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Review

MicroRNAs as Diagnostic Tools in Hepatocellular Carcinoma

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Abstract: Liver cancer is the fourth leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) accounting for approximately 80% of all liver cancers. The serum concentration of alpha-fetoprotein (AFP) is the only validated biomarker for HCC diagnosis. MicroRNAs (miRNAs) are small non-coding RNAs of 21–30 nucleotides playing a critical role in human carcinogenesis, with types of miRNAs with oncogenic (oncomiRs) or tumor suppressor features. The altered expression of miRNAs in HCC is associated with many pathological processes, such as cancer initiation, tumor growth, apoptosis escape, promotion of migration and invasion. Moreover, circulating miRNAs have been increasingly investigated as non-invasive biomarkers for HCC diagnosis. MiRNAs' expression patterns are altered in HCC and several single miRNAs or miRNAs panels have been found significantly up or downregulated in HCC with respect to healthy controls or non-oncological patients (cirrhotic or with viral hepatitis). However, any of the investigated miRNAs or miRNAs panels has entered clinical practice so far. This has mostly to do with lack of protocols standardization, small sample size and discrepancies in the measurement techniques. This review summarizes the major findings regarding the diagnostic role of miRNAs in HCC and their possible use together with standard biomarkers in order to obtain an early diagnosis and easier differential diagnosis from non-cancerous liver disease.

Keywords: microRNAs; HCC; hepatocellular carcinoma; diagnosis; prognosis

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1. Introduction

1.1. Hepatocellular Carcinoma

Liver cancer, with an estimated incidence of >1 million cases by 2025, is the fourth leading cause of cancer-related deaths worldwide, making it a global health challenge [1]. Hepatocellular carcinoma (HCC) is the dominant type of liver cancer, accounting for approximately 80% of all liver cancers [2]. Despite the incidence rates are decreasing in some high-rate areas, primary liver cancer remains the second-most common cause of cancer mortality in many low-rate areas [3]. HCC is one of the few cancers with well-defined major risk factors and geographical differences in incidence reflect variations of the main causal factors of HCC [4]. Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection are the most prominent risk factors for hepatocarcinogenesis, although alcoholic liver disease (ALD), non-alcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), associated with diabetes mellitus or metabolic syndrome, are becoming the leading etiology of HCC, particularly in the West [5–7]. Despite recent progress in

HCC therapy, the 5-year survival rate for late-stage HCC remains poor, because of its late diagnosis, resistance to therapy and high frequency of recurrence [8].

1.2. Diagnosis

The diagnosis of HCC, usually based on non-invasive criteria, is currently challenged by the need for molecular characterization of the tumor using tissue or liquid biopsies in clinical practice. Although clinical studies are focusing on biomarker discovery, the only blood-based biomarker currently accepted and validated for HCC is alpha-fetoprotein (AFP) [9].

The serum concentration of AFP is the most commonly used marker for early diagnosis, monitoring and recurrence of HCC, albeit its sensitivity is around 40%: most tumors do not produce AFP at all or only in advanced stages and on the other hand, elevation of AFP is found in patients with chronic liver diseases or acute viral hepatitis too. Given these limitations, HCC diagnosis should be performed using a combination of imaging (ultrasonography) and serum biomarkers [10,11].

HCC harbors a pathognomonic radiological presentation, often crucial for diagnosis. Compared with the background liver, the differential blood supply of the tumor, unbalanced in favor of arterial perfusion over portal perfusion, is responsible of distinctive radiological enhancement pattern on contrast-enhanced magnetic resonance imaging (MRI) of HCC. Hence, HCC lesions are characterized by hyperenhancement in the arterial phase (wash-in) and hypoenhancement (wash-out) in the venous/delayed phases of acquisition.

If these features are evident, the diagnosis of HCC can be obtained in most cases radiologically, without the need for biopsy confirmation.

According to the main European guidelines, abdominal ultrasonography (US) is the most commonly recommended surveillance modality of high-risk patients (affected by cirrhosis or chronic hepatitis infection) [10,11].

