World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i15.3907

World J Gastroenterol 2016 April 21; 22(15): 3907-3936
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Hepatitis B virus: Global view

MicroRNAs as possible biomarkers for diagnosis and prognosis of hepatitis B- and C-related-hepatocellular-carcinoma

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Author contributions: Fiorino S conceived the study and coordinated the search activity of colleagues; Visani M and Acquaviva G contributed to the design of the review and coordinated the preparation of the first draft of manuscript; Masetti M and Lombardi R independently and in a parallel manner, performed the literature search, identified and screened the articles; Fornelli A and Bacchi-Reggiani ML supervised the literature search analysis; Grizzi F and Di Tommaso L contributed to write the first draft of manuscript; Tura A and Domanico A checked the accuracy of data collection; Zanello M and Mastrangelo L independently extracted and tabulated all relevant data from included studies by means of a standardized flow path and contributed to writing the manuscript; Fabbri C and Leandri P commented on drafts of the manuscript; Pession A and Bondi A supervised and critically reviewed the manuscript; Jovine E and Sabbatani S were responsible for the final approval of manuscript; de Biase D contributed to the design of the study and commented on drafts of the manuscript; all authors approved the final version of the manuscript.

Conflict-of-interest statement: The authors have no conflict of interest to report.

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Received: January 19, 2016
Peer-review started: January 20, 2016
First decision: February 18, 2016
Revised: March 5, 2016

Accepted: March 18, 2016
Article in press: March 18, 2016
Published online: April 21, 2016

Gastroenterol 2016; 22(15): 3907-3936 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i15/3907.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i15.3907

Abstract

Aim of the present review is to summarize the current knowledge about the potential relationship between miRNAs and hepatitis B virus (HBV)-hepatitis C virus (HCV) related liver diseases. A systematic computer-based search of published articles, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Statement, was performed to identify relevant studies on usefulness of serum/plasma/urine miRNAs, as noninvasive biomarkers for early detection of HBV and HCV-induced hepatocellular carcinoma (HCC) development, as well as for its prognostic evaluation. The used Medical Subject Headings terms and keywords were: "HBV", "HCV", "hepatocellular carcinoma", "microRNAs", "miRNAs", "diagnosis", "prognosis", "therapy", "treatment". Some serum/plasma miRNAs, including miR-21, miR-122, mi-125a/b, miR-199a/b, miR-221, miR-222, miR-223, miR-224 might serve as biomarkers for early diagnosis/prognosis of HCC, but, to date, not definitive results or well-defined panels of miRNAs have been obtained. More well-designed studies, focusing on populations of different geographical areas and involving larger series of patients, should be carried out to improve our knowledge on the potential role of miRNAs for HCC early detection and prognosis.

Key words: Hepatitis B virus; Hepatitis C virus; Hepatocellular carcinomas; Liver diseases; MicroRNAs; Review

Core tip: A systematic computer-based search of published articles was performed to identify relevant studies on usefulness of serum/plasma/urine miRNAs, as noninvasive biomarkers for early detection of hepatitis B virus and hepatitis C virus-induced hepatocellular carcinoma (HCC) development. Some serum/plasma miRNAs might serve as biomarkers for early diagnosis/prognosis of HCC, but, to date, not definitive results or well-defined panels of miRNAs have been obtained. More well-designed studies should be carried out to improve our knowledge on the potential role of miRNAs for HCC early detection and prognosis.

Fiorino S, Bacchi-Reggiani ML, Visani M, Acquaviva G, Fornelli A, Masetti M, Tura A, Grizzi F, Zanello M, Mastrangelo L, Lombardi R, Di Tommaso L, Bondi A, Sabbatani S, Domanico A, Fabbri C, Leandri P, Pession A, Jovine E, de Biase D. MicroRNAs as possible biomarkers for diagnosis and prognosis of hepatitis B- and C-related-hepatocellular-carcinoma. *World J*

INTRODUCTION

Hepatitis B (HBV) and Hepatitis C (HCV) viruses are well-known etiological factors for liver damage. It has been estimated that nearly 5% of world population is chronically infected with HBV (approximately 350 million of people)[1]. The global prevalence of HCV is about 2%, with 180 million people who persistently carrier this pathogen[2]. However, wide variations in HBV/HCV infection rates exist among different countries[3]. A significant percentage of chronic HBV and HCV carriers develop a necroinflammatory liver disease with different patterns of severity and course, ranging from persistent injury to cirrhosis, hepatic failure and hepatocellular carcinoma (HCC)[4]. Liver carcinogenesis is a multi-step process, which is characterized by the perturbation of several key and crucial cellular functions[5]. Cell-cycle control, apoptosis, senescence, growth, migration and energy production are the most important deregulated activities during cancer development both in liver and other organs[6,7]. HCC is the sixth most frequent malignancy in the world, and, irrespective of the improvement in diagnostic approaches and in treatment of this neoplasm, it still represents the second cause of cancer death, because of its poor outcome[8-10]. The high morbidity and mortality rates of this type of cancer require the adoption of more specific methods and more effective strategies for HCC diagnosis and treatment. To date, HCC detection is generally based on imaging techniques, including ultrasonography, Computed Tomography (CT) and Magnetic Resonance (MRI) in association of laboratory tests (serum α-feto protein) and/or histopathology (*i.e.*, liver biopsy)[11]. All these diagnostic tools present potentially limiting factors, including their costs, availability and reproducibility[12]. Therefore, in the last years, some serum or tissue biomarkers have been developed to be used in clinical practice, such as microRNAs (miRNAs). These molecules are small (19-23 nucleotides) single-stranded non-coding RNAs, able to silence endogenous messenger RNA (mRNA) transcripts[13,14]. MiRNAs modulate gene expression, by degrading or inhibiting mRNAs, therefore they decrease or suppress protein translations, at post-transcriptional level. In the last years, an increasing number of studies have investigated the role of miRNAs in the regulation of different cellular processes, including energy production, protein synthesis, proliferation, differentiation and apoptosis[15]. It is well-known that each natural tissue harbours peculiar profiles of miRNAs expression. In addition, characteristic perturbed miRNA patterns have been described in

different liver diseases, ranging from chronic hepatitis to cirrhosis and HCC[16-19]. The identification of subjects with HCC at early stages, before the development of clinical signs and symptoms, represents a pressing need to improve long-term prognosis of these individuals[20].

The aim of the study is to review the available data describing: (1) potential usefulness of serum/plasma/urine miRNAs that may serve as novel non-invasive biomarkers for early detection of HBV and HCV-induced HCC development, as well as for prognostic assessment in these patients; and (2) perturbation of miRNAs expression in liver tissue of HBV- and HCV-related HCC.

SEARCH STRATEGY AND SELECTION OF STUDIES

A systematic computer-based search of published articles, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement[21], issued in 2009, was conducted through Ovid interface, in order to identify relevant studies on the usefulness of serum/plasma/urine miRNAs that may serve as novel noninvasive biomarkers for early detection of HBV and HCV-induced HCC development, as well as for prognostic assessment in these patients.

The literature review was performed in March 2015. The following electronic databases were used: MEDLINE (January, 2000 to March, 2015) and the Cochrane Library (until the first quarter of 2015) for all relevant articles. The search strategy and the search terms were developed with the support of a professional research librarian. The search text words were identified by means of controlled vocabulary, such as the National Library of Medicine' s MESH (Medical Subject Headings) and Keywords. Our review assessed the perturbation of miRNAs expression in HBV and HCV related liver diseases. The used MESH terms and keywords were: "HBV", "HCV", "hepatocellular carcinoma", "microRNAs", "miRNAs", "diagnosis", "prognosis", "therapy", "treatment".

The inclusion criteria for our analysis were: (1) studies investigating liver-originated miRNAs expression in patients with HCC and performed with the aim to improve the diagnosis of this malignancy or to evaluate their potential role as tools for assessing prognosis and efficacy of treatment for patients, suffering from this neoplasm; (2) study samples were represented by serum/plasma, urine and hepatic tissue specimens and obtained in these studies directly from the investigated liver lesions or extracted from extra-lesional material (*e.g.*, plasma, sera); (3) each of included studies contained at least 10 subjects for group; and (4) articles which were reported in English, as peer-reviewed, full-text publications.

On the other hand, exclusion criteria were: (1) conference abstracts, case reports, editorials, articles not published as full reports; (2) duplicates; and (3) studies performed in cell lines or in animal models.

The PubMed "related articles" features and the reference lists of retrieved articles were also searched to find additional pertinent studies. If a study was considered potentially eligible by either of the two reviewers, the full-text of this study was further evaluated. Full-text assessment was performed according to eligibility criteria developed to systematically include studies into this review. Therefore, we excluded all trials, reporting patients with HBV or HCV and HIV co-infection.

STUDY SELECTION

Two authors (M.M.. and R.L.), independently and in a parallel manner, performed the literature search, identified and screened relevant articles, based on title or title and abstract. If a study was considered potentially eligible by either of the 2 reviewers, the full article of this research was collected for further assessment. Other two authors (M.Z. and L.M.) independently extracted and tabulated all relevant data from included studies by means of a standardized flow path, according to the Cochrane handbook section 7.3a checklist of domains. The following information was obtained from each study, by means of a predefined data extraction form, including: first author's name, study design, inclusion and exclusion criteria, year of publication, country of origin, ethnicity, matching criteria, number of cases and controls, diagnostic methods to detect each malignancy, HCV detection assays. The accuracy of data collection was checked by A.T. and A.D. and any disagreements concerning the results were settled by consensus between all authors. With the purpose to prevent multiple inclusions of the same data, we searched the presence of possible duplicates, examining the first author's name as well as the place and the period of subjects' enrolment. When different versions of the same study were detected, only the most recent one was considered.

Bearing in mind the purpose of our review, the characteristics and the wide heterogeneity of the identified reports (such as the difference in study designs as well as in end points and the limited number of screened miRNAs, recognized as potentially involved in HCC development) and the lack of a definite and appropriate knowledge of miRNAs profiles, associated with diagnosis and outcome of this malignancy, sensitivity and subgroup analyses of identified articles were considered inappropriate. Therefore, no qualitative analysis and quantitative assessment of these studies was performed and all articles, meeting the predefined inclusion criteria, were included in our review. We decided to search the miRNAs, that were reported at least five or more times in available studies.

