Int J Clin Exp Med 2016;9(6):9705-9713
www.ijcem.com /ISSN:1940-5901/IJCEM0021593

Review Article

Prognostic role of microRNA 125b invarious cancers: a meta-analysis

Quanhui Mei[1], Ruizheng Shi[2]

[1]*Department of Intensive Care Unit, The First People's Hospital of Changde City, Changde 415000, Hunan, China;* [2]*Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, Changsha 410008, Hunan, China*

Received December 10, 2015; Accepted March 19, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Objectives: Recently, lots of studies have demonstrated that microRNAs (miRNA) exhibit altered expression in various cancers and maybe a prognostic biomarker of cancers. We performed a meta-analysis to evaluate the impact of miR-125b expressionin solid tumors on patients' overall survival (OS), release-free survival (RFS) and progress-free survival (DFS). Design: Meta-analysis: Data sources and study eligibility criteria: Studies were identified by searching PubMed, Embace, and Cochrane Library and were assessed by further quality evaluation. The pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to investigate the association between miR-125 bexpression and cancer patients OS, RFS and PFS. Results: Our analysis results showed that miR-125b predicted poorOS (HR = 1.14 (95% CI: 0.77-1.69), RFS (HR = 2.48, 95% CI 1.43-4.30) and PFS (HR = 1.00, 95% CI 0.45-2.23). The subgroups showed miR-125b was significantly associated with worse OS in gastric carcinoma (HR = 1.61, 95% CI 1.05-2.49; $P < 0.001$) and hepatocellular carcinoma (HR = 1.74, 95% CI 1.02-2.97; $P < 0.001$). Conclusion: The findings fromthis meta-analysis suggest that miR-125b could be a useful clinical prognostic biomarker of human cancers.

Keywords: Cancer, miR-125b, prognosis, meta-analysis

Introduction

MicroRNAs are a class of endogenous small noncoding RNAs, which had the length of 19~25 nucleotides and mainly regulate the mRNAs and the expression level of their target proteins by directly binding with the corresponding mRNAs on the 3' UTR or 5' UTR [1]. It is reported that miRNAs have an important role in the development of a variety of human diseases [2-4].

MiR-125b is validated to be transcribed from two loci situated on chromosomes 11q23 and 21q21 and its product is hsa-miR-125b-1 and hsa-miR-125b-2 respectively [5]. It is reported that miR-125b was involved in various tumor development [6-10]. Previous studies show that miR-125b suppresses the proliferation and migration of osteosarcoma cells through down-regulation of STAT3 [11], but promotes proliferation through down-regulation of Bak1 in prostate cancer cells [10]. These data suggest that miR-125b might act as a tumor suppressor or oncogene depending onthe cellular context.

The majority of cancers are often a serious problem for the clinical problem, Henceit is imperative for us to identify of predictive biomarkers to improve treatment of patients with various cancers [12]. From the different studies miR-125b maybe act as a significant tumor biomarker and a potential therapeutic target [13]. However, the result from single study is not enough to evaluate whether miR-125b can be considered as a promising biomarker. So we collected the date and performed meta-analysis to assess the prognostic value of miR-125 levels in different cancers.

Materials and methods

Search strategy

We performed a meta-analysis in accordance with the guidelines of observational studies in epidemiology (MOOSE) [14]. We searched the

