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Original Article

Diagnostic value of miR-153 and miR-203 in patients with cervical cancer and their correlation with human papillomavirus infection

Yanyan Wang[1], Bin Xu[2], Xiaoyong Shen[3], Li'na Sun[2]

Departments of [1]Pathology, [2]Obstetrics and Gynecology, [3]Radiology, Huzhou Central Hospital, Huzhou, Zhejiang Province, China

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Abstract: Objective: To explore the diagnostic value of miR-153 and miR-203 in patients with cervical cancer (CC). Methods: A total of 136 CC and suspected CC patients admitted to our hospital were enrolled in this prospective study. Among them, 80 cases had CC, 56 cases with cervical intraepithelial neoplasia, and 40 cases with cervicitis. The normal cervical tissues of the above 176 patients were taken as a control and the expression levels of miR-153, miR-203 and human papillomavirus (HPV) DNA in CC tissues were detected. Results: The relative expressions of miR-153 and miR-203 in the CC group were significantly lower than those in the cervicitis and cervical intraepithelial neoplasia groups (all P<0.01). The area under the ROC curve of miR-153 for the diagnosis of CC was 0.883 (95% CI: 0.828-0.938, P<0.001). When the cut-off value of miR-153 expression level in the diagnosis of CC was 0.27, its Youden index, specificity, and sensitivity were 0.748, 0.863, and 0.885, respectively. The area under the ROC curve of miR-203 for the diagnosis of CC was 0.752 (95% CI: 0.680-0.825, P<0.001). When the cut-off value of miR-203 expression level in the diagnosis of CC was 0.51, its Youden index, specificity, and sensitivity were 0.478, 0.615, and 0.863, respectively. Compared with the cervical intraepithelial neoplasia group, HPV infection rate in the CC group was significantly higher (P<0.001). The relative expression levels of miR-153 and miR-203 in HPV-positive patients were significantly lower than those in HPV-negative patients (P<0.001). Significantly lower levels of miR-153 and miR-203 were found in patients with myometrial infiltration, FIGO III-IV stage, and lymphatic metastasis (P<0.05). Conclusion: The expressions of miR-152 and miR-203 are down-regulated in patients with CC, which has diagnostic value for CC. The expressions of miR-153 and miR-203 are correlated with HPV infection and aggressiveness of tumor.

Keywords: miR-153, miR-203, cervical cancer, human papillomavirus infection, diagnosis, correlation

Introduction

Cervical cancer (CC) is a common gynecologic malignancy, and its incidence continues to increase in recent years. It ranks as fourth among female malignant tumors, causing great harm to women's health [1, 2]. Recent studies have shown that there is a certain correlation between the incidence of CC and the national economy. The incidence of CC is significantly reduced in high-income countries compared to that of low and middle-income countries. CC in low and middle-income countries was already at an advanced-stage when it was diagnosed [3]. In China, there is also late diagnosis and delayed treatment of CC, and the optimum time for surgical treatment is lost when the diagnosis is at advanced stage, with high recurrence rate of advanced CC after surgical treatment. Studies have shown that there are still a considerable number of CC patients who are diagnosed at advanced stage in China, and they often relapse after surgery, leading to poor prognosis. Therefore, early clinical diagnosis and radical surgery can effectively treat CC and improve the prognosis of patients [4, 5]. Clinical studies have shown that over 94% of CC patients are infected with human papillomavirus (HPV); however, less than 1% of HPV patients develop CC [6].

Studies have found that miRNA plays a crucial role in the regulation of tumorigenesis and development [7, 8]. miR-153 is a member of this family. It is reported that miR-153 has a low expression level in pancreatic cancer,

Table 1. Primers for RT-PCR

Primer	Forward primers 5'-3'	Reverse primers 5'-3'
miR-153	UUGCAUAGUCACAAAAGUGAUC	TCCACCACCCAGTTGCTGTA
miR-203	GUGAAAUGUUUAGGACCACUAG	CCAGUGGUUCUUAACAGUUCAAC
U6	CGGGTTTGTTTTGCATTTGT	AGTCCCAGCATGAACAGCTT

breast cancer, ovarian cancer, and colorectal cancer, mainly by promoting apoptosis of tumor cells to inhibit tumor production [9, 10]. Previous studies have shown that miR-203 can also inhibit tumor proliferation and it can inhibit tumor cell metastasis and invasion of colorectal cancer [11]. Another study has found that miR-203a-5p can inhibit the growth, proliferation, and invasion of CC tumor cells, but the role of miR-203 in CC is less reported [12]. Based on the above research, we studied the miR-153 and miR-203 expression in CC patients and their correlation with HPV infection to determine their diagnostic value for CC.

