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Observational Study

Construction and analysis of an ulcer risk prediction model after endoscopic submucosal dissection for early gastric cancer

Abstract

BACKGROUND

Endoscopic submucosal dissection (ESD) has been widely used in the treatment of early gastric cancer (EGC). A personalized and effective prediction method for ESD with EGC is urgently needed.

AIM

To construct a risk prediction model for ulcers after ESD for EGC based on LASSO regression.

METHODS

A total of 196 patients with EGC who received ESD treatment were prospectively selected as the research subjects and followed up for one month. They were divided into an ulcer group and a non-ulcer group according to whether ulcers occurred. The general data, pathology, and endoscopic characteristics of the groups were compared, and the best risk predictor subsets were screened by LASSO regression and tenfold cross-validation. Multivariate logistic regression was applied to analyze the risk factors for ulcers after ESD in patients with EGC. A receiver operating characteristic (ROC) curve was used to estimate the predictive model performance.

RESULTS

One month after the operation, no patient was lost to follow-up. The incidence of ulcers was 20.41% (40/196) (ulcer group), and the incidence of no ulcers was 79.59% (156/196) (non-ulcer group). There were statistically significant differences in the course of disease, *Helicobacter pylori* infection history, smoking history, tumor number, clopidogrel medication history, lesion diameter, infiltration depth, convergent folds, and mucosal discoloration between the groups. Gray's medication history, lesion diameter, convergent folds, and mucosal discoloration, which were the 4 nonzero regression coefficients, were screened by LASSO regression analysis. Further multivariate logistic analysis showed that lesion diameter [Odds ratios (OR) = 30.490, 95%CI: 8.584-108.294], convergent folds (OR = 3.860, 95%CI: 1.060-14.055), mucosal discoloration (OR = 3.191, 95%CI: 1.016-10.021), and history of clopidogrel (OR = 3.554, 95%CI: 1.009-12.515) were independent risk factors for ulcers after ESD in patients with EGC ($P < 0.05$). The ROC curve showed that the area under the curve of the risk prediction model for ulcers after ESD in patients with EGC was 0.944 (95%CI: 0.902-0.972).

CONCLUSION

Clopidogrel medication history, lesion diameter, convergent folds, and mucosal discoloration can predict the occurrence of ulcers after ESD in patients with EGC.

INTRODUCTION

Gastric cancer is a common, widespread cancer. According to the "2020 Latest Global Cancer Burden" released by the World Health Organization, there were 1.089 million new gastric cancer cases and 768000 deaths worldwide, of which 478000 new cases and 373000 deaths were in China, accounting for nearly half of the cases, equivalent to 1022 Chinese people dying every day due to gastric cancer[1]. The prognosis of early gastric cancer is significantly better than that of advanced gastric cancer due to the low rate of lymphatic metastasis and distant metastasis[2].

In recent years, with the development of endoscopic techniques, endoscopic submucosal dissection (ESD) has been widely used in the treatment of early gastric cancer (EGC)[3,4]. Compared to previous treatments, the scope of ESD treatment is expanded, the resection rate is improved, the residual lesion is reduced, the recurrence rate is reduced, and the cure rate of digestive tract lesions is improved[5]. Therefore, ESD is currently the main endoscopic resection treatment for early gastric cancer; however, due to the wide range of ESD peeling, deep lesion peeling, difficult operations, and relatively high risk of complications such as bleeding and perforation[6-8], personalized and effective methods to predict the outcome are urgently needed in clinical practice.

The Japanese Gastric Cancer Association proposed that the absolute indications for ESD for EGC radical resection initially included non-ulcerative, well-differentiated mucosal lesions ≤ 2 cm in diameter. However, the absolute indications are so strict that unnecessary surgery may be performed. Subsequently, after a rigorous investigation of surgical specimens, the indications for ESD were expanded to include a larger diameter, undifferentiated mucosal lesions, and differentiated lesions with mild submucosal infiltration[9,10].

A recent meta-analysis showed that the postoperative ulcer risk was relatively low in patients who met the absolute indications, suggesting that if radical endoscopic dissection is accurately predicted based on histopathology, it may be possible to avoid intraoperative specimen excision[11]. Nevertheless, it is difficult to determine the presence of histological ulcers before ESD, and the presence of ulcers in EGCs is closely related to their depth of invasion and lymphatic invasion. Ruptures are considered ulcers, which undoubtedly overestimate the disease and lead to unnecessary surgery[12,13]. In addition, an endoscopy study reported that EGC ulcers might heal spontaneously without mucosal rupture. The presence of an ulcer is critical in deciding on the treatment modality[14].

