Int J Clin Exp Pathol 2017;10(4):4756-4763
www.ijcep.com /ISSN:1936-2625/IJCEP0046254

Original Article

Circulating miR-106a high expression predicts worse prognosis in patients with hepatocellular carcinoma

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Received December 9, 2016; Accepted February 6, 2017; Epub April 1, 2017; Published April 15, 2017

Abstract: This study aimed to investigate the associations of miR-106a/b expression with hepatocellular carcinoma (HCC) clinical pathological features and prognosis. 152 HCC patients and 76 health controls (HCs) were recruited in this prospective cohort study. Plasma samples were collected from HCC patients before treatments and HCs. Total RNA was extracted from plasma and microRNA (miR)-106a/b expressions were determined by Quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Plasma miR-106a/b expressions were increased in HCC patients compared with health controls (both P<0.001). Plasma miR-106a expression was found to be positively correlated with tumor size (P=0.035), lymph node metastasis (P=0.042) and TNM stage (P=0.034); while miR-106b level was observed to be only associated with tumor size (P=0.015). No correlations of miR-106a/b expressions with other clinicopathological features were found in this study. Kaplan-Meier curve illustrated that HCC patients with low miR-106a expression in plasma had a longer OS compared with high expression (P=0.005), while no differences of OS were observed between high and low expressions in miR-106b (P=0.113). In addition, univariate and multivariate Cox's proportional hazards regression were performed, and we found miR-106a high expression (P=0.021) was an independent factor in predicting shorter OS, as well as lymph node metastasis (P=0.037) and vascular invasion (P=0.047). In conclusion, our study validated that circulating miR-106a expression could be regarded as a novel and promising biomarker of prognosis in HCC patients.

Keywords: Circulating, miR-106a/b, hepatocellular carcinoma (HCC), prognosis

Introduction

Hepatocellular carcinoma (HCC), an inflammation related malignant tumor, exhibits an increasing incidence worldwide which accounts for 6% of newly diagnosed carcinomas worldwide [1-3]. And it is one of the most frequent causes of carcinoma-related death all over the world as well as the major cause of death in cirrhosis patients [1, 4]. Regardless of improvement in HCC treatment, poor prognosis still exists in most patients, which mainly due to late diagnosis resulting from that few symptoms were able to be observed at an early stage [5, 6].

MicroRNA (miRNA) is a small class of non-coding RNA molecules, which consists of 21-13-nt fragments; it negatively regulates post-transcriptional expression by suppressing target mRNA translation or inducing its degradation by pairing with complementary sequences within 3'-untranslated regions (UTR) of targeted transcripts [7]. Accumulating researches demonstrate that dysregulations of miRNAs play critical roles in pathogenesis of HCC through regulating cell proliferation, differentiation, migration and apoptosis in tumors by multiple mechanisms such as activating insulin receptor substrate 1 (IRS1), survivin and NF-kappaB-inducing kinase (NIK) [8-13].

MicroRNA-106 (miR-106), consists of miR-106a and miR-106b, belongs to the miR-17 family and the dysregulation of miR-17 family is found in numerous carcinomas [14-16]. In non-small cell lung cancer, miR-106a is observed to reduce the phosphatase and tensin homolog (PTEN) expression therefore motivates the growth and metastasis of tumor [17]. Furthermore, miR-106b is found to further gastric carcinoma cell cycle by mediating p21 and E2F

transcription factor 5 protein (E2F5) target gene levels [18]. As to in esophageal squamous cell carcinoma, miR-106b is demonstrated to strengthen epithelial-mesenchymal transition (EMT) by down regulating mothers against decapentaplegic homolog (Smad) 7 hence promotes cell migration as well as invasion [19]. A meta-analysis result characterizes that miR-106a/b has a good accuracy in carcinoma diagnosis [20]. In addition, recent studies show that miR-106a is positively associated with tumor metastasis in gastric carcinoma patients and is negatively correlated with poor prognosis in glioma patients [21, 22].

However, the correlation of circulating miR-106a/b with HCC prognosis is still unclear. Thus, our study aimed to investigate the associations of miR-106a/b expression with HCC clinical pathological features and prognosis.

