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ORIGINAL RESEARCH

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Study on the relationship between serum *miR-146a-5p* and *miR-151a-3p* and the sensitivity of synchronized radiotherapy in patients with locally advanced cervical cancer

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Abstract

Background: This study aimed to analyze the relationship between serum *microRNA-146a-5p* (*miR-146a-5p*) and serum *microRNA-151a-3p* (*miR-151a-3p*) and the sensitivity to concurrent chemo-radiation (CCRT) in patients with locally advanced cervical cancer (LACC). **Methods**: A total of one hundred LACC patients were selected. The healthy control group consisted of 100 cases of physical examination health checks performed throughout the same period. Using the solid tumor effectiveness evaluation criteria, the patients with cervical cancer were split into two groups: the resistant group (31 instances) and the sensitive group (69 cases). By using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), serum *miR-146a-5p*, and *miR-151a-3p* levels were found. In patients with LACC, the association between serum *miR-146a-5p*/*miR-151a-3p* and the resistance to CCRT therapy was examined. **Results**: Patients with LACC had significantly greater serum levels of *miR-146a-5p* and *miR-151a-3p* than the healthy control group ($p < 0.05$). Serum levels of *miR-146a-5p* and *miR-151a-3p* were significantly higher in the resistant group's patients than in the sensitive group's ($p < 0.05$). Tumor diameter greater than 4 cm, lymph node metastasis, and higher serum *miR-146a-5p*/*miR-151a-3p* levels were identified as independent risk factors for resistance to CCRT ($p < 0.05$). For predicting resistance to CCRT, the area under the curve (AUC) for serum *miR-146a-5p* was 0.835 (95% confidence interval (CI): 0.748–0.902) and for serum *miR-151a-3p* it was 0.798 (95% confidence interval: 0.706–0.872). Additionally, a higher AUC value of 0.916 (95% confidence interval: 0.844–0.962) was achieved by combining serum *miR-146a-5p* and *miR-151a-3p*. **Conclusions**: Elevated levels of serum *miR-146a-5p* and *miR-151a-3p* serve as useful diagnostic biomarkers for non-invasive screening of resistance to CCRT in patients with LACC. These levels were found to be closely associated with the effectiveness of CCRT in these patients.

Keywords

microRNA-146a-5p; *microRNA-151a-3p*; Locally advanced cervical cancer; Concurrent chemo-radiation

1. Introduction

With a complex etiology, cervical cancer (CC) is one of the most frequent malignant tumors of the female reproductive system. Its morbidity and mortality rates are among the highest of all female malignancies [1]. Although early screening for cervical cancer and human papillomavirus (HPV) vaccination have been widely promoted in recent years, some patients are still diagnosed with locally advanced cervical cancer (LACC) [2]. Concurrent chemo-radiation (CCRT) is currently the main treatment for such patients. However, due to the heterogeneity of tumor cells and individual differences, some patients still show poor sensitivity to CCRT, leading to poor therapeutic outcomes [3]. Therefore, the search for markers that can predict and evaluate the sensitivity of radiotherapy is of great significance in improving the treatment outcome of cervical cancer patients.

MicroRNA is a short non-coding RNA that is essential to many biological processes. It is a key regulator of apoptosis, differentiation, and cell proliferation, among other functions [4]. To identify dysregulated miRNAs, Ma *et al*. [5] analyzed plasma samples from 97 cervical cancer patients and 87 normal controls. They identified four miRNAs, including *miR-146a-5p* and *miR-151a-3p*, whose expression was elevated in the plasma of CC patients. *miR-146a-5p* can promote cervical cancer metastasis by regulating the signaling pathway, suggesting that *miR-146a-5p* may be associated with disease progression in cervical cancer [6]. Although fewer studies have inves-

tigated the specific mechanism of *miR-151a-3p* in cervical cancer, but one study showed that aberrant expression of *miR-151a-3p* was correlated with the progression and prognosis of various tumors [7]. However, there has been limited discussion in the literature on the relationship between CCRT sensitivity and serum levels of *miR-146a-5p* and *miR-151a-3p* in patients with LACC. In light of this, the present study examined the relationship between blood levels of *miR-146a-5p* and *miR-151a-3p* in patients with LACC who also exhibited these markers and concomitant chemo-radiation resistance. The goal of this research is to establish a baseline for the detection and management of locally advanced cervical cancer.

