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Original Research Article

Risk Factors and Predictive Biomarkers for Anastomotic Leakage after Colorectal Cancer Surgery with the Double Stapling Technique

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Abstract

Objectives: Anastomotic leakage (AL) is a serious complication associated with morbidity, mortality, and poor prognosis. This study aimed to identify the risk factors and predictive biomarkers for AL after colorectal surgery with double stapling technique (DST) anastomosis.

Methods: We retrospectively analyzed 331 patients who underwent elective colorectal cancer surgery with DST anastomosis between April 2012 and July 2021. Patient-, tumor-, and surgery-related variables were examined using univariate and multivariate analyses to identify the risk factors for AL. Postoperative inflammatory biomarkers were also analyzed to identify the predictive factors for AL.

Results: AL occurred in 28 (8.5%) patients. In multivariate analysis, male sex, a history of diabetes mellitus and high ligation of inferior mesenteric artery (IMA) were significant risk factors for AL. Serum C-reactive protein (CRP) levels on postoperative day (POD) 3 and 7 were significantly correlated with AL (OR; 95% CI, 1.134; 1.044-1.232, p = 0.003, and 1.154; 1.036-1.286, p = 0.009, respectively). The cut-off value of CRP on POD 3 was 10.91 mg/dL (sensitivity 0.714, specificity 0.835, positive predictive value [PPV] 0.290, and negative predictive value [NPV] 0.969). The cut-off value of CRP on POD 7 was 4.58 mg/dL (sensitivity 0.821, specificity 0.872, PPV 0.377, and NPV 0.981).

Conclusions: Male sex, a history of diabetes mellitus and high ligation of IMA were risk factors for AL in colorectal cancer surgery with DST anastomosis. The predictive biomarkers for cases without AL were CRP levels on POD 3 and 7.

Keywords

anastomotic leakage, colorectal cancer, double stapling technique

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Introduction

Anastomotic leakage (AL) is a serious complication of colorectal surgeries. AL has been reported to be associated with increased postoperative morbidity and mortality, longer hospital stay, and higher costs[1,2]. Furthermore, AL is associated with worse oncological outcomes, which reduces overall and disease-free survival[3-7].

The double stapling technique (DST) has greatly facilitated intestinal reconstruction in colorectal surgery, especially for anastomosis of left-sided colon and rectal cancers. Despite technical improvements and instrumental developments, it is difficult to completely eliminate AL. It is reported that the overall incidence of colorectal AL is between 2% and 14%[1,8,9]; particularly, AL reconstructed with the DST is between 6.3% and 13.7%[7,10-12]. Various studies have evaluated the risk factors for AL development. These risk factors are related to the patient background, tumor, and surgery. They include age, sex, obesity, intraoperative bleeding, protective diverting stoma, anastomotic level, number of

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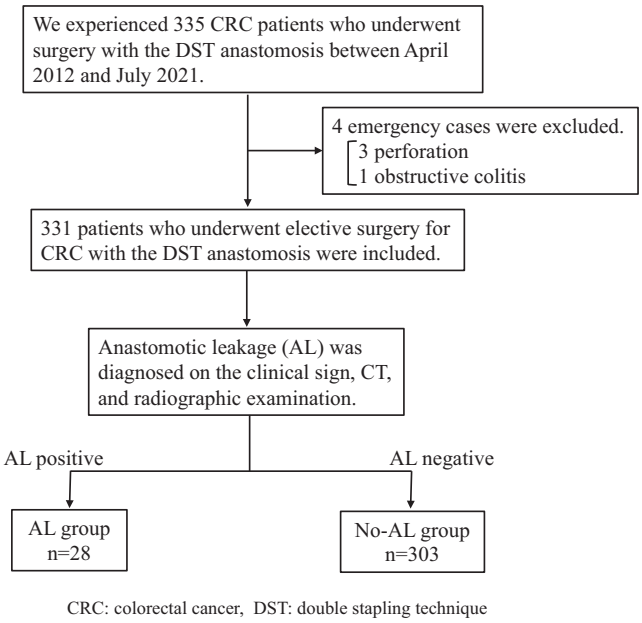

Figure 1. Flow diagram of study participants.

linear staples used, body mass index (BMI), smoking, alcohol intake, previous abdominal surgery, preoperative chemoradiotherapy, tumor location and stage, operation time, blood loss, transfusion, and pre-compression[13-24]. It is expected that serious conditions can be avoided by diagnosing and predicting AL early, before it becomes apparent. It has also been reported that serum C-reactive protein (CRP) levels, procalcitonin, and white blood cell (WBC) count are effective predictive biomarkers for AL[25-31]. Most data are from Europe and the United States. This study examined whether it would be equally useful in an Asian cohort.

