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Original Article

The correlation of the miR-29a/MMP9 axis with *Helicobacter pylori* infection in gastric cancer

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Abstract: Objective: This study was designed to investigate the association between the miR-29a/MMP9 axis expression levels and *Helicobacter pylori* (HP) infection in gastric cancer patients. Methods: A total of 100 gastric cancer patients referred to our hospital from June 2017 to June 2019 were recruited as the study cohort. Among them, 50 HP-positive patients were included in the experimental group and 50 HP-negative patients were included in the control group. The changes in the patients' conditions were compared, the miR-29a/MMP9 axis expression levels were recorded, and the correlation between the miR-29a/MMP9 axis and the HP infections was analyzed. All the discharged patients were followed up for one year to analyze the correlation between the HP infections and the serum miR-29a and MMP9 expression levels with the disease progression. Results: The experimental group had higher miR-29a expression levels and higher MMP9 chromogenic scores than the control group ($P<0.05$). A negative correlation was found between the miR-29 expression level and the MMP9 expression level ($r=-5.369$, $P<0.05$). One year after discharge, there were 27 patients with severe disease in the experimental group and 6 in the control group, with a significant difference between the two groups. Moreover, the expression levels of the miR-29a/MMP9 axis were significantly higher in the discharged patients than in the patients with severe disease ($P<0.05$). A receiver operating characteristic (ROC) curve was used to analyze the predictive value of miR-29/MMP9 in the diagnosis of gastric cancer, and the area under the curve was found to be 0.97. Conclusion: The miR-29a/MMP9 axis levels were increased in the HP positive patients but not in the HP negative patients. HP infection is considered to be closely related to gastric cancer cell spread, disease relapse, and high miR-29a/MMP9 axis expression levels.

Keywords: miR-29a/MMP9 axis, *Helicobacter pylori*, gastric cancer

Introduction

Gastric cancer, a malignant tumor that severely affects human health, may stem from severe gastropathy and bad living habits. Notwithstanding the well-rounded treatment techniques for gastric cancer in China, the mortality of gastric cancer remains at a high level and can be attributed to relapse and metastasis. The current early diagnostic techniques for gastric cancer leave much to be desired [1]. It has been shown that *Helicobacter pylori* (HP) infection can cause gastric mucosal injury, thereby triggering the occurrence and metastasis of cancer cells [2]. In addition, significant changes in the expression of miRNAs occur in the tissue cells of gastric cancer patients, suggesting that the miRNAs function as oncogenes or antioncogenes. Consequently, the quantification of the serum miRNA levels in gastric cancer patients is essential for the diagnosis of gastric cancer. Of the many miRNAs, miR-29a is shown to promote the expression of the MMP9 protein [3], and the expression levels of the miR-29a/MMP9 axis are reported to be closely associated with HP infection and indirectly lead to gastric carcinoma. Herein, we analyzed the correlation of the serum levels of miR-29a and MMP9 with HP infection in gastric cancer patients, and compared the number of patients with spread, metastasis, and disease recurrence between the HP positive and HP negative gastric cancer patients. The innovation of this study lies in the exploration of gastric cancer and its biological behavior at the genetic level. It was found that MMP-9 effectively decomposed type IV colla-

gen-the main component of the basement membrane, and the overexpression of MMP-9 led to enhanced metastasis and invasion of malignant tumors, which provided new targets for future treatment of gastric cancer.

Materials and methods

General data

Fifty HP positive (experimental group) and 50 HP negative (control group) gastric cancer patients who underwent treatment in our hospital from June 2017 to June 2019 were recruited as the study cohort. All the patients in the experimental group were 26 to 70 years old, and the patients in the control group were 30 to 71 years old.

Inclusion criteria

① Patients who were diagnosed with gastric cancer through pathological examinations. ② Patients who didn't undergo any radiotherapy or chemotherapy before the operation. ③ Patients who didn't undergo any anti-HP treatment in the 4 weeks before their enrollment in the study.

Exclusion criteria

① Patients with a recurrence of gastric cancer. ② Patients with other malignant tumors. ③ Patients with incomplete clinical data. ④ Patients with severe organ dysfunction.

This study was approved by the ethics committee of our hospital, and all the patients voluntarily participated in the study and signed an informed consent form (Ethics Committee Approval Number: 2016-03-24).

