

Risk factors for surgical-site infections after radical gastrectomy for gastric cancer: a study in China

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Abstract

Background: About 10% of patients get a surgical-site infection (SSI) after radical gastrectomy for gastric cancer, but SSI remains controversial among surgeons. The aim of this study was to explore the risk factors for SSIs after radical gastrectomy in patients with gastric cancer to guide clinical therapies and reduce the incidence of SSI.

Methods: The study was a retrospective cohort study in patients who underwent radical gastrectomy for gastric cancer. SSI was defined in accordance with the National Nosocomial Infection Surveillance System. We evaluated patient-related and peri-operative variables that could be risk factors for SSIs. The Chi-squared test and logistic regression analysis were used to assess the association between these risk factors and SSI.

Results: Among the 590 patients, 386 were men and 204 were women. The mean age was 56.6 (28–82) years and 14.2% (84/590) of these patients had an SSI. Among them, incisional SSI was observed in 23 patients (3.9%) and organ/space SSI in 61 patients (10.3%). Multivariate logistic regression analysis identified sex (odds ratios [ORs] = 2.548, and 95% confidence interval [CI]: 1.268–5.122, $P = 0.009$), total gastrectomy (OR = 2.327, 95% CI: 1.352–4.004, $P = 0.002$), albumin level (day 3 after surgery) <30 g/L (OR = 1.868, 95% CI: 1.066–3.274, $P = 0.029$), and post-operative total parenteral nutrition (OR = 2.318, 95% CI: 1.026–5.237, $P = 0.043$) as independent risk factors for SSI.

Conclusions: SSI was common among patients after radical gastrectomy for gastric cancer. The method supporting post-operative nutrition and the duration of prophylactic antibiotics may be important modifiable influencing factors for SSI.

Keywords: Radical gastrectomy; Gastric cancer; Risk factor; Surgical-site infection

Introduction

Gastric cancer (GC) is one of the most common malignancies and leading causes of cancer-related death in East Asia.^[1,2] Radical resection is the method of first choice for the treatment of GC.^[3–5] However, about 10% of patients worldwide get a surgical-site infection (SSI) after radical gastrectomy for GC,^[6,7] which prolongs hospitalization, increases medical costs, reduces patients' quality of life, and even causes death.^[8] Thus, to date, SSI remains controversial among surgeons.

Several studies investigated the factors that influence SSI after radical gastrectomy. Tu *et al*^[9] found that body mass

index (BMI) ≥ 25 kg/m², intraoperative blood loss ≥ 75 mL, surgical time ≥ 240 min, and peri-operative transfusion were adversely associated with organ/space SSIs. A similar study from Japan^[10] showed that male sex, chronic liver disease, total gastrectomy (TG), and surgical time ≥ 320 min were independently associated with SSI. However, the factors mentioned above cannot be easily altered. The patients' sex and BMI also cannot be changed before surgery, and these factors would not make much difference in lowering the incidence of SSI even if they were adverse factors. Therefore, the aim of the present study was to identify factors that can be modified to help prevent SSI after radical gastrectomy in a consecutive cohort of patients over 1 year at our center.

Yong-Qi Qiao and Li Zheng contributed equally to this research.

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Methods

Study design

The study was a retrospective analysis of a prospectively documented database comprising 590 patients who underwent radical gastrectomy for primary gastric cancer at the Department of Pancreatic and Gastric Surgery of National Cancer Center (NCC)/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from November 2017 to December 2018. The exclusion criteria were as follows: (1) pre-operative identification of infectious disease or febrile status within 24 h before surgery; (2) T4b stage or palliative resection; (3) American Society of Anesthesiologists (ASA) score ≥ 4 ; or (4) presence of post-operative anastomotic fistula that was diagnosed using gastroscopy, upper digestive tract radiography, or methylene blue trial. Risk factors for SSIs after radical gastrectomy for gastric cancer were determined based on other published studies, such as pre-operative and intra-operative factors. Several new factors were also included, such as albumin level on day 3 after surgery, prophylactic antibiotics duration, and nutrition support methods within 24 to 48 h after surgery.

