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Identification of Predictors of Surgical Site Infection in Patients With Gastric Cancer Undergoing Surgery With Curative Intent

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Surgical site infection (SSI) is a potentially morbid and costly complication of surgery. The purpose of this study was to determine preoperative and operative predictors of SSIs after gastric resection with lymphadenectomy in patients with gastric cancer (GC). Data on clinicopathologic factors, including operative and preoperative laboratory factors, for 384 patients with GC who had undergone curative surgery were analyzed in this retrospective study to assess their associations with SSIs. Superficial/deep incisional SSIs (iSSIs) and organ/space SSIs (o/sSSIs) occurred in 18 (4.6%), and 27 (7.0%), respectively. The o/sSSIs were significantly associated with surgery-related factors such as duration of operation, blood loss, and extent of tumor. Additionally, high levels of preoperative indicators of systemic inflammation, including neutrophil counts, neutrophil/lymphocyte ratio, and C-reactive protein concentrations, were significantly associated with o/sSSIs. Multivariate analyses demonstrated that preoperative neutrophil counts and duration of surgery were independent predictors for o/sSSIs, whereas only preoperative serum albumin concentration was predicted for iSSIs. In patients with GC undergoing curative surgery, preoperative neutrophil count and operation time are potentially valuable predictors of o/sSSIs, whereas only preoperative serum albumin predicts iSSIs.

Key words: Neutrophil – Surgical site infection – Operation time – Gastric cancer

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Gastrectomy is one of the most common gastrointestinal surgical procedures performed in Japan. Although innovation in devices and improvements in surgical technique and perioperative management have resulted in reduced mortality after gastrectomy, postoperative morbidity remains a clinically significant problem.[1] Surgical site infections (SSIs) are a leading cause of nosocomial infectious complications, accounting for 14%–16% of nosocomial infections overall and 38% of nosocomial infections among surgical patients.[2] SSIs remain clinically important issues after radical gastrectomy for patients with gastric cancer (GC), such infections being associated with prolonged hospitalization, increased costs of medical treatment, and decreased patient quality of life.[2–4] Furthermore, they remain a substantial cause of mortality.

According to the Centers for Disease Control and Prevention classification,[2] SSIs are categorized as superficial/deep incisional SSIs (iSSIs), and organ/space SSIs (o/sSSIs). Previous studies have reported several risk factors for SSIs after gastrectomy.[3–6] However, most of these studies did not assess iSSIs and o/sSSIs separately. The development of SSIs depends on complex interactions between patient- and procedure-related factors, intraoperative bacterial contamination, and compliance with the standard measures that should be implemented to prevent SSIs.[7] It is likely that the risk factors for iSSIs and o/sSSIs differ significantly.[8] These complications should therefore be assessed separately.

In this study, we investigated the risk factors for iSSIs, and o/sSSIs separately and identified distinct risk factors associated with these 2 complications. In addition, preoperative evaluation of risk of SSIs is clinically important because it optimizes selection of the duration of prophylactic antimicrobial treatment and use intensive antibiotics such as therapeutic antimicrobial agent. Thus, we assessed preoperative blood variables when evaluating the risk of SSIs in patients with GC who had undergone surgery with curative intent.

Methods

Patients

Data for 384 patients who had undergone potentially curative surgery for GC (stages I–III) at the Department of Gastrointestinal and Pediatric Surgery of Mie University Graduate School of Medicine from January 2001 to December 2011 were included in this retrospective study. The staging was performed according to the Japanese classification of gastric carcinoma.[9] The type of surgical resection (*i.e.*, distal subtotal gastrectomy, proximal subtotal gastrectomy, or total gastrectomy) and extent of lymph node dissection was selected according to the Japanese gastric cancer treatment guidelines.[9] Curative resection was defined as the absence of any residual tumor in the surgical bed and a surgical resection margin that was pathologically negative for tumor invasion. No patient received chemotherapy or radiotherapy before curative surgery and there was no perioperative mortality.

