Int J Clin Exp Med 2016;9(10):19607-19610
www.ijcem.com /ISSN:1940-5901/IJCEM0031975

Original Article

Clinical relevance of miR-92a in colorectal cancer: a meta-analysis

Jun-Xin Song[1], Zhen Zhang[2], Jun-Jun Sun[1]

Departments of [1]General Surgery, [2]Neurology, The First Affiliated Hospital, College of Clinical Medicine of Henan University of Science and Technology, No. 24 Jinghua Road, Luoyang 471003, China

Received May 10, 2016; Accepted July 26, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: MicroRNAs (miRNAs) are endogenous short non-coding RNAs that downregulate target gene expressions by binding to their 3'-UTR. miRNAs may play a strong role in disease progression by changing target gene expressions in many tumors. Recently, some studies investigated the association of miR-92a and colorectal cancer (CRC) prognosis. However, the result was still inconsistent. The aim of this study was to investigate whether there is an association between the miR-92a and CRC prognosis. Published reports were searched in PubMed, EMBASE, and Google Scholar. The strength of association between miR-92a and CRC prognosis was evaluated by calculating the HR and 95% CI. Six publications with 695 patients had met the inclusion criteria and were subjected to further examination. High expression of miR-92a was significantly associated with high clinical stage (OR=2.45; 95% CI, 1.16-7.28; I^2=0%), distant metastasis (OR=4.71; 95% CI, 1.74-12.69; I^2=0%), lymph node metastasis (OR=2.90; 95% CI, 1.64-5.13; I^2=0%), and depth of invasion (OR=1.79; 95% CI, 1.04-3.07; I^2=35%). Additionally, we found miR-92a was significantly associated with shorter overall survival (OS) in CRC (HR=2.90; 95% CI 1.76-7.28; I^2=71%). The shape of the funnel plot seemed symmetrical, suggesting that there was no obvious publication bias (P=0.99). In conclusion, miR-29a is associated with poor survival of CRC.

Keywords: Colorectal cancer, microRNAs, meta-analysis

Introduction

Colorectal cancer (CRC) accounts for 10% of new cancer cases and is one of the leading causes of death worldwide [1]. Despite dramatic improvements in the five-year survival rate of CRC patients diagnosed at the early stage, most patients are diagnosed too late to receive effective medical treatment. Thus, it is very important to find useful biomarkers which could predict the prognosis of CRC.

MicroRNAs (miRNAs) are endogenous short non-coding RNAs that downregulate target gene expressions by binding to their 3'-UTR [2]. MiRNAs may play a strong role in disease progression by changing target gene expressions in many tumors [3].

Recently, some studies investigated the association of miR-92a and CRC prognosis [4-9]. However, the result was still inconsistent. The aim of this study was to investigate whether there is an association between the miR-92a and CRC prognosis.

Methods

Publication search

Published reports were searched in PubMed, EMBASE, and Google Scholar, with the following key words: "Colorectal cancer" and "miR-92a". Publication language was not restricted in this search. Reference lists of articles retained for review were examined manually to further identify potentially relevant reports.

Inclusion criteria

Studies were considered eligible if they met the following criteria: (1) Study investigated the association between miR-92a and CRC prognosis; (2) Study provided sufficient data for estimating hazard ratio (HR) with 95% confidence interval (CI). Meanwhile, studies were excluded