Data collection

The required information was gathered from hospital records and through patient interviews. The potential risk factors for SSI included age, sex, co-morbidities, BMI, smoking, alcohol use, hemoglobin concentration, lymphocyte count, tumor stage, pre-operative chemo- or radiotherapy, surgical duration, surgery mode (laparoscopic-assisted/open), TG, bleeding, albumin level on day 3 after surgery, prophylactic antibiotics duration, and nutrition support methods at the early post-operative stage. All surgeries were performed by experienced senior surgeons and the surgical incision classification was clean-contaminated or contaminated.

The primary outcome was SSI. SSI is defined as an infection that occurs at an incisional site within 30 days after the incision is made, or within 1 year if a prosthesis is implanted, based on the Committee of Disease Control guidelines.^[8] SSI has been classified into the following three categories: (1) superficial incisional (involving only the skin and subcutaneous tissue at the site of the incision); (2) deep incisional (involving fascial and muscle layers); and (3) organ/space (involving a body cavity or visceral organs, diagnosis was made by surgeons).

Data analysis

Statistical analysis was performed using SPSS version 19.0 software (SPSS, Chicago, IL, USA). Categorical data are presented as the percentage. Chi-squared test and analysis of variance were used to screen the categorical factors that were associated with SSIs. Variables that showed a statistically significant difference in the univariate analysis were included in the subsequent multivariate analysis. The univariate analysis results were described by Chi-squared and *P* values, and multivariable analysis results were

described using odds ratios (ORs) and 95% confidence intervals (CIs). *P* < 0.05 was considered statistically significant.

Results

SSI incidence and characteristics

Among the 590 patients, 65.4% (386/590) were men and 34.6% (204/590) were women. The mean age was 56.6 (28–82) years. The patients' mean BMI was 23.8 (14.0–34.9) kg/m². Based on the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) Classification of Malignant Tumors, 8th Edition, 56.8% of patients (335/590) were classified as stage I-II and 43.2% (255/590) were classified as stage III. Additionally, 14.6% (86/590) of the patients received neoadjuvant chemotherapy and 22.7% (134/590) had co-morbidities. The mean pre-operative hemoglobin was 135.9 (range, 61–196) g/L and the mean surgical duration was 2.99 ± 0.88 h. The average blood loss was 117.6 (range, 10–2500) mL. Additionally, 18.3% (108/590) of the patients underwent TG and 48.8% (288/590) underwent laparoscopic gastrectomy.

Among the 590 patients, 84 (14.2%) had an SSI, including 23 incision SSIs and 61 organ/space SSIs. Among the 61 organ/space SSI patients, 41 presented with pleural effusion, 16 had intra-abdominal abscesses, and four had blood infection.

The most frequent antibiotic prescribed was latamoxef (441/590, 74.7%), followed by cefminox (135/590, 22.9%). In other patients, levornidazole, clindamycin, cefoselis, and meropenem were administered because of cephalosporin allergy. The prophylactic antibiotic for each patient was administered 30 min to 1 h before the skin incision, and an additional dose was administered every 3 h during surgery. The prophylactic antibiotics duration in 41.7% (246/590) of patients was less than 48 h. Table 1 presents additional characteristics of the study patients.

