Cancer Management and Research

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Elevated Levels of MUC and JADE1 Predict Poor Prognosis of Patients with Gastric Cancer

Zhaowei Zhu[1,2], Yanming Hua[2], Jianta Wu[2], Jianfeng Mei[2]

[1]Graduate School, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, People's Republic of China; [2]Department of General Surgery, The General Surgery of Lanxi People's Hospital, Jinhua, Zhejiang, 321100, People's Republic of China

Correspondence: Jianfeng Mei, Department of General Surgery, The General Surgery of Lanxi People's Hospital, 1359 Xishan Road, Lanjiang Street, Lanxi, Jinhua, Zhejiang, People's Republic of China, Email lxmjf1205@163.com

Objective: This study aimed to investigate the relationship between the expression of mucin (MUC) and JADE family PHD finger factor 1 (JADE1) and *Helicobacter pylori* (HP) infection as well as depth of tumor invasion in gastric cancer.

Methods: According to the results of immunohistochemical staining, 132 gastric cancer patients diagnosed and treated in our hospital from March 2018 to May 2019 were divided into MUC2 negative group (n=43), MUC2 positive group (n=89), JADE1 negative group (n=36) and JADE1 positive group (n=96). The relationship between MUC2 and JADE1 expression and clinicopathological features of gastric cancer was analyzed. The diagnostic value of MUC2 and JADE1 alone or in combination in gastric cancer was analyzed using ROC curve.

Results: The MUC2 and JADE1 expressions in gastric cancer tissues was increased (P<0.05). MUC2 and JADE1 expressions were related to different tumor size, differentiation degree, HP infection, lymph node metastasis, depth of tumor invasion and Lauren classification (P<0.05). Kaplan-Meier survival analysis showed that the survival rate of patients with negative expression of MUC2 and JADE1 was significantly lower than that of patients with positive expression of MUC2 and JADE1 (P<0.05). The area under the curve, sensitivity and specificity of MUC2 alone, JADE1 alone and the two combined in detection of gastric cancer was 0.774, 72.46% and 80.03%, 0.796, 82.14% and 76.48%, and 0.918, 91.34% and 89.57%, respectively.

Conclusion: The expressions of MUC2 and JADE1 in gastric cancer tissues were significantly increased, and their expressions were associated with tumor size, differentiation degree, HP infection, lymph node metastasis, depth of tumor infiltration, Lauren's staging. The combined detection of the two has a high value in the diagnosis of gastric cancer. Analysis of the relationship between MUC2 and JADE1 expression and HP infection is helpful for clinical medical staff to effectively evaluate the condition of patients.

Keywords: gastric cancer, MUC mucin, JADE1, HP infection, depth of tumor infiltration

Introduction

Gastric cancer is the most common malignant tumor of the digestive tract in men. With the change of people's living habits in recent years, such as irregular diet and disordered work and rest, the incidence of gastric cancer is increasing year by year. Its mortality ranks the fourth in the world, only after lung cancer, colorectal cancer and liver cancer. Gastric cancer has become a disease affecting the quality of life and even the health of patients worldwide.[1] Gastric cancer can be resulted from a variety of factors. *Helicobacter pylori* (HP) infection, age, high salt intake, and a diet low in fruits and vegetables are all risk factors for gastric cancer. Surgery is one of the main treatment methods for gastric cancer. The application of neoadjuvant chemotherapy before or after surgery has received increasing attention, and some patients will undergo surgery after neoadjuvant chemotherapy. However, due to the insidious onset of early gastric cancer, most patients are in the middle and advanced stages when diagnosed, and miss the best treatment time. Even if they can be treated in time, patients still have a high recurrence rate and a poor prognosis.[2] Vascular endothelial growth factor (VEGF) and microvessel density (MVD) are important indicators for clinical diagnosis of gastric cancer. VEGF can increase the permeability of microvessels and induce neovascularization. However, there are many factors affecting the expression of VEGF and MVD with low specificity.[3] Mucin (MUC) is a glycoprotein with high molecular weight, which can be divided into membrane-bound type and secretory type. Among them, MUC1 and MUC2 are mainly expressed in the stomach.[4] It has been found that MUC plays an important role in the normal physiological function and

