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Original Article

miR-122 and miR-197 expressions in hepatic carcinoma patients before and after chemotherapy and their effect on patient prognosis

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Abstract: Objective: To quantify the miR-122 and miR-197 expression levels in liver cancer (LC) patients before and after chemotherapy and to determine their prognostic implications. Methods: The present study included 169 patients with LC who were admitted to our hospital from January 2005 to December 2010. The miR-122 and miR-197 expression levels in the patients' cancerous and adjacent tissues were quantified, and their peripheral blood levels before and after chemotherapy were analyzed, as well as their prognostic implications. Results: The miR-122 and miR-197 levels in the LC tissues were lower than they were in the adjacent tissues, and they increased in the peripheral blood after chemotherapy. Higher miR-122 and miR-197 expression levels were observed in the LC tissues of sorafenib-sensitive patients. ROC curves demonstrated that miR-122 and miR-197 are predictive markers for the therapeutic effect of sorafenib. As shown by a K-M survival curve and a log-rank test, low miR-122 and miR-197 levels are responsible for low 5-year patient survival rates. Moreover, a univariate Cox analysis uncovered the association between the 5-year survival and the miR-122 and miR-197 expression levels, the size and number of tumors, vascular invasion, and TNM and BCLC staging. Also, a multivariate Cox analysis indicated that the independent risk factors for 5-year survival in LC included the miR-122 and miR-197 levels, the number of tumors, vascular invasion, and TNM and BCLC staging. Conclusion: miR-122 and miR-197 expression levels can predict LC patient responses to sorafenib chemotherapy, and their levels increase after chemotherapy. Moreover, decreased miR-122 and miR-197 levels are independent risk factors for LC progression.

Keywords: miR-122, miR-197, liver cancer, chemotherapy, prognosis

Introduction

Liver cancer (LC) ranks fifth in frequency and third in cancer deaths worldwide, with an increasing incidence and mortality [1] More than 550,000 new cases are diagnosed every year involving more than 400,000 males and more than 150,000 females [2]. Due to LC's invasive metastasis and recurrence, the long-term patient survival rate remains low; moreover, the overall 5-year survival rate of advanced LC is less than 5%, with a median overall survival time of 3 to 16 months [3, 4]. In recent years, great progress has been made in LC treatment, including progress in surgical resection, radiotherapy, and chemotherapy.

The identification of pre-treatment markers predictive of therapeutic benefits can avoid ineffective regimens and unnecessary toxicity, and minimize the treatment delays of effective alternative schemes [5]. Interestingly, microRNAs (miRNAs) have shown a potential use as LC biomarkers and are thought to indicate its molecular pathogenesis [6]. However, the relationship between miRNAs and chemotherapy efficacy has been poorly analyzed. One study verified the close relationship between miR-122 and LC, finding that a decrease in miR-122 in LC tissues affects patient survival and concluding that miR-122 is an independent prognostic factor for LC [7]. Another study also found that miR-122 is associated with liver cell chemosensitivity and the inhibition of multidrug-resistance genes through its targeting of the Wnt/β-catenin pathway, thereby enhancing the sensitivity of LC to oxaliplatin [8]. miR-197-3p is a prognostic biomarker inhibiting cell in-

