

# Risk factors for esophagojejunal anastomotic leakage after curative total gastrectomy combined with D2 lymph node dissection for gastric cancer

Journal of International Medical Research

49(3) 1–10

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DOI: 10.1177/03000605211000883

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## Abstract

**Objective:** To explore the risk factors associated with esophagojejunal anastomotic leakage (EJAL) after curative total gastrectomy combined with D2 lymph node dissection for gastric cancer.

**Methods:** We reviewed the data for 390 consecutive patients undergoing Roux-en-Y esophagojejunostomy reconstruction after total gastrectomy. Multivariate analysis was performed using a logistic regression model to identify the independent risk factors for EJAL.

**Results:** Of the 390 patients enrolled in this study, EJAL occurred in 10 patients (2.6%), and one patient (1/10) with EJAL died. Univariate analysis identified age, alcohol consumption, pulmonary insufficiency, and intraoperative blood loss as risk factors for EJAL. Of these four risk factors, age and alcohol consumption were retained as independent risk factors by multivariate analysis.

**Conclusion:** Surgeons should be very careful regarding anastomotic leakage after esophagojejunal anastomosis, perioperatively, especially in patients with advanced age and a history of alcohol consumption. Pulmonary insufficiency and intraoperative blood loss, although not identified as independent risk factors, should also be considered.

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## Keywords

Esophagojejunal anastomotic leakage, risk factor, total gastrectomy, mortality, complication, multivariate analysis

Date received: 24 January 2021; accepted: 16 February 2021

## Introduction

Esophagojejunal anastomotic leakage (EJAL) is a common and serious postoperative complication of total gastrectomy. Moreover, EJAL has been identified as an independent negative prognostic factor for long-term survival.<sup>1</sup> The reported incidence of EJAL varies between 0.5% and 11.5%,<sup>1-9</sup> and recently, Cetin et al.<sup>10</sup> reported an incidence of up to 16.2%. These data highlight the requirement for preventing perioperative complications. Inconsistent reports regarding the risk factors for EJAL, long-term clinical data, maturity regarding the learning curve, and the now widespread use of mechanical stapling devices make previous research data less relevant as reference material. To inform decision-making in gastric surgery, it is necessary to keep exploring the risk factors for EJAL. Therefore, this study aimed to explore in detail the risk factors for EJAL in patients who underwent curative total gastrectomy combined with D2 lymph node dissection in our unit.

## Methods

### Patients

All patients and their families provided written informed consent before surgery. The present study was approved by the Medical Ethics Committee of Peking University Cancer Hospital and was conducted in accordance with the guidelines of the Helsinki Declaration of the World Medical Association.

### Surgical technique

The reconstruction method after total gastrectomy was Roux-en-Y esophagojejunostomy. All esophagojejunal anastomoses were performed with a circular stapler (Ethicon<sup>TM</sup> Circular Stapler CDH25A; Ethicon Inc., Somerville, NJ, USA). The integrity of the ring of tissue that was retained by the circular stapler after completing the anastomosis was also examined. Finally, additional sutures were placed as needed to reinforce the anastomosis.

### Definitions and variables

The diagnosis of EJAL relies mainly on radiological and/or clinical findings. Upper gastrointestinal contrast swallow, which is feasible and low cost, was routinely performed for all patients after a median of 6 postoperative days in our unit.

Radiological leakage was defined as transudation outside the lumen seen on X-ray imaging as the patient was drinking the water-soluble contrast medium. Clinical leakage was defined as leakage of intestinal fluid or turbid content from the surgical drain accompanied by fever, abdominal pain, or elevated leukocyte count, or C-reactive protein (CRP) or procalcitonin (PCT) concentrations. The definition of EJAL was based on clinical leakage, in the present study. One patient with asymptomatic leakage that was diagnosed only radiologically was not included in the EJAL group. The definition of an older person was in accordance with the standards of the World

Health Organization (WHO).<sup>6,9</sup> Pulmonary insufficiency was defined as a forced expiratory volume measured for 1 s (FEV1)/forced vital capacity (FVC) <0.70 (obstructive lung disease) or total lung capacity (TLC) <80% (restrictive lung disease).<sup>6</sup> Gastric cancer histopathological staging was performed according to the seventh edition of the International Union Against Cancer TNM classification.<sup>11</sup> "Alcohol consumption" was defined as alcohol intake >1 U/day for women and >2 U/day (1 U of alcohol = 12 g of alcohol) for men, as stipulated in the Dietary Guidelines For Americans.<sup>12</sup>

