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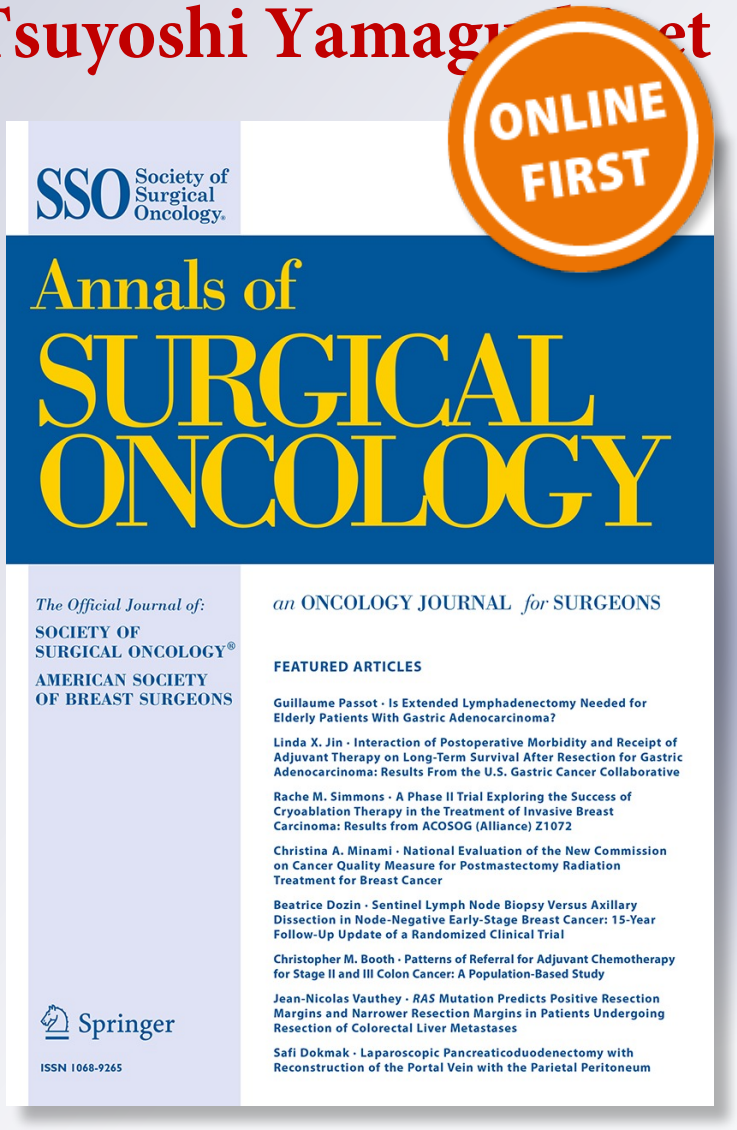

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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

Perioperative Adiponectin Measurement is Useful for Prediction of Postoperative Infection in Patients with Colorectal Cancer

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ABSTRACT

Background. Adiponectin (ADN) is a key molecule associated with obesity and metabolic syndrome, and functions as an immunomodulator. We have shown that the ADN ratio (i.e., postoperative ADN/preoperative ADN) can predict infection after gastrectomy in patients with gastric cancer . In the present study, we evaluated whether the ADN ratio could reliably predict the incidence of postoperative infection in patients undergoing colorectal cancer surgery.

Methods. We retrospectively analyzed 131 consecutive patients who underwent colorectal cancer surgery and measured their preoperative and postoperative ADN values. The outcome was postoperative infection, including surgical site and remote infections. The association between the ADN ratio and postoperative infection was assessed using logistic regression models. For the ADN ratio and other significant predictors, we conducted receiver operating characteristics (ROC) analyses.

Results. Forty-nine patients (37.4 %) experienced postoperative infections. Logistic regression analysis indicated that the ADN ratio was most significantly associated with postoperative infection [odds ratio per one standard deviation (1 SD) decrease 0.36; 95 % confidence interval 0.18–0.71] even after adjustment for diabetes, type of surgery, blood loss, C-reactive protein level, and preoperative ADN level. History of type 2 diabetes mellitus also significantly predicted postoperative infection (odds ratio per 1 SD increase 2.93; 95 % confidence interval 1.03–8.38). When predicting postoperative infection, the area under the ROC curve for the ADN ratio (0.707) was comparable to that for blood loss (0.698; $p = 0.975$).

Conclusions. ADN ratio is a clinically useful predictor of postoperative infection in patients undergoing colorectal cancer.