Received: 25 August 2024
Accepted: 8 February 2025
Published: 13 March 2025

lubrication of the stomach. It is rich in a variety of amino acids, and its secretion level may affect the adhesion, immune recognition, and metastasis of tumor cells.[5] It has been reported that MUC shows significantly abnormal expression in the occurrence and development of gastric cancer.[6] Jade family PhD index factor 1 (JADE1) is a tumor-related gene, with anti-proliferation and apoptosis-promoting effects. Von Hippel-Lindau (VHL) is a tumor suppressor gene that plays a role in tumor development through the VHL-hypoxia inducible factor (HIF)-dependent pathway, which can control the stability of the cell cycle genome and cell death. It has been found that JADE1 can interact with a variety of genes such as VHL, and then participate in the occurrence and development of diseases.[7] The expression of JADE1 has been discovered to be significantly abnormal in a variety of malignant tumors such as renal cancer, colorectal cancer and other malignant tumors.[8] The pathogenesis of gastric cancer is complex, and HP infection is an important cause of gastric cancer. The previous study has found that HP infection can induce the expressions of a variety of gastric cancer related factors.[9] MUC2 and JADE1 were selected for this study based on the following considerations. Firstly, as a glycoprotein widely expressed in epithelial cells, MUC2 is involved in the renewal and differentiation of epithelial cells and the maintenance of the integrity of epithelial cells, which is closely related to the occurrence and development of a variety of cancers.[10] Secondly, the expression of JADE1 is found to be significantly abnormal in renal clear cell carcinoma cells, and it can interact with a variety of genes to participate in the occurrence and development of diseases.[11] Therefore, we hypothesized that MUC2 and JADE1 might also play an important role in the pathogenesis of gastric cancer. Based on these findings, the aim of this study is to investigate the relationship between the expression of MUC and JADE1 in gastric cancer tissues and HP infection as well as the depth of tumor infiltration. We hope our results can help clinicians more effectively grasp the diagnostic value of MUC and JADE1 as markers in HP infection and pathogenesis of gastric cancer, and help to further evaluate the patient's condition.

Materials and Methods

General Materials

The surgical specimens of 132 patients with gastric cancer diagnosed and treated in our hospital from March 2018 to May 2019 were selected as the research subjects. According to the results of immunohistochemical staining, the subjects were divided into MUC2 negative group (n=43), MUC2 positive group (n=89), JADE1 negative group (n=36) and JADE1 positive group (n=96) based on immunohistochemical staining results. There were 79 males and 53 females, aged from 27 to 75 years, with the average age of (50.58 ± 7.26) years. Criteria inclusion: (1) All subjects met the criteria for the diagnosis and treatment of gastric cancer,[12] and were confirmed by pathological examination; (2) The subjects without endoscopic surgery, radiotherapy or chemotherapy before participating in the study; (3) All subjects signed the informed consent form and actively participated in the study; (4) The study was approved by the Ethics Committee of our hospital; (5) All subjects were able to cooperate with relevant research contents. Exclusion criteria: (1) The subjects combined with other malignant tumors; (2) The subjects with obviously abnormal liver and kidney function or heart function; (3) Pregnant or lactating subjects; (4) The subjects who were unable to cooperate with the study and poor compliance; (5) The subjects accompanied by mental disorders; (6) The subjects complicated with infectious diseases. The selection process of general materials was shown in Figure 1.

Immunohistochemical Staining

Gastric cancer tissues and adjacent normal tissues were routinely made into paraffin sections, and then were subjected to dry, dewaxing, hydration, antigen retrieval, block and membrane broken. MUC2 and JADE1 antibody diluents were prepared, then added to each tissue section in turn, and incubated at 4 °Covernight. Subsequently, the tissue sections were cleaned by addition of phosphate buffer solution (PBS), followed by addition of horseradish peroxidase secondary antibody to each tissue section in turn and incubation at 37 °C for 60 min. The sections were washed with PBS, and then being dehydration and transparent after DAB for color development and hematoxylin re-staining. The sections were sealed with resin, and observed under microscope.

The staining results were considered as positive expression when the tissues were stained as brown yellow and yellow. To be specific, positive expression: both staining intensity and the proportion of positive cells were considered as

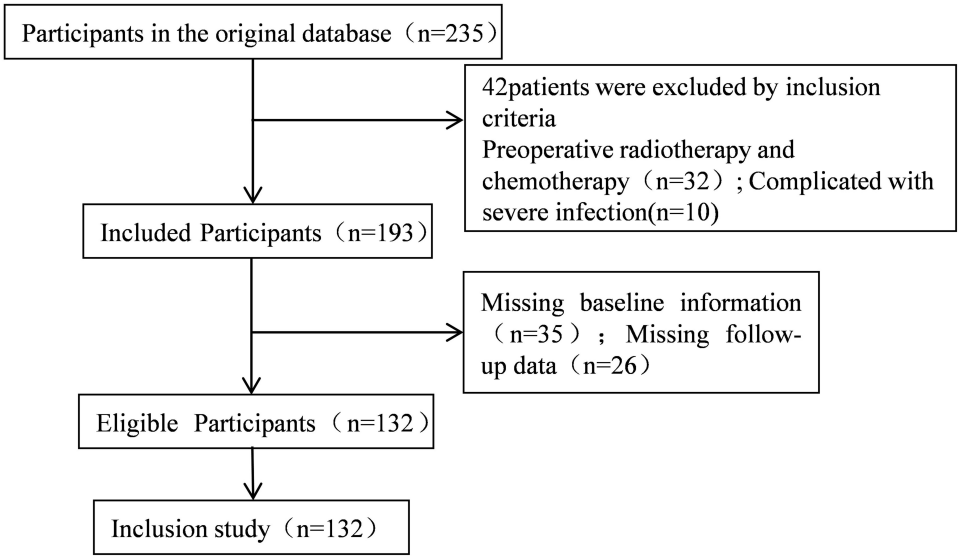

Figure 1 Selection process of general materials.