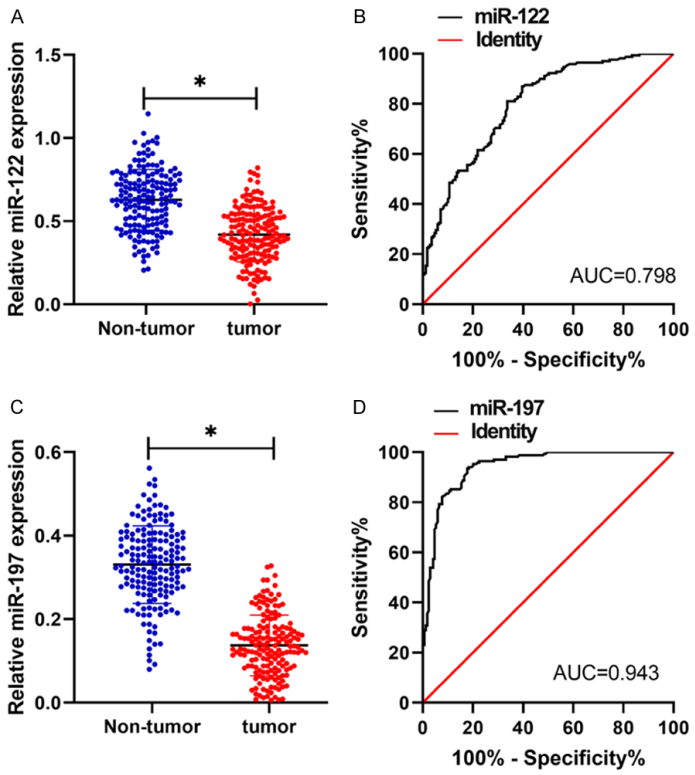

Figure 1. The miR-122 and miR-197 levels in LC. A: The miR-122 levels in LC. B: miR-122 for differentiating LC tissues. C: miR-197 levels in LC. D: miR-197 for differentiating LC tissues. *$P < 0.05$.

vasion in hepatocellular carcinoma (HCC) [9], but the role of miR-197 in LC has hardly been studied.

In the present study, qRT-PCR was used to quantify the miR-122 and miR-197 levels in LC patients before and after chemotherapy. And the associations between miR-122, miR-197, and chemotherapy were analyzed, as were their influences on patient prognosis.

Materials and methods

Patient recruitment and tumor collection

A total of 169 patients with LC, ranging in age from 35 to 83 years old and admitted to our hospital from January 2005 to December 2010, were recruited as the study cohort. The specimens were confirmed through histopathological examinations and the Edmondson grading system. The tumor stages were classified according to the sixth edition of the TNM staging system developed by the Union for International Cancer Control. The tumor differentiation was determined according to the Barcelona Clinical Liver Cancer (BCLC) staging system. The tissue specimens were stored at -80°C. All the patients underwent sorafenib chemotherapy, 400 mg twice a day, allowing for the discontinuation of treatment and a maximum of two dose reductions for drug-related adverse reactions. Patients who received neoadjuvant radiotherapy or chemotherapy within the 6 months before their operations were excluded from the study cohort. The ethics approval was granted by Central Theater General Hospital Medical Committee, and all the patients signed the consent form.

Assessment of the chemotherapy efficacy

The responses to the chemotherapy were classified by two radiologists as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) following the response evaluation criteria in solid tumors version 1.1 (RECIST). The 5-year survival rates were recorded.

RNA extraction and qRT-PCR

First strand cDNA was obtained (Revert Aid First Strand cDNA Synthesis kit, Thermo Fisher Scientific, Inc.) from the total RNA extracted from the tissue/peripheral blood (miRNeaseMini kit, Qiagen, Inc., Valencia, CA, USA). Next, cDNA amplification was conducted with iQ SYBR Green (Bio-Rad Laboratories, Inc.) on a CFX96 system (Bio-Rad Laboratories, Inc., Hercules, CA, USA). $2^{-\Delta\Delta Cq}$ was used to analyze the relative expression profiles of the miRNAs, with U6 as the internal reference. miR-122 forward (F): 5'-TTTGCTAGTGATGGATTGGAAACC-3', reverse (R): 5'-AGAGCCCCGGGATCTTGAATA-3'; miR-197-3p F: 5'-CACCACCTTCTCCACCCA-3', R: 5'-GGGACTGGACTTGGAGTC-3'; U6 F: 5'-CTCGCTTCGGCAGCACA-3', R: 5'-AACGCTTCACGAATTTGCGT-3'.

