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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Retrospective Study

Characterization of E-cadherin expression in normal mucosa, dysplasia and adenocarcinoma of gastric cardia and its influence on prognosis

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statement: This study was reviewed and approved by the Ethics Committee of Zhengzhou

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Abstract**BACKGROUND**

Gastric cardia adenocarcinoma (GCA), which has been classified as type II adenocarcinoma of the esophagogastric junction in western countries, is of similar

University.

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Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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geographic distribution with esophageal squamous cell carcinoma in China, and even referred as "sister cancer" by Chinese oncologists. The molecular mechanism for GCA is largely unknown. Recent studies have shown that decreased expression of E-cadherin is associated with the invasion and metastasis of multiple cancers. However, the E-cadherin expression has not been well characterized in gastric cardia carcinogenesis and its effect on GCA prognosis.

AIM

To characterize E-cadherin expression in normal gastric cardia mucosa, dysplasia and GCA tissues, and its influence on prognosis for GCA.

METHODS

A total of 4561 patients with GCA were enrolled from our previously established GCA and esophageal cancer databases. The enrollment criteria included radical surgery for GCA, but without any radio- or chemo-therapy before operation. The GCA tissue from 4561 patients and matched adjacent normal epithelial tissue ($n = 208$) and dysplasia lesions ($n = 156$) were collected, and processed as tissue microarray for immunohistochemistry. The clinicopathological characteristics were retrieved from the medical records in hospital and follow-up was carried out through letter, telephone or home interview. E-cadherin protein expression was determined by two step immunohistochemistry. Kaplan–Meier and Cox regression analyses were used to correlate E-cadherin protein expression with survival of GCA patients.

RESULTS

Of the 4561 GCA patients, there were 3607 males with a mean age of 61.6 ± 8.8 and 954 females with a mean age of 61.9 ± 8.6 years, respectively. With the lesions progressed from normal gastric cardia mucosa to dysplasia and GCA, the positive immunostaining rates for E-cadherin decreased significantly from 100% to 93.0% and 84.1%, respectively ($R^2 = 0.9948$). Furthermore, E-cadherin positive immunostaining rate was significantly higher in patients at early stage (0 and I) than in those at late stage (II and III) (92.7% vs 83.7% , $P = 0.001$). E-cadherin positive expression rate was significantly associated with degree of differentiation ($P = 0.001$) and invasion depth ($P < 0.001$). Multivariate analysis showed that the GCA patients with positive E-cadherin immunostaining had better survival than those with negative ($P = 0.026$). It was noteworthy that E-cadherin positive expression rate was similar in patients with positive and negative lymph node metastasis. However, in patients with negative lymph node metastasis, those with positive expression of E-cadherin had better survival than those with negative expression ($P = 0.036$). Similarly, in patients with late stage GCA, those with positive expression of E-cadherin had better survival than those with negative expression ($P = 0.011$).

CONCLUSION

E-cadherin expression may be involved in gastric cardia carcinogenesis and low expression of E-cadherin may be a promising early biomarker and overall survival predictor for GCA.

Key Words: E-cadherin expression; Immunohistochemistry; Gastric cardia adenocarcinoma; Dysplasia; Clinicopathological feature; Prognosis

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Core Tip: In previous reports, there is no consistent conclusion on the association between E-cadherin expression and gastric cardia carcinogenesis and its effect on prognosis with gastric cardia adenocarcinoma (GCA) patients. It was notable that the positive immunostaining rates of E-cadherin decreased significantly from normal mucosa to dysplasia and GCA, as well as higher in early stage than those in advanced stage of GCA. Moreover, we found high expression of E-cadherin represented a better survival, especially for patients with negative lymph node metastasis. In conclusion, E-

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cadherin may be involved in carcinogenesis and may be a predictor on prognosis for GCA.

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INTRODUCTION

Gastric cardia adenocarcinoma (GCA), which has been classified as type II adenocarcinoma of the esophagogastric junction in western countries[1], is of similar geographic distribution with esophageal squamous cell carcinoma in China[2], and even referred as "sister cancer" by Chinese oncologists. In contrast to esophageal squamous cell carcinoma, the incidence for GCA is increasing worldwide[3,4]. Most GCA patients lack early warning symptoms, and > 90% of patients are diagnosed at an advanced stage, resulting in poor prognosis, with < 20% 5-year survival[5,6]. Obviously, early detection for GCA is crucial in decreasing the high mortality. Identification of unique molecular biomarkers at the early stage of GCA is crucial for screening high-risk individuals and early detection of GCA. Unfortunately, the molecular mechanism of human gastric cardia carcinogenesis is largely unknown.

