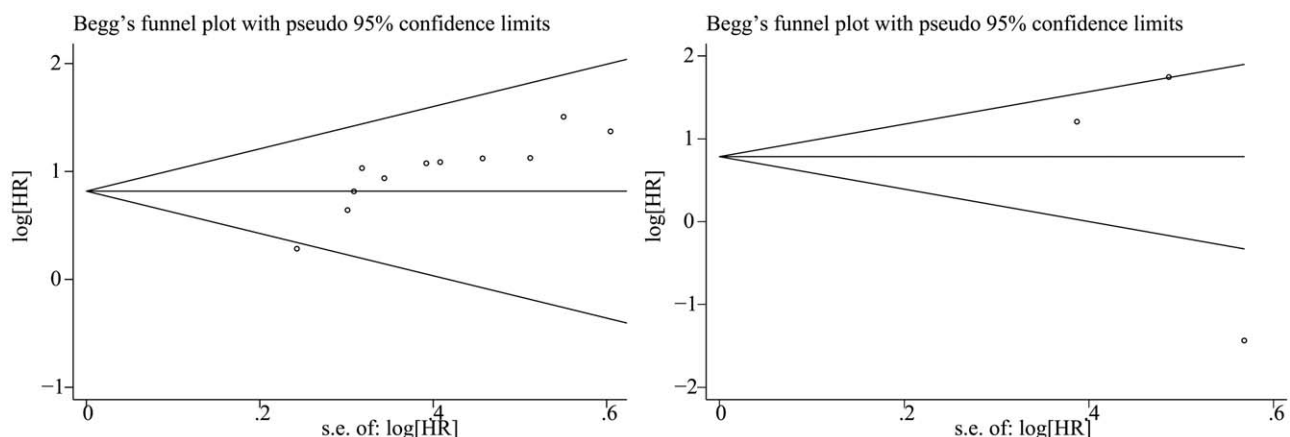


**Figure 8.** Begg funnel plots for the studies included in meta-analysis. OS (A) and DFS (B).

tumor size (OR = 1.47, 95% CI: 1.03–2.09, $P$ = .035), earlier lymph node metastasis (present vs absent, OR = 2.26, 95% CI: 1.63–3.14, $P$ < .001), earlier distant metastasis (present vs absent, OR = 2.60, 95% CI: 1.45–4.67, $P$ < .001), TNM stage (III-IV vs I-II, OR = 2.01, 95% CI: 1.35–2.99, $P$ = .001), and portal vein invasion (present vs absent, OR = 4.39, 95% CI: 2.23–8.64, $P$ < .001), but not associated with age, gender, tumor differentiation, and vascular invasion.

This meta-analysis also has some limitations, and the results should be interpreted with caution. First, data presented in the current meta-analysis were not applicable to all countries worldwide, because all the included studies were derived from China. Second, part of the HR value was calculated using a survival curve, which may lead to some error. Third, although all studies used qRT-PCR to evaluate the expression of miR-638, the cut-off value differed among studies, which might cause bias in the meta-analysis. Fourth, because of the relatively small sample size, we were unable to aggregate results based on a single type of tumor. Therefore, larger-scale, multicenter and high-quality studies are desperately necessary to confirm our findings.

## 5. Conclusions

In conclusion, our meta-analysis demonstrated that low expression of miR-638 was significantly correlated with poor OS and may serve as an effective predictive biomarker for tumor prognosis. Future larger scale prospective and standard investigations should be conducted to confirm our results.

## Author contributions

**Conceptualization:** Fanliang Kong.
**Data curation:** Lixia Hu, Mengqin Huang.
**Formal analysis:** Lixia Hu, Mengqin Huang, Qianqian Yuan.
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**Software:** Qianqian Yuan, Lixia Hu.
**Writing – original draft:** Lixia Hu, Mengqin Huang, Qianqian Yuan.
**Writing – review & editing:** Fanliang Kong.

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