2. Materials and methods

2.1 Patients

One hundred cases of LACC patients admitted to the People's Hospital of Danyang, Affiliated Danyang Hospital of Nantong University, were selected as study subjects. An additional 100 healthy individuals who underwent medical checkups during the same period were selected as healthy controls. The inclusion criteria were: (1) clinicopathologically confirmed diagnosis of cervical cancer [8]; (2) International Federation of Gynecology and Obstetrics (FIGO) stage IIB–IVA [9]; (3) first-time diagnosis; (4) age greater than 18 years; and (5) healthy controls were screened with cervical smears and had negative results. The exclusion criteria were: (1) allergy to chemotherapeutic drugs; (2) recent receipt of other anti-tumor therapy; (3) accompanied by mental disorders; (4) accompanied by endometritis, pelvic inflammatory disease or other malignant tumors; abnormal coagulation function, or hepatic or renal insufficiency; (5) combined with acute and chronic infections.

2.2 Treatment

All patients were given CCRT treatment: (1) Pelvic external beam radiation therapy: 1.8~2.0 Gy/fraction, 5 times/week, total 5 weeks, total dose 45.0~50.4 Gy; equivalent dose (EQD2) = $n \times d(1 + d/\alpha/\beta)/(1 + 2d/\alpha/\beta)$. n, the number of treatment; d, the single dose; α/β, the correction factor. In this study, n = 25, d = 2, α/β = 4, and EQD2 = 37.5 Gy. (2) Brachytherapy after external radiation reaches a dose of 45.0 Gy: 6.0~6.6 Gy/fraction, once a week, total 5 times; (3) During this period, patients also received concurrent chemotherapy: 30~40 mg/m^2 intravenous cisplatin, 1~2 times/week.

2.3 Data collection

Clinical data and routine blood indexes before CCRT treatment were collected from the study participants. Baseline data included age, body mass index, pathological type, degree of tissue differentiation, squamous cell carcinoma antigen (sCCAg), tumor diameter, and lymph node metastasis. Routine blood indices mainly included hemoglobin, white blood cell count, and the neutrophil-to-lymphocyte ratio (NLR).

2.4 Serum *miR-146a-5p* and *miR-151a-3p* level detection

Fasting venous blood was drawn from cervical cancer patients within 24 hours of hospital admission, and fasting venous blood was drawn from the healthy group on the day of the physical examination. Total RNA was extracted using Trizol lysis according to the kit instructions, and the integrity of the RNA was verified to ensure that it met the criteria for reverse transcription. The RNA was reverse transcribed into cDNA using a reverse transcription kit. PCR amplification was performed using real-time fluorescence quantitative polymerase chain reaction (qRT-PCR). The reaction conditions were: 15 minutes at 90 ℃, 5 seconds at 94 ℃, 30 seconds at 55 ℃, and 30 seconds at 70 ℃ for 40 cycles. The miRNA expression level was calculated using the $2^{-\Delta\Delta Ct}$ method with U6 as the internal reference. The Primers were as follows:

miR-146a-5p, F 5′-CAG TGC GTG TCG TGA GT-3′, R 5′-GGG TGA GAA CTG AAT TCC A-3′; *miR-151a-3p*, F 5′-GGA TGC TAG ACT GAA GCT CCT-3′, R 5′-CAG TGC GTG TCG TGG AGT-3′; *U6*, F 5′-CTT CGG CAG CAC ATA TAC-3′, R 5′-GAA CGC TTC ACG AAT TTG C-3′.

2.5 Determination of the efficacy of concurrent chemo-radiotherapy

Patients with LACC were classified as either sensitive or resistant based on their response to CCRT therapy. Patients with complete tumor disappearance and more than 30% reduction in tumor diameter were classified as sensitive, and *vice versa*, according to the solid tumor efficacy evaluation criteria [9].