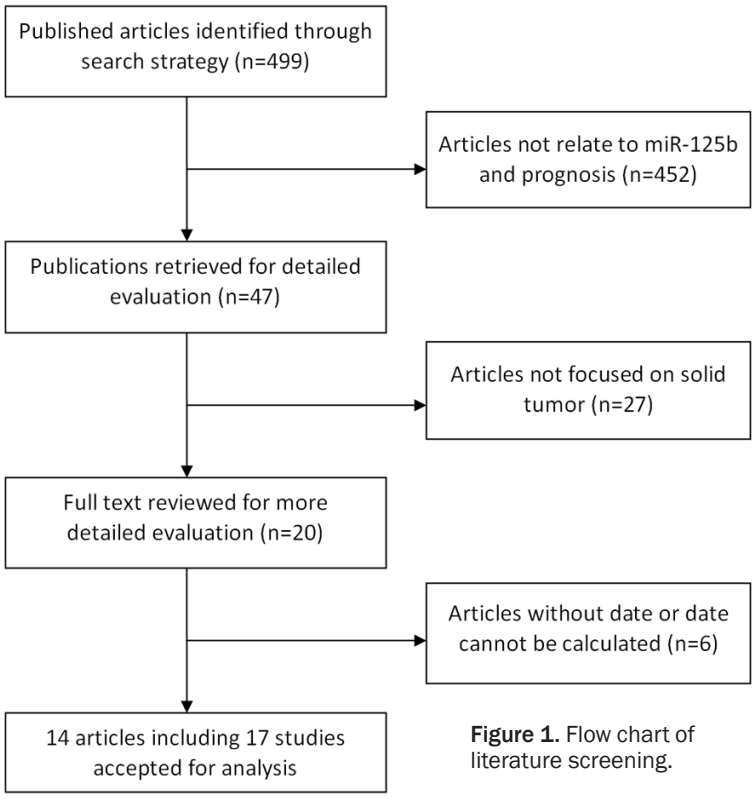

Figure 1. Flow chart of literature screening.

studies from PubMed, Embace, and Cochrane Library. The search strategy was "microRNA-125b OR miR-125b" AND "tumor OR neoplasm OR cancer OR "carcinoma" and "survival OR prognosis OR outcome". The database search was carried out by two authors (Quanhui Mei and Ruizheng Shi). The disagreements were resolved by consensus.

Inclusion and exclusion criteria

Eligible studies included in this meta-analysis according to the following criteria: (1) it reported miR-125b expression by the specific methods in tumor tissue or blood; (2) it invested the association between miR-125b expression and survivaloutcome; (3) it reported sufficient data to estimate the hazard ratio (HR) and 95% confidence intervals (CI) according to miR-125b expression. The candidate articles were screenedby author (Quanhui Mei). Articles were excludeif they were (1) a case reports; (2) letters and reviews; (3) animal trails; (4) hematological malignancies and autoimmune disorders; (5) or lack of important information such as hazard ratio (HR), 95% CI and *P* value. The full texts of the articles were carefully examined for comprehensive evaluation. The whole process was supervised by Ruizheng Shi.

Quality assessment

All the included studies was performed independently by two investigators (Quanhui Mei and Ruizheng Shi), based on the critical guidelines of the Dutch Cochrane Centre proposed by MOOSE for prognostic meta-analyses. The articles should included a basic criteria as follows: (1) clear report of study population and country; (2) clear definition of type of cancer; (3) clear demonstrated the outcome assessment; (4) clear definition of measurement of miR-125b. Otherwise the studies were excluded for the reason of the quality of the meta-analysis.

Data extraction

Two reviewers independently extracted the required information from all eligible studies to rule out any discrepancy. The following data were extracted: first author, study of year, type of carcinoma, source of patients, number of patients, method of testing miR-125b, and HR of miR-125b for overall survival (OS), Release-free survival (RFS) and Progression free survival (PFS), as well as the corresponding 95% CI. If the HR and CI were not reported directly, the total observed events and the numbers of patients in each group were extracted to calculate HR and its variance indirectly [15]. If only Kaplan-Meier curves are available, data was extracted from the graphical survival plots by Engauge Digitizer version 4.1. Only reported univariate analysis results for survival in eligible studies were considered for the aggregation of the survival data. All the data were resolved by consensus.