Accumulated evidence indicates that E-cadherin protein, a member of the cadherin family encoded by the *CDH1* gene, may play an important role in intercellular adhesion, maintaining the stability of epithelial structure and function, cell polarity, and regulating intracellular signaling pathways[7]. Reduced expression of E-cadherin has been reported as a molecular biomarker of a cellular process called epithelial-mesenchymal transition, which is often associated with cancer progression[8]. The latest studies have indicated that decreased expression of E-cadherin is involved in many different types of cancer[9-11]. However, E-cadherin expression in GCA has not been well characterized.

In the present study, we detected the expression of E-cadherin in GCA, precancerous lesions and normal mucosa. We also evaluated the relationship of E-cadherin expression and survival of GCA.

MATERIALS AND METHODS

Patients

All the patients were enrolled from the 500000 esophageal and gastric cardia carcinoma databases (1973–2020) established by the State Key Laboratory for Esophageal Cancer Prevention & Treatment and Henan Key Laboratory for Esophageal Cancer Research of the First Affiliated Hospital of Zhengzhou University (Zhengzhou, China). GCA patients were enrolled in the present study according to the following criteria: (1) Patients were diagnosed with GCA by postoperative histopathology; (2) Patients had tumors located in the esophagogastric junction; (3) Patients had no other malignant tumors except for GCA; (4) Patients received no chemotherapy or/and radiotherapy before surgery; and (5) The tissue samples of the patients were available. The exclusion criteria were: (1) Pathological type was not adenocarcinoma; (2) Clinicopathological information was incomplete; and (3) patients had received preoperative radiation or chemotherapy. A total of 4561 patients with GCA were enrolled in the study (Table 1). In addition, 208 matched adjacent normal epithelial tissue and 156 dysplasia lesions were selected.

The staged of patients with GCA were based on the 8th edition of the American Joint Committee. Positive smoking history was defined as having smoked continuously or accumulatively for 6 mo or more in one's lifetime and negative drinking history was defined less than 20 g of alcohol *per* day. Family history positive was defined as more than two patients with GCA in two consecutive generations.

Table 1 Clinical characteristics of patients with gastric cardia adenocarcinoma

Variables	Cases, n (%)	
Gender		
Female	954	20.9
Male	3607	79.1
Age at diagnosis (yr)		
< 60	1717	37.6
≥ 60	2844	62.4
Family history		
Negative	3366	73.8
Positive	1195	26.2
Cigarette smoking		
No	2166	47.5
Yes	2395	52.5
Alcohol consumption		
No	3206	70.3
Yes	1355	29.7
Differentiation		
Well	133	2.9
Moderate	2039	44.7
Poor	2389	52.4
T status		
T1	71	1.6
T2	308	6.8
T3	3044	66.7
T4	1138	25.0
Lymph node metastasis		
Negative	1637	35.9
Positive	2924	64.1
Staging		
Early stage	191	4.2
Advanced stage	4370	95.8

Histopathological diagnosis

Histopathological diagnoses for normal mucosa, dysplasia and adenocarcinoma of the gastric cardia were made according to established criteria[12]. The normal gastric cardia mucosa, composing of a single columnar epithelium and mucous glands composed only of mucous cells; dysplasia, neoplastic feature including nuclear atypia and/or architectural abnormalities confined to the gastric cardia epithelium, without invasion; GCA, invasion of neoplastic gastric cardia cells through the basement membrane.