Methods

Detection methods for HP infection: C^{13} breath tests were performed in both groups to determine whether the patients had HP infection and to facilitate the grouping. After the patients fasted for 8 hours, the breath tests was performed 30 min in the wake of the oral administration of urea capsules. The peak value of the C^{13} atom in the gas after the oral administration of the capsules was measured using Haidwei HP testers (HUBT20P; Chongqing Jiusheng Medical Device Co., Ltd.). The patients were confirmed to be HP-positive (HP infection) if the measurement result exceeded 5% of the specified value, otherwise, the diagnosis was HP negative (HP-uninfected) [4-6].

Study methods: Fasting venous blood (5 mL) was drawn from the patients in both groups before and after the tumor resections to determine the serum miR-29a and MMP9 levels using real-time quantitative reverse transcription polymerase chain reactions (RT-qPCR) and MMP9 assay kits (48t; Shanghai Future Industrial Co., Ltd.), respectively.

Fluorophore was added again to the PCR reaction system to observe and record the fluorescence signal changes, and the reaction curve was drawn. The curve obtained from the test was compared with the standard curve, and the patients' serum miR-29a expression levels were then measured.

The collected blood samples were centrifuged at 3000 rpm for 10 min to separate the serum from the erythrocytes. Subsequently, the supernatant of the separated cells was collected for later analysis. The number and depth of the color development of the serum samples were observed microscopically to determine the MMP9 expression levels in the patients [7-9].

Treatment and nursing methods: The patients in the two groups underwent the same nursing. In terms of the treatment, the experimental group was given antibiotics (clarithromycin 500-1000 mg/d or amoxicillin 2000 mg/d or metronidazole 800 mg/d) in addition to the treatment administered to the control group. The recovery of the two groups was observed. The patients were followed up for 1 year after discharge to record the number of patients with disease recurrence and cancer cell spread and metastasis after the tumor resections, and to determine the serum miR-29a and MMP9 expression levels in the patients with recurrences.

Evaluation indicators

The difference between the detection curve and the standard curve of miR-29a was beyond the safe range, suggesting abnormal serum miR-29a expression levels in the patients. The MMP expressions were measured in strict accordance with the instructions of the

Table 1. Comparison of the general data

Group	Sex (M/F)	Age (year)	Height (cm)	Weight (kg)
Experimental group	21/29	47.35±13.50	167.94±14.00	66.39±10.99
Control group	26/24	50.22±11.07	169.69±14.78	70.01±10.37
t		1.16	0.64	1.69
P	0.32	0.25	0.54	0.09

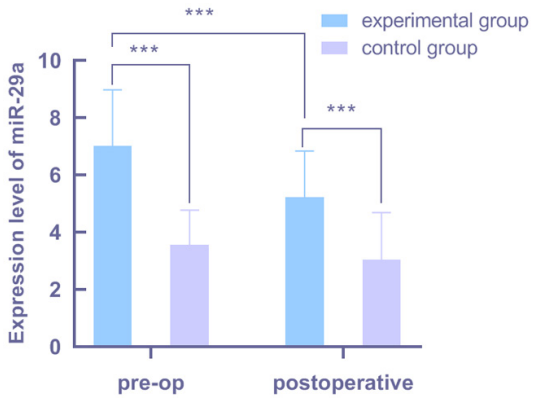

Figure 1. Comparison of the miR-29a expression levels. Notes: The abscissa indicates before the surgeries and after the surgeries from left to right, and the ordinate indicates the patients' serum miR-29a expression levels. The preoperative miR-29a expression levels in the experimental group were significantly higher than they were in the control group (7.01±1.97 *vs* 3.56±1.21; t=10.55). ***P<0.001. The postoperative miR-29a expression levels in the experimental group were significantly higher than they were was in the control group (5.21±1.63 *vs* 3.03±1.66; t=6.63); ***P<0.001. In the experimental group, the preoperative miR-29a expression levels were significantly higher than the postoperative levels (7.01±1.97 *vs* 5.21±1.63; t=4.98); ***P<0.001.