Materials and methods

Patients

152 HCC patients were recruited in this prospective cohort study, from Oct. 2010 to Sep. 2012 at the Department of General Surgery, the Affiliated Cangnan Hospital of Wenzhou Medical University. The inclusion criteria were: initial patients diagnosed as HCC by histopathological examination; no interventions for the tumor treatment were carried out such as chemotherapy, radiotherapy and surgery. While patients with serious infection, history of other malignant tumor, cognitive impairment, poor adherence or who were not able to understand the study protocol, were excluded.

HCC Patients were followed up by telephone calls or usual visits, and overall survival (OS) was calculated from recruiting time to the date of death or last follow-up, the last month of follow-up was Oct. 2016.

In the meanwhile, 76 age and gender matched health volunteers at the department of physical examination were also enrolled in this study as health controls.

This study was approved by the Ethics Committee of Cangnan Hospital, and all the participants (Both HCC patients and health controls) signed informed consent.

Samples

Peripheral blood was obtained from HCC patients and health controls and kept in ethylene diamine tetraacetic acid (EDTA) tube. After standing at room temperature for 2 hours, peripheral blood was centrifuged at 3000 r/min for 10 minutes at 4°C. The upper plasma were subsequently acquired and further centrifuged at 12000 r/min for 15 minutes at 4°C. The plasma were then collected and stored at -80°C.

Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

Total RNA was extracted from plasma by TRIzol LS Reagent (Invitrogen, Carlsbad, CA, USA), and the concentration as well as purity of RNA were evaluated by spectrophotometer. RNA was then reversely transcribed by the PrimerScript Real-time reagent kit (TaKaRa, Otsu, Shiga, Japan) and quantitative measurement of miRNAs expression wasperformed using SYBR Premix Ex TaqTM II according to the manufacturer's instructions (TaKaRa, Otsu, Shiga, Japan). U6 was used as internal reference, and miR-106a/b expressions were calculated by $2^{-\Delta\Delta t}$ method.

Statistical analysis

Statistical analysis was performed using the SPSS 21.0 program. Data were mainly presented as median and (25th-75th), count and (percentage). Differences between two groups were compared by Wilcoxon rank sum test or Chi-square test. Kaplan-Meier curve and Log-rank test were carried out to analyze OS in different groups cut off by miR-106a/b levels. Univariate Cox proportional hazards regression was performed to investigate factors at baseline which influence OS, and all factors with a *P*-value ≤0.1 were further included in the multivariate Cox proportional hazards regression analyses. A $P \leq 0.05$ was considered as significant.

Results

Characteristics of HCC patients

152 HCC patients with age 57 (50-67) years and 119 (78%) male were enrolled in this study and included in the final analysis, among which

Table 1. The correlations of miR-106a/b expressions with clinicopathological features in HCC patients

Parameters	Cases (n=152)	*miR-106a*		*P Value*	*miR-106b*		*P Value*
		High	Low		High	Low	
Age (years)							
≥60	72	40	32	0.194	37	35	0.745
<60	80	36	44		39	41	
Gender							
Male	119	62	57	0.325	63	56	0.168
Female	33	14	19		13	20	
HBsAg							
Positive	122	65	57	0.103	63	59	0.415
Negative	30	11	19		13	17	
AFP (ng/ml)							
≥20	112	58	54	0.461	60	52	0.141
<20	40	18	22		16	24	
Anti-HCV							
Positive	21	13	8	0.240	13	8	0.240
Negative	131	63	68		63	68	
Liver cirrhosis							
Yes	103	56	47	0.118	57	46	0.056
No	49	20	29		19	30	
Smoke							
Yes	47	24	23	0.861	22	25	0.599
No	105	52	53		54	51	
Drink							
Yes	72	39	33	0.330	37	35	0.745
No	80	37	43		39	41	
Differentiation							
Poor	68	39	29	0.103	38	30	0.192
Moderate/well	84	37	47		38	46	
Tumor size (cm)							
≥3	81	47	34	0.035*	48	33	0.015*
<3	71	29	42		28	43	
Lymph node metastasis							
Positive	23	16	7	0.042*	14	9	0.258
Negative	129	60	69		62	67	
Vascular invasion							
Yes	51	30	21	0.122	28	23	0.390
No	101	46	55		48	53	
TNM stage							
III/IV	67	40	27	0.034*	38	29	0.141
I/II	85	36	49		38	47	

*P<0.05. Data was presented as counts; The comparison was determined by Chi-square test; P<0.05 was considered as significant; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; HCV, hepatitis C virus.

