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Review Article

An update of the prognostic value of miR-155 in various tumors: a meta-analysis

Lian Li[1], Liangliang Xu[1], Peng Wang[1], Shengsheng Ren[1], Jianwei Tang[1], Mingqing Xu[1], Bo Li[1], Ming Zhang[1,2]

[1]*Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China;* [2]*Department of General Surgery, Mianzhu Hospital of West China Hospital, Sichuan University, Mianzhu, Sichuan Province, China*

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Abstract: Accumulated studies have proved the significant prognostic relevance of Micro-RNAs in many cancers, and miR-155 is one of the most potential Micro-RNAs. However, the association between miR-155 expression and prognostic outcomes of various tumors is still controversial. Therefore this study aims to comprehensively illustrate whether miR-155 has prognostic value for several cancers or not. According to the heterogeneity, pooled hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) and disease-free survival (DFS), including relapse-free survival (RFS), event-free survival (EFS), treatment-free survival (TFS), cancer-specific mortality (CSS), time to progression (TTP), and cancer-free survival (CFS) were estimated with the random or fixed effects models. A total of 46 studies containing 5925 cases were selected for analysis. Prognostic analyses on the pooled HR (hazard ratio) of OS and DFS were 1.67 (95% CI 1.44, 1.93) and 1.99 (95% CI 1.67, 2.36) for high miR-155 expression and low miR-155 expression, respectively. Further subgroup analyses were performed according to the region, sample sources, tumor types, HR resources, cut off values and independent factors. Most of the subgroup analyses indicated that high-expression of miR-155 cluster was associated with poor OS and DFS. Our study indicated that high expression of miR-155 was significantly related to the poor survival in several cancer patients, and thus could be an important predictor of poor prognosis.

Keywords: miR-155, prognosis, tumour, meta-analysis

Introduction

Micro-RNAs (miRNAs) have direct implications for fundamental biology as well as disease etiology and treatment [1], and are small and single-stranded noncoding RNAs consist of approximately 18-22 evolutionarily conserved nucleotides in length. Numerous studies have reported that up-regulation or down-regulation of miRNAs contribute to tumor initiation and progression in various malignancies via regulation the target genes [2, 3]. Among these Micro-RNAs, miR-155 family has been reported to develop prognostic role in multiple carcinomas [4-6].

Among all of the miRNAs, miR-155 was well studied in many tumors. Recent studies demonstrated that miR-155 can not only function as a tumor-promoting miRNA by targeting E2F2 in ccRcc [7], but can also play as a tumor-promoting role by regulating the BCL6/cyclin D2 axis in some cancers [8]. These results suggested that miR-155 has prognostic value in various cancers. In addition, some meta-analyses summarized that miR-155 had prognostic value in cancer patients and regularly measuring miR-155 expression may be useful in clinical practice [9]. But on the other hand, other study demonstrated that high expression of miR-155 in some tumors was not related to the patients' survival [10]. We conduct this meta-analysis to illustrate the relationship between the expression of miR-155 and prognosis of tumor patients.

Materials and methods

Literature searching strategy

Conducting a systematic literature search through the online databases of Pubmed, Embase and Web of Science, the searching key words included "microRNA-155 OR miR-155 OR MiRNA-155" (all fields). We conducted the search