MMP9 kit, and the proportion of chromogenic cells and the cell colors in the reagent sample were observed under a microscope. 0 point: the proportion of chromogenic cells was less than 5%; 1 point: the proportion of chromogenic cells was less than 30%; 2 points: the proportion of chromogenic cells was less than 60%; 3 points: the proportion of chromogenic cells was less than 80%; 4 points: the proportion of chromogenic cells was more than 80%. The chromogenic cells were yellowish for 1 point; dark yellow for 2 points; and tan for 3 points [10-12]. A total score of 0-3 suggests low expression of MMP9, and a total score of 3-7 suggests high expression. A follow-up visit was performed one year after the tumor resections to compare the numbers of patients with cancer cell spread and metastasis and disease recurrence between the two groups and to determine the association between the HP infections and the patients' serum miR-29a/MMP9 axis expression levels.

Statistical analysis

In this study, all the statistical analyses were conducted using SPSS 21.0. The measurement data were expressed as ($\bar{x}$±s) and examined using t-tests. The count data were represented as [n (%)] and examined using X^2 tests. Spearman's correlation coefficient analyses were used to analyze the correlations between the miR-29 and MMP9 expression levels. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the diagnostic value of the miR-29/MMP9 axis in gastric cancer. A statistically significant difference was determined at P<0.05.

Results

Comparison of the general information

The two groups did not differ in terms of their general clinical information (P>0.05, **Table 1**).

Comparison of the miR-29a expression levels

After the surgery, the miR-29a expression levels decreased significantly in both groups (P< 0.05) but were higher in the experimental group compared with the control group (P<0.05, **Figure 1**).

Comparison of the MMP9 positive rates

A significantly higher positive rate of MMP9 was found in the experimental group as compared to the control group (P<0.05, **Table 2**).

Comparison of the miR-29a expression levels between the MMP-positive and MMP-negative patients

The MMP-positive patients showed higher expression levels of miR-29a than the MMP-negative patients (P<0.05, **Figure 2**). A negative correlation was determined between the expression level of miR-29 and the expression level of MMP9 (r=-5.369, P<0.05, **Figure 3**).

Table 2. The MMP-9 expression levels in the two groups

Group	MMP-9 Negative	MMP-9 Positive
Experimental group (n=50)	22 (44)	28 (56)
Control group(n=50)	36 (72)	14 (28)
χ^2	8.046	
P	0.004	

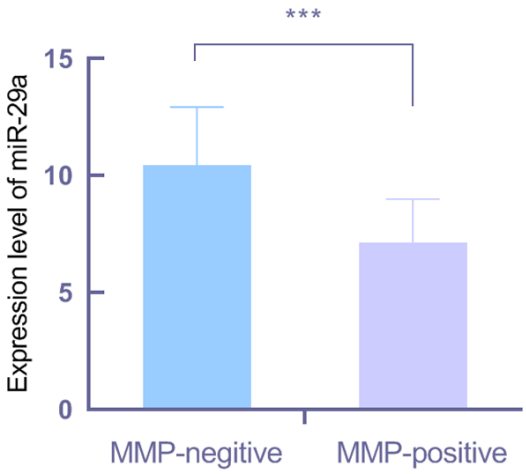

Figure 2. A comparison of the miR-29a expression levels in the MMP-positive and MMP-negative patients. Note: ***P<0.001.

Comparison of serum MMP9 levels before and after the operations

Similar to the expressions level of miR-29a, the serum MMP9 expression levels witnessed a downturn after the tumor resections in both groups (P<0.05), and the experimental group garnered a higher outcome than the control group (P<0.05, **Figure 4**).

Comparison of the follow-up results

The patients were followed up for one year after their discharge to record the spread and metastasis of cancer cells and the disease recurrence. The results showed a total of 33 cases with cancer cell spread, metastasis, and disease recurrence, including 27 patients in the experimental group and 6 patients in the control group. Among the 33 patients, 14 had cancer cell spread, 9 had cancer cell metastasis to other organs, and 10 had signs of disease recurrence after tumor resection. The patients in the experimental group were at a higher risk

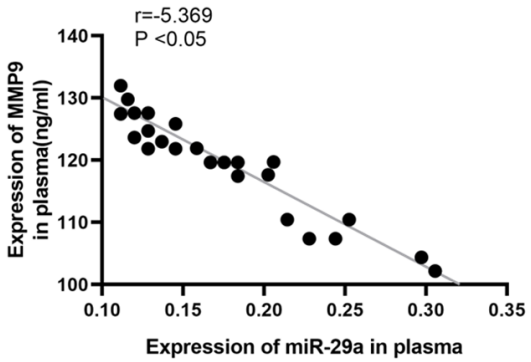

Figure 3. The correlation between the miR-29 and the MMP9 expression levels.

of cancer cell metastasis and spread, as well as disease recurrence than those in the control group (P<0.05, **Figure 5**).