NUMBER OF STUDIES REPORTING MIRNAS EXPRESSION IN HBV- AND HCV-RELATED HCC

The search of Medline and Cochrane Library identified a total of 2778 citations. Among these, 2579 were excluded after a preliminary review of the titles and/or abstracts. The full text of the remaining 199 articles was considered for a more detailed assessment. The full-text of these 199 articles was reviewed to determine whether they met our inclusion and exclusion criteria, 127 studies were excluded because of they were reviews, duplicates or not relevant to the miRNA expression in HCC. Finally, 72 reports were included in this systematic review and subdivided into three groups (Table 1, Table 2, Table 3, Table 4 and Table 5 and Supplementary Tables 1-3): (1) studies investigating miRNAs patterns in patients with only HBV-related HCC[22-64]; (2) studies showing miRNAs profiles in individuals with HBV and HCV-related HCC[65-85]; and (3) studies reporting miRNAs patterns in subjects with only HCV-related HCC[86-92].

The first subgroup included 43 articles (1): 36 performed in China, 3 in South Korea, one in Taiwan, one in India, one in Turkey and one in Italy; In the second subgroup 21 articles were available (2): 6 were carried out in Japan, 4 in China, 4 in Italy, 2 in United States, 2 in Taiwan, one in South Korea, one in France and one in Germany; and the subgroup consisted of 7 studies (3): 3 articles were performed in Egypt, 2 in Germany, one in China and one in Turkey.

Some studies enrolled only HCC patients, without comparison group, whereas most of them included controls as healthy subjects, patients with viral-related chronic hepatitis or cirrhosis, as well as hepatitis B surface antigen (HBsAg) positive subjects (defined as "asymptomatic carries" because of the evidence of liver active disease). Most of HCC patients included in these reports were male. In addition, a high heterogeneity among the studies is evident as reported in Tables 1-5 (and in Supplementary Tables 1-3), mainly due to differences in scope, end-points, reference control group, starting material and molecular techniques. In particular, some studies enrolled patients with HBV- or HCV-related HCC and the results, concerning the miRNA profiles, were not characterized on the basis of the viral infection etiology.

In Tables 2 and 4 we have tried to hypothesize two putative panels of deregulated miRNAs in HBV- and HCV-related HCCs, considering only miRNAs observed deregulated (with the same expression) in at least three papers. As shown in Table 2, in HCC patients with HBV-related infection, seven miRNAs (miR-221, miR-21, miR-222, miR-122a, miR-224, miR-18a and miR-223) have been observed as consistently up-regulated and only one miRNA (miR-101) has been described as down-regulated. Intriguingly, even if the vast majority of papers have obtained concordant results about the expression of these miRNAs, some studies have reported a different regulation of some of aforementioned miRNAs (miR-21, miR-222, miR-122a, miR-101)[22,28,61,93] (Table 2).

In Table 4, we have reported miRNAs observed deregulated in studies enrolling HCC patients with HBV and HCV-related infection in at least three papers. Two miRNAs (miR-21 and miR-224) were observed consistently up-regulated and two miRNAs (miR-130a and miR-195) as down-regulated (Table 4).

MIRNAS IN THE ASSESSMENT OF HCC DIAGNOSIS AND PROGNOSIS

Only a small number of circulating miRNAs has been assessed at least five or more times as potential and useful biomarkers in HCC diagnosis in the identified studies, because they have been reported as deregulated in cirrhosis and during development of hepatic malignancy. In particular, among the tested miRNAs profiles, miR-21, both in serum/plasma[45,49,56,61,63,82] and in liver cancerous tissue[24,29,72,77,83,87], miR-122 both in serum/plasma[43,49,50,55-57,71,88,93] and tissue samples[46,67,69,80,83], miR-125a/b in serum/plasma sample[30,43,90] and in tissue specimens[25,68,75,78,83,91], miR-199a/b in serum/plasma sample[50,65,76] and in tissue specimens[34,69,75,83,91], miR-221 both in serum plasma[49,52,88,94] and in hepatic specimens[29,63,68,69,83], miR-222 both in serum/plasma[49,52] and hepatic specimens[22,72,83], miR-223 both in serum/plasma[30,32,43,49] and in liver tissue[69], miR-224 both in serum plasma[45,57] and tissue samples[29,40,68,72,75] have been assessed more widely in comparison to other miRNAs. According to the reported results, these miRNAs represent the most important candidate biomarkers in term of diagnostic efficiency among the assessed ones, to compare circulating miRNA expression between HCC patients and healthy people as well as between subjects with liver malignancy and individuals with hepatic injury, such as persistent hepatitis or cirrhosis. Nevertheless, to date, no definitive conclusions may be drawn.

MIRNAS IN NON-VIRAL ASSOCIATED HUMAN HEPATOCARCINOGENESIS

Despite a wide series of efforts to investigate the roles of miRNAs both in malignant and in non-malignant liver diseases, little is known about the roles of miRNAs in non-viral associated human hepatocarcinogenesis, including non-alcoholic fatty liver disease (NAFLD) and/or non-alcoholic steatohepatitis (NASH), alcohol-related HCC, iron overload and primary biliary cirrhosis. Most of available studies have been performed in animal models, mimicking these pathological conditions. To date, only a small number of reports have been carried out to examine miRNA expression profiles and their potential impact, during the development

Table 1 miRNAs patterns in studies enrolling hepatocellular carcinoma patients with hepatitis B virus-related infection

References, period and state	Characteristics of the study	miRNAs Up-regulated	miRNAs Down-regulated	Conclusions
Bandopadhyay M, *BMC Cancer*, 2014 India Period: NR	Tissue samples obtained from: -16 healthy subjects -16 patients with advanced liver diseases (HBV positive cirrhosis and HCC)	ND	Decreased miR-21, miR-222 and miR-145 expression in patients with advanced liver diseases and HCC in comparison with healthy individuals	Differential modulation of miRNAs expression by HBx protein
Cheong JY, *J Korean Med Sci*, 2014 Korea Period: NR	Serum samples from: 1439 individuals with either past/present evidence of HBV infection: -HCC: 417; -LC: 305; -CHB: 313; -SR: 404.	NR	Higher rate of HBV persistence after infection subjects with miR-604 rs2368392 T allele in comparison with miR-604 rs2368392 C allele. Patients with miR-604 T allele may have a higher risk for HBV chronicity Higher rate of the miR-604 T allele in the chronic carrier without HCC	pre-miR-604 rs2368392 polymorphism might confer genetic susceptibility to the occurrence of HCC in HBV related chronic liver disease, and HBV persistence after HBV infection
Connolly E, *The American Journal of Pathology*, 2008 China Period: NR	Human HCC samples and matched non-tumor liver tissue (19 sets) were obtained from surgical resections of anonymous donors	Up-regulation of miR-17-92 (miR-17, miR-19a, miR-20, and miR-92) and miR-21 occurs in precancerous stages of liver disease and in HCC in comparison with normal liver	NR	The combination of assays presented in the present study supports a role for the miR-17-92 polycistron (all six members) or miR-21 in the maintenance of the malignant transformation of hepatocytes
Coppola N, *PLoS One*, 2013 Italy Period: April 2007 - March 2011	Tissue samples obtained from: twenty-seven consecutive HBsAg/anti-HBe/HBV-DNA-positive Caucasian patients who were naive to nucleos(t)ide analogues and interferon therapy	Higher miR-125a-5p liver concentrations observed in patients with HBV-DNA plasma levels > 10^3 IU/mL	NR	In HBsAg/anti-HBe-positive patients, the liver miR-125a-5p level correlated with liver and plasma HBV-DNA values and was associated to a more severe disease progression
Dang YW, *Asian Pac J Cancer Prev*, 2014 China Period: March 2010 and December 2011	89 pairs of HCC formalin-fixed paraffin-embedded and their adjacent tissue 74/89 pairs were obtained from HBV-related HCC samples	NR	Remarkably downregulation of miR-152 expression in HCC compared to that in adjacent hepatic tissues Lower expression was observed in HBV positive group than in the negative one	miR-152 underexpression is associated with hepatocarcinogenesis, acting as a tumor suppressor miRNA, its lack is related to the progression of HCC through deregulation of cell proliferation, motility and apoptosis

Fan MQ, *Journal of Experimental and Clinical Cancer Research*, 2013 China Period: 2002 -2007, patients were followed until December 2010	100 patients with HCC, undergoing LT 95/100 patients with HBV related cirrhosis Specimens obtained from formalin-fixed paraffin-embedded tissue	NR	Down-regulation of miRNA 20a	miR-20a is decreased in HCCs and correlates with HCC recurrence and prognosis. Its down-regulation increases the proliferation abilities of HCC cells. miR-20a may represent a novel Potential therapeutic target and biomarker for survival of HCC patients
Fu Y, *Oncol Letters*, 2013 China Period: NR	Serum and tissues (paired tissue specimens from 25 HCC tissues and adjacent noncancerous hepatic tissues (20 HBV-related HCC) were obtained from patients undergoing surgical resection and compared with 20 healthy subjects	miR-101 is upregulated in human HBV-related HCC serum	miR-101 is downregulated in human HBV-related HCC tissues	Serum miR-101 expression was closely associated with tumoral size of HCC-patients and provides a promising biochemical marker of HBV-related HCC
Gao P, *Hepatology*, 2011 Hong Kong Period: NR	Formalin fixed, paraffin embedded materials obtained from: -16 patients with dysplastic nodules -29 HCC nodules from 24 patients	Up-regulation of miR-224 in pre-malignant DNs Up-regulation of miR-10b, miR-21, miR-221, and miR-224 in the small HCCs	Down-regulation of miR-145 and miR-199b in pre-malignant DNs Down-regulation of miR-145 and miR-199b in the small HCCs	miRNA deregulation is an early event and accumulated throughout the various steps of HBV-associated hepatocarcinogenesis. Down-regulation of miR-145 and miR-199b and up-regulation of miR-224 were frequently observed in pre-malignant DNs and these changes persisted throughout HCC development miR-145 is a candidate tumor suppressive miRNA and may play an important role in HCC development
Giray BG, *Mol Biol Rep*, 2014 Turkey Period: NR	Plasma samples from: -66 HBV-positive patients (CHB: 24, cirrhosis: 22, HCC: 20) -28 healthy controls	mi125b-5p up-regulation in CHB, cirrhosis and HCC in comparison to healthy controls	miR-223-3p down regulation in CHB, cirrhosis and HCC in comparison to healthy controls	miR-125-5 p and miR-223 -3p could be used as novel non-invasive biomarkers of HBV-positive HCC in very early, even at CHB stage of liver disease
Gu H, *Mol Cell Biochem*, 2013 China Period: April 2001 - March 2009	Tissue samples obtained from 108 patients with HCC, undergoing surgical resection. HBsAg +: 92; HBsAg -: 16	Up-regulation of miR-372 associated with significant poorer recurrence-free survival and overall survival	NR	miR-372 may serve as a potent prognostic marker for tumor recurrence and survival of HCC patients as well as a promoter of tumorigenicity of HCC and may be a prospective therapeutic target for this malignancy