Early diagnosis of suspicious lesions is of utmost importance, in order to recognize promptly and treat adequately every lesion and to justify the cost-benefit balance of the surveillance. Therefore, the improvement of accurate diagnostic tools is in this setting highly desirable. For diagnosis of lesions $\geq$10 mm in diameter, both contrast-enhanced MRI and quadruple-phase Computer Tomography should be performed [10,11]; the use of Contrast Enhanced-Ultrasound (CEUS) is still controversial despite recent encouraging results [12,13]. Lesions smaller than 10 mm are too small to be properly characterized and should be monitored at regular intervals (3 to 4 months). MRI had the highest per-lesion sensitivity for HCC, superior to CT, 80% vs. 68%, respectively [14]. In the current scenario of non-invasive diagnosis of HCC, the role of hepatobiliary MRI contrast agents or diffusion weighted MRI or novel positron emission tomography (PET) radiotracers remains unclear, needing to be further validated before being included in the diagnostic algorithm.

In case of an unclear lesion or an atypical pattern, a second imaging method should be considered; if the diagnostic doubt persists, a biopsy with intra- and extra-injury sampling is indicated [10], especially for lesions <2 cm, which more rarely show the typical pattern [15]. The decision to proceed with a biopsy should take into account the complications associated with the procedure, the possibility of inadequate sampling and the risk of tumor seeding [16]. In case of a negative biopsy result, if well-differentiated HCC is suspected, the repetition of the biopsy may be indicated, reducing the risk of false negative [17]. (Figure 1). Staging of HCC is based on the use of CEMRI, showing high sensitivity in detecting small intrahepatic nodules, or of CECT, including chest imaging, in advanced HCC [1].