Immunohistochemical staining and evaluation

E-cadherin protein expression was detected by immunohistochemical staining on normal mucosa, dysplasia and GCA with tissue microarray. The focal area of the cancer tissue was marked on the paraffin-embedded specimens, and a 7 × 16 microarray was designed. Punch holes with a diameter of 1.5 mm were made in the samples. The tissue chip model was then made and fixed. Immunohistochemistry was

carried out by a two-step protocol using the Roche Benchmark XT. In brief, the paraffin-embedded tissue sections were deparaffinized with xylene and anhydrous ethanol for rehydration and heated in citrate buffer (G1202, pH 6.0) for 25 min at 95 °C for antigen repair. The sections were then cooled for 60 min at room temperature, and immersed in 3% hydrogen peroxide solution (G0115) to neutralize endogenous peroxidase. A mouse monoclonal anti-E-cadherin antibody was used (cat. no. GB13083-1; dilution 1:500; Wuhan Servicebio Technology Co., Ltd, Wuhan, China). The anti-E-cadherin antibody was added and incubated overnight at 4 °C. The secondary antibody was then added (cat. no. G1210-2). Between each incubation step, the slides were washed with phosphate buffered saline (PBS, pH 7.4, G0002) three times. Immunostaining was performed using the Roche Benchmark XT with diaminobenzidine (DAB, G1212-200) according to the manufacturer's instructions and the sections were subsequently counterstained with hematoxylin (G1004). The known positive sections were used as the positive control, and PBS was used as the negative control instead of the primary antibody. Observation was performed using a microscope at a magnification of 400 ×. The positive cells for E-cadherin protein expression showed yellow or brown staining in the cell membrane.

According to the staining intensity, the results were categorized as: 0 points, no staining; 1 point, light yellow; 2 points, brown yellow; and 3 points, tan. According to the ratio of the positive cell number, they were scored as 0 (< 10%), 1 (11%-25%), 2 (26%-50%) or 3 (> 50%). The two scores were multiplied, and the results were classified as negative (< 3) or positive (≥ 3). Immunohistochemical results were independently assessed by two pathologists. If the results were inconsistent, they were evaluated by the two pathologists together until a consensus was reached.

Follow-up

All the patients were followed up by letter, telephone or home interview every 3–6 mo after initial diagnosis and treatment. Before the 1990s, patients were usually followed up through letters. The data were saved in medical records. The patients who survived for > 5 years were followed up once a year until the end event (death) occurred. The last follow-up was on June 30, 2020. The median follow-up time was 5.4 [interquartile range (IQR) 3.4–7.6] years.

Statistical analysis

SPSS statistical software (version 25.0, IBM, Chicago, IL) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, California United States) were used to analyze the data. Variables with abnormal distribution were represented by a median (IQR). The χ^2 test and Fisher tests were used for the differences in clinicopathological characteristics and the protein expression of E-cadherin between the groups. The correlation of E-cadherin expression in normal mucosa, dysplasia and adenocarcinoma of the gastric cardia was evaluated by linear regression analysis (R^2 -value). The effect of a single factor on survival was analyzed by Kaplan-Meier method and log-rank test. Independent risk factors affecting survival were analyzed by Cox regression model. All the test levels were $\alpha = 0.05$. The statistical review of the study was performed by the biomedical statistician from Zhengzhou University.

RESULTS

Clinical characteristics of patients

From the clinical records, we retrieved the baseline clinical parameters for this group of GCA patients (Table 1). It shows the distribution of all GCA patients by gender, age, family history, cigarette smoking, alcohol consumption and histopathology. Among the 4561 patients with GCA, there were 954 women and 3607 men with a mean age of 61.6 ± 8.8 and 61.9 ± 8.6 , respectively. The number of male patients was 3.8 times that of female patients. Family aggregation for GCA patients was evident with a positive family history in 26.2% of the patients. In addition, 2395 (52.5%) patients had a history of cigarette smoking and 1355 (29.7%) patients had a history of alcohol consumption. Among male patients, 65.7% (2370/3607) had a history of smoking and 36.8% (1327/3607) had alcohol consumption. The depth of invasion and lymph node metastasis were also classified. There were 2924 (64.1%) patients with positive lymph node metastasis in postoperative pathology. There were 191 (4.2%) patients at early stage (0 and I) and 4370 (95.8%) patients at advanced stage (II and III).

