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Risk factors and laboratory markers used to predict leakage in esophagojejunal anastomotic leakage after total gastrectomy

Durmuş Ali Çetin[1], Ebubekir Gündeş[2], Hüseyin Çiyiltepe[3], Ulaş Aday[4], Orhan Uzun[5], Kamuran Cumhur Değer[5], Mustafa Duman[5]

ABSTRACT

Objective: Esophagojejunal anastomotic leakages, which occur in the reconstruction procedures performed after total or proximal gastrectomy, still account for one of the most significant causes of morbidity and mortality in spite of the developments seen in the perioperative management and surgical techniques in gastric cancer surgery. The aim of the presentstudy was to ascertain the risk factors for Esophagojejunal anastomotic leakages.

Materialand methods: A total of 80 patients with gastric cancer, who had total gastrectomy + D2 lymph node dissection and Esophagojejunal anastomotic between January 2013 and December 2016, were retrospectively evaluated. Patients who did not have anastomotic leakages during their clinical follow-ups were allocated to Group 1, whereasthose who had anastomotic leakages were allocated to Group 2.

Results: A total of 58 (72.5%) out of 80 patients were males, whereas 22 (27.5%) were females.The mean age of the patients was 61.2±11.2 years. There were no demographic differences between the groups. Postoperative recurrent fever (p=0.001), C-reactive protein values on postoperative days 3 and 5 (p=0.01), and neutrophil-to-lymphocyte ratio on postoperative day 5 (p=0.022) were found to be statistically significant with regardto Esophagojejunal anastomotic leakages and other postoperative complications. The duration of operation (p=0.032) and combined organ resection (p=0.008) were ascertained as risk factors for Esophagojejunal anastomotic leakages.

Conclusion: Surgeons should be careful about Esophagojejunal anastomotic leakages thatare significant postoperative complications seen especially in cases where the duration of operation is prolonged, and additional organ resections are performed. Recurrent fever, high C-reactive protein levels, and neutrophil-to-lymphocyte ratio may serve as warnings for complications in postoperative follow-ups.

Keywords: Anastomosis leakage, gastrectomy, risk factors

ORCID ID of the author:
D.A.Ç. 0000-0003-3012-6774;
E.G. 0000-0001-7944-8681;
H.Ç. 0000-0003-3048-1784;
U.A. 0000-0002-3161-0923;
O.U. 0000-0001-6550-0936;
K.C.D. 0000-0003-4083-3448;
M.D. 0000-0002-0276-0543.

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[1]Department of Gastroenterological Surgery, Şanlıurfa Training and Research Hospital, Şanlıurfa, Turkey
[2]Department of Gastroenterological Surgery, Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey
[3]Department of Gastroenterological Surgery, Fatih Sultan Mehmet Training and Research Hospital, İstanbul, Turkey
[4]Department of Gastroenterological Surgery, Elazığ Training and Research Hospital, Elazığ, Turkey
[5]Department of Gastroenterological Surgery, Kartal Koşuyolu High Speciality Training and Research Hospital, İstanbul, Turkey

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Corresponding Author
Durmuş Ali Çetin
e-mail: drdurmusalicetin@gmail.com

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INTRODUCTION

Surgical treatment focuses on the balance between risk and reward. The most important components of postoperative care include predicting the possible secondary problems regarding the procedure, preventing these problems, noticing them early on, and rightly performing the appropriate intervention for treatment on time. In spite of all these, complications may not always be prevented. As long as surgical procedures are performed, surgeons will have to deal with complications as well. Therefore, it is inevitable that novel findings and information on this issue will accumulate, and novel perspectives will develop in modern practices. Anastomotic leakages still prove to be a major problem for surgeons although many studies have been conducted on the issue.

Anastomotic leakage is one of the most significant complications of postoperative gastric surgery and has a high rate of morbidity and mortality (1, 2). Securing a safe and sound esophagojejunal anastomotic (EJA) after total gastrectomy is one of the most important problems of gastric surgeons. The incidence of EJA leakages has decreased with experiences achieved during the learning curve and the common use of mechanical stapler tools (3). It is, however, still challenging to completely prevent anastomotic leakage, and the incidence of EJA leakages has been reported to be between 1% and 11% (3-11).

The aim of the present study was to ascertain the risk factors for EJA leakage in patients who had total gastrectomy +D2 lymph node dissection due to gastric cancer and to unveil the presence of biochemical markers that could be utilized to predict them before they clinically developed.

