Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(5) 2116–2125
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DOI: 10.1177/0300060519834815
journals.sagepub.com/home/imr
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Serum level of miR-142-3p predicts prognostic outcome for colorectal cancer following curative resection

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Abstract

Objective: MicroRNA (miR)-142-3p may function as a tumor suppressor in the development of various cancers. In this study, we measured serum levels of miR-142-3p in patients with colorectal cancer (CRC) to evaluate the diagnostic and prognostic value of miR-142-3p.

Methods: Serum samples from 363 consecutive CRC patients and 156 healthy controls were retrospectively collected. Serum miR-142-3p levels were measured using real-time quantitative reverse transcription polymerase chain reaction. All patients were followed up regularly after tumor resection. The correlation between serum miR-142-3p level and survival outcomes was analyzed.

Results: Serum levels of miR-142-3p were significantly lower in CRC patients than in healthy volunteers. A low serum miR-142-3p level was significantly associated with advanced cancer. Survival analysis demonstrated that patients with a low serum miR-142-3p had a lower 5-year overall survival rate than patients with a high serum miR-142-3p level (67.4% vs. 76.9%). Serum miR-142-3p level was also shown to be an independent risk factor for CRC in multivariate analysis (hazard ratio, 2.68; 95% confidence interval: 1.21–7.95).

Conclusions: Serum miR-142-3p might serve as a useful diagnostic and prognostic marker for CRC.

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Keywords
Serum miR-142-3p, prognosis, colorectal cancer, biomarker, tumor suppression, microRNA

Date received: 6 November 2018; accepted: 8 February 2019

Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed and lethal gastrointestinal cancers in China and worldwide.[1,2] Although considerable advancements in diagnostic and therapeutic modalities have improved early detection and decreased mortality over the previous decades, the prognosis of CRC remains poor, especially for patients who are diagnosed at advanced stages.[3–5] Recurrence after treatment is one of the main contributors to unsatisfactory long-term prognosis for localized and operable CRC.[6,7] Moreover, in clinical practice, CRC patients present with heterogeneous prognosis and treatment responses. Therefore, efficient and effective risk stratification of patients is required for clinical management of CRC.[8] Previous studies have established several classical methods for the risk stratification of CRC patients and biomarkers to guide administration of adjuvant treatments, such as TNM classification and histological stage.[9,10] However, these biomarkers cannot be obtained until the postoperative histological evaluation of the carcinoma tissue has been completed, which is not conducive to determining preoperative neo-adjuvant treatments.[11–13] Therefore, more feasible and effective biomarkers that can be obtained before treatment are needed for CRC prognosis and risk stratification.

The microRNAs (miRNAs) are a subset of small noncoding RNAs consisting of approximately 18 to 22 nucleotides that can inhibit gene expression by specifically binding the 3′ untranslated regions of their target messenger RNAs (mRNAs), resulting in translation suppression of specific protein-coding genes.[14] Dysregulation of miRNAs plays a crucial role in the development of various malignancies.[15–20] Previous studies have demonstrated that miRNAs are remarkably stable in serum or plasma samples at measurable concentrations.[21–24] Serum miRNAs can bind to specific proteins or be packaged into apoptotic bodies or exosomes, rendering them resistant to endogenous ribonuclease activity.[25,26] Thus, expression of different serum miRNAs is a valuable biomarker for cancer.[27–29]

MicroRNA-142-3p is a tumor suppressor miRNA that targets several oncogenes and is strongly downregulated in various types of cancer.[30,31] The aberrant miR-142-3p expression not only has diagnostic value but also predicts prognosis for cancer patients.[32] Overexpression of miR-142-3p can inhibit the proliferation, invasion, and migration of gastric cancer cells.[33] However, no reports have established the significance of serum miR-142-3p levels in patients with CRC. Therefore, in the current study, we evaluated serum levels of miRNA-142-3p in CRC patients to determine the prognostic value.