Gui J, *Clinical Science*, 2011 China Period: November 2008 - January 2010	Serum samples from: 25 HBV-positive patients (LC: 10, HCC: 15) -10 age-matched healthy controls	Up-regulation of miR-885-5p, miR-574-3p, miR-224, miR-215 and miR-146a in the HCC and LC patients	NR	miR-885-5p is significantly elevated in the sera of patients with liver pathologies miRNAs could serve as novel complementary biomarkers for the detection and assessment of liver pathologies
Han Y, *PLoS One*, 2013 China Period: -September 2009 - June 2010 -October 2009 to September 2011	Serum samples from: 1,012 healthy controls, 302 HBV natural clearance subjects, 316 ASCs, 316 patients with CHB, 358 HBV-infected patients with LC, and 1,021 HBV-infected patients with HCC Pri-miR-34b/c rs4938723 HBV-HCC patients: 311 HBV-infected subjects without HCC: 210 Pre-miR-196a2 rs11614913 HBV-HCC patients: 255 HBV-infected subjects without HCC: 170	NR	NR	Association of pri-miR-34b/c rs4938723 with a significant increased risk of HCC, mainly in women No statistically significant association of pre-miR-196a2 rs11614913 with HCC risk. pre-miR-196a2 rs11614913 may enhance the effect of primiR-34b/c rs4938723 in women rs4938723 CC genotype and rs11614913 TC genotype might predispose the host to immune selection of T1674C/G, and G1896A, respectively The rs4938723 effect on HCC risk can be seriously affected by the HBV mutations
Hou J, *Cancer Cell*, 2011 China Period: NR	Tissue samples obtained from 40 HCC patients with CHB	NR	Consistent miR-199a/b-3p decrease in HCC, and its reduction significantly correlates with poor survival of HCC patients	miRNomes of human liver and HCC and contributes to better understanding of the important deregulated miRNAs in HCC and liver diseases
Huang J, *Hepatology*, 2010 China Period: NR	20 HBV-related HCC tissues and the corresponding nearby noncancerous livers	NR	Down-regulation of miR-152 in human HBV-related HCC Tissues	Tumor suppressive role of miR-152 in the epigenetic aberration of HBV-related HCC and the potential development of miRNA-based targeted approaches for the treatment of HBV-related HCC

Huang YH, *PLoS One*, 2012 China Period: July 1998 - Aug 2004	Tissue samples obtained from: 228 patients with HCC, 12 with known better and poorer prognosis subjected for the first-step (pilot) study; 6 patients had a RFS time for more than 5 yr (better prognosis) and 6 had rapid relapse within six-month after operation (poorer prognosis)	High expression levels of miR-30c, miR-155, miR-432, miR-15b, and miR-30b associated with shorter RFS High miR-15a, miR-486-3p, and miR-381 expression significantly predicted a longer RFS High expression level of miR-29a, miR-486-3p, and miR-876-5p significantly predicted a longer OS	NR	Significant prognostic miRNA predictors identified through examination of miRNA expression levels in paraneoplastic liver tissues. Functional analysis of miR-155, suggested that the prognostic miRNA predictors identified under this strategy could serve as potential molecular targets for anticancer therapy
Jiang R, *Clin Cancer Res*, 2011 China Period: January 2001 - August 2009	Liver tissue obtained from: 116 HBV-related HCC patients 48 subjects with benign conditions	up-regulation of miR-22 in male tumor adjacent tissue	NR	Overexpression of miR-22 in male tumor adjacent tissue associated with down-regulated ERa expression, potentially causing the attenuation of the protective effect of estrogen and inducing increased IL-1a expression. These results may explain the high incidence of HBV-associated HCC in the male population
Kim HY, *J Med Virol*, 2014 South Korea Period: NR	Serum samples obtained from: 1439 Korean patients with either past or present HBV infection, -404 control subjects with spontaneous Recovery; -1035 subjects with chronic HBV (313 with chronic hepatitis B, 305 with liver cirrhosis, 417 with HCC)	NR	NR	Protective effect of miR-196a-2 rs12304647 CC genotype against development of HCC in comparison to the AA or AC genotypes in patients with chronic hepatitis and cirrhosis
Kwak MS, *PLoS One*, 2012 South Korea Period: January 2001 - August 2003	1439 Korean subjects with past or persistent HBV infection: SR: 404 CHB: 313 chronic LC: 305 HCC : 417	Micro RNAs-371-372-373 (miRNAs-371-373), originating from the same pri-miRNA transcript, are upregulated in HCC	NR	Among chronic carriers and liver cirrhosis patients, the A allele of rs3859501 and the haplotype pri-miRNAs-371-373_ht2 were more protective to HCC than other genotypes and haplotypes
Lan SH, *Hepatology*, 2014 Taiwan Period: NR	Tissue and specimens, obtained from patients from Taiwan patients with HCC	The level of autophagy was low and inversely Correlated with miR-224 expression only in HBV associated HCC	NR	A noncanonical pathway links autophagy, miR-224, Smad4, and HBV-associated HCC

Li J, *Biochemical and Biophysical Research Communications*, 2011 China Period: NR	Serum samples of HCC were obtained from 46 patient (30 HBsAg positive) The healthy sera were collected from 50 age-matched healthy individuals who serves as normal controls	Serum miR-221, up-regulation in HCC, correlates with tumor size, cirrhosis and tumor stage	NR	Serum miR-221, upregulated in HCC, can provide predictive significance for prognosis of HCC patients
Li L, *Digestive Diseases and Sciences*, 2012 China Period: NR	Serum samples obtained from: HCC: 101 (HBsAg +) CLD and cirrhosis: 30 Healthy controls: 60	miR-18a significantly up-regulated in HBV-related HCC, chronic hepatitis or cirrhosis than those in healthy Controls	NR	Significant increase of elevated serum miR-18a in the patients of HBV-related HCC. It might serve as a novel noninvasive biomarker to distinguish patients with HBV-related HCC from healthy subjects, and further from those with HBV-related chronic hepatitis or cirrhosis
Li LM, *Cancer Research*, 2010 China Period: September 2007 - July 2008	Serum samples from: -120 HCC-affected individuals; -135 HBV carriers; -48 HCV carriers; -210 controls	Serum up-regulation of miR-375, miR-92a, miR-10a, miR-223, miR-423, miR-23b/a, miR-342-3p, miR-99a, miR-122a, miR-125b, miR-150, and let-7c. in HBV positive patients with HCC in comparison with healthy controls	NR	The expression profile of serum miRNAs can serve as novel non-invasive biomarkers for the diagnosis of HBV infection and HBV positive HCC. The use of 3 miRNAs: miR-25, miR-375, and let-7f could be used to separate HCC cases from controls, miR-375 alone had high specificity and sensitivity in HCC prediction
Li T, *Oncology Reports*, 2014 China Period: NR	Tissue and plasma obtained from: 31 patients with HBV-related HCC 31 age- and gender-matched CHB patients	Tissue miRNA-21, miRNA-221, miRNA-148b and miRNA-186 over-expression	Tissue miRNA-99a, miRNA-27b, miRNA-378a, miRNA-378e and miRNA-30 down-regulation Tissue and plasma miRNA-139 down-regulation in HCC *vs* non-HCC patients	miRNA-139 is downregulated in both cancerous tissue and plasma of HCC. The plasma miRNA-139 is a possible diagnostic biomarker for identifying HCC patients while combined with other biomarkers, it is also a prognostic factor for indicating patient survival

Li W, *Int J Cancer*, 2008 China Period: NR	Specimens obtained obtained from: 78 human primary hepatocellular carcinoma (68 HBsAg +) and matched noncancerous liver tissues	84 miRNAs identified with deregulated expression in tissues from HCC patients. 69/84 miRNAs resulted differentially expressed in normal or non-tumour liver tissue *vs* cancerous hepatic tissue with 29 miRNAs up-regulated -Noncancerous *vs* normal liver tissue: 27 miRNAs differentially expressed, with 14 up-regulated in noncancerous liver specimens -HCC *vs* normal tissue: 55 differentially expressed miRNAs, with 29 up-regulated in HCC tissues	84 miRNAs identified with deregulated expression in tissues from HCC patients. 69/84 miRNAs resulted differentially expressed in normal or non-tumour liver tissue *vs* cancerous hepatic tissue with 40 miRNAs down-regulated Noncancerous *vs* normal liver tissue: 27 miRNAs differentially expressed, with 13 down-regulated in noncancerous liver specimens -HCC *vs* normal tissue: 55 differentially expressed miRNAs, with 26 down-regulated in HCC tissue	miRNA signature identified as a HCC diagnostic discriminator from both noncancerous and normal liver tissues. This is the first report to identify single miRNA correlated to the HCC prognosis, *i.e.*, miR-125b as a HCC survival predictor
Liu AM, *BMJ Open*, 2012 China Period: 1990-2007	Serum and Cancerous/non tumors tissue samples collected from: - 96 cirrhotic patients with HCC (84 HBsAg positive) undergoing hepatectomy (exploration phase) -29 hepatitis B carriers, 57 patients with HCC and 30 healthy controls (validation phase)	Exploration phase in resected tumour/ adjacent non-tumour tissues: Upregulated miR in the AFP-low (< 400 ng/mL) HCC subgroup: miR-9, -9*, -15b, -21, -34c, -96, -130b, -183, -188, -196b, -216, -224, -301 and -324-5p Upregulated miR in all HCC samples of varying serum AFP levels: miR-15b, -21, -130b, -183, -224 and -301	Decreased serum miR-224 and miR-301 levels in HCC patients post-surgery in comparison with pre- surgery. Slight reduction of serum miR-15b and miR-130b levels in HCC patients post-surgery in comparison with pre- surgery	The combined miR-15b and miR-130b classifier is a serum biomarker with clinical value (high sensitivity and accuracy) for HCC screening. This classifier also identified early-stage HCC cases that could not be detected by AFP
Liu Y, *PLoS One*, 2012 China Period: January 2006-December-10 Controls screened for the HBV/HCV markers in 2004 and 2009	Serum samples collected from: - 1300 HBV positive HCC cases, -1344 HBV persistent carriers; - 1344 subjects with HBV natural clearance people These patients were matched to the HCC cases on age and gender	NR	NR	A genetic variant in the promoter region of miR-106b-25 cluster might provide a protective effect against chronic HBV infection but an increased risk for HCC in HBV persistent carriers by affecting the expression of miR-106b-25 cluster A to G base change of rs999885 may have a protective effect on the probability to develop chronic HBV infection, but increased the risk of HCC in HBV persistent carriers