2.6 Statistical analysis

The data for this investigation were processed using SPSS 25.0 (IBM Corp., SPSS Statistics, Armonk, NY, USA). The χ^2 test was used, and count results were reported as n (%). When analyzing continuous variables with a normal distribution, the Students' *t*-test was used to report the data as mean ± standard deviation. A multivariate logistic regression model was used to examine the factors impacting the resistance to CCRT in patients with LACC. $p < 0.05$ was considered a statistically significant difference.

3. Results

3.1 The levels of serum *miR-146a-5p*/*miR-151a-3p* were evaluated in LACC patients

The expression levels of serum *miR-146a-5p* ($t = 4.225$, $p < 0.001$) and *miR-151a-3p* ($t = 7.488$, $p < 0.001$) were significantly upregulated in patients with LACC compared to healthy controls ($p < 0.05$, Fig. 1).

3.2 Comparison of clinical data between CCRT-sensitive and resistant patients

According to the solid tumor efficacy evaluation criteria, after 100 patients with LACC were treated with CCRT for 5 weeks, 69 cases (69.00%) were classified as sensitive and 31 cases

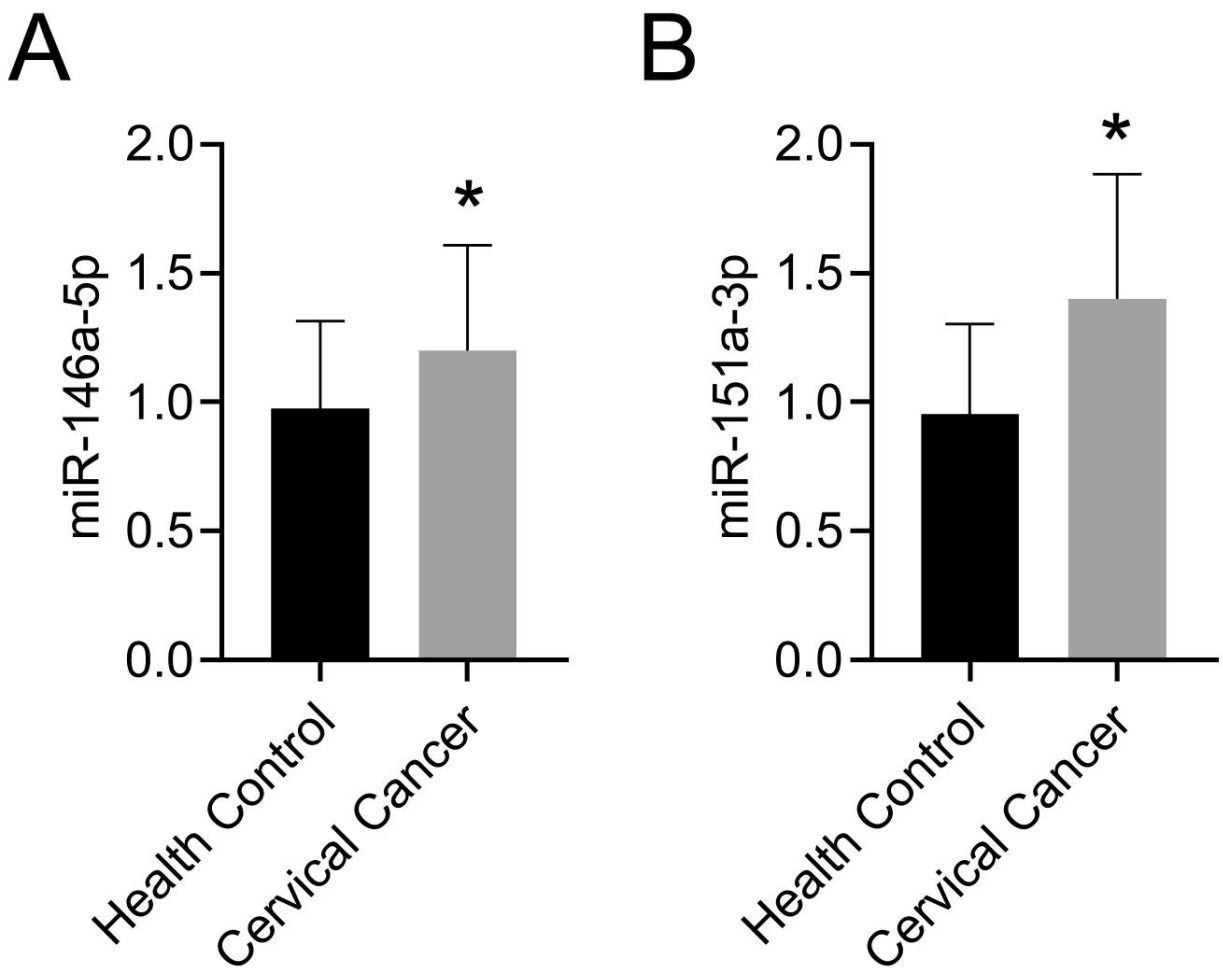

FIGURE 1. Elevated serum miR-146a-5p/miR-151a-3p levels in patients with LACC. (A) serum miR-146a-5p; (B) serum miR-151a-3p. *$p < 0.05$. *miR-146a-5p*: *microRNA-146a-5p*; *miR-151a-3p*: *microRNA-151a-3p*.

(31.00%) as resistant. There were no significant differences in age, body mass index, pathological type, degree of tissue differentiation, squamous cell carcinoma antigen levels, hemoglobin, leukocyte count, and NLR between the sensitive and resistant groups ($p > 0.05$, Table 1). Compared to patients in the sensitive group, those in the resistance group exhibited a significant increase in tumor diameter greater than 4 cm and a higher percentage of lymph node metastasis ($p < 0.05$, Table 1).