(≥10%); Negative expression: no staining or the staining intensity and the proportion of positive cells were less than 10%. The staining scores of MUC2 and JADE1 were evaluated using a semi-quantitative scoring system: Staining intensity: 0 points for colorless, 1 point for light yellow, 2 points for brown yellow, and 3 points for tan. Proportion of positive cells: The score was based on the proportion of positive cells in total cells, 0 points for 0% to 5%, 1 point for 6% to 25%, 2 points for 26% to 50%, 3 points for 51% to 75%, and 4 points for 76% to 100%. Final score: The staining intensity score was multiplied with the proportion of positive cells score to obtain the final score. According to the final score, the staining results were divided into four grades: negative (−, 0–2 points), weak positive (+, 3–4 points), positive (++, 5–8 points) and strong positive (+++, 9–12 points).

Collection of Clinical Pathological Data

The clinicopathological data of the patients were collected, including the age (≤ 55 years old, > 55 years old), sex (male, female), tumor size (≤ 4cm, > 5cm), location of onset (gastric antrum, gastric body, cardia), degree of differentiation (low differentiation, medium and high differentiation), HP infection (yes, no) (The surface and crypt of gastric mucosal tissue were stained with Warthin-Starry silver staining.[13] HP infection was considered positive if it was black dot, curved rod or short rod, otherwise it was negative), lymph node metastasis (yes, no), depth of tumor invasion (T1+T2, T3+T4) (Staging was performed according to the International Association for Cancer Control TNM staging scheme)[14] and Lauren typing (diffuse type, mixed type, intestinal type).

Follow-up

Follow-up using telephone interview and outpatient examination was conducted for 36 months, once every 3 months until 12 months and once every 6 months thereafter.

Outcome Measures

(1) Detection of the expression of MUC2 and JADE1: The expressions of MUC2 and JADE1 in tissues were detected by immunohistochemistry.
(2) The relationship between MUC2 and JADE1 expression in gastric cancer tissues and clinicopathological features was analyzed.
(3) The relationship between MUC2 and JADE1 expression and the survival and prognosis of patients: Kaplan-Meier survival curve was used to analyze the relationship between the expression of MUC2 and JADE1 and the survival

and prognosis of patients. In the survival analysis, the selected cancer tissue samples were all from the central region of the tumor and did not include the tissue edge part to avoid the influence of the edge effect on the results.

(4) Diagnostic value: The diagnostic value of MUC2 and JADE1 alone or in combination for gastric cancer was analyzed using receiver operating characteristic (ROC) curve.

Statistical Analysis

According to different observation indicators and data, SPSS 21.0 statistical software was used to analyze the data. Sex, the relationship between the expression of MUC2 and JADE1 with clinicopathological features and other enumeration data were expressed in [cases (%)], and compared using the χ^2 inspection. Age and other measurement data were tested by normal distribution, and all were consistent with the normal distribution. The measurement data were expressed in the form of mean ± standard deviation (SD), and compared using *t*-test between two groups. P<0.05 was regarded as statistically significant.

Results

Expression of MUC2 and JADE1 in Gastric Cancer and Non-Tumor Tissues

The positive expression rates of MUC2 and JADE1 in gastric cancer tissues were 67.42% (89/132) and 72.73% (96/132), respectively. The positive expression rates of MUC2 and JADE1 in adjacent normal tissues were 22.73% (30/132) and 27.27% (36/132), respectively. The expressions of MUC2 and JADE1 in gastric cancer tissues were significantly higher than that in adjacent normal tissues (P<0.05). MUC2 was mainly expressed in the cytoplasm and JADE1 was mainly expressed in the cytoplasm and cell membrane of gastric cancer tissues, in which the staining was brownish yellow (Figure 2).

Relationship Between the Expression of MUC2 and JADE1 and Clinicopathological Features in Gastric Cancer

The expressions of MUC2 and JADE1 in gastric cancer tissues were significantly different in patients with different tumor size, differentiation degree, HP infection, lymph node metastasis, depth of tumor invasion and Lauren classification (P<0.05). The expressions of MUC2 and JADE1 in gastric cancer tissues were closely related to tumor size, differentiation degree, HP infection, lymph node metastasis, depth of tumor infiltration and Lauren typing (P<0.05, Table 1).