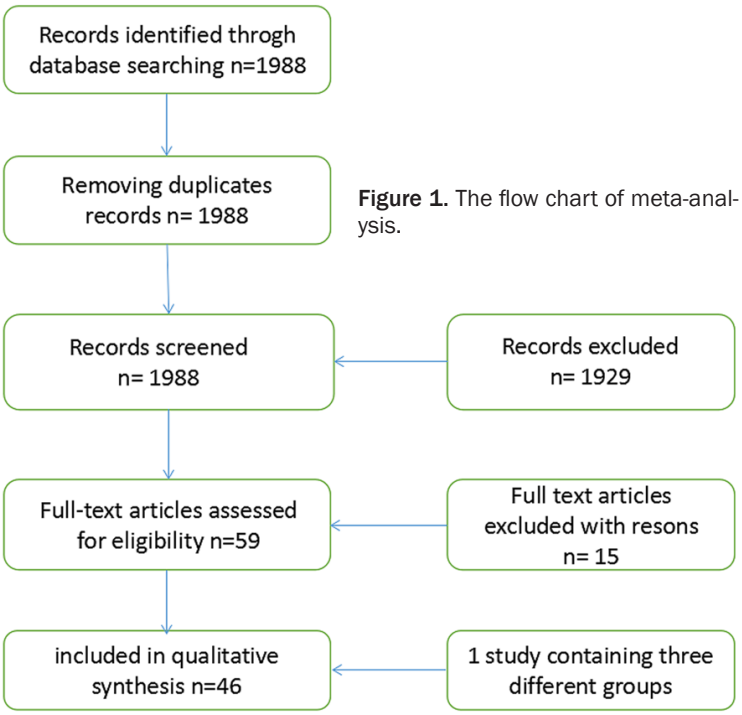

Figure 1. The flow chart of meta-analysis.

manually so as to cover all the concerned studies without using too many key words. The search was performed independently by two authors (Li, Xu).

Including and excluding criteria

Literatures meeting the following criteria were considered eligible: 1). Various associated human malignancies and survival outcomes with miR-155 expression; 2). Hazard ratios (HRs) and 95% confidence intervals (95% CI) were provided or could be estimated by kaplan-meier curves; 3). MiR-155 expression was detected by qRT-PCR, in situ hybridization or microarray; 4). Study including the patients' prognostic parameters of OS/DFS/PFS/RFS/MFS/TTP, and miR-155 was measured in tumor tissue, peripheral blood or body liquid. Articles were excluded based on the following items: 1). Case reports, reviews, conference abstracts, letters, and animals trials. 2). The study only conducted on animal models or tumor cell lines. 3). No more than 20 participants in order to make sure the persuasiveness.

Data extraction

Based on the including and excluding criteria, we extracted the relevant information from each eligible publication. The extracted information included the first author, publication year, study country, journal name, cancer type, sample source, test method, cutoff value, number of participants, survival outcome, independent factor, and the method of analysis. HR and 95% CI and the cut-off value were extracted. Sample source was stratified into tissue, blood, urine, formalin-fixed and paraffinembeded (FFPE). Test methods included in situ hybridization (ISA), reverse transcription-polymerase chain reaction (qRT-PCR) and microarray. Cancer types included solid cancer and more. The results from multivariate analyses or univariate analyses were allowed in the meta-analysis. Additionally, if both multivariate analysis and univariate analysis were not available, kaplan-meier curves were adopted to extract HR by Engauge Digitizer 4.1.

Statistical analyses

According to the cut-off value provided in the article, the miR-155 expression was defined as high expression or low expression. Pooled data was calculated by HRs and the corresponding 95% CIs. For the prognostic results, a combined HR > 1 indicated that high expression of miR-155 was associated with the poor outcome. Cochran's Q-test and Higgins-I^2 statistics (I^2) were used to test the heterogeneity of pooled HRs [11]. If the significant heterogeneity was observed at the percentage of I^2 was greater than 50% or the $P<0.05$, the random-effects model was applied to calculate the pooled HR and 95% CI of survival outcomes. Otherwise, the fixed-effects model was applied. In addition, we performed the sub-analysis to minimize the heterogeneity. Publication bias was assessed by Begg's test [12]. All of the statistical calculations were conducted by Stata version 12.0 (Stata Corporation, College Station. TX, USA). It was considered statistical significant if the *P* value was less than 0.05.