MATERIAL AND METHODS

Patients

A total of 80 patients with gastric cancer, who had total gastrectomy +D2 lymph node dissection and EJA between January 2013 and December 2016 at Kartal Koşuyolu Higher Specialty Training and Research Hospital's Gastroenterology Surgery Clinic, were retrospectively evaluated. The study was approved by the ethics committee of Kartal Koşuyolu Higher Specialty Training and Research Hospital

Table 1. Demographic features and preoperative laboratory results of patients

Variable		Anastomosis leakage (–) n: 67	Anastomosis leakage (+) n: 13	p
Gender#	Male	48 (60)	10 (12.5)	0.696
	Female	19 (23.8)	3 (3.8)	
Age* (year)		61±12	65±9	0.161
ASA#	1	10(14.9)	1(7.7)	0.612
	2	27(40.3)	7(53.8)	
	3	30(44.8)	5 (38.5)	
Comorbidities#	HT Yes	17 (25.4)	3 (23.1)	0.861
	No	50 (74.6)	10 (76.9)	
	DM Yes	15 (22.4)	2 (15.4)	0.572
	No	52 (77.6)	11 (84.6)	
	COPD Yes	13 (19.4)	1 (7.7)	0.309
	No	54 (80.6)	12 (92.3)	
	CRF Yes	1 (1.5)	0	0.658
	No	66 (98.5)	13 (100)	
	CAD Yes	7 (10.4)	3 (23.1)	0.208
	No	60 (89.6)	10 (76.9)	
History of smoking#	Yes	21 (31.3)	4 (30.8)	0.967
	No	46 (68.7)	9 (69.2)	
Weight loss#	Yes	30 (44.8)	6 (46.2)	0.927
	No	37 (55.2)	7 (53.8)	
BMI* (kg/m^2)		27±4.5	28±3.2	0.480
LVEF*		61±9	63±9	0.393
Pulmonary function test*	FEV1	97±17	91±22	0.318
	FVC	97±14	88±21	0.1
Preoperative laboratory results*	Hematocrit	35.7±5.5	37.6±4.7	0.249
	Albumin	3.9±0.5	3.9±0.5	0.970
	Creatinine	0.94±0.4	0.76±0.2	0.750

ASA: American Society of Anesthesiologists; HT: hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; CAD: coronary artery disease; BMI, body mass index; LVEF: left ventricular ejection fraction; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; SD: standard deviation
Datas are presented as *: mean±standard deviation, #: n (%)

(no. 2017.3/2-36). Informed consent was obtained from each patient for surgical intervention prior to surgery.

Patients who had immunosuppressive treatment; who had inflammatory diseases; who received neoadjuvant treatment; who had D1 lymph node dissection; who had surgical procedures due to gastrointestinal stromal tumor, gastric lymphoma, and other gastric tumors; who had palliative surgeries; and who had missing data in their files were excluded from the study.

All patients had oral intravenous contrasted thoracoabdominal computed tomography (CT) and positron emission tomography in suspected cases prior to surgical procedures. All patients for whom a surgical procedure was planned were started on preoperative enteral feeding. Feeding was reinitiated on postoperative day 1 through intraoperative nasojejunal catheters. Curative resection was performed for those patients without distant organ metastasis or major vascular invasion. Patients who did not have anastomotic leakages during their clinical follow-ups formed Group 1, whereas those who had anastomotic leakages formed Group 2.

Surgical technique

All patients received total gastrectomy +D2 lymph node dissection and omentectomy. The intestinal reconstruction was performed in the form of Roux-en-Y esophagojejunostomy. EJA was performed by a circular stapler ILS (Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA) in the form of end-to-side in all cases. The size of the stapler was determined based on the diameter of the esophagus of the patient and the judgment of the surgical team. A 25 mm stapler was generally used for patients with normal sized esophagus. Wider staplers (28–29

Table 2. Intraoperative and pathological data of patients

Variable		Anastomosis leakage (–) n: 67	Anastomosis leakage (+) n: 13	p
T stage#	T1	6 (9)	0	0.148
	T2	5 (.5)	0	
	T3	25 (37.3)	9 (69.2)	
	T4	31 (46.3)	4 (30.8)	
N stage#	N0	20 (29.9)	3 (23.1)	0.895
	N1	10 (14.9)	2 (15.4)	
	N2	18 (26.9)	3 (23.1)	
	N3	19 (28.4)	5 (38.5)	
No. of harvested lymph nodes*		26±11	29±14	0.603
No. of harvested metastatic lymph nodes*		5±8	5±6	0.587
Combined organ resection#	Yes	10 (14.9)	7 (53.8)	0.002
	No	57 (85.1)	6 (46.2)	
Duration of operation(min)#	<300	32 (47.8)	1 (7.7)	0.007
	≥300	35 (52.2)	12 (92.3)	
Intraoperative blood transfusion#	Yes	13 (19.4)	1 (7.7)	0.309
	No	54 (80.6)	12 (92.3)	

Datas are presented as *: mean±standard deviation, #: n (%)

Table 3. Multivariate analysis of the intraoperative findings of patients.

