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Original Article

Expression of microRNA (miR)-145 and miR-34a in different cervical lesion tissues of Uygur and Han females in Xinjiang, China

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Abstract: Objective: This study is to investigate the expression of microRNA (miR)-145 and miR-34a in different cervical lesion tissues of Uygur and Han females in Xinjiang, China. Methods: Totally 58 females (25 Uygur and 33 Han) with cervical cancer (CC), 60 females (26 Uygur and 34 Han) with cervical intraepithelial neoplasia (CIN) II-III, and 32 normal subjects (15 Uygur and 17 Han) were included. MiR expression was detected with quantitative real-time PCR. Association between the miR expression and CC clinicopathological features was analyzed, and the receiver operating curve (ROC) analysis was performed. Results: Expression levels of miR-145 and miR-34a in the cervical tissues were gradually decreased in the following order: normal, CIN II-III, and CC groups. No significant differences were observed in the miR expression between Uygur and Han females. The expression levels of miR-145 and miR-34a were positively associated. Moreover, the miR expression was significantly associated with the FIGO staging and lymph node metastasis of CC. The miR-145 expression was significantly associated with tissue differentiation, while the miR-34a expression was significantly associated with tumor size. However, the miR expression was not significantly associated with age, pathological type, myometrial invasion, or parametrial invasion. ROC analysis revealed significant AUC values, and high sensitivities and specificities, for miR-145 and miR-34a, in the diagnosis and assessment of CC. Conclusion: Expression of miR-145 and miR-34a is significantly declined in the CC tissues of Uygur and Han females, which might be used as tumor markers for the disease early diagnosis and prognosis prediction in clinic.

Keywords: MicroRNA (miR)-145 miR-34a, cervical cancer (CC), cervical intraepithelial neoplasia (CIN), Uygur and Han females

Introduction

Cervical cancer (CC) is one of the most common malignant tumors in females throughout the world. The incidence of CC ranks the first among the malignant tumors in the female reproductive system [1]. China is associated with the second highest incidence of CC in the world. Particularly, in Xinjiang, Northwest China, the incidence of CC and the related mortality rate for the Uygur females are significantly elevated, compared with the Han females living in the same environment [2].

In clinic, CC has been characterized by high malignancy, frequent relapse, invasion and metastasis, and poor prognosis. Moreover, no obvious symptoms and signs would be observed in the early disease phase, making it easy to be missed and misdiagnosed. Therefore, it is of great importance and significance to investigate the pathogenesis and development of CC, and find highly sensitive and specific tumor markers, for the disease early diagnosis, targeted therapy, and prognosis prediction in clinic.

MicroRNA (miR) is a class of highly conserved and specific endogenous non-coding single stranded RNAs, with 19-24 nucleotides in length, which are widely distributed in various tissues [3]. These miRs have been shown to participate in the modulation of proliferation, differentiation, and apoptosis of tumor cells, and thus involved in the disease pathogenesis and development [3]. In our previous study, the expression of miRs in the CC tissues has been detected by microarray, and down-regulated

Table 1. Expression levels of miR-145 and miR-34a in different cervical lesion tissues

	N	Relative expression of miR-145	Relative expression of miR-34a
Normal control	32	2.096 (0.991-4.885)	1.278 (0.553-4.221)
CIN II-III	60	1.166 (0.477-2.555)*	0.339 (0.219-0.999)*
CC	58	0.602 (0.258-1.538)*,#	0.117 (0.058-0.302)*,#

Note: compared with the control group, *$P < 0.01$; compare with the CIN group, #$P < 0.01$.

expression of miR-145 has been noted in the cancer tissues [4]. Moreover, miR-34a has been shown to be regulated by p53, and HPV-16/18 E6 could degrade p53 through the ubiquitin protein degradation pathway and decrease miR-34a in the CC cells [5]. In this study, the expression of CC-related miRs in different cervical lesion tissues was analyzed and compared between Uygur and Han females in Xinjiang, China. Association of the miR expression with clinicopathological features of CC and its significance in the disease diagnosis were also discussed.