122 (81%) were hepatitis B surface antigen (HBsAg) positive and 21 (14%) were anti-hepatitis C virus (HCV) positive. The other clinical and pathological characteristics of HCC patients were presented in **Table 1**.

Higher plasma miR-106a/b expression in HCC patients

Plasma miR-106a expression was increased in HCC patients (4.501 (3.486-5.828)) compared with health controls (3.001 (2.196-5.117)), P<0.001, (**Figure 1A**). And miR-106b level was also illuminated to be higher in HCC patients than controls (5.210 (4.491-6.838) vs. 3.995 (3.453-5.506), P< 0.001, **Figure 1B**).

Correlation of miR-106a/b levels with clinical and pathological characteristics

As shown in **Table 1**, plasma miR-106a expression was found to be positively correlated with tumor size (P= 0.035), lymph node metastasis (P=0.042) and TNM stage (P=0.034); while miR-106b level was observed to be only associated with tumor size (P=0.015). No correlations of miR-106a/b expressions with other clinicopathological features were found in this study.

Higher miR-106a level was associated with worse OS

HCC patients were divided into miR-126a high group and low group by the median value in HCC as cut off point, so as miR-126b. Kaplan-Meier curve illustrated that HCC patients with low miR-106a expression in plasma had a longer OS compared with high expression (P= 0.005, **Figure 2A**). While no differences of OS were observed between high and low expressions in miR-106b (P=0.113, **Figure 2B**).

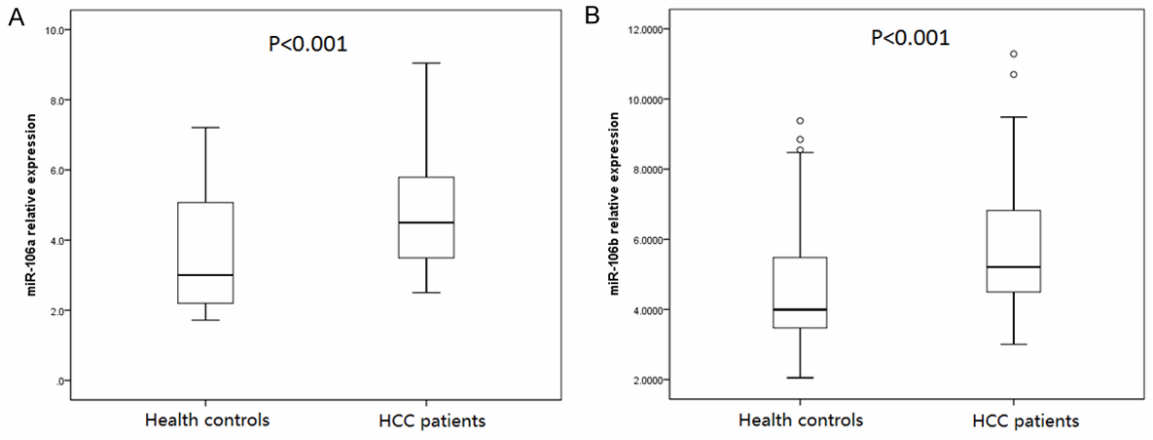

Figure 1. The relative expressions of miR-106a/b in HCC patients and Health controls. A. Relative expressions of miR-106a. B. Relative expressions of miR-106b. Comparisons between two groups were determined by Wilcoxon rank sum test. P<0.05 was considered as significant.