Variable	p	OR	95% CI
Combined organ resection	0.008*	6.329	0.040-0.623
Duration of operation(min)	0.032*	10.416	0.011-0.820

OR: odds ratio; CI: confidence interval
*Statistically significant at p<0.05

mm) were used for patients with a wider esophagus. The circle, which was removed after the anastomosis was completed, was immediately controlled in all cases. Additional organ resection was performed for patients with intraoperative organ invasion and/or iatrogenic additional organ injury (spleen, pancreas, colon, and liver).

Diagnosis of EJA leakage

Diagnosis of anastomotic leakage was predicted upon clinical and radiological results. Radiological leakage was defined as extravasation outside the lumen seen under endoscopy during the drinking of water-soluble contrast agent (WSCA), observation of the drank contrast agent outside the lumen in CT, determination of abscess with air collection at anastomotic neighboring, detection of defects at the anastomotic line, and observation of defects in the anastomosis as revealed by endoscopic assessment. Clinical leakage was defined as the leak of intestinal and/or purulent content from the surgical incision or drains, fever, deteriorating abdominal pain, increase in C-reactive protein (CRP) and leukocyte levels, and determination of leakage during relaparotomy for abdominal sepsis. The radiological imaging performed after WSCA was performed routinely for all patients.

Data

Data on age, sex, body mass index (BMI), left ventricular ejection fraction, respiratory function parameters (forced expiratory volume (FEV) and forced vital capacity (FVC)), preoperative albumin and peripheral blood results, durations of surgical procedures, presence or absence of additional organ resection, need for intraoperative blood transfusion, duration of hospitalization, postoperative clinical characteristics, and CRP and all blood values were recorded. Recurrent fever was defined as fever that lasted for at least 3 days and was over 38 °C.

Echocardiography was performed by a 2.5 MHz probe in the left lateral decubitus position. Ejection fraction was calculated according to the modified Simpson method.

The height (cm) and body weight (kg) of all patients were used to calculate their BMI for spirometric calculations. Each patient was asked to perform forced expiration after deep inspiration in a sitting position. Calculations were conducted by a dry spirometer tool according to the recommendations of the American Thoracic Society (ATS) (12). The best calculation out of three conducted for each case was recorded. FVC and FEV in one second (FEV1) were recorded within the scope of spirometric measurements. Expected values were assessed according to the ATS criteria (12).

Peripheral blood samples were extracted to determine hematocrit, leukocyte, neutrophil, lymphocyte, and platelet counts. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the number of neutrophils by the number of lymphocytes, whereas the platelet-to-lymphocyte ratio was calculated by dividing the number of platelets by the number of lymphocytes.

Table 4. Laboratory results and fever values in the postoperative period

Variable		No Complication (n: 46)	Anastomosis leakage (+) (n: 13)	Another Complicationa (n: 21)	p
CRP* (mg/dL)	Po day 1	6.8±2.4	9.8±3.9	9.9±8.8	0.201
	Po day 3	8.3±3.4	21.1±9.2	22.7±13.3	0.01
	Po day 5	8.8±4	17.4±7.2	10.7±5.3	0.01
WBC* (103/μL)	Po day 1	13.59±4.91	15.88±2.49	13.62±3.72	0.226
	Po day 3	8.8±3.11	12.02±3.79	9.87±5.93	0.077
	Po day 5	8.44±2.94	9.37±4.84	8.7±3.8	0.800
Neutrophil-to-lymphocyte ratio*	Po day 1	16.6±13.8	26.2±19.5	22.1±20.3	0.142
	Po day 3	11.2±7.8	16.7±13.5	9.7±7.7	0.146
	Po day 5	6.2±2.9	12.0±8.0	9.7±7.4	0.022
Platelet-to-lymphocyte ratio*	Po day 1	379.9±315.7	396.6±238.7	492.5±363.5	0.404
	Po day 3	290.8±132.1	303.4±221.5	344.9±274.2	0.682
	Po day 5	308.6±109.1	327.8±208.6	503.8±726.8	0.340
Fever#		16 (34.8)	7 (53.8)	12 (57.1)	0.168
Recurrent fever#		2 (4.3)	6 (46.2)	4 (19)	0.001