3.3 The levels of serum *miR-146a-5p* and serum *miR-151a-3p* were elevated in CCRT-resistant cervical cancer patients

Those in the sensitive group had substantially lower blood levels of *miR-146a-5p* and *miR-151a-3p* than those in the resistant group ($p < 0.05$, Fig. 2).

3.4 Multivariate examination of concurrent radiotherapy and chemotherapy resistance in individuals with LACC

In patients with LACC, elevated serum levels of *miR-146a-5p*, *miR-151a-3p*, tumor diameter greater than 4 cm, and lymph node metastasis were found to be independent risk factors for CCRT resistance ($p < 0.05$, Table 2).

3.5 Predictive value of serum *miR-146a-5p* and serum *miR-151a-3p* for CCRT resistance in LACC patients

The sensitivity of serum *miR-146a-5p* and *miR-151a-3p* for CCRT resistance in patients with LACC were 82.61% and 84.06%, respectively, and the area under the curves (AUCs) were 0.835 (95% CI: 0.748–0.902) and 0.798 (95% CI: 0.706–0.872), according to the receiver operating characteristic (ROC) results (Fig. 3). The two indicators mentioned above were incorporated into the logistic regression model, and the regression coefficients provided the following numerical formula for the union (parallel) of the two: Combined Score = 2.174 × *miR-151a-3p* + 2.054 × *miR-146a-5p*. The AUC of the combination was 0.916 (95% CI: 0.844–0.962), with a sensitivity of 86.96% and a specificity of 80.65%, according to the ROC findings (Fig. 3, Table 3).

4. Discussion

Cervical cancer is the second leading cause of cancer deaths among women. An estimated 570,000 new cases and 300,000 deaths are attributed to cervical cancer annually [10]. Early symptoms of cervical cancer are not obvious, and as the disease progresses, symptoms such as vaginal bleeding and abdominal pain may occur. For patients with LACC, surgical treat-

TABLE 1. Comparison of clinical data of patients in sensitive and resistant groups.