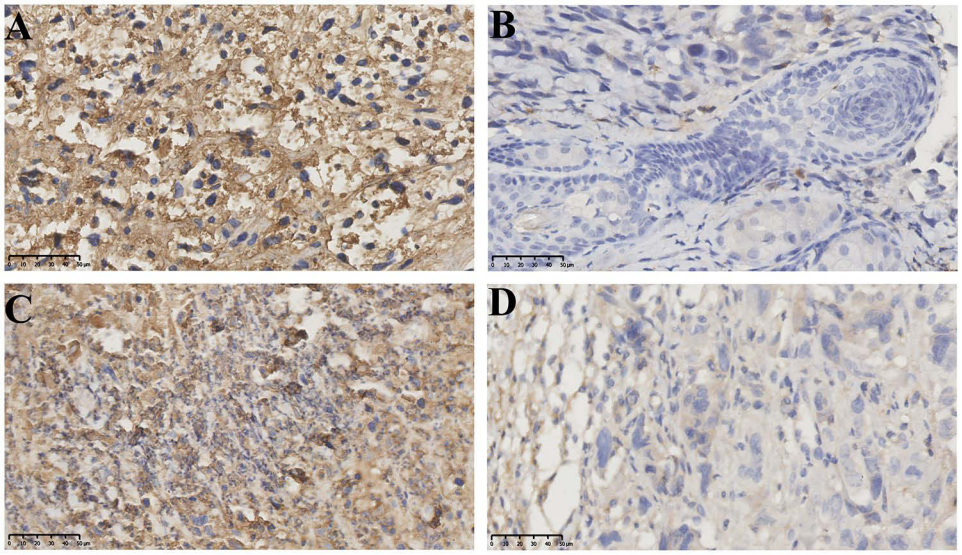

Figure 2 Expression of MUC2 and JADE1 in gastric cancer and adjacent normal tissues. (**A**) Expression of MUC2 in gastric cancer tissues; (**B**) Expression of MUC2 in adjacent normal tissues; (**C**) Expression of JADE1 in gastric cancer tissues; (**D**) Expression of JADE1 in adjacent normal tissues.

Table 1 Relationship Between Expression of MUC2 and JADE1 With Clinic-Pathological Features in Gastric Cancer [n (%)]

Clinic-Pathological Features	Cases	MUC2		χ^2	P	JADE1		χ^2	P
		Negative n=43	Positive n=89			Negative n=36	Positive n=96		
Age (year)				1.994	0.158			0.253	0.615
≤55	56	22 (39.29)	34 (60.71)			14 (25.00)	42 (75.00)		
>55	76	21 (27.63)	55 (72.37)			22 (28.95)	54 (71.05)		
Gender (%)				0.230	0.632			1.030	0.310
Female	53	16 (30.19)	37 (69.81)			17 (32.08)	36 (67.92)		
Male	79	27 (34.18)	52 (65.82)			19 (24.05)	60 (75.95)		
Tumor size (cm)				3.938	0.047			5.704	0.017
≤5	89	34 (38.20)	55 (61.80)			30 (33.71)	59 (66.29)		
>5	43	9 (20.93)	34 (79.07)			6 (13.95)	37 (86.05)		
Location of onset (%)				1.111	0.574			4.544	0.103
Gastric antrum	73	21 (28.77)	52 (71.23)			18 (24.66)	55 (75.34)		
Gastric body	34	13 (38.24)	21 (61.76)			7 (20.59)	27 (79.41)		
Cardia	25	9 (36.00)	16 (64.00)			11 (44.00)	14 (56.00)		
Differentiation (%)				25.482	<0.001			13.586	<0.001
Low-differentiation	78	18 (23.08)	60 (76.92)			12 (15.38)	66 (84.61)		
Medium + high differentiation	54	25 (46.30)	29 (53.70)			24 (44.44)	30 (55.56)		
HP infection (%)				5.096	0.024			10.709	0.001
Yes	80	32 (40.00)	48 (60.00)			30 (37.50)	50 (62.50)		
No	52	11 (21.15)	41 (78.85)			6 (11.54)	46 (88.46)		
Lymph node metastasis (%)				8.726	0.003			18.147	<0.001
Yes	74	32 (43.24)	42 (56.76)			31 (41.89)	43 (58.11)		
No	58	11 (18.67)	47 (81.03)			5 (8.62)	53 (91.38)		
Depth of tumor infiltration (%)				5.441	0.020			7.207	0.007
T1+T2	46	9 (19.57)	37 (80.43)			6 (13.04)	40 (86.96)		
T3+T4	86	34 (39.53)	52 (60.47)			30 (34.88)	56 (65.12)		
Lauren typing (%)				7.805	0.020			10.099	0.006
Diffuse type	49	17 (34.69)	32 (65.31)			14 (28.57)	35 (71.43)		
Mixed type	31	4 (6.56)	27 (44.26)			2 (3.28)	29 (47.54)		
Intestinal type	52	22 (42.31)	30 (57.69)			20 (38.46)	32 (61.54)		

Univariate Analysis of 3-year Survival Rate of Patients with Gastric Cancer

The followed up time was 0.9~36 months, and the median survival time was 23.5 months. The 1-year survival rate was 100.00% (132/132), and the 3-year survival rate was 90.91% (120/132). Univariate analysis showed that tumor size, differentiation degree, lymph node metastasis, depth of tumor infiltration, expression of MUC2 and JADE1 were the influencing factors of 3-year survival rate of patients with gastric cancer (P<0.05, Table 2).

Cox Regression Analysis of Risk Factors Affecting the 3-year Survival Rate of Patients with Gastric Cancer

Multivariate Cox regression analysis showed that tumor size, differentiation degree, lymph node metastasis, depth of tumor infiltration, and MUC2 and JADE1 expression were risk factors for the 3-year survival rate of patients with gastric cancer (Table 3).