In our study, LASSO regression was performed to screen the factors influencing the risk of ulcers in EGC patients after ESD. Based on the differential indicators, we aimed

to build a personalized prediction model that may provide a theoretical basis for the prevention of ulcers in EGC patients after ESD.

MATERIALS AND METHODS

Study subjects

This study was approved by the ethics committee of the hospital. After signed informed consent was obtained, 196 EGC patients who received ESD treatment in our hospital from March 2019 to March 2021 were enrolled in our study. The inclusion criteria were as follows: (1) met the diagnostic criteria for early gastric cancer confirmed by pathological examination; (2) the depth of invasion was limited to the mucosa and submucosa without lymph node metastasis; and (3) all patients provided informed consent and signed the consent form. The exclusion criteria were as follows: (1) gastric cancer combined with tumors in other parts; (2) epithelial tumor, adenocarcinoma or gastric adenoma; and (3) received radiotherapy, chemotherapy and/or surgery before ESD[15]. The occurrence of postoperative ulcers was evaluated 1 mo after ESD. At the same time, according to previous literature reports and clinical references, the baseline data and endoscopic characteristics of patients before ESD treatment were collected, and the factors influencing postoperative ulcers were discussed. A risk prediction model for ulcers after ESD in patients with early gastric cancer was constructed, and receiver operating characteristic (ROC) curves were drawn to verify the effectiveness of the prediction model.

Scheme of ESD treatment

General intravenous anesthesia was performed on all patients during ESD in our study. The size and scope of the lesions were determined by endoscopy before surgery, and the depth of invasion of the lesions was determined to exclude the possibility of lymph node metastasis. The detailed scheme of EDS treatment was as follows: (1) marking: the periphery of the lesion was marked by electrocoagulation at a distance of 5.0 mm from the outer edge of the lesion by subion coagulation; (2) submucosal injection: indigo

rouge injection (Southwest Pharmaceuticals; batch no. H50021944; 10 mL: 40 mg) for multipoint submucosal injection to ensure that the lesion mucosa was uplifted; (3) circular incision: a needle knife was used to cut the outer edge of the lesion along the marked point of the lesion edge; (4) mucosal peeling: repeated submucosal injection and separation to strip and excise the lesion from the submucosa; (5) wound treatment: thermal biopsy forceps and titanium clips were used to treat the postoperative bleeding points and lesion edges; and (6) postoperative treatment: the size of the lesion was measured, it was fixed with 4% formaldehyde solution and sent for histopathology to clarify the nature of the lesion.

Data collection and data quality control

The data collection included the general information of the patients, their pathological features and the endoscopic features. The general information of the patients included age, sex (male/female), course of disease, body mass index [weight (kg)/height (m^2)], history of *Helicobacter pylori* (*H. pylori*) infection, family history of gastric cancer, lesion site, comorbid diseases (hypertension, diabetes, coronary heart disease), residence (rural, urban), smoking history, drinking history, and drug history (aspirin, clopidogrel). The pathological features included lesion diameter, pathological type (differentiated carcinoma, undifferentiated carcinoma), number of tumors (single, multiple), depth of invasion (submucosal, muscularis mucosa), and vascular invasion. The endoscopic features included the lesion site (upper 1/3 of the stomach, middle 1/3 of the stomach, lower 1/3 of the stomach), lesion surface (convex, flat, depressed), mucosal rupture (regardless of the depth of invasion, any mucosal defect represents the presence of mucosal ruptures), mucosal discoloration (discoloration of any part of the lesion or the entire lesion contrasts with that of the surrounding mucosa, indicating a color change), and converging folds (the presence of any centripetal folds in the lesion indicates converging folds).

Data quality control was performed according to the inclusion and exclusion criteria, which were strictly implemented to ensure the authenticity of the patient data.

Specialized personnel collected and checked the general data of the patients, and the data were double-entered in parallel into EpiData software to ensure accuracy.

Follow-up and ulcer occurrence criteria

Follow-up and observation were performed for one month. Endoscopic review within 1 mo after the operation, local anesthesia and gastroscopic observation of the patient's lesions were performed. Then, 500 mL of 400% degassed distilled water was injected into the stomach, and endoscopic examination was performed under immersion. The occurrence of ulcers after ESD in the patients was recorded. The criteria for ulceration were mucosal defects involving the submucosa, muscularis propria malformation, or fibrosis in the submucosa or deeper layers under endoscopy[16,17].

