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ORIGINAL RESEARCH

Prognostic significance of microRNA-100 in solid tumors: an updated meta-analysis

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Objective: The aim of this study was to identify prognostic significance of microRNA-100 (miR-100) in solid tumor.

Methods: Literature search was conducted in databases such as PubMed, Embase, and Web of Science, using the following words "(microRNA-100 OR miR-100 OR mir100) AND (tumor OR neoplasm OR cancer OR carcinoma OR malignancy)." The search was updated up until July 10, 2016. Newcastle–Ottawa scale was used to evaluate the quality of studies. Pooled hazard ratio (HR) with 95% confidence interval (CI) for patients' survival was calculated by using a fixed-effects or a random-effects model on the basis of heterogeneity. Subgroup analysis, sensitive analysis, and meta-regression were used to investigate the sources of heterogeneity. Publication bias was evaluated by using Begg's and Egger's tests.

Results: A total of 16 articles with 1,501 patients were included in the present meta-analysis. It was demonstrated that a lower expression of miR-100 plays a negative role in the overall survival (OS) of patients with solid tumor (HR =1.92; 95% CI =1.25–2.94). In addition, the association between miR-100 and prognosis was also revealed in the following subgroups: non-small-cell lung cancer (NSCLC; HR =2.46; 95% CI =1.98–3.06), epithelial ovarian cancer (EOC; HR =2.29, 95% CI =1.72–3.04), and bladder cancer (BC; HR =4.14, 95% CI =1.85–9.27).

Conclusion: This meta-analysis indicates that lower expression of miR-100 is related to poorer OS in patients with solid tumor, especially in those with NSCLC, EOC, and BC. MiR-100 is a promising prognosis predictor and may be a potential target for therapy in the future.

Keywords: microRNA-100, prognosis, meta-analysis

Introduction

MicroRNAs, noncoding small RNAs, regulate mRNA at the posttranscriptional level, leading to degradation or inhibition of the target mRNA. Research on microRNAs began in 1993.[1,2] Since then, an increasing number of microRNAs were discovered, and it was found that play an important role in a variety of biological activities including proliferation, differentiation, invasion, and apoptosis.[3–5] The association between microRNAs and cancer was first reported in 2002 by Calin et al, who observed that miR-15 and miR-16 acted as negative regulators of Bcl-2 in cancer, especially chronic lymphocytic leukemia.[6] It is now clear that microRNAs play a crucial role in cancer cells. Moreover, the clinical use of microRNA is being widely investigated. As a result, currently, multiple research studies have been exploring the prognostic function of microRNA-100 (miR-100) in cancer patients in order to find a reliable biomarker to guide for cancer treatment.[7,8]

As a member of the miR-99 family, miR-100 is located on Chromosome 11 at 11q24.1.[9] Its aberrant expression was reported in various cancers including nasopharyngeal cancer (NPC),[10] oral squamous cell carcinoma,[11] esophageal adenocarcinoma (EA),[12]

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small cell carcinoma of the cervix (SCCC),[13] non-small-cell lung cancer (NSCLC),[14,15] endometrioid endometrial carcinoma (EEC),[16] epithelial ovarian cancer (EOC),[17,18] bladder cancer (BC),[19,20] renal cell carcinoma (RCC),[21] esophageal squamous cell carcinoma (ESCC),[22,23] hepatocellular carcinoma (HCC),[24] colorectal cancer (CRC),[25,26] and pancreatic adenocarcinoma.[27] This aberrant expression of miR-100 not only has diagnostic implications but also can predict cancer patient survival.[28] From this perspective, it may be feasible to predict prognosis based on miR-100 expression level. However, the correlation between them remains controversial to some extent. In some studies, miR-100 was reported as a tumor suppressor, whose low expression level was a negative prognostic factor.[16,17] In contrast, in some articles, miR-100 was regarded as an oncogene.[21,27] Therefore, this meta-analysis was conducted to identify the relationship between miR-100 expression level and the survival of cancer patients, by pooling the hazard ratio (HR) from studies addressing the correlation between miR-100 and overall survival (OS) of patients with solid tumor.