SSIs include iSSIs and o/sSSIs, and were classified according to the criteria of the Centers for Disease Control and Prevention.[2] The o/sSSIs included anastomotic leakage and intraabdominal abscesses, defined as the presence of septic fluid in the peritoneal space proven by surgical drainage or needle aspiration and bacteriologic culture. iSSIs included wound infections, which were demonstrated by the presence of purulent fluid or pus in the wound incision. Hyperemia and local warming at the surgical site was also accepted as a criterion for superficial iSSIs. In addition, postoperative anastomotic leakage was diagnosed by performing contrast radiography.

All patients received prophylactic first-generation cephalosporin antibiotics (cefazolin) for 1 day, according to Japanese guidelines on hospital-acquired infection; 1.0 g of cefazolin being administered by an anesthesiologist. Infusions were started soon after induction of anesthesia to ensure achievement of peak blood levels of antibiotics during surgery. Further doses of antibiotics were given every 3 hours during the operation.

Associations between postoperative iSSIs and o/sSSIs and clinicopathologic factors, operative factors and preoperative laboratory data were analyzed in 384 patients with GC who had undergone curative gastrectomy with D1 or D2 lymphadenectomy according to the clinical stage.

Blood collection and subsequent analyses were approved by the Institutional Review Boards of Mie University Hospital in Japan. The study was conducted in accordance with the guidelines of the 1975 Declaration of Helsinki. The need for informed patient consent was waived because of the retrospective nature of the study.

Statistical analysis

Data are presented as means ± standard deviation (SD). Comparisons were made using the Mann–

Whitney, Kruskal–Wallis test, or χ^2 test, as appropriate. Receiver operating characteristic (ROC) analysis was performed to determine which factors distinguished study patients with SSIs from those without. Sensitivity versus 1 − specificity was plotted at each cutoff threshold; the area under the curve (AUC) values reflect the probability of correctly identifying patients with SSIs from those without. The optimal cutoff thresholds for making this distinction were determined by using Youden's index. In brief, the optimal cutoff threshold values were at the point on the ROC curve at which Youden's index (sensitivity + specificity − 1) was maximal. All P values were 2-sided and $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using MedCalc 7.2 for Windows (Mariakerke, Belgium).

Results

Patient characteristics

The study group comprised 264 men and 120 women aged 32 to 88 years (median: 67 years). The average body mass index (BMI) was 22.34 ± 3.45 kg/m^2. Of the 384 registered patients with GC, 178 (46.3%) had undergone open gastrectomy and 206 (53.7%) had laparoscopic gastrectomy. Total gastrectomies had been performed in 111 patients (28.9%), distal gastrectomy in 217 patients (56.5%), proximal gastrectomy in 27 patients (7.0%), and partial gastrectomy in 29 (7.6%). Roux-en-Y reconstruction had been performed in 244 patients (63.6%), Billroth I in 119 (31.0%), Billroth II in 14 (3.6%), and other forms of reconstruction in 7 (1.8%). According to the Japanese classification of GC, 244 patients (63.6%) had stage I disease, 68 (17.7%) had stage II, and 72 (18.7%) had stage III disease. Median tumor diameter was 30 mm (4–150 mm), median operation time 307 minutes (103–780 minutes), median blood loss 260 mL (7–2311 mL), and median number of dissected lymph nodes per patient 26 (0–77).

Association between clinicopathologic findings and postoperative SSIs

iSSIs and o/sSSIs with anastomotic leakage occurred in 18 cases (4.6%) and 27 cases (7.0%), respectively (Table 1). There were no significant associations between postoperative iSSIs and the following factors: age, sex, American Society of Anesthesiologists classification, operative factors, BMI, and pathologic characteristics of tumors (Table 1). Conversely, male sex (P = 0.0335), longer operation time (P = 0.0166), advanced pathologic N stage (P = 0.0244), and advanced TNM stage (P = 0.0344) were significantly associated with occurrence of postoperative o/sSSIs (Table 1).

