Logistic regression analysis of the risk factors of anastomotic fistula after radical resection of esophageal-cardiac cancer

Jinxi Huang1, Yi Zhou2, Chenghu Wang1, Weiwei Yuan1, Zhandong Zhang1, Beibei Chen3 & Xiefu Zhang4

1 Department of General Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China
2 Department of Anesthesiology, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China
3 Department of Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China
4 Department of General Surgery, First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Keywords
Anastomotic fistula; esophageal-cardiac cancer; logistic regression analysis; risk factors; surgical treatment.

Correspondence
Yi Zhou, Department of Anesthesiology, The Affiliated Cancer Hospital of Zhengzhou University, Dongming Road, Zhengzhou City, Henan Province, 450003, China.
Tel: +86 371 6558 7230
Fax: +86 371 6596 1505
Email: yizhouhn675@126.com

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Abstract
Background: This study was conducted to investigate the risk factors of anastomotic fistula after the radical resection of esophageal-cardiac cancer.

Methods: Five hundred and forty-four esophageal-cardiac cancer patients who underwent surgery and had complete clinical data were included in the study. Fifty patients diagnosed with postoperative anastomotic fistula were considered the case group and the remaining 494 subjects who did not develop postoperative anastomotic fistula were considered the control. The potential risk factors for anastomotic fistula, such as age, gender, diabetes history, smoking history, were collected and compared between the groups. Statistically significant variables were substituted into logistic regression to further evaluate the independent risk factors for postoperative anastomotic fistulas in esophageal-cardiac cancer.

Results: The incidence of anastomotic fistulas was 9.2% (50/544). Logistic regression analysis revealed that female gender (P < 0.05), laparoscopic surgery (P < 0.05), decreased postoperative albumin (P < 0.05), and postoperative renal dysfunction (P < 0.05) were independent risk factors for anastomotic fistula in patients who received surgery for esophageal-cardiac cancer. Of the 50 anastomotic fistulas, 16 cases were small fistulas, which were only discovered by conventional imaging examination and not presenting clinical symptoms. All of the anastomotic fistulas occurred within seven days after surgery. Five of the patients with anastomotic fistulas underwent a second surgery and three died.

Conclusion: Female patients with esophageal-cardiac cancer treated with endoscopic surgery and suffering from postoperative hypoproteinemia and renal dysfunction were susceptible to postoperative anastomotic fistula.
mortality rates of anastomotic fistula in patients with esophageal cancer who have undergone surgery range from 8% to 24% and 11% to 35.7%, respectively.5,7 In this study, the records of 544 patients diagnosed with esophageal-cardiac cancer and treated in our hospital were retrospectively analyzed to explore the risk factors of anastomotic fistula by logistic regression analysis.

Methods

Patients

The data of 558 patients who underwent radical surgery at The Affiliated Cancer Hospital of Zhengzhou University from June 2012 to February 2015 was retrospectively analyzed. Cardiopulmonary, hepatic, and renal function had been tested before surgery to eliminate contraindications. The patients were diagnosed by gastroscopy and pathologic examination, and results revealed esophageal-cardiac adenocarcinoma. Of the 558 patients, five cases without sufficient clinical data and nine who suffered from distant metastasis were excluded from the study. Of the 544 remaining cases, 391 manifested esophagus-jejunum anastomosis and 153 exhibited esophagus-stomach anastomosis. The great omentum of the patients was removed when the tumor invaded around 3 cm of the esophagus, and thoraco-abdominal joint incision surgery was then performed.

Anastomotic fistula symptoms and diagnosis

In clinical manifestations, most of the patients suffered from continuous high fever, a cough with large amounts of purulent sputum, intense chest pain, difficulty breathing, and hydro pneumothorax on the surgical side. Some of the patients experienced toxic shock caused by delayed diagnosis and treatment. In auxiliary examination, encapsulated effusion or hydro pneumothorax was detected by gastrointestinal radiography.8