Materials and methods

Study subjects

Totally 58 patients with CC, 60 patients with cervical intraepithelial neoplasia (CIN) II-III, and 32 normal subjects were included in this study, who were admitted to the First Affiliated Hospital of Xinjiang Medical University, from November 2010 to February 2013. The exclusion criteria included acute inflammation, severe chronic disease, pregnancy, having received chemotherapy, topical medication, and other treatments. In these 58 CC patients, there were 25 Uygur and 33 Han females, with a median age of 50.0 years, ranging from 32 to 79 years. Moreover, in the 60 CIN patients, there were 26 Uygur and 34 Han females, with a median age of 44.0 years, ranging from 28 to 75 years. Furthermore, there were 15 Uygur and 17 Han normal female subjects, with a median age of 40.5 years, ranging from 30 to 71 years. Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of the First Affiliated Hospital of Xinjiang Medical University.

Quantitative real-time PCR

Total RNA was extracted with the miRNeasy FFPE Kit (Qiagen, Hilden, Germany), according to the manufacturer's instructions. Reverse transcription was performed with the miScriptII RT kit (Qiagen) to obtain cDNA. Real-time PCR was conducted with the miScript SYBR Green PCR kit (Qiagen) on the RGQ-5PLEX HRM machine (Qiagen). The primer sequences were synthesized by Sangon, Shanghai, China: miR-145, forward 5'-TGCGCGTCCAGTTTTCCCAGGAA-3' and reverse 5'-CCAGTGCAGGGTCCGAGGTATT-3'; miR-34a, forward 5'-TGCGCTGGCAGTGTCTTAGCT-3' and reverse 5'-CCAGTGCAGGGTCCGAGGTATT-3'; U6, forward 5'-CGCTTCGGCAGCACATATAC-3' and reverse 5'-AAATATGGAACGCTTCACGA-3'. The 20 μL PCR system consisted of 1 μL cDNA, 10 μL 2×SYBR Green Mix, 1 μL primer each, and 7 μL ddH_2O. The reaction conditions were as follows: 95°C for 15 min; 94°C for 15 s, 55°C for 30 s, and 70°C for 30 s, for 40 cycles. Relative expression levels of the target genes were calculated with the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

SPSS 17.0 software was used for statistical analysis. The relative expression levels of miRs were expressed as median and interquartile range (QL-QU). Nonparametric rank sum test was performed for the difference analysis between groups, with Mann-Whitney U and Kruskal-Wallis H tests. Correlation analysis was performed with the Spearman rank correlation analysis. $P<0.05$ was considered as statistically significant.

Results

Expression of miR-145 and miR-34a in cervical tissues of Uygur and Han females

To investigate the expression levels of miRs in the cervical tissues of Uygur and Han female subjects, quantitative real-time PCR was performed. Our results showed that, the relative expression levels of miR-145 and miR-34a in the cervical tissues were gradually decreased in the following order: normal, CIN II-III, and CC groups (all $P<0.05$) (**Table 1**). Moreover, no significant differences were observed in the expression of miR-145 and miR-34a between the Uygur and Han subjects, for all the normal, CIN, and CC groups ($P>0.05$) (**Table 2**). Furthermore, correlation analysis showed that, the relative expression levels of miR-145 and miR-34a

Table 2. Expression of miR-145 and miR-34a between the Uygur and Han subjects

	Relative expression of miR-145			Relative expression of miR-34a		
	Normal control	CIN II-III	CC	Normal control	CIN II-III	CC
Uygur	1.955 (0.741-4.309)	0.626 (0.198-1.494)	0.549 (0.332-1.720)	1.742 (0.551-4.496)	0.264 (0.148-0.890)	0.122 (0.049-0.232)
Han	2.727 (1.203-5.227)	1.360 (0.851-3.005)	0.649 (0.144-1.499)	0.834 (0.541-2.726)	0.412 (0.262-1.133)	0.116 (0.066-0.371)

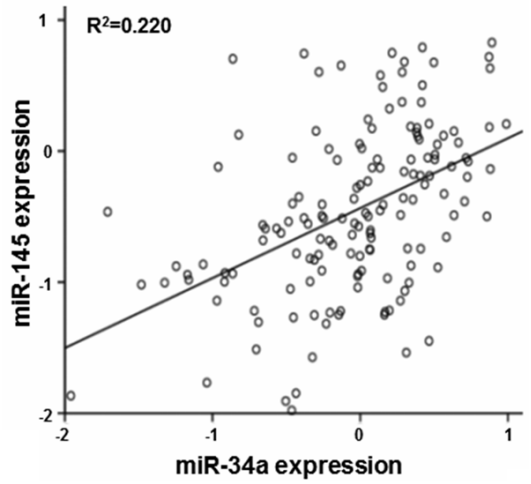

Figure 1. Association between miR-145 and miR-34a expression in cervical tissues.

were positively associated (r=0.495; *P*<0.01) (**Figure 1**). These results suggest that, significantly declined expression of miR-145 and miR-34a would be observed in the cervical lesion tissues, which might contribute to the disease pathogenesis.