Analysis of factors associated with SSI

Tables 2–4 show the univariate analysis results of pre-, intra-, and post-operative factors, respectively. Sex (*P* = 0.001) and smoking (*P* = 0.039) were the two pre-operative factors that were significantly associated with SSI, while TG was the only intra-operative factor with statistical significance (*P* = 0.001). For post-operative factors, we found that the prophylactic antibiotics duration (*P* = 0.029) and post-operative nutrition supporting methods (*P* = 0.007) were significantly associated with SSI. Age (*P* = 0.067) and serum albumin (day 3 after surgery) < 30 g/L (*P* = 0.074) were two factors with a *P* value lower than 0.1 and were also included in multivariable logistic regression analysis. The multivariate analysis revealed that male sex (OR = 2.548, 95% CI: 1.268–5.122, *P* = 0.009), TG (OR = 2.327, 95% CI: 1.352–4.004, *P* = 0.009), serum albumin (day 3 after surgery) < 30 g/L (OR = 1.868, 95% CI: 1.066–3.274, *P* = 0.029), and post-operative total parenteral nutrition (TPN) (OR = 2.318, 95% CI: 1.026–5.237, *P* = 0.043) were the adverse risk factors for SSI [Tables 5 and 6].

Table 1: Patient and surgical characteristics of 590 patients with gastric cancer.

Characteristics	Value
Mean age (years)	56.6 (10.2)
Sex	
Male	386 (65.4%)
Female	204 (34.6%)
Body mass index (kg/m ²)	23.8 (14.0–34.9)
Smoker	255 (43.2%)
Alcohol consumer	210 (35.6%)
Co-morbidities*	134 (22.7%)
Tumor stage	
I–II	335 (56.8%)
III–IV	255 (43.2%)
Pre-operative chemo- or radio-therapy	86 (14.6%)
Pre-operative hemoglobin (g/L)	135.9 (61–196)
Absolute lymphocyte count (×10 ⁹ /L)	1.78 (0.44–4.84)
Duration of surgery (hours)	2.99 (0.88)
Bleeding (mL)	117.6 (10–2500)
Mode of surgery	
Laparoscopic assisted	288 (48.8%)
Open	302 (51.2%)
Total gastrectomy	108 (18.3%)
Infections	84 (14.2%)

Data are expressed as mean (standard deviation), mean (range) or *n* (%).

* Co-morbidities include diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, congestive heart failure, and human immunodeficiency virus infection/acquired immune deficiency syndrome and other immunocompromised states.

Discussion

SSIs have been a global challenge for a long time. In 2002, a project was conducted by the Committee of Disease Control to decrease the incidence of SSIs, and for decades, tremendous efforts were made, but the incidence of SSIs showed only a small decrease. To date, the overall incidence of SSIs is about 10% to 20%, and infections account for nearly half of the causes of death after major abdominal surgery.^[6,7,11–14] It is crucially important to determine all the SSI risk factors, especially those factors that are modifiable so that SSIs can be prevented.

An anastomotic leakage space/organ SSI is almost inevitable. Anastomotic leakage is an independent influencing factor of SSI and the SSI treatment methods are different if there is an anastomotic leakage. Several studies investigated the factors that influence anastomotic leakage, including ischemia, low pre-operative serum albumin, anemia, malnutrition, and SSI.^[15–18] Thus, SSI can also be a reason for an anastomotic leakage, and the relationship between SSI and anastomotic leakage is complex. In this research, we excluded patients with SSIs and anastomotic leakage and determine the precise influencing factors that are associated with SSI.

Several studies have reported risk factors for SSIs after gastrectomy, including male sex, chronic liver disease, longer surgical time, advanced age, a BMI of 25 kg/m² or higher, diabetes mellitus, blood loss, TG, and combined resection procedures.^[6,7,9,10,19] Similarly, male sex and TG

were also risk factors in our study. However, other factors did not show a statistically significant difference. For the longer surgical time factor, other studies defined a longer surgical time as longer than 240 or 320 min, but in our study, nearly all the surgical time was less than 240 min. We set a surgical time cut-off of 180 min for the analysis, and thus, the results were different compared with the other studies. A BMI of 25 kg/m² or higher is usually a risk factor for SSI,^[19,20] but we defined a BMI of less than 18 kg/m² as malnutrition, which might also influence the incidence of SSI. Thus, we combined patients with a BMI of less than 18 kg/m² or greater than 24 kg/m² into a group, so our results were also different compared with these studies. In this study, few patients had accompanying diabetes mellitus or underwent combined resection procedures, so these two factors were excluded.