Materials and methods

Search strategy

A literature search was conducted in databases such as PubMed, Embase, and Web of Science, using the following words "(microRNA-100 OR miR-100 OR mir100) AND (tumor OR neoplasm OR cancer OR carcinoma OR malignancy)." The search was updated up until July 10, 2016. In order not to miss the potentially related articles, reference lists were also screened.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) studies exploring any of the following solid tumor (eg, head and neck, thyroid, non-small-cell or small cell lung, breast, esophageal, gastric, pancreatic, hepatobiliary, colorectal, anal, prostate, bladder, renal, cervical, endometrial and ovarian carcinoma, melanoma, and sarcomas); 2) studies dealing with miR-100 expression and OS; 3) studies that categorized patients into low- and high-expression groups based on the miR-100 expression; 4) studies providing HR directly or key information to calculate HR indirectly, such as Kaplan–Meier curves and original survival data; and 5) studies assessing miR-100 expression in tissue or blood. The following were the exclusion criteria: 1) studies on myelomas, lymphomas, or leukemia; 2) nonoriginal articles, such as reviews, articles, or letters; 3) laboratory studies on cell lines or animals level; 4) studies on a set of microRNAs but not miR-100 alone; and 5) studies on nondichotomous miR-100.

Qualitative assessment

Newcastle–Ottawa scale was used to evaluate the quality of the studies based on the following three aspects: selection, comparability, and outcome.[29] A study can be given a maximum of one star for each item within the selection and outcome categories, and a maximum of two stars can be given for comparability category. The total stars that can be given for a study ranges from 0 to 9. Studies with $\geq$6 stars were considered as of high quality.[30] Otherwise, studies were excluded from the final meta-analysis.

Data extraction

Data extraction was carried out by Wang and Cheng. The following details of each article were recorded: publication year, first author's last name, cancer type, treatment, sample size, stage of disease, miR-100 assay, the cutoff value to discriminate high or low expression of miR-100, sample sources, follow-up time, and HR (low versus high expression). HR >1 indicates that lower expression of miR-100 is an unfavorable prognostic factor, and HR <1 suggests that lower expression of miR-100 confers survival advantage to the patients. If the HR value was calculated by a multivariate analysis, then it was extracted directly; if multivariate analysis was not available, then results from univariate analysis were also accepted in the meta-analysis. If both multivariate analysis and univariate analysis were not offered, Kaplan–Meier curves were used to estimate HR value by using the described method.[31] In addition, original survival data obtained, if possible, can also be used to calculate HR by conducting survival analysis.

Statistical analysis

In order to test the heterogeneity of pooled HR, Cochran's Q-test and Higgins I^2 statistics were performed. $P<0.05$ was considered statistically significant. Random-effects model was used to calculate pooled HR when between-study heterogeneity was revealed ($P<0.05$), and fixed-effects model was conducted when between-study heterogeneity did not reach the statistical significance ($P>0.05$). Subgroup analysis, sensitive analysis, and meta-regression were used to investigate the sources of heterogeneity. Publication bias was assessed by using Begg's test and Egger's test.[32,33] STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used to perform all the analyses.

Results

Study selection

In total, 179, 482, and 292 records were identified from PubMed, Embase, and Web of Science, respectively

(Figure 1). After excluding the replicate records, 272 articles were left. Reviewers Wang and Huang carefully read the abstract or full text as required and removed 658 records because they were review articles, laboratory studies, and so on. Then, 23 publications were retrieved for further analysis; of these studies, two studies focused on biochemical-free survival and recurrence-free survival of prostate cancer instead of OS;[34,35] three articles did not address solid tumor.[36–38] In addition, a study by Wang et al used malignant effusion, rather than tissue or blood, to assess miR-100 expression in NSCLC patients.[39] Therefore, according to the inclusion and exclusion criteria in the present study, 17 articles were accepted for Newcastle–Ottawa scale.

Qualitative assessment

Results from Newcastle–Ottawa scale demonstrated that two studies received eight stars, eight articles received seven stars, six articles received six stars, and one article received one star. Thus, a study by Zhang et al was excluded as it was a low-quality article (Table 1).[40]

Summary of the analyzed studies

After filtering, 16 studies published between 2011 and 2016 were considered for the final meta-analysis (Table 2). The cancer types included EA, SCCC, EEC, human EOC, BC, NSCLC, RCC, ESCC, HCC, CRC, and pancreatic ductal adenocarcinoma. Only four studies clearly stated the research-related treatment. As revealed in Table 2, most studies (11 of 16) did not clarify whether patient received adjuvant therapy after surgery. Study sample sizes ranged from 42 to 172 with a total of 1,501 patients from the People's Republic of China, the USA, Poland, Iran, and Germany. Nine studies enrolled patients with stages I–IV, whereas a study by Dhayat only explored miR-100 in patients with Stage II pancreatic ductal adenocarcinoma.[27] Four studies did not specify the stage of disease in the study population. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to assess miR-100 expression in all the studies, and the cutoff value varied among studies with median expression of miR-100 the most widely used. All the authors used tissues as the source of miR-100. The majority of HRs (13 of 16) were reported in the present analysis, all of which were calculated by using a multivariate analysis, whereas four HRs were estimated by analyzing Kaplan–Meier curves.