Association between miR expression and clinicopathological features of CC

Relationship between the expression of miR-145 and miR-34a with the clinicopathological features of CC was next investigated, including FIGO staging, lymph node metastasis, tissue differentiation, tumor size, pathological type, myometrial invasion, and parametrial invasion. Our results showed that, the expression of miR-145 and miR-34a was significantly associated with the FIGO staging and lymph node metastasis of CC (*P*<0.01) (**Figure 2**). Moreover, the miR-145 expression was significantly associated with the tissue differentiation of CC (*P*<0.01), while the miR-34a expression was significantly associated with the tumor size (*P*<0.01) (**Figure 2**). However, neither the expression of miR-145 nor miR-34a was associated with the subject age, pathological type, myometrial invasion, or parametrial invasion (*P*>0.05). The results from the Spearman rank correlation analysis showed that, the expression of miR-145 was negatively associated with the tissue differentiation (r=-0.283, *P*=0.031), FIGO staging (r=-0.437, *P*=0.001), and lymph node metastasis (r=-0.404, *P*=0.002). On the other hand, the miR-34a expression was negatively associated with tumor size (r=-0.413, *P*=0.001), FIGO staging (r=-0.491, *P*=0.000), and lymph node metastasis (r=-0.370, *P*=0.004) (**Table 3**). These results suggest that, the expression of miR-145 and miR-34a is associated with several clinicopathological features of CC.

Evaluation of miR detection in clinical diagnosis of CC

The application of miR detection in the clinical diagnosis of CC was then evaluated. Our results from the ROC analysis showed that, the AUC of miR-145 in distinguishing the tissue differentiation of CC was 0.786 (95% CI: 0.642-0.931; *P*=0.002), while the evaluation threshold of miR-145 expression was 0.636, the sensitivity was 91.7%, and the specificity was 65.2%. Moreover, the AUC of miR-34a in distinguishing the tumor size was 0.748 (95% CI: 0.609-0.886; *P*=0.002), while the evaluation threshold of miR-34a expression was 0.110, the sensitivity was 70.3%, and the specificity was 76.2%. Furthermore, the AUC values for miR-145 and miR-34a in distinguishing CC with and without lymph node metastasis were 0.779 (95% CI: 0.629-0.930; *P*=0.002) and 0.756 (95% CI: 0.620-0.893; *P*=0.005), respectively. The evaluation threshold of miR-145 expression was 0.340, the sensitivity was 77.8%, and the specificity was 61.5%. The evaluation threshold of miR-34a expression was 0.081, the sensitivity was 73.3%, and the specificity was 69.2%.

On the other hand, the application of miR-34a detection in distinguishing CC patients from CIN and normal subjects was also evaluated. Our results from the ROC analysis showed that, the AUC of miR-34a in distinguishing CC patients from normal subjects was 0.889 (95% CI:

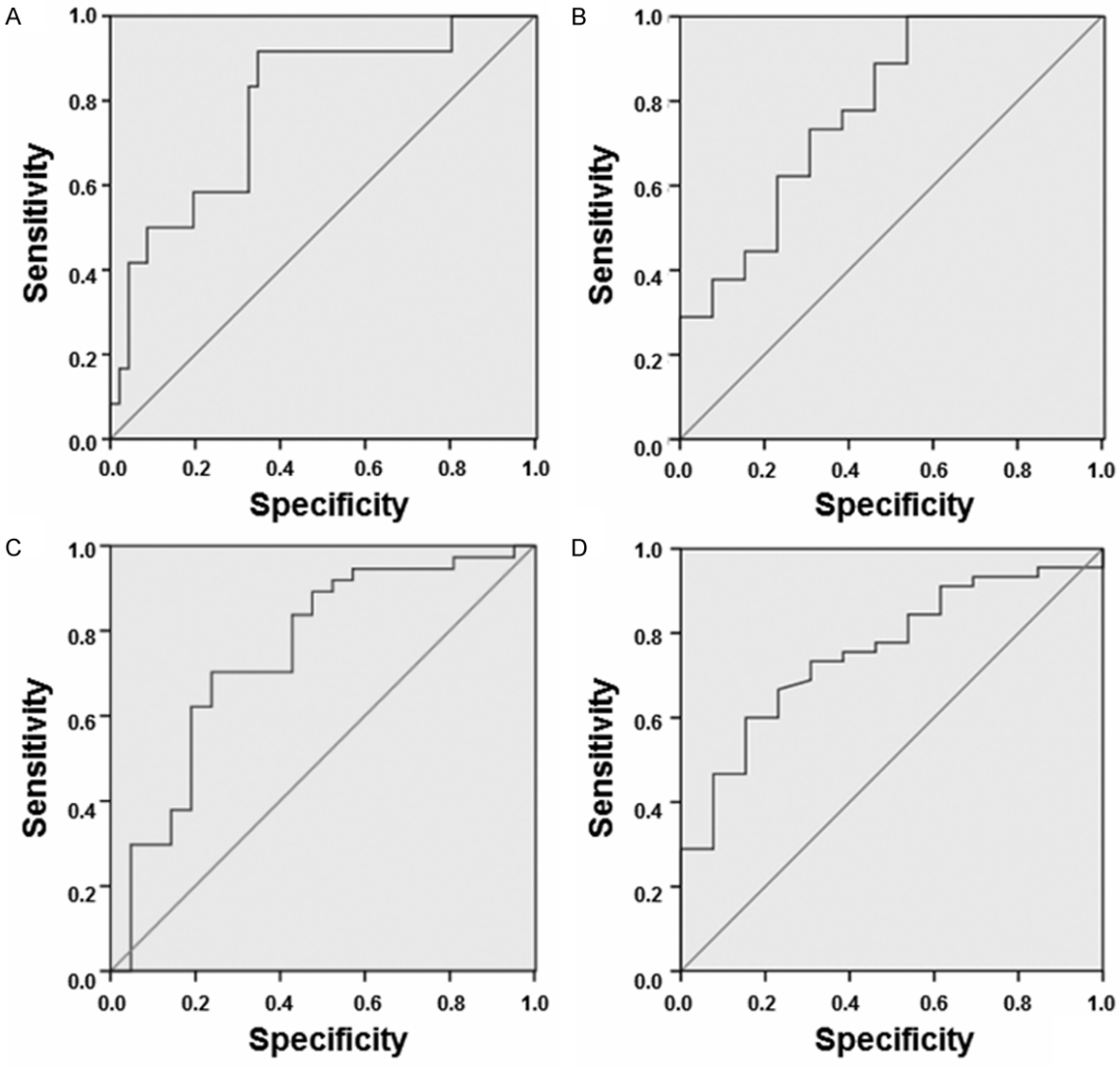

Figure 2. ROC analysis for miRs in distinguishing clinicopathological features of CC. (A, B) ROC analysis for miR-145 in distinguishing tissue differentiation (A) and lymph node metastasis (B). (C, D) ROC analysis for miR-34a in distinguishing tumor size (C) and lymph node metastasis (D).

0.814-0.957; *P*=0.000), while the evaluation threshold of miR-34a expression was 0.406, the sensitivity was 87.5%, and the specificity was 81.0% (**Figure 3**). Moreover, the AUC of miR-34a in distinguishing CC patients from CIN patients and normal subjects was 0.810 (95% CI: 0.737-0.882; *P*=0.000), while the evaluation threshold was 0.211, the sensitivity was 83.7%, and the specificity was 70.7% (**Figure 3**), indicating high diagnostic value. Furthermore, the AUC in distinguishing CC patients from CIN patients was 0.767 (95% CI: 0.680-0.854; *P*=0.000), while the evaluation threshold was 0.211, the sensitivity was 78.3%, and the specificity was 70.7% (**Figure 3**), indicating moderate diagnostic value. These results suggest that the detection of miR-145 and miR-34a expression would contribute to the diagnosis of CC in clinic.