Potential risk factors of postoperative anastomotic fistula

The potential risk factors of anastomotic fistula were statistically analyzed in accordance with previously described methods.9 General patient information included: age (≤65 or >65 years); gender (male, female); diabetes (positive, negative); smoking history (positive, negative); nutritional screening table (NRS2002) score (<3 or ≥3); and preoperative chemotherapy (positive, negative). The following surgical parameters were considered: laparoscopic surgery (yes, no); T staging (T1–2, T3–4); N staging (N0–1, N2–3); surgical duration (≤200 or >200 min); blood loss (≤300 or >300 mL); resection of adjacent organs (yes, no); chest open surgery (yes, no); esophageal-jejunum anastomosis (yes, no); number of dissected lymph nodes (≤15, >15); Borrmann type invasion (yes, no); and postoperative early enteral nutrition (yes, no). The biochemical parameters included: preoperative hemoglobin (≤90 or >90 g/L); preoperative albumin (≤34 g, >34 g/L); albumin within seven days after the surgery (≤28 or >28 g/L); and blood urea nitrogen and abnormal creatinine levels within seven days after surgery (yes, no). The abnormal levels of postoperative blood urea nitrogen and creatinine were described as urea nitrogen ≥15 mM or creatinine ≥200 μM.

Logistic regression was used to screen the independent risk factors and to determine whether a postoperative anastomotic fistula was a dependent variable (Y: Y1 = Yes, Y0 = No) or other risk factors were independent variables (X1, X2...). The potential risk factors obtained were assigned and substituted to the logistic regression equation, and the independent risk factors of postoperative anastomotic fistula in esophageal-cardiac cancer were calculated.

Statistical analysis

Potential risk factors were detected using single-factor analysis. The potential risk factors with P < 0.05 were further assigned, imported into the logistic regression equation and analyzed. P < 0.05 was considered statistically significant. The odds ratio (OR) and 95% confidence interval were calculated. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Incidence rate of anastomotic fistula

The incidence rate of anastomotic fistula was 9.2% (50/544). All of the patients underwent radiographic examination with an oral liquid contrast agent after surgery, and their diagnosis was clear (Fig 1).

Single-factor analysis of the relationship between clinical data and anastomotic fistula

After the patients with esophageal-cardiac cancer completed surgery, anastomotic fistula incidence was examined using single-factor analysis. The results revealed that clinical data, such as patient age, history of diabetes, smoking history, preoperative NRS score, and chemotherapy before surgery, were not related to incidence.
The incidence of postoperative anastomotic fistula in women was significantly higher than in men \((P = 0.006)\) (Table 1).

### Single-factor analysis of the relationship between surgery-related data and anastomotic fistula

On the basis of the relevant surgical conditions of the patients, we observed that laparoscopic surgery \((P = 0.002)\), prolonged surgical procedure \((P = 0.001)\), and excessive intraoperative blood loss \((P = 0.009)\) promoted the occurrence of anastomotic fistula. However, tumor staging, lymph node staging, adjacent organ resection, anastomotic methods, anastomotic strengthening, number of dissected lymph nodes, tumor invasiveness, and early enteral feeding were not significantly correlated with the development of anastomotic fistula \((P > 0.05)\) (Table 2).

### Single-factor analysis of the relationship between laboratory index and anastomotic fistula

Single-factor analysis revealed that preoperative moderate anemia \((P = 0.044)\), significantly decreased albumin level after surgery \((P < 0.001)\), and postoperative renal dysfunction \((P < 0.001)\) were risk factors of anastomotic fistula. Conversely, a slight decrease in albumin levels before surgery was not significantly related to the development of anastomotic fistula \((P > 0.05)\) (Table 3).

### Logistic regression analysis of anastomotic fistula after surgery for esophageal-cardiac cancer

The single factors described in the preceding sections were examined through logistic regression analysis, and our results indicated that female gender \((P < 0.05)\), laparoscopic surgery \((P < 0.05)\), decreased postoperative albumin level \((P < 0.05)\), and postoperative renal dysfunction \((P < 0.05)\) were independent risk factors of developing anastomotic fistula after esophageal-cardiac cancer patients underwent surgery (Table 4).

### Prognostic analysis of patients with anastomotic fistula

Of the 50 cases of anastomotic fistula, 16 cases were small fistulas, detected only by postoperative conventional imaging examination and not characterized by any clinical...
symptoms. All anastomotic fistulas developed within seven days after surgery. Five of the patients with anastomotic fistulas underwent a second surgery and three died.

