Risk Factors for Anastomotic Leakage: A Retrospective Cohort Study in a Single Gastric Surgical Unit

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Purpose: Although several studies report risk factors for anastomotic leakage after gastrectomy for gastric cancer, they have yielded conflicting results. The present retrospective cohort study was performed to identify risk factors that are consistently associated with anastomotic leakage after gastrectomy for stomach cancer.

Materials and Methods: All consecutive patients who underwent gastrectomy at a single gastric surgical unit between May 2003 and December 2012 were identified retrospectively. The associations between anastomotic leakage and 23 variables related to patient history, diagnosis, and surgery were assessed and analyzed with logistic regression.

Results: In total, 3,827 patients were included. The rate of anastomotic leakage was 1.88% (72/3,827). Multiple regression analysis showed that male sex (P=0.001), preoperative/intraoperative transfusion (P<0.001), presence of cardiovascular disease (P=0.023), and tumor location (P<0.001) were predictive of anastomotic leakage. Patients with and without leakage did not differ significantly in terms of their 5-year survival: 97.6 vs. 109.5 months (P=0.076).

Conclusions: Male sex, cardiovascular disease, perioperative transfusion, and tumor location in the upper third of the stomach were associated with an increased risk of anastomotic leakage. Although several studies have reported that an anastomotic complication has a negative impact on long-term survival, this association was not observed in the present study.

Key Words: Stomach neoplasms; Gastrectomy; Complication; Anastomotic leak

Introduction

Stomach cancer is the fourth most common cancer and, the second most common cause of cancer-related death worldwide after lung cancer.[1] Although the strategies used to treat stomach cancer depend on its oncological stage, surgical resection is generally considered the first choice of treatment.[2] Recently, minimally invasive surgery such as laparoscopy-assisted or robotic-assisted gastrectomy has become a common procedure for stomach cancer.[3,4] Numerous studies have assessed the oncological outcomes and complications of both open and laparoscopic gastrectomy.[5-8]

Of the various postoperative complications that are associated with gastrectomy, a particularly detrimental one is anastomotic leakage.[9,10] This complication not only has immediate clinical consequences and increases postoperative mortality, but it can also affect the long-term outcomes.[11-13] Anastomotic leakage has been reported to occur in 1% to 6% of patients undergoing gastrectomy.[5,10,14-17] While several studies have identified risk factors for anastomotic leakage, they have yielded inconsistent results. Furthermore, these studies have only examined the risk factors associated with a single gastrectomy method and were focused on the negative impact of anastomotic leakage.

Since identifying risk factors that are associated consistently

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with anastomotic leakage after gastrectomy would promote the development and implementation of preventive measures, this retrospective cohort study was performed. Its aims were to determine the anastomotic leakage rates in a single gastric surgical unit and to identify the preoperative and intraoperative risk factors.

Materials and Methods

1. Patients

All consecutive patients who underwent gastric resection for cancer between May 2003 and December 2012 at a single, stomach surgical unit at Seoul National University Bundang Hospital, Korea were identified through a retrospective search of the medical database. Patients who underwent palliative gastrostomy or a bypass procedure were excluded from the study. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (IRB No: B-1411-274-101).

2. Study variables

All patients underwent surgery performed by the same surgical team. Patient demographic characteristics were recorded along with the following clinical, surgical, and pathological characteristics: the operators of the surgical team (A, B, or C), presence of cardiovascular or pulmonary disease, history of diabetes, American Society of Anesthesiologists (ASA) score, Charlson comorbidity score, smoking habit, history of previous laparotomy, preoperative blood tests, tumor location, intraoperative blood loss, surgical approach (open, laparoscopy-assisted, or conversion to open), pre/intraoperative blood transfusion, duration of operation, combined organ resection, type of resection, type of reconstruction, presence of proximal or distal margin involvement, numbers of harvested lymph nodes, TNM stage, and time to first flatus. Patients with and without anastomotic leakage were compared in terms of these clinicopathological and surgical factors.

