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

Jiadi Xing*, Maoxing Liu*, Xinyu Qi*, Jianhong Yu, Yingcong Fan, Kai Xu, Pin Gao, Fei Tan, Zhendan Yao, Nan Zhang, Hong Yang, Chenghai Zhang, Ming Cui and Xiangqian Su

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 esophagojejunalostomy 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.

*These authors contributed equally to this work.

Corresponding author:
Xiangqian Su, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Surgery IV, Peking University Cancer Hospital and Institute, 52 Fucheng Road, Haidian District, Beijing 100142, China.
Email: suxiangqian@bjmu.edu.cn

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Surgery IV, Peking University Cancer Hospital and Institute, Beijing, China

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
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. The reported incidence of EJAL varies between 0.5% and 11.5%, and recently, Cetin et al. 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.

Surgical technique

The reconstruction method after total gastrectomy was Roux-en-Y esophagojejunostomy. All esophagojejunal anastomoses were performed with a circular stapler (Ethicon Circular Stapler CDH25A; Ethicon Inc., Somerville, NJ, USA). The integrity of the ring of tissue that was retained by the circular staple 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 Medical Association.

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.
Health Organization (WHO). 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). Gastric cancer histopathological staging was performed according to the seventh edition of the International Union Against Cancer TNM classification. “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.

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/m²), 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 nasojejunal 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                                  |             |             |          |         |
| Male                                 | 287         | 10          | 3.214    | 0.073   |
| Female                               | 93          | 0           |          |         |
| Age (years)                          |             |             |          |         |
| $\leq 65$                             | 275         | 4           | 5.014    | 0.025   |
| $>65$                                | 105         | 6           |          |         |
| ASA category                         |             |             |          |         |
| I                                    | 303         | 7           | 3.975    | 0.137   |
| II                                   | 71          | 2           |          |         |
| III                                  | 6           | 1           |          |         |
| Smoking                              |             |             |          |         |
| No                                   | 246         | 6           | 0.096    | 0.757   |
| Yes                                  | 134         | 4           |          |         |
| Alcohol consumption                  |             |             |          |         |
| No                                   | 305         | 5           | 5.473    | 0.019   |
| Yes                                  | 75          | 5           |          |         |
| Hypertension                         |             |             |          |         |
| No                                   | 291         | 8           | 0.064    | 0.801   |
| Yes                                  | 89          | 2           |          |         |
| Diabetes                             |             |             |          |         |
| No                                   | 343         | 10          | 1.076    | 0.300   |
| Yes                                  | 37          | 0           |          |         |
| BMI (kg/m²)                          |             |             |          |         |
| $<25$                                 | 266         | 5           | 1.838    | 0.175   |
| $\geq 25$                            | 114         | 5           |          |         |
| Neoadjuvant chemotherapy             |             |             |          |         |
| No                                   | 303         | 9           | 0.641    | 0.423   |
| Yes                                  | 77          | 1           |          |         |
| Pulmonary insufficiency              |             |             |          |         |
| No                                   | 292         | 5           | 3.866    | 0.049   |
| Yes                                  | 88          | 5           |          |         |
| Preoperative hemoglobin (g/L)        |             |             |          |         |
| $<90$                                | 21          | 0           | 0.584    | 0.445   |
| $\geq 90$                            | 359         | 10          |          |         |
| Preoperative serum albumin (g/L)     |             |             |          |         |
| $<35$                                | 49          | 3           | 2.467    | 0.116   |
| $\geq 35$                            | 331         | 7           |          |         |
| Preoperative carcinoembryonic antigen (µg/mL) |             |             |          |         |
| $<0.005$                             | 292         | 8           | 0.055    | 0.815   |
| $\geq 0.005$                         | 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 ($P < 0.05$).
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.

**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 factors for EJAL.
factors associated with EJAL. However, patients who had suffered extensive intraoperative 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. 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.
that reported an incidence of EJAL after total gastrectomy of 2.5%. 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. Goh et al. 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, but also intestinal anastomoses. Kazuhiro et al. 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 also failed to find an association between diabetes and EJAL. Therefore, this issue deserves further discussion.

Although Isozaki et al. and Sauvanet et al. successively reported that pulmonary insufficiency was not a risk factor for EJAL, Wu et al. 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. found that the risk of EJAL was 49% lower in patients who received 80% FiO2 than in those who received 30% FiO2 during and 6 hours

| Variable            | $P$ value | Odds ratio | 95% CI          |
|---------------------|-----------|------------|-----------------|
| Age (years)         | 0.043     | 3.882      | 1.045–14.422    |
| Alcohol consumption | 0.043     | 3.828      | 1.043–14.050    |

There were statistically significant differences for the data in italics ($P < 0.05$). CI, confidence interval.
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.21,22 Rullier et al. and Sorensen et al.23,24 reported that smoking and alcohol abuse were major risk factors for anastomotic leakage in colorectal surgery. Thomas et al.25 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.26,27

Cardiac insufficiency, immunosuppression, and hemostasis have also been demonstrated in symptom-free alcohol abusers with postoperative complications.28 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.22 Several studies21–25 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 studies1,6,10 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.;6 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 ≥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).