Liu Y, *J Med Virol*, 2014 China Period: April 2008 - November 2011 Newly diagnosed HCC patients included from January 2006 - December 2010 HBV carriers and patients with signs oif past HBv infection, screened from 2004 to 2009	Samples obtained from: 29 pairs of HCC and adjacent noncancerous liver tissues	NR	In noncancerous liver tissues, subjects with a CA genotype exhibited significantly lower expression level of pri-miR-122 than those carrying the CC genotype. Positive or inverse correlation between the expression levels of pri-miR-122 and mature miR-122 were observed in HCC tissues or oncancerous tissues, respectively	The C to A base change of rs4309483 may alter the expression of miR-122, thus providing protective effect from chronic HBV infection but an increased risk for HCC in HBV carriers
Meng FL, *Med Oncol*, 2014 China Period: January 2009 - December 2011	Tissue obtained from: 84 patients with HBV-related HCC 31 with CLDs 46 with healthy controls	Tissue miR-24-3p over-expression in HCC in comparison with healthy controls and CLD	NR	The combination of serum miR-24-3p and AFP improves the diagnostic accuracy for HCC prediction compared to each biomarker alone. High serum miR-24-3p level is an independent predictor of overall survival and disease free-survival. In patients with HBV-related HCC
Qi, F, *PLoS One*, 2014 China Period: NR	Serum samples obtained from 331 patients with HBV-related HCC in either intermediate or advanced stage of disease without surgery	NR	NR	miR-106b-25 cluster plays oncogenic roles in cancers through influencing tumor growth, cell survival, and angiogenesis. rs999885 is associated with prognosis of intermediate or advanced HBV-related hepatocellular carcinoma (HCC) . rs999885 variant could influence miR-106b-25 expression and the expression levels of miR-106b-25 were significantly higher in AG/GG carriers than that in AA carriers G allele of rs999885 may provide a protective effect on the prognosis of intermediate or advanced HCC in Chinese

Qi P, *PLoS One*, 2011 China Period: NR	Study divided into four phases. Serum samples obtained from: (Ⅰ phase) -10 HBV-positive HCC patients and -10 age- and sex-matched healthy subjects; (Ⅱ phase) before surgery, sera from another 48 HBV-positive HCC patients, from 48 chronic HBV infection patients without HCC and 24 age- and sex-matched healthy subjects; (Ⅲ phase) 14 HCC patients before and after surgery, (Ⅳ phase) correlation between the expressions of candidate serum miRNAs with clinical parameters of HCC patients	Up-regulation of serum miR-122, miR-222 and miR-223 in HCC patients in comparison with healthy controls	Down-regulation of serum miR-21 in HCC patients in comparison with healthy controls	Serum miR-122 might serve as a novel and potential biomarker for detection of HCC in healthy subjects and it might serve as a novel biomarker for liver injury but not specifically for detection of HCC in chronic HBV infection patients
Tan Y, *PLoS One*, 2014 China Period: August 2010 - June 2013	Serum samples obtained from: HCC: 261, LC: 133; Healthy controls:173	up-regulation: miR-190b; miR-141-3p; miR-4532; mir-6127; miR-99b-3p; miR-1228-5p between HCC and healthy controls up-regulation: miR-206, mir-1285-1-p5, miR-10a-5p ,miR-511-5p, miR-433-3p between HCC and cirrhosis groups	Down-regulation: miR-30a-3p; miR-199a-5p ; let-7f-5p ; miR-122-5p ; miR-192-5p; miR-98-5p; miR-574-3p; miR-30e-3p; miR-6852-5p between HCC and healthy controls Down-regulation: miR-100-5p; miR-483-5p, miR-584-5p; miR-28-5p miR-30b-5p; miR-30c-5p ; miR-26a-5p; miR-4454; let-7e-5p; let-7c-5p; miR-4433b-5p between HCC and cirrhosis groups	A serum panel of miRNA with considerable clinical value in HCC diagnosis was identified. miR-206, miR-141-3p, miR-433-3p, miR-1228-5p, miR-199a-5p, miR-122-5p, miR-192-5p, and hsa-miR-26a-5p as potential circulating markers for HCC diagnosis
Wei X, *Cellular Signalling*, 2013 China Period: NR	Serum and tissues (paired tissue specimens from HBV-related HCC tissues and adjacent noncancerous hepatic tissues)	NR	miR-132 is more frequently downregulated in HBV-positive HCCs tumor tissues than in adjacent noncancerous tissues and has a significant inverse correlation with HBx expression in HBV-related HCCs	miR-132 may play a tumor-suppressive role in HBV-related HCC development. Serum miR-132 levels are closely correlated with miR-132 expression levels in tumor tissues. miR-132 may be a promising biochemical marker and may have therapeutic applications in HBV-related HCC

Wen Y, *Int J Cancer*, 2015 China Period (3 phases): December 2010- December 2011 January 2010- December 2012 2004-2005	Multicenter, three-phase study to screen liver-originated HCC-associated plasma miRNAs in both plasma and tissue samples The training set consisted of 35 HCC cases and 50 cancer-free HBV carriers who were frequency matched for age and sex, whereas the validation set consisted of 32 HCC cases and 32 matched cancer-free HBV carriers	Up-regulation of miR-221, miR-222, miR-31	Down-regulation of miR-126, and miR-122a miR-223	miR-223 may represent a potential target in cancer therapy because it regulates Stathmin 1
Xiang Y, *Mol Biol Rep*, 2012 China Period: December 2009 - February 2011	Specimens obtained from: -100 patients with HCC (73 HBV positive); -100 patients with CHB; -100 healthy subjects	NR	NR	miRNA 499 polymorphisms is associated with susceptibility in HBV-related HCC in Chinese population. The risk of HCC development is increased in patients with miR-399 C/C was higher in comparison with subjects with miR 499 T/T
Xie Y, *Cancer Biology and Therapy* China Period: NR	Specimens and tissue samples obtained from: -67 HBV-HCC patients, -61 HBV-LC patients, -79 CHB patients, -30 Healthy subjects	Elevated miR-101 levels in the sera and liver tissues of HBV-LC patients and decreased in HBV-HCC patients	NR	Serum miR-101 as a potential biomarker for monitoring the development of HBV-HCC from HBV-LC and the development of HBV-LC from CHB
Xing TJ, *Genetics and Molecular Research*, 2014 China Period: NR	Serum samples obtained from: HCC: 20 patients; LC: 20 patients; CHB: 29 patients; ASC: 20 patients; Healthy controls: 20	Increased miRNA-122 levels in patients with HCC and CHB *vs* patients with HC, LC, and ASC	lower miRNA-29 serum levels in LC patients than those in the healthy controls	The elevation in miR-122 was correlated with liver damage in CHB patients and with the pathogenesis of liver cancer in HCC patients. The decrease in miR-29 expression was related to the incidence of liver fibrosis
Xu J, *Molecular Carcinogenesis*, 2011 China Period: NR	Serum samples obtained from: -101 patients with advanced primary HCC (78 HBsAg +), -48 patients with CHB, -89 healthy controls	Higher serum miR-21, miR-122, and miR-223 levels in patients with HCC or CHB, compared with healthy controls	NR	Serum miR-21, miR-122 and miR-223 are elevated in patients with HCC or chronic hepatitis and these miRNAs have strong potential to serve as novel biomarkers for liver injury but not specifically for HCC

Zhang H, *WJG*, 2012 China Period: NR	Serum samples obtained from patients with: -34 CHB, -20 NASH -34 healthy donors Serum samples from 10 CHB patients and 10 controls were subjected to miRNA microarray analysis to obtain serum miRNA profiles	Up-regulation of miR-122, miR-138, miR-638, hsv1-miR-H1, miR-575, miR-572, kshv-miR-K12-3, miR-1915, miR-623, miR-1268, miR-939, miR-498	Down-regulation of: miR-421, miR-598, miR-155, miR-424, miR-23b, miR-195, miR-487b, miR-224, miR-495, miR-181c, miR-654-3p, let-7e, miR-382, miR-171, miR-128, miR-625, miR-30e1, miR-139-5p, miR-30c, miR-744, miR-374b, miR-376c	Serum levels of miR-122, -572, -575, -638 and -744 are deregulated in patients with CHB or NASH. The levels of these miRNAs may serve as potential biomarkers for liver injury caused by CHB and NASH
Zhang T, *Neoplasia*, 2013 China Period: NR	Samples obtained from cancerous tissues of thirty-three patients with HBV-related HCC and their corresponding nearby nontumorous liver tissues	NR	HBx-mediated downregulation of miR-205 through the induction of miR-205 promoter hypermethylation	HBx is able to inhibit tumor suppressor miR-205. miR-205 may be useful in the treatment of HCC
Zhang ZZ, *WJG*, 2011 China Period: NR	miRNA expression profiles obtained from 78 HCC patients from Gene Expression Omnibus study	8/ 10 differentially expressed miRNAs common to the AHB infection and HCC datasets were inversely changed, only 3/8 differentially expressed miRNAs common to the chronic HBV infection and HCC datasets exhibited opposite alterations	8/ 10 differentially expressed miRNAs common to the AHB infection and HCC datasets were inversely changed, only 3/8 differentially expressed miRNAs common to the chronic HBV infection and HCC datasets exhibited opposite alterations	miRNA level is correlated in HBV infection and HCC
Zhao Q, *PLoS One*, 2014 China Period: February 2012 - January 2013	Serum and cancerous and non-tumors tissue samples obtained from: -66 patients with HBV-related HCC patients -11 hepatic hemangioma Patients	Up-regulation of miR-545/374a cluster in HBV-HCC tissue	NR	The overexpression of miR-545/374a cluster is partially responsible for a poor prognosis, and monitoring sera levels of miR-545/374a may be a useful diagnostic marker for HCC
Zhou J, *J Clin Oncol*, 2011 China Period: August 2008 - June 2010	934 blood samples, from healthy subjects patients with CHB, cirrhosis or HCC	High expression levels of miR-192, miR-21, and miR-801 in patients with HCC compared with those in the control group	Low expression levels of miR-122, miR-223, miR-26a, and miR-27a observed in patients with HCC compared with those in the control group	miR panel with considerable clinical value in diagnosing early-stage of HBV-related HCC
Zhu HT, *PLoS One*, 2012 China Period: January 2004 - December 2008	Tissue obtained from:	Up-regulation in microdissected HCC tissue with early recurrence: miR-29a-5p, miR-27b*, miR-204, miR-29c, miR-10b, miR-	Down-regulation in microdissected HCC tissue with early recurrence:	In the multivariate analyses, miR-29a-5p was identified as an independent factor for tumor recurrence. miR-29a-5p might be a useful marker for the prediction of early tumor recurrence after HCC resection, especially in BCLC 0/A stage HCCs

