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

Jun-Xin Song¹, Zhen Zhang², Jun-Jun Sun¹

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

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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; I²=0%), distant metastasis (OR=4.71; 95% CI, 1.74-12.69; I²=0%), lymph node metastasis (OR=2.90; 95% CI, 1.64-5.13; I²=0%), and depth of invasion (OR=1.79; 95% CI, 1.04-3.07; I²=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; I²=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
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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; \(P=35\%\)). 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,
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Table 1. Characteristics of the studies included in this meta-analysis

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

NA, not available.

Table 2. Results of the meta-analysis

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Test of association</th>
<th>Model</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR/OR (95% CI)</td>
<td>P Value</td>
<td>I² (%)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>4</td>
<td>2.90 (1.16-7.28)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>3</td>
<td>2.45 (1.42-4.24)</td>
<td>0.001</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>3</td>
<td>4.71 (1.74-12.69)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>3</td>
<td>2.90 (1.64-5.13)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Depth of invasion</td>
<td>3</td>
<td>1.79 (1.04-3.07)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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.
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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