Materials and methods

General information

The Ethics Committee of our hospital approved this study and all patients signed an informed consent form. A total of 136 CC patients and suspected CC patients admitted to our hospital from March 2017 to August 2020 were enrolled in this prospective study. The patients included in the study were between 25-71 years old. The pathologic results confirmed that 80 patients had CC, with an average age of 43.1±10.0 years, and 56 patients had cervical intraepithelial neoplasia, with an average age of 42.8±9.8 years. In addition, 40 patients with cervicitis were enrolled into the study at the same period, and their average age was 43.6±9.7 years.

Inclusion criteria: (1) patients met the diagnostic criteria for CC, cervical intraepithelial neoplasia, or cervicitis [13]; (2) patients were aged 18-75 years old; (3) patients received cervical biopsy or radical cervical resection in our hospital to obtain cervical tissue samples, and the diseased and normal tissues of their cervix were sampled separately.

Exclusion criteria: (1) patients with incomplete clinical data; (2) patients with severe heart, liver, and kidney related diseases; (3) patients with mental illness or cerebrovascular disease; (4) patients with other cancers or not primary CC; (5) patients participating in clinical research for other projects.

Methods

Determination of the relative expression levels of miR-153 and miR-203 in cervical tissues: RT-PCR technology was used to reverse transcribe miRNA into cDNA using a reverse transcription kit (Fernentas, Canada), which was used as a template for DNA amplification. The expression levels of miR-153 and miR-203 in cervical tissue samples were determined by probe-based fluorescence quantitative PCR. The $2^{-\Delta\Delta CT}$ method was applied to calculate relative expression levels and experiments were repeated in triplicate to take the average value. U6 was used as an internal control. The primer sequences are shown in **Table 1**.

Detection of the HPV DNA in cervical tissue samples: The PCR amplifications were performed to amplify HPV DNA and the second-generation hybrid capture methods were used to identify 14 high-risk types of HPV. In the hybridization reactions, the DNA load was used to determine HPV infection in the cervical tissue samples. When the DNA load ≥1 ng/L, the sample is HPV-positive; otherwise, it is HPV-negative [6].

Statistical analysis

Statistical analysis was conducted by statistical software SPSS 17.0. Normally distributed measured data were expressed as $\bar{x}$ ± sd and the measured data conforming to the homogeneity of variance were tested by t-test. Independent sample t test was performed for comparison between groups; paired sample t test was used for intra-group comparison. The counted data were expressed as a percentage and tested by the Pearson chi-square test. The ROC curve was used to estimate the value of miR-153 and miR-203 in diagnosing CC, and the pictures were drawn by Medcalc software. Differences with $P<0.05$ were considered significant.

Results

Comparison of general information in the three groups

The expressions of tumor markers CEA, Ca199, and Ca125 in the CC group were significantly higher than those in the cervicitis group and cervical intraepithelial neoplasia group (P<

Table 2. Comparison of general information in the three groups ($\bar{x}$ ± sd)

