Expression and diagnostic value of miR-34c and miR-141 in serum of patients with colon cancer

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Abstract. Expression of miR-34c and miR-141 in serum of colon cancer patients and their association with clinicopathological features and diagnostic value for colon cancer were investigated. A total of 64 patients with colon cancer admitted to Hubei Cancer Hospital from January 2016 to March 2018 were included in the experimental group, and 64 healthy subjects undergoing physical examination during the same period were the control group. The expression of miR-34c and miR-141 in serum of patients in the two groups were detected by RT-qPCR, and the association of miR-34c and miR-141 with the clinicopathological characteristics of colon cancer patients was analyzed. The receiver operating characteristic (ROC) curve was used to assess the diagnostic efficiency of miR-34c and miR-141 in colon cancer. The expression of miR-141 in serum of patients in the experimental group was significantly higher than that in the control group (P<0.05). Expression of miR-34c in serum of patients in the experimental group was significantly lower than that in the control group (P<0.05) and the expression of miR-34c and miR-141 in serum of the experimental group were associated with tumor diameter, clinical stage, degree of differentiation and lymph node metastasis (P<0.05). AUC of serum miR-34c in the diagnosis of colon cancer was 0.857 (95% CI: 0.795-0.919), with the cut-off value of 0.800, the diagnostic sensitivity of 84.38%, and the specificity of 68.75% and AUC of serum miR-141 in the diagnosis of colon cancer was 0.876 (95% CI: 0.810-0.941), with the cut-off value of 0.282, the diagnostic sensitivity of 70.31%, and the specificity of 96.88%. The ROC curve for the diagnosis of colon cancer was further plotted in combination with serum miR-34c and miR-141. AUC of the two combined for the diagnosis of colon cancer was 0.929 (95% CI: 0.884-0.974), with the cut-off value of 0.566, the diagnostic sensitivity of 84.38%, and the specificity of 93.75%. In conclusion, miR-34c and miR-141 might be involved in the occurrence and progression of colon cancer and could be used as biological indicators for early diagnosis of colon cancer.

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Introduction

Colon cancer is one of the most common malignant tumors in the clinical practice. Its morbidity and mortality worldwide are gradually increasing, posing a great threat to human life (1). There is lack of specific early stage symptoms and the digestive system signs appear in the middle and late stages, which can cause serious adverse effects (2,3). At present, the main treatment for clinical colon cancer is still surgical resection, but due to the lack of sensitive diagnostic indicators, most patients have already developed lymph nodes or distant metastases at the time of diagnosis, and the surgical resection rate and prognosis are not ideal (4,5). Therefore, it is very important to find a biomarker for early diagnosis of colon cancer.

It has been found that miRNAs are differentially expressed in colon cancer cells (6). They are closely related to the biological and clinical characteristics of colon cancer, and play an important role in the occurrence and progression of colon cancer (7). As studies have shown, miRNAs are thought to have a regulator role in tumor suppression and tumorigenesis. For example, miR-185 can inhibit the proliferation and invasion of colon cancer cells by targeting Wnt1, and regulating the level of miR-185 may have a therapeutic effect on colon cancer patients (8). miR-223-3p can promote the progression of colon cancer by negatively regulating PRDM1 (9). Based on these results, miRNAs are attracting attention as a potential target for the treatment and diagnosis of colon cancer. Recently, the role of miR-141 in tumor growth has been described. Expression level of miR-141 in patients with colon cancer at stage IV has increased, which can easily distinguish patients with distant metastasis, other stages and healthy control, showing that plasma miR-141 is a potential prognostic factor for predicting poor survival of colon cancer patients (10). miR-34C is a tumor suppressor regulator, which is down-regulated in most forms of cancer, and can inhibit the growth of malignant tumors by inhibiting genes related to proliferation, anti-apoptosis

and migration (11). A study has shown that the expression of miR-34C is down-regulated in colon cancer, and the loss of expression is consistent with the data of colon cancer cell lines (12).

There are few previous studies on the diagnosis of colon cancer with serum miR-34c and miR-141 (13-15), and the study on the role of miRNA expression in colon cancer provided new diagnostic methods and thinking for the diagnosis and treatment of colon cancer. In this study, by observing the expression of miR-34c and miR-141 in the serum of colon cancer patients, the diagnostic value of miR-34c and miR-141 in colon cancer and their relationship with clinicopathological features were investigated.