Therefore, this study aimed to evaluate the risk factors and predictive biomarkers for AL in colorectal cancer surgery cases where DST anastomosis was performed.

Methods

Consecutive series of patients with primary colorectal cancer who underwent elective surgery with DST anastomosis at our hospital between April 2012 and July 2021 were evaluated retrospectively. Patients who underwent emergency surgery and those with preoperative infections such as perforation, bowel obstruction, and enterocolitis were excluded from this study. Patients were divided into two groups according to the presence of AL and categorized into AL and No-AL groups (Figure 1). The medical ethics committee of Fukushima Medical University reviewed and approved the study design (Approval No. 2022-150). Patients provided their informed consent for the use of their data. We use only anonymized and unidentifiable data.

Anastomotic leakage was diagnosed based on clinical signs of peritonitis and/or evidence of fecal or pus-like fluid emerging from the drain site. Under clinical suspicion, an abdominal to pelvic computed tomography (CT) scan was performed to confirm fluid collection or air bubbles around the anastomotic site. CT scan was performed for all symptomatic patients, but it was not done in asymptomatic patients diagnosed with radiographic examination. Before closure of the diverting stoma, we performed a radiographic examination to confirm healing of the anastomosis by injection of water-soluble contrast enema. Even if there were no symptoms, a leak of contrast medium around the anastomotic site was diagnosed as AL. It is highly unlikely that such cases can be evaluated based on clinical symptoms or inflammatory biomarkers, only cases requiring therapeutic intervention were considered in this study.

For anastomotic procedures, after transection by linear stapler, we used a circular stapler with a diameter of 25 mm for the DST anastomosis. A linear stapler contains of three rows of staples, and a circular stapler contains of two rows of staples. After DST anastomosis, we performed a 'leakage test' to confirm air tightness in all patients. For the leakage test, the large intestine was clamped at the proximal side of the anastomotic site, and air was injected through the anus to inflate the anastomotic site. The leakage test was defined as positive if an air bubble was recognized around the anastomotic site. We routinely placed a drain behind the anastomotic site. If the anastomotic site was within 5 cm from the anal verge or the leak test was positive or male patients with a narrow pelvis, we usually constructed a protective diverting stoma. A narrow pelvis was determined by the surgeon's judgment when it was difficult to handle around rectum during surgery or when it was difficult to insert a stapling device.

Patient characteristics, tumors, and surgery-related factors were evaluated as risk factors for AL. These factors included sex, age, smoking, diabetes mellitus, antithrombotic drugs, preoperative serum albumin (ALB) level, BMI, and prognostic nutritional index (PNI), tumor location, the maximum diameter of the tumor, neoadjuvant chemotherapy (NAC), operative procedure (laparotomy or laparoscopy), level of ligation of the inferior mesenteric artery (IMA), leakage test, construction of diverting stoma (DS), placement of transanal drainage tube, operative time, and blood loss during surgery. Diabetes mellitus was defined as patients with current or previous treatment with oral medications or insulin. The PNI was calculated as ALB level (g/L) + 0.005×total lymphocyte count (per mm^3), and initially used to evaluate the nutritional status of patients undergoing surgery[32].

The location of the tumor was diagnosed using a CT scan. The inferior margin of the second sacral vertebra was defined as the lower border of the sigmoid colon. The upper rectum was defined as the segment from the lower edge of the sigmoid colon to the peritoneal reflection. The lower

Table 1. Characteristics of 28 AL Group Patients.