Comparison of the symptom-free survival times

As shown in **Figures 6** and **7**, the control group yielded a promising outcome in its symptom-free survival times compared to the experimental group (17.35±3.57 *vs* 14.57±3.18, P<0.05).

The miR-29a and MMP-9 expressions in the patients who experienced recurrence

All the patients with recurrent disease had HP infections, and presented with significantly higher miR-29a and MMP9 expression levels compared with the expression levels recorded at discharge (P<0.05, **Tables 3** and **4**).

ROC curve analysis of the miR-29/MMP9 axis for predicting gastric cancer

An ROC curve was used to analyze the predictive value of miR-29/MMP9 in the diagnosis of gastric cancer. It was found that the area under the curve was 0.97 (**Figure 8**), suggesting that the miR-29/MMP9 axis has a great potential in the prediction of gastric cancer.

Discussion

Gastric cancer is a public health concern with a high mortality. Poor living habits, primary gastropathy, and other critical illnesses are all factors leading to gastric cancer [13, 14]. Despite the substantial achievements made in the treatment of gastric cancer in China, there are

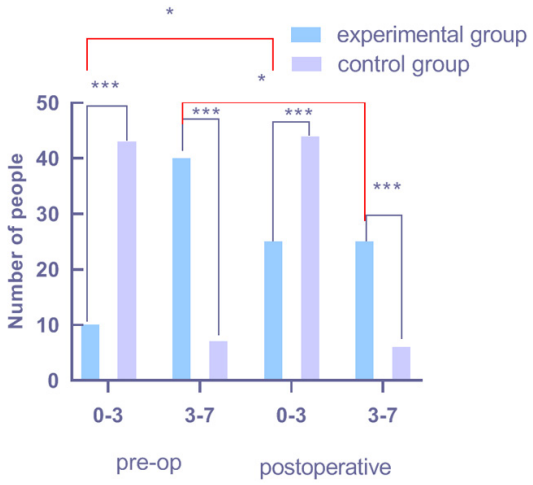

Figure 4. A comparison of the MMP9 expression levels. Note: The abscissa represents the score range of the MMP9 expression levels before and after the tumor resections, and the ordinate represents the number of patients. The number of patients with preoperative low MMP9 expressions in the experimental group was significantly less than the number in the control group (10 *vs* 43, X^2=43.71); ***P<0.001; The number of patients with preoperative high MMP9 expressions in the experimental group was significantly greater than the number in the control group (40 *vs* 7, X^2=43.71); ***P<0.001; The number of patients with postoperative low MMP9 expressions in the experimental group was significantly less than the number in the control group (25 *vs* 44, X^2=16.88); ***P<0.001; The number of patients with postoperative high MMP9 expression in the experimental group was significantly greater than that in the control group; 25 *vs* 6, X^2=16.88); ***P<0.001; In the experimental group, the number of patients with low MMP9 expression before surgery was significantly less than that after surgery (10 *vs* 25, X^2=9.89), *P=0.002. In the experimental group, the number of patients with high MMP9 expressions before surgery was significantly greater than the number after surgery (40 *vs* 25, X^2=9.89); *P=0.002.