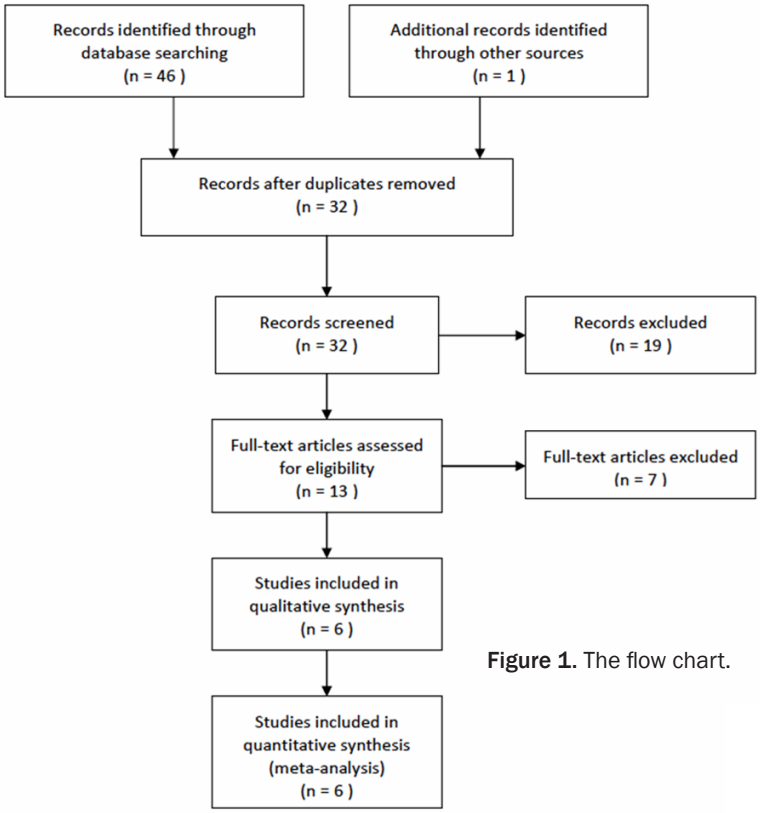

Figure 1. The flow chart.

based on the following criteria: (1) Duplicate publications; (2) Lack of key information for further analysis; (3) Reviews, meeting abstracts, editorials, and case reports; (4) Nonhuman research. Two investigators judged study eligibility and disagreements were resolved by discussion.

Data extraction

The following information was extracted from all eligible studies independently by two investigators: first author's name, year of publication, country, age, gender, sample size, follow-up duration, clinical stage, distant metastasis, lymph node metastasis, depth of invasion, and prognosis.

Statistical analysis

The strength of association between miR-92a and CRC prognosis was evaluated by calculating the HR and 95% CI. Moreover, X^2 based Q and I^2 test were performed to evaluate the between-study heterogeneity and P<0.1 was defined as statistical significance. The random-effects was used to calculated the OR if significant heterogeneity existed. Otherwise, the fixed-effects model was applied. Publication bias was assessed by asymmetry of funnel plots. We conducted all the analyses by using STATA 11.0 software (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

The flow chart in **Figure 1** summarizes this literature review process. We identified a total of 47 relevant publications after initial screening. Among these, 6 publications with 695 patients had met the inclusion criteria and were subjected to further examination. One study was conducted in Europe, 5 were conducted in Asia. Characteristics of the included studies are shown in **Table 1**.

Results of meta-analysis

The results of the association between miR-92a and clinicopathological factors are summarized in **Table 2**. High expression of miR-92a was significantly associated with high clinical stage (OR=2.45; 95% CI, 1.16-7.28; I^2=0%), distant metastasis (OR=4.71; 95% CI, 1.74-12.69; I^2=0%), lymph node metastasis (OR=2.90; 95% CI, 1.64-5.13; I^2=0%), depth of invasion (OR=1.79; 95% CI, 1.04-3.07; I^2=35%). When all eligible studies were pooled into one dataset for the meta-analysis, we found miR-92a was significantly associated with shorter overall survival (OS) in CRC (HR=2.90; 95% CI 1.76-7.28; I^2=71%; **Figure 2**).

We conducted Begg's funnel plot and Egger's test to access the publication bias of all included studies. The shape of the funnel plot seemed symmetrical (**Figure 3**), suggesting that there was no obvious publication bias (P=0.99).

Discussion

Some studies have investigated the relation of miR-92a with prognosis of CRC, but the conclusions are still controversial. In view of this issue,

Table 1. Characteristics of the studies included in this meta-analysis

First author	Year	Country	Age group	Gender	Case number (n)	Follow-up duration (m)	Clinical stage	Depth of invasion	Distant metastasis	Lymph node metastasis	Overall survival
Nishida	2012	Japan	Adult	Mixed	24	NA	NA	Reported	Reported	Reported	NA
Zhou	2012	China	Adult	Mixed	82	5-66	I-IV	Reported	Reported	Reported	Reported
Schee	2012	Norway	Adult	Mixed	193	0.4-61	I-III	NA	NA	NA	Reported
Yamada	2013	Japan	Adult	Mixed	38	NA	0-IV	Reported	NA	NA	NA
Liu	2013	China	Adult	NA	200	36.4	I-IV	NA	NA	NA	Reported
Ke	2015	China	Adult	Mixed	158	57.6	I-IV	Reported	Reported	Reported	Reported

NA, not available.