3. Definition of anastomotic leakage

Clinical signs of anastomotic leakage included abdominal pain, fever, pus or complicated discharge from the abdominal drain catheter, and peritonitis. Clinical suspicion of leakage was documented reoperation or confirmed by a radiographic examination demonstrating contrast leakage from a viscus into a body cavity.

4. Statistical analysis

The association of leakage with independent variables was examined by performing univariate analysis. Some continuous variables were converted into dichotomous variables, namely, age (<60 vs. ≥ 60 years), body mass index (BMI; <25, ≥ 25 and <30, ≥ 30), ASA grade (<3 vs. ≥ 3), Charlson comorbidity score (<3 vs. ≥ 3), blood loss (<500 vs. ≥ 500 ml), and duration of operation (≤ 300 vs. >300 minutes). Continuous variables were analyzed by using the Mann-Whitney U-test. Categorical variables were analyzed by using the chi-squared test or Kruskal-Wallis test. Survival interval was measured from the date of gastrectomy to the date of death. Survival data were analyzed by using the Kaplan-Meier method, and the log-rank test was used to detect differences between patients with and without anastomotic leakage in terms of cancer-related deaths. All variables with $P<0.05$ in the univariate analyses were included in the multivariate analysis; $P<0.05$ was considered to indicate statistical significance. Patient groups were compared in terms of categorical variables by using binary logistical regression. All statistical analyses were performed by using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA).

Results

In total, 4,219 patients underwent gastrectomy for stomach cancer during the study period. Of these, 392 were excluded because patients underwent palliative gastrostomy (n=152) or a bypass procedure (n=240). The remaining 3,827 patients were included in the study. Table 1 shows the clinicopathological and operative characteristics of these patients.

1. Risk factors for anastomotic leakage after gastrectomy

In total, 72 patients had an anastomotic leakage. Thus, the leakage rate was 1.88%. Table 2 shows details of anastomotic leakage sites. Among them, 10 patients underwent reoperation and 62 had percutaneous drainage and conservative management. Mean hospital stay of patients with anastomotic leakage was 15.8 days (9~33 days) and there was no in-hospital mortality. The variables that achieved statistical significance by univariate analyses were sex (P=0.001), presence of cardiovascular disease (P=0.046) and diabetes (P=0.011), history of previous laparotomy (P=0.045), tumor location (P<0.001), time to first flatus (P=0.014), intraoperative blood loss (P=0.001), pre/intra-

Table 1. Clinicopathological and operative characteristics of the 3,827 patients who underwent gastrectomy

Variable	Number (%)
Age (yr)	
<60	1,722 (45.0)
≥60	2,105 (55.0)
Sex	
Male	2,602 (68.0)
Female	1,225 (32.0)
Body mass index, (kg/m^2)	
<25	2,683 (70.1)
≥25 and <30	1,045 (27.3)
≥30	99 (2.6)
Cardiovascular disease	
Absent	2,886 (75.4)
Present	941 (24.6)
Diabetes	
Absent	3,435 (89.8)
Present	392 (10.2)
Pulmonary disease	
Absent	3,776 (98.7)
Present	40 (1.0)
ASA score	
<3	3,476 (90.8)
≥3	351 (9.2)
Charlson comorbidity score	
<3	2,507 (65.5)
≥3	1,320 (34.5)
Smoking habits	
Non-smoker	2,475 (64.7)
Smoker	711 (18.6)
Ex-smoker	641 (16.7)
Previous laparotomy	
Absent	3,248 (84.9)
Present	578 (15.1)
Preoperative blood results	
Anemia*	982 (25.7)
Leukocytosis[†]	227 (5.9)
Hypoalbuminemia[‡]	467 (12.2)
Tumor location	
Upper third stomach	733 (19.2)
Middle third stomach	1,013 (26.5)
Lower third stomach	1,935 (50.6)
Entire stomach	81 (2.1)
T stage	
T1	2,099 (54.9)
T2	444 (11.6)
T3	626 (16.4)
T4	644 (16.8)