	266 patients, undergoing curative liver resection for HCC 48 patients subdivided into: -group with early recurrence (24) -group without early recurrence (24) 218 patients enrolled into: training (106) and validation (112) cohort	196b, miR-216a, miR-217, miR-517a, miR-518e, miR-518f, miR-518b, miR-519a, miR-519d, miR-522, miR-486-5p, miR-181c, miR-210, miR-215 Up-regulation in microdissected non-tumorous liver tissue with early recurrence: miR-486-5p, miR-181c, miR-193b*, miR-643, miR-409-3p, miR-424*, miR-139-3p, miR-766	miR-193b*, miR-643, miR-22, miR-15b, miR-505, miR-107, miR-142-5p, miR-135a, miR-34c-5p, miR-98, miR-483-5p Down-regulation in microdissected non-tumorous liver tissue with early recurrence: miR-210, miR-215, miR-22, miR-409-5p, miR-200a*, miR-10b*

ABH: Acute B hepatitis; ASCs: Asymptomatic HBsAg carriers; BCLC: Barcelona clinic liver cancer staging system; CHB: Chronic hepatitis B; CLD: Chronic liver disease; ER-α: Estrogen receptor-α; FNH: Focal nodular hyperplasia; HCC: Hepatocellular carcinoma; HC: Healthy controls; HCA: Hepatocellular adenoma; LC: Liver cirrhosis; LT: Liver transplantation; NR: Not reported; OS: Overall survival; RFS: Recurrence-free survival; SR: Spontaneously recovered.

Table 2 miRNA observed deregulated in studies enrolling hepatocellular carcinoma patients with hepatitis B virus-related infection in at least three papers

miRNA	Type of deregulation (number of papers)	Type of Sample (number of papers)	Ref.
miR-221	Upregulated (6)	Tissue (5), serum (1)	Gao P, *Hepatology*, 2011 Li J, *Biochemical and Biophysical Research Communications*, 2011 Li T, *Oncology Reports*, 2014 Li W, *Int J Cancer*, 2008 Wen Y, *Int J Cancer*, 2015 Zhang ZZ, *WJG*, 2011
[1]miR-21	Upregulated (5)	Tissue (4), serum (1)	Bandopadhyay M, *BMC Cancer*, 2014 Connolly E, *The American Journal of Pathology*, 2008 Gao P, *Hepatology*, 2011 Li T, *Oncology Reports*, 2014 Xu J, *Molecular Carcinogenesis*, 2011
[2]miR-222	Upregulated (4)	Tissue (3), serum (1)	Li W, *Int J Cancer*, 2008 Qi P, *PLoS One*, 2011 Zhang ZZ, *WJG*, 2011 Wen Y, *Int J Cancer*, 2015
[3]miR-122a	Upregulated (4)	Serum (4)	Li LM, *Cancer Research*, 2010 Qi P, *PLoS One*, 2011 Xing TJ, *Genetics and Molecular Research*, 2014 Xu J, *Molecular Carcinogenesis*, 2011
miR-224	Upregulated (4)	Tissue (3), serum (1)	Gao P, *Hepatology*, 2011 Gui J, *Clinical Science*, 2011 Li W, *Int J Cancer*, 2008 Zhang ZZ, *WJG*, 2011
[4]miR-101	Downregulated (4)	Tissue (4)	Fu Y, *Oncol Letters*, 2013 Li W, *Int J Cancer*, 2008 Xie Y, *Cancer Biology and Therapy*, 2014 Zhang ZZ, *WJG*, 2011
miR-18a	Upregulated (3)	Tissue (2), serum (1)	Li L, *Digestive Diseases and Sciences*, 2012 Li W, *Int J Cancer*, 2008 Zhang ZZ, *WJG*, 2011
miR-223	Upregulated (3)	Serum (3)	Li LM, *Cancer Research*, 2010 Qi P, *PLoS One*, 2011 Xu J, *Molecular Carcinogenesis*, 2011

[1]miR-21: in one paper by Zhou [Zhou J, *J Clin Oncol* 2011] starting from serum samples, miR-21 was observed as down-regulated; [2]miR-222: in one paper by Bandopadhyay [Bandopadhyay M, *BMC Cancer* 2014] starting from tissue samples, miR-222 was observed as down-regulated; [3]miR-122a: in two papers by Tan *et al* and Zhou *et al* [Tan Y, *PLoS One* 2014; Zhou J, *J Clin Oncol* 2011] both starting from serum samples, miR-122 was observed as down-regulated; [4]miR-101: in paper by Fu *et al*, miR-101 was observed as down-regulated in tissue but up-regulated in serum [Fu Y, *Oncol Letters* 2013].

Table 3 miRNAs patterns in studies enrolling hepatocellular carcinoma patients with hepatitis B virus and hepatitis C virus-related infection

Ref.	Characteristics of the study	miRNAs Up-regulated	miRNAs Down-regulated	Conclusions
Chung GE, *Oncol Rep*, 2010 Korea Period: 2001-2004	Tissue samples obtained from twenty-five pairs of primary HCC (18 HBV positive patients, 2 HCV positive subjects, 5 HBV/HCV negative) and adjacent non-tumor liver tissues were evaluated in this study	Up-regulation of miR-15b, miR-105 and miR-339, let-7d, miR-107, miR-103, miR-210, miR-25, let-7a, miR-93, miR-345, miR-30d, miR-423, miR-320	miR-422b, miR-22, miR-497, miR-195, miR-199a*, miR-199[a], miR-130a	miR-15b expression in HCC tissues may predict a low risk of HCC recurrence. In addition, the modulation of miR-15b expression may be useful as an apoptosis-sensitizing strategy for HCC treatment
Cong N, *Tumor Biol*, 2014 China Period: January 2007 - February 2012	Serum samples obtained from: -206 patients with HCC -217 controls	NR	NR	The miR-146a GG genotype and G allele carried an increased risk of HCC HBV-positive subjects carrying but not in HCV-infected patients
Coulouarn C, *Oncogene*, 2009 USA Period: NR	Specimens obtained from 64 HCC tissues (18 pts HBsAg +, 13 HCV +, 3 with HBV and HCV coinfection, 30 with different etiologies) and 28 matched non-tumor surrounding liver tissues from patients undergoing partial hepatectomy as treatment for HCC	NR	Down-regulation of miRNA-122 in HCC	miR-122 as a diagnostic and prognostic marker for HCC progression
Diaz G, *Int J Cancer*, 2013 Italy Period: NR	Tissue samples obtained from: -HCV-associated HCC (HCC), -HCC-associated non-tumours cirrhosis (HCC-CIR), -HCV- associated cirrhosis without HCC (CIR), -HBV-associated acute liver failure (ALF), -normal liver tissue surrounding angioma (NL), -normal liver from liver donors (LD)	Up-regulation of: miR 221, miR-224 and miR-224-3p, miR-452, miR-1269	Down-regulation of: miR-125a-5p , miR-130a, miR-139-5p, miR-139-3p, miR-195, miR-199a-5 and miR-199a-3p, miR-214, miR-424-3p, miR-497	18 miRNAs exclusively expressed in HCV-associated HCC and characterized by high specificity and selectivity *vs* all other liver diseases and healthy conditions were identified Among the 18 HCC-exclusive miRNAs identified in this research, miR-221 and miR-224, miR-199a-5p, miR-195, miR-214, miR-199a-3p, miR-125a-5p, miR-139-5p, miR-130a, miR-199b-3p, miR-139-3p, miR-224-3p and miR-452 were already reported in previous studies miR-497, miRNA-1269 miR-424-3p were never described in previous reports

Gramantieri L, *Cancer Research*, 2007 Italy Period: NR	Tissue obtained from: 60 patients (HBV: 5, HCV: 31, HBV+ HCV: 5, HCV+ pas tHBV: 5, past HBV: 1; HBV + ethanol: 1, HCV + ethanol: 2, ethanol: 3)	Up-regulation of: miR-221	Down-regulation of : let-7a-1, let-7a2, let-7a3, let-7b, let-7c, let-7d, let-7e, let-7f2, let-7g, miR-122a, miR-124a, miR-130a, miR-132, miR-136, miR-141, miR-142, miR-143, miR-145, miR-146, miR-150, miR-155, miR-181a-1, miR-181a-2, miR-181c, miR-195, miR-199a1-5p, miR-199a2-5p, miR-199b, miR-200b, miR-214, miR-223	The aberrant expression of a restricted panel of miRNAs could participate in the molecular events leading to HCC development
Hao YX, *Asian Pac J Cancer Prev*, 2013 China Period: January 2010 - April 2012	Serum samples from: -285 patients with HCC 133 HBsAg-positive 36 anti-HCV positive 8 with coinfection -Residents without HCC who entered the hospital for health check-ups were enrolled into control group Each control was pair-matched by sex and age (± 5 yr) to a patient with HCC	NR	NR	miR-196a2 CC genotype and C allele have an important role in HCC risk in Chinese patients, especially in HBV infection carriers No significant association observed between miR-146aG>C and miR-499A>G genetic polymorphisms and HCC risk
Köberle V, *Eur J Cancer*, 2013 Germany Period: February 2009 - July 2012	Serum samples obtained from: 195 patients with HCC (33 HBV+; 87 HCV +, 14 NASH, 65 Alcohol, 8 Haemochromatosis, 9 Cryptogenic) 54 patients with liver cirrhosis (2 HBV +; 41 HCV +, 0 NASH, 16 Alcohol, 0 Haemochromatosis, 0 Cryptogenic)	Longer OS in patients with higher miR-1 and miR-122 serum levels	Reduced OS in patients with lower miR-1 and miR-122 serum levels	At age-, sex-, tumor stage and treatment-adjusted multivariate Cox regression analysis miR-1 serum levels were independently associated with OS, whereas serum miR-122 was no. t miR-1 may improve the predictive value of classical HCC staging scores
Ladeiro Y, *Hepatology*, 2008 France Period: 1992-2004	109 liver samples, collected from 93 patients surgically treated. Analysed cases: HCC: 28, HC: 13, FNH: 5, non-tumor liver samples: 4 Two sets of samples were considered:(first set of samples (n = 50, 16 HBV positive, 9 HCV positive) and validation set of samples (n = 59, 18 HBV positive, 17 HCV positive)	- miR-96 overexpressed in HBV tumors - miR-21, miR-222, miR-10b overexpression in HCC - miR-224 overexpression in HCC *vs* benign tumours	-miR-422b, miR-122a down-regulation both in benign and malignant tumors - miR-200c and miR-203 underexpression in benign tumours - low expression of miR-375 in both HCA and HCC mutated for β-catenin	Hepatocellular tumors may have a distinct miRNA expression fingerprint according to malignancy, risk factors, and oncogene/tumor suppressor gene alterations

