—Original—

Worse Preoperative Status Based on Inflammation and Host Immunity Is a Risk Factor for Surgical Site Infections in Colorectal Cancer Surgery

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Objective: The modified Glasgow Prognostic Score (mGPS) is an inflammation-based measure of malnutrition that reflects a state of cachexia in cancer patients. We evaluated mGPS as an index to predict surgical site infection (SSI) incidence in patients undergoing colorectal cancer surgery.

Subjects and Methods: We retrospectively analyzed 351 patients who underwent colon cancer resection. Factors correlated with the incidence of SSIs were identified by logistic analysis and stepwise selection.

Results: SSIs were observed in 32 patients, with an incidence of 9.1%. Univariate logistic analysis revealed mGPS (Score 2), laparotomy, resection of other organs, colostomy, excessive blood loss (>423 mL), long duration of surgery (>279 minutes), pulmonary dysfunction, prognostic nutritional index (PNI) ≤40, neutrophil lymphocyte ratio (NLR)(>4), and controlling nutritional status (CONUT) ≥2 to be associated with an increased incidence of SSIs. Multivariate analysis with variables selected by the stepwise procedure also revealed mGPS (Score 2) (Odds ratio (OR)=3.55, 95% Confidence interval (CI) 1.30−9.56; p=0.01), colostomy (OR=6.56, 95%CI 1.60−31.38; p=0.01), excessive blood loss (OR=3.20, 95%CI 1.23−8.42; p=0.02), and NLR (>4)(OR=3.24, 95%CI 1.31−8.17; p=0.01) to be independent risk factors.

Conclusion: mGPS is an independent risk factor for SSIs. Our results suggest that cachexia before surgery in patients with colorectal cancer might predict the incidence of SSIs.

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Key words: modified Glasgow Prognostic Score (mGPS), surgical site infection (SSI), colorectal cancer surgery

Introduction

Cancer cachexia is a complex metabolic abnormality syndrome characterized by skeletal muscle atrophy occurring regardless of loss of body fat mass[1]. In cancer tissue, IL-6 is produced, tumor-host interactions occur, systemic metabolic abnormalities are induced, and cancer-induced weight loss (CIWL) owing mainly to skeletal muscle atrophy occurs[2]. This systemic metabolic abnormality reflects the pathology of cancer cachexia[2].

C-reactive protein concentration (CRP) is induced by IL-6 in the liver, and objectively represents the actual nature of cancer cachexia[3]. CRP correlates with IL-6 and serum albumin (Alb) is inversely correlated with CRP[4]. The modified Glasgow Prognostic Score (mGPS) is classified by CRP and Alb, and is an indicator of inflammation-based nutritional disorders[4]. mGPS also correlates with muscle atrophy and CIWL[4], and is frequently used as an indicator of cachexia[5]. mGPS is divided into three groups by score (Score 0−2), with a score of 2 (CRP >1.0 mg/dL and Alb <3.5 g/dL) reflecting cachexia[6].

Cachexia is observed in the early phase of diagnosis in 10−20% of colorectal cancer patients[7]. Moreover, cachexia accompanied by a systemic inflammatory response following invasive surgery reportedly induces postoperative

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infectious complications[7]. Infectious complications are classified as surgical site infections (SSIs) and remote infections (RIs)[8]. Adaptive measures and elucidation of risk factors for SSIs are important because their incidence is high, and since patients with SSIs tend to be in a serious condition[9]. To our knowledge, only a few reports have examined the relationship between mGPS and SSIs[10,11]. Accordingly, we examined factors that affect SSI incidence in colorectal cancer surgery, with a particular focus on cachexia using mGPS as an index.

Methods

Subjects

A total of 351 patients who underwent colorectal surgery between January 2005 and December 2008 were enrolled for analysis. Subjects were those who underwent colon cancer resection with anastomosis. Those who underwent colon cancer resection without anastomosis were excluded. The study population did not include patients who underwent surgery for benign disease.

Informed Consent

We followed the retrospective observational research information disclosure procedure (opt-out) of Tokyo Women's Medical University for obtaining informed consent from research subjects. This study was approved by the Ethics Committee of Tokyo Women's Medical University (No. 4150).