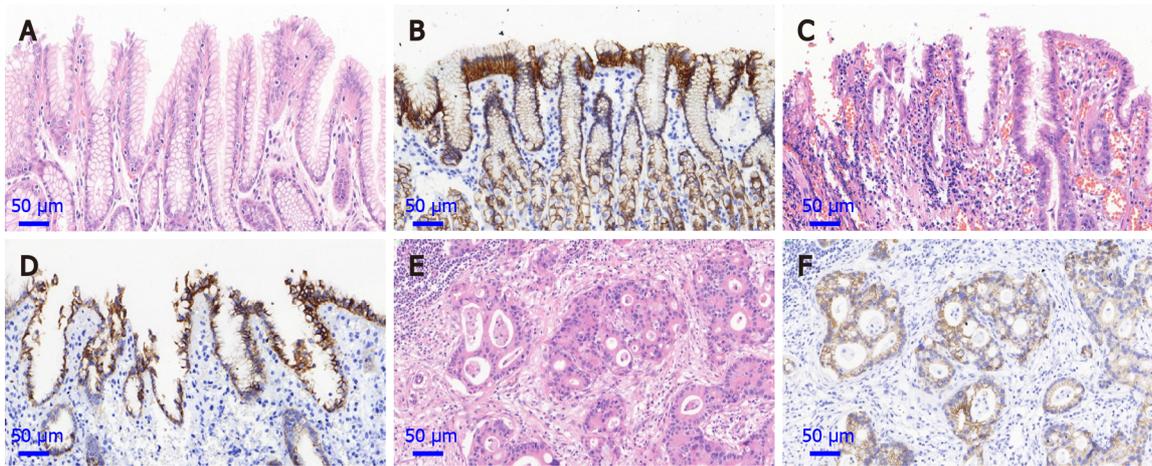


Figure 1 Hematoxylin and eosin staining sections and expression of E-cadherin of normal gastric cardia mucosa, dysplasia and gastric cardia adenocarcinoma (magnification, 400 ×). A: Hematoxylin and eosin staining (HE) section of normal gastric cardia mucosa; B: Positive protein expression of E-cadherin in normal gastric cardia mucosa; C: HE section of dysplasia (DYS); D: Positive protein expression of E-cadherin in DYS tissue; E: HE section of gastric cardia adenocarcinoma (GCA) tissue; F: Positive protein expression of E-cadherin in GCA.

Expression of E-cadherin protein in normal mucosa, dysplasia and GCA

The positive immunostaining reaction of E-cadherin protein expression was mainly located in the cell membrane (Figure 1). With the lesions progressed from normal gastric cardia mucosa to dysplasia and GCA, the positive immunostaining rates for E-cadherin decreased significantly from 100.0% (208/208), to 93.0% (145/156) and 84.1% (3836/4561), respectively ($\chi^2 = 47.439$, $P < 0.001$; Table 2). In the linear analysis of E-cadherin protein expression in normal mucosa, dysplasia and GCA, the decreasing tendency was observed ($y = -0.08x + 1.0833$, $R^2 = 0.9948$, Figure 2).

Association of E-cadherin expression with clinicopathological features in patients with GCA

By comparing the relationship between E-cadherin expression and clinicopathological characteristics, the expression rate of E-cadherin in male patients was lower than that in female patients (83.5 *vs* 86.4%, $\chi^2 = 4.645$, $P = 0.031$, Table 3). It was found that the positive rate of E-cadherin expression gradually decreased with the degree of differentiation (92.5% *vs* 85.4% *vs* 82.5%, $\chi^2 = 14.259$, $P = 0.001$, Table 3). E-cadherin expression differed according to degree of tumor invasion ($\chi^2 = 22.490$, $P < 0.001$, Table 3). The E-cadherin positive immunostaining rate was significantly higher in the patients at early stage (0 and I) than advanced stage (II and III) (92.7% *vs* 83.7%, $\chi^2 = 10.941$, $P = 0.001$, Table 3). There was no significant difference in the expression of E-cadherin protein according to age at diagnosis, family history, cigarette smoking, alcohol consumption and lymph node metastasis ($P > 0.05$, Table 3).