Meta-analysis results

Due to obvious heterogeneity (I^2=85.9%; $P<0.001$), random-effects model was used to calculate pooled HR

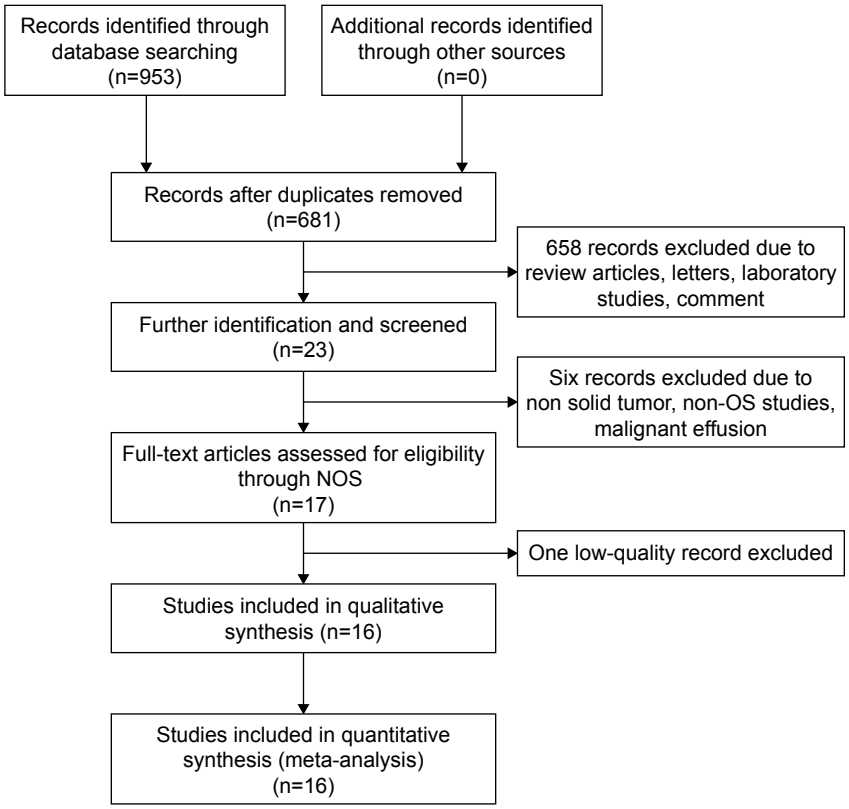

Figure 1 Flow diagram of filtering studies.
Abbreviations: NOS, Newcastle–Ottawa scale; OS, overall survival.

Table 1 Newcastle–Ottawa scale

	Selection	Comparability	Outcome	Total
Feber et al[12]	4	0[e,f]	2[g]	6
Huang et al[13]	4	0[e,f]	2[g]	6
Torres et al[16]	4	0[e,f]	2[g]	6
Peng et al[17]	4	1[e]	2[g]	7
Wang et al[19]	4	1[e]	2[g]	7
Liu et al[14]	4	1[e]	2[g]	7
Wang et al[21]	4	1[e]	2[g]	7
Sun et al[22]	4	2	1[g,h]	7
Chen et al[24]	4	1[e]	2[g]	7
Chen et al[25]	4	1[e]	2[g]	7
Zhou et al[23]	4	1[e]	3	8
Cao et al[20]	4	1[e]	2[g]	7
Zhang et al[40]	0[a–d]	0[e,f]	1[g,h]	1
Luo et al[15]	4	0[e,f]	2[g]	6
Dhayat et al[27]	4	1[f]	3	8
Zhang et al[26]	4	1[e]	1[g,i]	6
Azizmohammadi et al[18]	4	1[e]	1[g,h]	6

Notes: Reasons for lost stars: [a]no description of the derivation of the cohort; [b]no description of the derivation of the nonexposed cohort; [c]no description of exposure ascertainment; [d]no description of whether outcome of interest was not present at the start of study; [e]study not controlling the most important factor such as TNM stage; [f]study not controlling other additional factors, such as age, gender, and smoke; [g]no description of outcome assessment; [h]inadequacy of follow-up of cohorts; [i]follow-up not long enough for outcomes to occur.

(HR =1.92; 95% confidence interval [CI] =1.25–2.94), suggesting that lower expression level of miR-100 significantly predicted poorer OS in patients with solid tumor (Figure 2).