Discussion

Cervical cancer (CC) is one of the common malignancies in females, with increasing incidence rate in recent years [1]. At present, the treatment for CC is mainly limited to surgery, supplemented by radiotherapy and chemotherapy. However, CC is prone to metastasize and spread, with the 5-year survival rates of 90% for the early cancer, and 66% for the advanced

Table 3. Association between the miR expression and the clinicopathological features of CC

	N	Expression of miR-145	Expression of miR-34a
Age (years)			
≤ 50	32	0.619 (0.221-1.794)	0.107 (0.052-0.383)
> 50	26	0.505 (0.290-1.461)	0.120 (0.056-0.229)
P		0.796	0.994
Tumor diameter (cm)			
≤ 4	37	0.650 (0.335-1.499)	0.178 (0.081-0.493)
> 4	21	0.367 (0.157-1.811)	0.056 (0.028-0.112)
P		0.344	0.002
Differentiation			
High	12	1.759 (0.926-2.390)	0.111 (0.067-0.545)
Moderate/poor	46	0.482 (0.203-1.191)	0.135 (0.049-0.295)
P		0.002	0.845
FIGO staging			
I	21	1.087 (0.437-2.356)	0.181 (0.110-0.859)
II	28	0.555 (0.221-1.382)	0.108 (0.057-0.245)
III-IV	9	0.198 (0.058-0.661)	0.031 (0.015-0.060)
P		0.004	0.001
Pathological type			
Squamous cell carcinoma	53	0.588 (0.245-1.499)	0.114 (0.056-0.285)
Adenocarcinoma	5	0.698 (0.253-2.189)	0.208 (0.096-0.761)
P		0.589	0.339
Myometrial invasion			
≤ 1/2	36	0.636 (0.344-2.030)	0.139 (0.089-0.325)
> 1/2	22	0.360 (0.136-1.475)	0.061 (0.030-0.215)
P		0.106	0.058
Parametrial invasion			
No	36	0.674 (0.344-2.002)	0.122 (0.057-0.383)
Yes	22	0.438 (0.133-1.131)	0.099 (0.056-0.225)
P		0.061	0.336
Lymph node metastasis			
No	45	0.698 (0.346-1.922)	0.130 (0.066-0.371)
Yes	13	0.198 (0.058-0.745)	0.059 (0.022-0.107)
P		0.002	0.005

cancer [6]. The development and metastasis of CC is a multi-stage and multi-factor process. It is of great importance to investigate the disease pathogenesis and find highly sensitive and specific markers, for the diagnosis and treatment of CC.

In 2002, Calin *et al.* [7] has first reported the association between abnormal miR expression and tumorigenesis. Differential expression patterns of miR could be noted between tumors, precancerous lesions, and normal tissues, which might be used as markers for the disease early diagnosis and prognosis prediction [8, 9]. In recent years, several studies have revealed that the miR expression profile is closely associated with the development of CC. However, only few miRs and the involved target genes have been well elucidated. MiR-145 is located on chromosome 5q32-33, which down-regulates the expression of c-MYC, RTKN, MUC1, and K-RAS. MiR-145 participates in the P53-miR-145-MDM2 feedback pathway, which inhibits the proliferation of tumor cells, and promotes cycle arrest and apoptosis [9, 10]. Moreover, miR-145 could down-regulate the expression of tumor stem cell markers that are positively associated with CC differentiation (such as KLF4, SOX2, and OCT4), and interfere with the epithelium-interstitial transformation (EMT) signaling pathway, thus inhibiting tumor differentiation, metastasis, and invasion [11]. On the other hand, miR-34a is located on human chromosome 1p36.23, whose transcription is directly induced by p53. MiR-34a could down-regulate the E3F3 expression and up-regulate the p53 expression through the p53-miR-34a-E2F3-p53 pathway, which would activate the expression of miR-34a and inhibit the tumor cell proliferation [12]. Targeted inhibition of SIRT1 by miR-34a could activate the expression of p53, and activate the p53-miR-34a-SIRT1-p53 positive feedback pathway. The function of miR-34a and p53 would be enhanced, which further promotes cell cycle arrest and cellular apoptosis [13]. The inactivation and/or deletion of miR-34a might be asso-