Statistical analysis

The data described as the mean ± standard deviation were processed statistically by SPSS 19.0. χ^2 tests and Student's t tests were used for the categorical and continuous data, respectively. ROC curves measured the predictive val-

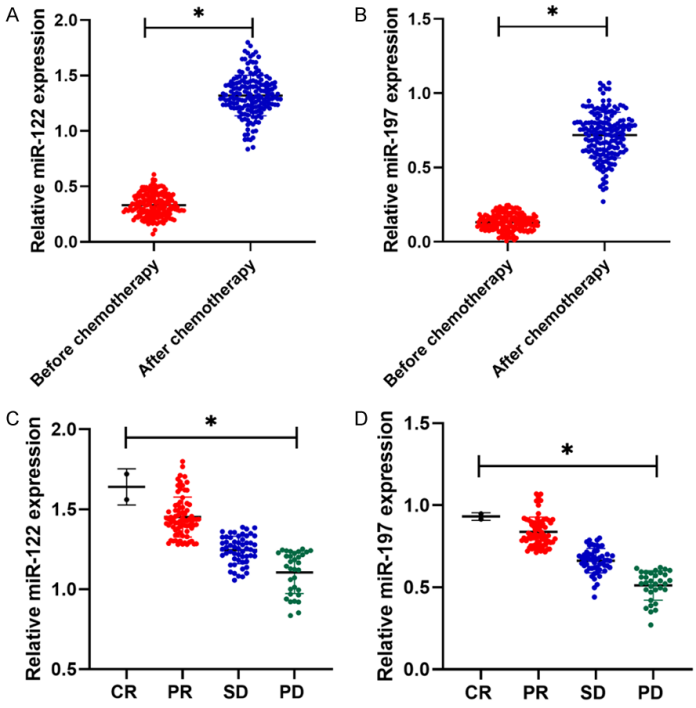

Figure 2. Changes in the miR-122 and miR-197 levels after the chemotherapy. A: Changes in the miR-122 levels after the chemotherapy. B: Changes in the miR-197 levels after the chemotherapy. C: The miR-122 levels in the patients with different curative effects. D: The miR-197 levels in the patients with different curative effects. $^{*}P < 0.05$.

ues of miR-122 and miR-197 in assessing the chemotherapeutic efficacy, and the patient survival was visualized using Kaplan-Meier curves and analyzed using log-rank tests. Multivariate COX analyses were carried out based on the significant variables as determined in the univariate COX analyses. The level of statistical significance was set at $P < 0.05$.

Results

Quantification of the miR-122 and miR-197 expression levels in LC patients

The miR-122 and miR-197 expression levels decreased in the LC tissues compared to the adjacent tissues, as demonstrated by qRT-PCR. ROC curves showed that the areas under the ROC curve (AUC) of miR-122 and miR-197 for distinguishing the cancerous tissues from the normal tissues were 0.799 and 0.943, respectively (**Figure 1**).

Changes in the miR-122 and miR-197 levels following chemotherapy

The miR-122 and miR-197 levels were elevated following the chemotherapy. According to RECIST version 1.1, of the 169 patients with LC, 2 achieved CR after sorafenib chemotherapy, 79 achieved PR, 55 achieved SD, and 33 had PD. Further analyses showed that patients sensitive to sorafenib presented with higher miR-122 and miR-197 levels than the insensitive patients did (**Figure 2**).

Predicting the efficacy of miR-122 and miR-197 on sorafenib chemotherapy

According to our assessment of sorafenib efficacy using RECIST version 1.1, we allocated the patients into effective (CR + PR) and ineffective (SD + PD) groups. The ROC curves demonstrated that the AUC of miR-122 for predicting the efficacy of sorafenib was 0.960, and the AUC of miR-197 for predicting the efficacy of sorafenib was 0.971 (**Figure 3**).