E-cadherin expression is an independent risk factor for GCA prognosis

To evaluate the potential association of clinical factors with overall survival, we performed univariate Cox regression analysis. In univariate analysis, age at diagnosis ($P < 0.001$), degree of differentiation ($P < 0.001$), invasion depth ($P < 0.001$), lymph node metastasis ($P < 0.001$) and E-cadherin expression ($P = 0.003$) were survival factors (Table 4). There was no significant difference in overall survival among patients with different gender, family history, cigarette smoking and alcohol consumption (Table 4). Kaplan-Meier analysis showed that positive E-cadherin expression predicted better overall survival ($P = 0.003$; Figure 3A). Similarly, it showed that age < 60 years at diagnosis, well differentiation, T1 and negative lymph node metastasis predicted better overall survival ($P < 0.001$; Supplementary Figure 1). In multivariate analysis, E-cadherin expression was an independent factor of GCA survival ($P = 0.026$; Table 4).

Stratification analysis of the effect of E-cadherin expression on patient survival

According to the clinicopathological features, the patients were divided into different groups. In the group with negative lymph node metastasis, survival was better in patients with positive E-cadherin expression than negative expression ($P = 0.036$; Figure 3B). A similar result was found in the group with positive lymph node

Table 2 The difference of E-cadherin protein expression in normal tissue, dysplasia and gastric cardia adenocarcinoma

Lesion type	Total	E-cadherin protein expression		χ^2	P value
	n	Positive, n (%)	Negative, n (%)		
Normal	208	208 (100.0)	0 (0)	47.439	< 0.001
DYS	156	145 (93.0)	11 (7.0)		
GCA	4561	3836 (84.1)	725 (15.9)		

DYS: Dysplasia; GCA: Gastric cardia adenocarcinoma.

metastases ($P = 0.048$; **Figure 3C**). With regard to the patients at advanced stage (II and III), patients with positive E-cadherin expression survived better than those with negative expression ($P = 0.011$; **Figure 3D**).

DISCUSSION

As we know, the present study is the first report about the E-cadherin protein expression in the lesions progressed from normal gastric cardia mucosa to dysplasia and GCA, and the largest sample study of the expression of E-cadherin protein and its influence on survival with GCA[13,14].

It is well known that loss of E-cadherin expression resulting from CDH1 gene alterations is the primary carcinogenetic event in hereditary diffuse gastric cancer[15]. However, there was few report concerning the expression of E-cadherin in the gastric cardia carcinogenesis, progressed from normal gastric cardia to dysplasia and GCA. It is showed that, in our study, the significantly decreased immunostaining rate of E-cadherin protein presented from normal gastric cardia to dysplasia and GCA, which indicated that E-cadherin protein may be involved in the gastric cardia carcinogenesis and low expression of E-cadherin protein may accelerate the process. The result in our study was consistent with those reported on gastric cancer[16].

It was found that the positive rate of E-cadherin expression gradually decreased with the decline of the degree of differentiation (92.5% vs 85.4% vs 82.5%, $\chi^2 = 14.259$, $P = 0.001$). The worse the differentiation, the lower the positive expression rate of E-cadherin. This is consistent with previous studies[17,18]. We think that E-cadherin may be a differentiation marker.

The present study demonstrated that patients with positive expression of E-cadherin protein had better survival than those with negative expression. Cox regression analysis indicated that positive expression of E-cadherin protein was an independent factor for better prognosis of patients with GCA, considered together with age at diagnosis, degree of differentiation, invasion depth and lymph node metastasis. The mechanism for the E-cadherin expression and cancer prognosis is largely unknown. E-cadherin gene, also known as CDH1, has been recognized as a tumor suppressor gene. Decreased expression of E-cadherin is reported to be related to prognosis in breast, colorectal and hepatocellular cancers[19,20]. However, less research has been conducted on GCA and controversial results have been observed in gastric cancer[21,22]. A meta-analysis of E-cadherin expression in 4383 patients with gastric cancer showed that the down-regulation of E-cadherin expression was significantly correlated with TNM stage, tumor invasion depth, lymph node metastasis, tumor differentiation, vascular invasion, tissue type and distant metastasis [23]. This study showed that negative E-cadherin was associated with poor differentiation and deep invasion of tumors, which suggested that tumor differentiation was related to cell adhesion, while tumors lacking adhesion were prone to regional lymph node or distant metastasis and had a relatively poor prognosis. The results of our study did not indicate that E-cadherin was associated with lymph node metastasis of GCA, which still needs to be confirmed by further studies.