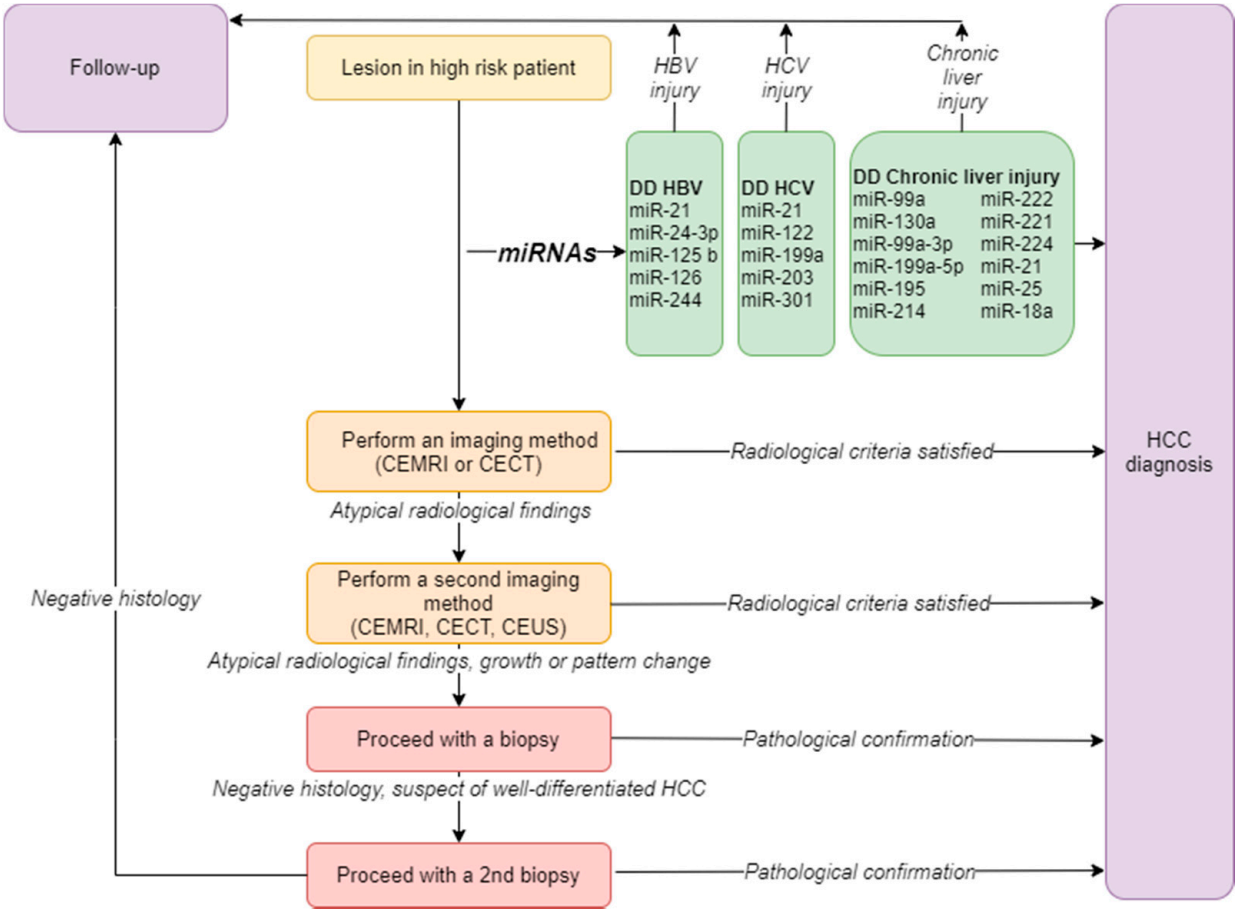

Figure 1. HCC diagnostic flow diagram. According to current guidelines, in case of detection of a suspicious liver lesion, imaging is the main diagnostic tool, followed by pathological diagnosis in case of persistence of atypical characteristics. The introduction of microRNAs analysis in the diagnostic algorithm would allow a more precise differential diagnosis between HCC, HBV, HCV or chronic liver damage. Legend: CECT: Contrast Enhanced-Computer Tomography; CEUS: Contrast Enhanced-Ultrasound; CEMRI: Contrast Enhanced Magnetic Resonance Imaging; DD: differential diagnosis; miRNA: microRNA.

1.3. MicroRNAs

MicroRNAs (miRNAs) are small non-coding RNAs of 21–30 nucleotides in length, highly conserved across different animal species, that have been increasingly investigated in the last few years for their ability to modulate more than 15,000 genes [18]. In the nucleus, RNA polymerase II generally transcribes miRNAs genes in order to generate primary miRNA transcripts (pri-miRNAs). Pri-miRNAs consists of one or more hairpin structures that finally produce on or more functional miRNAs. Transcription is an important step for miRNA expression. Indeed, promoters of miRNAs' genes harbor many features in common with protein-coding genes, such as presence of TATA box and GpG islands [19]. A single miRNA can modulate more than 200 mRNAs [20]. Despite the important roles of miRNAs in the modulation of mRNA expression are well established, their precise functions remain elusive. Circulating miRNAs have been increasingly investigated as non-invasive biomarkers of disease, including liver disease. By modulating the expression of approximately 30% of all human genes, many of which are tumor-associated or located in regions of instability in the genome, miRNAs play a critical role in human carcinogenesis, with types of miRNAs with oncogenic (oncomiRs) or tumor suppressor features [21]. While oncomiRs induce carcinogenesis by inhibiting the expression of tumor suppressors, tumor suppressor miRNAs inhibit oncogene expression in normal cells and are lacking in cancer cells [22]. Data on the expression of miRNAs mainly come from real time polymerase chain

reaction (PCR)-based and microarray-based profiling. More recently, new technologies such as next generation sequencing (NGS) have led to the identification of new miRNAs, providing also a detailed characterization of miRNAs isoforms [23,24].

1.4. MicroRNAs and HCC

The relationships between miRNAs and HCC have been described by several studies and potential miRNA biomarkers for HCC diagnosis and treatment have been identified. The altered expression of miRNAs in HCC is associated with many pathological processes, such as cancer initiation, tumor growth, apoptosis escape, promotion of migration and invasion [25]. Normal liver tissues express a limited number of miRNAs (e.g., miR-199a and miR-122) [26], while HCC often presents loss of these miRNAs together with over-expression of others (e.g., miR-21, miR-221/222 and miR-517) [27–29]. Polymorphisms in miRNAs' genes can determine production of mature miRNA forms with liver carcinogenic potential [25]. For example, a G > C polymorphism in the stem region of miR-146a is associated with HCC development [30]. In addition, other mechanisms through which miRNAs' expression is modulated during liver carcinogenesis are chromosomal rearrangement, promoter methylation, transcriptional induction and delivery between cells trough exosomes [25].

The major clinical implications of miRNAs in HCC include the diagnostic and prognostic role for the disease together with the predictive role of response to anticancer treatment. Moreover, several clinical trials testing miRNAs-based therapeutics are ongoing [25].