Characteristic	Cervicitis group (n=40)	Cervical intraepithelial neoplasia group (n=56)	CC group (n=80)	χ^2/F	P
Age (years)	43.6±9.7	42.8±9.8	43.1±10.0	0.077	0.926
BMI	23.82±1.62	24.22±1.46	23.99±1.58	0.811	0.446
Comorbidity (n, %)					
Hypertension	6 (15.00)	9 (16.07)	15 (18.75)	0.320	0.852
Coronary heart disease	2 (5.00)	4 (7.14)	10 (12.50)	2.192	0.334
Type 2 diabetes	4 (10.00)	8 (14.29)	12 (15.00)	0.595	0.942
Hyperlipidemia	3 (7.50)	5 (8.23)	13 (16.25)	2.648	0.266
Cerebral infarction	3 (7.50)	6 (10.71)	10 (12.50)	0.693	0.707
CEA (μg/L)	0.92±0.43	1.22±0.74	1.72±0.93$^{***,###}$	17.231	<0.001
Ca199 (kU/L)	3.44±1.34	4.22±1.93	5.63±2.64$^{***,###}$	15.765	<0.001
Ca125 (kU/L)	5.41±1.73	7.92±2.74	13.6±2.62$^{***,###}$	32.458	<0.001
CRP (mg/L)	7.60±2.62	7.93±2.83	7.13±2.44	0.876	0.445
Smoking (n %)	4 (10.00)	8 (14.29)	14 (17.50)	1.224	0.521

Note: Compared with the cervicitis group, ***P<0.001; compared with the cervical intraepithelial neoplasia group, $^{###}$P<0.001. CEA: Carcinoembryonic antigen; Ca199: Carbohydrate antigen Ca199; Ca125: Carbohydrate antigen Ca125; CRP: C-reactive protein; CC: cervical cancer.

Table 3. Comparison of expression levels of miR-153 and miR-203 in the three groups of patients and the normal group ($\bar{x}$ ± sd)

Group	n	Relative expression levels of miR-153	Relative expression levels of miR-203
Control group	176	0.43±0.12	0.81±0.33
Cervicitis group	40	0.40±0.11	0.75±0.31
Cervical intraepithelial neoplasia group	56	0.33±0.09$^{***,###}$	0.47±0.21$^{***,###}$
CC group	80	0.21±0.08$^{***,###,@@@}$	0.36±0.20$^{***,###,@@}$
F		65.076	36.190
P		<0.001	<0.001

Note: Compared with the control group, ***P<0.001; compared with the cervicitis group, $^{###}$P<0.001; compared with the cervical intraepithelial neoplasia group, $^{@@}$P<0.01, $^{@@@}$P<0.001. CC: cervical cancer.

0.001). The remaining clinical characteristics were not different (P>0.05, **Table 2**).

Comparison of expression levels of miR-153 and miR-203 among groups

The present study demonstrated that relative expression levels of miR-153 and miR-203 in the CC group were significantly lower than those in the other three groups (P<0.01); furthermore, those in the cervical intraepithelial neoplasia group were significantly lower than those in the control and cervicitis groups (P<0.001, **Table 3**).

Diagnostic values of miR-153 and miR-203 for CC

The area under the ROC curve of miR-153 for the diagnosis of CC was 0.883 (95% CI: 0.828-0.938, P<0.001). When the cut-off value of miR-153 expression level in the diagnosis of CC was 0.27 ($2^{-\Delta\Delta CT}$), its Youden index, specificity, and sensitivity were 0.748, 0.863 and 0.885, respectively. The area under the ROC curve of miR-203 for the diagnosis of CC was 0.752 (95% CI: 0.680-0.825, P<0.001). When the cut-off value of miR-203 expression level in the diagnosis of CC was 0.51 ($2^{-\Delta\Delta CT}$), its Youden index, specificity, and sensitivity were 0.478, 0.615, and 0.863, respectively (**Figure 1**).

Comparison of HPV infection in the three groups

Compared with the cervicitis group, HPV infection rates in the CC and cervical intraepithelial neoplasia groups were significantly higher (P<0.001), and the CC group had significantly higher HPV infection rate (P<0.001, **Table 4**).