Disruption of the cell adhesion molecule E-cadherin causes dysregulation of cell-cell adhesion properties. E-cadherin expression may be associated with epithelial-mesenchymal transition through activating the Akt and mitogen-activated protein kinase signaling pathways[24], and negative expression of E-cadherin could lead to a decline of proliferation and metastasis. Medicines for CDH1 mutations are being developed and it has been suggested that non-steroidal anti-inflammatory drugs

Table 3 Association of E-cadherin expression with clinicopathological features in patients with gastric cardia adenocarcinoma

Variables	Total	E-cadherin protein expression		χ^2	P value
	n	Positive, n (%)	Negative, n (%)		
Gender				4.645	0.031
Female	954	824 (86.4)	130 (13.6)		
Male	3607	3012 (83.5)	595 (16.5)		
Age at diagnosis (yr)				0.709	> 0.05
< 60	1717	1434 (83.5)	283 (16.5)		
≥ 60	2844	2402 (84.5)	442 (15.5)		
Family history				1.018	> 0.05
Negative	3366	2820 (83.8)	546 (16.2)		
Positive	1195	1016 (85.0)	179 (15.0)		
Cigarette smoking				1.408	> 0.05
No	2166	1841 (85.0)	325 (15.0)		
Yes	2395	2005 (83.7)	390 (16.3)		
Alcohol consumption				0.011	> 0.05
No	3206	2706 (84.4)	500 (15.6)		
Yes	1355	1142 (84.3)	213 (15.7)		
Differentiation				14.259	0.001
Well	133	123 (92.5)	10 (7.5)		
Moderate	2039	1742 (85.4)	297 (14.6)		
Poor	2389	1971 (82.5)	418 (17.5)		
T status				22.490	< 0.001
pT1	71	63 (88.7)	8 (11.3)		
pT2	308	278 (90.3)	30 (9.7)		
pT3	3044	2580 (84.8)	464 (15.2)		
pT4	1138	915 (80.4)	223 (19.6)		
Lymph node metastasis				0.481	> 0.05
Negative	1637	1385 (84.6)	252 (15.4)		
Positive	2924	2451 (83.8)	473 (16.2)		
Staging				10.941	0.001
Early stage	191	177 (92.7)	14 (7.3)		
Advanced stage	4370	3659 (83.7)	711 (16.3)		

can inhibit CDH1 methylation in human gastric mucosa[25].

Another interesting finding in the present study was that positive expression of E-cadherin protein in GCA patients at dysplasia lesion was higher than in GCA stage (93% *vs* 84.1%, $P = 0.003$), which indicates that E-cadherin protein may be an early potential biomarker for gastric cardia carcinogenesis. Accumulated evidence demonstrates that the germline mutations of E-cadherin gene are highly correlated with hereditary diffuse gastric cancer and lobular breast cancer, and are considered to be promising biomarkers, combined with endoscopy, for early detection of hereditary diffuse gastric cancer and breast cancer[26-29].

Lastly, we found that in the GCA patients with negative lymph node metastasis, positive expression of E-cadherin protein indicated better survival than negative expression. The difference in E-cadherin expression can further stratify the prognosis of patients with negative lymph node metastasis, indicating that E-cadherin protein expression may be a promising prognostic biomarker for non-surgical GCA patients. It

Table 4 Univariate and multivariate analyses of survival of patients with gastric cardia adenocarcinoma

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Gender			> 0.05			
Female	1					
Male	1.063	0.979-1.153				
Age at diagnosis (yr)			< 0.001			< 0.001
< 60	1			1		
≥ 60	1.335	1.246-1.431		1.352	1.262-1.449	
Family history			> 0.05			
Negative	1					
Positive	1.060	0.983-1.143				
Cigarette smoking			> 0.05			
No	1					
Yes	1.004	0.929-1.084				
Alcohol consumption			> 0.05			
No	1					
Yes	0.947	0.869-1.031				
Differentiation			< 0.001			< 0.001
Well	1			1		
Moderate	1.316	1.067-1.623		1.234	1.000-1.522	
Poor	1.791	1.454-2.206		1.480	1.199-1.827	
T status			< 0.001			< 0.001
pT1	1			1		
pT2	1.916	1.289-2.849		1.604	1.078-2.387	
pT3	2.829	1.949-4.107		2.074	1.426-3.018	
pT4	3.390	2.328-4.936		2.272	1.555-3.320	
Lymph node metastasis			< 0.001			< 0.001
Negative	1			1		
Positive	1.952	1.815-2.099		1.805	1.676-1.944	
E-cadherin			0.003			0.026
Positive	1			1		
Negative	1.144	1.048-1.248		1.104	1.012-1.206	