The associations between miR-122, miR-197 and the clinicopathological features in LC

Taking the median expressions of miR-122 and miR-197 as critical values, the patients were assigned into high and low expression groups. It turned out that there was an association between miR-122, miR-197, and higher AFP levels (≥ 20 g/L), multiple tumors (n ≥ 2), and vascular invasion, and miR-122 was also related to larger tumors (≥ 5 cm) (**Table 1**).

The effects of miR-122 and miR-197 on patient prognosis and survival

Furthermore, we tried to determine the correlation of levels of miR-122 and miR-197 with prognosis after chemotherapy. The K-M survival curve and a log-rank test indicated that the 5-year survival rate was lower in patients with low miR-122 and miR-197 expression levels (**Figure 4**).

In a univariable COX analysis, the 5-year survival rate of patients was associated with the miR-122 and miR-197 levels, the size and number of tumors, vascular invasion, and the TNM and BCLC staging. Our multivariable COX analysis showed that the independent risk factors for 5-year survival included the miR-122 and

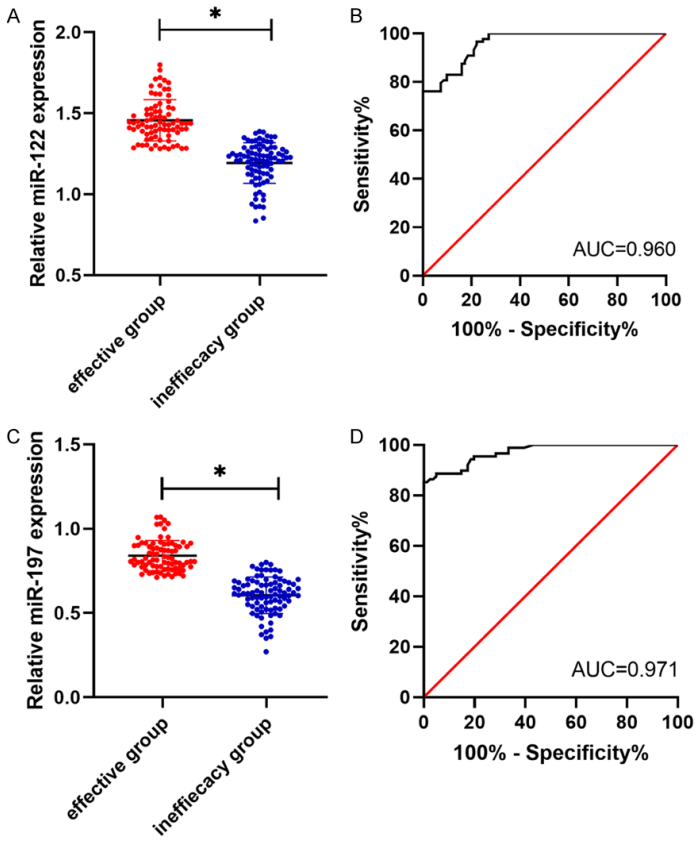

Figure 3. Using miR-122 and miR-197 to predict the efficacy of sorafenib chemotherapy. A: miR-122 levels in the effective and ineffective groups. B: Using miR-122 to predict the efficacy of sorafenib chemotherapy. C: The miR-197 levels in the effective and ineffective groups. D: Using miR-197 to predict the efficacy of sorafenib chemotherapy. $^{*}P < 0.05$.

miR-197 levels, the number of tumors, the vascular invasion, and the TNM and BCLC staging (**Table 2**).

Discussion

Mature miRNAs, a class of non-coding single-stranded small RNAs 20-23 nt in length, are usually deregulated in tumor genomes [10, 11]. miRNAs have been found to closely relate to the differentiation, metastasis, and recurrence of tumors [12]. A kind of regulatory factor, miRNAs suppress the levels of target mRNAs through complete or incomplete complementary binding with them, thereby regulating the expressions of the tumor-related genes at the post-transcriptional level [13]. miRNAs have high anti-degradation capacities in formalin-fixed and paraffin-embedded materials and the blood and are suitable as biomarkers, so they have become an attractive target for predicting the development of biomarkers [14, 15].

