Systematic Review and Meta-Analysis: Circulating miRNAs for Diagnosis of Hepatocellular Carcinoma

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Because early-stage hepatocellular carcinoma (HCC) is difficult to diagnose using the existing techniques, identifying better biomarkers would likely improve the patients’ prognoses. We performed a systematic review and meta-analysis of published studies to appraise the utility of microRNAs (miRNAs) for the early diagnosis of HCC. Pertinent literature was collected from the Medline, Embase, and Chinese National Knowledge Infrastructure databases. We analyzed 90 studies that included 3,423 cases of HCC, 2,403 chronic hepatic disease (CH) patients, and 1,887 healthy controls in 16 articles. Summary receiver operating characteristic analyses of all miRNAs showed an area under the curve (AUC) of 0.82, with 75.8% sensitivity and 75.0% specificity in discriminating patients with HCC from healthy controls. miR-21 and miR-122 individually distinguished patients with HCC from healthy controls, with an AUC of 0.88 for miR-21 and 0.77 for miR-122. The sensitivity and specificity for miR-21 were 86.6% and 79.5%, respectively, those for miR-122 were 68.0% and 73.3%. We conclude that circulating miRNAs, particularly miR-21, and miR-122, are promising biomarkers for the early diagnosis of HCC.


Hepatocellular carcinoma (HCC) is diagnosed in more than half a million people worldwide each year; it is the fifth most common cancer in men and the seventh most common in women. The mortality rate of HCC is extremely high, with five-year overall survival rates of no more than 10% (El-Serag, 2011; Forner et al., 2012). Several risk factors for HCC have been identified. The highest incidence of HCC has been reported in eastern Asia and sub-Saharan Africa, where hepatitis B virus (HBV) infection, which is the major cause of HCC, occurs commonly. In 2010, HBV infection contributed to about half of HCC mortality (Trepo et al., 2014). Recently, we determined that HBV infection was a key factor that influenced tumorigenesis in HCC using droplet digital PCR (ddPCR) measurement of HBV copy number in formalin-fixed paraffin-embedded (FFPE) HCC tissue (Huang et al., 2015). In most developed countries, hepatitis C virus (HCV) infection and alcohol-related cirrhosis are the major risk factors, with trends in the incidence of HCC that parallel those of HCV (Bosetti et al., 2008; Qu et al., 2009; Huang et al., 2015). Other risk factors for HCC include non-alcoholic fatty liver, exposure to aflatoxin B1 (Ji et al., 2009), and diabetes (El-Serag et al., 2004). Obese patients with HCC, particularly those with a body mass index greater than 40, have a mortality rate that is five times higher than that of other patients (Calle et al., 2003). Surgical

Abbreviations: ACC, adrenocortical carcinoma; AFP, alpha-fetoprotein; AUC, area under the curve; CH, chronic hepatic disease; CIs, confidence intervals; CNKI, Chinese National Knowledge Infrastructure databases; DCP, des-gamma carboxyprothrombin; ddPCR, droplet digital PCR; DOR, diagnostic odds ratio; EOCs, epithelial ovarian cancers; FN, false negatives; FP, false positives; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; miRNAs, microRNAs; NLR, negative likelihood ratio; PCa, prostate cancer; PLR, positive likelihood ratio; PRISMA, preferred reporting items for systematic reviews and meta-analyses; qRT-PCR, quantitative real-time polymerase chain reaction; QUADAS, quality assessment of diagnostic accuracy studies; SNPs, single-nucleotide polymorphisms; SROC, summary receiver operator characteristic curve; TN, true negatives; TP, true positives.

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resection of HCC in patients with cirrhosis also raises the risk of perioperative morbidity and mortality (Llovet et al., 2005; Kapitanov et al., 2015).