Liu YX, *BioMed Research International*, 2014 China Period: January 2004 - December 2008	Tissue obtained from: -207 HCC liver tissue and patients and adjacent noncancerous tissue samples. HBV + : 174 patients; HCV+ : 3 patients	miR-24 up-regulation in HCC tumor tissues relative to adjacent noncancerous tissue samples	NR	High expression of miR-24 could promote AFB1-DNA formation and increase adducts mount. High expression of miR-24 was significantly correlated with larger tumor size, higher microvessel density, and tumor dedifferentiation
Liu WH, *Gastroenterology*, 2009 Taiwan Period: 2002-2006	Tissue obtained from: -80 HCC patients (40 HBV+ and 40 HCV +), -16 focal nodular hyperplasia cases -7 adenoma cases	Specifically increased miR-18a miRNA in samples from female HCC patients. miR-18a expression in tumor tissues not different from the non-tumoral tissues in either male or female patient FNHs and adenomas	NR	miR-18a prevents translation of ER, potentially blocking the protective effects of oestrogen and promoting the development of HCC in women
Lu CY, *Genes Chromosomes and Cancer*, 2013 Taiwan Period: NR	Tissue and sera obtained from: -41 patients with HCC (19 HBV positive, 11 HCV positive, 2 HBV/HCV positive, 8 HBV/HCV negative and 1 not determined) -8 patients with cirrhosis (6 HBV positive, 2 HCV positive, 1 HBV/HCV positive), -10 Healthy subjects	In 39/41 HCC, the methylation levels of miR-129-2 were significantly increased in tumor tissues compared with adjacent normal tissues miR-129-2 methylation was detectable in plasma samples from HCC patients, but not in plasma samples from healthy individuals or patients with liver cirrhosis	NR	miR-129-2 methylation is highly accurate in distinguishing HCC patients from cirrhosis patients and healthy individuals, implying its potential utility as an early diagnostic marker for HCC
Murakami Y, *Oncogene*, 2006 Japan Period: NR	miR expression profiles in 25 pairs of hepatocellular carcinoma (HCC) and adjacent nontumorous tissue (NT) and nine additional CHB specimens was performed, using a human miRNA microarray HBV +: 6; HCV +: 26	Major expression of miR-18, precursor miR-18, and miR-224 in HCC *vs* non-cancerous tissue	Minor expression of miR-199a*, miR-195, miR-199a, miR-200a, and miR-125[a] in HCC *vs* non-cancerous tissue	Higher expression of three miRNAs in the HCC samples *vs* NT samples, demonstrated lower expression of five miRNAs in the HCC samples *vs* NT samples

Qu KZ, *J Clin Gastroenterol*, 2011 USA Period: NR	283 subjects studied: -105 patients with HCC (20 HBV +, 66 HCV +, 1 with coinfection); -107 individuals with CLDs; -71 healthy controls	NR	Significantly lower serum levels of miR-16 and miR-199a in HCC than in CLD patients or control subjects	Measurement of serum levels of miR-16 improves differentiation of HCC from non-HCC CLD. The combination of miR-16, AFP, AFP-L3, and DCP yielded greater sensitivity and specificity for HCC detection than any other single marker or marker combination examined
Salvi A, *Intern J Oncol*, 2012 Italy Period: NR	Tissue specimens obtained from: human HCC samples, corresponding peritumoral and non-tumor samples (resected 1-2 cm from the malignant tumor) 15 HCV + patients, 10 HBV+ patients 4 HBV+/HCV + subjects 7 HBV -/ HCV - patients 5 patients with no available informations (25 cirrhosis, 15 hepatitis, 1 steatosis)	Up-regulation of: miR-21 in HCC tissues *vs* the corresponding peritumoral tissues, particularly in non-cirrhotic HCC	Down-regulation of: miR-24 and miR-27a in HCCs from cirrhotic liver tissues in comparison to those from non-cirrhotic liver tissues. The downregulation of miR-24 was correlated with poorer prognosis in patients with HBV and HCV virus infections	Differential expression of miRNAs in cirrhotic and non-cirrhotic HCCs, thereby contributing to advances in the discovery and validation of novel molecular biomarkers of HCC progression
Sato F, *PLoS One*, 2011 Japan Period: January 1997 - March 2007	73/639 patients with HCC and satisfying enrollment criteria, underwent hepatic resection Patients HBsAg +: 12; Patients HCV +: 51	Recurrence-related miR in tumor tissues: miR22, miR99a, miR99b, miR100, miR 125a-5p, miR125b, miR129-5p, miR 140-3p, miR145, miR195, miR221, miR378, miR497	Recurrence-related miRNA in non-tumor tissues: miR18a, miR18b, miR21, miR23a, miR24, miR27a, miR96, miR103, miR 107, miR126, miR142- 3p, miR 148a, miR 191, miR 222, miR362-3p, miR 425, miR378, miR1202, let 7e, let-7f	miRNA profiling can predict HCC recurrence in Milan criteria cases miR-96 in non-tumor tissues is the most strongly associated with HCC recurrence
Shigoka M, *Pathology International*, 2010 Japan Period: NR	Serum and tissue samples obtained from: -22 HCC cases (6 HBV +, 10 HCV +, 6 non-HBV/HCV) -5 pairs of fresh HCC and non-tumorous LCD samples surgically resected from HCC patients -10 healthy subjects	Higher levels of miR-92a expression in HCC sections *vs* adjacent LC sections	Decreased ratio of miR-92a to miR-638 in the plasma samples from the HCC patients compared with that from the normal donors	Deregulation of miR-92 expression in cells and plasma could be implicated in the development of HCC

Spaniel C, *PLoS One*, 2013 Japan/USA Period: NR	Tissue samples obtained from: a) Paired tumor and nontumor tissues collected from 26 patients undergoing surgical resection of HCC: -16 with concomitant chronic HCV infection, -10 infected with HBV b) 9 with non-infected 'normal' liver tissue collected from patients undergoing resection of metastases of non-hepatic primary cancers	Possible miR-191 increased expression in HBV-associated HCC	Significant reduction of miR-122 abundance in HBV associated HCC in comparison with "normal" liver tissue, but not in liver cancer associated with HCV. Significant differences in miR-122 expression exist in non-tumor tissue, with miR-122 abundance reduced from "normal" in HCV- but not HBV-infected liver	miR-122 abundance varies between HBV- and HCV-related liver HCC as well as in non-tumor tissue
Toffanin S, *Hoshida Cabellos Gastroenterology*, 2011 Italy Period: NR	Tissue samples obtained from: - 89 fresh-frozen HCC samples (surgical resection or LT); - Formalin-fixed paraffin-embedded tissues of 165 HCCs (validation set) caused by HCV, HBV, alcohol, and others Subjects subdivided into: Training set: 79 patients Validation set: 161 patients Training set:, HCV +: 79/79 patients Validation set: HCV +: 74/161; HBV +: 43/161; Alcohol: 12/161; Other: 25/161	Up-regulation of 23 miRNAs in cluster C2 (miR-517a, miR-517b, miR-517c, miR-520g, miR-520h, miR-519b, miR-519d, miR-516-5p, miR-519a,miR-520c, miR-520b, miR-520f, miR-526b, miR-524, miR-516-1, miR-526b, miR-519e, miR-512-3p, miR-522, miR-526a, miR-518f, miR-518b, and miR-525 Up-regulation of 16 miRNAsin cluster C3 (miR-376a, miR-494, miR-409-3p, miR-376b, miR-377, miR-368, miR-382, miR-369-3p, miR-410, miR-432, miR-154, miR-379, miR-299-5p, miR-431, miR-381, miR-495)	Down-regulation of miR-26a and miR-26b in cluster C2 and C3	miRNA-based classification of 3 subclasses of HCC is proposed. Among the proliferation class, miR-517a is an oncogenic miRNA, promoting tumor progression A rationale for developing therapies that miRNA 517 for patients with HCC is proposed A hierarchical clustering of miRNA data identified 3 main clusters of HCC: clusters A (32/89), B (29/ 89) and C (28/89). The C cluster divided into 3 sub-clusters with distinct miRNA expression patterns: C1 (15/89), C2 (8/89) and C3 (5/89)
Tomimaru Y, *J Hepatol*, 2011 Japan Period: January2010 - February 2010	Serum samples obtained from: -10 patients before and after curative resection of HCC (HBV/HCV-: 1, HBV: /3/ HCV+: 6/); -126 patients with HCC, -30 patients with CLD, -50 healthy volunteers	Significantly higher plasma miR-21 level in the HCC patients in comparison with CLD patients and healthy volunteers	Significantly diminished plasma miRNA-21 levels after surgery compared with the pre-operative values	Plasma miRNA-21 level is a promising biochemical marker for HCC