miRNAs can distinguish malignant tumors from benign ones; moreover, they have been identified as potential biomarkers for LC diagnosis and are highly predictive of metastasis and prognosis in LC [16, 17]. We analyzed 169 samples of LC tissues to quantify the differential levels of miR-122 and miR-197 in cancerous and adjacent tissues. miR-122 is an integral liver-specific miRNA involved in the growth and differentiation of hepatocytes [18]. Glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme of the pentose phosphate pathway (PPP), produces the NADPH required for lipid synthesis; miR-122 inhibits the expression of G6PD and hinders the redirection of carbon flux towards PPP, thereby inhibiting biomass production and proliferation in cancer cells [19, 20]. In addition, miR-122 is able to inhibit Bcl-2 responsible for cell apoptosis, Wnt1 for cell proliferation, ADAM17 for metastasis, and Ccgn1 for cell-cycle progression [21, 22]. Also, miR-122 is effective at restricting angiogenesis and intrahepatic metastasis by lowering the levels of the tumor necrosis factor-α-converting enzyme [23]. Furthermore, its role in regulating the therapeutic effects of drugs in LC has been revealed, that is, coptisine has an anti-cancer effect in LC by upregulating miR-122 [24]. However, there are few studies on miR-197 in LC. miR-197 is considered to be a potential therapeutic target that inhibits the growth of LC cells through the mutual regulation with the IL-6/STAT3 pathway [25]. A low level of miR-197-3P is related to the invasiveness of HCC, making it a predictor of poor prognosis, and an inhibitory role of miR-197-3p in HCC cell growth *in vivo* has been reported [26].

In the present study, both miR-122 and miR-197 had decreased levels in LC tissues, indicating their capabilities of distinguishing the cancerous tissues from the adjacent tissues. In addition, we found that their levels in the peripheral blood increased after sorafenib chemotherapy, and that miR-122 and miR-197 were predictive of the efficacy assessment of sorafenib chemotherapy. Next, we noticed that low miR-122 and miR-197 were associated with

Table 1. The association between miR-122 and miR-197 and the clinicopathological features in LC

	miR-122				miR-197			
	High (n = 84)	Low (n = 85)	χ^2	P	High (n = 84)	Low (n = 85)	χ^2	P
Sex			0.053	0.818			0.629	0.428
Male	76	76			74	78		
Female	8	9			10	7		
Age (years)			0.725	0.395			0.005	0.942
≥ 55	37	43			40	40		
< 55	47	42			44	45		
Tumor size (cm)			5.118	0.024			1.040	0.307
≥ 5	29	44			33	40		
< 5	55	41			51	45		
HBsAg			0.211	0.459			0.001	0.974
Positive	70	73			71	72		
Negative	14	12			13	13		
AFP (μg/L)			49.765	< 0.001			41.242	< 0.001
Positive	10	55			12	53		
Negative	74	30			72	32		
Cirrhosis			1.704	0.192			0.145	0.703
Yes	40	49			43	46		
No	44	36			41	39		
Number of tumors			5.118	0.024			10.202	0.001
Multiple	29	44			26	47		
Single	55	41			58	38		
Vascular invasion			4.984	0.026			6.453	0.011
Yes	34	49			33	50		
No	50	36			51	35		
TNM staging			0.324	0.569			1.440	0.230
I-II	31	35			29	37		
III-IV	53	50			55	48		
BCLC staging			0.330	0.566			0.004	0.952
A-B	30	34			32	32		
C-D	54	51			52	53		