Table 2. Results of the meta-analysis

	No. of studies	Test of association		Model	Heterogeneity	
		HR/OR (95% CI)	*P* Value		I^2 (%)	*P* Value
Overall survival	4	2.90 (1.16-7.28)	0.02	R	71.0	0.02
Clinical stage	3	2.45 (1.42-4.24)	0.001	F	0.0	0.62
Distant metastasis	3	4.71 (1.74-12.69)	0.002	F	0.0	0.54
Lymph node metastasis	3	2.90 (1.64-5.13)	0.0003	F	0.0	0.92
Depth of invasion	3	1.79 (1.04-3.07)	0.04	F	35.0	0.20

R, random-effects model; F, fixed-effects model.

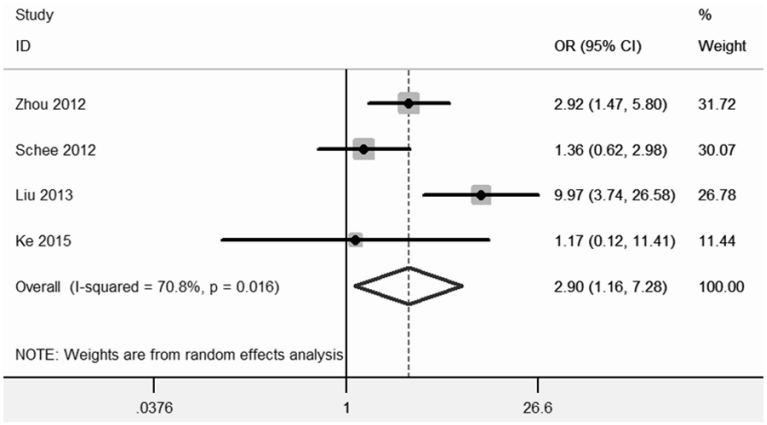

Figure 2. Meta-analysis for the association between miR-92a and OS of CRC.

we comprehensively analyzed the association between miR-92a and OS of CRC via the method of meta-analysis, and found that miR-92a was linked to poor survival of CRC. Furthermore, high expression of miR-92a was significantly associated with high clinical stage, distant metastasis, lymph node metastasis, and depth of invasion. Thus, miR-92a might be a prognostic factor of CRC.

Chang et al. suggested that combined analysis of miR-223 and miR-92a yielded the highest sensitivity and the specificity for CRC detection [10]. Yang et al. indicated that miR-92a might be a novel potential biomarker in the diagnosis of CRC [11]. Zhang et al. found that miR-92a induced EMT and regulated cell growth, migration and invasion in the SW480 cells, at least partially, via suppression of PTEN expression [12]. Wang et al. suggested that serum miR-29a has strong potential as a novel noninvasive biomarker for early detection of CRC with liver metastasis [13].

This study has some limitations. First, the sample size was relatively small. Second, significant heterogeneity was detected in included studies and the accuracy of results would be affected in spite of utilizing the random-effects model to calculate pooled ORs. Third, this study is a meta-analysis of cohort study. Confounding cannot be avoided and should be considered.

In conclusion, miR-29a is associated with poor survival of CRC. It could be used as a prognostic biomarker for CRC.

Disclosure of conflict of interest

None.