Indicators	Sensitive group (n = 69)	Resistant group (n = 31)	t/χ^2	p
Age				
≤50 yr	40 (57.97%)	14 (45.16%)	1.413	0.235
>50 yr	29 (42.03%)	17 (54.84%)		
Body mass index (kg/m^2)	23.29 ± 2.91	22.38 ± 2.33	1.543	0.126
Pathologic type (n (%))				
Phosphate cancer	14 (20.29%)	9 (29.03%)	0.923	0.337
Adenocarcinoma	55 (79.71%)	22 (70.97%)		
Differentiation (n (%))				
Moderately or highly differentiated	44 (63.77%)	19 (61.29%)	0.056	0.812
Lowly differentiated	25 (36.23%)	12 (38.71%)		
Tumor diameter				
≤4 cm	42 (60.87%)	10 (32.26%)	7.015	0.008
>4 cm	27 (39.13%)	21 (67.74%)		
Lymph node metastasis (n (%))				
No	39 (56.52%)	9 (29.03%)	6.476	0.011
Yes	30 (43.48%)	22 (70.96%)		
Squamous cell carcinoma antigen (ng/mL)	1.51 ± 0.30	1.49 ± 0.29	0.376	0.707
Hemoglobin (g/L)	112.01 ± 15.99	111.49 ± 16.30	0.151	0.880
Leukocytes (×10^9/L)	9.48 ± 1.77	9.24 ± 1.98	0.616	0.539
NLR	6.44 ± 0.74	6.48 ± 1.04	0.245	0.807

NLR: neutrophil-to-lymphocyte ratio.

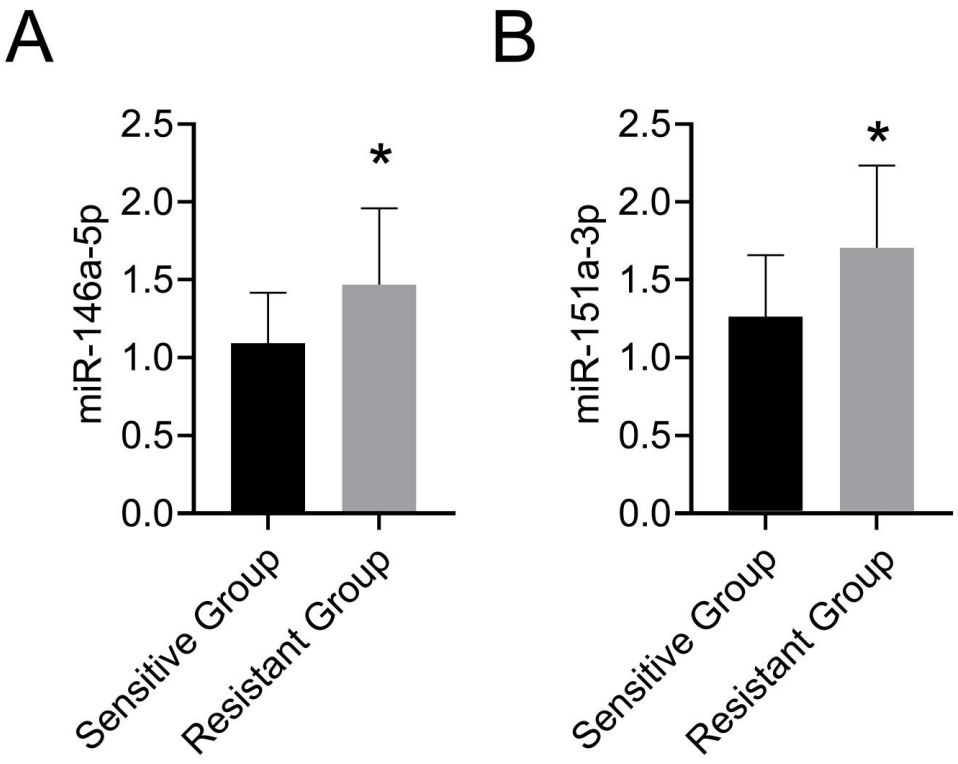

FIGURE 2. The levers of serum *miR-146a-5p* and serum *miR-151a-3p* were elevated in CCRT resistant cervical cancer patients. (A) Serum *miR-146a-5p*; (B) Serum *miR-151a-3p*. *$p < 0.05$. *miR-146a-5p*: *microRNA-146a-5p*; *miR-151a-3p*: *microRNA-151a-3p*.