Table 1. Continued

Variable	Number (%)
N stage	
N0	2,298 (60.1)
N1	482 (12.6)
N2	369 (9.6)
N3	671 (17.5)
Stage	
I	2,249 (58.8)
II	579 (15.1)
III	875 (22.9)
IV	113 (3.0)
Blood loss (ml)	
≤500	3,722 (97.3)
>500	105 (2.7)
Laparoscopy-assisted	
Open	1,343 (35.1)
Laparoscopy-assisted	2,367 (61.9)
Conversion to open	117 (3.1)
Preoperative/intraoperative blood transfusion	
No	3,427 (89.6)
Yes	400 (10.5)
Duration of operation (min)	
≤300	3,616 (94.5)
>300	211 (5.5)
Combined organ resection	
Not performed	3,420 (89.4)
Performed	
Single	331 (8.6)
Multiple	76 (2.0)
Type of resection	
Distal gastrectomy	2,913 (76.1)
Total gastrectomy	752 (19.6)
Proximal gastrectomy	162 (4.2)
Type of reconstruction	
Billroth I	1,798 (47.0)
Billroth II	272 (7.1)
Roux-en-Y gastrojejunostomy	843 (22.0)
Roux-en-Y esophagojejunostomy	752 (19.7)
Esophagogastrostomy	71 (1.9)
Double tract reconstruction (after proximal gastrectomy)	91 (2.4)

Tumor stages are based on the TNM classification system from the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer. ASA = American Society of Anesthesiologists. *Anemia is defined as blood hemoglobin concentration <12 g/dl in females or <13 g/dl in males. [†]Leukocytosis is defined as white blood cell >10,000/μl. [‡]Hypoalbuminemia is defined as serum albumin <3.5 g/dl.

operative blood transfusion (P<0.001), duration of operation (P=0.04), combined organ resection (P<0.001), type of resection (P<0.001), and type of reconstruction (P=0.003).

Multiple regression analysis revealed that sex (P=0.001), presence of cardiovascular disease (P=0.023), tumor location (P=0.001), and pre/intraoperative transfusion (P=0.001) were independent risk factors for the occurrence of anastomotic leakage. Table 3 lists the odds ratios, 95% confidence intervals, and P-values for the variables that achieved statistical significance after being entered into the multivariate logistic regression model.

The rate of anastomotic leakage was similar for patients who underwent laparoscopic gastrectomy and those who underwent open gastrectomy (P=0.517).

2. Association between anastomotic leakage and cancer-related survival

The median follow-up time was 58.5 months (range: 0~136.0 months). In total, 21 patients (29.2%) with anastomotic leakage died, compared with 777 patients (20.7%) without leakage (P=0.082). The patients with and without leakage did not differ significantly in terms of overall mean survival: 97.6 vs. 109.5 months (P=0.076).

Table 4 summarizes the results of the univariate and multivariate survival analyses. The univariate analyses showed that the presence of anastomotic leakage was not associated significantly with cancer-related death (P=0.624). Multivariable analyses revealed that an age ≥60 years, Charlson comorbidity score ≥3, tumor location in the upper third of the stomach, preoperative leukocytosis, preoperative hypoalbuminemia, proximal or distal margin involvement, T stage, and M stage were independent prognostic factors for gastric cancer-related death.