Because the risk factors for HCC are so numerous and complex, its diagnosis, especially in the case of early-stage HCC, can be clinically challenging. Currently, most doctors, and investigators base their diagnoses of HCC on imaging techniques, such as abdominal ultrasonography, magnetic resonance imaging, and contrast-enhanced computed tomography, and on laboratory analyses, including tests for serum α-fetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP) (Collier and Sherman, 1998; Qi et al., 2013). However, the accuracy of these tests for early-stage HCC is modest and AFP analysis missed one-third of patients with tumors smaller than 3 cm in diameter (Collier and Sherman, 1998; Qi et al., 2013). In another study, elevated DCP activity was present in only 44–47% of HCC patients with tumors smaller than 3 cm in diameter (Abdalla and Haj-Ahmad, 2012). The biomarkers for the difference in survival or cure rates observed in patients with early- or late-stage HCC are essential for the early diagnosis of hepatocellular carcinoma. The lack of good diagnostic biomarkers for early-stage HCC surely contributes to the low five-year overall survival rate of 5–9%.

Thus, discovering sensitive and specific biomarkers for the early diagnosis of HCC could prove vital to improving the prognosis of HCC patients.

It has become increasingly clear that the circulation of certain aberrant microRNAs (miRNAs) in the blood may increase the risk of HCC and, consequently, that miRNAs may be useful as biomarkers for early-stage HCC (Qi et al., 2013). miRNAs are small noncoding RNAs that regulate mammalian gene expression by binding with miRNAs. The deregulation of miRNAs results in the degradation of their targets or the inhibition of their expression (Bartel, 2009; Tian et al., 2013; Wang et al., 2014a) and thereby plays an important role in oncogenesis and metastasis. Aberrant miRNAs has been measured in formalin-fixed paraffin-embedded tissues of several tumor types, including HCC, lung cancer, melanoma, pancreatic cancer, papillary thyroid carcinoma, and renal tumors (Wang et al., 2014a, 2015). Moreover, a recent study reported that eight circulating miRNAs (miR-20a-5p, miR-25-3p, miR-30a-5p, miR-92a-3p, miR-132-3p, miR-185-5p, miR-23a-5p, and miR-324-3p) are significantly overexpressed in HBV-positive HCC patients compared with HBV-positive cancer-free controls (Sidhu et al., 2015). Our previous research showed that single-nucleotide polymorphisms in miR-196-a2C > T and miR-499C > T elevate the risk of HCC (Qi et al., 2014). These aberrant miRNAs may thus prove to be useful biomarkers for HCC risk assessment, diagnosis, and prognosis, especially in HBV-positive patients (Lu et al., 2005). To test this hypothesis and evaluate the diagnostic efficacy of miRNAs as biomarkers for early HCC, we reviewed the literature, and performed a detailed meta-analysis.

Methods

Systematic review, study design, and data collection

We performed our review and meta-analysis according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). A set of evaluation criteria has been proposed for literature selection. The exclusion criteria were as follows: meeting abstracts, editorials, commentaries, or studies without complete data, studies unrelated to HCC, studies without comparison groups, and duplicate publications. We conducted a comprehensive literature search for original articles analyzing the diagnostic value of miRNAs in patients with HCC using the Medline, Embase, and Chinese National Knowledge Infrastructure (CNKI) databases. We identified the studies by searching for the following medical subject heading (MeSH) terms: “liver neoplasms” or “liver cancer” or “hepatocellular” or “carcinoma” or “hepatocellular carcinoma” and “microRNAs” or “miRNAs” and “diagnosis” or “sensitivity” and “specificity” or “receiver operating characteristic”. We did not restrict our search by language or publication date. We also scanned the reference lists of review articles and selected papers published at any time until July 2015 to identify any additional acceptable articles.

To be included in our final data set, studies had to (1) evaluate the diagnostic value of miRNAs in HCC, (2) have confirmed all HCC cases by a standard test (such as histological examination), and (3) report the sample types, sensitivity, specificity, or enough information to reconstruct a diagnostic four-fold contingency table. All patients had pathologically confirmed HCC or chronic hepatic disease (CH). Two of the authors independently extracted the following data from the full text of the selected articles: first author’s name; year and country of publication; subjects’ ethnicity, sex, and age; total number of cases and controls; miRNAs studied; type of specimen used for miRNA testing; sensitivity, specificity, true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) values of tested miRNAs; and information needed for quality assessment.