In order to identify the potential source of heterogeneity, subgroups analysis was conducted based on the patient origin, cancer type, and the methods used to calculate HR (Table 3). The association between miR-100 and OS was also revealed in the following subgroups: NSCLC (HR =2.46; 95% CI =1.98–3.06; fixed-effects model), EOC (HR =2.29; 95% CI =1.72–3.04; fixed-effects model), and BC (HR =4.14; 95% CI =1.85–9.27; fixed-effects model). Notably, significant heterogeneity was not found among these studies, with *P*-value of heterogeneity being 0.696, 0.07, and 0.146, respectively. However, no statistic difference was reported in esophageal carcinoma (HR =1.82; 95% CI =0.32–10.32; random-effects model) and CRC (HR =1.70; 95% CI =0.93–3.09; random-effects model). The prognostic role of miR-100 was also significant in the following subgroups: HR by report or multivariate analysis (HR =1.91; 95% CI =1.91–3.06; random-effects model) and Asian patients (HR =2.38; 95% CI =1.56–3.66; random-effects model).

Sensitivity analysis was conducted by sequentially omitting individual studies, indicating that there was not a single study that significantly contributed to heterogeneity (Figure 3). Furthermore, a meta-regression was also conducted to explore the potential factors that are responsible for heterogeneity. The results showed that the following factors could partly explain the heterogeneity but did not reach statistical significance: patient origin (I^2=85.68%; adjusted R^2=16.54%; P=0.06), cancer type (I^2=83.65%; adjusted R^2=10.95%; P=0.59), and multivariate analysis (I^2=86.84%, adjusted R^2=−8.60%; P=0.97).

Publication bias was evaluated by using Begg's funnel plot and Egger's test. Although the funnel plot revealed slight publication bias, *P*-values of Begg's and Egger's tests were 0.753 and 0.056, respectively, showing no evidence for significant publication bias (Figure 4).

Discussion

Lack of a reliable biomarker to predict prognosis is a main hurdle to realize individualized treatment. Fortunately, emerging data favor the potential use of miR-100 as a cancer prognostic predictor. In recent years, downstream targets of miR-100 have widely been investigated in several signal pathways, which may provide evidence for its potential clinical use at a molecule level. First, miR-100 facilitated cancer cell proliferation and growth by targeting the mammalian target of rapamycin (mTOR) and fibroblast growth factor receptors (FGFRs). By using GeneChip® miRNA Array and qRT-PCR, Xu et al[41] identified decreased expression of miR-100 in bladder tumor tissues and found that ectopic restoration of miR-100 expression suppressed tumor cell proliferation. Furthermore, bioinformatic analysis indicated that mTOR was the direct target of miR-100.[41] Consistently, another study on esophageal squamous cell cancer also supported this report. Sun et al transfected esophageal squamous cell cancer cell lines with miR-100 precursor molecules and reported the subsequent inhibition of cell proliferation, which was attributed to the fact that miR-100 downregulated the expression of mTOR by directly targeting its 3′UTR in a post-transcriptional manner.[22] In gynecologic cancer, this interaction exists. Torres et al observed that decreased miR-100 in EEC tissues coexisted with increased mTOR kinase.[16] With respect to cell growth, another potential target of miR-100 may be FGFRs. Bi et al transfected U2OS cells (human osteosarcoma line) with a miR-100 construct or with an antisense of miR-100.[42] It was observed that overexpression of miR-100 led to decreased expression of FGFR3 protein. Conversely, inhibition of miR-100 induced FGFR3 protein expression. Bioinformatics analysis and luciferase reporter assay implied that 3′UTR of FGFR3 mRNA was the direct target of miR-100. Based on these experimental results, Bi et al[42] pointed out that miR-100 served as a tumor suppressor by

