cancers

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Review

Liquid Biopsy in Hepatocellular Carcinoma: Where Are We Now?

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Citation: Pelizzaro, F.; Cardin, R.; Penzo, B.; Pinto, E.; Vitale, A.; Cillo, U.; Russo, F.P.; Farinati, F. Liquid Biopsy in Hepatocellular Carcinoma: Where Are We Now? *Cancers* **2021**, *13*, 2274. https://doi.org/10.3390/cancers13092274

Academic Editor: Anna Kakehashi

Received: 16 April 2021
Accepted: 6 May 2021
Published: 10 May 2021

Supplementary Table 1. Studies on use of microRNAs (miRNAs) as biomarkers in HCC.

Diagnosis				
Study	**Type of miRNA**	**Number of patients**	**Comparator**	**Main findings (sensitivity/specificity, AUC)**
Zhou et al, 2011 [1]	miRNA panel: miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a and miR-801	Training phase: 204 HCC, 60 LC, 75 CLD (HBV), healthy subjects 68 Validation phase: 196 HCC, 56 LC, 72 CLD (HBV), 66 healthy subjects	AFP (cut-off 400 ng/mL)	Training cohort: 68.6%/90.1%, 0.864 Validation cohort: 81.8%/83.5%, 0.888 AUC according to BCLC stage: 0 = 0.888, A = 0.888, B = 0.901, and C = 0.881 In AFP <400 ng/mL: 77.7%/84.5%, 0.879 In AFP ≥400 ng/mL: 87.7%/83.5%, 0.910 HCC vs. healthy subjects: 83.2%/93.9%, 0.941 HCC vs. CLD: 79.1%/76.4%, 0.842 HCC vs. LC: 75%/91.1%, 0.884
Tomimaru et al, 2012 [2]	miR-21	126 HCC 30 CLD 50 healthy subjects	AFP (cut-off 19 ng/mL in HCC vs. CLD and 6 ng/mL in HCC vs. healthy subjects)	HCC vs. CLD: miR-21: 61.1%/83.3%, 0.773 AFP: 59.5%/83.3%, 0.743 miR-21 + AFP: 81%/76.7%, 0.823 HCC vs. healthy subjects: miR-21: 87.3%/92%, 0.953 AFP: 77.8%/96%, 0.882 miR-21 + AFP: 92.9%/90%, 0.971
Lin et al, 2015 [3]	miRNA classifier: miR-29a, miR-29c, miR-133a, miR-143, miR-145, miR-192, and miR-505	Training cohort: 108 HCC, 47 LC, 51 CLD (HBV), 51 healthy subjects Validation cohort: 2020 HCC, 181 CLD + LC, 108 healthy subjects	AFP (cut-off 20 ng/mL)	Validation cohort 1: miRNA classifier: 74.5%/88.9%, 0.817 AFP: 56.9%/84.9%, 0.709 ($p<0.05$ vs. miRNA classifier) Validation cohort 2: miRNA classifier: 85.7%/91.1%, 0.884 AFP: 59.2%/100%, 0.796 ($p<0.05$ vs. miRNA classifier) miRNA classifier vs. AFP (AUC): Small HCC: 0.833 vs. 0.727 ($p<0.05$) Early-stage HCC: 0.824 vs. 0.754 ($p<0.05$) miRNA classifier in AFP negative patients (AUC): 0.825
El-Tawdi et al, 2016 [4]	lncRNA-CTBP +miR-16-2 + miR-21-5p + LAMP2	78 HCC 36 CLD (HCV) 44 healthy subjects	NR	HCC vs. CLD + healthy subjects: 79.5%/100%, 0.938
Amr et al, 2016 [5]	miR-21 and miR-199a	23 HCC 17 CLD	AFP	miR-21: 100%/81.2%, 0.943 miR-199a: 54.5%/100%, 0.856 AFP: 100%/69.2%, 0.832
Okajima et al, 2016 [6]	miR-224	87 HCC 55 healthy subjects	AFP (cut-off 20 ng/mL) DCP (cut-off 40 mAU/mL)	93.1%/80.0%, 0.908 Early-stage HCC (TNM stage I) vs. healthy subjects: AUC=0.0899 miR-224 in the detection of tumor <18 mm (sensitivity, AUC): First cohort: 80%, 0.802 (DCP 45%, 0.741; AFP 50%, 0.475) Second cohort: 63.6%, 0.731 (DCP 50%, 0.595; AFP 20%, 0.726)