Sex	
male/female	25/3
Age (years)	
median (range)	69 (49-83)
Location	
sigmoid colon/upper rectum/lower rectum/other	15/5/7/1
Diverting stoma	
have/none	7/21
Onset of AL (POD)	
median (range)	5 (1-37)
Severity (Clavien-Dindo classification)	
Grade I	4
Grade II	1
Grade IIIa	16
Grade IIIb	7
Treatment	
none	4
antibiotics	22
drainage	16
surgery	7
stoma creation	6
re-anastomosis	2

AL, anastomotic leakage; POD, postoperative day

rectum was defined as a segment under the peritoneal reflection. Regarding the level of ligation of the IMA, high ligation was defined as ligation near its origin, and low ligation was defined as preservation of the left colic artery.

CRP level, WBC count, and neutrophil ratio were evaluated on postoperative days (POD) 1, 3, and 7 to determine predictive biomarkers for AL. In our clinical pathway of colorectal cancer surgery, patients are scheduled to have blood chemical analysis on POD 1, 3, and 7.

Statistics

Continuous variables were presented as medians and ranges. Categorical variables were presented as frequencies and percentages. Differences between the groups were evaluated using the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Statistical significance was set at $p < 0.05$. The receiver operating characteristic (ROC) curves of CRP level, WBC count, and neutrophil ratio were used to determine the best cut-off values for anastomotic leakage. The ROC curves are a plot of the test's sensitivity (true positives) against 1-specificity (false positives) for each test threshold. The area under the ROC curve (AUC) is a direct measure of the test's diagnostic accuracy. A test with an AUC greater than 0.80 was considered to have high diagnostic accuracy and is a candidate predictive factor of AL. Risk factors for AL were determined using multivariate logistic regression analysis, and factors with $p < 0.05$ in univariate analysis were included in the model. To determine the predictive factors of AL, factors with an AUC greater than 0.80 were included in the model. Statistical analysis was performed using the Bell Curve for Excel version 2.20 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

A total of 331 patients were included in this study. There were 28 (8.5%) patients with AL (AL group) and 303 (91.5%) patients without AL (No-AL group).

Characteristics of 28 patients of anastomotic leakage group

The characteristics of the 28 AL group patients are summarized in Table 1. There were 25 men and 3 women. Their median age was 69 years (range 49-83 years). The tumor was located in the sigmoid colon in 15 patients, upper rectum in 5, lower rectum in 7, and others in 1. Seven patients had a diverting stoma (DS). Of the seven patients, three were symptomatic and four were asymptomatic. Of the three symptomatic patients, one patient required surgery, and two patients recovered conservatively. The four asymptomatic patients were diagnosed using radiographic examination before surgery for stoma closure. AL was diagnosed between POD 1 and 37, and the median AL onset was POD 5. The severity of AL was determined using the Clavien-Dindo classification[33]. There were 4 grade I, 1 grade II, 16 grade IIIa, and 7 grade IIIb patients. Regarding the treatment for AL, 16 patients were treated with drainage. Intraoperative drains were used for drainage, and no new drains were added to any patient. Surgery was performed in seven patients. Six patients underwent stoma creation, one of whom simultaneously underwent re-anastomosis. The remaining patient had DS. Re-anastomosis was performed, and the DS was retained. Twenty-one patients who underwent these treatments were administered antibiotics, and one patient recovered with fasting and antibiotics alone. No additional treatments were performed for the four asymptomatic patients diagnosed using radiographic examination before surgery for stoma closure. These four patients were diagnosed on POD 9, 15, 28, and 37.

Analyses of the factors for anastomotic leakage

Patient characteristics and tumor- and surgery-related factors are shown in Table 2. There were no significant differences between the two groups regarding age, tumor location, smoking, administration of antithrombotic drugs, administration of NAC, preoperative ALB level, BMI, PNI, construction of DS, placement of transanal drainage tube, leakage test, and operative procedure. However, there were more male patients in the AL group (n = 25, 89.3%) than in the No-AL group (n = 191, 63.0%) ($p < 0.001$). Furthermore,

Table 2. Patients' Baseline and Clinical Characteristics.