Association between preoperative laboratory findings and postoperative SSIs

Table 2 shows the associations between preoperative laboratory findings and postoperative infectious complications. Only preoperative serum albumin concentration differed significantly between the iSSIs negative and positive groups (P = 0.04674). In addition, preoperative neutrophil counts were significantly higher in o/sSSIs positive than negative patients (P = 0.000371).

Identification of factors associated with postoperative o/sSSIs

Using the factors identified as significant by univariate analysis, we performed multivariate analysis to identify factors independently associated with o/sSSIs, as shown in Table 1 and Table 2. We found that high neutrophil counts (>4190) and lengthy operations (>307 minutes) were independent predictors of postoperative o/sSSIs [neutrophil count, HR (95% CI) = 3.5658 (1.5507–8.1933), P = 0.0028; operation time, HR (95% CI) = 3.5568 (1.3970–90.555), P = 0.0078] (Table 3).

High neutrophil counts and long operation duration predict o/sSSIs

ROCs revealed that AUC for preoperative neutrophil counts for prediction of postoperative o/sSSIs was 0.705 (sensitivity, 59.26%; specificity, 75.56%; cut-off value, 4190) (Fig. 1a). In contrast, AUC for operation duration for prediction of postoperative o/sSSIs was 0.605 (sensitivity, 69.23%; specificity, 59.09%; cut-off value, 318 minutes) (Fig. 1b). In addition, study patients with both of these risk factors had significantly higher percentages of o/sSSIs (29%; $P < 0.0001$) than those without these factors (Fig. 1c).

Discussion

In this study, we found that o/sSSIs was significantly associated with surgery-related factors, namely longer duration of operation and more blood loss, and extent of tumor. In addition, high

Table 1 Associations between clinicopathologic factors and SSIs in patients with gastric cancer undergoing curative surgery

Category	iSSI(−)	iSSI(+)	*P* value	o/sSSI(−)	o/sSSI(+)	*P* value
Age						
≦67 y	190	7	0.4022	185	12	0.5894
> 67 y	176	11		172	15	
Gender						
Male	254	10	0.3288	240	24	0.0335
Female	112	8		117	3	
ASA classification						
I–II	347	17	0.6345	337	27	0.4156
III–V	19	1		20	0	
Open vs Laparoscopic						
Open	166	12	0.1265	163	15	0.427
Lap	200	6		194	12	
Reconstruction						
B 1	115	4	0.5512	112	7	0.5846
B 2	14	0		12	2	
R-Y	230	14		226	18	
Others	7	0		7	0	
Operation methods						
Total G	103	8	0.3613	99	12	0.2898
Distal G	208	9		205	12	
Proximal G	26	1		25	2	
Partial G	29	0		28	1	
Operation time						
≦307.5 (min)	183	9	0.8092	185	7	0.0166
> 307.5 (min)	183	9		172	20	
Blood loss						
≦260 (mL)	186	7	0.4551	183	10	0.2203
> 260 (mL)	180	11		174	17	
BMI						
≦22.2	186	6	0.2274	181	11	0.4247
> 22.2	180	12		176	16	
Tumor size						
≦30 mm	160	6	0.5324	159	7	0.0928
> 30 mm	206	12		198	20	
Pathologic T stage						
T1–2	256	10	0.3029	251	15	0.1658
T3–4	110	8		106	12	
Pathologic N stage						
N−	253	13	0.9870	253	13	0.0244
N+	113	5		104	14	
Pathologic differentiation						
differentiation	201	9	0.8676	198	12	0.3367
undifferentiation	165	9		159	15	
TNM classification						
I	234	10	0.5999	231	13	0.0408
II	65	3		64	4	
III	67	5		62	10	

ASA, the American Society of Anesthesiologists; BMI, body mass index; iSSI, incisional surgical site infection; o/sSSI, organ/space SSI.

levels of preoperative indicator of systemic inflammation, namely neutrophil counts, were significantly associated with o/sSSIs. Furthermore, multivariate analyses demonstrated that high preoperative neutrophil counts and long duration of operation were independent predictors of o/sSSIs. However, only preoperative serum albumin concentration was significantly associated with iSSIs in the study patients.