Methods

Patients

This study was conducted according to the relevant global and local guidelines or regulations. All subjects provided written informed consent before enrollment. Our study was also approved by the institutional review boards of the Second Affiliated

Hospital of Zhejiang Chinese Medical University.

Data of primary colorectal cancer patients who underwent curative surgery between June 1, 2013, and June 1, 2017, were retrospectively collected. A number of cases were excluded from the study because of the following exclusion criteria: histology other than adenocarcinoma, preoperative acute and severe comorbidity, distant metastasis, preoperative neo-adjuvant chemotherapy, unavailable clinical and histopathological data, and life expectancy less than 24 weeks. All patients underwent R0 resection and postoperative adjuvant radiotherapy or chemotherapy, or both, according to 2015 NCCN Colorectal Cancer Practice Guidelines,[34] and all of the tumor specimens were pathologically evaluated as colorectal adenocarcinoma. The control group consisted of age-matched healthy subjects without history of cancer and in good health status based on self-report.

Clinical and pathological data of all patients were collected and checked, including sex, age, tumor site and size, tumor invasion depth, lymph node involvement, TNM stage, histopathological differentiation, and surgery records. Tumor stages were evaluated based on the Union for International Cancer Control (UICC) classification system. All patients were regularly followed up through clinical visits or telephone. Clinical follow-up lasted from the surgery day to either death or June 2018. The primary outcome of interest was 5-year overall survival (OS) rate; OS was defined as the duration from surgery day to death.

Sample preparation and RNA isolation

Five milliliters of sterile peripheral venous blood was collected from each patient on the day before surgery and from healthy controls in the corresponding period. Serum was extracted from blood samples by centrifugation and then transferred to RNase/DNase-free tubes and immediately stored at $-80\,^{\circ}C$ until further processing. Total RNA was extracted from serum by use of a miRNEasy Serum/Plasma Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. The RNA concentration and integrity were quantified by using a NanoDrop ND-1000 spectrophotometer (Nanodrop Technologies LLC, Wilmington, DE, USA).

Quantification of miRNA by qRT-PCR

Total RNA from study participants was applied to reverse transcribe miRNAs to cDNA using a miScript Reverse Transcription Kit (Qiagen). Amplifications were performed using a miScript SYBR Green PCR kit (Qiagen) and real-time quantitative (qRT)PCR was run on an Applied Biosystems 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). The sequence of the primer used in reverse transcription for miR-142-3p was GTCGTATCCAGTGCAGGGTC CGAGGTATTCGCACTGGATACGAC TCCATAA. The expression levels of each miRNA were normalized against miR-16 expression, and threshold cycle (Ct) values ≥ 40 were considered undetectable. The relative expression of serum miR-142-3p was quantitatively analyzed by the $2^{-\Delta\Delta CT}$ method. Each sample was analyzed in triplicate.

Statistical analysis

All statistical analyses in this study were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). The results were considered statistically significant when $p < 0.05$ (two sided). Continuous variables expressed as means $\pm$ standard deviations were compared by using analysis of variance, and comparisons of categorical

variables were conducted using χ^2 or Fisher's exact test and presented as frequencies and percentages. Receiver operating characteristic (ROC) curve analysis was conducted to assess the feasibility of serum miRNA-142-3p levels as a diagnostic indicator for CRC detection. The cut-off value for the serum miRNA-142-3p levels predicting survival was also evaluated by ROC analysis. Kaplan–Meier survival curves were analyzed by log-rank test in the univariate analysis. A multivariate Cox hazard regression model was used to confirm the independent prognostic factors for CRC.

Results

Patients

Data of 363 primary colorectal cancer patients who underwent curative surgery were retrospectively collected. The control group consisted of 156 age-matched healthy individuals.

Serum miR-142-3p expression profiling in patients with CRC

Serum miR-142-3p was detected in all blood samples from 363 patients with CRC and 156 controls. The serum levels of miR-142-3p were significantly lower in CRC patients than in healthy control subjects ($p < 0.01$; Figure 1). Furthermore, ROC curve analysis showed that serum miR-142-3p level could serve as a diagnostic biomarker, distinguishing patients CRC and healthy individuals with a sensitivity of 68.5% and a specificity of 73.7%. The area under the curve was 0.74 [95% confidence interval (CI): 0.68–0.86, $p < 0.01$; Figure 2].