	No-AL group (n=303)	AL group (n=28)	*p* value
Sex			
male	191 (63.0%)	25 (89.3%)	< 0.001
female	112 (37.0%)	3 (10.7%)	
Age			
median (range)	68 (37-93)	69 (49-83)	0.410
Location			
sigmoid colon	203 (66.9%)	15 (53.6%)	0.492
upper rectum	35 (11.6%)	5 (17.9%)	
lower rectum	60 (19.8%)	7 (25.0%)	
others	5 (1.7%)	1 (3.6%)	
Smoking			
positive	53 (17.5%)	5 (17.9%)	0.961
negative	250 (82.5%)	23 (82.1%)	
Diabetes mellitus			
positive	42 (13.9%)	10 (35.7%)	0.002
negative	261 (86.1%)	18 (64.3%)	
Antithrombotic drug			
used	46 (15.2%)	6 (21.4%)	0.385
never	257 (84.8%)	22 (78.6%)	
NAC			
done	25 (8.3%)	3 (10.7%)	0.654
never	278 (91.7%)	25 (89.3%)	
Maximum diameter of the tumor (mm)			
median (range)	35 (7-97)	49 (8-98)	0.015
Albumin (mg/dl)			
median (range)	4.1 (2.0-4.1)	4.0 (2.9-4.9)	0.693
BMI			
median (range)	24.4 (16.2-32.9)	23.2 (15.9-39.2)	0.327
PNI			
median (range)	49.5 (23.0-65.4)	47.8 (30.1-61.4)	0.427
Diverting stoma			
have	81 (26.7%)	7 (25.0%)	0.843
none	222 (73.3%)	21 (75.0%)	
Transanal drainage tube			
have	31 (10.2%)	6 (21.4%)	0.072
none	272 (89.8%)	22 (78.6%)	
Leak test			
positive	52 (17.2%)	3 (10.7%)	0.541
negative	251 (82.8%)	25 (89.3%)	
Operative procedure			
laparoscopy	271 (89.4%)	25 (89.3%)	0.980
laparotomy	32 (10.6%)	3 (10.7%)	
Site of IMA ligation			
low	162 (53.5%)	8 (28.6%)	0.012
high	141 (46.5%)	20 (71.4%)	
Operative time (minute)			
median (range)	229 (61-587)	274 (170-776)	0.021
Blood loss (g)			
median (range)	40 (1-2962)	79 (10-1962)	0.049

NAC, neoadjuvant chemotherapy; BMI, body mass index; PNI, prognostic nutritional index; IMA, inferior mesenteric artery

Table 3. Multivariate Analysis of Clinical Factors Associated with Anastomotic Leakage.

valuables	Odds Ratio	95% CI*	*p* value
Male	4.682	1.359-16.13	0.015
Diabetes mellitus	3.027	1.268-7.224	0.013
Site of IMA ligation	3.121	1.306-7.461	0.011

*CI: confidence interval

there were more patients with diabetes mellitus in the AL (n = 10, 35.7%) than in the No-AL group (n = 42, 13.9%) (p = 0.002). The maximum tumor diameter was larger in the AL (49 mm) than in the No-AL group (35 mm) (p = 0.015). Regarding surgical factors, the rate of high ligation of the IMA was higher in the AL (n = 20, 71.4%) than in the No-AL group (n = 141, 46.5%) (p = 0.012). The operative time was longer in the AL group (274 min) than in the No-AL group (229 min) (p = 0.021). Blood loss during surgery was greater in the AL group (79 g) than in the No-AL group (40 g) (p = 0.049). Considering the number of AL events, multivariate analysis was performed for the three factors with low p-values. In the multivariate analysis including male sex, a history of diabetes mellitus and site of the IMA ligation, all three factors were significantly correlated with AL (Table 3) (Odds ratio [OR]; 95% confidence interval [CI]: 4.682; 1.359-16.13; p = 0.015 and 3.027; 1.268-7.224; p = 0.013 and 3.121; 1.306-7.461; p = 0.011 respectively).