Statistical analysis

Statistical heterogeneity was assessed by visual inspection of forest plots, by performing the Chisquaretest (assessing the *P* value) and calculating the I^2 statistic [16]. If the *P* value was less than 0.05 and/or I^2 exceeded 50%, indicat-

Table 1. Characteristics of studies

Study	Year	Type	Country	Sample	Survival	Obtain	Method	HR(CI)
Li WX [17]	2008	Hepatocellular carcinoma	China	75	OS	Original	qRT-PCR	OS: 2.43 (1.13-5.24)
Naohiro Nishida [18]	2010	Colorectal cancer	Japan	89	OS	Engauge	qRT-PCR	OS: 1.6 (0.52-4.90)
Zhang Y [19]	2011	Breast cancer	China	105	OS	Engauge	qRT-PCR	OS: 0.49 (0.19-1.26)
Feng JJ [20]	2012	glioma	America	277	OS	Original	qRT-PCR	OS: 1.08 (0.86-1.35)
Ma YX [21]	2012	Non-small cell lung cancer	China	193	OS	Original	qRT-PCR	OS: 2.46 (1.80-3.38)
Song FJ [22]	2013	Gastric cancer	China	358	OS+PFS	Original	qRT-PCR	OS: 1.8 (1.19-2.72) PFS: 1.76 (1.2-2.58)
M Shiiba [23]	2013	Oral squamous cell carcinoma	Japan	50	OS	Engauge	qRT-PCR	OS: 0.77 (0.1-6.19)
Federico Cappuzzo [24]	2014	Colorectal cancer	Italy	183	OS+PFS	Calculate	microarray	OS: 1.8 (1.19-2.72) PFS: 0.68 (0.43-1.07)
Li XX [25]	2014	Glioma	China	45	OS	Original	qRT-PCR	OS: 2.43(1.13-5.24)
Felice H Tsang [26]	2014	Hepatocellular carcinoma	China	49	OS+RFS	Engauge	qRT-PCR	OS: 1.28 (0.2-8.36) RFS: 1.51 (0.42-5.42)
Wu JG [27]	2014	Gastric cancer	China	149	OS	Engauge	qRT-PCR	OS: 1.03 (0.4-2.67)
Fu Q [28]	2014	Clear-cell renal cell carcinoma	China	259	RFS	Original	qRT-PCR	OS: 1.8 (1.19-2.72) RFS: 2.40 (1.37-3.78)
Yu XZ [29]	2015	None-small cell lung cancer	China	42	PFS	Engauge	qRT-PCR	PFS: 0.94 (0.38-2.36)
Vilquin P [30]	2015	Breast cancer	France	65	RFS	Original	qRT-PCR	RFS: 6.8 (1.35-35.26)