Despite improvements in surgical procedures and perioperative management, postoperative infection remains associated with morbidity and mortality.[1, 2] Postoperative infection causes prolonged hospital stays and increased medical costs.[3] In addition, postoperative infection after colorectal resection for cancer is associated with patient survival.[4] Infections are important causes of postoperative morbidity after abdominal surgery; currently, although several risk factors have been identified for postoperative infection, including obesity and type 2 diabetes mellitus (T2DM), no factors have been shown to predict postoperative infection.[5]

Adiponectin (ADN) is an adipocyte-derived secretory protein that plays a key role in metabolism.[6] Decreased ADN levels are associated with obesity and insulin resistance; moreover, they are predictive of T2DM, dyslipidemia, and coronary artery disease.[7–14] These

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obesity and obesity-related comorbidities are known risk factors for surgical site infection (SSI) after colon surgery.[5] The ADN ratio can be calculated as the ADN value on postoperative day (POD) 1 divided by the preoperative ADN value. Recently, we demonstrated that the ADN ratio was an independent and useful predictor of postoperative infection after gastric surgery.[15] However, compared to gastric cancer surgery, colorectal cancer surgery tends to be associated with a higher risk of postoperative infection as a result of the release of intestinal bacteria during surgery.[16]

In the present study, we therefore examined the usefulness of the ADN ratio as a predictive marker of postoperative infection after colorectal surgery.

MATERIALS AND METHODS

Patient Population and Study Design

We retrospectively analyzed 131 consecutive patients admitted to the Shiga University of Medical Science Hospital (Shiga, Japan) who underwent elective colorectal cancer surgery from 1997 to 2010. All patients received conventional and prophylactic antibiotic therapy for 3 days after surgery in the absence of clinical signs of postoperative infection.[17] Traditionally, prophylactic antibiotic therapy for 3–4 days after surgery has been applied in Japan to prevent the appearance of drug-resistant bacteria.[18]

Blood samples were collected to measure plasma ADN levels before surgery and on POD1 using a latex particle-enhanced turbidimetric assay (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan), as described previously.[15,19] In addition, the C-reactive protein (CRP) levels were measured on POD1.

The primary outcome of interest was the incidence of postoperative infection, including SSI and remote infection, during the 21-day postoperative observation period. SSI was defined using the criteria of the Centers for Disease Control and Prevention (CDC).[20] Superficial and deep incisional SSIs were characterized by the presence of purulent discharge from the incision site. Organ/space SSIs included anastomotic leakage and intra-abdominal abscesses characterized by purulent discharge when a drain was placed into the organ/space or abscess that involved an organ/space. Remote infections included respiratory, urinary, and gastrointestinal tract infections, as well as catheter infections. All patients were checked daily for signs of infection. If a diagnosis of infection was suspected during hospitalization, we aseptically obtained and cultured a sample of the fluid, tissue, or other material; if infectious organisms were isolated, infection was diagnosed.

The study conformed to the Clinical Research Guidelines of Shiga University of Medical Science, and it was approved by the institutional ethics committee. We obtained written informed consent from all participants.

Statistical Analysis

Baseline characteristics were summarized as mean [standard deviation (SD)] or median (interquartile range) for continuous variables, and as number (%) for categorical variables. The baseline characteristics of patients with bacterial infection were compared against those without infection by Wilcoxon or χ^2 tests. Predictors of bacterial infection were assessed by univariable and multivariable logistic regression models. Candidate predictors were age, body mass index, blood loss, CRP (POD1), ADN ratio, and preoperative ADN as continuous variables and gender (female vs. male), T2DM (yes vs. no), location of cancer (rectal vs. colon and the others vs. colon), and open surgery (yes vs. no). Factors associated with infections in crude analysis ($p < 0.05$) were included in the multivariable model. We show the odds ratios for continuous variables per 1 SD increase or decrease. To investigate the prognostic value and cutoff level of factors that significantly predicted bacterial infection, we plotted receiver operating characteristics (ROC) curves and obtained the area under the ROC curve (AUC). The AUCs of different predictors were compared using an algorithm suggested by DeLong et al..[21] The cutoff value of predictors that optimized the ability to predict the risk of bacterial infection was determined as the point closest to 1-specificity of 0 and sensitivity of 1 on the ROC curve. A standard level of significance ($p < 0.05$) was used, and the data were reported with 95 % confidence intervals (CIs). Analyses were performed by SAS 9.4 (SAS Institute, Cary, NC, USA) and Stata 13 (StataCorp, College Station, TX, USA).