[a]Patients' postoperative complication without anastomosis leakage (surgical site infection, pneumonia, postoperative atelectasis, chylous leakage, evisceration, acute renal failure, and intra-abdominal bleeding)
[b]Postoperative body temperature over 38 °C in more than one measurement
Po: postoperative; CRP: C-reactive protein; WBC: white blood cell
Datas are presented as *: mean±standard deviation, #: n (%)

The duration of hospitalization was accepted to be the period from the day of surgical procedure to discharge, whereas in-hospital mortality was accepted to be the case of mortality seen during hospitalization or during the first 30 days following surgery. Postoperative complications were ranked according to the Clavien–Dindo Classification of surgical complications (13). Patients without anastomotic leakage but with postoperative complications were set as other complications. Postoperative other complications included surgical site infection, pneumonia, postoperative atelectasis, cheilosis leakage, evisceration, acute renal failure, and intra-abdominal hemorrhage. The American Joint Committee on Cancer classification system's seventh TNM staging was used for the histopathological staging of all cases (14).

Statistical Analysis

The Statistical Package for the Social Sciences software (SPSS Inc., Chicago, IL, USA) was used in all biostatistical analyses. Data from the study were expressed in mean figures, standard deviation values, and percentages as necessary. The Kolmogorov–Smirnov test was used to check the distribution of the collected data. The ANOVA test was utilized for the multiple group comparisons of normally distributed data, whereas the Student's t-test was used for binary group comparisons. The multiple group comparisons of non-parametric data were conducted through the Kruskal–Wallis analysis, whereas binary group comparisons were performed by the Mann–Whitney U test. The comparison of categorical groups was conducted by the chi-square test. Multivariate analysis was conducted for intraoperative results that were found to be statistically significant according to univariate analysis. The results were set at 95% confidence interval (CI). A $p<0.05$ was considered as statistically significant.

RESULTS

Of the 80 patients, 58 (72.5%) were males, whereas 22 (27.5%) were females. The mean age of the patients was 61.2±11.2 years. There were 67 (83.8%) patients in Group 1 with no EJA leakage findings during their clinical follow-ups, whereas 13 (16.2%) patients in Group 2 with EJA leakage. Both groups had similar demographic characteristics and preoperative laboratory results (Table 1).

When intraoperative findings and pathological results were investigated, it was ascertained that additional organ resection ($p=0.002$) and prolonged intraoperative time ($p=0.007$) significantly increased the rate of EJA leakage. It was seen that all patients with EJA leakage had T3 (69.2%) and T4 (30.8%) tumors, but no statistically significant difference was found. The total number of excised and the number of metastatic lymph nodes, the N stage of tumor, and intraoperative blood transfusion were not found to be statistically significant with regard to EJA leakage. Table 2 shows the intraoperative and pathological data of patients. The results of the multivariate analysis revealed that additional organ resection ($p=0.008$, odds ratio (OR) 6.329, 95% CI 0.040–0.623) and the duration of operation ($p=0.032$, OR 10.416, 95% CI 0.011–0.820) were independent risk factors for EJA leakage (Table 3).

Further, all patients were divided into three subgroups according to those with EJA leakage, those with postoperative complications other than anastomotic leakage, and those without. When data on these patients' postoperative fever and laboratory results up to postoperative day 5 were investigated, it was seen that 7 out of 13 patients with EJA leakage had fever, and 6 had recurrent fever. Of 21 patients, 12 had postoperative

complications, but no anastomotic leakage had fever, and 4 had recurrent fever. The rate of EJA leakage and postoperative complications in patients with postoperative recurrent fever was found to be significantly higher (p=0.01). When CRP values were assessed, it was observed that CRP values on postoperative days 3 and 5 were higher in patients with postoperative complications including EJA leakage than in those with no complications, and the difference was statistically significant (p=0.01). There was, however, no statistically significant difference with regard to CRP values between patients with EJA and those with postoperative complications other than anastomotic leakage. Moreover, when the patients were evaluated according to their NLR, it was seen that NLR on postoperative day 5 was significantly higher in the EJA leakage and other postoperative complications group (p=0.022). There was no statistically significant difference regarding NLR on postoperative days 1 and 3. Table 4 shows the patients' postoperative laboratory results and fever values.

The average duration from operation to the day on which the leakage was identified among 13 patients with EJA leakage was 6.3 (3–8) days. The average duration of hospitalization for patients with EJA leakage was 35±30 days, whereas it was 13±7 days for patients without EJA leakage. When the cases of patients with EJA leakage were ranked according to the modified Clavien–Dindo Classification of surgical complications, it was seen that 4 patients had grade 2, 4 patients had grade 3a, 2 patients had grade 3b, 2 patients had 4a, and 1 patient had grade 5 complications. Covered self-expandable metal stents were endoscopically placed in 2 out of 13 patients with EJA leakage. One (7.7%) patient with stent died due to multiorgan failure. Two patients needed reoperation. Five patients received radiological percutaneous drainage under local anesthesia due to intra-abdominal abscess. Four patients were treated conservatively.