Methods

We analyzed clinicopathological factors associated with SSIs, categorized as follows: mGPS (Score 0・1/Score 2), sex (male/female), age (≥75/<75 years), depth of tumor invasion(≤MP/≥SS), approach (laparotomy/laparoscopy), location (colon/rectum), resection of other organs (yes/no), colostomy (yes/no), timing of operation (emergency/elective), blood loss (large/small), duration of surgery (long/short), histology (tub1, 2/others), ileus (yes/no), diabetes mellitus (yes/no), pulmonary dysfunction (yes/no), performance status (0/≥1), American Society of Anesthesiologists classification (ASA) (1・2/3), body mass index (BMI)(<18.5/≥25.0), prognostic nutritional index (PNI) (≤40/>40), neutrophil lymphocyte ratio (NLR) (>4/≤4), controlling nutritional status (CONUT) (0・1/≥2), and smoking habit (yes/no). Pulmonary dysfunction was defined as less than 80% of percentage vital capacity (%VC) or less than 70% of forced expiratory volume in one second percentage (FEV1.0%).

Blood biochemical values represent results immediately prior to surgery after hospitalization. mGPS[6] was scored as follows: score 2, CRP >1.0 mg/dL and Alb <3.5 g/dL; score 1, CRP >1.0 mg/dL or Alb <3.5 g/dL; and score 0, CRP ≤1.0 mg/dL and Alb ≥3.5 g/dL. PNI was calculated using the following formula, as proposed by Onodera at al.[12]: serum albumin levels (g/dL)×10+total lymphocyte count (per mm^3)×0.005. NLR was calculated by dividing the number of neutrophils by the number of lymphocytes[13]. The CONUT Score takes the serum albumin value, total lymphocyte count, and total cholesterol value, and integrates them to evaluate nutritional status using the "CONUT score" (0–12 points) in 4 levels[14]. Specifically, patients with CONUT scores of 0–1 have a normal nutritional status, those with CONUT scores of 2–4 are at mild risk, those with CONUT scores of 5–8 are at moderate risk, and those with CONUT scores of 9–12 are at severe risk of malnutrition[14]. Blood loss, duration of surgery, and NLR beyond the 75th percentile based on the cumulative frequency distribution were considered poor.

Assessment of SSIs and Complications

SSI was diagnosed based on National Nosocomial Infection Surveillance (NNIS) System standards prescribed by the Centers for Disease Control and Prevention. Surgeons examined the wound site daily and added a description of the findings to the subject's medical records. Surveillance was conducted by a group of doctors until postoperative day 30. The authors confirmed and summarized the subject's medical records. Grade II or higher complications according to the Clavien-Dindo classification[15] were considered an incident for calculation of incidence rate.

Statistical Analysis

Statistical analyses were performed with SAS ver.9.2 (SAS Institute, Inc., Cary, NC, USA). Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables were used for between-group comparisons. Univariate and multivariate logistic regression analyses were performed to identify factors associated with SSI incidence. Variables for inclusion in the multivariate analysis were selected by the stepwise procedure with all variables (stepwise forward selection with entry and stay criteria both set to p=0.25). $P<0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics of Subjects

This study involved 351 subjects (206 men 58.7% and 145 women 41.3%). The median age of subjects was 68 years (range: 27–92 years). Subject characteristics are shown in **Table 1**.

Table 1 Demographic and clinical characteristics of subjects

Variables		n	%		n	%
modified Glasgow prognostic score (Score)	2	38	10.8	0/1	313	89.2
Sex	M	206	58.7	F	145	41.3
Age (years)			68※ (27–92)			
Postoperative hospital days			15※ (8–92)			
Depth of tumor invasion	M/SM/MP/SS/≥SE		11 (3.1%)/43 (12.3%)/18 (5.1%)/127 (36.2%)/152 (43.3%)			
Blood loss (mL)			155※ (0–3,250)∮			
Duration of surgery (min)			226※ (94–701)∮			
Pulmonary dysfunction (%)	%VC		102.1※ (42.2–152.1)∮			
	FEV1.0%		80.6※ (34.6–127.8)∮			
Performance status	0/1/2/3		301 (85.8%)/36 (10.2%) /7 (2.0%)/7 (2.0%)			
American Society of Anesthesiologists classification	1/2/3		184 (52.4%)/139 (39.6%) /28 (8.0%)			
Body mass index (kg/m^2)			22.6※ (13.4–34.1)∮			
Prognostic nutritional index			46.6※ (22.2–61.1)∮			
Neutrophil lymphocyte ratio			2.5※ (0.4–50.4)∮			
Controlling nutritional status	0/1/2/≥3		130 (37.0%)/70 (20.0%) /48 (13.7%)/103 (29.3%)			

※median ∮range

		n	%		n	%
Approach	laparotomy	285	81.2	laparoscopy	66	18.8
Location	rectum	103	29.3	colon	248	70.7
Resection of other organs	yes	61	17.4	no	290	82.6
Colostomy	yes	27	7.7	no	324	92.3
Timing of operation	emergency	16	4.6	elective	335	95.4
Histology	others	66	18.8	tub1, 2	285	81.2
Ileus	yes	35	10.0	no	316	90.0
Diabetes mellitus	yes	75	21.4	no	276	78.6
Smoking habit	yes	127	36.2	no	224	63.8

mGPS was scored as follows: score 2, CRP >1.0 mg/dL and Alb <3.5 g/dL; score 1, CRP >1.0 mg/dL; and score 0, CRP ≤1.0 mg/dL and Alb ≥3.5 g/dL.