Table 2 Univariate Analysis of 3-year Survival Rate in Patients With Gastric Cancer

Factors	Cases	3-year Survival	χ^2	P
Age (year)			1.641	0.200
≤55	56	53 (94.64)		
>55	76	67 (88.16)		
Gender (%)			1.261	0.261
Female	53	50 (94.34)		
Male	79	70 (88.61)		
Tumor size (cm)			15.483	<0.001
≤5	89	87 (97.75)		
>5	43	33 (76.74)		
Location of onset (%)			5.500	0.064
Gastric antrum	73	69 (94.52)		
Gastric body	34	32 (94.12)		
Cardia	25	20 (80.00)		
Differentiation (%)			5.795	0.016
Low-differentiation	78	67 (85.90)		
Medium + high differentiation	54	53 (98.15)		
HP infection (%)			0.203	0.652
Yes	80	72 (90.00)		
No	52	48 (92.31)		
Lymph node metastasis (%)			6.794	0.009
Yes	74	63 (85.14)		
No	58	57 (98.28)		
Depth of tumor infiltration (%)			4.606	0.031
T1+T2	46	45 (97.83)		
T3+T4	86	75 (87.21)		
Lauren typing (%)			0.081	0.960
Diffuse type	49	45 (91.84)		
Mixed type	31	28 (90.32)		
Intestinal type	52	47 (90.38)		
MUC2			6.985	0.008
Negative	43	35 (81.40)		
Positive	89	85 (95.51)		
JADE1			10.328	0.001
Negative	36	28 (77.78)		
Positive	96	92 (95.83)		

Table 3 Cox Regression Analysis of Risk Factors Affecting the 3-year Survival Rate of Patients With Gastric Cancer

Index	*Wald* value	SE	Odds Ratio	P value	OR	95% CI	
						Lower Limit	Upper Limit
Tumor size	1.104	0.521	4.382	0.026	3.041	1.061	8.451
Differentiation	0.942	0.419	5.113	0.013	2.482	1.126	5.920
Lymph node metastasis	1.115	0.683	3.115	0.003	3.421	0.861	12.115
Depth of tumor infiltration	1.660	0.570	8.512	0.005	5.241	1.711	12.026
MUC2	0.887	0.360	6.066	0.013	2.412	1.120	4.857
JADE1	0.589	0.276	8421	0.009	2.625	2.187	5.429

Table 4 Differences Among Various Factors

Factors	HR	P	95% CI	
			Lower Limit	Upper Limit
MUC2 negative vs MUC2 positive	2.503	<0.001	1.213	3.766
JADE1 negative vs JADE1 positive	3.336	<0.001	2.130	7.765

Relationship Between the Expression of MUC2 and JADE1 in Gastric Cancer Tissue and the Survival and Prognosis of Patients

The patients were followed up for 36 months, and the Kaplan-Meier survival curve was established. The analysis showed that the survival rate of patients with negative expression of MUC2 and JADE1 was significantly lower than that of patients with positive expression of MUC2 and JADE1 (P<0.05, Table 4 and Figure 3).

Analysis of the Diagnostic Value of MUC2 and JADE1 in Gastric Cancer Tissue Alone or in Combination in Gastric Cancer

Based on the ROC curve, the area under the curve of MUC2 in gastric cancer tissues alone in detection of gastric cancer was 0.774, with the sensitivity and specificity of 72.46% and 80.03%, respectively. The area under the curve of JADE1 in gastric cancer tissues alone in detection of gastric cancer was 0.796, with the sensitivity and specificity of 82.14% and 76.48%, respectively. The area under the curve of the combined detection of the two was 0.918, with the sensitivity and specificity of 91.34% and 89.57%. The results indicated that the combined detection of MUC2 and JADE1 had a high diagnostic value in the pathogenesis of gastric cancer (Table 5 and Figure 4).

Discussion

Surgery is one of the main treatment methods for gastric cancer. Especially for patients with early gastric cancer, a high cure rate can be achieved by radical resection of the diseased tissue, but there are still some patients with poor long-term survival and prognosis after surgery.[15] The pathogenesis of gastric cancer is relatively complex, and it is believed that it may be the result of the comprehensive effect of genetics, HP infection, environment and other factors.[16] Early diagnosis

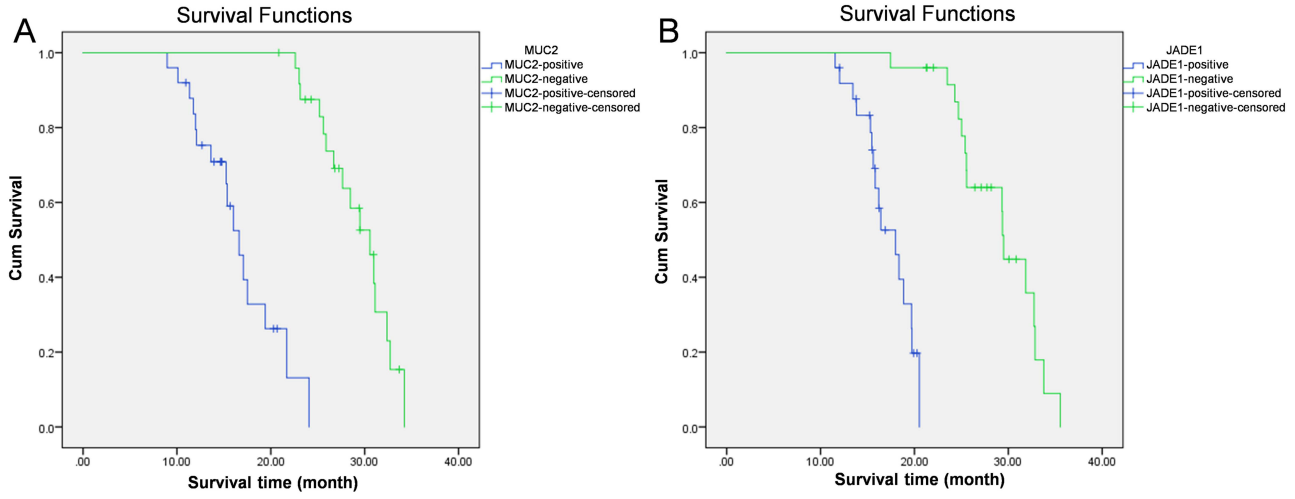

Figure 3 The relationship between the expression of MUC2 and JADE1 in gastric cancer tissue and the survival and prognosis of patients. (**A**) Survival curve of different expression of MUC2; (**B**) Survival curve of different expression of JADE1.