Numerous risk factors have been identified as associated with SSIs after gastrectomy, including advanced age,[10] BMI of 25 or above,[11] sex,[12] open gastrectomy,[10] blood loss,[3] and operation duration.[5,10,13] In several large-scale surveys, multivari-

Table 2 Associations between preoperative laboratory findings and SSIs in patients with gastric cancer undergoing curative surgery

	iSSI(−), mean (SD)	iSSI(+), mean (SD)	*P* value	o/sSSI(−), mean (SD)	o/sSSI(+), mean (SD)	*P* value
Neutrophil	3547 (1390)	4061 (1843)	0.34722	3491 (1365)	4630 (1664)	0.000371
Lymphocyte	1792 (621)	1818 (908)	0.65087	1779 (624)	1979 (758)	0.098414
NLR	2.29 (1.73)	3.45 (4.24)	0.39139	2.30 (1.85)	3.02 (2.74)	0.094986
CRP	0.52 (1.52)	0.82 (1.53)	0.36546	0.52 (1.53)	0.77 (1.33)	0.182187
Alb	3.97 (0.51)	3.68 (0.60)	0.04674	3.95 (0.51)	3.98 (0.59)	0.590084
CEA	8.5 (41.7)	5.5 (4.6)	0.38233	6.0 (19.7)	38.8 (131.5)	0.131783
CA19-9	27.8 (86.5)	25.6 (28.1)	0.12093	26.5 (84.8)	42.9 (81.4)	0.817353

Alb, albumin; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; iSSI, incisional surgical site infection; NLR, neutrophil/lymphocyte ratio; o/sSSI, organ/space SSI; SD, standard deviation.

ate regression analyses have shown that operation duration is one of the most significant risk factors for SSIs after gastrointestinal surgery, including gastrectomy.[5,10,13] In the present study, univariate analysis showed that several patient-related (sex), procedure-related (operation duration), and tumor-related factors (advanced N and TNM stage) were significantly associated with o/sSSIs; however, according to multivariate analysis, operation duration was one of the most important independent risk factor for o/sSSIs.

Our subanalyses showed that male patients had significantly greater blood loss ($P = 0.0004$; Fig. 2a) than female patients. BMI had significant direct positive correlations with operative time (Rho = 0.273, $P < 0.0001$; Fig. 3a) and intraoperative blood loss volume (Rho = 0.138, $P = 0.007$; Fig 3b). In addition, extent of tumor (large tumor, advanced T, N, and TNM stage) was also significantly associated with intraoperative blood loss (advanced T stage, $P < 0.0001$; large tumor, $P = 0.0004$; advanced N stage, $P < 0.0001$; advanced TNM stage, $P < 0.0001$; Fig 2b–e). Furthermore, there was a significant positive correlation between operative time and blood loss (Rho = 0.211, $P < 0.0001$; Fig. 3c). Thus, increased operative duration secondary to being male and having a high BMI and advanced tumor resulting in greater blood loss may be responsible for o/sSSIs.

An interesting aspect of our study is the relationship between preoperative serum indicators of systemic inflammation and postoperative SSIs. We believe this is the first reported study to find that high neutrophil counts are an independent predictor of o/sSSIs. Although an explanation for this association in patients with GC is speculative, we pose the following two possibilities. First, we recently showed that high preoperative neutrophil elastase, which correlates with neutrophil counts, is associated with SSIs in patients with ulcerative colitis.[14] Additionally, removing activated leukocytes from the peripheral blood by perioperative leukocyte apheresis can lead to a reduced incidence of postoperative SSIs in patients with ulcerative colitis.[15,16] These findings imply that perioperative neutrophil activation is a risk factor for SSIs.