TABLE 2. Multivariate study of individuals with LACC who also had concomitant chemo-radiation resistance.

Variables	β	S.E.	Wald	OR	95% CI	*p*
Tumor diameter >4 cm	1.419	0.648	3.144	3.155	1.665–4.135	<0.001
Lymph node metastasis	1.099	0.358	9.424	3.001	1.711-4.273	<0.001
miR-146a-5p	1.728	0.529	10.670	5.629	4.596-6.295	<0.001
miR-151a-3p	1.572	0.625	6.326	4.816	4.095-5.414	<0.001

miR-146a-5p: microRNA-146a-5p; miR-151a-3p: microRNA-151a-3p; β: regression coefficient; S.E.: standard error; OR: Odds Ratio; CI: confidence interval.

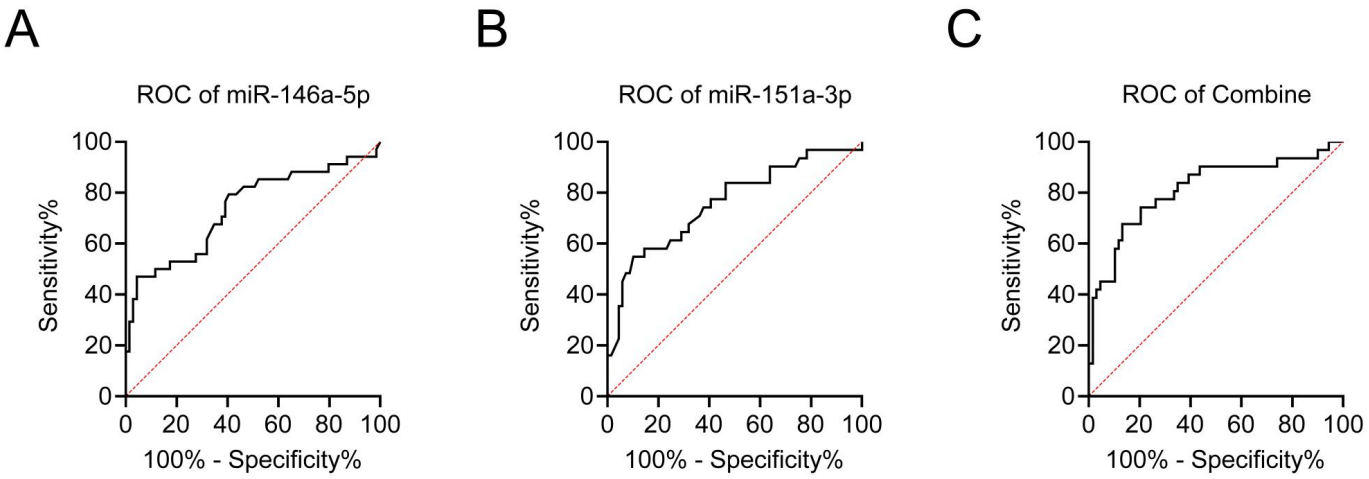

FIGURE 3. ROC curves of *miR-146a-5p*, *miR-151a-3p* predicting CCRT resistance in patients with LACC. (A) Serum *miR-146a-5p*; (B) Serum *miR-151a-3p*; (C) Combine. *miR-146a-5p*: *microRNA-146a-5p*; *miR-151a-3p*: *microRNA-151a-3p*; ROC: receiver operating characteristic.

TABLE 3. Predictive value of serum *miR-146a-5p* and *miR-151a-3p* for CCRT resistance in patients with LACC.