CI: Confidence interval; GCA: Gastric cardia adenocarcinoma; HR: Hazard ratio.

is well known that lymph node metastasis is a useful indicator for poor survival in almost all cancer patients, including GCA. However, clinically, GCA patients with negative lymph node metastasis also showed different survival. E-cadherin protein expression may shed a light on these phenomena.

This study has some limitations. Firstly, there might be some missing data about clinical information. Secondly, the patients' time span was long and the fact that they came from different hospitals also might have caused some bias. Further studies are needed to confirm the new findings.

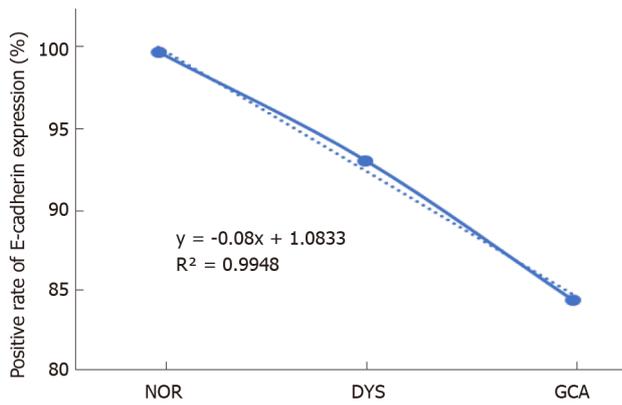


Figure 2 The linear analysis of E-cadherin protein expression in normal gastric cardia mucosa, dysplasia and gastric cardia adenocarcinoma. With the lesions progressed from normal gastric cardia mucosa to dysplasia and gastric cardia adenocarcinoma, the positive immunostaining rates for E-cadherin decreased significantly from 100% to 93.0% and 84.1%, respectively ($y = -0.08x + 1.0833$, $R^2 = 0.9948$).