Statistical analysis

SPSS 22.0 statistical software was used in our study. The measurement data were first tested for normality; the normally distributed data are expressed as the mean ± SD, and two independent samples *t*-tests were used for comparisons between groups. Count data are given as *n* (%), and differences between groups were compared using the χ^2 test. Based on *R* software (glmnet package), LASSO regression was performed, and the tenfold cross-validation method was used to screen the best risk predictor subset. Multivariate logistic regression analysis was performed to evaluate the odds ratio. ROC analysis was performed to evaluate the effectiveness of the prediction model. A *Z* score test was performed to compare the ROC curves of the different indicators. A *P* value less than 0.05 represents a significant difference.

RESULTS

General information of the patients

One month after the operation, no cases were lost to follow-up, the incidence of ulcers was 20.41% (40/196) (ulcer group), and the incidence of no ulcers was 79.59% (156/196) (non-ulcer group). There was no significant difference in age, sex, body mass index,

drinking history, family history of gastric cancer, number of tumors, comorbidities, residence, or aspirin medication history between the two groups ($P > 0.05$). There were significant differences in the course of disease ($P = 0.032$), history of *H. pylori* infection ($P = 0.041$), smoking history ($P = 0.045$), and proportion of clopidogrel medication history ($P < 0.001$) between the two groups ($P < 0.05$) (Table 1).

Comparison of pathological features between the ulcer group and the non-ulcer group

The pathological features in the ulcer group ($n = 40$) and non-ulcer group ($n = 156$) were compared. There was no significant difference in pathological type or vascular invasion between the two groups ($P > 0.05$), but there were statistically significant differences in lesion diameter ($P < 0.001$), the number of tumors ($P = 0.041$), and infiltration depth ($P = 0.046$) between the two groups (Table 2).

Comparison of endoscopic features between the ulcer group and the non-ulcer group

The endoscopic features in the ulcer group ($n = 40$) and non-ulcer group ($n = 156$) were compared. There was no significant difference in lesion site or lesion surface between the two groups ($P > 0.05$), but there were statistically significant differences in mucosal discoloration ($P < 0.001$) and convergent folds ($P < 0.001$) between the two groups, as shown in Table 3.

LASSO regression analysis

After the differential information of the patients, pathological features and endoscopic features was obtained, LASSO regression analysis was performed on the above independent variables (the course of disease, history of *H. pylori* infection, smoking history, clopidogrel medication history, lesion diameter, number of tumors, infiltration depth, mucosal discoloration, and convergent folds) (Figure 1). With the change in the penalty coefficient λ, the coefficients of the independent variables initially included in the model were gradually compressed, and finally, the coefficients of some independent variables were compressed to 0. Then, the 10-fold cross-validation method was used to

validate the independent variables. After validation, clopidogrel medication history, lesion diameter, convergent folds, and mucosal discoloration were the 4 independent variables that predicted postoperative ulceration (Figure 2).

Multivariate logistic regression analysis of the risk of ulcers after ESD in EGC patients

Taking the occurrence of ulcers as the dependent variable (ulcer occurrence = 1, no ulcer occurrence = 0), the above variables with statistically significant differences were used as independent variables for logistic regression analysis, and variable selection was performed by the stepwise method (α in = 0.05, α out = 0.1). Multivariate logistic analysis showed that lesion diameter [Odds ratios (OR)= 30.490, 95%CI: 8.584-108.294], convergent folds (OR = 3.860, 95%CI: 1.060-14.055), mucosal discoloration (OR = 3.191, 95%CI: 1.016-10.021) and clopidogrel medication history (OR = 3.554, 95%CI: 1.009-12.515) were independent risk factors for ulcers after ESD in EGC patients ($P < 0.05$) (Table 4).

Evaluation of the ROC risk prediction model for ulcer occurrence after ESD in EGC patients

ROC curve analysis showed that the area under the curve (AUC) of the risk prediction model for ulcers after ESD in patients with EGC was 0.916 (95%CI: 0.865-0.967), as shown in Figure 3. In addition, ROC curves of the lesion diameter, convergent folds, mucosal discoloration and clopidogrel medication history for ulcer occurrence after ESD in EGC patients were also evaluated. Among the four indicators alone, the AUC of the lesion diameter was the best, 0.885 (95%CI: 0.814-0.955), and the AUCs of convergent folds, mucosal discoloration and clopidogrel medication history were 0.651 (95%CI: 0.549-0.753), 0.648 (95%CI: 0.554-0.742) and 0.693 (95%CI: 0.601-0.785), respectively. Compared to the four indicators alone, the combined prediction model should significantly increase the accuracy of the prediction of ulcer occurrence after ESD in EGC patients (Table 5).