Variables	AUC	Cut-off value	95% CI	Sensitivity (%)	Specificity (%)	Youden index
miR-146a-5p	0.835	1.07	0.748-0.902	82.61	74.19	0.568
miR-151a-3p	0.798	1.68	0.706-0.872	84.06	70.97	0.550
Combine	0.916	-	0.844-0.962	86.96	80.65	0.676

miR-146a-5p: microRNA-146a-5p; miR-151a-3p: microRNA-151a-3p; AUC: area under the curve; CI: confidence interval.

ment is difficult, and CCRT protocols are primarily used for clinical treatment. CCRT is a combination of radiotherapy and chemotherapy, which, to some extent, can effectively reduce the tumor volume in patients with LACC and eliminate potential tiny metastatic foci to improve the clinical cure rate. However, the overall efficacy still needs to be improved due to differences in patients' sensitivity to radiotherapy and chemotherapy [11]. For patients with low sensitivity, poor treatment outcomes, disease progression or even death may occur [12]. In this study, the incidence of resistance was 31%, seen in 31 out of 100 patients with LACC who received CCRT. Patients with cervical cancer have a poor overall 5-year survival rate and are particularly susceptible to developing radiation resistance, according to previous clinical research [13]. Therefore, to provide patients with LACC-improved treatment options, objective indications associated with the prediction of CCRT resistance need to be identified.

Non-coding RNAs known as miRNAs have about 22 nucleotides and are important for regulating gene expression in several biological processes. Increasing evidence suggests that miRNAs play a key role in tumorigenesis and development. miRNAs can affect tumor cell proliferation, apoptosis, invasion, and metastasis by regulating the expression of oncogenes or tumor suppressor genes [14–16]. The results of this study indicate that blood levels of *miR-146a-5p* and *miR-151a-3p* were significantly higher in the disease group than in the healthy group, suggesting the potential involvement of these molecules in the development of cervical cancer. Consistent with the findings of this investigation, a study by Bloomfield J *et al.* [17], reported that *miR-146a-5p* and *miR-151a-5p* were overexpressed in the serum of endometrial cancer patients compared with healthy individuals and showed some diagnostic utility in endometrial cancer. The upregulated expression of *miR-146a-5p* and *miR-151a-3p* in the serum of patients with cervical cancer may represent novel biomarkers for the diagnosis of cervical cancer [5]. *miR-146a-5p* is expressed at high levels in several cancer cell lines and solid tumors, including cervical cancer, gastric cancer, and prostate cancer. The biological targets of *miR-146a-5p* have been partially identified, and it can promote the prolif-

eration and metastasis of cervical cancer cells by regulating key genes associated with proliferation and metastasis, such as the WW and C2 domain-containing protein (WWC2) and the Histone modifier lysine-specific demethylase 2B (KDM2B) [6, 18]. Additionally, *miR-151a-3p* can regulate the biological characteristics of cancer cells through various mechanisms. For instance, by inhibiting *p53*, *miR-151a-3p* may induce an anti-apoptotic response, trigger epithelial-to-mesenchymal transition (EMT), and encourage the development of tumors via controlling genes linked to *p53*-related tumor progression [19]. Therefore, drug development targeting *miR-146a-5p* and *miR-151a-3p* molecules may be a promising avenue for treating cervical cancer.