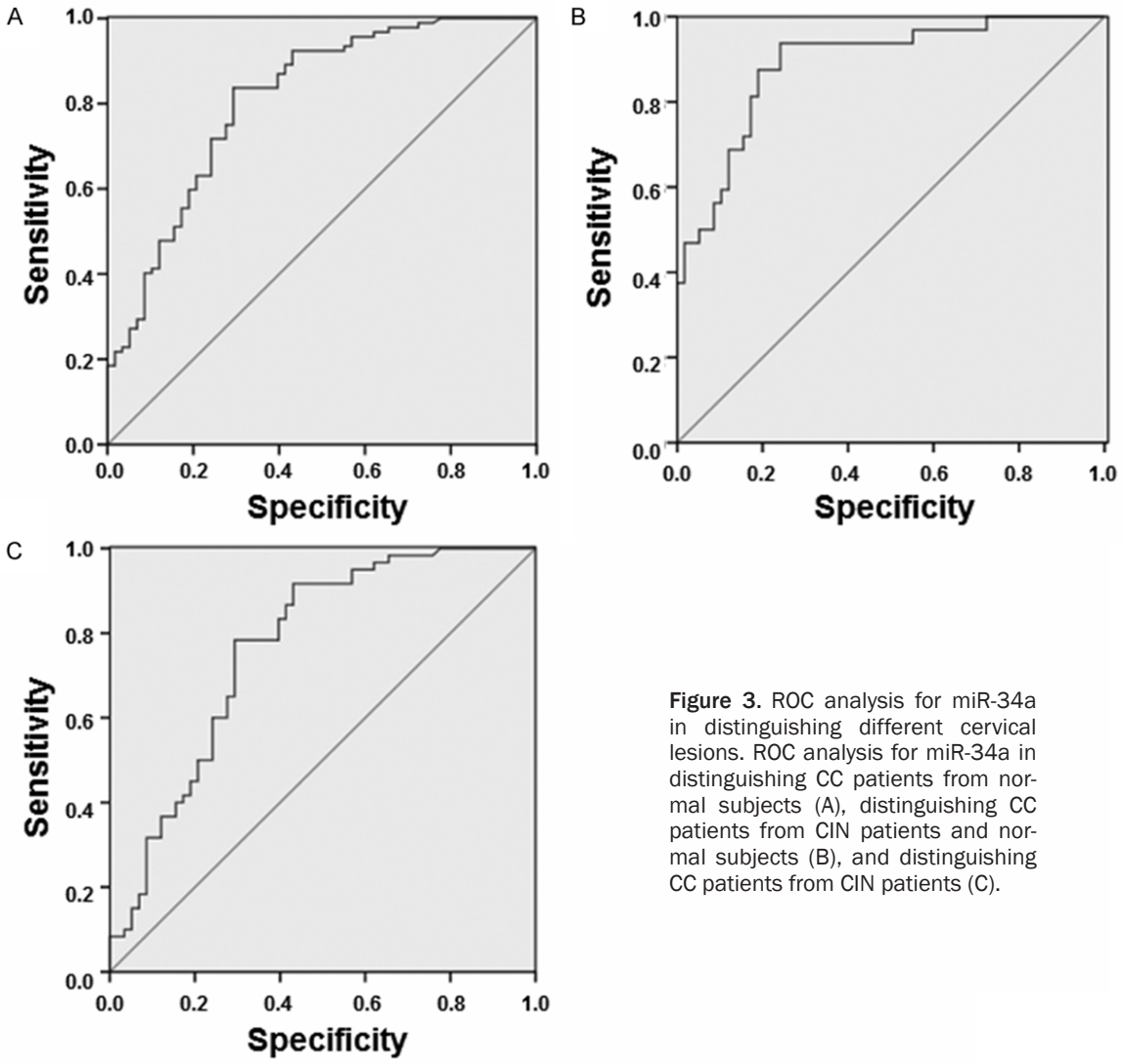

Figure 3. ROC analysis for miR-34a in distinguishing different cervical lesions. ROC analysis for miR-34a in distinguishing CC patients from normal subjects (A), distinguishing CC patients from CIN patients and normal subjects (B), and distinguishing CC patients from CIN patients (C).

ciated with the pathogenesis and development of tumors.