Statistical analysis

All statistical analyses were performed using the Stata 12.0 software (Stata-Corp LP, College Station, TX). To identify the most commonly defined diagnostic microRNAs, we extracted the number of participants with TP, FP, FN, and TN from each study. We calculated the pooled sensitivity (TP/[TP+FP]), specificity (TN/[TN+FP]), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and corresponding 95% confidence intervals (CIs) for the miRNAs studied. In addition, we determined the sensitivity and specificity of the miRNAs in each study using a bivariate summary receiver operating characteristic (SROC) curve. We calculated the area under the SROC curve (AUC) and the maximum point of intersection between sensitivity and specificity (Q value) (Walter, 2002). We explored potential publication bias using Deeks funnel plots (Deeks et al., 2005). All statistical tests were two-sided, and \( P < 0.05 \) was considered statistically significant.

Results

Systematic review and quality assessment of diagnostic studies of HCC for meta-analysis

Our primary literature search of the Medline, Embase, and CNKI databases identified 92 eligible articles examining the diagnostic efficacy of single miRNAs in patients with HCC (Fig. 1). We identified an additional nine eligible articles by scanning the reference lists. Upon screening the titles, abstracts, and keywords, we excluded 39 duplicate studies and 32 reviews and commentaries, studies irrelevant to HCC, and studies unrelated to diagnostic analysis. Of the remaining 30 candidate articles, whose full text we reviewed, 14 lacked key information. Ultimately, sixteen articles were analyzed for our study. Ultimately, 11 articles that examined the efficacy of single miRNAs for diagnosing HCC compared with healthy individuals were included in this review (Tan et al., 2008; Qi et al., 2011; Xu et al., 2011; Li et al., 2012; Liu et al., 2012; Tomimaru et al., 2012; Luo et al., 2013; Shen et al., 2013; Zheng et al., 2013, 2014; Jiang et al., 2015).

The 11 selected articles, which were published between 2011 and 2015, reported 24 studies that assessed the diagnostic efficacy of single miRNAs for distinguishing cases of HCC from healthy controls. Zhang et al.’s article included two
Sensitivity and specificity of circulating miRNAs for the diagnosis of HCC

The overall pooled sensitivity and specificity for the single miRNA analyses were 75.8% (95%CI: 70.1–80.8%) and 75.0% (95%CI: 67.8–81.0%), respectively, for distinguishing patients with HCC from healthy individuals (Fig. 2A and 2B). The diagnostic sensitivity and specificity of single miRNA for discriminating HCC from chronic hepatic disease (CH) were 70.0% (95% CI: 64.5–74.9%) and 73.1% (95% CI: 65.7–79.4%), respectively (Fig. 2C and 2D). The PLR, NLR, and DOR for single miRNA levels to differentiate patients with HCC from healthy controls were 3.03 (95% CI: 2.36–3.90), 0.32 (95% CI: 0.26–0.40), and 9.41 (95% CI: 6.44–13.73), respectively (Table 2). The PLR, NLR, and DOR for single miRNA levels to differentiate HCC from CH were 2.60 (95% CI: 2.07–3.27), 0.41 (95% CI: 0.35–0.48), and 6.34 (95% CI: 4.63–8.68), respectively (Table 2). Estimates of the sensitivity and specificity for all 24 studies comparing patients with HCC and healthy controls are shown, together with the SROC point (pooled sensitivity against 1-pooled specificity), in Fig. 3A. The AUC was 0.82 (95% CI: 0.78 to 0.85). Estimates of the sensitivity and specificity for all 26 studies comparing patients with HCC and those with CH are shown, together with the SROC point in Fig. 3C. The AUC was 0.77 (95% CI: 0.73–0.81), which indicates that tests for single miRNAs are highly accurate for the early diagnosis of HCC.

Diagnostic efficacy of circulating miR-21 and miR-122 in HCC

In the studies of the diagnostic efficacy of single miRNA, the aberrant miRNAs most commonly examined were miR-21 and miR-122. As a result, we further analyzed the diagnostic efficacy of these two miRNAs in distinguishing patients with HCC from healthy individuals. In the three studies about miR-21, the pooled sensitivity was 86.6% (95% CI: 82.1–90.2%), and the specificity was 79.5% (95% CI: 65.7–88.7%) (Fig. 4A and 4B). The PLR was 4.24 (95% CI: 2.40–7.49), the NLR was 0.17 (95% CI: 0.12–0.24), and the DOR was 25.17 (95% CI: 11.02–54.47). The AUC for miR-21 was 0.88 (95% CI: 0.85–0.90) (Table 2 and Fig. 5A). In the four studies about miR-122, the pooled sensitivity and specificity were 68.0% (95% CI: 55.8–78.2%), 73.3% (95% CI: 66.0–79.6%), respectively (Figs. 4C and 4D). The PLR, NLR, and DOR for miR-122 in HCC diagnosis were 2.55 (95% CI: 2.08–3.13), 0.44 (95% CI: 0.32–0.59), and 5.85 (95% CI: 3.85–8.90), respectively (Table 2). The AUC of miR-122 was 0.77 (95% CI: 0.73–0.80) (Fig. 5B).