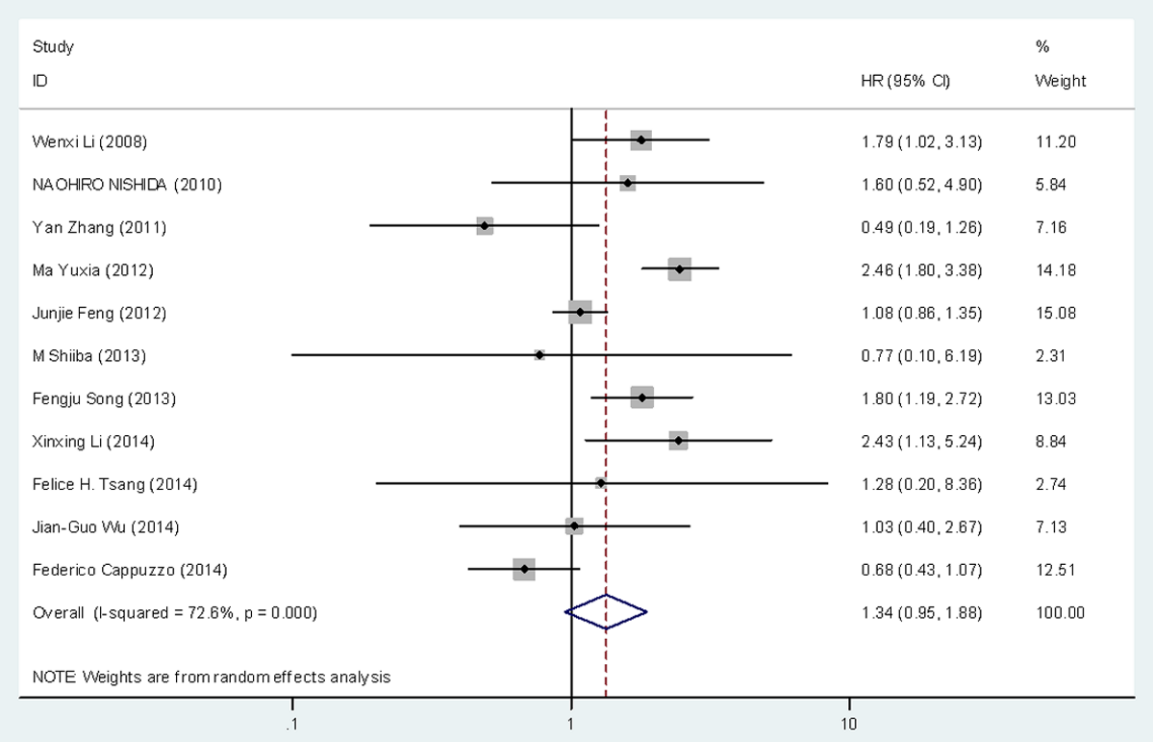

Figure 2. Meta-analysis of miR-125b expression and solid tumors' overall survival.

ing the presence of heterogeneity, a random-effects model (the DerSimonian-Laird method) was used. Otherwise, the fixed-effects model (the Mante-Haenszel method) was used. Subgroup analysis was further performed to explore the source of heterogeneity. Heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$. Subgroup and sensitivity analysis was carried out by investigating the influence of a single study on the overall HR. Furthermore, Begg's test was performed to provide quantitative evidence of publication bias. All analyses were performed using STATAvision 12.0 (Stata Corporation, College Station, TX, USA).