Background and operative outcomes of patient with diverting stoma

In this study, there was no significant difference in the incidence of AL between the patients with and without DS. However, since DS is an important factor that may reduce symptomatic AL, we investigated the background and operative outcomes of patients with or without DS (Table 4). Regarding tumor location, the rectum was more common in patients with DS, and the sigmoid colon was more common in patients without DS (p < 0.001). Patients with DS were significantly more likely to receive NAC (P < 0.001). Patients with DS had larger maximum tumor diameter (p = 0.013), lower preoperative serum albumin levels (p = 0.033), were less likely to undergo laparoscopic surgery (p < 0.001), and had longer operative times (p < 0.001) and more intraoperative bleeding (p < 0.001). There were more patients with DS who had a positive leakage test (p < 0.001).

Analyses of postoperative values for the systemic inflammatory markers for anastomotic leakage

We investigated whether postoperative inflammatory biomarkers can predict AL after colorectal surgery with DST anastomosis. The WBC count on POD 7, CRP levels, and neutrophil ratios on POD 1, 3, and 7 were significantly higher in the AL group (WBC count, p = 0.003; CRP level, p = 0.008, p < 0.001, p < 0.001; and neutrophil ratio, p = 0.010, p < 0.001, p < 0.001, respectively) (Table 5). To establish a threshold for the relationship between the WBC count, CRP level, neutrophil ratio, and AL, ROC curves were plotted for factors with p < 0.05 (Figure 2). AUC values were as follows: WBC count on POD 7 0.67; CRP levels on POD 1, 3, and 7 were 0.64, 0.81, and 0.86, respectively; and neutrophil ratios on POD 1, 3, and 7 were 0.64, 0.82, and 0.71 respectively. An AUC greater than 0.80 was considered a candidate predictive factor of AL. The CRP levels on POD 3 and 7 and neutrophil ratio on POD 3 were evaluated for correlations with AL in the multivariate analysis (Table 6).

Sensitivity, specificity, and predictive values for each cut-off value of CRP level

CRP levels on POD 3 and 7 were significantly correlated with AL (OR 1.134; CI 1.044-1.232; p = 0.003 and OR 1.154; CI 1.036-1.286; p = 0.009, respectively) (Table 6). The cut-off value of CRP level on POD 3 calculated from the AUC curve was 10.91 mg/dL (sensitivity 0.714, specificity 0.835, positive predictive value [PPV] 0.290, and negative predictive value [NPV] 0.969). The cut-off value of the CRP level on POD 7 was 4.58 mg/dL (sensitivity 0.821, specificity 0.872. PPV 0.377, and NPV 0.981) (Table 7). Furthermore, Table 7 shows the sensitivity, specificity, PPV, and NPV when both CRP levels of 10.91 mg/dL and 4.58 mg/dL on POD 3 and POD 7, respectively, are applicable, and when only one value is applicable. The negative predictive value when CRP levels on both POD 3 and POD 7 were below the cut-off value was 0.986.

Discussion

AL is one of the most serious complications of gastrointestinal surgery. In particular, AL associated with colorectal cancer surgery may lead to fecal peritonitis and sepsis. Despite technical improvements and instrumental developments in recent years, it is difficult to completely eliminate AL. DST anastomosis, which is frequently used for anastomosis of left-sided colon and rectal surgery, is known to the occurrence of AL to a certain rate[7,10-12]. Although it is difficult to completely eliminate AL, if we can identify cases with a low risk of AL, removal of the drain, early discharge from the hospital, and early closure of the diverting stoma will be possible. This would lead to earlier social reinstatement and lower medical costs. Symptoms, such as fever and abdominal distension, in the early postoperative period are nonspecific, and it is difficult to predict and diagnose AL at an early stage based only on clinical symptoms. Therefore, it is useful to identify risk factors and predictive biomarkers for AL for early diagnosis.

Table 4. Background and Operative Outcomes of Patients with or without Diverting Stoma.