This review summarizes the major findings regarding the diagnostic role of miRNAs in HCC and their possible use together with standard biomarkers in order to obtain an early diagnosis and easier differential diagnosis from non-cancerous liver disease.

2. The Diagnostic Role of microRNAs in HCC

For decades, serum α-fetoprotein (AFP), in association with hepatic ultra-sound imaging, has been the most commonly used serological biomarker for HCC detection and surveillance, even if with poor specificity [31]. Given the need for sensitive and specific biomarkers able to be evaluated in readily accessible tissues, several studies have reported the potential role of circulating miRNAs, since they circulate in a highly stable cell-free form in the circulation, as predictive and diagnostic non-invasive biomarkers in this setting [32]. Aberrant expression of circulating miRNAs has been reported in chronic liver injury, liver inflammation and HCC (Table 1) and to date, discovering a panel of miRNAs able to distinguish HCC from non-cancerous liver disease is therefore needed [33,34].

In regions where hepatitis B (HBV) remains endemic such as Africa, the Western Pacific region and Asia, circulating miR21, miR-24-3p, miR125b, miR-126 and miR-224 can be used to distinguish HCC from HBV [35], as well as miR-21, miR-122, miR-199a, miR-203 and miR-301 can be used to identify patients with HCC from ones with chronic hepatitis C [36–40]. Although it is still difficult to differentiate chronic liver injury from HCC with high accuracy, six most consistently downregulated miRNAs (miR99a, miR-130a, miR-199a-3p, miR-199a-5p, miR-195and miR-214) and six upregulated miRNAs (miR-222, miR-221, miR-224, miR-21, miR-25 and miR-18a) were identified in different profiling studies comparing miRNA dysregulation in HCC tissues and corresponding non-tumor liver tissues [41,42]. The serum level of miR-17-5p was down-regulated in a group of HCC resected patients. On the contrary, it was found upregulated in the HCC relapsed group and significantly associated with worse metastasis status and TNM stage [43].

Evaluation of circulating microvesicles and exosomes may be useful in early diagnosis of HCC, as well. Exosomes were characterized based on morphological aspect, molecular weight, protein markers CD63, CD9, and CD81, and miR-21-5p and miR-92a-3p exosomal expression levels. Expression profile analysis indicated that miR- 21-5p was upregulated ($p = 0.017$), and miR-92a-3p was downregulated ($p = 0.0005$) in plasma-derived exosomes from HCC subjects, regardless of patient characteristics patient characteristics. The clinical risk prediction model for HCC diagnosis based on AFP only had an AUROC score of

0.72, while it improved significantly to 0.85 after the integration of AFP with the exosomal expression of miR-21-5p and miR-92a-3p [44].

Moreover, different miRNAs have been reported to target several key driver genes in HCC. The miR-99 family, with its three members miR-99a, miR-99b and miR-100, has been reported to have potential role as tumor suppressor in multiple types of cancer [45,46]. MiR-99a, involved in blocking cell cycle at G1/S transition, is the sixth most bountiful microRNA in the miRNome of normal human liver and it is significantly down-regulated in HCC [47]. Decreased expression of miR-99a, which seemed independent of HCV or HBV infection, correlates with worse prognosis of HCC patients [48]. Lower miR-130a levels, associated with the better overall survival rates of HCC patients, have been associated with a decreased inhibition of the proliferation, migration and invasion of HCC cells by targeting Rho-associated kinases 2 (ROCK2) [49,50]. MiR-199a-3p and miR-199a-5p are consistently decreased in HCC patients, correlating with poor survival [51]. Remarkably, miR-199a-5p downregulation increased autophagy activation, inducing cell proliferation [52,53]. Moreover, recent studies revealed that HCC growth seems to be suppressed by miR-199a/b-3p through inhibiting PAK4/Raf/MEK/ERK pathway [54]. MiR-195 inhibits the invasion, migration and epithelial-mesenchymal transition of HCC cells with the decrease of E-cadherin expression and increase of vimentin expression and is significantly downregulated in HCC patients [55]. Lower miR-214 expression levels correlate with the hypervascularity and portal vein invasion, hallmarks of HCC, and with the increase of β-catenin, resulting in the upregulation of cyclinD1, c-Myc and Lymphoid Enhancer Binding Factor 1 [56]. Moreover, miR-214 indirectly targets *CTNNB1* via suppressing the enhancer of zeste homologue 2 (*EZH2*), a driver-mutation gene in HCC progression, and it is associated with the invasion of HCC cells [57]. High circulating miR-18a expression levels promotes HCC cell migration augmenting HCC proliferation [58]. Similarly, upregulation of miR-21, by activating the pyruvate dehydrogenase kinase 1 (PDK1)/AKT pathway and downregulating the expression of the tumor suppressor phosphatase and tensin homolog (*PTEN*) promotes cancer cell migration and invasion with secretion of angiogenic molecules by cancer cells [59]. MiR-21 and mi-R25 levels permit the differentiation of HCC from chronic hepatitis with 61.1% sensitivity and 83.3% specificity and to distinguish between HCC and healthy controls showing a sensitivity of 86.6% and specificity of 79.5% [60].