Table 2 Characteristics of the included articles

Authors	Year	Origin	Cancer type	Treatment	Number of patients	Stage	miR-100 assay	Cutoff	Sample source	Follow-up (months)	Hazard ratio	Multivariate analysis
Feber et al[12]	2011	The USA	EA	Surgery[a]	45	I–IV	qRT-PCR	Median	Tissue	21.8[c]	K–M	No
Huang et al[13]	2012	People's Republic of China	SCCC	Surgery[a]	42	I–IV	qRT-PCR	6.515[b]	Tissue	23.6[d]	K–M	No
Torres et al[16]	2012	Poland	EEC	Surgery + radiotherapy + chemotherapy	73	I–IV	qRT-PCR	Median	Tissue	150[e]	Report	Yes
Peng et al[17]	2012	People's Republic of China	EOC	Surgery[a]	98	I–IV	qRT-PCR	Median	Tissue	72[e]	Report	Yes
Wang et al[19]	2012	People's Republic of China	BC	Surgery + chemotherapy	126	NR	qRT-PCR	Median	Tissue	36[e]	Report	Yes
Liu et al[14]	2012	People's Republic of China	NSCLC	Surgery[a]	110	I–III	qRT-PCR	Mean	Tissue	60[e]	Report	Yes
Wang et al[21]	2013	People's Republic of China	RCC	Surgery[a]	96	NR	qRT-PCR	Median	Tissue	81.8[c]	Report	Yes
Sun et al[22]	2013	People's Republic of China	ESCC	Surgery[a]	61	I–III	qRT-PCR	NR	Tissue	120[e]	K–M	No
Chen et al[24]	2013	People's Republic of China	HCC	Surgery[a]	134	I–IV	qRT-PCR	Mean	Tissue	60[e]	Report	Yes
Chen et al[25]	2014	People's Republic of China	CRC	Surgery[a]	138	I–IV	qRT-PCR	Median	Tissue	60[e]	Report	Yes
Zhou et al[23]	2014	People's Republic of China	ESCC	Radiotherapy	120	I–IV	qRT-PCR	Median	Tissue	60[e]	Report	Yes
Cao et al[20]	2015	People's Republic of China	BC	Surgery[a]	92	NR	qRT-PCR	Median	Tissue	60[e]	Report	Yes
Luo et al[15]	2015	People's Republic of China	NSCLC	Surgery[a]	48	NR	qRT-PCR	Median	Tissue	18[e]	K–M	No
Dhayat et al[27]	2015	Germany	PDA	Surgery + chemotherapy	91	II	qRT-PCR	5[b]	Tissue	30.5[c]	Report	Yes
Zhang et al[26]	2015	People's Republic of China	CRC	Surgery[a]	172	I–IV	qRT-PCR	Median	Tissue	50[e]	Report	Yes
Azizmohammadi et al[18]	2016	Iran	EOC	NR	55	I–IV	qRT-PCR	Median	Tissue	40[c]	Report	Yes

Notes: [a]No description of postoperative adjuvant therapy; [b]did not state the definition of cutoff; [c]median; [d]mean; [e]maximum duration of follow-up.

Abbreviations: BC, bladder cancer; CRC, colorectal cancer; EA, esophageal adenocarcinoma; EEC, endometrioid endometrial carcinoma; EOC, epithelial ovarian cancer; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; K–M, Kaplan–Meier curves; NR, not reported; NSCLC, non-small-cell lung cancer; PDA, pancreatic ductal adenocarcinoma; qRT-PCR, quantitative real-time polymerase chain reaction; RCC, renal cell carcinoma; ROC, receiver operating characteristic; SCCC, small cell carcinoma of the cervix.