DISCUSSION

With advances in endoscopic techniques, ESD has become widely used in EGC treatment. ESD can provide a higher quality of life than surgical resection in terms of long-term outcomes[18]. To select ESD patients who may benefit from this treatment, personalized prediction of the outcome of EGC treatment is needed; therefore, previous studies have analyzed various clinicopathological factors and imaging modalities for personalized prediction[19]. Compared with non-ulcer EGCs, the incidence of lymph node micro-metastases in ulcerative EGC is significantly increased, so the presence or absence of ulcers has been identified as the key to a personalized treatment strategy for EGC.

However, currently, the presence of ulcers in the current ER criteria does not refer to endoscopic ulcers but to histological ulcers, which are based on data from surgically resected specimens. It is difficult to assess histological ulcers from biopsy specimens prior to treatment. Although the histological appearance of ulcers is considered to be an important factor in EGC treatment decisions and ESD curability, they should also be distinguished from biopsy-derived scars[20,21]. Mucosal rupture cannot be defined as an ulcer alone, but some clinicians believe that it could be described as an endoscopic ulcer, which may lead to overestimation of ulcerative EGC. To avoid unnecessary surgery, careful examination and personalized assessment of the ulcer under endoscopy is urgently needed in clinical practice[22].

In terms of endoscopic features, a previous study of endoscopic images of EGC patients showed that the diagnostic accuracy was 28.2% in the case of superficial mucosal ruptures without converging folds; in cases with confluent folds without mucosal ruptures and in patients with pathological ulcerative lesions, the diagnostic accuracy was only 35.9%[23]. The reason for this may be that most endoscopists tend to consider sunken lesions or lesions with mucosal ruptures as endoscopic ulcers. In another study[24], the lesion surface was irregular, and concentric folds of the diseased tissue were observed during the postoperative healing process of mixed EGC.

Converging folds of the EGC being a risk factor for ulceration was confirmed in our study. We believe that converging folds may originate from previous ulcers during the healing process, which indicates the presence of histological ulcers, and the presence of ulcer scars is negatively related to the effect of ESD. If converging folds are observed during endoscopy, it should be concluded that the lesion is accompanied by ulcer scars, and the probability of postoperative ulceration is high, so the procedure should be handled by a skilled endoscopist.

In addition, a recent study reported that white discoloration was associated with undifferentiated histology of EGC[25]. It was also shown that well-differentiated or moderately differentiated adenocarcinoma tumors have abundant and dense blood vessels, while low-grade adenocarcinoma tumors have sparse and loose blood vessels[26]. These findings are associated with cancerous mucosal redness in well-differentiated or moderately differentiated adenocarcinomas and pallor in undifferentiated carcinomas. A retrospective study showed that a color change (OR = 2.33) was an independent factor for predicting histological ulcers[27]. These results were also confirmed in our study.

The relationship between clinicopathological features and postoperative ulceration is also a hot topic in various studies, and previous studies have confirmed that the diameter of the lesion is a predictor of ulceration after ESD[28], because the larger the tumor diameter is, the greater the resection range. The larger the size, the longer the treatment time, which was also observed in this study.

In addition, some studies identified antithrombotic therapy as an independent risk factor for ESD ulcers[29]. A history of clopidogrel use was associated with the occurrence of ulcers after ESD[30]. In our study, a history of clopidogrel medication was also an independent risk factor for ulcers after ESD in EGC patients. The reason may be that the long-term use of clopidogrel before surgery may lead to changes in the patients' coagulation function and increase the risk of postoperative ulcers. However, it is worth noting that aspirin and clopidogrel are both antithrombotic drugs, and aspirin does not increase the risk of postoperative ulcers, which may be related to the relatively small

sample size of this study, so the relationship between aspirin and the risk of postoperative ulcers should be examined in a future study.

However, there are still some shortcomings in our study. First, our study was a single-center study, which may have selection bias in the collection of clinical case data. A multicenter study should be performed in the future. Second, the sample size was relatively small, and the predictive model of ulcers after ESD in EGC patients needs to be confirmed in a much larger study. Third, although a risk prediction model for EGC was built, the model was not validated. A prospective study should be performed to further confirm these results.

CONCLUSION

In summary, clopidogrel medication history, lesion diameter, convergent folds, and mucosal discoloration can predict the occurrence of ulcers after ESD in patients with EGC. The LASSO regression-based ulcer risk prediction model for EGC may be feasible and meaningful, and its clinical application value can effectively help clinicians identify high-risk groups for ulcers after ESD for EGC and provide targeted treatment measures.

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Figure Legends

Figure 1 Coefficient curves of nine clinical features included in LASSO regression.