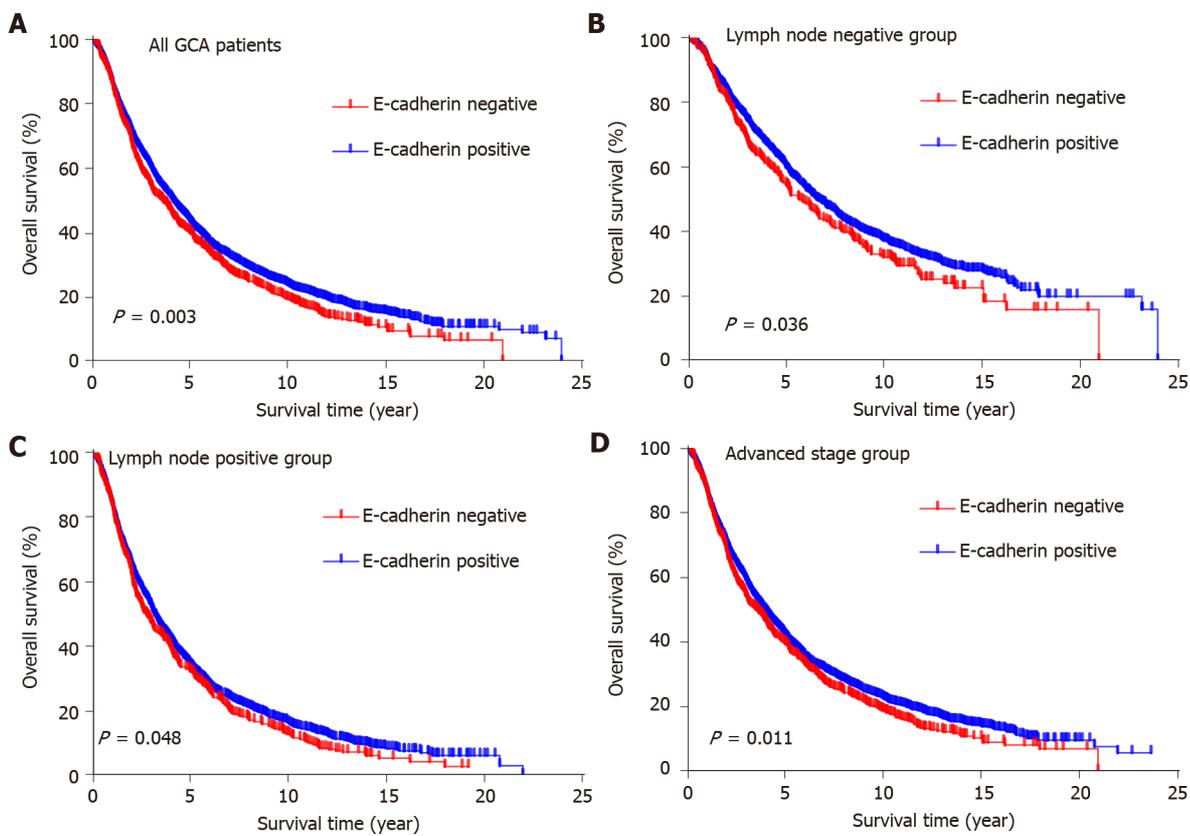


Figure 3 Kaplan–Meier analysis of the effect of E-cadherin expression on survival of gastric cardia adenocarcinoma patients. A: Kaplan–Meier curves of overall survival according to the E-cadherin expression in gastric cardia adenocarcinoma (GCA) patients ($n = 4651$; $P = 0.003$); B: Kaplan–Meier curves of overall survival in GCA patients with negative lymph node metastasis ($n = 1637$; $P = 0.036$); C: Kaplan–Meier curves of overall survival in GCA patients with positive lymph node metastasis ($n = 2924$; $P = 0.048$); D: Kaplan–Meier curves of overall survival in GCA patients with advanced stage ($n = 4370$; $P = 0.011$). GCA: Gastric cardia adenocarcinoma.

CONCLUSION

E-cadherin plays an important role in carcinogenesis of GCA. E-cadherin may be a promising biomarker for early warning and overall survival predictor for GCA patients. E-cadherin protein expression may also shed light on the clinical phenomena for the GCA patients with negative lymph node metastasis with different survival.

ARTICLE HIGHLIGHTS

Research background

Gastric cardia adenocarcinoma (GCA), which has been classified as type II adenocarcinoma of the esophagogastric junction in western countries, is of similar geographic distribution with esophageal squamous cell carcinoma in China, and even referred as "sister cancer" by Chinese oncologists. The molecular mechanism for GCA is largely unknown. Recent studies have shown that decreased expression of E-cadherin is associated with the invasion and metastasis of multiple cancers. However, the E-cadherin expression has not been well characterized in gastric cardia carcinogenesis and its effect on GCA prognosis.

Research motivation

In previous reports, there is no consistent conclusion on the association between E-cadherin expression and gastric cardia carcinogenesis and its effect on prognosis with GCA.

Research objectives

This study aimed to characterize E-cadherin expression in normal gastric cardia epithelium, dysplasia lesions and GCA tissues, and its influence on prognosis for GCA.

Research methods

Immunohistochemistry staining of E-cadherin was performed on GCA and matched adjacent normal epithelial tissue and dysplasia. The correlation on E-cadherin protein expression and prognosis of patients with GCA were analyzed using Kaplan–Meier and Cox regression test.

Research results

With the lesions progressed from normal gastric cardia mucosa to dysplasia and GCA, the positive immunostaining rates for E-cadherin decreased significantly from 100% to 93.0% and 84.1%, respectively ($R^2 = 0.9948$). E-cadherin had better survival than those with negative expression ($P = 0.026$). In the group with negative lymph node metastasis, survival was better in patients with positive E-cadherin expression than negative expression ($P = 0.036$). Similarly, in patients with late stage GCA, those with positive expression of E-cadherin had better survival than those with negative expression ($P = 0.011$).

Research conclusions

E-cadherin expression may be involved in gastric cardia carcinogenesis and low expression of E-cadherin may be a promising early biomarker and overall survival predictor for GCA.

Research perspectives

E-cadherin protein expression is expected to be a molecular marker for early detection and prognosis prediction for GCA.

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