Table 1. Subgroup analysis between miR-155 expression and prognosis of patients

Subgroup	OS (n = 27)					DFS (n = 29)				
	No. of studies	Model	Pooled HR (95% CI)	*P* value	HG I^2 %	No. of studies	Model	Pooled HR (95% CI)	*P* value	HG I^2 %
	27	random	1.67 (1.44, 1.93)	<0.00001	79	29	random	1.99 (1.67, 2.36)	<0.00001	60
Tumor type										
Colorectal cancer	2	fixed	3.30 (2.04, 5.33)	<0.00001	0	2	fixed	2.72 (1.55, 4.77)	0.0005	0
Blader cancer						3	random	4.13 (1.37, 12.45)	0.0004	53
Renal carcinoma						3	fixed	2.15 (1.35, 3.42)	0.001	0
Oral squamous carcinoma						2	fixed	2.87 (1.15, 7.12)	0.02	26
Lymphoma						3	fixed	2.06 (1.40, 3.03)	0.0003	0
Leukemia	6	random	1.76 (1.31, 2.37)	<0.00001	57	3	fixed	1.41 (1.17, 1.69)	0.0003	5
Lung cancer	5	Random	1.52 (0.77, 2.98)	0.0001	78	7	Random	1.60 (1.16, 2.20)	<0.0001	51
Pancreatic cancer	4	random	1.59 (0.81, 3.13)	0.003	72	1	ND	3.33 (1.20, 9.25)	0.02	ND
Glioma	1	ND	1.74 (0.21, 14.53)	0.61	ND	ND	ND	ND	ND	ND
Gallblader carcinoma	1	ND	1.44 (1.04, 2.00)	0.03	ND	1	ND	1.96 (1.17, 3.27)	0.01	ND
Hepatocellular	2	Random	2.95 (1.02, 8.55)	<0.0001	74	3	Random	2.60 (1.66, 4.06)	<0.00001	56
Breast cancer	3	fixed	2.42 (1.66, 3.52)	<0.00001	0					
Liposarcoma	1	ND	2.90 (1.38, 6.10)	0.005	ND	1	Random	2.11 (1.06, 4.21)	0.03	ND
Chordoma	1	ND	6.35 (1.53, 26.4)	0.001	ND	ND	ND	ND	ND	ND
GBM	1	ND	0.78 (0.63, 0.96)	0.02	ND	ND	ND	ND	ND	ND
Sample type										
Tissues	11	Random	2.03 (1.37, 3.00)	0.0004	83	12	fixed	2.04 (1.67, 2.50)	<0.00001	0
FFPE	8	Random	1.62 (1.14, 2.31)	0.007	77	8	fixed	2.29 (1.80, 2.93)	<0.00001	21
Plasma	1	ND	1.09 (1.02, 1.16)	0.008	ND	2	Random	1.74 (0.64, 4.69)	0.004	75
Urine						2	Random	3.42 (0.79, 14.81)	0.005	56
Blood sample	3	fixed	1.82 (1.40, 2.37)	<0.00001	0	3	fixed	1.41 (1.17, 1.69)	0.0003	5
Serum	1	ND	3.86 (1.58, 9.44)	0.003	ND	2	fixed	2.60 (1.62, 4.18)	<0.0001	0
Marrow	3	Random	1.73 (1.01, 2.99)	0.05	62					
HR resource										
Reported	17	Random	1.55 (1.32, 1.82)	<0.00001	83	21	fixed	1.83 (1.61, 2.07)	<0.00001	43
SC	10	Fixed	1.84 (1.53, 2.23)	<0.00001	7	8	Random	1.74 (1.27, 2.39)	<0.00001	63
Region										
Asian	15	Random	1.61 (1.33, 1.93)	<0.00001	81	17	fixed	2.12 (1.81, 2.48)	<0.00001	18
Europe	4	Random	2.06 (0.83, 5.11)	0.12	85	6	fixed	1.23 (1.11, 1.38)	0.0002	44
America	8	Random	1.86 (1.39, 2.50)	<0.0001	60	5	fixed	1.47 (1.21, 1.79)	<0.0001	50
Egypt						1	ND	2.64 (1.51-4.63)	0.004	ND
Cut-off value										
Median	21	Random	1.83 (1.45, 2.31)	<0.00001	76	21	Random	1.88 (1.55, 2.30)	<0.00001	63
Mean	4	Random	1.13 (1.08, 1.19)	<0.0001	86	4	fixed	2.95 (1.79, 4.88)	<0.0001	0
Others	2	fixed	2.52 (1.63, 3.92)	<0.0001	0	4	fixed	1.94 (1.48, 2.55)	<0.00001	0
Independent risk factor										
Yes	22	Random	1.72 (1.47, 2.02)	<0.00001	81	22	Random	2.06 (1.70, 2.51)	<0.00001	67
NR	5	Random	1.52 (0.83, 2.79)	0.17	65	7	fixed	1.69 (1.22, 2.35)	0.001	0