	Diverting stoma (n=88)	No stoma (n=243)	*p* value
Sex			
male	62 (70.5%)	154 (63.4%)	0.232
female	26 (29.5%)	89 (36.6%)	
Age			
median (range)	68 (37-86)	69 (37-93)	0.410
Location			
sigmoid colon	14 (15.9%)	204 (84.0%)	< 0.001
upper rectum	18 (20.5%)	22 (9.1%)	
lower rectum	56 (63.6%)	11 (4.5%)	
others	0 (0%)	6 (2.4%)	
Smoking			
positive	19 (21.6%)	39 (16.0%)	0.241
negative	69 (78.4%)	204 (84.0%)	
Diabetes mellitus			
positive	10 (11.4%)	35 (14.4%)	0.456
negative	78 (88.6%)	208 (85.6%)	
Antithrombotic drug			
used	14 (15.9%)	39 (16.0%)	0.733
never	74 (84.1%)	204 (84.0%)	
NAC			
done	22 (25.0%)	6 (2.5%)	< 0.001
never	66 (75.0%)	237 (97.5%)	
Maximum diameter of the tumor (mm)			
median (range)	40 (8-98)	34 (7-95)	0.013
Albumin (mg/dl)			
median (range)	4.0 (2.0-4.7)	4.1 (2.7-4.9)	0.033
BMI			
median (range)	23.1 (15.9-30.5)	23.4 (16.2-39.2)	0.208
PNI			
median (range)	49.2 (23.0-65.4)	49.7 (30.1-64.1)	0.103
Leak test			
positive	28 (31.8%)	27 (11.1%)	< 0.001
negative	60 (68.2%)	216 (88.9%)	
Operative procedure			
laparoscopy	70 (79.5%)	226 (93.0%)	< 0.001
laparotomy	18 (20.5%)	17 (7.0%)	
Site of IMA ligation			
low	48 (54.5%)	121 (49.8%)	0.445
high	40 (45.5%)	122 (50.2%)	
Operative time (minute)			
median (range)	308 (61-776)	217 (132-558)	< 0.001
Blood loss (g)			
median (range)	127 (1-1899)	35 (2-2962)	< 0.001

NAC, neoadjuvant chemotherapy; BMI, body mass index; PNI, prognostic nutritional index; IMA, inferior mesenteric artery

In this study, male sex and a history of diabetes mellitus were significant risk factors for AL. A higher risk of AL in male patients has been reported in other studies[9,13,15-17,21,22]. This may be due to their narrow pelvis, leading to a more complicated operation compared to female patients with a broader pelvis. Some studies have also shown that androgens might exert inhibitory effects on intestinal epithelial function[34]. Diabetes mellitus was also reported as a risk factor for AL in another study[35]. This may be due to insufficient blood supply to the anastomosed area because of microcirculatory disorders, insufficient glycogen stores, and delayed tissue healing because of hyper-

Table 5. Postoperative Values of Systemic Inflammation Markers.

	No-AL group (n=303)	AL group (n=28)	*p* value
WBC count (/μl)			
POD 1	9500 (2000-25000)	9680 (3500-23900)	0.569
POD 3	6745 (2100-16880)	8200 (3500-19200)	0.061
POD 7	6300 (2700-16500)	8100 (3100-13200)	0.003
CRP level (mg/dl)			
POD 1	3.17 (0.28-20.96)	4.12 (0.59-24.61)	0.008
POD 3	4.83 (0.28-32.71)	16.16 (1.29-37.52)	<0.001
POD 7	1.26 (0.06-20.44)	8.75 (0.29-29.45)	<0.001
Neutrophil ratio (%)			
POD 1	82.4 (39.8-93.6)	84.4 (79.1-93.3)	0.010
POD 3	69.4 (45.7-96.3)	85.3 (63.4-94.1)	<0.001
POD 7	63.9 (10.6-91.7)	73.2 (46.5-88.8)	<0.001