Patients and methods

General data. A total of 64 patients diagnosed with colon cancer and treated in Hubei Cancer Hospital (Wuhan, China) were selected as the experimental group, including 44 males and 20 females. The patients were aged 25-65 years, with an average age of (46.5±8.4) years. According to TNM staging system, there were 22 cases of stage I+II, and 42 cases of stage III. There were 19 cases of lymph node metastasis, and 15 cases of poor differentiation, 49 cases of high and medium differentiation. Sixty-four healthy subjects were included in the control group, including 38 males and 26 females. The controls were aged 26-57 years, with an average age of (44.5±7.9) years. The study was approved by the Ethics Committee of the Hubei Cancer Hospital, and the subjects and/or their families were informed and signed an informed consent.

Inclusion and exclusion criteria. Inclusion criteria were: Patients met NCCN colon cancer tumor clinical practice guidelines (16). CT, color Doppler ultrasound and MRI were performed to rule out distant metastasis. According to TNM staging system there were Stage I, II and III. Patients did not receive previous chemotherapy, or radiotherapy. Patients were diagnosed for the first time, with detailed clinicopathological data. Exclusion criteria were: Patients without other malignant tumors, hematological diseases. Patients with severe complications and immune system diseases. Patients with poor treatment compliance caused by severe mental illness, and patients unwilling to participate in the present study.

Main instruments and reagents. ABI PRISM 7500 quantitative PCR instrument (Beijing Image Trading Co., Ltd.; cat. no. 100005). M-MLV reverse transcription kit (Beijing Shengkeboyuan Biotechnology Co., Ltd.; cat. no. RTP50). TRIzol extraction kit (Shanghai Xinfan Biological Technology Co., Ltd.; cat. no. XFR1030). UV-visible spectrophotometer (Bioteke corporation; cat. no. ND5000). microRNA PCR premix kit (AcebioX; cat. no. PAMI000). The primers of miR-34c, miR-141 and U6 were synthesized by Beijing Lvyuanbode Biotechnology Co., Ltd. (Table I).

RT-qPCR detection. Elbow venous blood (5 ml) of the subjects were taken, after 10-15 min, the blood was centrifuged at 1,500 x g and 4˚C for 10 min, and then stored at -70˚C. The total RNA in the serum was extracted using TRIzol kit (Takara), and the absorbance values of RNA at 260 and 280 nm were measured by ultraviolet-visible spectrophotometer. The RNA concentration and purity were analyzed. Then, 2 μl of total RNA was taken to reversely transcribe the first strand cDNA, according to the reverse transcription kit. Reverse transcription reaction conditions: 42˚C for 30 min, 95˚C for 5 min. The synthesized cDNA sample was stored at -80˚C. U6 was used as an internal reference. The total volume of 20 μl includes 10 μl of PCR Premix, 2 μl of upstream primer, 2 μl of downstream primer and dd water (Rnase and Dnase free). PCR amplification cycle conditions were: 92˚C for 5 min, 95˚C for 5 sec, 65˚C for 30 sec, 72˚C for 5 sec, a total of 45 cycles. $2^{-\Delta\Delta Cq}$ method was used to analyze the relative expression of the target gene.

Statistical analysis. SPSS19.0 (IBM Corp.) statistical software was used to analyze the data. Enumeration data in the group were represented by numbers of case/percentage [n (%)] and were analyzed by Chi-square test. Measurement data were expressed by mean ± standard deviation. Independent sample t-test was used for comparison of measurement data between two groups. ROC curve was used to assess the diagnostic efficiency of miR-34c and miR-141 on colon cancer. $P<0.05$, was considered statistically significant.

Results

General data. There was no difference between the experimental group and the control group in gender, age, body mass index (BMI), smoking history, drinking history, residence, educational level or other general clinical data ($P>0.05$) (Table II).

Expression levels of miR-34c and miR-141 in colon cancer. The relative expression of miR-34c and miR-141 in the serum of subjects in the two groups were detected, and it was found that the serum level of miR-34c in the experimental group was significantly lower than that in the control group ($P<0.05$), and the relative expression of miR-141 in serum of patients in the experimental group was significantly higher than that in the control group ($P<0.05$) (Table III and Fig. 1).

Association of the expression of miR-34c and miR-141 with clinicopathologic features of patients with colon cancer. The expression of miR-34c and miR-141 in serum of colon cancer was not associated with the clinicopathological parameters such as age, gender, local tumor invasion, vascular invasion, degree of differentiation, and neural invasion ($P>0.05$), but was associated with tumor diameter, lymph node metastasis, carcinoembryonic antigen, and TNM staging ($P<0.05$) (Table IV).