OS-overall survival, DFS-disease free survival, ND-no data, GBM-glioblastoma multiform, FFPE-formalin-fixed paraffin embedded samples, SC-survival curve, NR-not reported, HG-heterogeneity, HR-hazard ratio, Random-random-effect model, fixed-fixed-effect model.

Results

Characteristics of included studies

A total of 46 studies including 5925 cases were involved in this meta-analysis (**Figure 1**). The basic characteristics were summarized in **Table 1**. Of all the studies, except one from Egypt, 32 were from Asia, 13 were from America, 10 were from Europe. Tumor types included the colon cancer [13, 14], bladder cancer [15, 16], renal carcinoma [17-19], oral squamous carcinoma [20, 21], lymphoma [22-24], leukemia [25-31], lung cancer [10, 32-39], glioma [40], gallblader carcinoma [41], hepatocellular carcinoma [42, 43], breast cancer [44, 45], liposarcoma [46], pancreatic cancer [47-50], chordoma [51], and glioblastoma multiforme [52]. Meanwhile, there

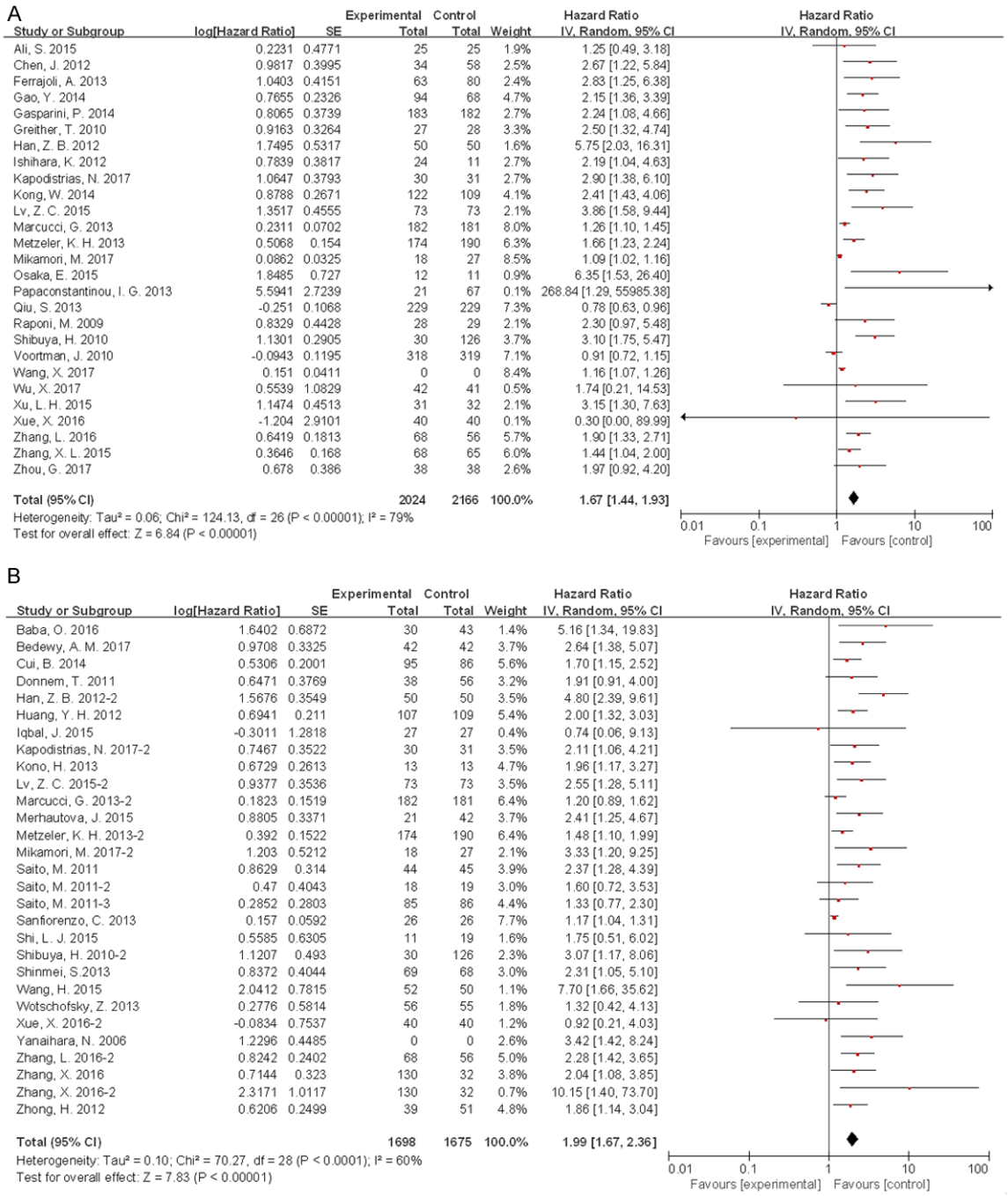

Figure 2. A. One way sensitivity analysis of high-expression of miR-155 in various tumors with OS under different types of analysis. B. One way sensitivity analysis of high-expression of miR-155 in various tumors with DFS under different types of analysis.

are such sample types as FFPE, tissue, blood, urine. As for the test methods, most studies applied qRT-PCR, except one study used in situ hybridization (ISH), and another two studies adopted microarray. Most of the cut-off values were median or mean. 44 studies were divided into two datasets: 27 studies for OS analysis and 29 studies for DFS (including DFS, PFS, RFS, etc) analysis.

Meta-analysis of OS

27 studies were involved to evaluate the relation between miR-155 expression and progno-