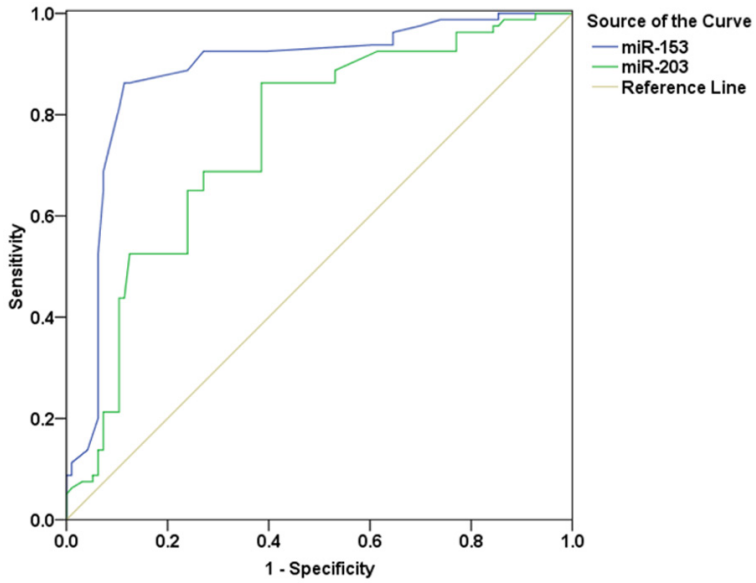

Figure 1. ROC curves of miR-153 and miR-203 for CC diagnosis. CC: cervical cancer.

Table 4. Comparison of HPV infection in the three groups (n, %)

Group	HPV-positive
Cervicitis group (n=40)	8 (20.00)
Cervical intraepithelial neoplasia group (n=56)	27 (48.21)***
CC group (n=80)	78 (97.50)***,###
χ^2	76.586
P	<0.001

Note: compared with the cervicitis group, ***P<0.001; compared with the cervical intraepithelial neoplasia group, ###P<0.001. HPV: Human papillomavirus; CC: cervical cancer.

Table 5. Expression of miR-153 and miR-203 under different HPV infection conditions ($\bar{x}$ ± sd)

Group	Relative expression level of miR-153	Relative expression level of miR-203
HPV-positive group (n=113)	0.25±0.11	0.43±0.24
HPV-negative group (n=63)	0.36±0.11	0.59±0.30
t	6.238	4.055
P	<0.001	<0.001

Note: HPV: Human papillomavirus.

Comparisons of expression levels of miR-153 and miR-203 under different HPV infection conditions

The relative expression levels of miR-153 and miR-203 in HPV-positive patients were significantly lower than those in HPV-negative patients (P<0.001, **Table 5**).

Correlation between the relative expression levels of miR-153 and miR-203 and the clinical and pathologic characteristics of 80 CC patients

Significantly lower expressions of miR-153 and miR-203 were found in patients with myometrial infiltration, FIGO III-IV stage, and lymphatic metastasis (P<0.05, **Table 6**).

Discussion

The early diagnosis of malignant tumors determines the prognosis and quality of life of patients, which is getting more attention in clinical practice. How to find biomarkers quickly and effectively has become a focus of clinical research. More and more clinical studies have been conducted on the diagnostic value of miRNAs in tumor patients, and studies have shown that miRNAs are closely related to the occurrence and development of tumors [14, 15]. Existing studies have found that miRNAs are abnormally expressed in CC patients, and different miRNAs play a role in inhibiting or promoting tumor cells in CC patients [16, 17].

In this study, it was shown that the expressions of miR-153 and miR-203 were both low in CC tissues. This suggests that the low expressions of miR-153 and miR-203 in patients with CC may be related to an antineoplastic effect. Previous studies have shown that the low expression of miR-153 in breast cancer tissues has an antitumor function. This may be achieved by regulating the TGF-β signaling pathway to inhibit the migration, invasion, and epithelial mesenchymal transition (EMT) of breast cancer cells [18]. Low expression of miR-153 also exists in glioma patients, and research has shown that

Table 6. Correlation between the relative expression levels of miR-153 and miR-203 and the clinical and pathologic characteristics of 80 patients with CC ($\bar{x}$ ± sd)