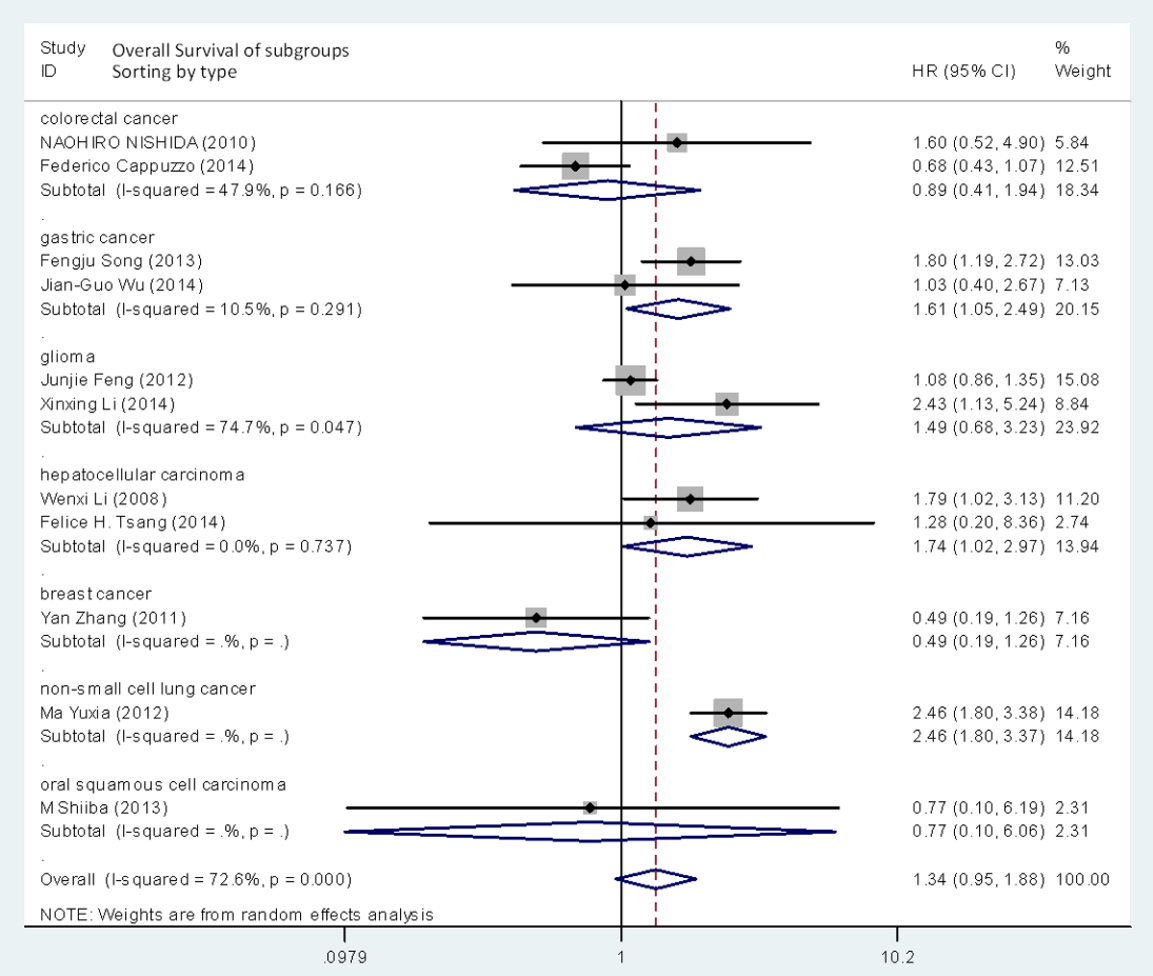

Figure 3. Subgroups analysis of miR-125b expression and solid tumors' overall survival.

Results

Study characteristics

According to the criteria mentioned in materials and methods, 499 abstracts were initially selected. However, 452 irrelevant abstracts were excluded by the first choosing. Forty-seven full-text articles were reviewed for further evaluation and twenty-seven were excluded because they were the solid tumor. The remaining twenty articles had further read and six articles were excluded because of not including the OS analysis. At last we selected fourteen articles including 1939 patients, which were published between 2008 and 2015 (**Figure 1**). The category of cancers included breast cancer (2 studies), gastric cancer (2 studies), hepatocellular carcinoma (2 studies), colorectal cancer (2 studies), non-small cell lung cancer (2 studies), glioma (2 studies), oral squamous cell carcinoma and clear-cell renal cell carcinoma. Quantitative RT-PCR and microarray were used to detect miRNAs expression in all studies. HRs wereestimated in 6 studies by engauge software and directly reported in five studies. Themajor characteristics of the 14 eligible studies are listed in **Table 1**.

Overall survival (OS) associated with miR-125b expression

For studies evaluating OS for miR-125b, a random-effects model was used to calculate the pooled HR and its 95% CI because of the high significant heterogeneity (I^2 = 72.6%, P = 0.000). The result demonstrated that high level of miR-125b may predict poorer OS, with the pooled HR being 1.14 (**Figure 2**). The subgroups were analyzed according to the main characteristics such as tumor type. In the subgroup of tumor type, we found the miR-125b was signifi-