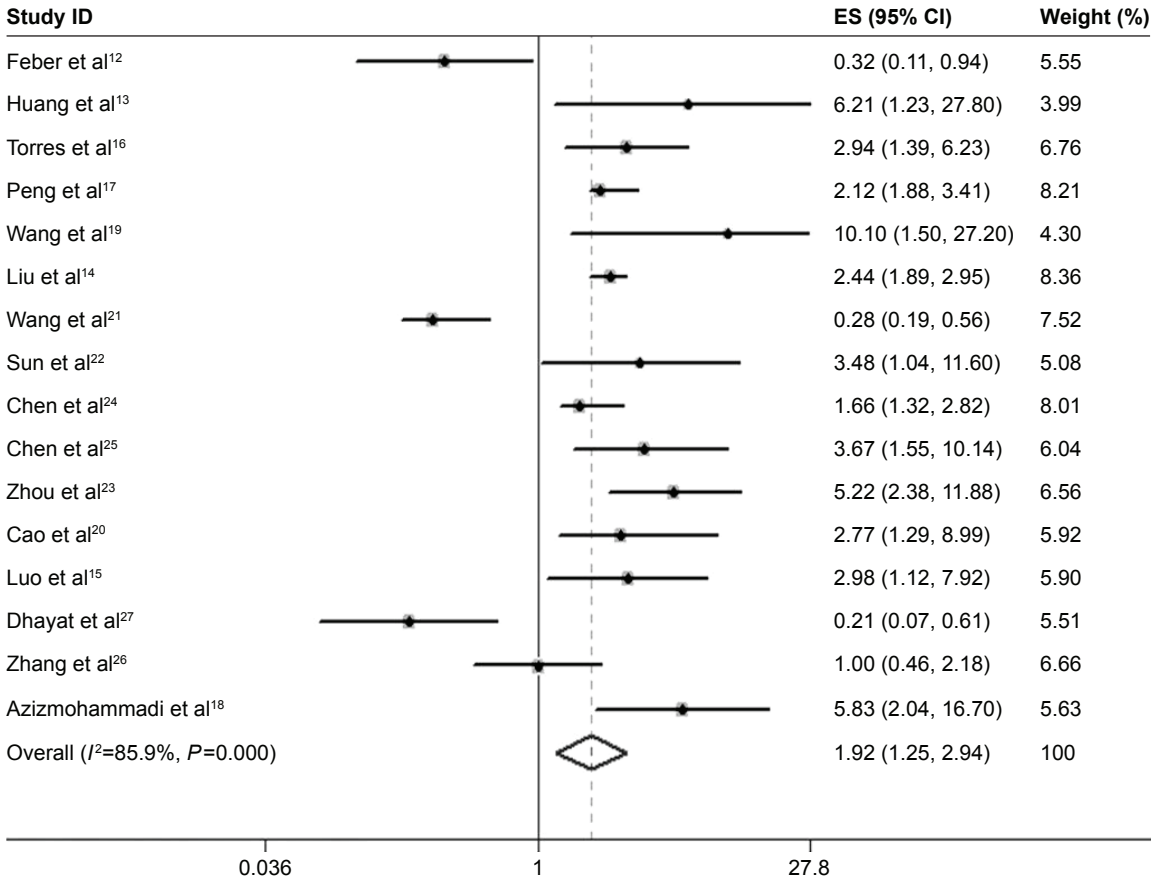

Figure 2 Forest plot of the relationship between miR-100 and overall survival in solid tumor.
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; ES, effect size.

preventing translation of FGFR3s. Another study on BC also revealed that the reduction of miR-100 expression induced sixfold upregulation of FGFR3 protein through an interaction with FGFR3 mRNA.[43] Similar result was also reported in non-small-cell lung.[15] Second, miR-100 participated in cancer cell apoptosis, which also determines the development of the tumor. Chen et al observed that miR-100 precursor elevated expression of cleaved caspase-3 and pro-caspase-3 protein, which are two key apoptosis proteins.[24] In order to find the mechanism, flow cytometry and Western blot analysis were used to assess the apoptosis in siRNA/plk 1-transfected human hepatocellular cells. The outcome showed that

Table 3 Subgroup analysis

Subgroup	Heterogeneity		HR (95% CI)	*P*-value
	I^2	*P*-value		
Patient origin				
Asian	84.6%	<0.001	2.38 (1.55–3.66)[a]	<0.001
Non-Asian	90.0%	<0.001	0.60 (0.10–3.50)[a]	0.574
Cancer type				
Non-small-cell lung cancer	0	0.696	2.46 (1.98–3.06)[b]	<0.001
Epithelial ovarian cancer	69.6%	0.070	2.29 (1.72–3.04)[b]	<0.001
Bladder cancer	52.7%	0.146	4.14 (1.85–9.27)[b]	0.001
Esophageal cancer	88.5%	<0.001	1.82 (0.32–10.32)[a]	0.497
Colorectal cancer	77.1%	0.037	1.7 (0.93–3.09)[b]	0.084
Multivariate analysis				
Yes	88.0%	<0.001	1.91 (1.19–3.06)[a]	0.007
No	79.4%	0.002	2.03 (0.55–7.42)[a]	0.286

Notes: [a]Random-effects model; [b]fixed-effects model.
Abbreviations: CI, confidence interval; HR, hazard ratio.

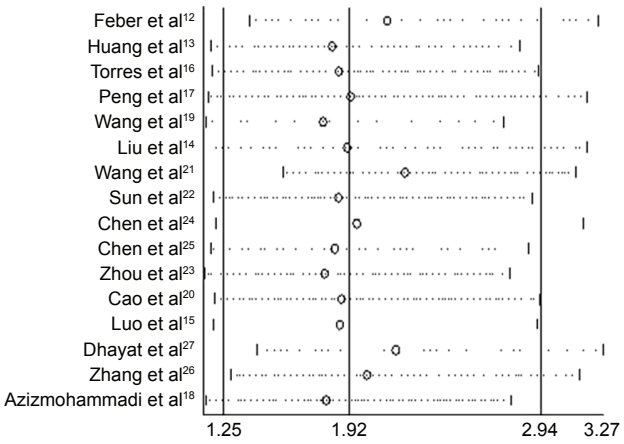

Figure 3 Sensitivity analysis: meta-analysis of random-effects estimates (exponential form) with studies omitted.