The relative expression of serum miR-34c and miR-141 in the diagnosis efficiency of colon cancer. ROC curve of relative expression of serum miR-34c and miR-141 for the diagnosis of colon cancer was drawn. AUC of serum miR-34c for the diagnosis of colon cancer was 0.857 (95% CI: 0.795-0.919), its cut-off value was 0.800; diagnostic sensitivity was 84.38%, and specificity was 68.75%. AUC of serum miR-141 for

Table I. Primer sequences of miR-34c, miR-141 and U6.

Gene	Forward primers	Reverse primers
miR-34c	5'-CGCGGATCCTCTATTTGCCATCGTCTA-3'	5'-CTGAAGCTTCAGGCAGCTCATTTGGAC-3'
miR-141	5'-GCGAAGCATTTGCCAAGAA-3'	5'-CAATCACAGACCTGTTATTGC-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

Table II. General data in the experimental group and control group [n (%), mean ± SD].

Class	Experimental group (n=64)	Control group (n=64)	t/χ^2	P-value
Sex			0.131	0.717
Male	44 (68.75)	38 (59.38)		
Female	20 (31.25)	26 (40.62)		
Age (years)	46.5±8.4	44.5±7.9	1.388	0.168
BMI (kg/m^2)	22.94±4.06	22.49±3.72	0.654	0.514
Smoking history			0.283	0.595
Yes	36 (56.25)	33 (51.56)		
No	28 (43.75)	31 (48.44)		
Drinking history			1.647	0.199
Yes	44 (68.75)	37 (57.81)		
No	20 (31.25)	27 (42.19)		
Place of residence			0.142	0.707
City	20 (31.25)	22 (34.38)		
Country	44 (68.75)	42 (65.62)		
Education level			2.050	0.152
>Senior high school	33 (51.56)	41 (64.06)		
≤Senior high school	31 (48.44)	23 (35.94)		

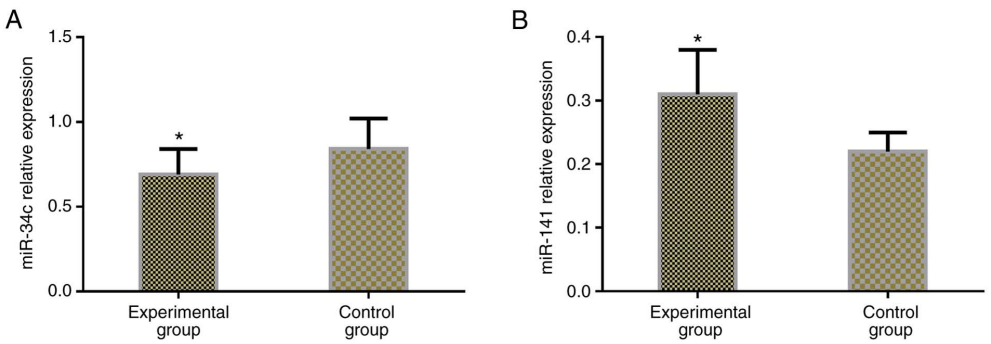

Figure 1. Expression of miR-34c and miR-141 in the serum of colon cancer. (A) Serum level of miR-34c in the experimental group was significantly lower than that in the control group (P<0.05). (B) The relative expression of miR-141 in serum of patinets in the experimental group was significantly higher than that of the control group (P<0.05). *P<0.05, compared with the normal control group.

diagnosis of colon cancer was 0.876 (95% CI: 0.810-0.941), its cut-off value was 0.282; diagnostic sensitivity was 70.31%, and specificity was 96.88%. ROC curve for the diagnosis of colon cancer combined with serum miR-34c and miR-141 was further drawn. The combined AUC of serum miR-34c and miR-141 for the diagnosis of colon cancer was 0.929 (95% CI: 0.884~0.974), the cut-off value was 0.566; diagnosis sensitivity was 84.38% and the specificity was 93.75%. More details are shown in Table V and Fig. 2.

Table III. Expression levels of miR-34c and miR-141 in serum of colon cancer (mean ± SD).

Groups	n	miR-34c	miR-141
Experimental group	64	0.69±0.15	0.31±0.07
Control group	64	0.84±0.18	0.22±0.03
t	-	5.121	9.454
P-value	-	<0.001	<0.001

Table IV. Correlation of miR-34c and miR-141 expression levels with the clinicopathologic features of patients with colon cancer (mean ± SD).