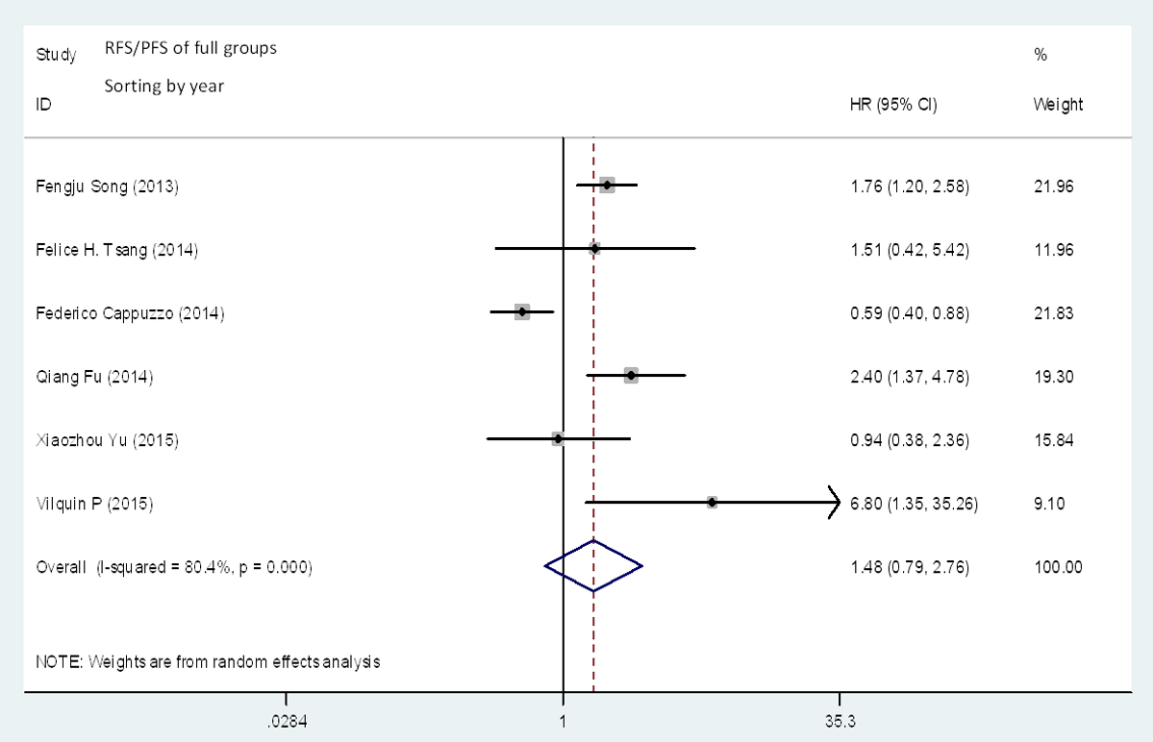

Figure 4. Meta-analysis of miR-125b expression and solid tumors' RFS/PFS.