※median ∮range

Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables were used for between-group comparisons.

Incidence of SSIs

SSIs were observed in 32 patients, with an incidence of 9.1%. Superficial and deep SSIs were noted in 22 subjects (6.3%). Twelve subjects had organ/space SSIs, including eight subjects (2.3%) with anastomotic failure and four subjects with intra-abdominal abscess (1.1%). Baseline characteristics by presence of SSI are shown in **Table 2**.

Predictive Factors for SSIs in Colorectal Cancer Surgery (Table 3)

Univariate logistic regression analyses: In univariate logistic analysis, a significantly high incidence of SSIs was associated with mGPS (Score 2), laparotomy, resection of other organs, colostomy, excessive blood loss (>423 mL), long duration of surgery (>279 minutes), pulmonary dysfunction, PNI ≤40, NLR (>4), and CONUT ≥2.

Multivariate logistic regression analyses: In multivariate analysis with variables selected by the stepwise procedure, mGPS (Score 2) (Odds ratio=3.55, 95% Confidence interval (CI) 1.30−9.56; p=0.01), colostomy (OR= 6.56, 95%CI 1.60−31.38; p=0.01), excessive blood loss (OR =3.20, 95%CI 1.23−8.42; p=0.02), and NLR (>4)(OR=3.24, 95%CI 1.31−8.17; p=0.01) were found to be independent risk factors.

Discussion

Since SSI not only extends hospital stay, but also increases recurrence and worsens prognosis, it is not a complication to be taken lightly[14]. In the present study, we examined factors that affect SSI incidence with a particular focus on cachexia, using mGPS as an index.

Table 2 Baseline characteristics by presence of SSI

Variables		n	(%)		n	(%)	p-value
modified Glasgow prognostic score (Score)	2	12	31.6	0·1	20	6.4	<.0001
Sex	male	19	9.22	female	13	9.0	1.00
Age	≥75 years	7	8.1	<75	25	9.4	0.83
Depth of tumor invasion	≥SS	27	9.7	≤MP	5	7.0	0.65
Approach	laparotomy	31	10.9	laparoscopy	1	1.5	0.02
Location	rectum	13	12.6	colon	19	7.7	0.16
Resection of other organs	yes	11	18.0	no	21	7.2	0.01
Colostomy	yes	9	33.3	no	23	7.1	0.0001
Timing of operation	emergency	2	12.5	elective	30	9.0	0.65
Blood loss	Large (>423 mL)	19	22.4	small	13	4.9	<.0001
Operating time	Long (>279 min)	14	16.1	short	18	6.8	0.02
Histology	others	7	10.6	tub1, 2	25	8.8	0.64
Ileus	yes	3	8.6	no	29	9.2	1.00
Diabetes mellitus	yes	11	14.7	no	21	7.6	0.07
Pulmonary dysfunction	yes	12	14.8	no	20	7.4	0.049
Performance status	≥1	7	14.0	0	25	8.3	0.19
American Society of Anesthesiologists classification	3	4	14.3	1·2	28	8.7	0.31
Body mass index kg/m^2	<18.5	2	7.7	≥18.5	30	9.2	1.00
	≥25	5	6.1	<25	27	10.0	0.38
Prognostic nutritional index	≤40	14	24.1	>40	18	6.1	0.0001
Neutrophil lymphocyte ratio	>4	19	20.2	≤4	13	5.1	<.0001
Controlling nutritional status	≥2	21	13.9	0·1	11	5.5	0.008
Smoking habit	yes	11	8.7	no	21	9.4	1.00

Pulmonary dysfunction was defined as less than 80% of % vital capacity (%VC) or less than 70% of forced expiratory volume in one second % (FEV1.0%).
mGPS was scored as follows: score 2, CRP >1.0 mg/dL and Alb <3.5 g/dL; score 1, CRP >1.0 mg/dL; and score 0, CRP ≤1.0 mg/dL and Alb ≥3.5 g/dL.
Blood loss, duration of surgery, and NLR were divided into 75th percentile groups based on a cumulative frequency distribution. Baseline characteristics were divided by the presence of SSI.
Fisher's exact test for categorical variables was used for between-group comparisons.