Patient-related, surgery-related, and tumor-related variables potentially associated with EJAL were recorded. Table 1 summarizes the patient-related variables, namely sex (female, male), age ( $\leq 65$ ,  $> 65$  years), American Society of Anesthesiologists (ASA) category (I–III), smoking, alcohol consumption, hypertension, diabetes, body mass index (BMI) ( $< 25$ ,  $\geq 25$  kg/m<sup>2</sup>), neoadjuvant chemotherapy, pulmonary insufficiency, preoperative hemoglobin ( $< 90$ ,  $\geq 90$  g/L), preoperative serum albumin ( $< 35$ ,  $\geq 35$  g/L), and preoperative carcinoembryonic antigen ( $< 0.005$ ,  $\geq 0.005$  ng/mL). Table 2 summarizes the surgery-related variables, namely operative approach (open, laparoscopic), duration of operation ( $< 240$ ,  $\geq 240$  minutes), intraoperative blood loss ( $< 200$ ,  $\geq 200$  mL), combined resection of other organs (spleen, pancreas, liver), and perioperative blood transfusion. Additionally, Table 3 summarizes the tumor-related variables, namely tumor location (lower, middle, upper, entire stomach), tumor size ( $< 4$ ,  $\geq 4$  cm), lymph node dissection ( $n < 16$ ,  $n \geq 16$ ), pathological tumor type (well-, moderately-, poorly-differentiated, other), depth of invasion (T0–4), and lymph node status (N0–3). In total, 23 potential risk factors were considered and analyzed in the present study.

## EJAL interventions

The interventions for EJAL were as follows: (1) conservative treatment (with or without percutaneous drainage): fasting, antibiotics, nutritional support (enteral or parenteral), and insertion of a nasojejun tube, and (2) surgical treatment: drainage, repair, or repeat surgery to repair the anastomosis.

## Statistical analyses

Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables were dichotomized according to the clinical situation, and standard values were stipulated by state-of-the-art guidelines or using the median value of each variable as the cutoff point. Patients were divided into two groups according to whether they experienced EJAL, and the groups were analyzed using the chi-squared test or Fisher's exact test. Variables with a  $P$  value  $< 0.05$  in the univariate analysis and other factors considered to have important clinical significance were entered into the multivariate analysis. The multivariate analysis involved a logistic regression model to investigate the risk factors associated with the incidence of EJAL, and a  $P$  value  $< 0.05$  was considered statistically significant. Odds ratios (OR) and their 95% confidence intervals (CI) were also provided.

## Results

### Patients

From April 2009 to April 2019, 398 patients with gastric cancer underwent curative total gastrectomy combined with D2 lymph node dissection in our unit. The patients' demographics are as follows: There were 297 men and 93 women, with a mean age of 59.5 (range: 22–80) years. Two patients with duodenal stump leakage and a gastric stromal tumor, respectively, were excluded from the study. Two patients with positive proximal

**Table 1.** Univariate analysis of patient-related variables associated with esophagojejunal anastomotic leakage.

Variable	Leakage (-)	Leakage (+)	$\chi^2$	P value
Sex			3.214	0.073
Male	287	10		
Female	93	0		
Age (years)			5.014	0.025
≤65	275	4		
>65	105	6		
ASA category			3.975	0.137
I	303	7		
II	71	2		
III	6	1		
Smoking			0.096	0.757
No	246	6		
Yes	134	4		
Alcohol consumption			5.473	0.019
No	305	5		
Yes	75	5		
Hypertension			0.064	0.801
No	291	8		
Yes	89	2		
Diabetes			1.076	0.300
No	343	10		
Yes	37	0		
BMI (kg/m <sup>2</sup> )			1.838	0.175
<25	266	5		
≥25	114	5		
Neoadjuvant chemotherapy			0.641	0.423
No	303	9		
Yes	77	1		
Pulmonary insufficiency			3.866	0.049
No	292	5		
Yes	88	5		
Preoperative hemoglobin (g/L)			0.584	0.445
<90	21	0		
≥90	359	10		
Preoperative serum albumin (g/L)			2.467	0.116
<35	49	3		
≥35	331	7		
Preoperative carcinoembryonic antigen (μg/mL)			0.055	0.815
<0.005	292	8		
≥0.005	88	2		

ASA, American Society of Anesthesiologists; BMI, body mass index;  $\chi^2$ , chi-square test. There were statistically significant differences for the data in italics ( $P < 0.05$ ).