RESULTS

In total, 49 patients (37.4 %) experienced postoperative infections during the 21-day observation period or until the day of discharge. Of the 37 patients who developed SSIs, 22 had incisional infections and 15 had organs/space infections. However, 15 patients developed remote infections, including five cases of pneumonia, six cases of enterocolitis, one case of catheter-related infection, one case of cholecystitis, and two cases of urinary tract infection. Three patients developed more than one postoperative infection, and one patient died of pneumonia. Three of the six cases of enterocolitis were associated with postoperative paralytic ileus. Postoperative infection was confirmed on mean postoperative day 7.2 (range 2–21 days).

Table 1 shows the surgery-related risk factors and characteristics of patients with and without postoperative

TABLE 1 Baseline characteristics of patients with and without postoperative infection

Characteristic	No infection ($n = 82$)	Infection ($n = 49$)	p^a
Age (y)	67.7 (11.2)	66.7 (9.9)	0.410
Male gender	54 (66 %)	33 (67 %)	0.861
BMI	23.3 (3.0)	22.8 (3.0)	0.414
Body weight (kg)	58.4 (10.1)	58.5 (12.5)	0.914
Height (cm)	160.1 (10)	162 (10.9)	0.236
History of diabetes mellitus	12 (15 %)	14 (33 %)	0.028
Total operation time (min)	287 (106)	340 (153)	0.057
Blood loss (g)	193 (70–400)	410 (90–1415)	0.007
Location of cancer			
Colon	41 (50 %)	20 (41 %)	0.253
Rectum	38 (46 %)	24 (49 %)	
Others	3 (4 %)	5 (10 %)	
Type of surgical procedure			
Laparoscopic	34 (41 %)	11 (22 %)	0.027
Open	48 (59 %)	38 (78 %)	
Preoperative CRP (mg/dl)	0.12 (0.07–0.50)	0.18 (0.10–0.60)	0.139
CRP POD1 (mg/dl)	8.90 (4.20)	10.65 (4.13)	0.016
Preoperative ADN (μg/dl)	7.90 (6.20–11.1)	9.20 (6.91–12.80)	0.122
ADN POD1 (μg/dl)	6.38 (4.88–9.80)	6.40 (5.09–9.08)	0.999
ADN ratio	0.84 (0.13)	0.72 (0.14)	0.0001

Data are presented as mean (standard deviation) for continuous variables without skewed distribution, median (interquartile range) for continuous variables with skewed distribution, and *n* (%) for categorical variables

BMI body mass index, *CRP* C-reactive protein, *POD1* postoperative day 1, *ADN* adiponectin

[a] Difference between groups was tested by Wilcoxon rank sum test for continuous variables and χ^2 test for categorical variables

infections . The baseline data for history of T2DM, blood loss, type of surgical procedure (laparoscopic vs. open), CRP level (POD1), and ADN ratio were significantly different between the two groups.

Logistic regression analyses were performed to identify independent risk factors for postoperative infection (Table 2). Type of surgical procedure and CRP level showed significant associations with the rate of infection in crude analysis, but not in multivariable analysis. Blood loss showed a marginal trend toward significance in multivariable analysis. History of T2DM and the ADN ratio were independent variables, and both remained significant independent variables when type of surgical procedure blood loss and CRP were adjusted. The multivariable-adjusted odds ratio of history of T2DM was 2.93, whereas the odds ratio of the ADN ratio per 1 SD decrease was 2.78 (1/0.36).

The ROC analysis indicated that the ADN ratio and blood loss were equally predictive of postoperative infection. The AUCs of the ADN ratio and blood loss were 0.707 (95 % CI 0.609–0.805) and 0.698 (95 % CI 0.593–0.803), respectively (Fig. 1). The AUCs of the ADN ratio and blood loss were not significantly different ($p = 0.975$). The optimal cutoff value for the ADN ratio was 0.77, with a sensitivity and specificity of 0.612 and 0.793, respectively . The optimal cutoff value for blood loss was 400 ml, with a sensitivity and specificity of 0.571 and 0.744, respectively (Fig. 1). Positive and negative predictive values for the ADN ratio were 0.638 and 0.774, respectively. Positive and negative predictive values for blood loss were 0.571 and 0.744, respectively.

To identify determinant factors of high ADN ratio, cutoff value for the ADN ratio (0.77) from the ROC analysis was used to calculate related factors. Location of cancer, type of surgical procedure, blood loss, and CRP level showed significant associations with high ADN ratio in crude analysis. Multivariable analysis revealed that blood loss and the CRP level were significant independent variables (Table 3).