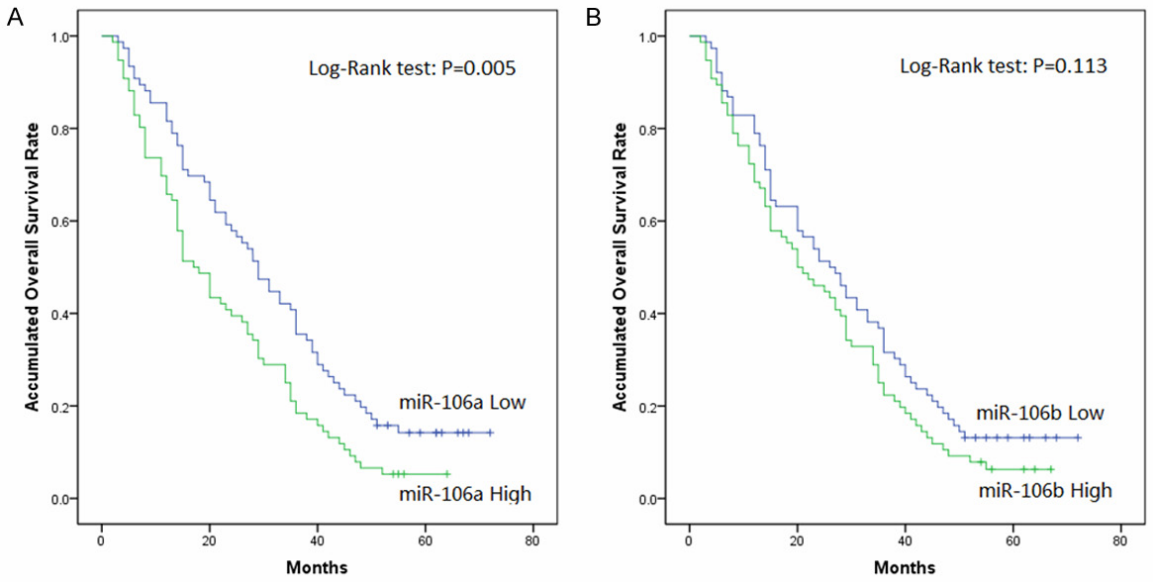

Figure 2. OA of HCC patients with high or low miR-106a/b expressions. A. OA of patients with high or low miR-106a expressions. B. OA of patients with high or low miR-106b expressions. OS in different groups cut off by miR-106a/b expressions were analyzed by Kaplan-Meier curve and log-rank test. P<0.05 was considered as significant.

MiR-106a expression was an independent factor in predicting OS

As to explore the factors at baseline in predicting OS in HCC patients, Univariate Cox's proportional hazards regression was performed, and miR-106a high expression (P=0.006), poor differentiation (P=0.036), lymph node metastasis (P=0.039), vascular invasion (P=0.042) as well as TNM stage III/IV (P=0.028) were manifested to be correlated with worse OS (**Table 2**). All the factors with a *P* value ≤0.1 were subsequently analyzed by mutilvariate Cox proportional hazards regression, which confirmed that miR-106a high expression (P=0.021) was an independent factor in predicting shorter OS (**Table 2**), as well as lymph node metastasis (P=0.037) and vascular invasion (P=0.047).

Discussion

The results of our study presented that (1) miR-106a/b expressions were elevated in HCC patients compared with health controls; (2) the

Table 2. Factors at baseline affecting the overall survival in HCC patients

	Univariate				Multivariate			
	P value	HR	95% CI		*P* value	HR	95% CI	
			Lower	Higher			Lower	Higher
miR-106a								
High vs. Low	0.006*	1.603	1.143	2.247	0.021#	1.563	1.070	2.283
miR-106b								
High vs. Low	0.121	1.304	0.932	1.826	-	-	-	-
Age (years)								
≥60 vs. <60	0.533	1.113	0.795	1.559	-	-	-	-
Gender								
Male vs. Female	0.138	1.376	0.902	2.099	-	-	-	-
Gender								
Positive vs. Negative	0.566	1.130	0.745	1.714	-	-	-	-
AFP (ng/ml)								
≥20 vs. <20	0.431	1.162	0.799	1.692	-	-	-	-
AFP (ng/ml)								
Positive vs. Negative	0.750	1.079	0.677	1.718	-	-	-	-
Liver cirrhosis								
Yes vs. No	0.072	1.404	0.970	2.033	0.264	1.250	0.845	1.849
Smoke								
Yes vs. No	0.603	1.091	0.760	1.566	-	-	-	-
Smoke								
Yes vs. No	0.607	1.092	0.780	1.529	-	-	-	-
Differentiation								
Poor vs. Moderate/well	0.036*	1.436	1.024	2.015	0.109	1.325	0.940	1.868
Tumor size (cm)								
≥3 vs. <3	0.084	1.351	0.960	1.900	0.211	1.251	0.881	1.776
Lymph node metastasis								
Positive vs. Negative	0.039*	1.622	1.025	2.567	0.037#	1.697	1.033	2.788
Vascular invasion								
Yes vs. No	0.042*	1.441	1.013	2.049	0.047#	1.453	1.006	2.099
Vascular invasion								
III/IV vs. I/II	0.028*	1.461	1.043	2.048	0.100	1.339	0.946	1.895

*P<0.1, #P<0.05. Data was presented as *P* value and 95% CI. Significance was determined by univariate and multivariate Cox's proportional hazards regression analysis. A *P* Value <0.05 was considered significant. HCC, hepatocellular carcinoma; HR, hazard ratio; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; HCV, hepatitis C virus.

miR-106a expression was positively associated with tumor size, lymph node metastasis and TNM stage, while miR-106b was only correlated with tumor size; (3) HCC patients with high expression of plasma miR-106a had a worse OS compared with low expression, and miR-106a was an independent predicting factor of shorter OS.