Zhuang et al, 2016 [7]	miR-21, miR-26a and miR-101	52 HCC 42 CLD 43 healthy subjects	AFP (cut-off NR)	HCC vs. healthy subjects: miR-21 + miR-26a + miR-101: 88.2%/58.5%, 0.803 miR-21 + miR-26a + miR-101 + AFP: 87%/78%, 0.914 HCC vs. CLD: miR-26a + miR-101: 70.6%/80.2%, 0.822 miR-26a + miR-101 + AFP: 72.5%/86.7%, 0.854
Zekri et al, 2016 [8]	Several miRNAs	192 HCC 96 LC 96 CLD (HCV) 95 healthy subjects	AFP (cut-off NR)	HCC vs. healthy subjects: miR-122 + miR-885-5p + miR-29b + AFP: AUC = 1 HCC vs. LC: miR-122 + miR-885-5p + miR-221 + miR-22 + AFP: AUC = 0.982 HCC vs. CLD: miR-22 + miR-199a-3p + AFP: AUC = 0.988
Shi et al, 2017 [9]	miR-106b	25 HCC 310 non-HCC	NR	Patients with HCC had higher serum miR-106b levels. 90%/66.7% (0.855)
Guo et al, 2017 [10]	miR-21	175 HCC 64 CLD (HBV) 78 LC 136 healthy subjects	AFP (cut-off 16.42 ng/mL)	HCC vs. LC: miR-21: 80.8%/72.9%, 0.814 AFP: 70.4%/71.5%, 0.686 HCC vs. CLD: miR-21: 76.9%/85.7%, 0.789 AFP: 59.3%/69.7%, 0.634
Zhang et al, 2017 [11]	miRNA panel: miR-92-3p, miR-107 and miR-3126-5p	115 HCC 40 healthy subjects	AFP (cut-off NR)	miR-3126-5p: AUC = 0.881 miR-107: AUC = 0.730 miR-92a-3p: AUC = 0.705 miRNA panel: AUC = 0.969 vs. AFP: AUC=0.848 miRNA panel + AFP: AUC = 0.994
Moshiri et al, 2018 [12]	miR-106b-3p, miR-101-3p and miR-1246	62 HCC 41 LC 25 healthy subjects	NR	HCC vs. healthy subjects: 100%/100%, 1.00 HCC vs. LC: 100%/92.9%, 0.99s
An et al, 2018 [13]	miR-375, miR-10a, miR-122 and miR-423	84 HCC 84 normal controls	NR	miR-375: AUC = 0.918 miR-10a: AUC =0.838 miR-122: AUC = 0.871 miR-423: AUC =0.898 miR-375, miR-10a, miR-122 and miR-423: AUC = 0.995
Han et al, 2019 [14]	miR-148a	155 HCC 96 LC 95 healthy subjects	AFP (cut-off NR)	HCC vs. healthy subjects: 97.9%/92.9%, 0.980 HCC vs. LC: AFP: 88.4%/84.4%, 0.941 miR-148a: 89.6%/89%, 0.919 (in patients with low AFP: 90.6%/92.6%, 0.949)
Weis et al, 2019 [15]	miR-122-5p, miR-486-5p and miR-142-3p	20 HCC 20 LC 20 CLD	AFP (cut-off 20 ng/mL)	miR-122 + miR-486 + miR-142: 80%/95%, 0.94 AFP: 25%/90%, 0.64 (p=0.06 vs. miRNA panel) miR-122 + miR-486 + miR-142 + AFP: 0.94