https://doi.org/10.2147/CMAR.S493015

Table 5 Analysis of the Diagnostic Value of MUC2 and JADE1 in Gastric Cancer Tissue Alone or in Combination in the Diagnosis of Gastric Cancer

Indicators	The Area Under the Curve	Sensitivity (%)	Specificity (%)	P	95% CI	
					Lower Limit	Upper Limit
MUC2	0.774	72.46	80.03	<0.05	0.718	0.830
JADE1	0.796	82.14	76.48	<0.05	0.736	0.856
Combination of MUC2 and JADE1	0.918	91.34	89.57	<0.05	0.848	0.988

of gastric cancer plays an important role in improving the survival rate and prognosis of patients. No previous study has reported the relationship between the expression of MUC and JADE1 and HP infection. The aim of this study was to investigate the relationship between the expression of MUC and JADE1 in gastric cancer tissue and HP infection as well as the depth of tumor infiltration, so as to provide relevant theoretical learning basis for clinicians to evaluate the condition of patients in time and provide effective treatment.

MUC is a glycoprotein widely expressed in epithelial cells, which can participate in the renewal and differentiation of epithelial cells and maintain the integrity of epithelial cells. In addition, it also has a certain protective and lubricating effect. MUC2 is a subtype of MUC, and is mainly expressed in goblet cells of the intestine. MUC2 is not expressed in gastric mucosa under normal condition, but its expression is significantly increased upon gastric cancer. MUC2 may participate in the recognition and adhesion between cells.[17] Evaluation of MUC2 expression in gastric cancer patients revealed that MUC2 was more frequently detected in multiple histologically negative lymph nodes.[18] Additionally, relevant data show that MUC2 is not expressed in normal lymph nodes, but specifically expressed in perigastric lymph nodes of patients with pT1 gastric cancer, suggesting that the expression of MUC2 has certain sensitivity and specificity. It is helpful to detect lymph node micrometastasis of gastric cancer, and is conducive to early detection and minimally invasive surgery.[19] The study has also showed that different concentrations of MUC2 antisense oligonucleotides have a significant inhibitory effect on the growth of SGC7901 cells.[20] Thus, the expression of MUC2 protein may play an important role in the biological behavior of gastric cancer. In addition, it has been reported that the expression level of MUC2 is significantly up-regulated in colorectal cancer tissues, and the upregulation of MUC2 is an indicator of high

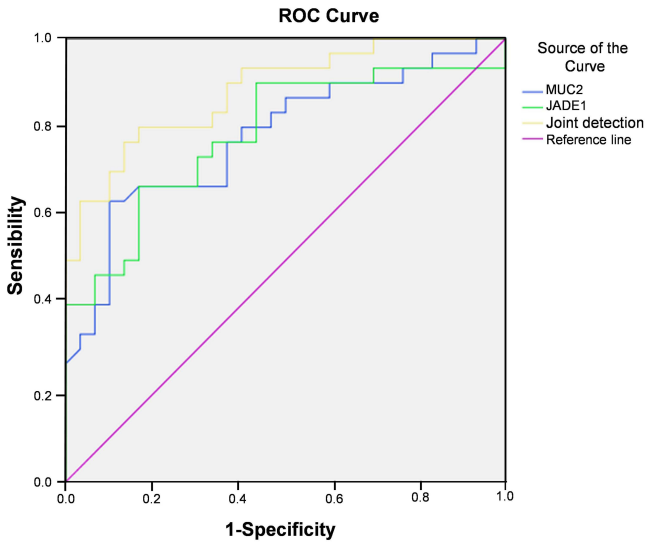

Figure 4 ROC curve analysis.

treatment resistance and poor prognosis in patients with colorectal cancer.[21] In the present study, the results showed that the expression level of MUC2 in gastric cancer was significantly increased, and its expression level was closely related to tumor size, differentiation degree, HP infection, lymph node metastasis, depth of tumor infiltration and Lauren's classification. Moreover, the survival rate of patients with positive expression of MUC2 was significantly lower than that of patients with negative expression. This result was similar to previous studies in other tumor types, which showed that MUC2 expression was closely related to the degree of differentiation, tumor stage, and lymph node metastasis of gastric cancer, and that the 5-year survival rate of MUC2-positive gastric cancer patients after surgery was significantly higher than that of MUC2-negative patients.[22]