In recent years, serologic biomarkers have received a lot of attention due to their low cost and ease of performing the assays. miRNAs can be released from cancer cells into the bloodstream and remain stable in the peripheral circulation, thus enabling their detection in the bloodstream [20]. Because circulating miRNAs are stable in serum and plasma and exhibit constant and repeatable expression levels among individuals, it is possible that they could be used as non-invasive biomarkers [21, 22]. Therefore, miRNAs are considered promising serum biomarkers for disease diagnosis and prognostic assessment. Circulating miRNAs may be an encouraging noninvasive diagnostic tool for individuals with cervical cancer, according to a systematic review and meta-analysis [23]. Notably, some miRNAs can predict the efficacy of surgical treatment, radiotherapy, and chemotherapy for cervical cancer [24–26]. Reduced levels of *miR-1228-5p*, *miR-33a-5p*, *miR-3200-3p*, and *miR-6815-5p* and elevated levels of *miR-146a-3p* were linked to the degree of early progression and metastasis in patients with cervical cancer receiving CCRT therapy [27]. Furthermore, some miRNAs associated with CCRT resistance in cervical cancer patients have been identified, and these miRNAs may serve as useful biomarkers for predicting chemotherapy sensitivity [28]. In this study, we found that serum *miR-146a-5p* and *miR-151a-3p* were associated with CCRT in patients with LACC, and showed predictive value for CCRT. *miR-146a-5p* exerts its role in tumorigenesis and development by targeting multiple genes associated with cell proliferation, apoptosis, and migration. For example, *miR-146a-5p* inhibits key molecules of the inflammatory signaling pathway, such as the tumor necrosis factor receptor associated factor 6 (TRAF6) and the interleukin 1 receptor-associated kinases 1 (IRAK1), thereby attenuating the inflammatory response in the tumor microenvironment. However, this inhibitory effect may promote the survival of tumor cells and the development of drug resistance in some cases. Previous studies have found [29, 30] that serum *miR-146* and *miR-151* levels showed a gradual increase with higher malignancy such as tumor stage, infiltration depth, and lymph node metastasis. According to a study by Zhuang *et al*. [31], tumor-stromal crosstalk mediated by *miR-146a-5p* derived from cancer-associated fibroblasts promoted the formation of ecological niches for cancer stem cells and cancer stemness. It also improved chemoresistance in uroepithelial bladder cancer, indicating a possible link between *miR-146a-5p* and chemosensitivity. In addition, Lee *et al*. [19] emphasized the important role of *miR-151a-3p* as a biomarker in enhancing sensitivity to radiation therapy. miR-151a-3p exerts its biological functions mainly by targeting genes related to the cell cycle, apoptosis and DNA repair. For example, *miR-151a-3p* inhibits the expression of cyclin-dependent kinase 6 (CDK6), thereby blocking the cell cycle process; it also inhibits apoptosis of tumor cells by down-regulating the expression of apoptosis-related genes. Together, these mechanisms of action promote the proliferation of tumor cells and the emergence of drug resistance. Therefore, serum *miR-146a-5p* and *miR-151a-3p* may serve as helpful biomarkers for predicting the efficacy of CCRT therapy in patients with LACC. Furthermore, miRNA panels are more effective in diagnosing diseases than individual miRNAs [32, 33]. For instance, *let-7d-3p* and *miR-30d-5p* together have shown high diagnostic effectiveness in detecting cervical cancer [34]. Furthermore, for patients with LACC, the current study found that serum *miR-146a-5p* and *miR-151a-3p* jointly improved the prognostic power of CCRT treatment. In a clinical setting, patients with LACC who have both low serum *miR-146a-5p* and low serum *miR-151a-3p* are less likely to develop CCRT resistance. However, patients with LACC who develop both high serum *miR-146a-5p* and high serum *miR-151a-3p* should be given special attention or treated aggressively. This finding may provide important guidance for improving the prognosis of patients with LACC.

There are several limitations of this study. First, this study only examined the diagnostic significance of serum *miR-146a-5p* and serum *miR-151a-3p* concerning the efficacy of CCRT in LACC patients, without performing predictive analyses. Second, considering the limited sample size, a multicenter, large sample size prospective inquiry is still required to assess the predictive value of serum *miR-146a-5p* and serum *miR-151a-3p* in CCRT efficacy in LACC patients. Moreover, additional investigation is necessary to ascertain the specific functions of *miR-146a-5p* and *miR-151a-3p* in the development of LACC.

5. Conclusions

In conclusion, increased serum levels of *miR-146a-5p* and *miR-151a-3p* are linked to CCRT resistance in LACC patients, and the combination of these two miRNA-based signatures in serum has the potential to predict the effectiveness of CCRT in LACC patients.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

WC, WZ—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. WC, WZ, XYJ, YNJ—supervised the data collection; analyzed the data; interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of The People's Hospital of Danyang (Approval no. 20210810). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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