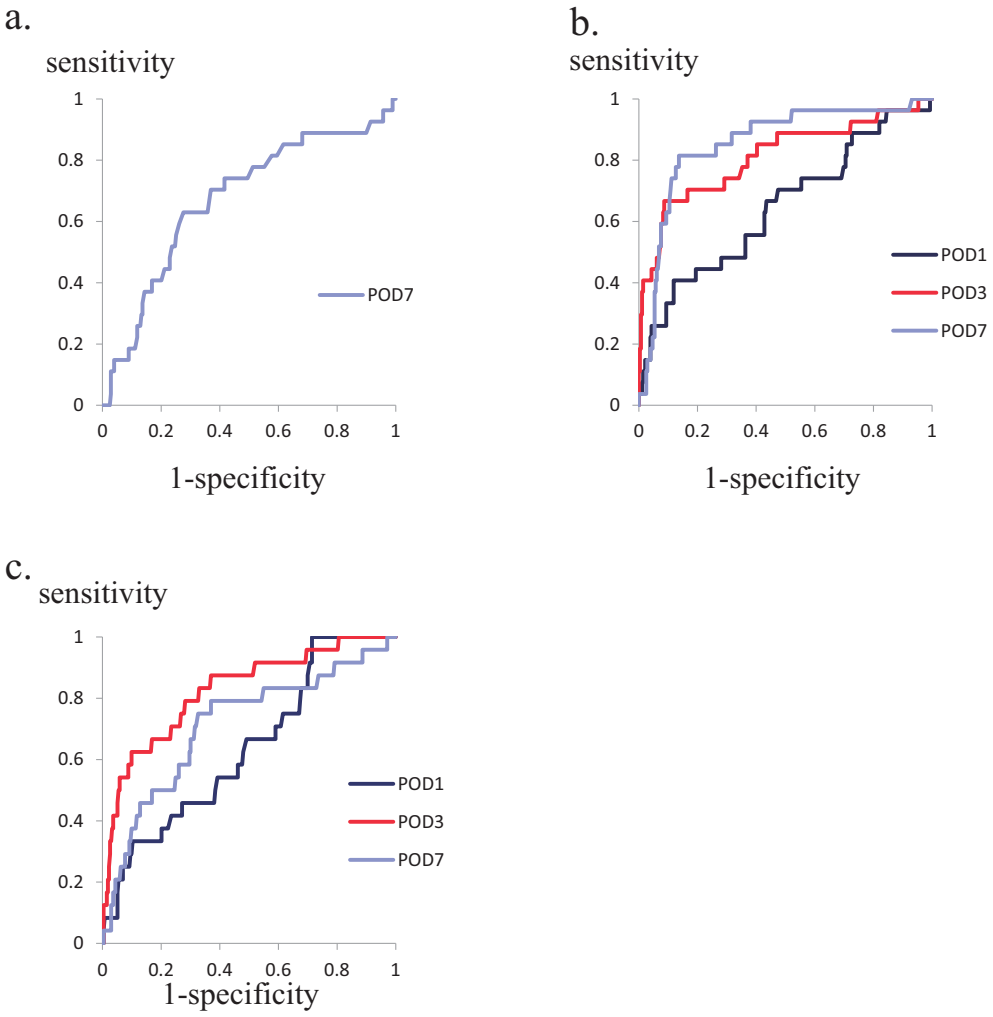

Figure 2. Receiver operating characteristic curve for systemic inflammation markers.
a. WBC, b. CRP, c. Neutrophil ratio.

glycemia[36].

Tension-free anastomosis and adequate blood supply are important for preventing AL. If the anastomotic site becomes tense, mobilization of the splenic flexure is necessary. The indocyanine green assay and measurement of anastomotic blood flow via Doppler sonography are effective in

assessing blood flow and oxygenation in the reconstructed intestinal tract[37,38]. In this study, high ligation of the IMA was also significantly associated with a higher risk of AL in the multivariate analysis. Preservation of the LCA appears to be associated with a lower risk of AL and overall morbidity[39]. However, two Japanese RCTs[40,41] and recent meta-analysis[42] shows that high ligation of the IMA does not increase the incidence of AL in anterior resection for rectal cancer. This matter is still controversial. It has also been reported that reduction of intraluminal pressure at the anastomotic site is important for preventing AL, and transanal drainage tube placement might reduce the pressure in the rectum[43]. However, in this study, there was no difference in the incidence of anastomotic leakage due to the placement of the transanal drainage tube. Whether DS can reduce the rate of AL also remains controversial. Some previous studies have reported that DS could reduce the incidence of AL and diminish the severity of leakage[44,45]. In contrast, a recent large multicenter cohort study using propensity-score matching analysis reported that DS could not reduce the incidence rate of AL but could reduce the reoperation rate[46]. It is generally recognized that DS can reduce the incidence of severe complications of AL, including fecal peritonitis and sepsis. In this study, DS was created in high-risk patients with rectal cancer, positive leak test results, administration of NAC, larger tumors, and poor nutritional status. However, the univariate analysis showed no statistical difference in the incidence of AL between patients with and without DS. Of the seven patients with AL and DS, only three (42.9%) patients were symptomatic, and only one patient (14.3%) required surgery. These results were consistent with those of a previous study.