Anti-microbial prophylaxis (AMP) can effectively prevent SSI in gastric cancer surgery. A single dose of AMP was recommended in the current research,^[21–23] but prolonged post-operative use of prophylactic antibiotics after gastric cancer surgery remains common in Asia.^[24] In the guidelines for clinical application of antibiotics in China, it is recommended that AMP can be extended for up to 48 h after gastrointestinal surgery. A prophylactic antibiotic duration of more than 48 h was thought to be a factor that was associated with SSI, which is supported by the results of this study.

Based on the guidelines for enhanced recovery after surgery,^[25,26] TPN is not recommended as a method of nutritional support after upper gastrointestinal surgery. The existing routine of nil-by-mouth for upper gastrointestinal surgery remains unchallenged. Recently, we conducted a study comparing food-at-will and TPN after gastrectomy, and the results showed that the incidence of infectious complications with TPN was much higher compared with food-at-will. Additionally, the study by Lassen *et al*^[27] showed that the infectious incidence associated with allowing food-at-will was lower compared with an enteral tube feeding. These results showed that a relatively low number of calories within the first 3 to 5 post-operative days were associated with fewer infectious complications. Eating food, especially through the activation of normal digestive reflexes, has an important impact on overall recovery after gastrointestinal surgery. As an influencing factor for SSI, it is modifiable and can be easily controlled by each surgeon.

Data collection in our study showed that pre-operative albumin levels among all the patients was above 35 g/L, which reflects a good nutrition status in the patients before surgery. Numerous studies have shown that post-operative hypoalbuminemia is a risk factor for complications after surgery.^[28–31] Exudate after surgery is necessary for wound healing, but it causes a decrease in serum albumin. However, systemic inflammatory response syndrome or SSI may cause higher levels of exudate, which will lead to a low serum albumin level.^[32] Post-operative serum albumin was mainly considered to be an acute-phase protein. We found that serum albumin that was lower than 30 g/L on day 3 after surgery was significantly associated with SSI, and this factor might be used as an indicator of SSI.

Table 2: Pre-operative factors associated with surgical site infections in 590 patients with gastric cancer.

Factors	Total, <i>n</i>	SSI, <i>n</i>		Incidence (%)	χ^2	<i>P</i>
		Yes <i>N</i> = 84	No <i>N</i> = 506			
Sex						
Male	386	68	318	17.6	10.441	0.001
Female	204	16	188	7.8		
Age						
≥ 60 years	255	44	211	17.3	3.349	0.067
< 60 years	335	40	295	11.9		
Tumor stage						
I-II	335	44	291	13.1	0.772	0.380
III-IV	255	40	215	15.7		
Pre-operative chemo- or radio-therapy						
Yes	86	10	76	11.6	0.561	0.454
No	504	74	430	14.7		
Smoker						
Yes	255	45	210	17.6	4.276	0.039
No	335	39	296	11.6		
Alcohol consumer						
Yes	210	30	180	14.3	0.001	0.980
No	380	54	326	14.2		
Co-morbidities						
Yes	134	17	117	12.7	0.341	0.559
No	456	67	389	14.7		
BMI						
> 24 or < 18.5 kg/m ²	288	38	250	13.2	0.501	0.479
$18.5 \leq$ BMI ≤ 24 kg/m ²	302	46	256	15.2		
Pre-operative hemoglobin						
≥ 120 g/L	464	67	397	14.4	0.073	0.787
< 120 g/L	126	17	109	13.5		
Absolute lymphocyte count						
$< 1 \times 10^9/m^3$	553	76	477	13.7	1.763	0.184
$\geq 1 \times 10^9/m^3$	37	8	29	21.6		

SSI: Surgical-site infection; BMI: Body mass index.

Table 3: Intra-operative factors associated with surgical site infections in 590 patients with gastric cancer.