DISCUSSION

It has been stated that the developments in surgical techniques and perioperative management decreased the rate of EJA leakage after total or proximal gastrectomy. The incidence of EJA leakage was reported to be between 1.0% and 11.5% (3-11). The rate of leakage reported by high-volume Japanese centers, however, was 1.0%–2.1% (2, 3, 5, 8). The Japanese National Clinical Database on digestive surgery reported that the incidence of anastomotic leakage after total gastrectomy in 2014 was 4.4% (881/20011) (15). Surgeons should be careful when forming an anastomosis in order to prevent this dangerous complication. Therefore, appropriate anastomosis techniques and a detailed observation of anastomosis are required in order to prevent this complication (11).

Esophagojejunal anastomotic leakage prolongs the duration of hospitalization while increasing the risk of reoperation. It, at the same time, may lead to a fatal result. Sierzega et al. (5) reported that postoperative mortality rates increase, whereas survival rates decrease in patients with EJA leakage after total gastrectomy. Migita et al. (11) also reported that the mortality rate is 1.8% in 327 patients. The authors stated that 3 out of 21 patients with EJA leakage died. Isozaki et al. (2) concluded that aggressive surgery for advanced stage gastric cancer increases the risk of anastomotic leakage as well. The results of our study, however, showed that 16.2% of the patients with EJA had anastomotic leakage, and this figure was higher than those reported in the literature. We believe that the reason why our EJA leakage rates were high is related to the fact that the majority of our patients had advanced stage tumors and received radical aggressive surgery. Although our leakage rate was high, our mortality rate was at an acceptable level at 1.2%.

Deguchi et al. (8) reported that pulmonary failure and the duration of operation are markers of EJA leakage in 1640 patients after total and proximal gastrectomy in their retrospective study. In our study, the duration of operation was markedly longer in the EJA leakage group than in the group with no leakage, and it was found to be statistically significant by both univariate and multivariate analyses. Various studies have also reported that prolonged duration of operation is related to morbidity after gastrectomy (16-18).

Many factors affect prolonged duration of operation. Complicated surgical procedures result in longer duration of operation and increase the risk of morbidity (19). Procedural duration is generally prolonged in advanced tumor cases, but it does not always lead to EJA leakage. Some studies have also reported that patients' risk of postoperative complications related to additional organ resections including splenectomy or pancreatectomy is higher (20, 21). Deguchi et al. (8) found that the effects of additional organ resection on EJA leakage are statistically significant as revealed by univariate analysis. They, however, reported that the results of their multivariate analysis reveal that it does not have a determinant role on EJA leakage.

Migita et al. (11) reported that chronic renal failure, proximal gastrectomy, high levels of hemoglobin A1c, and problems seen in anastomoses during EJA construction are independent risk factors for EJA leakage, whereas combined additional organ resection is not related to EJA leakage in 327 patients. The results of our study, however, showed that additional organ resection was statistically significant.

Kiudelis et al. (22) ascertained that a 4-day average body temperature, leukocyte levels, and CRP levels during the early postoperative period are considerably related to anastomotic leakage as revealed by univariate analysis in 175 patients. The results of our study also demonstrated that the rates of EJA leakage and postoperative complications were significantly higher in patients with recurrent fever in the postoperative period (p=0.01). When CRP values were investigated, it was seen that the CRP values on postoperative days 3 and 5 were higher in patients with postoperative complications including EJA leakage than in those without complications, and the difference between the two groups was statistically significant (p=0.01). When the patients were assessed with regard to NLR, it was observed that NLR on postoperative day 5 was significantly higher in the EJA leakage and other postoperative complication group (p=0.022). All these mentioned factors are essentially a result of the inflammatory effect of EJA leakage and are not specific to EJA leakage.

Study limitations

The limitations of our study included the fact that it was retrospective, had a small patient population, and was conducted at a single center.

CONCLUSION

Surgeons should be careful about anastomotic leakage, which is a significant postoperative complication, especially in cases where the duration of operation is prolonged, and additional organ resection is required. Recurrent fever, high CRP levels, and NLR may serve as warnings for complications in postoperative follow-ups.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Kartal Koşuyolu Higher Specialty Training and Research Hospital (2017.3/2-36).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

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