Table 6. Multivariate Analysis of Systemic Inflammation Markers.

valuables	Odds Ratio	95% CI*	*p* value
POD 3 CRP level	1.134	1.044-1.232	0.003
POD 7 CRP level	1.154	1.036-1.286	0.009
POD 3 neutrophil ratio	1.044	0.968-1.126	0.262

*CI: confidence interval

In this study, the predictive biomarkers for AL were CRP levels on POD 3 and 7. Based on the clinical pathway of colorectal cancer surgery used in our hospital, blood chemical analyses were performed on POD 1, 3, and 7. If clinical symptoms such as defecation, flatus, fever, abdominal pain, and getting out of bed are not a problem, the drain is often removed on POD 5, and the patient is discharged on POD 7. In clinical practice, the CRP level on POD 3 is more important, and there have been some reports that the CRP level on POD 3 is an effective predictor, as in this study[25,28,30]. The cut-off values ranged from 14 to 17 mg/dL. Moreover, some reports have stated that serum procalcitonin and CRP trajectories were more accurate in predicting AL[26,27,29,31]. However, the role of procalcitonin as a predictor of AL remains controversial. In all cases, it is not common to measure from the viewpoint of cost. Regarding the trajectory of CRP levels, daily blood chemical analyses are not common in terms of cost, patient distress, and staff labor. The sensitivity and PPV of the CRP levels on POD 3 and 7 in this study were not very high, making it difficult to determine effective predictors. On the other hand, it should be noted that negative predictive values were good at 0.969% and 0.981%. This indicates that ruling out AL is more suitable than being an effective predictor of AL. If the CRP levels on POD 3 and 7 were below the cut-off value, the drain could be safely removed, and the patient could be discharged from the hospital. If these values were above the cut-off value, early interventions would be needed to prevent AL. When the CRP levels on POD 3 and 7 were both below the cut-off value, the NPV was 0.986, which was even better than that of CRP levels on POD 3 or 7 alone. Therefore, we attempted early closure of the diverting stoma within 1 month for patients with CRP levels below the cut-off value on both POD 3 and 7.

The present study had several limitations. First, it was conducted at a single center and was retrospective in design. There may have been a selection bias. Second, we did not assess postoperative infectious complications other than AL. However, there were no complications except AL, which changed the treatment policy and clinical course.

In conclusion, in colorectal cancer surgery where DST anastomosis was performed, the risk factors for AL were male

Table 7. Sensitivity, Specificity, and Predictive Values for Each Cut-Off Point of CRP Level.

Cutoff value of CRP level (mg/dL)	Sensitivity	Specificity	PPV	NPV
POD 3 (10.91)	0.714	0.835	0.290	0.969
POD 7 (4.58)	0.821	0.872	0.377	0.981
POD 3 (10.91) and POD 7 (4.58)	0.643	0.942	0.514	0.965
POD 3 (10.91) or POD 7 (4.58)	0.892	0.710	0.225	0.986

PPV, positive predictive value; NPV, negative predictive value

sex, a history of diabetes mellitus and high ligation of IMA. The predictive biomarkers for cases without AL were CRP levels on POD 3 and 7.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Planning and conducting the study was performed by SE and NI. Data collection was performed by NI, TN, DN, MA and KU. Drafting the manuscript was performed by NI. All authors critically revised the report, commented on drafts of the manuscript. SE and KT read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

This study was approved by the Medical Ethics Committee of Fukushima Medical University (No. 2022-150).

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