Figure 2 The most suitable clinical features were selected by LASSO regression and ten-fold cross-validation.

Table 1 Comparison of general information of ulcer group and non-ulcer group, *n* (%)

General Information	Ulcer group (n = 40)	Non-ulcer group (n = 156)	t/χ^2 value	P value
Sex			0.83	0.362
Male	26 (65.00)	89 (57.05)		
Female	14 (35.00)	67 (42.95)		
Age	48.98 ± 8.23	47.11 ± 9.02	1.257	0.213
BMI	22.25 ± 2.01	21.83 ± 1.98	1.183	0.242
Course of disease (yr)	2.85 ± 0.48	2.66 ± 0.52	2.195	0.032
History of *H. pylori* infection	7 (17.50)	11 (7.05)	4.168	0.041
Family history of GC	8 (20.00)	22 (14.10)	0.854	0.355
Drinking history	9 (22.50)	26 (16.67)	0.739	0.39
Smoking history	24 (60.00)	66 (42.31)	4.013	0.045
Comorbidities				
Hypertension	9 (22.50)	26 (16.67)	0.739	0.39
Diabetes	6 (15.00)	22 (14.10)	0.021	0.885
Coronary heart disease	7 (17.50)	23 (14.75)	0.187	0.666
Residence			0.116	0.733
Rural	25 (62.50)	102 (65.38)		
Town	15 (37.50)	54 (34.62)		
Medication history				
Aspirin	12 (30.00)	28 (17.95)	2.847	0.092
Clopidogrel	19 (47.50)	27 (17.31)	16.158	< 0.001

BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; GC: Gastric cancer.

Table 2 Comparison of pathological features of ulcer group and non-ulcer group, *n* (%)

Pathological features	Ulcer group (*n* = 40)	Non-ulcer group (*n* = 156)	t/χ^2 value	*P* value
Lesion diameter (cm)	4.40 ± 0.97	2.97 ± 0.62	8.871	< 0.001
Number of tumors			4.185	0.041
Single shot	18 (45.00)	98 (62.83)		
Multiple	22 (55.00)	58 (37.18)		
Pathological type			0.268	0.605
Differentiated carcinoma	19 (47.50)	67 (42.95)		
Undifferentiated carcinoma	21 (52.50)	89 (57.05)		
Infiltration depth			3.988	0.046
Submucosa	21 (52.50)	55 (35.26)		
Mucosal layer	19 (47.50)	101 (64.74)		
Vascular invasion	2 (5.00)	6 (3.85)	0.108	0.742

Table 3 Comparison of endoscopic features of ulcer group and non-ulcer group, *n* (%)

Endoscopic features	Ulcer group (*n* = 40)	Non-ulcer group (*n* = 156)	χ^2 value	*P* value
Lesion site			2.132	0.344
Upper 1/3 of stomach	12 (30.00)	61 (39.10)		
1/3 of stomach	20 (50.00)	76 (48.72)		
Lower 1/3 of stomach	8 (20.00)	19 (12.18)		
Mucosal discoloration	28 (70.00)	63 (40.38)	11.227	< 0.001
Convergence folds	28 (60.00)	49 (31.41)	19.877	< 0.001

Lesion surface			1.105	0.576
Bulge	11 (27.50)	52 (33.33)		
Flat	15 (37.50)	62 (39.74)		
Sag	14 (35.00)	42 (26.93)		

Table 4 Multivariate logistic regression analysis on the risk of ulcers after endoscopic submucosal dissection in early gastric cancer patients

Related indicator	β	SE	Wald	*P* value	OR	95%CI	
						Lower	Upper
Lesion diameter	3.417	0.647	27.927	< 0.001	30.490	8.584	108.294
Clopidogrel medication history	1.268	0.642	3.899	0.048	3.554	1.009	12.515
Convergent folds	1.351	0.659	4.195	0.041	3.860	1.060	14.055
Mucosal discoloration	1.160	0.584	3.950	0.047	3.191	1.016	10.021

OR: Odds ratios.

Table 5 Evaluation of prediction model for ulcer occurrence after endoscopic submucosal dissection in early gastric cancer patients

Indicator	AUC	SD	*P* value	95%CI	
				Lower	Upper
Lesion diameter	0.885	0.036	< 0.001	0.814	0.955
Clopidogrel medication history	0.651	0.052	0.003	0.549	0.753
Mucosal discoloration	0.648	0.048	0.004	0.554	0.742
Convergent folds	0.693	0.047	< 0.001	0.601	0.785
Prediction model	0.916	0.026	0.000	0.865	0.967

AUC: Area under the curve.

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