MiR-221, miR-222 and miR-224 are the most highly deregulated miRNAs in HCC tissues. MiR-221 correlates with tumor size and tumor stage; patients with higher serum miR-221 levels show poor overall survival with shorter time to local recurrence than individuals with lower levels [61]. MiR-221 promotes HCC cells migration via targeting plant homeodomain finger 2 gene (*PHF2*), a cancer suppressor [62]. Mir-221, miR222 and miR224 are key oncogenic players in HCC when they are overexpressed or dysregulated and can serve as predictive factors for HCC patients' poor outcome [28,63–66].

Circulating miR-122, a sensitive biomarker for liver injury, has been associated with both HCC and liver pathologies, even if with contradictory results [57]. Zhou et al. observed down-regulation of circulating miR-122 in mainly HBV-related HCC patients compared to healthy group, whereas Xu et al. and Qi et al. found miR-122 significantly upregulated in patients diagnosed with HCC [67–69]. Several target genes of miR-122a able to play a role in epithelial mesenchymal transition and tumorigenesis have been identified. The expression of cyclin G1, directly down-regulated by miR-122a, has been shown to be associated with genomic instability [70]. Deregulation of miR-122 in HCC patients has been correlated with AFP elevation, alanine aminotransferase increases and a more aggressive phenotype in HCC, with shorter recurrence-free and overall survival due to increased expression of Cut Like Homeobox 1 (*CUX1*), another direct target of miR-122 [71]. Moreover, increased serum levels of miR-122 have been described in NAFLD and decreased levels have been noted in liver tissues of NASH patients [72]. Accordingly, miR-122 is a good candidate biomarker for early liver pathology, but not specifically for HCC [67]. Cheng et al. recently identified VEGF signaling pathway as one of the most represented miRNA-regulated pathways in HCC: overexpression of miR-146a and miR-638

has been showed to repress angiogenesis by reducing VEGF secretion, on the other hand lower miR-338-3p levels have been related to promote angiogenesis [73].

Table 1. Downregulated and upregulated circulating miRNAs in HCC.

MiRNAs	Targets	Mechanisms	Expression	References
miR-99a	*PLK1*, IGF-1R		Down	[45–48]
miR-130a	*ROCK2*	metastasis	Down	[49,50]
miR199a-3p	mTOR, PAK4, caveolin-2	drug resistance, cell growth	Down	[50–54]
miR199a-5p	*DDR1*, *ATG7*	invasion, autophagy	Down	[52,53]
miR-195	cyclin D1, CDK6, *E2F3*, *LATS2*	cell cycle, tumorigenesis, apoptosis	Down	[55]
miR-214	HDGF, β-catenin	cell growth, angiogenesis, metastasis	Down	[56,57]
miR-18a	ER1a	proliferation	Up	[58]
miR-21	*PTEN*, *RHOB*, *PDCD4*	metastasis, drug resistance	Up	[59]
miR-25	*TRAIL*	apoptosis	Up	[6]
miR-221	p27, p57, *ARNT*, CDK inhibitors	apoptosis, proliferation, angiogenesis	Up	[61–64]
miR-222	p27, *DDIT4*	tumorigenesis	Up	[28,65,66]
miR-224	*ATG5*, *SMAD4*, autophagy, *API5*	tumorigenesis, autophagy	Up	[64]
miR-24-3p	Metallothionein 1M	proliferation, apoptosis	Up	[35]
miR122	BCL-w, ADAM17, *WNT1*	apoptosis, proliferation, angiogenesis	Up/Down	[67–72,74]
miR-17-5p	*PTEN*, *GALNT7*, vimentin	proliferation, invasion	Up/Down	[43]
miR-92a-3p	*PTEN*, AKT/Snail	proliferation	Down	[44]

3. Discussion

The principal objective of HCC biomarker research is to find new molecules and optimize the use of the existing ones to diagnose the disease earlier in at-risk population. At the same time, the advent of new biomarkers may cause unnecessary testing and abuse of wasteful and needless follow-up examinations in absence of proper validation and algorithms for further management, given that only a small proportion of the at-risk population will eventually develop the disease [75].