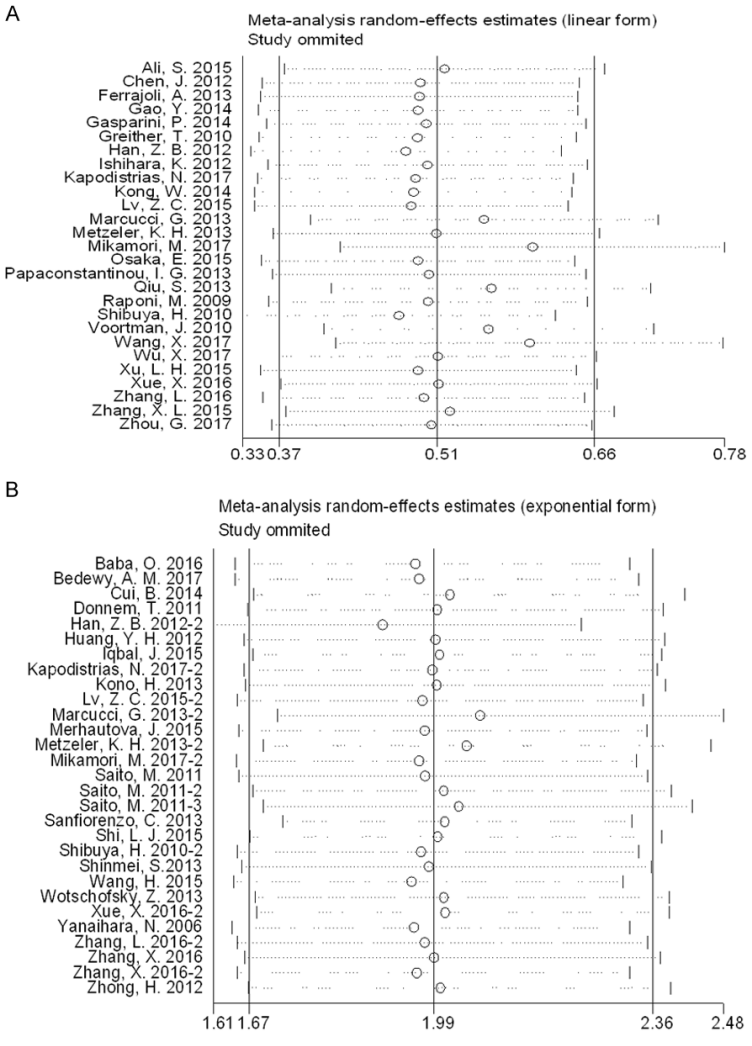

Figure 3. A. One-way sensitivity analysis of high-expression of miR-155 in various tumors. B. One-way sensitivity analysis of high-expression of miR-155 in various tumors.

sis. The results demonstrated that high expression of miR-155 in various tumors was associated with relatively poor OS (HR = 1.67, 95% CI = 1.44, 1.93, P<0.00001; **Figure 2A**). Because of the heterogeneity among studies (I^2 = 79%, P<0.00001), subgroup analysis was performed. Interestingly, high expression of miR-155 could predict worse OS regardless of the region, sample types, tumor types, HR resources, cut off values, independent factors (**Table 1**). We found the HRs of these tumor types, including lung cancer, pancreatic cancer, were not related to the patients' survival. Similarly, studies from Europe were different from other regions, where there was no relationship between HR and prognosis. Considering the obvious heterogeneity of the results from meta-analysis, a random model was used to calculate the pooled HR and 95% CI from the 29 studies provided the OS of patients.

Meta-analysis of DFS

Besides OS, all of the following survival data were taken into consideration: PFS, DFS, RFS, EFS, TFS, EFS, CSS, TTP, CFS. We found there were significant association between the survival data and the prognosis (HR = 1.99, 95% CI = 1.67, 2.36, P<0.00001, **Figure 2B**). Also, since the heterogeneity, we performed sub-analysis and found that except the plasma and urine samples shown no relationship between HR and survival, other sample types, regions, tumor types, HR resources, cut off values, independent factors have certain association with miR-155 expression **Table 1**. Considering the heterogeneity among the studies, random models were performed to HR and 95% CI.

Sensitivity analysis

To eliminate individual studies, sensitivity analysis was performed. In order to explore the potential factors contribute to heterogeneity in OS and DFS, a meta-regression was conducted. The results indicated that there was no stu-dy responsible for *heterogeneity*. The pooled results analyses were shown in **Figure 3A** and **3B**.

Publication bias

The funnel plots, Begg's analyses were shown in **Figure 3A** and **3B** formed. In order to explore the potential factors contribute to heterogeneity in OS and DFS, a meta-regression was conducted. The result *P* value shown no evidence of significant publication bias (Pr > |z| = 0.359 > 0.05) (**Figure 4A**). Unpublished studies may existed. Similarly, *P*-value of Begg's test for DFS