Our second proposal is derived from *in vitro* and *in vivo* experiments. Neutrophils are first-line effector immune cells against microbial invasion, their effects being exerted mainly in injured or infected tissues; however, excessive activation or activation at inappropriate sites may lead to destruction of host tissue.[17,18] Therefore, appropriate neutrophil recruitment into sites of local inflammation is essential for host defense against infection. Hidemura *et al* have shown that patients with gastrointestinal cancer who develop postoperative

Table 3 Multivariate analysis of predictors of organ/space SSIs in gastric cancer patients undergoing curative surgery[a]

	Multivariate analysis		
Factors	HR	95% CI	*P* value
Neutrophil (>4190/≦4190)	3.5658	1.5507 to 8.1933	**0.0028**
Gender (Male versus Female)	3.1573	0.8982 to 11.098	0.073
Operation time (> median/≦median)	3.5568	1.3970 to 9.0555	**0.0078**
Pathologic N stage (N+ versus N−)	1.6192	0.4895 to 5.3557	0.4297
TNM stage (III versus I–II)	1.9688	0.5527 to 7.0132	0.2959

CI, confidence interval; HR, hazard ratio.

[a]The median operation time is 307 min.

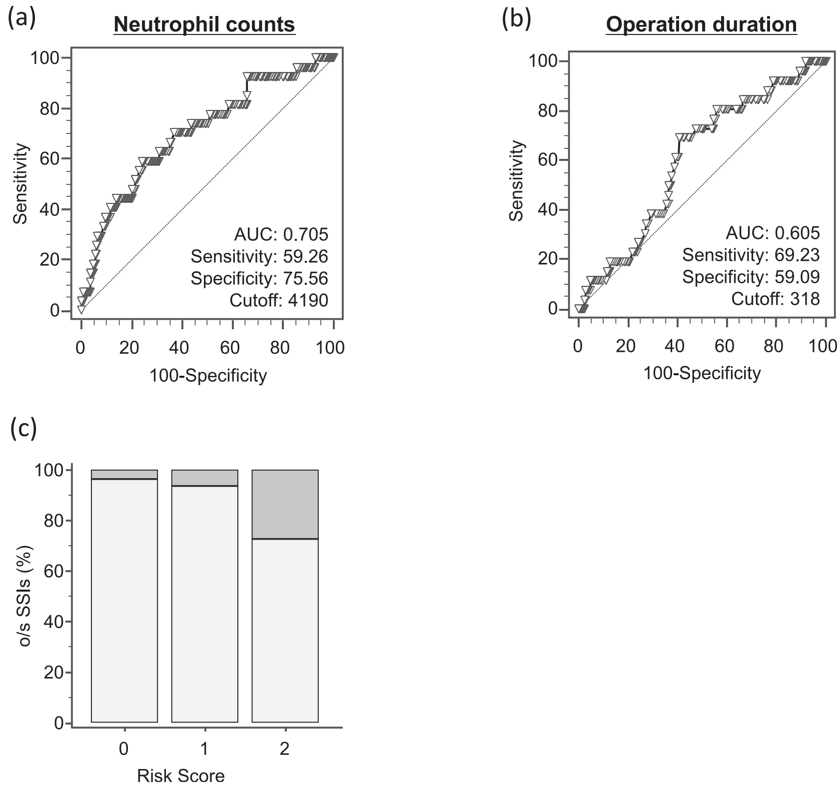

Fig. 1 (a) Receiver operative curve (ROC) showing the accuracy of preoperative neutrophil counts for prediction of postoperative organ/space SSIs (o/sSSIs). (b) ROC curve showing the accuracy of operation duration for prediction of postoperative o/sSSIs. (c) 100% stacked column to show the percentages of organ/space SSIs (o/sSSIs) subdivided by risk scores (0, both negative; 1, one positive; 2, both positive). White, SSIs negative; Gray, SSIs positive.