Relationship between serum miR-142-3p and clinicopathological variables

In this study, we analyzed associations between serum miR-142-3p levels and clinicopathological characteristics by using the χ^2 test. The results showed that a low serum miR-142-3p levels were significantly associated with advanced T stage ($p < 0.01$) and TNM stage ($p < 0.01$). We detected no significant differences between high and low serum miR-142-3p groups for other clinicopathological characteristics, including sex, age, tumor site and size, or pathological differentiation and N stage (Table 1).

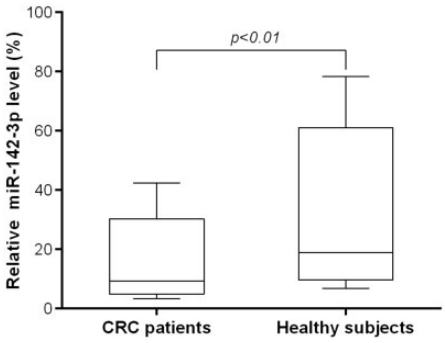

Figure 1. Serum microRNA (miR)-142-3p level in patients with colorectal cancer (CRC) and healthy controls. The serum miR-142-3p levels of 363 patients with CRC was significantly lower than that of 156 age-matched healthy volunteers ($p < 0.01$). The box indicates the interquartile range, the line indicates the median, and the whiskers indicate the standard deviation.

Prognostic value of serum miR-142-3p level in patients with CRC

The median follow-up period was 35.4 months (range, 6.1–85.1 months). During follow-up, there were 79 (21.8%) tumor-specific deaths in the group of patients with CRC. In the univariate survival analysis, we found that patients with low expression of serum miR-142-3p had a significantly worse 5-year OS rate compared with those with high expression of miR-142-3p (67.4% vs. 76.9%, $p = 0.03$; Table 2, Figure 3).

The multivariate analysis included age and sex of patients, tumor size, lymph

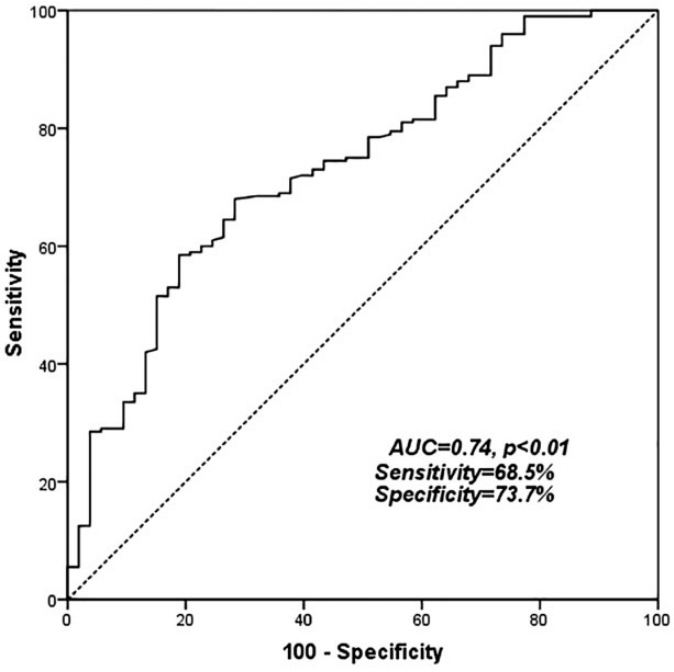

Figure 2. Receiver operator characteristic (ROC) curve for colorectal cancer detection. ROC analysis showed an area under the curve (AUC) of 0.74 for microRNA (miR)-142-3p with a 95% confidence interval of 0.68–0.86 ($p < 0.01$).

Table 1. Correlation between serum microRNA (miR)-142-3p level and clinical variables of patients with colorectal cancer.