The serum concentration of AFP is the only used marker for the diagnosis of HCC. Other serological biomarkers such as Golgi protein 73 (GP73), Glypican-3 (GPC3) and aldo-keto reductase family 1 member 10 (AKR1B10) appear promising but require further validation [75]. Osteopontin (OPN) has been reported as one of the most promising markers for HCC, as well. However, a meta-analysis demonstrated that OPN had comparable accuracy to AFP for HCC diagnosis, while the value of the combination AFP-OPN was not clear deserving further investigation [76]. MiRNAs can serve as diagnostic and prognostic tools in HCC and are being used as therapeutic targets, as well. MiRNAs participate in various processes such as HCC proliferation, apoptosis, invasion, metastasis, epithelial-mesenchymal transition, angiogenesis and drug resistance. Exosomes can vehiculate miRNAs between cells, and autophagy is a primary regulatory mechanism of miRNAs in HCC [77]. However, consistency of the results obtained with miRNAs is poor, with subsequent challenges in the process of clinical validation. Variability is one of the main reasons explaining the discrepancies observed in studies involving miRNAs in HCC. Indeed, miRNAs are found in higher concentrations in plasma rather than serum because of the platelet mediated degradation during the clotting process [75]. Moreover, the polymorphic sites of various miRNAs are associated with HCC, and prevalence of polymorphisms varies with ethnicity [78]. In addition, several miRNAs whose expression

is increased in plasma and serum of HCC patients are expressed at lower levels in HCC tumor tissue compared with non-tumoral tissue.

A recent meta-analysis evaluated the diagnostic efficacy of miRNAs in distinguishing HCC at early stages from healthy individuals. A total of 34 studies were included, with 2747 HCC patients and 2053 healthy individuals. The diagnostic efficacy of serum and plasma-derived miRNAs was the same. Three different subgroups were compared, single miRNA, miRNAs' panel and multiple miRNAs. The miRNAs' panel had better diagnostic efficacy, with a sensitivity of 86% and specificity of 93%. Among miRNAs that were initially found to be promising as diagnostic tools in HCC, miR-21 and miR-122 did not show a different expression in cancer patients in an analysis using RNA sequencing. Differently, miR-101-3p, miR-106b-3p and miR-1246 showed a good diagnostic accuracy, either individually or in combination, when evaluated in HCC patients versus healthy controls or cirrhotic patients [79].

Therefore, miRNAs could be used as valid biomarkers for HCC early diagnosis and prediction of prognosis. Moreover, understanding the regulatory mechanisms of miRNAs in HCC development and progression could allow the development of new molecular drugs. The main limitation of early-phase studies involving miRNAs is the scarce translation of experimental findings into clinical practice. Moreover, the technical reliability of miRNAs measurements in HCC diagnosis requires further assessments and development.

Future research of miRNAs in HCC should focus both on miRNAs taking part in HCC carcinogenesis and on miRNAs deregulated due to changes in the metabolic and structural profile of tumor cells. Therefore, consensus is necessary in order to reduce heterogeneity in techniques used, samples involved (tissue versus serum versus plasma) and groups compared to HCC patients (cirrhotic patients, patients with chronic hepatitis, healthy controls).

4. Conclusions

MiRNAs' expression patterns are altered in HCC. Significant progress has been made in the evaluation of circulating miRNAs as potential diagnostic biomarkers for HCC. However, any of the investigated miRNAs or miRNAs panels has entered clinical practice so far. This has mostly to do with lack of protocols standardization, small sample size and discrepancies in the measurement techniques. Larger and prospective studies are warranted in order to eliminate biases and possibly identify new useful biomarkers for HCC diagnosis, together or in place of AFP, which remains nowadays the only validated available biomarker.

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