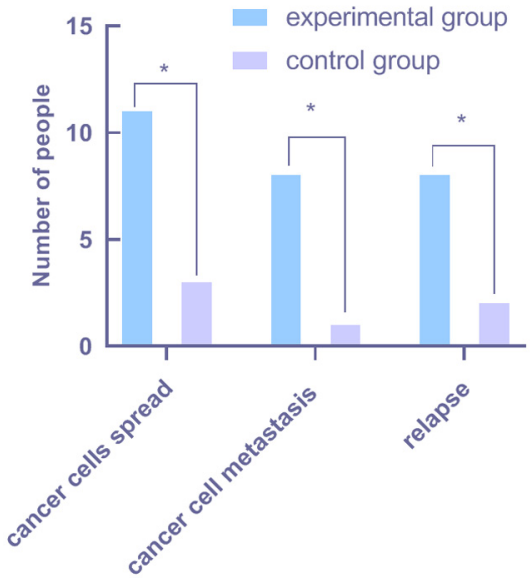

Figure 5. Comparison of the cancer cell spread and metastasis and the disease recurrence. Note: The abscissa indicates the disease progression of patients during follow-up, which was specifically classified as cancer cell spread, cancer cell metastasis, and gastric cancer recurrence from left to right, and the ordinate indicates the number of patients. The number of patients with cancer cell spread in the experimental group was significantly less than the number in the control group (11 *vs* 3, X^2=5.32), *P=0.021; The number of patients with cancer cell metastasis in the experimental group was significantly less than the number in the control group (8 *vs* 1, X^2=5.98), *P=0.014. The number of patients with gastric cancer recurrence in the experimental group was significantly less than the number in the control group (8 *vs* 2, X^2=5.83), *P=0.016. Additionally, it was found that all the patients with disease recurrence developed HP infections, and their expression levels of miR-29a and MMP9 were remarkably higher than those at discharge 1 year earlier. *P* values <0.05 were considered statistically significant.

still many advanced patients with little improved or even deteriorated conditions, which may be attributed to unsatisfactory diagnoses resulting from the non-specific symptoms of the disease in the early stages [15]. It is reported that HP infection is an important factor in the development of gastric cancer, and there is a close relationship between the serum miR-29a and MMP9 expression levels and HP infection in patients [16, 17].

To determine the effect of HP infection on the disease progression of gastric cancer patients and to understand the association between the expression levels of the serum miR-29a/MMP9 axis and HP infection, this study analyzed the disease progression of 100 gastric cancer patients admitted to our hospital from June 2017 to June 2019. The results showed that the serum miR-29a expression levels in the patients with HP infections in the experimental group were higher than they were in the control group. After the surgeries, the serum miR-29a expression levels decreased significantly in both groups (P<0.001), with higher levels in the experimental group compared to the control group (P<0.05). This finding indicates that the serum miR-29a expression shows a great potential in the early diagnosis and prevention of gastric cancer, and the inhibition of the miR-

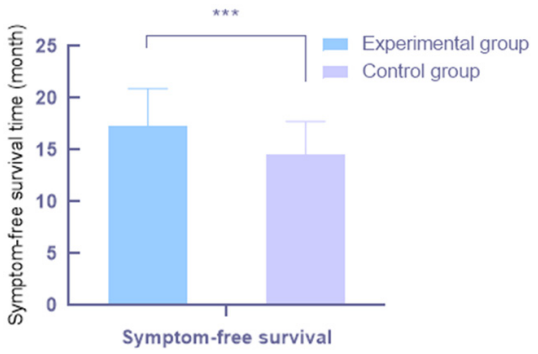

Figure 6. Symptom-free survival times of the two groups. Note: The symptom-free survival times were (17.35±3.57) months in the control group and (14.57±3.18) months in the experimental group. ***P<0.001.

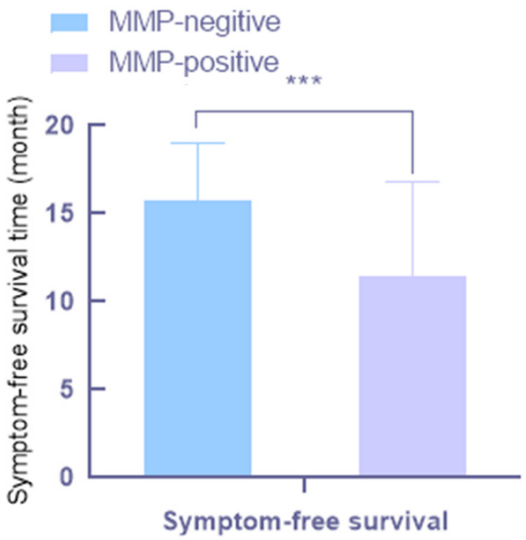

Figure 7. The symptom-free survival times of the MMP-negative and MMP-positive patients. Note: The symptom-free survival times of the MMP-negative patients were 15.75±3.25 m, and the symptom-free survival times of the MMP-positive patients were 11.48±5.32 m. ***P<0.001.