ORCID iDs
Jaodi Xing https://orcid.org/0000-0001-6463-7594
Ming Cui https://orcid.org/0000-0001-6463-7594

References
1. Sierzega M, Kolodziejczyk P, Kulig J, et al. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. Br J Surg 2010; 97: 1035–1042.
2. Hyodo M, Hosoya Y, Hirashima Y, et al. Minimum leakage rate (0.5%) of stapled esophagojejunostomy with sacrifice of a small part of the jejunum after total gastrectomy in 390 consecutive patients. Dig Surg 2007; 24: 169–172.
3. Isozaki H, Okajima K, Ichinona T, et al. Risk factors of esophagojejunal anastomotic leakage after total gastrectomy for gastric cancer. Hepatogastroenterology 1997; 44: 1509–1512.
4. Ichikawa D, Kurioka H, Yamaguchi T, et al. Postoperative complications following gastrectomy for gastric cancer during the last decade. Hepatogastroenterology 2004; 51: 613–617.
5. Meyer L, Meyer F, Dralle H, et al. Insufficiency risk of esophagojejunal anastomosis after total abdominal gastrectomy for gastric carcinoma. Langenbecks Arch Surg 2005; 390: 510–516.
6. Deguchi Y, Fukagawa T, Morita S, et al. Identification of risk factors for esophagojejunal anastomotic leakage after gastric surgery. World J Surg 2012; 36: 1617–1622.
7. Migita K, Takayama T, Matsumoto S, et al. Risk factors for esophagojejunal anastomotic leakage after elective gastrectomy for gastric cancer. J Gastrointest Surg 2012; 16: 1659–1665.
8. Zilling T, Olseen P and Walther BS. Prediction of hospital stay after total
gastrectomy. *Anticancer Res* 1997; 17: 1355–1359.

9. Tu RH, Lin JX, Zheng CH, et al. Development of a nomogram for predicting the risk of anastomotic leakage after a gastrectomy for gastric cancer. *Eur J Surg Oncol* 2017; 43: 485–492.

10. Cetin DA, Gündüz E, Ciyiltep H, et al. Risk factors and laboratory markers used to predict leakage in esophagojejunal anastomotic leakage after total gastrectomy. *Turk J Surg* 2019; 35: 6–12.

11. Sobin LH, Gospodarowicz MK and Wittekind C (editors). *International Union Against Cancer (UICC). TNM Classification of Malignant Tumours*. 7th ed. New York: Wiley-Blackwell, 2010.

12. U.S. Department of Agriculture and U.S. Department of Health and Human Services. In: *Dietary Guidelines for Americans*. 7th ed. Washington, DC: U.S. Government Printing Office, 2010.

13. Makuuchi R, Irino T, Tanizawa Y, et al. Esophagojejunal anastomotic leakage following gastrectomy for gastric cancer. *Surg Today* 2019; 49: 187–196.

14. Inokuchi M, Otsuki S, Fujimori Y, et al. Systematic review of anastomotic complications of esophagojunostomy after laparoscopic total gastrectomy. *World J Gastroenterol* 2015; 21: 9656–9665.

15. Tsou CC, Lo SS, Fang WL, et al. Risk factors and management of anastomotic leakage after radical gastrectomy for gastric cancer. *Hepatogastroenterology* 2011; 58: 218–223.

16. Black E, Vibe-Petersen J, Jorgensen LN, et al. Decrease of collagen deposition in wound repair in type 1 diabetes independent of glycemic control. *Arch Surg* 2003; 138: 34–40.

17. Onodera H, Ikeuchi D, Nagayama S, et al. Weakness of anastomotic site in diabetic rats is caused by changes in the integrity of newly formed collagen. *Dig Surg* 2004; 21: 146–151.

18. Sauvanet A, Mariette C, Thomas P, et al. Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. *J Am Coll Surg* 2005; 201: 253–262.

19. Wu WG, Gu J, Zhang WJ, et al. ERCP for patients who have undergone Billroth II gastroenterostomy and Braun anastomosis. *World J Gastroenterol* 2014; 20: 607–610.

20. Schietroma M, Cecilia EM, Carlei F, et al. Prevention of anastomotic leakage after total gastrectomy with perioperative supplemental oxygen administration: a prospective randomized, double-blind, controlled single-center trial. *Am Surg Oncol* 2013; 20: 1584–1590.

21. Van Rooijen S, Carli F, Dalton SO, et al. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. *Acta Oncol* 2017; 56: 329–334.

22. Kennedy ND and Winter DC. Impact of alcohol & smoking on the surgical management of gastrointestinal patients. *Best Pract Res Clin Gastroenterol* 2017; 31: 589–595.

23. Rullier E, Laurent C, Garrelon JL, et al. Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg* 1998; 85: 355–358.

24. Sorensen LT, Jorgensen T, Kirkeby LT, et al. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. *Br J Surg* 1999; 86: 927–931.

25. Nickelsen TN, Jørgensen T and Kronborg O. Lifestyle and 30-day complications to surgery for colorectal cancer. *Acta Oncol* 2005; 44: 218–223.

26. Tønnesen H, Petersen KR, Højgaard L, et al. Postoperative morbidity among symptom-free alcohol misusers. *Lancet* 1992; 340: 334–337.

27. Tønnesen H, Schutten BT and Jorgensen BB. Influence of alcohol on morbidity after colonic surgery. *Dis Colon Rectum* 1987; 30: 549–551.

28. Gloria L, Cravo M, Camilo ME, et al. Nutritional deficiencies in chronic alcoholics: relation to dietary intake and alcohol consumption. *Am J Gastroenterol* 1997; 92: 485–489.