Discussion

We reviewed the articles about the diagnostic accuracy of single miRNA in distinguishing patients with HCC from healthy individuals, and 19 miRNAs were included in this study (Table 1). In addition, 24 miRNAs were analyzed with regard to distinguishing patients with HCC from those with chronic hepatic disease (Supplemental Table 1). The quantitative real-time polymerase chain reaction (qRT-PCR) assay was used in all studies to measure the levels of circulating miRNAs, and normalization was performed using the endogenous gene RNU6B as a control in almost all studies. Overall, 50 studies in 16 articles were evaluated: 11 articles with 24 studies assessed 19 single miRNAs for their accuracy in discriminating patients with HCC from healthy individuals (Table 1), whereas nine articles with 26 studies in our meta-analysis assessed 24 single miRNAs for their accuracy in distinguishing patients with HCC from those with chronic hepatic disease (Supplemental Table 1).
TABLE 1. The main features of hepatocellular carcinoma (HCC) studies about HCC distinguishing from healthy control in circulating miRNA analysis by qRT-PCR

<table>
<thead>
<tr>
<th>miRNA</th>
<th>Serum/plasma</th>
<th>Number</th>
<th>Age</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Ethnicity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-21</td>
<td>Serum</td>
<td>101</td>
<td>n.a.</td>
<td>84.0</td>
<td>73.5</td>
<td>Asian</td>
<td>Xu J (2011)</td>
</tr>
<tr>
<td>miR-21</td>
<td>Plasma</td>
<td>136</td>
<td>63 ± 10</td>
<td>87.3</td>
<td>92.0</td>
<td>Asian</td>
<td>Tomimaru Y (2012)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>57</td>
<td>n.a.</td>
<td>89.5</td>
<td>71.2</td>
<td>Asian</td>
<td>Liu AM (2012)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>101</td>
<td>n.a.</td>
<td>70.7</td>
<td>69.1</td>
<td>Asian</td>
<td>Xu J (2011)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>70</td>
<td>49</td>
<td>81.6</td>
<td>83.3</td>
<td>Asian</td>
<td>Qi P (2011)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Plasma</td>
<td>85</td>
<td>53.60 ± 12</td>
<td>70.6</td>
<td>67.1</td>
<td>Asian</td>
<td>Luo J (2013)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>135</td>
<td>53.57 ± 11.50</td>
<td>48.9</td>
<td>82.2</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
<tr>
<td>miR-18a</td>
<td>Serum</td>
<td>101</td>
<td>54 ± 11</td>
<td>86.1</td>
<td>75.0</td>
<td>Asian</td>
<td>Li J (2012)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>50</td>
<td>38</td>
<td>81.6</td>
<td>83.3</td>
<td>Asian</td>
<td>Qi P (2011)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>60</td>
<td>52 ± 16</td>
<td>68.9</td>
<td>74.4</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>90</td>
<td>40.20 ± 6.61</td>
<td>48.9</td>
<td>82.2</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>36</td>
<td>54.60 ± 11.2</td>
<td>76.6</td>
<td>80.6</td>
<td>Asian</td>
<td>Li J (2015)</td>
</tr>
<tr>
<td>miR-122</td>
<td>Serum</td>
<td>95</td>
<td>52 ± 6.98</td>
<td>73.0</td>
<td>83.0</td>
<td>Asian</td>
<td>Zhang ZQ (2014)</td>
</tr>
<tr>
<td>miR-183</td>
<td>Serum</td>
<td>57</td>
<td>n.a.</td>
<td>57.9</td>
<td>69.5</td>
<td>Asian</td>
<td>Liu AM (2012)</td>
</tr>
<tr>
<td>miR-192</td>
<td>Serum</td>
<td>135</td>
<td>53.57 ± 11.50</td>
<td>71.9</td>
<td>75.6</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
<tr>
<td>miR-199a</td>
<td>Serum</td>
<td>135</td>
<td>53.57 ± 11.50</td>
<td>59.3</td>
<td>66.7</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
<tr>
<td>miR-206</td>
<td>Serum</td>
<td>135</td>
<td>53.57 ± 11.50</td>
<td>48.1</td>
<td>78.8</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
<tr>
<td>miR-215</td>
<td>Serum</td>
<td>95</td>
<td>52.58 ± 6.98</td>
<td>80.0</td>
<td>91.0</td>
<td>Asian</td>
<td>Zhang ZQ (2014)</td>
</tr>
<tr>
<td>miR-223</td>
<td>Serum</td>
<td>101</td>
<td>n.a.</td>
<td>80.0</td>
<td>76.5</td>
<td>Asian</td>
<td>Xu J (2011)</td>
</tr>
<tr>
<td>miR-433</td>
<td>Serum</td>
<td>135</td>
<td>53.57 ± 11.50</td>
<td>79.3</td>
<td>64.4</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
<tr>
<td>miR-483</td>
<td>Serum</td>
<td>49</td>
<td>61.10 ± 11.70</td>
<td>55.7</td>
<td>85.7</td>
<td>Caucasian</td>
<td>Shen J (2013)</td>
</tr>
<tr>
<td>miR-128</td>
<td>Serum</td>
<td>135</td>
<td>53.57 ± 11.50</td>
<td>79.3</td>
<td>27.8</td>
<td>Asian</td>
<td>Tan Y (2014)</td>
</tr>
</tbody>
</table>