**Discussion**

Although surgical techniques have improved, anastomotic fistula is still the most common serious postoperative complication. Surgeons should focus on the clinical conditions of patients and carefully choose surgical options to minimize the occurrence of anastomotic fistula. We retrospectively analyzed the data of 544 patients who were surgically treated for esophageal-cardiac cancer and our results indicated that female patients, laparoscopic surgery, decreased postoperative albumin level, and postoperative renal dysfunction were independent risk factors of developing postoperative anastomotic fistula.

A previous study demonstrated that decreased lung function, great omentum resection, and long-term use of steroids are associated with the development of anastomotic fistula. Primary screening was performed on the patients in our study to determine cardiopulmonary insufficiency, and patients ineligible for surgery were excluded from risk factor analysis. All of the patients with esophageal-cardiac cancer were subjected to standard D2 and D2 plus radical surgery and routine great removal. Only two patients in this study had used steroids long-term, thus there was insufficient data to include this factor in our analysis. As such, lung function, great omentum resection, and long-term use of steroids were not analyzed in this study.

According to previous studies, prolonged surgical procedures, excessive intraoperative blood loss, and preoperative anemia are independent risk factors in esophageal-cardiac cancer patients of developing anastomotic fistula. Single-factor analysis demonstrated that these factors were associated with a higher risk of developing anastomotic fistulas, but were not correlated with postoperative anastomotic fistula in the final logistic analysis.

Previous studies have reported that a preoperative NRS score of <3 is considered an independent risk factor. However, as any malnourished patients in our sample were treated for this issue before surgery, our analysis yielded no significant results relating to NRS score.

Studies have reported that resection of combined multiple organs is related to the development of anastomotic fistula. However, if a clear tendency of combined organ resection is observed in preoperative multidisciplinary discussion, National Comprehensive Cancer Network guidelines recommend that preoperative neoadjuvant chemotherapy be administered and surgery performed only after the tumor has been reduced. Therefore, few cases of resection of combined organs, such as liver and pancreas,
have been documented, whereas resection of mesentery, gall bladder, and spleen are commonly reported. This policy may account for the lack of such data in our final results.

In this study, female gender was considered an independent risk factor for developing anastomotic fistula in esophageal-cardiac cancer patients who underwent surgery. This risk factor might be related to the predominance of overweight female patients in northern China, difficulty conducting surgery, and the lack of postoperative activities. However, the specific reasons need to be elucidated.

Among the laboratory factors examined in this study, a significantly decreased postoperative albumin level and renal dysfunction were identified as independent risk factors, possibly because patients that usually suffer from systemic inflammatory response syndrome exhibit an increased catabolic rate in their protein tissue, and display a decrease in the synthetic rate once anastomotic fistula occurs. As a result of developing anastomotic fistula, the blood albumin level decreases and serum creatinine and urea nitrogen levels increase. If the two laboratory indexes of the patients are abnormal in the early stage, the occurrence of anastomotic fistula should be considered when imaging examination is unavailable.

A diagnosis of anastomotic fistula in our study sample was based on radiological examination. The results revealed a high probability of small fistula occurrence; therefore, our results are more reliable than other studies. As a retrospective analysis of a data from a single research center, this study inevitably has some limitations; however, all patients were analyzed simultaneously without selectivity. The comparatively large number of samples and controlled surgical quality made for reliable results.

Our study findings indicate that female patients with esophageal-cardiac cancer treated with endoscopic surgery and suffering from postoperative hypoproteinemia and renal dysfunction were susceptible to developing postoperative anastomotic fistula.

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**Table 4** Logistic regression analysis of anastomotic fistula after surgery for esophageal-cardiac cancer

| Variables                          | Coefficient | SE   | Wald     | Freedom | P       | OR    |
|------------------------------------|-------------|------|----------|---------|---------|-------|
| Gender                             | −0.961      | 0.358| 7.203    | 1       | 0.007   | 0.382 |
| Laparoscopic surgery               | 0.993       | 0.348| 8.136    | 1       | 0.004   | 2.699 |
| Postoperative Hypoproteinemia      | 1.594       | 0.388| 16.922   | 1       | 0.000   | 4.925 |
| Postoperative renal dysfunction    | 3.505       | 0.689| 25.842   | 1       | 0.000   | 33.267|

OR, odds ratio; SE, standard error of the mean.

**Disclosure**

No authors report any conflict of interest.

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