siRNA/plk 1 could mimic the effect of miR-100, indicating plk1 as a potential target of miR-100. In another digestive cancer, gastric cancer, Notch pathway was reported to participate in the miR-100-mediated apoptosis, which is initiated by the interaction between miR-100 and HS3ST2.[44] Third, miR-100 regulated several components of Wnt/β-catenin pathway, including β-catenin, metalloproteinase-7, T-cell factor-4, and lymphoid enhancing factor-1, which were closely related to cell invasion and tumor metastasis.[45] Transwell migration and invasion assay by Jiang showed that transfection of miR-100 mimic suppressed migration and invasion of breast cancer compared to the control group. The direct target of miR-100 in Wnt/β-catenin pathway may be FZD-8.[46] Bhushan et al also found that downregulation of miR-100 may account for less invasion of breast cancer cells.[47] In addition, Fu et al also consolidated the role miR-100 played in invasion and metastasis of esophageal squamous cell cancer by using bioinformatics analyses.[48] Fourth, cell cycle arrest, which is responsible for radio-resistance or chemo-resistance, was mediated by miR-100. Xiao et al discovered that the introduction of miR-100 mimic in H69 cells (human small cell lung cancer cell line) led to downregulation of HOXA1 protein, inducing G0-G1 and G1-M cell cycle arrest, which was associated with drug resistance.[49] A study by Shi et al documented that miR-100 can target plk1 and mediated G2/M arrest in NPC.[10] Together, miR-100 might be a promising prognostic predictor.

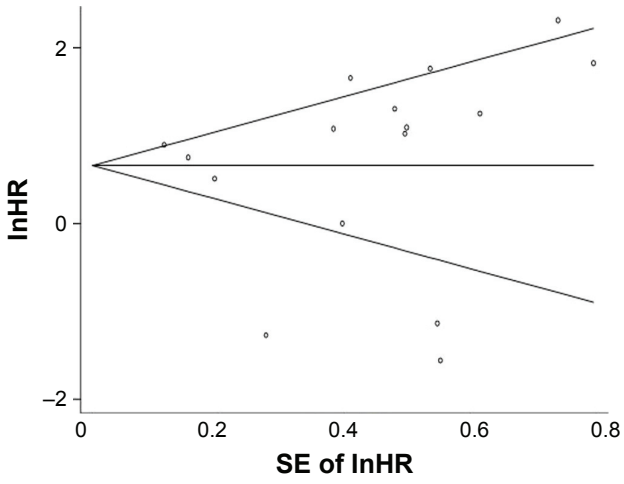

Figure 4 Publication bias: Begg's funnel plot with pseudo 95% confidence limits.
Abbreviations: HR, hazard ratio; SE, standard error.

Despite the sort of inconsistency, clinical investigations favor predictive use of miR-100 for the survival of cancer patients. Peng et al retrospectively collected fresh surgical tissues from 98 patients with EOC and used qRT-PCR assay to assess the expression level of miR-100.[17] It is revealed that the expression of miR-100 was significantly lower in epithelial ovarian tumor tissue than in adjacent normal tissue. Multivariate analysis demonstrated that lower expression of miR-100 was accompanied by shorter survival (HR =2.12; 95% CI =1.88–3.41). Further evidence on endometrial carcinoma also supported the finding that decreased expression level of miR-100 worsens prognosis, with a HR of 2.94 (low/high).[16] Similar results were obtained for digestive system cancers. Zhou investigated 120 patients with esophageal squamous cell cancer who received radiotherapy alone and concluded that HRs for locoregional progression-free survival (PFS), distant PFS, and OS (low/high) were 8.9, 8.34, and 8.02, respectively, suggesting that downregulation of miR-100 indicated poor prognosis.[23] In BC, Wang et al reported that 3-year OS and 3-year PFS for high expression level of miR-100 were 33 and 26 months, respectively; on the other hand, for low expression level of miR-100, they were merely 23 and 16 months, respectively.[19] However, it should be noted that literature on the prognostic value of miR-100 reveals conflicting findings. Wang et al found increased miR-100 expression in cancer tissues compared with normal tissues in patients with renal cell cancer.[21] HRs for OS and tumor-specific survival were 0.28 and 0.41, respectively, both of which were statistically significant, suggesting that lower expression of miR-100 confers survival advantage. Dhayat et al focused on pancreatic ductal adenocarcinoma Union for International Cancer Control stage II and found that lower level of miR-100 is a favorable factor to predict treatment response and OS.[27] Apart from studies revealing the survival difference, a study by Zhang showed that the difference in miR-100 expression level did not lead to statistic difference in the survival of patients with CRC.[26] In order to clarify the relationship between miR-100 and survival of patients with solid tumor, this meta-analysis was conducted.