Discussion

The overall anastomotic leakage rate of 1.88% observed in this study is similar to other reported anastomotic leakage rates ranging from 1.0% to 4.2%.[5,10,14-17]

The present study revealed that male sex was a risk factor for anastomotic leakage: men were 4.2 times more likely to develop anastomotic leakage than women (P=0.001). Several studies on

Table 2. Anastomotic leakage site

Anastomotic leakage site	Number (%)
Esophagojejunostomy	26 (36.1)
Gastroduodenostomy	20 (27.8)
Duodenal stump	14 (19.4)
Gastrojejunostomy	5 (6.9)
Jejunojejunostomy	7 (9.7)
Total	72 (100.0)

Table 3. Multivariate analysis to identify clinicopathological and operative variables that are associated with an anastomotic leakage

Variable	Total	No leakage	Leakage	Odds ratio	95% CI	P-value
Sex						0.001
Female	1,225 (32.0)	1,216 (32.4)	9 (12.5)	1		
Male	2,602 (68.0)	2,539 (67.6)	63 (87.5)	4.289	1.941~9.477	
Cardiovascular disease						0.023
Absent	2,886 (75.4)	2,828 (75.6)	58 (80.6)	1		
Present	941 (24.6)	927 (24.4)	14 (19.4)	1.826	1.088~3.067	
Tumor location						<0.001
Lower third stomach	1,935 (50.6)	1,908 (51.7)	27 (37.5)	1		
Middle third stomach	1,013 (26.5)	1,003 (27.2)	10 (13.9)	0.705	0.340~1.461	
Upper third stomach	733 (19.2)	702 (19.0)	31 (43.1)	3.121	1.849~5.265	
Entire stomach	81 (2.1)	77 (2.1)	4 (5.6)	3.671	1.254~10.751	
Preoperative/intraoperative blood transfusion						<0.001
No	3,427 (89.6)	3,374 (89.9)	53 (73.6)	1		
Yes	400 (10.5)	381 (10.2)	19 (26.4)	2.775	1.597~4.824	

Values are presented as number (%). CI = confidence intervals.

Table 4. Univariate and multivariate analyses to identify clinicopathological and operative variables that are associated with overall survival

Variable	Number (%)	Univariate analysis		Multivariate analysis	
		Hazard ratio (OR, 95% CI)	P-value	Hazard ratio (OR, 95% CI)	P-value
Age (yr)			<0.001		<0.001
<60	1,722 (45.0)	1		1	
≥60	2,105 (55.0)	1.031 (1.024~1.039)		1.032 (1.025~1.039)	
Charlson comorbidity score			<0.001		<0.001
<3	2,507 (65.5)	1		1	
≥3	1,320 (34.5)	1.430 (1.182~2.498)		1.221 (1.159~1.286)	
Preoperative blood results					
Leukocytosis*	227 (5.9)	1.429 (1.101~1.855)	0.022	1.320 (1.025~1.700)	0.032
Hypoalbuminemia†	467 (12.2)	1.485 (1.231~1.793)	<0.001	1.543 (1.287~1.850)	<0.001
Tumor location			0.039		<0.001
Lower third of stomach	1,935 (50.6)	1		1	
Middle third of stomach	1,013 (26.5)	0.875 (0.621~1.017)		0.716 (0.528~1.052)	
Upper third of stomach	733 (19.2)	2.110 (1.324~3.234)		2.058 (1.298~3.363)	
Entire stomach	81 (2.1)	2.324 (1.549~6.231)		2.208 (1.429~5.328)	
Distal margin involved	41 (1.1)	2.591 (1.751~3.835)	<0.001	2.292 (1.561~3.365)	<0.001
Proximal margin involved	35 (0.9)	2.147 (1.357~3.399)	<0.001	2.298 (1.475~3.581)	<0.001
TNM stage			<0.001		<0.001
IA	1,837 (47.7)	1		1	
IB	412 (10.8)	1.650 (1.160~2.348)		1.525 (1.021~2.194)	
IIA	344 (9.0)	2.831 (2.070~3.871)		2.730 (1.938~3.483)	
IIB	235 (6.1)	4.213 (3.070~5.783)		4.028 (2.839~4.827)	
IIIA	232 (6.1)	3.994 (2.887~5.525)		3.520 (2.539~5.239)	
IIIB	293 (7.7)	9.750 (7.608~12.494)		9.540 (7.209~10.823)	
IIIC	350 (9.2)	19.599 (15.683~24.493)		17.238 (13.238~18.223)	
IV	113 (3.0)	28.920 (22.000~38.017)		24.235 (19.232~34.028)	
Laparoscopic assisted			<0.001		<0.001
Open	1,343 (35.1)	1		1	
Laparoscopic assisted	2,367 (61.9)	0.616 (0.502~0.754)		0.672 (0.552~0.820)	
Open conversion	117 (3.1)	1.042 (0.743~1.461)		1.197 (0.863~1.662)	
Operative duration (min)			0.010		0.006
≤300	3,616 (94.5)	1		1	
>300	211 (5.5)	1.168 (0.808~1.68)		1.467 (1.114~1.933)	
Anastomotic leakage			0.624		
No	3,755 (98.1)	1			
Yes	72 (1.9)	0.813 (0.506~1.307)			