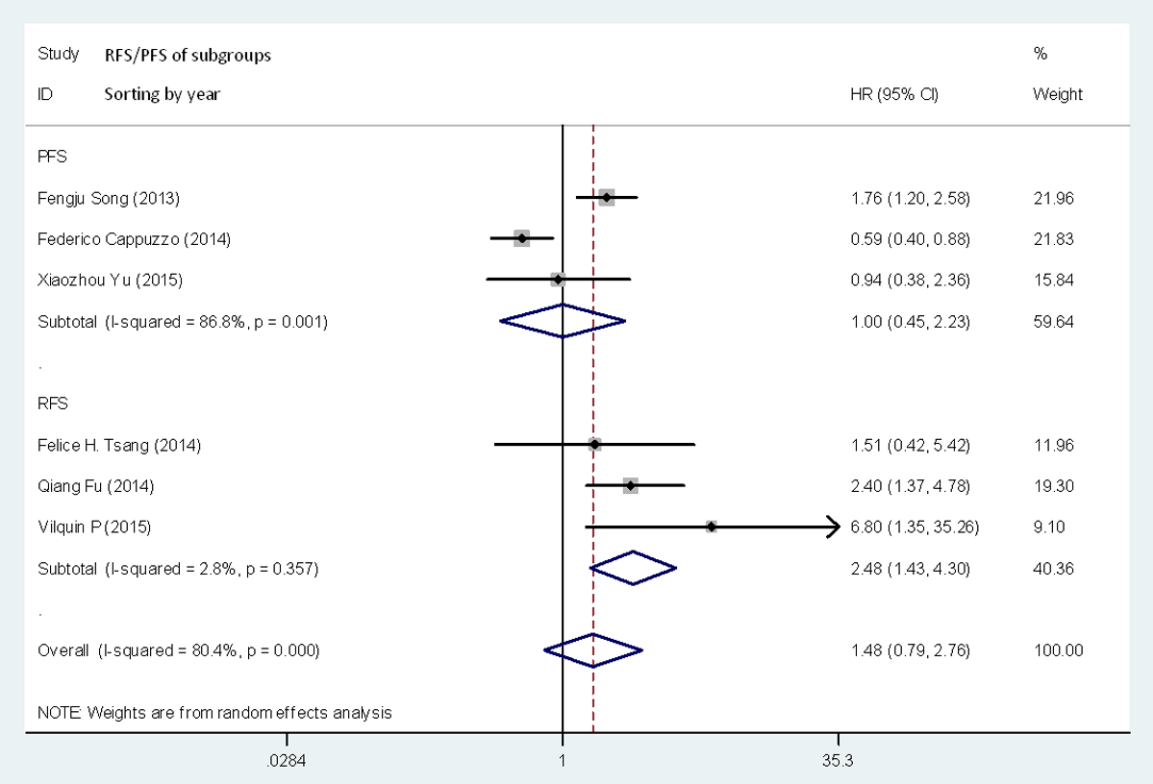

Figure 5. Subgroups analysis of miR-125b expression and solid tumors' RFS/PFS.

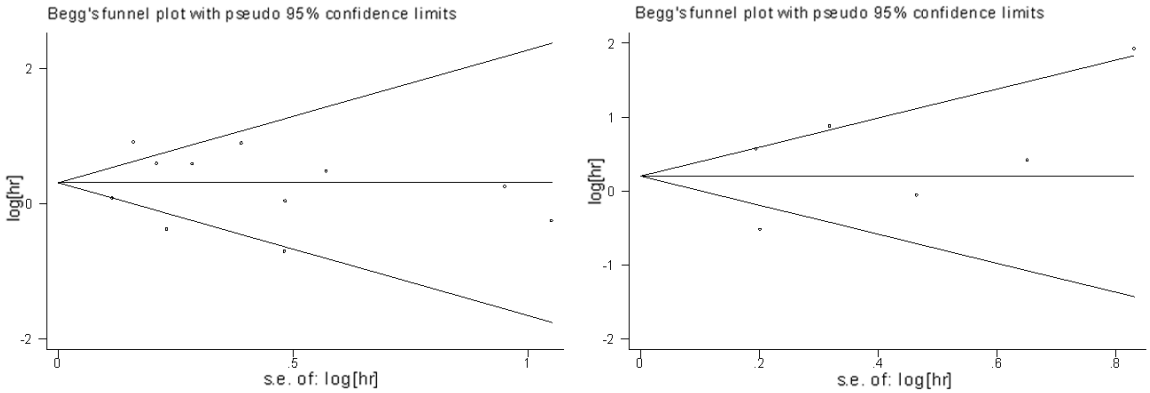

Figure 6. Begg's funnel plot of publication bias.

cantly associated with worse OS in gastric carcinoma (HR = 1.61, 95% CI 1.05-2.49; $P < 0.001$; fixed-effects model), hepatocellular carcinoma (HR = 1.74, 95% CI 1.02-2.97; $P < 0.001$; fixed-effects model), without any heterogeneity in thedata ($I^2 = 10.5\%$, $P = 0.291$; $I^2 = 0.0\%$, $P = 0.737$, resp) (**Figure 3**).