In order to ensure reliable outcome, the inclusion criteria were strictly limited. First, source of RNA was restricted to tissue or blood. As a result, a study by Wang et al was not accepted, because it explored miR-100 in malignant effusion in NSCLC.[39] Second, Newcastle–Ottawa scale was used. As shown in Table 1, most studies (16 of 17) were evaluated as of high quality; however, only two studies received nine stars, the highest score. The most common reasons why the research was deprived of stars lay in the comparability and outcome aspects. In terms of comparability, majority of the studies (15 of 17) did not control the most important factor such as TNM stage; some studies (6 of 17) did not control other less important factors, such as age, gender, and smoking status of the patients, which would bring potential bias to the survival outcome. In addition, it is necessary for prognosis studies to describe whether the survival outcome was attained by self-report or blind assessment, which was stated in Newcastle–Ottawa scale. However, only two studies mentioned this category.[23,27] Lastly, follow-up rate is not fully recorded. Only a minority of studies described the number of lost patients and offered the reason for loss. Considering these reasons, more stars have been provided in outcome category. It is noteworthy that Zhang et al analyzed survival data from the TCGA database and did not provide sufficient related information to get at least six stars according to Newcastle–Ottawa scale.[40] Hence, although it investigated the association between miR-100 expression and OS, it was excluded as a study of low quality.

Finally, 16 studies were included. According to the present study, decreased miR-100 expression level confers survival disadvantage in patients with solid tumor (HR =1.92; 95% CI =1.25–2.94). This relationship was also found in the following subgroups: NSCLC (HR =2.46; 95% CI =1.98–3.06; fixed-effects model), EOC (HR =2.29; 95% CI =1.72–3.04; fixed-effects model), and BC (HR =4.14; 95% CI =1.85–9.27; fixed-effects model). In order to find the potential source of heterogeneity, first, subgroup analysis was conducted, which revealed that heterogeneity declined dramatically in NSCLC group (I^2=0; P=0.70), EOC group (I^2=69.6%; P=0.07), and BC group (I^2=52.7%; P=0.15). Therefore, cancer type might partly account for heterogeneity. Previously, several meta-analyses classified subgroups according to the method used to assess RNA (qRT-PCR versus in situ hybridization) and the source of RNA (blood versus tissue).[30] Nonetheless, these variants were similar between the studies included in the present meta-analysis. As a result, the possibility of these variants as the source of heterogeneity was eliminated, and there was no requirement to perform further subgroup analysis. Owing to the results that sensitivity analysis did not reveal the source of heterogeneity, meta-regression was further conducted, which revealed that P-value of patient origin, the method used to calculate HR, and cancer type were all >0.05, with adjusted R^2 being 16.54%, −8.6%, and −10.95%, respectively. Meta-regression results showed that although these factors might explain part of heterogeneity, but it did not reach statistical significance. Meta-regression could have been used to analyze whether other factors such as follow-up time, related treatment methods, and cutoff value had an impact on heterogeneity, but, due to insufficient information on or remarkably different definition of cutoff value, the necessity and scientific implication to carry out this meta-regression in these variants were uncertain.

As it is well known, meta-analysis results are more robust than the result of single research. However, it is noteworthy that strict inclusion and exclusion criteria are a prerequisite for pooled data, which made the present results more reliable than the previous ones.[50,51] Despite careful assessment of study quality, there are limitations in the present study. First, heterogeneity among the studies included is relatively high. According to subgroup analysis, tumor type could partly explain the source of heterogeneity. Nonetheless, other potential factors may also exist. For instance, pathological type may be a potential source. The pooled HR from ESCC subgroup was 4.61 (95% CI =2.36–8.99; I^2=0; fixed-effects model) compared to esophageal cancer (HR =1.82; 95% CI =0.32–10.32; I^2=88.5%; random-effects model).[22,23] In addition, because of insufficient data, it was difficult to further assess the effects of other variants on heterogeneity. For instance, TNM stage, postoperative treatment, and follow-up method were not clearly stated in all the studies. Second, the power of miR-100 as a stand-alone biomarker is presumably weak and varies for different tumor types, given the fact that interaction between microRNA and its target is complicated. Undoubtedly, microRNA signature may be a better option that has been investigated in other microRNAs.[52] However, to date, such microRNA signature comprising miR-100 was not reported. Third, the definition of cutoff value varied among the studies. Some research studies chose median value to define the expression level of miR-100, yet some used mean value or value calculated by receiver operating characteristic curve. Finally, although publication bias was not revealed by Begg's and Egger's tests, the funnel plot is slightly asymmetric. The limitations emphasize the need for well-designed and well-conducted prognostic studies on miR-100 in the future.

Conclusion

This meta-analysis indicated that lower expression level of miR-100 is related to poorer OS in solid tumor, especially in patients with NSCLC, EOC, and BC.

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Disclosure

The authors report no conflicts of interest in this work.

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