Ura S *Hepatology*, 2009 Japan Period: 1999-2004	12 patients with HBV-related HCC 14 patients with HCV-related HCC	NR	Commonly repressed miR in CH-B, CH-C, HCC-B, and HCC-C compared with normal liver: miR-219, miR-320, miR-154, miR-29c; miR-338; miR-26a; miR-126; miR-325	miRNAs as important mediators of HBV and HCV infection as well as liver disease progression, they could be potential therapeutic target molecules Major miRNAs expression in HCC *vs* CLD: miR21, miR-98, miR183, miR221, miR222, miR301. Minor miRNAs expression in HCC *vs* CLD: miR17-3p, miR30a-3p, miR30e, miR92, miR 99a, miR122, miR125b, miR130a, miR139, miR187, miR199a, miR200a, miR200b, miR223, miR326
Zhou B *Tumor Biol*, 2014 China Period: January 2010 - February 2012	Serum samples obtained from: -266 patients with HCC -281 Healthy controls	NR	NR	Subjects with miR-146a GG and G allele had an enhanced risk of HCC in comparison with homozygote CC genotype. Individuals with miR-196a2, TT and T allele significantly decreased the risk of HCC in comparison with CC genotype. miR-196a2C>T polymorphisms associated with a decreased risk of HBV-related HCC, but not in HCV-related HCC cases

ABH: Acute B hepatitis; ASCs: Asymptomatic HBsAg carriers; BCLC: Barcelona Clinic Liver Cancer staging system; CHB: Chronic hepatitis B; CLD: Chronic liver disease; ER-α: Estrogen receptor-α; FNH: Focal nodular hyperplasia; HCC: Hepatocellular carcinoma; HC: Healthy controls; HCA: Hepatocellular Adenoma; LC: Liver cirrhosis; LT: Liver transplantation; NR: Not reported; OS: Overall survival; RFS: Recurrence-free survival; SR: Spontaneously recovered.

of HCC in this different spectrum of human diseases. Concerning NAFLD/NASH, most of available articles have studied the circulating or tissue miR signature associated with NAFLD progression and predictive power, as well as the role of miRs in disease biology and the relationship between circulating miRNA and features of the metabolic syndrome. In particular, a report has assessed tissue miRNA patterns in patients with NASH in comparison with normal controls. Forty-six miRNAs have resulted to be differentially expressed in these two distinct groups, 23 miRNAs were up-regulated (miR-125b, miR-16, miR-21, miR-23a, miR-23b, miR-24, miR-27b, miR-34a, miR-99b, miR-100, miR-127, miR-128a, miR-128b, miR-146b, miR-181b, miR-199a, miR-199a*miR-200a, miR-214, miR-221, miR-222, miR-224, miR-455) and 23 down-regulated (miR-126, miR-28, miR-26b, miR-30d, miR-122, miR-361, miR-574, miR-92b, miR-768-5p, miR-375, miR-203, miR-223, miR-145, miR-671, miR-139, miR-191*, miR-563, miR-188, miR-601, miR-765, miR-198, miR-641. miR-617)[95]. MiR-122 levels were significantly decreased in subjects with NASH. Estep

Table 4 miRNA observed deregulated in studies enrolling hepatocellular carcinoma patients with hepatitis B virus and hepatitis C virus-related infection in at least three papers

miRNA	Type of deregulation (number of papers)	Type of Sample (number of papers)	Ref.
miR-130a	Downregulated (4)	Tissue (4)	Gramantieri L, *Cancer Research*, 2007 Diaz G, *Int J Cancer*, 2013 Chung GE, *Oncol Rep*, 2010 Oksuz Z, *Mol Biol Rep*, 2015
miR-21	Upregulated (3)	Tissue (2), serum (1)	Ladeiro Y, *Hepatology*, 2008 Salvi A, *Intern J Oncol*, 2012 Tomimaru Y, *J Hepatol*, 2011
miR-224	Upregulated (3)	Tissue (3)	Diaz G, *Int J Cancer*, 2013 Ladeiro Y, *Hepatology*, 2008 Murakami Y, *Oncogene*, 2006
miR-195	Downregulated (3)	Tissue (3)	Gramantieri L, *Cancer Research*, 2007 Diaz G, *Int J Cancer*, 2013 Chung GE, *Oncol Rep*, 2010

Table 5 miRNAs patterns in studies enrolling hepatocellular carcinoma patients with hepatitis C virus-related infection

Ref.	Characteristics of the study	miRNAs Up-regulated	miRNAs Down-regulated	Conclusions
Abdalla MA, 2012 Egypt Period: NR	Urine samples collected from: -32 patients with HCC post-HCV infection, -74 patients with chronic HCV infection --12 normal individuals	Up-regulation of: - miR-765, miR200a and miR-610, in the HCC-post HCV group; - miR-335, miR-618, miR-625, miR-532, miR-7 were in both the HCC-post HCV positive group and in the HCV positive group, relative to the control group	Down-regulation of: -miR-765, miR200a and miR-610 in the HCV positive group; - miR-323, miR-449, miR-502d, miR-92b, miR-516-5p and miR-650 in both the HCC-post HCV positive group and in the HCV positive group, relative to the control group	The predictive sensitivity and specificity values of miR-618/650 in tandem for detecting HCC among HCV-positive individuals were 58% and 75%, respectively. These values were higher, compared to the traditional α-feto protein (AFP) level-based detection method
Bihrer V, *PLoS One*, 2011 Germany Period: NR	Tissue and serum samples obtained from: -CHC: 62; -CHC plus HCC: 29; -Healthy subjects: 29; An -Independent cohort of 47 CHC patients	ND	ND	The serum miR-21 level is a marker for necroin-flammatory activity, but does not differ between patients with HCV and HCV-induced HCC
El-Garem H, *WJG*, 2014 Egypt Period: March-June 2012	Serum samples obtained from: -30 with chronic HCV alone (CH); -30 with HCV-related cirrhosis (LC); -30 with HCV-related HCC; -10-age and gender-matched healthy volunteers	Up-regulation of miR-122, miR-221	NR	Serum miR-221 has a strong potential to serve as one of the novel non-invasive biomarkers of HCC

Elhelw DS, *Biomedical Reports*, 2014 Egypt Period: NR	Serum, liver tissues and peripheral mononuclear cells samples obtained from patients infected with genotype 4-HCV: -72 patients chronically infected with HCV - 22 age-matched controls. The patients classified as: 24 naïve-patients, 11 SVRs pre-treatment, 15 SVRs post-treatment, 12 NRS pre-treatment and 10 NRS post-treatment	*miR-181a* significantly higher in the serum of naïve patients compared to controls, no difference in *miR-181a* expression observed in the liver tissues and PBMCs of patients compared to controls up-regulation of *miR-181a* post-interferon/ribavirin treatment in the serum of SVRs compared to non-responders and treatment-naïve SVR	NR	The up-regulation of miR-181a in the serum of HCV patients as an indication of good prognosis Any decrease during follow-up may be an early marker for progression to HCC
Oksuz Z, *Mol Biol Rep*, 2015 Turkey Period: NR	Serum samples obtained from: -26 patients with CHC; -30 patients with HCV-related cirrhosis; -8 patients with HCV-positive HCC; -28 patients with control group	Deregulated miR-30a-5p, miR-30c-5p, miR-206, miR302c-3p in CHC Deregulated miR-17-5p, miR-30c-5p, miR-93-5p, miR-130a-3p, miR-223-3p, miR-302c-3p, miR-302c-5p	Deregulated miR-17-5p, miR-30c-5p, miR-223-3p, miR-302c-3p in cirrhosis and HCC	miR-17-5p, miR-30c-5p, miR-223-3p, miR-302c-3p could serve as novel non-invasive biomarkers in the early phases of HCV-related HCC and in the cirrhosis stage of liver disease
Varnholt H *Hepatology*, 2008 Germany Period: 1995-2007	Tissue samples obtained from: 52 primary liver tumors from 39 patients induced by HCV infection	Increased expression of miR-9, miR-10a, miR-15a, miR-16, miR-299, miR-370 miR-326, miR-let-7g, miR-100, miR-125b in HCC in comparison with normal liver	Decreased expression of miR-198, miR-302b, miR-302b, miR-145, miR-368, miR-218, miR-330, miR-137, miR-147, miR-104, miR-9, miR-106a, miR-204, miR-159a, miR-134, miR-29c, miR-95, miR-199b, miR-185 in HCC in comparison with normal liver	A subset of miRNAs are aberrantly expressed in primary liver tumors, serving both as putative tumor suppressors and as oncogenic regulators
Zhang Y *Hepatology*, 2012 China Period: NR	Tissue specimens obtained from: -Healthy controls: 7; -NASH:12; -Chronic HCV infection; patients: 34; -HCV-HCC patients:10	Up-regulation of: miRNA-155	NR	HCV-induced miR-155 expression promotes hepatocyte proliferation and tumorigenesis by activating Wnt signaling

BCLC: Barcelona Clinic Liver Cancer staging system; CLD: Chronic liver disease; ER-α: Estrogen receptor-α; FNH: Focal nodular hyperplasia; HCC: Hepatocellular carcinoma; HC: Healthy controls; HCA: Hepatocellular adenoma; LC: Liver cirrhosis; LT: Liver transplantation; NASH: Nonalcoholic steatohepatitis; ND: Not detected; NR: Not reported; NRS: Non-responder; OS: Overall survival; RFS: Recurrence-free survival; SR: Spontaneously recovered; SVRs: Sustained viral responses.