Characteristic	n	miR-153	t	P	miR-203	t	P
Age			1.973	0.052		1.071	0.281
≥50	46	0.20±0.09			0.35±0.18		
<50	34	0.23±0.06			0.39±0.21		
Pathologic type			0.584	0.561		0.102	0.919
Squamous cancer	71	0.21±0.08			0.37±0.19		
Adenocarcinoma	9	0.23±0.03			0.36±0.26		
Histologic grade			0.854	0.341		0.324	0.746
Highly differentiated	59	0.21±0.10			0.36±0.21		
Poorly differentiated	21	0.23±0.08			0.37±0.23		
Muscle infiltration			2.765	0.017		2.627	0.019
Yes	32	0.19±0.06			0.31±0.17		
No	48	0.25±0.10			0.39±0.23		
FIGO stage			3.114	0.008		3.411	<0.001
I-II	65	0.24±0.11			0.38±0.24		
III-IV	15	0.18±0.07			0.32±0.19		
Lymphatic metastasis			3.476	<0.001		4.014	<0.001
No	61	0.25±0.11			0.38±0.25		
Yes	19	0.18±0.09			0.30±0.18		

Note: CC: cervical cancer.

the promotion of miR-153 expression can enhance the radiosensitivity of glioma cells [19]. Also, low expression of miR-153 in renal cancer patients can promote the proliferation and invasion of renal cancer cells [20]. A study on the effect of miR-153 in CC has indicated that miR-153 can inhibit the occurrence and development of CC cells through the targeted regulation of GALNT7 [21]. miR-203 also plays an inhibitory role in the occurrence and development of tumors, and a study has shown that miR-203 can inhibit the proliferation and migration of oral cancer cells [22]. miR-203 can inhibit the proliferation of glioma cancer cells by regulating alpha-interferon [23]. It has found that miR-203 showed a low expression in CC tissues, and in the case of folic acid deficiency, the level of miR-203 can be down-regulated to induce CC [24]. The above results show that the low expressions of miR-153 and miR-203 have anti-cancer effects, which is consistent with the results of this study. This study further showed that miR-153 and miR-203 had value for diagnosis of CC and could be used as early markers for the diagnosis of CC. In this study, the areas under the ROC curve of miR-153 and miR-203 for the diagnosis of CC were 0.883 and 0.752, respectively, and the specificity/sensitivity of miR-153 and miR-203 were 0.927/0.688 and 0.525/0.875, respectively. It suggests that both miR-153 and miR-203 have high diagnostic value. Previous studies showed that miR-153 level in patients with CC was significantly lower than that of the control group. The above results suggested that miR-153 may be a tumor suppressor gene, and its decreased expression may be involved in the occurrence and development of CC. The optimal cut-off value of serum miR-153 expression level in the diagnosis of CC was 1.31, and the area under the ROC curve was 0.817, respectively. The sensitivity and specificity were both good. These results suggested that miR-153 could be used as a biological indicator for the diagnosis of CC [25]. The sensitivity/specificity of miR-203 molecule in endometrial carcinoma and healthy people were 85.9%/74.6%, respectively, which had a high diagnostic value [26].

In this study, HPV infection of CC reached 97.50%, and more than 94% of CC patients were found to be infected with HPV in clinical studies [6]. Research has shown that HPV virus enhances its activity through the mediation of viral proteins E6 and E7, and can inhibit miR-

203 to increase its life cycle [27]. As for miR-153, there is no relevant report on HPV infection at present, and its mechanism still has yet to be further clarified. Previous studies on the relationship between clinicopathologic features of CC and miR-153 and miR-203 have found that the low expressions of miR-153 and miR-203 are related to age, clinical stage, lymphatic metastasis, and myometrial invasion [28, 29]. In this study, myometrial invasion, FIGO III-IV stage, and lymphatic metastasis were associated with the expressions of miR-153 and miR-203.

This study has some limitations. This was a single-center study with a small sample size, so it may be possible to further expand the sample size and conduct a multi-center randomized controlled study.

In conclusion, low expressions of miR-153 and miR-203 in patients with CC have certain diagnostic value for CC, and the expressions of miR-153 and miR-203 are correlated with HPV infection and tumor aggressiveness.

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Disclosure of conflict of interest

None.

Address correspondence to: Bin Xu, Department of Obstetrics and Gynecology, Huzhou Central Hospital, No. 198 Hongqi Road, Huzhou 313000, Zhejiang Province, China. Tel: +86-13645729883; E-mail: xb-flower@yeah.net

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