Clinicopathologic features	n	miR-34c (n=64)	t	P-value	miR-141 (n=64)	t	P-value
Sex			1.577	0.120		1.783	0.079
Male	44	0.65±0.12			0.32±0.08		
Female	20	0.71±0.18			0.28±0.09		
Age, years			0.712	0.479		1.445	0.154
<50	21	0.67±0.13			0.30±0.09		
≥50	43	0.70±0.17			0.33±0.11		
Tumor diameter, cm			3.177	0.002		1.612	0.112
<5	47	0.74±0.13			0.33±0.12		
≥5	17	0.61±0.18			0.33±0.16		
TNM stage			4.512	<0.001		3.438	0.018
Grade I+II	22	0.81±0.18			0.29±0.05		
Grade III	42	0.64±0.12			0.34±0.09		
Grade of differentiation			1.862	0.673		0.904	0.369
High and moderate differentiation	49	0.70±0.12			0.32±0.07		
Poor differentiation	15	0.63±0.15			0.30±0.09		
Lymph node metastasis			8.204	<0.001		2.318	0.024
With	19	0.43±0.12			0.34±0.07		
Without	45	0.80±0.18			0.30±0.06		
Local tumor invasion			1.842	0.703		1.592	0.116
With	33	0.71±0.17			0.33±0.08		
Without	31	0.64±0.13			0.30±0.07		
Vascular invasion			0.533	0.596		1.500	0.139
With	35	0.68±0.14			0.33±0.04		
Without	29	0.70±0.16			0.30±0.11		
Neural invasion			1.033	0.306		1.013	0.315
With	40	0.67±0.15			0.34±0.08		
Without	24	0.71±0.15			0.32±0.07		
Carcinoembryonic antigen, μg/l			3.968	0.002		2.667	0.009
≥3.4	34	0.61±0.17			0.34±0.07		
<3.4	30	0.77±0.15			0.29±0.08		

Table V. Relative expression of serum miR-34c and miR-141 in the diagnostic efficiency of colon cancer.

Diagnostic indicator	AUC	95% CI	Standard error	Cut-off value	Sensitivity (%)	Specificity (%)
miR-34c	0.857	0.795-0.919	0.032	0.800	84.38	68.75
miR-141	0.876	0.810-0.941	0.033	0.282	70.31	96.88
miR-34c+miR-141	0.929	0.884-0.974	0.023	0.566	84.38	93.75

Discussion

Colon cancer is a malignant lesion in mucosal epithelium caused by a variety of carcinogenic factors. It is mainly related to a high-fat, high-protein and low-fiber diet, and is one of the common malignant tumors (17). The onset of colon cancer is insidious and most of its onset is slow. In the early stage, there is no obvious symptoms, patients are often diagnosed in the middle or late stage, thus losing the best time for treatment (18). Therefore, how to improve the diagnostic rate of colon cancer and overall survival is a major problem for clinicians. Surgery is an early treatment method for colon cancer. In recent years, the treatment of colon cancer has improved to a certain extent, but the high postoperative complication rate of colon cancer has not changed (19). Hence, actively looking for indicators with high sensitivity is

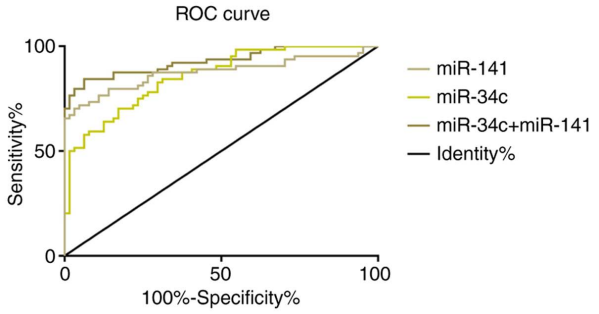

Figure 2. The relative expression of serum miR-34c and miR-141 in the diagnosis of colon cancer. The AUC of serum miR-34c for the diagnosis of colon cancer was 0.857 (95% CI: 0.795-0.919), its cut-off value was 0.800, diagnostic sensitivity was 84.38%, and specificity was 68.75%. AUC of serum miR-141 for diagnosis of colon cancer was 0.876 (95% CI: 0.810-0.941), its cut-off value was 0.282, diagnostic sensitivity was 70.31%, and specificity was 96.88%. ROC curve for the diagnosis of colon cancer combined with serum miR-34c and miR-141 was drawn, the combined AUC of serum miR-34c and miR-141 for the diagnosis of colon cancer was 0.929 (95% CI: 0.884-0.974), the cut-off value was 0.566, diagnosis sensitivity was 84.38% and the specificity was 93.75%.

of great significance for the early diagnosis and improvement of prognosis of colon cancer.

Colonoscopy is the current choice for clinical screening of colon cancer (20,21). Due to its high cost and invasive characteristics, colonoscopy is not widely used in clinical practice. The other choice, fecal occult blood test, has extremely high dietary requirements for patients due to its low sensitivity (22), so invasive biomarkers are urgently needed to detect colon cancer. miRNAs can form specific inclusion bodies and exosomes, which are suitable for detection in body fluids, serum and feces (23), making it possible to detect miRNAs in serum as biomarkers for nasopharyngeal cancer.