JADE1, a member of the JADE protein family, can promote the massive acetylation of histone 4 (H4) by interacting with endogenous histone acetyltransferase (HAT). It has been found that the JADE1S and JADE1L isoforms of JADE1 also seem to play different cellular roles, and that the JADE1 protein is able to directly regulate the process of cell cycle.[23] JADE1 is an important regulator of cytokinesis. It has been reported that JADE1 can also act as an E3 ubiquitin ligase by targeting β-Catenin for proteasomal degradation, thus regulating the proliferation, differentiation and distant metastasis of tumor cells.[24] The study of the role of JADE1 in pancreatic cancer showed that the expression level of JADE1 in pancreatic tissue was significantly increased, in which JADE1 might regulate phosphatidylinositol 3-kinase/protein kinase B/rapamycin target protein (PI3k/AKT/mTOR) signaling pathway, thereby affecting the development of renal cell carcinoma.[8] The results of this study showed that the expression level of JADE1 was highly increased in gastric cancer tissues, and its expression level was closely related to the clinicopathological data and the prognosis of patients. The results were similar to those of Seidl et al[25] in other tumor types, in which multivariate Cox regression analysis showed that positive expression of JADE1 was one of the independent risk factors for poor prognosis of patients with gastric cancer, and the HR value was 2.141, indicating that the prognosis of patients with positive expression of JADE1 was poor. These results suggested that the high expression of JADE1 in gastric cancer might be closely related to the poor prognosis of patients, and it could be used as a potential biomarker to evaluate the prognosis of gastric cancer patients.

HP is a pathogen isolated from gastric mucosa and has been classified as a class I carcinogen. Previous studies have found that HP infection is closely related to the occurrence and development of chronic gastritis, gastric cancer and other diseases.[24,26] HP may cause inflammation of gastric mucosa for a long time, and bind to the specific receptors of normal gastric mucosal epithelial cells through a variety of adhesion factors. In addition, HP can also damage the normal gastric mucosal barrier by secreting urinary hormones, and then cause the gastric mucosa to develop into gastric cancer. The study has determined the depth of tumor invasion and regional lymph node involvement are determined by detecting HP infection and endoscopic ultrasonography, and the results showed that HP might affect the occurrence and development of gastric cancer by regulating the Wnt/β-catenin pathway and inducing the expression of angiogenic factors.[27] The results of this study showed that MUC2 and JAD1 in gastric cancer tissue were closely related to HP infection and tumor infiltration depth, and the combined detection of MUC2 and JAD1 had important value in predicting the incidence of gastric cancer.

In conclusion, the expressions of MUC2 and JADE1 in gastric cancer tissue are significantly increased, and their expressions are closely related to tumor size, differentiation degree, HP infection, lymph node metastasis, depth of tumor infiltration, Lauren's classification and the survival prognosis of patients. Combined detection of MUC2 and Jade1 has high value in the diagnosis of gastric cancer.

Data Sharing Statement

All data, models, and code generated or used during the study appear in the submitted article.

Ethics Approval and Consent to Participate

This research was approved by the Ethics Review Committees of The General Surgery Of Lanxi People's Hospital and conducted according to the Declaration of Helsinki.

Consent for Publication

The patients participating in the study all agree to publish the research results.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no conflicts of interest in this work.