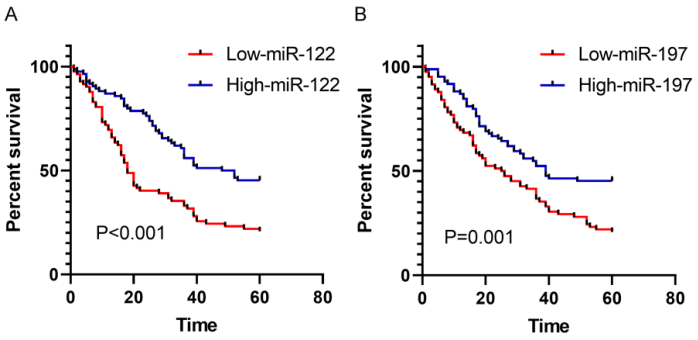

Figure 4. Effects of miR-122 and miR-197 on prognosis and survival of patients. A: The K-M survival curve and log rank test indicated that the 5-year survival was low-mir-122 was lower than high-mir-122. B: The K-M survival curve and log rank test indicated that the 5-year survival was low-mir-197 was lower than high-mir-197.

lower 5-year survival rates and were independent risk factors for reduced survival in LC. The AUCs of miR-122 in diagnosing colorectal cancer (CRC) and CRC metastasis to the liver are 0.89 and 0.81, suggesting that it is an independent prognostic marker of CRC [27]. miR-197 is a newly identified biomarker for diagnosing non-small cell lung cancer, with an AUC of 0.864 [28]. Also, miR-122 has been reported to target SerpinB3 and to participate in the sorafenib resistance of HCC [29]. Therefore, miR-122 and miR-197 are candidate biomarkers for pre-

Table 2. Univariate and multivariate COX analyses for the assessment of the 5-year survival rates

		Univariate factor			Multivariate factor		
		HR	95% CI	P	HR	95% CI	P
Sex	Male *vs.* Female	0.936	0.836-3.061	0.147			
Age (years)	≥ 55 *vs.* < 55	0.913	0.733-1.442	0.829			
Tumor size (cm)	≥ 5 *vs.* < 5	3.462	1.745-3.486	< 0.001	1.475	0.986-2.152	0.054
HBsAg	Positive *vs.* Negative	1.468	0.648-1.84	0.827			
AFP (μg/L)	Positive *vs.* Negative	0.958	0.714-1.422	0.977			
Cirrhosis	Yes *vs.* No	0.836	0.617-1.176	0.346			
Number of tumors	Multiple *vs.* Single	2.945	1.687-3.384	< 0.001	1.865	1.266-2.764	0.001
Vascular invasion	Yes *vs.* No	3.613	2.536-5.238	< 0.001	2.769	1.868-4.074	< 0.001
TNM staging	I-II *vs.* III-IV	3.028	1.782-3.527	< 0.001	3.826	1.915-6.638	< 0.001
BCLC staging	A-B *vs.* C-D	3.138	1.746-3.495	< 0.001	2.625	1.854-3.757	< 0.001
miR-122	High *vs.* Low	1.931	1.379-2.768	< 0.001	1.475	1.328-2.685	0.001
miR-197	High *vs.* Low	2.384	1.148-4.975	0.009	1.687	1.072-3.781	0.012

dicting the therapeutic effects of sorafenib. Nevertheless, we only included patients undergoing sorafenib chemotherapy, so the responses of miR-122 and miR-197 to other drugs remain unknown.

The limitation of the present study is that the mechanisms of action of miR-122 and miR-197 affecting the efficacy of sofetinib were not elaborated. It has been reported that miR-122 sensitizes HCC cells to sofetinib [30] and that miR-122 confers sorafenib resistance to HCC cells by targeting IGF-1R to regulate the RAS/RAF/ERK signaling pathways [31], which may be the possible reason why miR-122 affects the efficacy of sofetinib. Nevertheless, there is a lack of studies on miR-197 and sofetinib resistance, and the RAS/RAF/ERK signaling pathway may be a breakthrough, which we will further verify in future studies.

Overall, this study proposes that miR-122 and miR-197 are available candidate biomarkers to predict the therapeutic effects of sorafenib. And their downregulation in LC also suggests that they are qualified biological indicators for the prognoses of patients with LC.

Disclosure of conflict of interest

None.

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