Among the few reports that have examined mGPS in the context of SSI incidence, only one report by Haruki et al.[10] found GPS (Scores 1, 2) to be an independent risk factor for SSIs in patients undergoing hepatic resection for colorectal liver metastases. Other reports described mGPS as a risk factor for infectious complications including RIs[7]. Unlike the study by Haruki et al.[10], we focused only on mGPS (Score 2), but our results were similar with respect to SSI incidence.

Current discussions on the effects of cachexia on infectious complications include whether or not cases are limited to SSIs[11]. We thus plan to conduct a further study to examine how mGPS affects the incidence of SSIs relative to RIs.

The mechanism underlying the relationship between elevated mGPS before surgery and postoperative SSI is unknown[7]. However, Alb values have been reported to be correlated with lymphocyte count[17] and NLR[13], and to be inversely correlated with granulocyte count[17] and GL ratio[17]. Moreover, CRP values have been reported to be correlated with lymphocyte count[18], NLR[11], disease progression[18], and weight loss rate[18]. One characteristic of patients with elevated mGPS in whom the two indicators (Alb and CRP) worsened may be malnutrition and a reduction in preoperative immunocompetence, suggesting the possibility that compromised immunocompetence may influence the incidence of SSIs[7].

Resolvin was recently found to reduce this inflammatory response[19], effectively inhibiting signal transduction downstream of Toll-like receptors expressed in many cancer cells and normalizing abnormal neutrophil activity as well as IL-6 production. As resolvin is derived from docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)[19], efforts have been made to improve cachexia with oral nutritional supplements (ONS) containing these components[20].

Table 3 Predictive factors for SSIs in colorectal cancer surgery

Variables		n	(%)	Univariate logistic regression crude OR	95%CI	p-value	multivariate logistic regression adjusted OR	95%CI	p-value
modified Glasgow prognostic score (Score)	2	38	10.8	6.76	2.93–15.28	0.0001	3.55	1.30–9.56	0.01
Sex	male	206	58.7	1.03	0.50–2.21	0.93			
Age	≥75 years	86	24.5	0.85	0.33–1.95	0.72	0.46	0.15–1.23	0.14
Depth of tumor invasion	≥SS	279	79.5	1.44	0.58–4.36	0.47	0.29	0.08–1.18	0.07
Approach	laparotomy	285	81.2	7.93	1.65–142.43	0.04	6.47	0.94–131.66	0.10
Location	rectum	103	29.3	1.74	0.81–3.65	0.15	0.39	0.10–1.29	0.15
Resection of other organs	yes	61	17.4	2.82	1.24–6.11	0.01	2.15	0.79–5.71	0.13
Colostomy	yes	27	7.7	6.54	2.56–15.96	0.0001	6.56	1.60–31.38	0.01
Timing of operation	emergency	16	4.6	1.45	0.22–5.53	0.63			
Blood loss	large (>423 mL)	85	24.2	5.60	2.65–12.18	0.001	3.20	1.23–8.42	0.02
Operating time	long (>279 min)	87	24.8	2.62	1.23–5.51	0.01			
Histology	others	66	18.8	1.23	0.47–2.85	0.64			
Ileus	yes	35	10.0	0.93	0.21–2.81	0.91			
Diabetes mellitus	yes	75	21.4	2.09	0.93–4.47	0.06	2.22	0.86–5.56	0.09
Pulmonary dysfunction	%VC<80 or FEV1.0%<70	81	23.1	2.17	0.99–4.61	0.046	2.08	0.78–5.37	0.13
Performance status	≥1	50	14.2	1.80	0.68–4.22	0.20			
American Society of Anesthesiologists classification	3	28	8.0	1.76	0.49–4.91	0.33			
Body mass index kg/m^2	<18.5	26	7.4	0.82	0.13–2.95	0.80			
	≥25	82	23.3	0.58	0.19–1.44	0.28			
Prognostic nutritional index	≤40	58	16.5	4.86	2.23–10.46	0.001			
Neutrophil lymphocyte ratio	>4	94	26.8	4.75	2.26–10.29	0.001	3.24	1.31–8.17	0.01
Controlling nutritional status	≥2	151	43.0	2.78	1.32–6.15	0.008			
Smoking habit	yes	127	36.2	0.92	0.41–1.93	0.82			