**Table 2.** Univariate analysis of surgery-related variables associated with esophagojejunal anastomotic leakage.

Variable	Leakage (-)	Leakage (+)	$\chi^2$	P value
Operative approach			0.183	0.669
Open	178	4		
Laparoscopic	202	6		
Operative duration (minutes)			1.441	0.230
<240	147	2		
≥240	233	8		
Blood loss (mL)			5.885	0.015
<200	330	6		
≥200	50	4		
Combined organ resection			0.242	0.622
No	371	10		
Yes	9	0		
Perioperative blood transfusion			0.063	0.802
No	331	9		
Yes	48	2		

There were statistically significant differences for the data in italics ( $P < 0.05$ ).  $\chi^2$ , chi-square test.

margins, and four patients with missing data were also excluded from the study; thus, 390 patients remained eligible for analysis.

### Incidence of EJAL

Of the 390 patients, EJAL was diagnosed in 10 (2.6%) patients. Among these 10 patients with EJAL, all patients had intestinal fluid or turbid content emerging from their drain; 9 had increased leukocyte counts or elevated CRP or PCT concentrations; 8 patients developed fever; and 4 patients experienced abdominal pain. Of the 10 patients, 5 patients recovered with conservative treatment, and 4 patients underwent surgery. Only 1 of the 10 patients (1/10) died in-hospital owing to septic shock caused by EJAL.

### Patient-related risk variables

Table 1 displays the results of the univariate analysis of the patient-related variables associated with EJAL. All 10 patients who developed EJAL were men, but this finding

was not statistically significant. There were no statistically significant differences in ASA category, smoking, hypertension, diabetes, BMI, neoadjuvant chemotherapy, or preoperative hemoglobin, preoperative serum albumin, or carcinoembryonic antigen concentrations between the two groups. EJAL was a more frequent manifestation in older patients ( $P = 0.025$ ) and in patients who had preoperative pulmonary insufficiency ( $P = 0.049$ ). Moreover, patients with a history of excessive alcohol consumption were more likely to develop EJAL than those for whom no alcohol consumption had been reported ( $P = 0.019$ ).

### Surgery-related variables

Table 2 shows the results of the univariate analysis of the surgery-related variables associated with EJAL. The operational approach, operation duration, combined resection with other organs (spleen, pancreas, liver), and perioperative blood transfusion were not statistically significant risk

**Table 3.** Univariate analysis of tumor-related variables associated with esophagojejunal anastomotic leakage.

Variable	Leakage (-)	Leakage (+)	$\chi^2$	P value
Tumor location			1.761	0.623
Lower	23	0		
Middle	94	3		
Upper	229	7		
Whole stomach	34	0		
Tumor size (cm)			0.033	0.855
<4	163	4		
≥4	217	6		
Lymph node dissection (n)			0.497	0.481
<16	18	0		
≥16	362	10		
Pathological tumor type (differentiation)			2.768	0.429
Well	10	0		
Moderate	97	2		
Poor	247	6		
Other	26	2		
Depth of invasion			1.395	0.845
T0	3	0		
T1	45	1		
T2	41	2		
T3	168	5		
T4	123	2		
Lymph node status			4.492	0.481
N0	140	5		
N1	67	0		
N2	83	4		
N3	90	1		

$\chi^2$ , chi-square test.

factors associated with EJAL. However, patients who had suffered extensive intra-operative blood loss were more likely to develop EJAL than those who had not ( $P = 0.015$ ).

### Tumor-related variables

Table 3 lists the results of the univariate analysis of the tumor-related variables associated with EJAL. Tumor location, tumor size, lymph node dissection, pathological tumor type, depth of invasion, and lymph node status were not risk factors significantly associated with EJAL.