Values are presented as number (%). Tumor stages are based on the TNM classification system from the 7th edition of the Union for International Cancer Control/American Joint Committee on Cancer. Univariate P-values were obtained by Mann-Whitney U-test, the chi-squared test or the Kruskal-Wallis test. OR = odds ratio; CI = confidence interval. *Leukocytosis is defined as white blood cell >10,000/μl. †Hypoalbuminemia is defined as serum albumin <3.5 g/dl.

colorectal surgery have also shown that men have higher rates of anastomotic leakage than women.[18-20] Similarly, the study by Kim et al.[15] on stomach surgery found that men were more likely to have anastomotic leakage. However, several other studies on anastomotic leakage after gastrectomy have failed to demonstrate statistically significant associations between sex and anastomotic leakage.[7,12,13] The reason for this disparity between Kim et al.[15]'s study and our study compared to others is unclear. While it is not apparent why men may be more susceptible to anastomotic leakage, the study by Kunisaki et al.[21] suggests that it could relate to the tendency of men to have large visceral fat areas (VFAs). They found that large VFAs are associated with intraoperative and postoperative complications in laparoscopic-assisted distal gastrectomy for gastric cancer. We could not assess this association in our study because the VFAs of our patients were not recorded. Although BMI is related to VFA, we did not find that BMI was associated significantly with anastomotic leakage (P=0.434).

The present study also showed that preoperative or intraoperative transfusion was a risk factor for anastomotic leakage. The decision to provide intraoperative blood transfusion is largely determined by preexisting anemia and by the volume of blood lost during the operation. An association between perioperative transfusion and anastomotic leakage has not been reported previously, although several studies have shown that intraoperative blood loss increases the risk of peritoneal recurrence after curative resection for gastric cancer[22] and decreases the long-term survival of patients who undergo surgery for colon cancer.[23] Several studies have also revealed that perioperative transfusion is associated with a poor cancer prognosis.[24-26] The reason for the association between perioperative transfusion and anastomotic leakage that we observed is not clear, but it is likely related to the high intraoperative blood loss in these patients. For the 400 patients who underwent a transfusion in the perioperative period, the average intraoperative blood loss was 262±13.11 ml, whereas that of the remaining 3,427 patients was 110±1.88 ml. This difference was statistically significant (P=0.001). While this difference did not remain significant on multivariate analysis, perioperative transfusion was associated significantly with anastomosis leakage on multivariate analysis (P<0.001): the patients who received a blood transfusion in the perioperative period had a 2.775-fold higher risk of anastomotic leakage than the untransfused patients. Several studies report that transfusion causes a variety of hematological or immunological complications.[25,27]

However, it seems unlikely that the association between perioperative transfusion and anastomotic leakage was due to these transfusion-related complications.

The present study also revealed that tumor location in the upper third of the stomach was a risk factor for anastomotic leakage. This may reflect the fact that esophagojejunostomy leakage was the most common leakage in the study; it accounted for 24.1% of the leakages. When the tumor is located in the upper third of the stomach, resection of the tumor must be followed by esophagojejunostomy, regardless of whether open surgery or a laparoscopic procedure is being performed. Several studies have shown that esophagojejunostomy is a technically difficult and complex procedure and new techniques to prevent esophagojejunostomy leakage have been suggested.[17,28-31] Thus, the association between anastomotic leakage and tumor location probably relates to the difficulty of the esophagojejunostomy procedure.