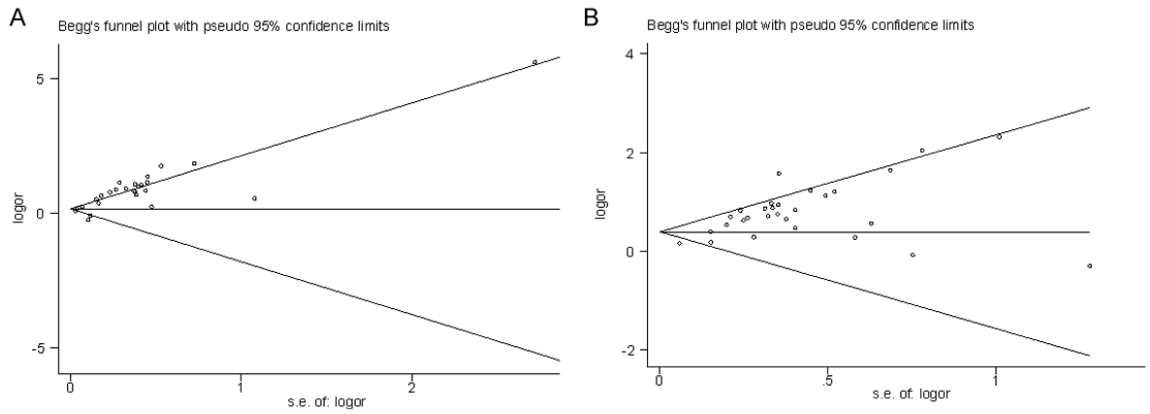

Figure 4. A. Begg's funnel plot of OS for publication bias test (Pr > |z| = 0.359 > 0.05); B. Begg's funnel plot of DFS for publication bias test (Pr > |z| = 0.103 > 0.05).

demonstrated that there was no publication bias (Pr > |z| = 0.103 > 0.05) (**Figure 4B**).

Discussion

Recently, more and more evidences demonstrated that miR-155 was widely expressed in various tumors, and its aberrant expression was reported in many tumors. These results have verified miR-155 as a potential biomarker for prognostic value. A research suggested that associated with lower RAD51 expression, high miR-155 levels indicated better overall survival of patients in breast cancers [44]. Other researches hold the opposite opinion, for example, Jiang S. found that overexpression of miR-155 in breast cancer cells can stimulate breast cancer cells [53]. Our analysis verified that high expression of miR-155 is correlated with poor cancer outcome.

The relation between miR-155 expression and the prognosis of patients with solid tumors was performed by Jing He [9]. However, the analysis is not comprehensive enough to collect all relevant evidence. Compared with former meta-analysis, this study contained more studies and patients, conducted more subgroup analyses and collected new evidences, thus providing powerful new evidence.

Admittedly, there were some inevitable limitations. Firstly, some of the HRs and CIs data were calculated based on the survival curves, despite the method has been previously validated, statistical errors were inevitable due to inaccurate readings. Secondly, tumor type, cut-off value, analysis type, miR-155 detection method, country, follow-up time and publication year might also contribute to the heterogeneity. Thirdly, studies regarding various tumors without a consistent cut-off value may influence the ultimate results, Meanwhile, we might ignore some undiscovered factors like adjustment for surgery, radiation, chemotherapy, socioeconomic status, tumor characteristics, and so on, which might contribute to the heterogeneity. Finally, although no significant publication bias was detected in this meta-analysis, the funnel plots of the OS analysis were not so symmetric, the results still need to be verified by a large number of studies.

In conclusion, although this study was not the first meta-analysis designed to illustrate the relationship between miR-155 and prognosis, more robust evidence had been revealed through our detailed subgroup analysis, updated data and more studies.

Conclusions

Our study indicated that high expression of miR-155 was significantly related to the poor survival in several cancer patients, and thus could be an important predictor of poor prognosis.

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Disclosure of conflict of interest

None.

Address correspondence to: Ming Zhang, Department of Liver Surgery, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu 610041, Sichuan Province, China. Tel: +86-028-85422469; E-mail: 48284728@qq.com

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