References

1. Virgilio E, Giarnieri E, Carico E, et al. Prognostic role of intragastric cytopathology and microbiota in surgical patients with stomach cancer. *J Cytol*. 2021;38(2):82–87. doi:10.4103/JOC.JOC_238_20
2. Shinohara H, Kurahashi Y, Ishida Y. Gastric equivalent of the 'Holy Plane' to standardize the surgical concept of stomach cancer to mesogastric excision: updating Jamieson and Dobson's historic schema. *Gastric Cancer*. 2021;24(2):273–282. doi:10.1007/s10120-020-01142-9
3. Chang Y, Niu W, Lian PL, et al. Endocan-expressing microvessel density as a prognostic factor for survival in human gastric cancer. *World J Gastroenterol*. 2016;22(23):5422–5429. doi:10.3748/wjg.v22.i23.5422
4. Kim YI, Pecha RL, Keihanian T, et al. MUC1 expressions and its prognostic values in US gastric cancer patients. *Cancers*. 2023;15(4):998. doi:10.3390/cancers15040998
5. Gundamaraju R, Chong WC. Consequence of distinctive expression of MUC2 in colorectal cancers: how much is actually bad? *Biochim Biophys Acta Rev Cancer*. 2021;1876(1):188579. doi:10.1016/j.bbcan.2021.188579
6. Hu LN, Su W, Guo XZ, et al. Prognostic role of MUC-2 expression in patients with gastric carcinoma: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2021;25(10):3700–3708. doi:10.26355/eurrev_202105_25936
7. Shafique S, Rashid S. Structural basis for renal cancer by the dynamics of pVHL-dependent JADE1 stabilization and β-catenin regulation. *Prog Biophys Mol Biol*. 2018;14(1):65–77.
8. Han J, Lachance C, Ricketts MD, et al. The scaffolding protein JADE1 physically links the acetyltransferase subunit HBO1 with its histone H3–H4 substrate. *J Biol Chem*. 2018;293(12):4498–4509. doi:10.1074/jbc.RA117.000677
9. Zhang MJ, Chen DS, Li S, et al. Helicobacter pylori infection as a potential favorable factor for immune checkpoint inhibitor therapy for gastric cancer. *Invest New Drugs*. 2021;39(5):1436–1438. doi:10.1007/s10637-021-01122-5
10. Cox KE, Liu S, Lwin TM, Hoffman RM, Batra SK, Bouvet M. The mucin family of proteins: candidates as potential biomarkers for colon cancer. *Cancers*. 2023;15(5):1491. doi:10.3390/cancers15051491
11. Kalantzakos T, Hooper K, Das S, et al. MicroRNA-155-5p targets JADE-1, promoting proliferation, migration, and invasion in clear cell renal cell carcinoma cells. *Int J Mol Sci*. 2023;24(9):7825. doi:10.3390/ijms24097825
12. Mönig S, Ott K, Gockel I, et al. [S3 guidelines on gastric cancer-diagnosis and treatment of adenocarcinoma of the stomach and esophagogastric junction: version 2.0-August 2019. AWMF register number: 032/009OL]. *Chirurg*. 2020;91(1):37–40. German. doi:10.1007/s00104-020-01112-y
13. Peng J, Fan Z, Zheng H, Lu J, Zhan Y. Combined application of immunohistochemistry and Warthin-Starry silver stain on the pathologic diagnosis of cat scratch disease. *Appl Immunohistochem Mol Morphol*. 2020;28(10):781–785. doi:10.1097/PAI.0000000000000829
14. Son T, Sun J, Choi S, et al. Multi-institutional validation of the 8th AJCC TNM staging system for gastric cancer: analysis of survival data from high-volume Eastern centers and the SEER database. *J Surg Oncol*. 2019;120(4):676–684. doi:10.1002/jso.25639
15. Meng W, Ya-di H, Wei-Bo C, et al. Clinical effect and follow-up of laparoscopic radical proximal gastrectomy for upper gastric carcinoma. *Front Oncol*. 2023;13:1167177. doi:10.3389/fonc.2023.1167177
16. Uno Y. Risk factors and incidence of gastric cancer after eradication of Helicobacter pylori. *Gastroenterology*. 2020;159(1):404–405. doi:10.1053/j.gastro.2020.02.067
17. Znalesniak EB, Salm F, Hoffmann W. Molecular alterations in the stomach of Tff1-deficient mice: early steps in antral carcinogenesis. *Int J Mol Sci*. 2020;21(2):644. doi:10.3390/ijms21020644
18. Lee YM, Park JP, Jung YH, et al. Melatonin restores Muc2 depletion induced by V. vulnificus VvpM via melatonin receptor 2 coupling with Gαq. *J Biomed Sci*. 2020;27(1):21. doi:10.1186/s12929-019-0606-x
19. Sonoda H, Yamamoto K, Kushima R, Okabe H, Tani T. Detection of lymph node micrometastasis in gastric cancer by MUC2 RT-PCR: usefulness in pT1 cases. *J Surg Oncol*. 2004;88(2):63–70. doi:10.1002/jso.20143
20. Kerckhoffs K, Liu D, Saragoni L, et al. Mucin expression in gastric- and gastro-oesophageal signet-ring cell cancer: results from a comprehensive literature review and a large cohort study of Caucasian and Asian gastric cancer. *Gastric Cancer*. 2020;23(5):765–779. doi:10.1007/s10120-020-01086-0
21. Chou CL, Chen TJ, Tian YF, et al. Upregulated MUC2 is an unfavorable prognostic indicator for rectal cancer patients undergoing preoperative CCRT. *J Clin Med*. 2021;10(14):3030. doi:10.3390/jcm10143030
22. Companioni O, Bonet C, García N, et al. Genetic variation analysis in a follow-up study of gastric cancer precursor lesions confirms the association of MUC2 variants with the evolution of the lesions and identifies a significant association with NFKB1 and CD14. *Int J Cancer*. 2018;143(11):2777–2786. doi:10.1002/ijc.31839
23. Jian Y, Wang M, Zhang Y, et al. Jade family PHD finger 3 (JADE3) increases cancer stem cell-like properties and tumorigenicity in colon cancer. *Cancer Lett*. 2018;428:1–11. doi:10.1016/j.canlet.2018.04.012
24. Zhou J, Wang H, Che J, et al. Silencing of microRNA-135b inhibits invasion, migration, and stemness of CD24+CD44+ pancreatic cancer stem cells through JADE-1-dependent AKT/mTOR pathway. *Can Cell Inter*. 2020;20(1):134. doi:10.1186/s12935-020-01210-1
25. Seidl C, Port M, Apostolidis C, et al. Differential gene expression triggered by highly cytotoxic alpha-emitter-immunoconjugates in gastric cancer cells. *Invest New Drugs*. 2010;28(1):49–60. doi:10.1007/s10637-008-9214-4
26. Sayed IM, Sahan AZ, Venkova T, et al. Helicobacter pylori infection downregulates the DNA glycosylase NEIL2, resulting in increased genome damage and inflammation in gastric epithelial cells. *J Biol Chem*. 2020;295(32):11082–11098. doi:10.1074/jbc.RA119.009981
27. Piao JY, Kim SJ, Kim DH, et al. Helicobacter pylori infection induces STAT3 phosphorylation on Ser727 and autophagy in human gastric epithelial cells and mouse stomach. *Sci Rep*. 2020;10(1):15711. doi:10.1038/s41598-020-72594-3