The multivariate analysis revealed that age ( $P = 0.043$ ; OR: 3.882 [95%

CI: 1.045–14.422]) and alcohol consumption ( $P = 0.043$ ; OR: 3.828 [95% CI: 1.043–14.050]) were independent risk factors associated with EJAL (Table 4).

### Discussion

EJAL is a serious and potentially fatal complication after gastric surgery. It has been reported that EJAL has a mortality rate of up to 50%, and is the major reason for postoperative death after surgery.<sup>13</sup> The present study identified an incidence of EJAL of 2.6% (10/390), which was similar to a recent high-quality meta-analysis involving 2484 patients with gastric cancer

**Table 4.** Multivariate analysis of the risk factors associated with esophagojejunal anastomotic leakage.

Variable	<i>P</i> value	Odds ratio	95% CI
Age (years)	<i>0.043</i>	3.882	1.045–14.422
Alcohol consumption	<i>0.043</i>	3.828	1.043–14.050

There were statistically significant differences for the data in italics ( $P < 0.05$ ).  
CI, confidence interval.

that reported an incidence of EJAL after total gastrectomy of 2.5%.<sup>14</sup> Moreover, the present study also found a mortality rate of 10% (1/10), which further highlights why the risk of developing perioperative EJAL should be evaluated.

Identifying the risk factors for EJAL helps reduce the incidence of this condition, clinically. The previously reported risk factors were mainly patient-, surgery-, and tumor-related factors. In the present study, the univariate analysis revealed that age  $>65$  years, alcohol consumption, pulmonary insufficiency, and intraoperative blood loss were risk factors associated with EJAL. The multivariate analysis demonstrated that age  $>65$  years and alcohol consumption were independent risk factors associated with EJAL in gastric surgery.

The present study also found that EJAL was more likely to occur in patients of advanced age, similar to findings in two previous studies.<sup>6,9</sup> Goh et al.<sup>15</sup> reported that older patients often had poorer physical physiological function, combined with several comorbidities and poor healing ability, making it more difficult for them to cope with surgery. Of the six advanced-age patients ( $>65$  years) in our study who developed anastomotic leakage, one patient had hypertension, three had pulmonary insufficiency, and one had concurrent hypertension and pulmonary insufficiency. Owing to the poor ability of older patients to respond to stimuli, the early clinical symptoms of anastomotic leakage might be atypical and prone to be missed or

misdiagnosed; thus, more attention should be paid to EJAL in older patients.

It is worth noting that whether diabetes affects the incidence of anastomotic leakage remains controversial. Diabetes affects wound healing, not only regarding surgical incisions,<sup>16</sup> but also intestinal anastomoses.<sup>17</sup> Kazuhiro et al.<sup>7</sup> reported that poor preoperative diabetic control was an independent risk factor for EJAL. However, none of the 10 patients who developed EJAL in our study had diabetes, and several previous reports<sup>1,3,5,6,9,10</sup> also failed to find an association between diabetes and EJAL. Therefore, this issue deserves further discussion.

Although Isozaki et al.<sup>3</sup> and Sauvanet et al.<sup>18</sup> successively reported that pulmonary insufficiency was not a risk factor for EJAL, Wu et al.<sup>19</sup> found that respiratory disease was associated with postoperative complications after gastric surgery. The present study revealed that pulmonary insufficiency was associated with EJAL, but was not an independent risk factor for EJAL. This may be explained by poor oxygen supply owing to pulmonary insufficiency, combined with restricted breathing owing to pain after abdominal surgery, both of which may affect the healing process after gastric surgery. Moreover, anastomotic leakage could aggravate impaired lung infection, creating a vicious circle. A high-quality randomized controlled trial by Schietroma et al.<sup>20</sup> found that the risk of EJAL was 49% lower in patients who received 80% FiO<sub>2</sub> than in those who received 30% FiO<sub>2</sub> during and 6 hours



after open total gastrectomy; this issue deserves further attention.