Yamamoto et al, 2020 [16]	8 miRNA panel: miR-320b, miR-663a, miR-4448, miR-4651, miR-4749-5p, miR-6724-5p, miR-6877-5p, and miR-6885-5p	353 HCC 93 LC 46 CLD 1033 healthy subjects	AFP (cut-off 10 ng/mL) DCP (cut-off 40 mAU/mL)	HCC vs. healthy subjects: 97.7%/98.4%, 1.00 HCC vs. CLD + LC: 97.7%/94.7%, 0.99 In TNM stage I, the 8 miRNAs panel: 100%/94.7%, 1.00
Prognosis				
Study	**Type of miRNA**	**HCC patients**	**Stage /Treatment**	**Main findings**
Koberle et al, 2013 [17]	miR-1 and miR-122	N = 195	BCLC stage A/B/C/D: 24%/39%/30%/7% Treatment: LR 9%, ABL+IAT 53%, SOR 24%, LT 11%	At univariate analysis, longer survival in: High miR-1 group: HR = 0.44 (0.23-0.83) High miR-122 group: HR = 0.49 (0.25-0.96) High miR-1 was an independent predictor of better OS: adjusted HR = 0.45 (0.24-0.86)
Xu et al, 2015 [18]	miR-122	N = 122	Stage: NR Treatment: NR	High miR-122 associated with longer OS: adjusted HR = 0.26 (0.14-0.47)
Cho et al, 2015 [19]	miR-122	N = 120	TNM stage I+II/III+IV: 73.3%/26.7% Treatment: LR 52.5%, ABL 47.5%	miR-122 levels were not associated with OS in the entire cohort and in LR patients. In ABL patients, high miR-122 associated with shorter OS: adjusted HR = 2.67 (1.12-6.35).
Okajima et al, 2016 [6]	miR-224	N = 87	TNM stage I/II-IV: 71%/29% Treatment: LR	miR-224 was significantly reduced in post-LR samples (p=0.006). Tumor >2 cm, advanced stage and presence of recurrences correlated with high levels of miR-224 (p=0.0005, 0.04 and 0.003, respectively).
Cho et al, 2017 [20]	miR-21, miR-26a and miR-29a	N = 120	TNM stage I+II/III+IV: 73.3%/26.7% Treatment: LR 52.5%, ABL 47.5%	Poorer DFS was demonstrated for: Low miR-26a levels: adjusted HR = 1.72 (1.04-2.83) Low miR-29a levels: adjusted HR = 1.75 (1.04-2.94) Shorter LT-free survival was demonstrated for: Low miR-26a: adjusted HR = 3.41 (1.32-8.82) Low miR-29a: adjusted HR = 2.75 (1.10-6.85)
Fornari et al, 2017 [21]	miR-221	N = 90 (50 in training set and 43 in validation set)	Stage: advanced HCC without extrahepatic metastases Treatment: sorafenib	Both in training and in validation cohorts: Higher pre-treatment miR-221 levels in non-responders vs. responders. After 2 months of treatment: increase of miR-221 in responders; non-significant decrease in non-responders.
Nishida et al, 2017 [22]	miR-181a-5p and miR-339-5p	N = 53	BCLC stage A/B/C: 15%/28.3%/56.6% Treatment: sorafenib	miR-181a-5p independently predicted DC: adjusted HR = 0.14 (0.01–0.66). High miR-181a-5p was associated with longer OS: adjusted HR = 0.27 (0.07-0.82).
Kim et al, 2018 [23]	miR-21, miR-26a and miR-29a-3p	N = 198	BCLC stage: A-B/C-D: 73.2%/26.8% Treatment: TACE	High miR-21, high miR-26a and low miR-29a-3p levels associated with overall TACE refractoriness (no after adjustment for confounders). miRNA combination panel (high miR-21 and miR-26a and low miR-29a-3p) independently predict early TACE refractoriness: adjusted HR = 2.32 (1.08-4.99).