An overwhelming majority of HCC cases are developed from chronic liver diseases, among which HBV is the most common risk factor [1, 2]. More importantly, the mortality of HCC patients is approaching incidence rate over years, which indicates HCC is of extremely poor prognosis that needs to be improved [23]. In the last decade, miRNAs have been proved to mediate HCC pathogenesis through regulating various cell activities such as proliferation, apoptosis, differentiation as well as migration [8-10]. For instance, in the study of Qiao et al, up regulation of miR-210 is reported to mediate cell migration and invasion in HCC by targeting vacuole membrane protein 1 (VMP1) [24]. In

another study, Wei, Wang et al reports that down regulation of miR-203 mediates cell proliferation in HCC through targeting survivin [12].

MiR-106a, a miR-106-163 cluster member, participates in the processes of multiple carcinogenesis [25]. For example, according to the study of Xiao Xie et al, miR-106a stimulates cell growth and metastasis in non-small cell lung carcinoma through reducing the expression of PTEN [17]. And Wang Z et al reported that in glioma stem cell, tissue inhibitor of metalloproteinases-2 (TIMP-2) is targeted by mirR-106a thus promoted the invasion of glioblastoma [26]. In this present study, the results showed that miR-106a level was increased in HCC patients compared with health controls, and miR-106a level was positively associated with tumor size, lymph node metastasis and TNM stage, which Indicated miR106a is an oncogenic factor. Our results were in accordance with previous studies in other cancers, which revealed miR-106a expression is dysregulated in numerous cancers such as colorectal cancer, gastric cancer and lymphoma [27-29].

In addition, miR-106a is detected to promote drug resistance of the cisplatin therapy in human ovarian carcinoma cells through targeting PDCD4 [30]. Accordingly, in metastatic colorectal carcinoma patients treated with first-line oxaliplatin-based treatment, miR-106a is one of the miRNAs that predict clinical outcome [31]. And epithelial miR-106a level predicts short disease free survival (DFS) and OS in stage II colorectal carcinoma in a cohort study of 50 participants [32]. In our study, we validated that high miR-106a level was an independent predictor of shorter OS in HCC patients, which might due to (1) high miR-106a was associated with tumor size, lymph node positive and TNM stage in HCC patients that indicates worse condition in patients, and resulted in shorter OS; (2) high miR-106a improved drug resistance in cisplatin-based therapy which influences the OS in HCC patients.

MiR-106b, located on chromosome 7q 22.1, is a member of miR-106b~25 cluster [33]. Previous studies have illuminated miR-106b as a tumor metastasis miRNA in different cancers, for instance, colon carcinoma with lymph node metastasis and breast carcinoma [33, 34]. A study conducted in Kazakh's esophageal squamous cell carcinoma patients illustrates that miR-106b stimulates carcinoma cell migration and invasion by reinforcing EMT [19]. And Yu et al reportedthat miR-106b signaled transforming growth factor (TGF)-β/Smad in Cluster of Differentiation 44 (CD44)-positive gastric carcinoma cells to modulate characteristics of tumor stem cell [35]. Our study observed miR-106b expression was increased in HCC patients compared with health controls, and miR-106b was positively associated with tumor size. However, no correlation of miR-106b and OS was found in our study, which might result from that miR-106b was only correlated with tumor size but not pathological stage, lymph node positive or TNM stage, so little effects were found on OS.

Some limitations occurred in our study: (1) no data were analyzed about treatments on participants were carried out after recruited, which might result in the bias in our study; (2) in this cohort study, the sample size that included 152 HCC patients and 76 health controls is relatively small, which means a large sample size study is needed in the future; (3) the mechanism of the impact on miR-106a/b target gene expression was not investigated in this study.

In conclusion, our study validated that circulating miR-106a expression could be regarded as a novel and promising biomarker of prognosis in HCC patients.

Disclosure of conflict of interest

None.

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