Although anastomotic leakage might be a complication that is driven by many factors, alcohol consumption has previously been associated with increased postoperative complications in patients with colorectal cancer.<sup>21,22</sup> Rullier et al. and Sorensen et al.<sup>23,24</sup> reported that smoking and alcohol abuse were major risk factors for anastomotic leakage in colorectal surgery. Thomas et al.<sup>25</sup> further demonstrated that an alcohol intake of more than 60 g/day was associated with an increased risk of anastomotic leakage in colorectal surgery. However, such analyses have rarely been published in studies of gastric cancer. To the best of our knowledge, ours is the first study to report alcohol abuse being associated with EJAL following gastric surgery. Alcoholism may affect the healing process and lead to impaired anastomotic integrity in various ways. Alcohol has been recognized as an influential factor in hemostasis, and excessive alcohol consumption may lead to increased perioperative bleeding because of bone marrow toxicity and decreased levels of fibrinogen, factor VII, and von Willebrand factor.<sup>26,27</sup>

Cardiac insufficiency, immunosuppression, and hemostasis have also been demonstrated in symptom-free alcohol abusers with postoperative complications.<sup>28</sup> Therefore, preoperative use of alcohol should be identified and managed appropriately before surgery. Moreover, it is important to remember that a history of alcohol consumption is an influential factor in the development of postoperative complications. To obtain beneficial short-term reversibility of physiological impairments, 4 weeks of alcohol abstinence prior to surgery has been advised.<sup>22</sup> Several studies<sup>21-25</sup> also revealed that smoking was a risk factor for anastomotic leakage and increased the incidence of postoperative complications following rectal surgery. Although 40% of

patients (4/10) with a history of smoking developed EJAL in our study, this factor failed to reach statistical significance but warrants further discussion.

The advent of the “minimally invasive” era has led to a significant reduction in intraoperative bleeding. Although intraoperative blood loss was not an independent risk factor for EJAL in this study, we consider that this factor should not be ignored in gastric surgery. On one hand, extensive intraoperative blood loss might impair the blood supply around the anastomosis, resulting in insufficient blood supply and further increasing the risk of anastomotic leakage. On the other hand, decreased hemoglobin resulting from extensive blood loss weakens oxygen-carrying capacity, thereby causing anastomotic leakage. Three previous studies<sup>1,6,10</sup> reported that longer operation duration and combined organ resection, namely splenectomy or pancreatectomy, were associated with anastomotic leakage, increasing the morbidity risk. However, the present study failed to reach this conclusion, and the main reason may lie in staff experience and the use of optimized mechanical devices, which make the surgery faster and more secure, ultimately decreasing the incidence of anastomotic leakage. Recently, neoadjuvant chemotherapy has been used more frequently in the treatment of advanced gastric cancer. However, only one patient (1/78) who received neoadjuvant chemotherapy developed EJAL after surgery, in this study, and the result was not statistically significant. This finding was consistent with those of Deguchi et al.,<sup>6</sup> therefore, neoadjuvant chemotherapy might not be a risk factor for EJAL.

One of the most important findings of this study was identifying alcohol consumption as an independent risk factor for EJAL in patients undergoing surgery for gastric cancer. However, several limitations should also be considered. First, the



incidence of EJAL was much lower (2.6%) than in most previous studies, which might have hindered discovering more risk factors for EJAL in this study, such as gender, combined organ resection, and other tumor-related variables. Second, patient selection bias and difficulty collecting data were also inevitable owing to this study's retrospective design. Third, no survival analysis was performed owing to inadequate 5-year follow-up data available for analysis, which was also a limitation, in this study. However, research involving survival analysis is ongoing in our unit and will also be reported in the future.

## Conclusions

Although postoperative anastomotic leakage is associated with a high mortality rate, this complication is controllable. Perioperatively, surgeons should pay attention to the risk of anastomotic leakage after gastric surgery, especially in older patients (>65 years) and in patients with a history of alcohol consumption of >2 U/day. Pulmonary insufficiency and intraoperative blood loss  $\geq 200$  mL, although not identified as independent risk factors in the present study, also deserve attention.

## Declaration of conflicting interest


The authors declare that there is no conflict of interest.


## Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (81672439, 81450028, 81272766, 81470129, 81402346), Beijing Natural Science Foundation (7162039, 7132054, 7172042), Beijing Health System High-level Health Technical Personnel Training Program (20153-074), Capitals Funds for Health Improvement and Research (CFH 20182-2153),

and the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (XM201309, ZYLX201701).

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