DISCUSSION

We demonstrated the surgery-related risk factors and patient characteristics that predict postoperative infection after colorectal cancer and gastric cancer surgery were similar. Previously, we found that the ADN ratio and T2DM were independent predictors for postoperative infection in gastric cancer patients. Similarly, we identified both ADN ratio and T2DM as independent predictors of

TABLE 2 Predictors of postoperative infection

Risk factor	Crude		Multivariable (adjusted)[a]	
	Odds ratio (95 % CI)	*p*	Odds ratio (95 % CI)	*p*
Age	0.91 (0.64–1.30)	0.603		
Female vs. male	0.94 (0.44–1.98)	0.861		
BMI	0.82 (0.57–1.19)	0.294		
Diabetes	2.65 (1.09–6.44)	0.031	2.93 (1.03–8.38)	0.044
Location of cancer				
Rectal vs. colon	1.29 (0.62–2.71)	0.494		
Other vs. colon	3.42 (0.74–15.74)	0.115		
Open surgery	2.45 (1.10–5.46)	0.029	0.70 (0.24–2.02)	0.512
Blood loss	2.13 (1.29–3.5)	0.003	1.94 (0.94–3.99)	0.073
CRP POD1	1.52 (1.05–2.21)	0.026	1.09 (0.69–1.73)	0.707
ADN ratio	0.37 (0.23–0.61)	<0.0001	0.36 (0.18–0.71)	0.003
Preoperative ADN	1.45 (0.98–2.14)	0.062		

Odds ratio for each continuous variable was expressed for 1 standard deviation increase (age 10.7 years, BMI 3.0 kg/m^2, blood loss 883 ml, CRP POD1 4.24 mg/dl, ADN ratio 0.14, preoperative ADN 6.39)

CI confidence interval, *BMI* body mass index, *CRP* C-reactive protein, *POD1* postoperative day 1, *ADN* adiponectin

[a] Multivariable model included statistically significant ($p < 0.05$) factors in crude analysis

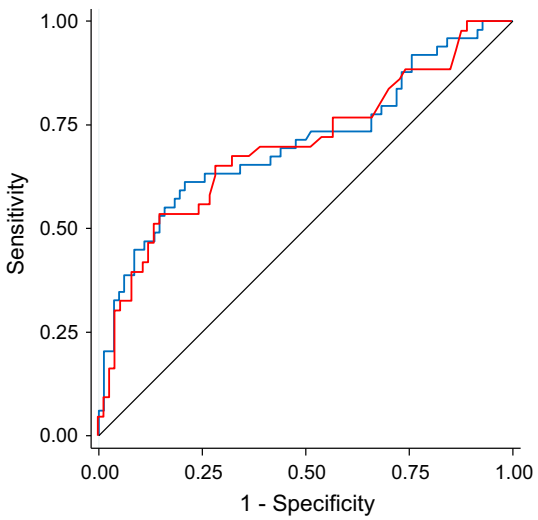

FIG. 1 Receiver operating characteristics (ROC) curves of adiponectin (ADN) ratio for prediction of postoperative infection. *Red line* represents blood loss, *blue line* ADN ratio. Areas under ROC curves of ADN ratio and blood loss were 0.707 (95 % CI 0.609–0.805) and 0.698 (95 % CI 0.593–0.803), respectively. There was no significant difference in areas under ROC curves between ADN ratio and blood loss ($p = 0.975$). Optimal cutoff values (sensitivity/specificity/positive predictive value/negative predictive value) for predicting ADN ratio and blood loss were 0.77 (0.612/0.793/0.638/0.774) and 400 g (0.571/0.744/0.571/0.744), respectively

postoperative infection after colorectal cancer. These results confirm the importance of perioperative ADN measurement for gastrointestinal cancer surgery.

In colorectal cancer surgery, the baseline history of T2DM, blood loss, type of surgical procedure, CRP level on POD1, and ADN ratio were significantly different between groups (Table 1). In the logistic regression analysis, both ADN ratio and T2DM were significant, even after controlling for type of surgical procedure, blood loss, CRP, and preoperative ADN (Table 2). Although the preoperative ADN level has been reported to be a risk factor for postoperative infection, we found that this was not the case.[22] These differences may result from differences in patient characteristics or the number of cases studied.

The acute reduction in ADN levels after surgery could result from plasma ADN levels decreasing with blood dilution because of blood loss and fluid replacement. Indeed, blood loss showed a marginal trend toward significance (Table 2). However, in our previous study, we excluded the possibility that a postoperative decrease in plasma ADN levels was due to blood loss or blood dilution by infusion because the ADN levels were unchanged after the removal of 400 ml of blood for autotransfusion.