29a expression can serve as a therapeutic approach. The MMP9 expression levels were measured using chromogenic tests. The results showed that the serum MMP9 expression levels were reduced significantly after the tumor resections in both groups (P<0.05), with a higher positive rate in the experimental group compared with the control group (P<0.05). Moreover, the expression of MMP9 decreased with the recovery of each patient's condition and the use of antibiotics (P<0.05). The results indicated that the MMP9 expression levels are higher in HP-infected gastric cancer patients and decreased in patients with gradual relief from their HP infection symptoms. Hence, the quantification and inhibition of MMP9 expression levels *in vivo* show a great potential in the diagnosis and treatment of HP-infected gastric cancer, which is consistent with the conclusion proposed by Chuanwen Zhao et al. [18], namely that Capn4 promotes the metastasis and progression of gastric cancer by increasing the MMP9 expressions in patients.

Furthermore, all the patients were followed up for one year after discharge. The results demonstrated that a total of 33 patients had disease aggravation within 1 year, including 27 patients in the experimental group and 6 patients in the control group. Among the 33 patients, 14 had cancer cell spread, 9 had cancer cell metastasis to other organs, and 10 had signs of gastric cancer relapse after their tumor resections. It was then revealed through surveys that all the patients with aggravated disease experienced HP infection, with significantly increased expression levels of miR-29a and MMP9 compared with the levels recorded at discharge (P<0.001). This can be attributed to the lack of strict diet control, a failure to maintain healthy living habits after discharge, and poor adherence to medication and follow-up examinations [19, 20]. Gastric cancer, one of the leading causes of cancer-related deaths in developing countries, is mainly triggered by HP infection. Active inflammation caused by HP infection and maintained by innate immune disorders further promotes cancer progression and postoperative recurrence. Conversely, the absence of HP in tumors is associated with a better prognosis, which may be due to the induction of anti-tumor immunity. Moreover, tumor-associated macrophages and neutrophils indicate a poor prognosis. The elevated serum MMP-9, MMP-12, and MMP-21 levels are closely related to the low survival rate in gastric cancer. Consequently, further emphasis should be placed on the integration of these biomarkers to clarify their value in predicting the postoperative prognosis of gastric cancer in a large cohort. Qu et al. [21] showed that the HOXA-AS3/miR-29a-3p/LTβR/NF-κB regulatory axis contributes to the progression of gastric cancer, thereby offering novel targets for the prognosis and treatment of the disease. The

Table 3. Comparison of the serum miR-29a expression levels in patients with recurrence and their levels at discharge

Group	Level at admission	Level at discharge	t	P
Expression level	6.95±2.54	3.99±2.07	6.39	<0.001

Table 4. Chromogenic MMP9 scores in the patients with recurrence

Group	Score at admission	Score at discharge	X^2	P
0-3	5	26	26.83	<0.001
3-7	28	7		

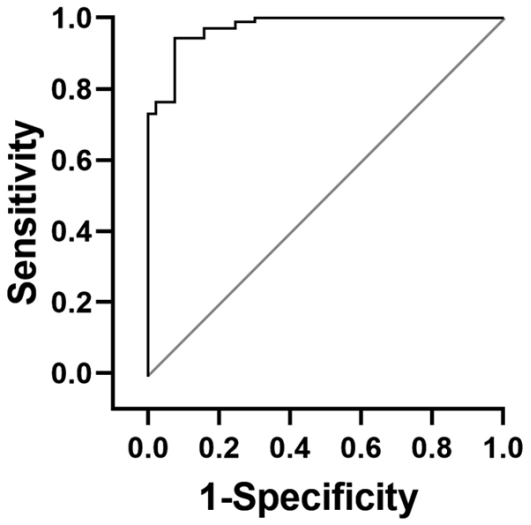

Figure 8. An ROC curve analysis of miR-29/MMP9 in predicting gastric cancer.

present study confirmed the involvement of the miR-29a/MMP9 axis in the progression of gastric cancer, which also provided new clinical targets for gastric cancer prognosis and treatment. The limitation of this study lies in the absence of drug trials, so further research is needed to investigate the effects of drugs on the miR-29a and MMP-9 expressions as well as tumor recurrence to obtain reliable clinical evidence and provide new targets for clinical treatment.

Taken together, the expression of the miR-29a/MMP9 axis is closely associated with HP infection in gastric cancer patients and directly correlates with the progression of gastric cancer. Therefore, measuring the expression levels of the miR-29a/MMP axis carries huge clinical implications for the early diagnosis and treatment of gastric cancer and is worthy of clinical application and promotion.

Disclosure of conflict of interest

None.

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