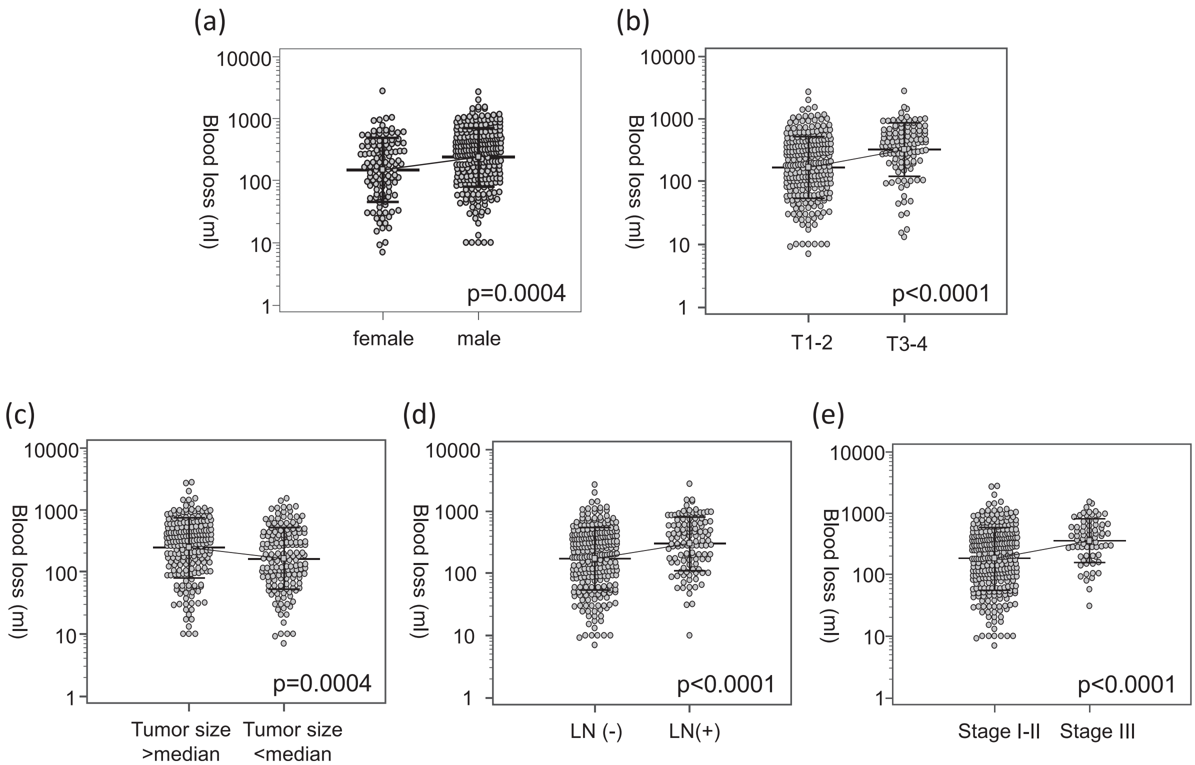

Fig. 2 Volume of blood loss according to various factors. (a) Sex, (b) pathologic T stage, (c) tumor size, (d) pathologic N stage, and (e) pathologic TNM stage