The present results, demonstrating that the ADN ratio is one of the best predictors of postoperative infectious complications in patients with colorectal cancer, are similar to those of our previous results in patients with gastric cancer. Blood loss was also comparable to the ADN ratio as a predictor of postoperative infection in patients with gastric cancer. Moreover, the cutoff values for the ADN ratio (0.77) and blood loss (400 ml) in the current study were similar to those in patients with gastric cancer (ADN ratio 0.76; blood loss 405 ml), suggesting that these results can be applied to gastrointestinal cancer surgery in general.[15] Recent studies of predicting values regarding postoperative infectious complications have focused on

TABLE 3 Determinant factors of high ADN ratio

Risk factor	Crude		Multivariable (adjusted)[a]	
	Odds ratio (95 %CI)	*p*	Odds ratio (95 %CI)	*p*
Age	0.91 (0.64–1.30)	0.590		
Female vs. male	1.03 (0.49–2.17)	0.937		
BMI	1.08 (0.76–1.55)	0.664		
Diabetes	1.88 (0.78–4.52)	0.159		
Location of cancer				
Rectal vs. colon	5.89 (2.59–13.42)	<0.0001	2.34 (0.58–6.48)	0.102
Others vs. colon	4.55 (0.98–21.03)	0.053	1.84 (0.28–11.96)	0.521
Open surgery	5.43 (2.18–13.49)	0.0003	1.57 (0.54–4.62)	0.411
Blood loss	10.99 (3.83–31.58)	<0.0001	2.09 (0.98–4.46)	0.002
CRP POD1	1.72 (1.18–2.52)	0.005	1.61 (1.03–2.53)	0.039

High ADN ratio is defined as ADN ratio > 0.77. Odds ratio for each continuous variable was expressed for 1 standard deviation increase (age 10.7 years, BMI 3.0 kg/m^2, blood loss 883 ml, CRP POD1 4.24 mg/dl)

CI confidence interval, *BMI* body mass index, *CRP* C-reactive protein, *POD1* postoperative day 1, *ADN* adiponectin

[a] Multivariable model included statistically significant ($p < 0.05$) factors in crude analysis

CRP.[23–25] Our present study failed to show postoperative CRP level as a useful predictor of postoperative infection in the multivariate analysis. There are several potential reasons for this difference. One possibility is the way the statistical analysis was performed. In our statistical analysis, we used CRP on POD1 as a continuous variable and did not use thresholds for CRP, as others have. Another possibility is the timing of measuring CRP. Others have measured CRP on POD3 or POD4. In our study, we focused on early postoperative (POD1) predictors of postoperative infections and measured CRP on POD1. In our preliminary study, among 49 patients with postoperative infection after colorectal cancer surgery, ADN ratio was comparable between CRP level on POD1 in the $\geq$ 10 mg/dl group and the $<$ 10 mg/dl group. This observation suggested that inflammatory reaction as assessed by CRP on POD1 is not associated with decreased ADN ratio in patients with postoperative infection. Other researchers will need to verify significant factors, including ADN ratio and CRP, for the detection of infectious complications.

Our previous report and a recent study by another group have shown that the administration of ADN secretagogues improved survival with increased ADN levels in a rat and mouse sepsis model.[26, 27] Given that the ADN ratio or postoperative ADN levels increase with the administration of ADN secretagogues, the development of postoperative infection after gastrointestinal surgery may be reduced. Because ADN secretagogues can be used as antidiabetic drugs, a prospective study is warranted that includes patients with diabetes undergoing gastrointestinal surgery, with an end point that assesses the postoperative infection rate.

The CDC guidelines for the prevention of SSIs recommend the administration of surgical antibiotic prophylaxis for 24 h in clean-contaminated surgeries, such as colectomy.[20] In contrast, the recommended duration of surgical antibiotic prophylaxis is 3–4 days in Japan.[28] A multicenter examination by the Japanese Society for Surgical Infection evaluated prophylactic surgical antibiotic administration for 24 h and for 4 days after several types of major surgery, including low anterior resection of the rectum. In patients undergoing elective rectal surgery, the incidence of SSI was not significantly different between those receiving a single dose of postoperative antibiotic and those receiving multiple doses of antibiotics.[29] However, in clinical practice, surgeons use antibiotics when faced with high-risk patients on POD1 after colorectal surgery. Thus, it is important to identify patients at high risk of postoperative infection to provide them with continued antibiotics after POD1. Because the ADN ratio can be assessed within a day after surgery, it could be used to predict the necessity of antibiotic continuation to control and prevent infection.

CONCLUSIONS

The ADN ratio is a clinically useful predictor of postoperative infection in patients with colorectal cancer. The ADN ratio may be used to identify patients at high risk of postoperative infection on POD1 and to individualize treatment to their needs, thereby preventing infection and potentially reducing costs.

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CONFLICT OF INTEREST The authors declare no conflict of interest.

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