Factors	Total, <i>n</i>	SSI, <i>n</i>		Incidence (%)	χ^2	<i>P</i>
		Yes <i>N</i> = 84	No <i>N</i> = 506			
Duration of surgery						
≥ 3 h	279	45	234	16.1	1.551	0.213
< 3 h	311	39	272	12.5		
Mode of surgery						
Laparoscopic-assisted	288	40	248	13.9	0.056	0.813
Open	302	44	258	14.6		
Total gastrectomy						
Yes	108	26	82	24.1	10.476	0.001
No	482	58	424	12.0		
Bleeding						
≥ 200 mL	126	17	109	13.5	0.073	0.787
< 200 mL	464	67	397	14.4		

SSI: Surgical-site infection.

Table 4: Post-operative factors associated with surgical site infections in 590 patients with gastric cancer.

Factors	Total, <i>n</i>	SSI, <i>n</i>		Incidence (%)	χ^2	<i>P</i>
		Yes <i>N</i> = 84	No <i>N</i> = 506			
Albumin (the third day after surgery)						
≥ 30 g/L	465	60	405	12.9	3.199	0.074
< 30 g/L	125	24	101	19.2		
Duration of prophylactic antibiotics						
≤ 2 days	352	41	311	11.6	4.792	0.029
> 2 days	238	43	195	18.1		
Post-operative parenteral nutrition						
Yes	469	76	393	16.2	7.249	0.007
No	121	8	113	6.6		

SSI: Surgical-site infection.

Table 5: Multivariable logistic regression analysis of factors associated with surgical site infection in 590 patients with gastric cancer.

Predictor variables	χ^2	<i>P</i>	OR	95% CI
Male	6.896	0.009	2.548	1.268-5.122
Age ≥ 60 years	1.196	0.274	1.314	0.805-2.145
Smoker	0.289	0.591	1.168	0.663-2.058
Total gastrectomy	9.301	0.002	2.327	1.352-4.004
Albumin (the third day after surgery) < 30 g/L	4.764	0.029	1.868	1.066-3.274
Duration of prophylactic antibiotics > 2 days	1.823	0.177	1.420	0.854-2.362
Post-operative parenteral nutrition	4.085	0.043	2.318	1.026-5.237

OR: Odds ratio; CI: Confidence interval.

Table 6: Culture isolates in cases of surgical site infection in 590 patients with gastric cancer.

Organism	<i>n</i>
<i>Staphylococcus saprophyticus</i>	2
<i>Staphylococcus epidermidis</i>	1
<i>Staphylococcus aureus</i>	1
<i>Staphylococcus capitis</i>	1
<i>Enterococcus faecalis</i>	1
<i>Enterobacter cloacae</i>	1
<i>Streptococcus salivarius</i>	1
<i>Burkholderia cepacia</i>	1
<i>Pseudomonas aeruginosa</i> + <i>Enterococcus avium</i>	1
<i>Enterococcus faecalis</i> + <i>Acinetobacter baumannii</i>	1
<i>Enterococcus faecalis</i> + <i>Klebsiella pneumoniae</i>	2
α -Hemolytic streptococcus + <i>Klebsiella pneumoniae</i>	1
<i>Pseudomonas aeruginosa</i> + <i>Klebsiella pneumoniae</i>	1

There were some limitations in this study. First, in this retrospective study, we gave the patients high-caloric sip-feeds instead of normal food, and the optimal number of calories was not investigated. Second, there was selection bias, and some important risk factors were not included. Finally, more data on SSI treatment should be included in this study.

In addition to male sex, TG, and lower serum albumin level on day 3 after surgery, this study showed that routine TPN after gastrectomy was an adverse risk factor of SSI

compared with food-by-mouth in the first 3 to 5 days after surgery. Univariate analysis showed that a prophylactic antibiotic duration more than 48 h was significantly associated with SSI. These findings will provide direction for subsequent clinical trials to reduce the incidence of SSI after radical gastrectomy.

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Conflicts of interest

None.

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