Characteristic	Serum miR-142-3p High (n = 127)	Low (n = 236)	*p*-value
Age (years)			0.38
≥60	61	102	
<60	66	134	
Sex			0.70
Male	79	142	
Female	48	94	
Tumor site			0.07
Colon	56	81	
Rectum	71	155	
Tumor size (cm)			0.92
≥5	48	88	
<5	79	148	
T stage			<0.01
T1 + T2	84	107	
T3	43	129	
Node involvement			0.80
N0	51	98	
N1	76	138	
Clinical stage (TNM)			<0.01
I + II	79	81	
III	48	155	
Pathological differentiation			0.24
Good/moderate	71	147	
Poor	56	89	

OS, overall survival; CI, confidence interval; HR, hazard ratio; miR-142-3p, microRNA-142-3p.

Table 2. Prognostic characteristics of patients with colorectal cancer.

	Univariate			Multivariate		
Characteristic	n	5-year OS rate (%)	*p*-value	HR	95% CI	*p*-value
Age (years)			0.82			
≥60	163	67.2				
<60	200	72.1				
Sex			0.12			
Male	221	72.5				
Female	142	71.7				
Tumor site			0.37			
Colon	137	70.4				
Rectum	226	69.6				
Tumor size (cm)			0.16			
≥5	136	69.3				
<5	227	72.8				
Tumor invasion depth			0.02			
T1 + T2	191	75.3				
T3 + T4	172	69.2				
Lymph node involvement			0.01			
N0	149	74.2				
N1	214	67.6				
Clinical stage (TNM)			0.04	3.32	1.98–8.62	<0.01
I + II	160	75.3				
III	213	6412				
Pathological differentiation			0.01	1.27	1.02–3.67	0.01
Good/moderate	218	75.1				
Poor	145	64.2				
Serum miR-142-3p			0.03	2.68	1.21–7.95	<0.01
Low	236	67.4				
High	127	76.9				

OS, overall survival; HR, hazard ratio; CI, confidence interval; miR-142-3p, microRNA-142-3p.

node involvement, clinical stage, histological differentiation type, and preoperative miR-142-3p level in a Cox regression model to determine independent prognostic biomarkers for patients with CRC. After adjustment for potential confounders, a low serum miR-142-3p level ($p < 0.01$; hazard ratio, 2.68; 95% CI: 1.21–7.95) was identified as an independent predictive risk factor for survival outcome of CRC patients, independent of classical prognostic biomarkers such as TNM stage ($p < 0.01$; hazard ratio, 3.32; 95% CI: 1.98–8.62) and pathological differentiation ($p = 0.01$; hazard ratio, 1.27; 95% CI: 1.02–3.67) (Table 2).

Discussion

In the current study, we found that the serum level of the tumor suppressor miR-142-3p was significantly downregulated in patients with CRC compared with healthy controls. Moreover, serum miR-142-3p was evaluated and determined to be a good indicator to discriminate CRC patients from

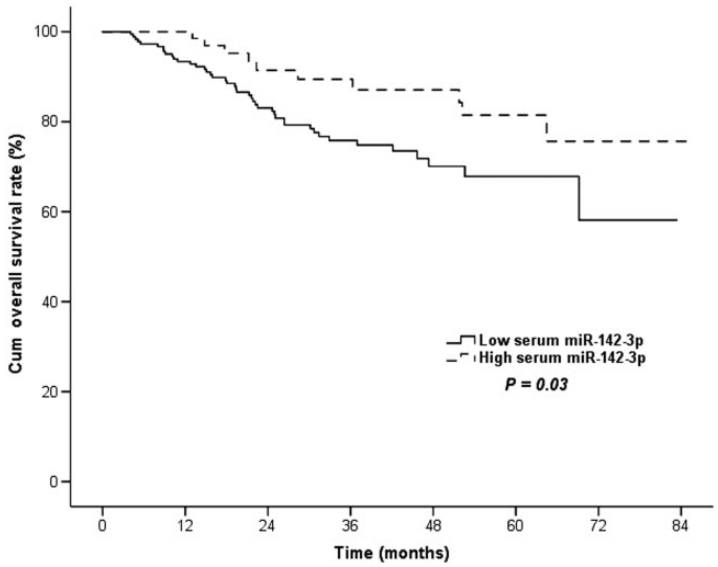

Figure 3. Lower plasma microRNA (miR)-142-3p level was associated with a worse prognosis for colorectal cancer. Prognostic analysis revealed that a low serum miR-142-3p level was significantly associated with a worse cumulative overall survival rate ($p = 0.03$).