Fig. 2. The pooled sensitivity (A, C) and specificity (B, D) of single miRNA for discriminating HCC from healthy controls (A, B), and for discriminating HCC from chronic hepatic disease with Forest plots analysis (C, D).
hepatic disease in this meta-analysis (Supplemental Table 1). To minimize the publication bias and ensure the quality of our meta-analysis, we followed the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) guidelines (Supplemental Fig. 1) (Whiting et al., 2011) and analyzed the potential publication bias using Deeks’ funnel plots. The Deeks’ funnel plots for potential publication bias showed some asymmetry (Fig. 3B and 3D). However, the P-values for the Deeks test were 0.16 for all single miRNAs for discriminating HCC from healthy individuals, 0.90 for all single miRNAs for discriminating HCC from chronic hepatic disease, 0.79 for miR-21 (Supplemental Fig. 2A), and 0.02 for miR-122 (Supplemental Fig. 2B), which indicated that there was no publication bias in our meta-analysis.

Ideal biomarkers of HCC must show a high sensitivity and specificity (Wang et al., 2014b; Tian et al., 2015). Our meta-analysis found that two miRNAs, miR-21, and miR-122, demonstrated potential value as biomarkers of HCC. We hypothesized that high levels of circulating miR-21 could serve as a biomarker of HCC because previous studies have shown that the overexpression of miR-21 in patients with HCC inhibits tumor suppressor genes, such as PDCD4, and PTEN, and is associated with cell proliferation and the suppression of apoptosis (Meng et al., 2006, 2007; Si et al., 2007; Asangani et al., 2008; Liu et al., 2010). Our results confirm that miR-21’s high sensitivity and specificity make it a good candidate biomarker of HCC. Further, our meta-analysis shows that miR-122, which is also involved in tumorigenesis, is another promising biomarker of HCC. miR-122 constitutes up to nearly 70% of all liver miRNAs (Girard et al., 2008), and previous studies have linked it to the development and differentiation of hepatocytes, the metabolism of hepatic fatty acids, and cholesterol, and liver fibrosis, and cirrhosis (Hu et al., 2012;...
Tsai et al., 2012). Zeisel and colleagues (Zeisel et al., 2013) have demonstrated that miR-122 acts as a tumor suppressor in HCC. Low levels of miR-122 have also been correlated with metastasis and poor prognosis in patients with liver cancer (Nakao et al., 2014). In a previous analysis, which was included in our meta-analysis, the utility of other miRNAs as biomarkers of HCC was studied. miR-483-5p alone had a sensitivity of 55.1% and a specificity of 85.7% (Shen et al., 2013). miR-483-5p, and miR-483-3p, which originate from miR-483, were upregulated in HCC tissue (Li et al., 2014a). Circulating miR-483-5p was a promising biomarker for the diagnosis and prognosis of various cancers, such as adrenocortical carcinoma (ACC) (Chabre et al., 2013), epithelial ovarian cancers (EOCs) (Zheng et al., 2013a) and myeloma (Qu et al., 2014). The level of miR-483-5p was also upregulated in urine samples of patients with prostate cancer (PCa) (Korzeniewski et al., 2015).