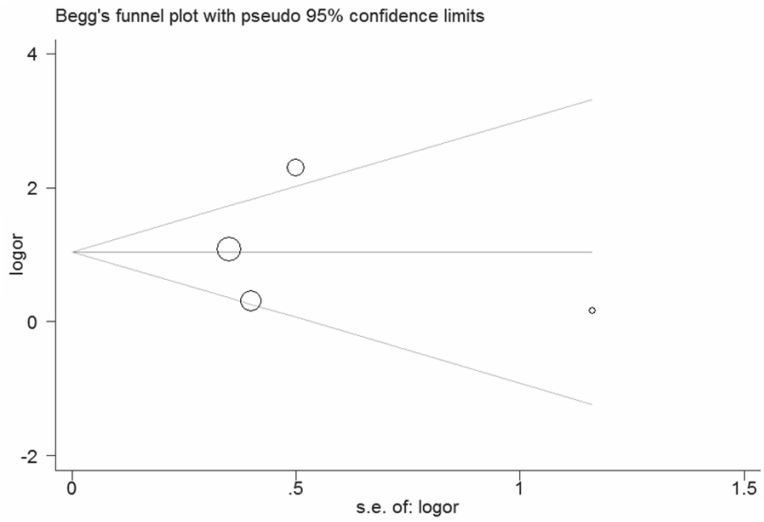

Figure 3. Funnel plot for the association between miR-92a and OS of CRC.

Address correspondence to: Jun-Jun Sun, Department of General Surgery, The First Affiliated Hospital, College of Clinical Medicine of Henan University of Science and Technology, No. 24 Jinghua Road, Luoyang 471003, China. Tel: 86-0379-64907159; E-mail: sjjhnly@163.com

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004; 116: 281-97.

[3] Jafri MA, Zaidi SK, Ansari SA, Al-Qahtani MH, Shay JW. MicroRNAs as potential drug targets for therapeutic intervention in colorectal cancer. Expert Opin Ther Targets 2015; 19: 1705-23.

[4] Schee K, Boye K, Abrahamsen TW, Fodstad O, Flatmark K. Clinical relevance of microRNA miR-21, miR-31, miR-92a, miR-101, miR-106a and miR-145 incolorectal cancer. BMC Cancer 2012; 12: 505.

[5] Yamada N, Nakagawa Y, Tsujimura N, Kumazaki M, Noguchi S, Mori T, Hirata I, Maruo K, Akao Y. Role of Intracellular and Extracellular MicroRNA-92a in Colorectal Cancer. Transl Oncol 2013; 6: 482-92.

[6] Nishida N, Nagahara M, Sato T, Mimori K, Sudo T, Tanaka F, Shibata K, Ishii H, Sugihara K, Doki Y, Mori M. Microarray analysis of colorectal cancerstromal tissue reveals upregulation of two oncogenic miRNA clusters. Clin Cancer Res 2012; 18: 3054-70.

[7] Ke TW, Wei PL, Yeh KT, Chen WT, Cheng YW. MiR-92a Promotes Cell Metastasis of Colorectal Cancer Through PTEN-Mediated PI3K/AKT Pathway. Ann Surg Oncol 2015; 22: 2649-55.

[8] Zhou T, Zhang G, Liu Z, Xia S, Tian H. Over expression of miR-92a correlates with tumor metastasis and poor prognosis in patients with colorectal cancer. Int J Colorectal Dis 2013; 28: 19-24.

[9] Liu GH, Zhou ZG, Chen R, Wang MJ, Zhou B, Li Y, Sun XF. Serum miR-21 and miR-92a as biomarkers inthe diagnosis and prognosis of colorectal cancer. Tumour Biol 2013; 34: 2175-81.

[10] Chang PY, Chen CC, Chang YS, Tsai WS, You JF, Lin GP, Chen TW, Chen JS, Chan EC. MicroRNA-223 and microRNA-92a in stool and plasma samples act as complementary biomarkers to increase colorectal cancer detection. Oncotarget 2016; 7: 10663-75.

[11] Yang X, Zeng Z, Hou Y, Yuan T, Gao C, Jia W, Yi X, Liu M. MicroRNA-92a as a potential biomarker in diagnosis of colorectal cancer: a systematic review and meta-analysis. PLoS One 2014; 9: e88745.

[12] Zhang G, Zhou H, Xiao H, Liu Z, Tian H, Zhou T. MicroRNA-92a functions as an oncogene in colorectal cancer by targeting PTEN. Dig Dis Sci 2014; 59: 98-107.

[13] Wang LG, Gu J. Serum microRNA-29a is a promising novel marker for early detection of colorectal liver metastasis. Cancer Epidemiol 2012; 36: e61-7.