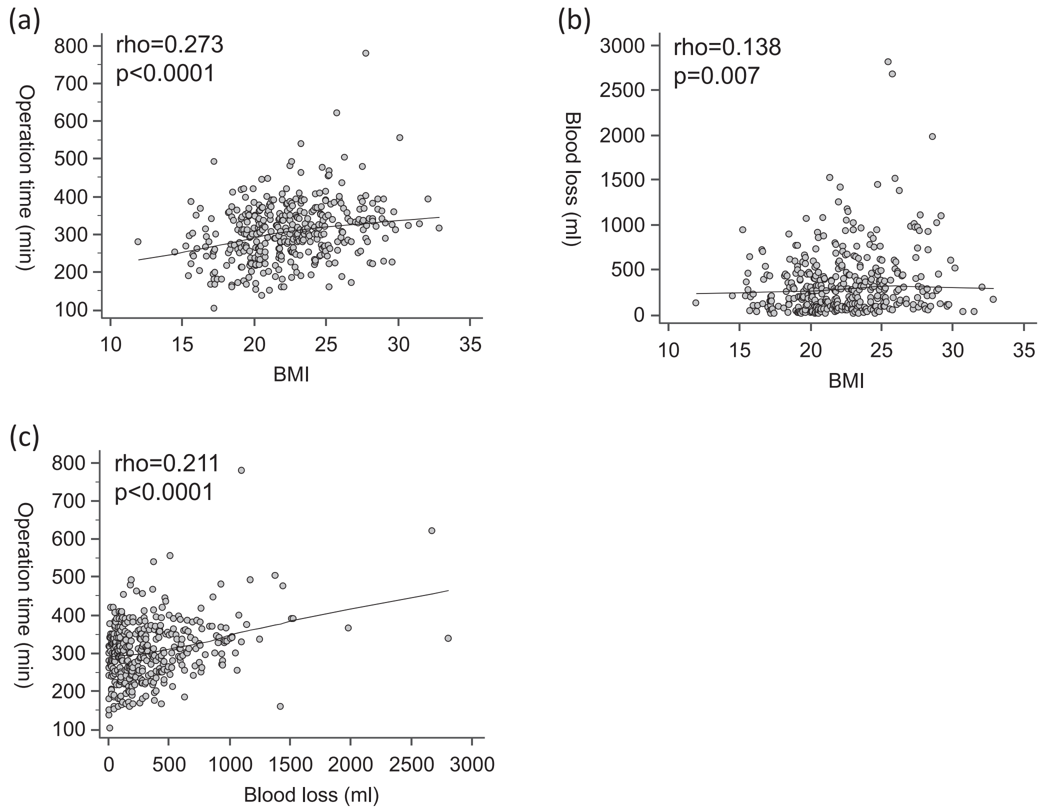

Fig. 3 Correlation between BMI and (a) operation time and (b) blood loss. (c) Correlation between operation time and blood loss.

infections tend to have higher preoperative neutrophil counts than those who do not develop infection group and that high preoperative neutrophil adhesion capacity is closely associated with postoperative infections.[19] Demers *et al* demonstrated that cancers can result in increased numbers of peripheral blood neutrophils that are sensitized to formation of neutrophil extracellular traps *in vivo*.[20] Under these conditions, spontaneous microthrombosis associated with neutrophil extracellular trap generation form in the circulation and at sites of low-grade infection or surgical stress.[20] Collectively, adhesive neutrophils and neutrophil extracellular trap-induced microthrombosis may lead to plugging of microvessels, impairment of microcirculation, and subsequent inappropriate immune responses at surgical sites, resulting in increased rates of postoperative infections.

Another possible measure for preventing SSIs is the use of laparoscopy. Although laparoscopic gastrectomy was not identified as a significant risk factor for SSIs in this study, another large-scale study has shown it to be associated with fewer SSIs than open surgery.[21] At our institution, the number of patients undergoing laparoscopic gastrectomy is increasing every year. Therefore, the use of laparoscopy may contribute to reducing the incidence of post-gastrectomy SSIs with increasing experience. The present study did have several potential limitations; namely, it was a retrospective, single-institution small study. However, the surgical procedures, administration of preventive antibiotics, implementation of standard precautions against SSIs, laboratory tests, and follow-up were uniform throughout the entire study period.

In conclusion, we have demonstrated that high preoperative neutrophil counts and long duration of operation are independent risk factors for o/sSSIs. Having both of these factors is associated with a high risk of SSIs in patients with GC undergoing curative surgery. These two factors should therefore be considered when deciding on the duration of administration of prophylactic antimicrobial agents or whether to administer intensive therapeutic antimicrobial agents preoperatively in these patients.

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