In this study, the expression of miR-145 and miR-34a in different cervical lesion tissues was detected with quantitative real-time PCR. Our results showed that, compared with normal tissues, the expression levels of miR-145 and miR-34a were significantly declined in the CC and CIN II-III tissues, along with the increasing cervical lesion severity. In line with this, declined expression of these miRs has also been noted in other tumors, including breast and colon cancers [14]. Moreover, our results indicated the altered expression of miR-145 and miR-34a in the precancerous tissues, which might participate in the pathogenesis and development of CC. Therefore, miR-145 and miR-34a would be used as markers for the diagnosis of CC in clinic. Moreover, positive correlation was observed between the expression of miR-145 and miR-34a, indicating that these miRs could synergistically affect the disease pathogenesis. The down-regulated expression of miR-145 and miR-34a was associated with the malignancy of CC. Lower miR expression was accompanied with more advanced FIGO staging, lower degree of differentiation, and larger tumor size, as well as lymph node metastasis. Therefore, the down-regulation of tumor suppressors would compromise the regulation of tumor cell cycle and apoptosis, leading to the excessive proliferation, metastasis, and invasion of tumor cells. These findings primarily suggest the roles of miR-145 and miR-34a in the pathogenesis and development of CC.

Similar results have been obtained by Huang *et al.* [15] and Weng *et al.* [16] about the roles of miR-145 and miR-34a in the small cell carcinoma of cervix and kidney cancer, respectively. In clinic, no obvious lesions could be observed in cervical carcinoma *in situ* and microinvasive carcinoma, which might lead to misdiagnosis. Based on our results, the detection of miR-145 and miR-34a might be used as indicator for the precancerous lesions and early CC diagnosis.

In clinic, pelvic lymph node metastasis is an important factor for the diagnosis, treatment, and prognosis evaluation for CC. At present, the evaluation of pelvic lymph node metastasis is mainly dependent on the preoperative radiology and the pathological detection of lymph node after surgery. However, there would still be the possibility of misdiagnosis of lymph node metastasis. Moreover, the determination of tissue differentiation and clinicopathological parameters of CC mainly depend on the histopathology after surgery. According to our results from the ROC analysis, the AUC values for miR-145 and miR-34a in distinguishing patients with and without lymph node metastasis were 0.779 and 0.756, respectively. The sensitivity and specificity for miR-145 detection were 77.8% and 61.5%, while the sensitivity and specificity for miR-34a detection were 73.3% and 69.2%, respectively, suggesting satisfactory diagnostic performance. Moreover, the AUC of miR-145 in distinguishing CC malignant differentiation was 0.786, and the sensitivity and specificity were 91.7% and 65.2%, respectively, suggesting high diagnostic value. These results suggest that, detection of miR-145 and miR-34a would be potential tumor markers for the diagnosis of CC, which might contribute to the targeted therapy of CC in clinic.

In Xinjiang, Northwest China, Uygur females have been known for the high incidence of CC. In this study, our results showed no significant differences in the expression of miR-145 and miR-34a between the Uygur and Han females. Based on these results, the higher incidence of CC in Uygur females might not be associated with the expression of miR-145 and miR-34a, and instead it would be related to the genetic susceptibility based on the gene polymorphism [17]. Further studies are still needed to address this issue. In addition, epidemiological studies indicate that the social factors, such as the peculiar habits of Uygur females, lower economic level, and poor awareness of cancer prevention, might contribute to the higher morbidity in these people [2].

In conclusion, our results showed that, the expression levels of miR-145 and miR-34a in the CC tissues were significantly declined, while no significant differences were observed in the miR expression between the Uygur and Han females. Moreover, the expression levels of miR-145 and miR-34a were positively associated. Furthermore, the expression of miR-145 and/or miR-34a was associated with the FIGO staging, lymph node metastasis, tissue differentiation, and tumor size of CC. In addition, ROC analysis revealed significant AUC values, and high sensitivities and specificities, for miR-145 and miR-34a, in the disease diagnosis and assessment. These results suggest that miR-145 and miR-34a might contribute to the pathogenesis and development of CC. Based on these findings, miR-145 and miR-34a could be used as tumor markers for the early diagnosis, targeted therapy, and prognosis prediction of CC in clinic.

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Disclosure of conflict of interest

None.

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