Univariate logistic regression analyses: In the univariate analysis, a significantly high incidence of SSIs was associated with mGPS (Score 2), laparotomy, resection of other organs, colostomy, excessive blood loss (>423 mL), long duration of surgery (>279 minutes), pulmonary dysfunction, PNI ≤40, NLR (>4), and CONUT ≥2.

multivariate logistic regression analyses: In multivariate analysis with variables selected by the stepwise procedure, mGPS (Score 2) (Odds ratio=3.55 95% Confidence interval (CI) 1.30–9.56; p=0.01), colostomy (OR=6.56 95%CI 1.60–31.38; p=0.01), excessive blood loss (OR=3.20 95%CI 1.23–8.42; p=0.02), and NLR (>4) (OR=3.24 95%CI 1.31–8.17; p=0.01) were found to be independent risk factors.

Univariate and multivariate logistic regression analyses were performed to identify factors associated with SSI incidence. Variables for inclusion in the multivariate analysis were selected by the stepwise procedure with all variables (stepwise forward selection with entry and stay criteria both set to p=0.25). P<0.05 was considered statistically significant.

Preoperative administration of immune-modulating nutrients (supplemented with arginine and omega-3 fatty acids) containing DHA reportedly decreased the incidence of SSIs significantly in colon cancer patients[20]. ONS containing EPA have also been reported to decrease CRP values, increase Alb, and maintain weight gain two weeks after administration was initiated in patients with rectal cancer undergoing chemotherapy[21]. In patients with esophageal cancer, a significantly smaller portion (8%) of those administered EPA had a ≥5% decrease in body weight compared to the control group (39%) during the perioperative period (5 days before and 21 days after surgery)[22]. However, there is no consensus with regard to reduced SSI incidence or prolonged survival, and the effects of early introduction or co-administration with antitumor therapies, such as molecular targeted therapy, are anticipated in the future[23]. Cachexia was once regarded as an irreversible condition, but given that a reduction in the activity of inflammation-induced substances and suppression of inflammatory cytokine production could be achieved by initiating nutrition therapy before the patient falls into an intractable state of cachexia, active multimodal therapy may prove effective[24].

NLR, which together with mGPS, was found to be an independent risk factor for the development of SSIs, is an index related to inflammatory conditions and reflects the

balance between a tumor promoting environment and antitumor immunity[13]. NLR is associated with mGPS, PNI, and serum zinc levels[25], and the incidences of infectious complications[25] and anastomotic leakage increase at high NLR values[26]. In the present study as well, the incidence of SSI was higher with increased NLR values, suggesting the potential involvement of a systemic inflammatory reaction and reduced immunity, which are enhanced in the cancerous state[26].

In addition to mGPS and NLR, we found excessive blood loss and colostomy, both of which are factors for which interventions are difficult preoperatively, to be independent risk factors for the development of SSIs.

Following abdominoperineal resection with colostomy, dehiscence[27] and wound infection[28] are known to occur at high rates due to stool leakage or contamination of the operative field. In the present study, SSIs that frequently occurred included wound infection and dehiscence, consistent with these previous reports.

In cases for which colostomy requires a long operating time, patients with large pelvic defects may be prone to pelvic infection; this is also indicated as a reason for increased SSI incidence[29]. Therefore, measures should be taken against contamination, such as protecting the incision wound[30]. Yet, since colostomy is a patient-specific factor determined by the condition of systemic or local lesions in the patient, this too is an unavoidable factor.

Blood loss is a factor related to surgical technique and operation, and SSI incidence decreases with reduced blood loss[31]. Horzic et al.[32] suggested that, based on the idea that preoperative anemia is a risk factor for postoperative infection in colon cancer, further bleeding during surgery may increase the risk of SSIs. Consistent with these reports, we also found blood loss to be an independent risk factor.

Blood loss can be reduced by choosing appropriate surgical instruments (e.g., ultrasonic scalpel or vessel sealing systemasuch as LigaSure®), or selection of laparoscopic surgery over laparotomy, as it is known to cause less bleeding, although cases are limited as indications need to be assessed according to criteria such as the stage of progression[31].

The present study investigated the effects of cachexia on SSI incidence using mGPS, which was found to be an independent risk factor along with colostomy, excessive blood loss, and NLR (>4). Performing early preoperative assessments of the state of cachexia and improving the condition of patients through appropriate nutrition therapy are important.

Conclusion

mGPS was found to be an independent risk factor for SSIs. Cachexia before surgery in patients with colorectal cancer might predict the incidence of SSIs.

Conflict of Interest: The authors declare no conflicts of interest.

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