Chuma et a, 2019 [24]	miR-1246	N = 121	BCLC stage 0/A/B: 27.3%/67.8%/5% Treatment: LR	miR-1246 levels higher in patients with early tumor recurrence. High levels of miR1246 associated with: Early tumor recurrence: adjusted HR = 3.42 (1.33-8.82) Shorter DFS (p<0.001) Shorter OS (p<0.001); adjusted HR = 2.78 (1.53-5.07)
Ali et al, 2019 [25]	miR-133b, miR-26a, miR-107 and miR-106	N = 51	Stage: single tumor 57% Treatment: TACE	Baseline miR-106b, miR-107 and miR-133b elevated in TACE-responders; miR-26a in non-responders (all p<0.001). Prediction of TACE response (sensitivity/specificity, AUC): miR-26a: 100%/100%, 1.00 in CR vs. NR; 94%/83%, 0.958 in CR vs. PR miR-133b: 100%/94%, 0.997 in CR vs. NR; 93%/88%, 0.919 in CR vs. PR; 94%/83%, 0.935 in PR vs. NR miR-26a + miR-133 (AUC): 1.00 in CR vs. NR; 0.997 in PR vs. NR; 0.919 in CR vs. PR; 0.998 in CR+PR vs. NR
Ning et al, 2019 [26]	miR-155, miR-96 and miR-99a	N = 30	TNM stage I+II/III+IV: 40%/60% Treatment: LR	Decreased OS in patients with: High miR-155 levels (p=0.004) High miR-96 levels (p=0.02) miR-99a levels were not significantly associated with OS.
Jin et al, 2019 [27]	miR-128, miR-139-5p, miR-382-5p, miR-410, miR-424-5p and miR-101-3p	N = 116	Stage: multifocal 29% Treatment: NR	Higher expression of miR-128, miR-139-5p, miR-382-5p and miR-410 and lower levels of miR-424-5p and miR-101-3p associated with worse prognosis.
Han et al, 2019 [14]	miR-148a	N = 155	Stage: metastases 30% Treatment: TACE or ABL	miR-148a increased significantly after treatment (p<0.0001).
Teufel et al, 2019 [28]	miR-30a, miR-122, miR-125b, miR-200a, miR-374b, miR-15b, miR-107, miR-320 and miR-645	N = 243	BCLC stage A/B/C: <1%/14%/86% (in RESORCE trial) Treatment: regorafenib	Increased miR-30a, miR-122, miR-125b, miR-200a, and MIR374B, decreased miR-15b, miR-107, and miR-320b, and absence of miR-645 predictive of survival benefit. miR-15b, miR-320b, and miR-200a were prognostic for OS (p<0.05)
Loosen et al, 2020 [29]	miR-193a-5p	N = 41	TNM stage T1-2/T3-4: 75%/25% Treatment: LR 19.5%, LT 80.5%	High levels of miR-193a-5p independently associated with poorer OS: adjusted HR = 3.71 (1.35-10.16)
Pratedrat et al, 2020 [30]	miR-223-3p	N = 70	BCLC stage 0-A/B/C-D: 30%/34.3%/35.7% Treatment: NR	High levels of miR-223-3p independently associated with poorer OS: adjusted HR = 6.61 (2.36-18.55)

Abbreviations: ABL, ablation; AFP, alpha-fetoprotein; AUC, area under the curve; BCLC, Barcelona Clinic Liver Cancer; CLD, chronic liver disease; CR, complete response; DC, disease control; DCP, des-γ-carboxyprothrombin; DFS, disease-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; IAT, intrarterial therapies; LC, liver cirrhosis; LR, liver resection; LT, liver transplantation; miRNA, microRNA; NR, not reported; OS, overall survival; PR, partial response; SOR, sorafenib; TACE, trans-arterial chemoembolization.

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