Tumor progression (RFS/PFS) associated with miR-125b expression

We analyzed tumor progression associated with miR-125b expression. Six studies included the RFS and PFS analysis. Meta-analysis of the eligible studies predicted that high level of miR-125 was significantly associated with poor DFS/PFS (pooled HR = 1.48, 95% CI: 0.79-2.76). There was significant heterogeneity was observed ($I^2 = 80.4\%$, $P = 0.000$) and the random-effects model was applied (**Figure 4**). In the subgroup of tumor type, we found the miR-125b was significantly associated with worse RFS (HR = 2.48, 95% CI 1.43-4.30; $P < 0.001$; fixed-effects model) (**Figure 5**).

Heterogeneity and publication bias analysis

Sensitivity analysis was performed by deletion of individual studies using the fixed-effects model. By excluding this study from the analysis, similar pooled HR and significance were obtained.Bgger's test wasused to evaluate the publication bias (**Figure 6**). The P values of Begg's tests wasover 0.05 ($P = 0.15$). Hence, there was noevidence for significant publication bias in themeta-analysis.

Discussion

Cancer is a global and growing problem which is potentially life-threatening that should be recognized immediately with decisive intervention in order to decreased mortality and morbidity. The signs and symptoms of tumor may present at any time. However, despite the advances technology was used to treatment the cancer, the five years survival was also lower mainly due to the late diagnosis and lack of prognostic markers for various cancers. There are few defined prognostic and diagnostic biomarkers available in cancers. So it is imperative for us to identify the newer biomarker of various cancer [31]. MiR-125b exhibits a large range of correlation with different cancers. Acting as tumor suppressor, miR-125b shows a lower expression in hepatocellular carcinoma, chronic lymphocytic leukemia, cutaneous squamous cell carcinoma, melanoma, Ewing's sarcoma, bladder cancer head and neck cancer. As a tumor promoter, miR-125b increased carcinogenesis in B-cell leukemia, myeloid leukemia, non-small cell lung cancer, clear-cell renal carcinoma, glioblastoma, prostate cancer, pancreatic cancer and oligodendroglia, in which miR-125 is overexpressed [28, 32-53]. In a word, miR-125b can be acted as a different role in the tumors. MiR-125b can regulate thetumor cell proliferation, apoptosis, invasion and metastasis. For example, Liu LH et al [11] found miR-125b might inhibit tumor cell proliferation by down-regulating STAT3. MiR-125b also influenced the expression of survivin protein by modulating the STAT3 signaling. Such regulation accelerates tumor cell apoptosis [54].

In terms of this, a total of 1939 participants from 14 studies were included into the meta-analysis. This result showed that high expression of miR-125b maybepredict a unsatisfactory outcome of some cancers (HR = 1.14,2.48,

1.00 for OS, RFS, and PFS, resp). For OS, the data displayed that miR-125b was anundesirably prognostic marker ingastric carcinoma (HR = 1.61, 95% CI 1.05-2.49; $P < 0.001$) and hepatocellular carcinoma (HR = 1.74, 95% CI 1.02-2.97; $P < 0.001$). Additionally, there was no obvious riskof publication bias in our meta-analysis. From the aboveresults, we found that high expression of tissue miR-125b was a negative prognostic factor in some cancer patients.

Although the present meta-analysis showed that theexpression of miR-125b maybe play a worse role in the prognosis in several cancers, some limitation was still in this meta-analysis. Firstly, the obvious heterogeneity existedin our meta-analysis. Secondly, several HRs were unreported in the original article that we have to calculate the HR from the survival curve. Thirdly, the number of studies in subgroup analyses was relativelysmall. More studies on these cancers are needed in the future.

In sum, in this meta-analysis, we got a concluded that miR-125b was acted as a biomarker in various carcinomas. Increased miR-125b level incancerous tissues was associated with unsatisfactory OS, PFS and RFS. However, our results should be regarded attention because of the limitations of the present analysis listedabove. There should be moremulticenter studies needed to focus on the relationship between miR-125b and cancer prognosis.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ruizheng Shi, Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, Changsha 410008, China. Tel: 086-731-84327694; Fax: 086-731-84327695; E-mail: xysrz2010@sina.com

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