healthy individuals. We also evaluated the potential value of serum miR-142-3p obtained before surgery as a candidate indicator to predict postoperative prognosis of CRC. We showed that low serum miR-142-3p was significantly related to poor survival of CRC patients. Low serum miR-142-3p levels were significantly correlated with unfavorable clinicopathological characteristics in CRC patients. According to these results, we propose that miR-142-3p could be used for diagnosis and optimal risk stratification of CRC patients, and that serum miR-142-3p is a promising biomarker for postoperative prognosis of CRC patients.

MiR-142-3p is generally expressed in human tissues and organs, and it has critical roles in biological processes of cancer cleavage and inhibiting translation.[35] This microRNA has been confirmed as a tumor suppressor that is downregulated in colon cancer.[36] It has been reported that miR-142-3p binds to the 3′-untranslated regions and coding sequences (thus inhibiting gene expression) of three risk genes associated with poor outcomes in colon cancer: CD133, ABCG2 (ATP binding cassette G2), and Lgr5 (leucine-rich-repeat-containing G-protein coupled receptor 5).[37] Levels of miR-142-3p were shown to be decreased in color cancer samples and negatively correlated with expression of these three genes.[37] Moreover, miR-142-3p may be involved in the regulation of cancer cell proliferation and metastasis in colorectal cancer by targeting transcription factor 7 (TCF-7), fatty acid synthase (FASN), and MYC oncogene.[38] In the current study, we showed that miR-142-3p is highly downregulated and correlated with poor prognosis in CRC patients, which is consistent with results from the earlier studies.

The function, mechanism, and origin of circulating miR-142-3p in cancer patients have not yet been fully elucidated. Several mechanisms for the release of circulating miRNAs have been suggested, including passive leakage from cells due to injury,

chronic inflammation, or necrosis; active secretion via membrane vesicles such as exosomes; and active secretion by complex formation with lipoproteins or RNA binding proteins. Furthermore, circulating miRNAs secreted from cancer cells can induce tumorigenesis in recipient cells.[23,39,40] Wu et al.[41] reported that miR-142-3p directly and negatively regulated RAC1 in hepatocellular carcinoma cells. Wang et al.[33] reported that miR-142-3p acts as a tumor suppressor in gastric cancer carcinogenesis partly by downregulating CCNT2. Increased expression of certain miRNAs is significantly associated with advanced clinical stages of cancer.[42] Our results were consistent with these previous studies. Therefore, serum miR-142-3p level could be a novel treatment target for patients CRC.

This study is the first to report, in a large group of patients, that miR-142-3p level is depleted in the serum of CRC patients and that miR-142-3p can serve as both a serum biomarker and a novel therapeutic target for CRC. However, the present study has several limitations, one of which is that the study was conducted at a single center and used a retrospective design. A large-scale, multicenter prospective study with a longer follow-up is needed to confirm our results. Furthermore, the roles of miR-142-3p in development of colorectal cancer and the underlying mechanisms are not yet fully understood. Further experiments must be conducted to elucidate the mechanisms of miR-142-3p in carcinogenesis.

Conclusions

We demonstrated that serum miR-142-3p levels were downregulated in patients with CRC. Moreover, low serum miR-142-3p levels were positively correlated with poor prognosis of CRC, suggesting that miR-142-3p may function as a tumor suppressor gene in CRC. Serum miR-142-3p might serve not only as a diagnostic and prognostic indicator for operable CRC but also as a potential novel treatment target.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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