Fig. 4. The pooled sensitivity (A, C) and specificity (B, D) of miRNA-21 (A, B) and miR-122 (C, D) in discriminating HCC from healthy controls with Forest plots analysis.

Fig. 5. The diagnostic performance of miR-21 (A) and miR-122 (B) for discriminating HCC from healthy controls using SROC analysis.
Moreover, the overexpression of miR-483 inhibited liver fibrosis in mice induced by CCl4 (Li et al., 2014a) and regulated the proliferation of hepatoma cells by targeted Socs3 (Ma et al., 2012). Thus, miR-483 may serve as a novel biomarker for the diagnosis of HCC and a potential target for hepatocellular carcinoma therapy.

However, some studies have also found that combining miRNA analysis with older methods for diagnosing and assessing the risk of HCC may yield more sensitive and specific tests than does either method on its own. Neither single miRNAs nor traditional biomarkers are sufficiently accurate to reliably diagnose liver cancer. Although single miRNAs show only acceptable sensitivity, traditional biomarkers demonstrate only satisfactory specificity. For instance, the combination of the expression of miR-483 and HCV status was much more sensitive (75.5%) and specific (89.8%) than miR-483 alone (Shen et al., 2013). Similarly, the combination of miR-21 and AFP has been found to increase the diagnostic discrimination ability compared with miR-21 alone or AFP alone (Luo et al., 2013). Thus, the combination of miR-21 and AFP also increased significantly the diagnostic discrimination ability over miR-2122a alone or AFP alone (Luo et al., 2013). Thus, the literature suggests that combining single miRNA analysis with traditional biomarkers, such as AFP and DCP, and risk factors, such as HBV and HCV infection, can enhance the diagnostic ability to identify patients with HCC from healthy controls. Our results suggest that circulating levels of miR-21 and miR-122 could be used either alone or in combination with other diagnostic tools as a first-line detection method of HCC.

Based on our review and analysis of the published data, we conclude that it is important to identify HCC-specific miRNAs in serum, plasma and to establish a signature that is capable of differentiating HCC from healthy controls, patients with hepatitis, and patients with cirrhosis. It might be helpful to us to clarify that studies have found that miRNAs are better at differentiating HCC from hepatitis or other liver injuries, such as cirrhosis. In our meta-analysis, the AUC increased from 0.77 for the single chronic hepatitis analyses for differentiating HCC from chronic hepatic disease to 0.82 for differentiating patients with HCC from healthy controls. The ROC curves also help determined the overall pooled sensitivity and specificity for the single miRNA analyses at various cut-off values. Using the optimal cut-off point, the sensitivity, and specificity were 70% and 73% for differentiating HCC from CH and 76% and 75% for differentiating patients with HCC from healthy controls (Table 2). These results demonstrate that single miRNA analyses have significantly improved our ability to differentiate between HCC patients and healthy controls compared with distinguishing HCC from chronic hepatic disease. It will also be necessary to clarify whether the differential expression of miRNAs that has been detected in HCC tumors and normal tissues is related solely to HCC. In the future, the most clinically pertinent candidate biomarkers need to be identified in more comprehensive reviews and meta-analyses of the available data about miRNAs as biomarkers in HCC. Stratified prospective studies of this important and controversial issue are also needed to consolidate the findings of these meta-analyses such that the results will be valuable to the greatest number of HCC patients. The ultimate goal is to correlate clinical variables with those available in public databases to develop novel biomarkers for improving the detection and diagnosis in patients with hepatitis and cirrhosis in early-stage HCC.

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Literature Cited


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