Several investigators have discussed how to prevent and manage esophagojejunostomy leakage.[32-34]

In our multivariate analysis, the presence of cardiovascular disease (hypertension or coronary artery disease) remained as an independent risk factor for anastomotic leakage (odds ratio 1.826, P=0.023). Similarly, Jeong et al.[35] reported that patients with heart or liver disease have higher morbidity rates after gastric surgery than patients without these comorbidities. Kim et al.[36] also reported that comorbidity has a negative impact on the surgical outcomes of laparoscopy-assisted distal gastrectomy. In our study, although we assessed the association between anastomotic leakage and several comorbidities and the Charlson comorbidity index, none showed a statistically significant association except for cardiovascular disease. This association may reflect the importance of adequate microcirculation to the anastomotic site for healing and the fact that patients with risk factors such as cardiovascular disease have insufficient microcirculation.[37]

Several other reported risk factors for anastomotic leakage include prolonged operating time, pulmonary insufficiency, chronic renal failure, and procedure type.[17,30] However, the present study did not find that these variables were statistically significant risk factors. Similarly, although several studies found that obese patients have higher risks of anastomotic leakage,[38,39] a statistically significant association between anastomotic leakage and BMI was not detected in our study. Nevertheless, it cannot be concluded as yet that these variables are not true risk factors of anastomotic leakage.
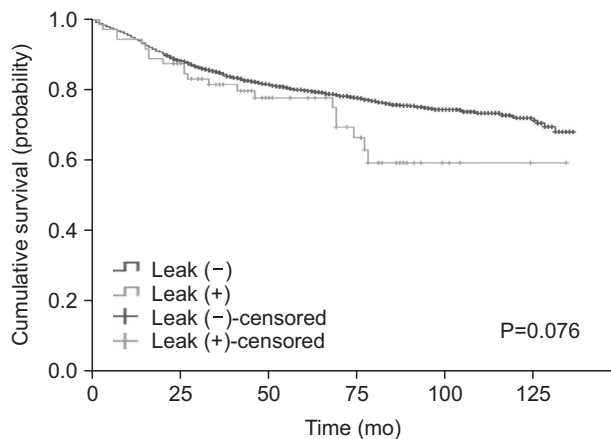
Fig. 1. Kaplan-Meier curve presenting the overall survival rate.

Nagasako et al.[40] reported that anastomotic complications have a negative impact on long-term survival: the hazard ratio for anastomotic complication regarding overall survival was 2.45 (P=0.009). Similarly, Sierzega et al.[11] and Yoo et al.[12] reported that anastomotic leakage is an independent risk factor for a worse survival rate; they reported hazard ratios of 3.47 and 3.58, respectively. However, in our study, anastomotic leakage was not associated significantly with decreased survival, even when we stratified patients according to their pathological stage and performed multivariate analysis (Fig. 1).

Being a retrospective analysis, the present study has several limitations. First, although most of our data was originally collected at the time of the patient's initial treatment, several characteristics were examined retrospectively at the time of this study. Second, the relatively low anastomotic leakage rate made the statistical analysis very sensitive. Indeed, when we used the random sampling method, different results were obtained. Third, we could not analyze immeasurable factors such as tension on the suture line, blood supply, and technical error that can be associated with anastomotic leakage. Furthermore, the definition of cardiovascular disease in our study was too broad, and intake history of anticoagulant was not analyzed. These limitations could yield biased results.

In conclusion, the identification of risk factors for anastomotic leakage may help to change techniques and preoperative management. Although the exact mechanism by which anastomotic leakage occurs is unknown, it is important to understand the clinicopathological and operative factors that may promote the development of this complication. To determine which variables consistently act as risk factors for anastomosis leakage after resection for gastric cancer, further studies should be conducted.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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