et al[96] have studied miRNA expression in the visceral adipose tissue of patients with non-alcoholic fatty liver disease. A total of 113 species of miRNAs were differentially expressed in the visceral adipose tissue of NASH patients compared with those with non-NASH type of NAFLD. After multiple test correction, a significant down-regulation in the expression of seven miRs (miR-132, miR-150, miR-433, miR-28-3p, miR-511, miR-517a, miR-671) was detected[96]. Functional analysis of these seven miRNAs differentially expressed in NASH showed significant association with paths involved in the liver carcinogenesis. In addition, two miRNAs (miR-197 and miR-99), were significantly associated with pericellular fibrosis in NASH patients. A significant correlation was detected between serum and hepatic miR-122 expression in a series of 67 patients with NAFLD[97]. Patients with mild steatosis (< 33%) had significantly lower levels of hepatic miR-122 in comparison with subjects with severe steatosis (> 33%). Hepatic and serum miR-122 levels were significantly higher in patients with mild fibrosis than in those with severe fibrosis. The serum miR-122 level has resulted to be a useful predictive marker of liver fibrosis in patients with NAFLD, but no correlation was assessed between miR-122 and risk of HCC development[97]. A further study has evaluated serum miRNA profiles in patients with NASH[98]. This paper shown that miR-122, miR-192, miR-19a/miR-19b, miR-125b, and miR-375 were up-regulated > 2-fold either in simple steatosis or NASH and that, at a regression analysis for an ordinal multinomial distribution, miR-122, miR-192 and miR-375 were significantly associated with the histological disease severity and significantly up-regulated in NASH compared with patients, suffering from simple steatosis. In addition, few data are available, concerning expression pattern of miRNAs in alcohol-related liver cancer. Only some studies has evaluated miRNA profiles in a small number of patients with liver cancer and history of alcohol abuse, but some of them had a coexisting HBV- or HCV- infection[69,81]. Ladeiro *et al*[72] found that miR-21, miR-222, and miR-10b were significantly over-expressed in patients with HCCs, associated with both viral- and non-viral risk factors, but only under-expression of miR-126* was specifically related to alcohol abuse. Primary biliary cirrhosis (PBC) is also characterized by an altered expression pattern of miRNAs in comparison with healthy individuals. In particular, in liver tissue miR-346, miR-145, miR-328, miR-371, miR-299, miR-374, miR-506, miR-202, miR-186, miR-341, miR-25 were up-regulated, whereas miR-122a, miR-23b, miR-26a, miR-192, miR-126, miR-130b, miR-192, miR-194, miR-24, miR-107, miR-455-3p, miR-16, miR-193b, miR-103, miR-100, miR-27b, miR-19b, let-7d, miR-99a, miR-30c, miR-422b, miR-30e-5p, miR-92, miR-101b resulted down-regulated[99], whereas, in serum, miR-1273g-5p, miR-33a-5p, miR-3960 were up regulated and miR-766-5p, miR-505-3p, miR-30b-3p, miR-139-5p, miR-197-3p, miR-500a-3p were down-regulated[100]. However, no data exist, concerning the roles of miRNAs in hepatocarcinogenesis in patients with this pathology. In addition, no results are available, concerning a specific miRNA signature and liver cancer in subjects with hemochromatosis. In conclusion, no definite miRNA patterns, associated with an increased risk of HCC development in these non-viral diseases, have been described.

DISCUSSION

It is well-known that miRNAs act as key factors in several biological processes, such as growth, cell proliferation, differentiation, apoptosis and carcinogenesis. To date, most of the current diagnostic approaches for cancer screening are invasive, not specific as well as generally little effective or unable to detect malignancies in the early phases of development. Accumulating evidence indicates that miRNAs are perturbed both in non-cancerous human diseases and in the course of human carcinogenesis, from the early- to the late-phases of this process, in a large series of malignancies, including lung, colon, stomach, kidney and prostate and breast tumours. HBV- and HCV-related HCC development and progression is also associated with a significant and important deregulation of serum/plasma and liver tissues profiles of miRNAs, as it has been widely reported by several studies. Therefore, this evidence makes miRNAs potential non-invasive biomarkers for diagnosis, staging, progression, prognosis and response to treatment not only in non-cancerous diseases, but also in different malignancies. In particular, whether a definitive and reliable correlation between specific miRNAs levels and/or profiles in body fluids and HCC could be defined, these molecules might become a very useful tool for early detection of this type of neoplasm, in particular in the pre-symptomatic phases of its development. Therefore, in the last years, a large series of studies has been performed with these purposes. Ideal biomarkers should allow to diagnose and to monitor a disease, with an adequate sensibility and specificity, to define its stage as well as to permit an easy and reproducible screening in the general population, with a low cost. MiRNAs possess some peculiar and usefulness characteristics, including the possibility to detect these molecules in serum/plasma samples, that may be easily collected, and their high stability, even in conditions that are generally known to induce RNAs degradation, such as fluctuations in temperature and pH levels as well as long-term storage[101-103]. Unfortunately, several factors may strongly influence and decrease the possible helpfulness and benefit of miRNAs use in diagnostic and prognostic assessment of patients with cancers, such as bioptic or surgical procedures for

samples collection, methods of specimens freezing and RNA detection, aetiology of neoplasms and changing miRNAs profiles in the different phases of carcinogenetic process. Taking advantage from these elements, several Authors have evaluated miRNAs expression patterns in serum/plasma of patients with HBV- and or HCV-related HCC and compared these profiles with those detectable in serum/plasma of subjects with HBV- and/or HCV-positive hepatitis or cirrhosis as well as of healthy individuals with the aim to assess their potential role in the early diagnosis, prognosis and treatment outcome of patients at high risk of HCC development. In our review we specifically focused on these reports to summarize the available knowledge on this topic. Although the results of these studies seem to suggest that the use of miRNAs might be a feasible tool for the diagnosis of HCC, to date several important questions remain unresolved and incompletely defined. Therefore the utility and feasibility of miRNAs employment in clinical practice is still debatable and no definitive conclusions may be drawn. A doubtful point emerges from available results and has to be taken into account: the extreme heterogeneity among the different available studies. In particular the following factors have to be considered.

Study design and end-points. A high number of reports include a small sample sizes, very low number of screened miRNAs as well as a poor research methodology. In particular, in a high series of studies, only one or two miRNAs were considered for data analysis.

Most reports (in particular, studies investigating miRNAs patterns in HBV-related HCC) were carried out in China or in South East Asia, such as South Korea and Taiwan, in people of Asian ethnicity. These countries are high HBV-endemic areas, although, in the last years, long-term vaccination programs have contributed to decrease HBsAg positivity rate in the general population. On the other hand, only a small number of studies have been carried out in Europe, America and Africa. Therefore, the substantial variation in serum prevalence of HBV-related antigens/antibodies (*i.e.*, the antibodies patterns of HBsAg negative individuals, with signs of past HBV infection, a frequent conditions, at least in subjects of Southern Europe), as well as difference in geographical distribution of HBV genotypes, should be taken into account. All these factors, mainly for HBV, might have a substantial impact on the results obtained by available reports and could limit their validity.

It is possible that several miRNAs with potential important roles in HCC development have not been yet identified and validated as possible specific and useful biomarkers in the process of liver carcinogenesis and their activity has not yet been assessed in the available scientific works.

The potential inter-relations and cooperation among host- and viral-miRNAs, during the development of this malignancy, the potential cooperation between viruses and host in the process of liver carcinogenesis requires further evaluations. Cellular miRNAs may directly affect replication and pathogenesis of HBV and HCV viruses. It has been reported that miRNA-122 is essential for maintaining the adult phenotype in hepatocytes[104]. Moreover miR-122 is able to modulate the activities of genes controlling some important liver functions, as metabolism of lipid and cholesterol[105]. MiR-122 is also able to facilitate HCV replication, by targeting a 50 non-coding region of the viral genome[106]. HBV genome includes targets for human encoded miRNAs, as miR-7, miR-196b, miR-205, miR-345, miR-433, miR-511 and also miR-122. This last binds to the region of HBV pregenomic RNA, which codes both for the viral polymerase and for the 3' untranslated region and for the core protein. Therefore, HBV gene expression and replication are negatively modulated[107]. It has been reporteded that several miRNAs (miR-7, miR-196b, miR-433 and miR-511) interact with some viral DNA sequences and influence their activities[108]. A study by Novellino *et al*[109] has showed that, during HBV chronic infection, circulating HBsAg particles represent the carriers of selective pools of hepatocellular miRNAs (miR-27a, miR-30b, miR-122, miR-126 and miR-145), with specific liver functions.

Actually it has not yet been defined which is the best human biological sample (*i.e.*, serum, plasma, urine or tissue) to establish both which is the type of miRNAs and the range of their levels useful to an early diagnosis of HCC diagnosis or the risk of its recurrence. It should be considered that also different starting material could lead to different miRNA expression results. For example, a miRNA found as up-regulated in tissue specimen could be observed as not-deregulated (or down-regulated) in serum sample (*e.g.*, miR-122, Table 2).

Distinct molecular techniques are used in different studies, as microarrays, reverse-transcription polymerase chain reaction-based assays and next-generation sequencing, making it difficult to compare the results from different studies.

It should be considered that different studies have compared miRNA expression profiles of patients with several different control groups (*e.g.*, non-neoplastic liver, non-neoplastic liver adjacent to the tumor, chronic hepatitis, hepatic tissue from alcoholic cirrhosis). The selection of reference control group is still a big issue also in miRNA studies performed in other tumors (*e.g.*, in brain neoplasia[110]). This variability in selection of reference groups is another reason explaining the different expression profiles of some miRNAs observed throughout different studies (Tables 1-5 and Supplementary Tables 1-3).

Therefore, our knowledge of this field of search is still far from complete. Taken into account the results available in literature, although some studies have pointed out the potential role of some serum/

plasma miRNAs, including miR-21, miR-122, miR-125a/b, miR199a/b, miR-221, miR-222, miR-223, miR-224, as biomarkers for an early diagnosis of HCC development as well as for the assessment of its prognosis in HBV- or HCV- positive patients with this type of malignancy, their efficiency and usefulness require further evaluation and several issues have to be addressed to establish circulating miRNAs as definite reliable and useful diagnostic and prognostic tools. It is conceivable that different panels of miRNAs should be defined to obtain this end-point. Because of extreme biological complexity of miRNAs system, where each single miRNA may not only possess many targets and may modulate several pathways but also it may be influenced by a large series of distinct miRNAs, it is very improbable that a single miRNA may be sufficient for this purpose. Therefore, more well-designed and well-adjusted studies, focusing on populations of different geographical areas and involving larger series of patients, should be carried out to improve our knowledge on the potential role of miRNAs in HCC detection and allow us to define efficient panels of miRNAs. These trials should also allow us to establish which is the better type of sample and of test to be used for miRNAs search. In addition, these studies might provide the opportunity to design new treatments and anticancer approaches as well as to assess the efficacy and the side effects of these therapies.

ACKNOWLEDGMENTS

The Authors thank Dr. Simonetta Righi, Biblioteca Centralizzata, Policlinico S. Orsola-Malpighi, Università di Bologna, Bologna, Italy for her support in the search of scientific bibliography and Mr. Fabio Castellini, Dipartimento di Emergenza-Urgenza, Ospedale di Budrio, Budrio, Bologna, Italy for his active support in clinical research. The authors thank Thomas Brand (University of Bologna) for the linguistic revision.

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P- Reviewer: Bock CT, Lee SW, Rezaee-Zavareh MS, Striker R, Toyoda T
S- Editor: Ma YJ **L- Editor**: A **E- Editor**: Liu XM

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ISSN 1007-9327
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