Micro non-coding microRNAs (miRNAs) contribute to the development and progression of cancer and are differentially expressed in normal tissues and cancer (24). miRNAs have a 'dual identity' of oncogene and cancer suppressor gene in the process of tumor progression, which is closely related to the occurrence, progression and metastasis of tumors (25). By regulating different signaling pathways, miR-141 indirectly regulates physiological and pathological conditions and plays an important role in the progression of the disease. It has been shown to be low expressed in a variety of tumors, and to be significantly decreased in tumor tissues, lymph nodes, and sera of colon cancer patients. Studies have revealed that the expression of miRNA-141 is down-regulated in colon cancer, which improves the expression level of MAP4K4, changes the anti-tumor response, and further increases tumor proliferation, invasion and metastasis (26). miR-34c is down-regulated in many different malignancies. Previous studies have revealed that the down-regulation of miR-34c in endometrial cancer may be an important factor for poor prognosis. Its overexpression can inhibit cell proliferation, colony formation, invasion, metastasis and apoptosis, and plays an important role in the formation, occurrence and progression of a variety of tumors (27). For example, in the study of Yang *et al* (28), the silencing of tumor suppressors such as miR-34c was related to the development of colorectal cancer, and showed that the overexpression of miR-34c induced apoptosis by silencing its target cytokines and inhibited the invasion and proliferation of colorectal cancer cells, indicating that miR-34c was a promising target. In the study of Gao *et al* (29), the dysregulation of miR-141 depended on the type of cancer. It played a dual role in tumorigenicity, and regulated cell movement and controlling 'dryness'. This phenomenon strongly suggested that miR-141 was an oncogene or tumor suppressor gene and provided new options for targeting cancer therapies. In this study, the relative expression of miR-34c and miR-141 in serum of patients in the two groups were detected. The serum level of miR-34c in the experimental group was significantly lower than that in the control group, while the expression of miR-141 was significantly higher than that of the control group, and was associated with tumor diameter, carcinoembryonic antigen, lymph node metastasis and TNM staging ($P<0.05$), indicating that miR-34c and miR-141 might be involved in the occurrence and progression of colon cancer, and miR-34c might act as a tumor suppressor gene in colon cancer, and miR-141 might act as an oncogene.

It has been reported that miR-34c and miR-141 can be used as biomarkers in a variety of tumors. For example, in the study of Tao *et al* (30), miR-34c played a key role in ovarian cancer and could be used as a potential diagnostic biomarker and a powerful therapeutic target for ovarian cancer. Wang *et al* (31) reported that the overexpression of miR-141 was not only closely related to the classification and size of osteosarcoma, but also inhibited the growth and metastasis of osteosarcoma cells by regulating epidermal growth factor and affecting downstream pathway proteins. The results of this study showed that the sensitivity and specificity of serum miR-34c for the diagnosis of colon cancer were 84.38 and 68.75%, respectively, and the sensitivity and specificity of serum miR-141 for the diagnosis of colon cancer were 70.31 and 96.88%, respectively. The sensitivity and specificity of the combined diagnosis of colon cancer were 84.38 and 93.75%, respectively. It suggested that miR-34c and miR-141 could be used as biological indicators with good sensitivity and specificity in the diagnosis of colon cancer, and their combination could improve the sensitivity in the diagnosis of colon cancer. Therefore, miR-34c and miR-141 might play important roles in the occurrence, progression and prognosis of colon cancer.

The research subjects were screened strictly in accordance with the inclusion and exclusion criteria, and there were no significant differences between the experimental group and the control group in the general clinical baseline data of gender and age, which ensured the preciseness and reliability of the study. Although this study confirmed the role of miR-34c and miR-141 in the occurrence, progression and prognosis of colon cancer, the functions of miR-34c and miR-141 in the prognosis of patients were not observed. These deficiencies needed to be further supplemented in future studies to support the results of this study.

In conclusion, miR-34c and miR-141 might be involved in the occurrence and progression of colon cancer. Serum miR-34c and miR-141 were detected to have a good sensitivity and specificity in the diagnosis of colon cancer, and combined detection could improve the sensitivity in the diagnosis of colon cancer. The combination of the two might be a new biomarker for colon cancer diagnosis.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HW and HY conceived and designed the study, acquired, analyzed and interpreted the experiment data, drafted the manuscript, and revised the manuscript critically for important intellectual content. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Hubei Cancer Hospital (Wuhan, China). Signed informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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