Asian Journal of Surgery (2016) xx, 1—9

Available online at www.sciencedirect.com

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journal homepage: www.e-asianjournalsurgery.com

Asian Journal of Surgery

ORIGINAL ARTICLE

Monitoring perioperative serum albumin can identify anastomotic leakage in colorectal cancer patients with curative intent

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Received 1 April 2016; received in revised form 14 June 2016; accepted 21 June 2016

KEYWORDS
anastomotic leakage;
colorectal cancer;
postoperative hypoalbuminemia

Summary *Background:* Preoperative hypoalbuminemia is a well-known risk factor for anastomotic leakage after colorectal surgery, but the association between perioperative albumin level and anastomotic leakage has not been fully investigated in curative colorectal cancer (CRC) patients.
Methods: In total, 200 CRC patients (Stage I—III) undergoing curative laparoscopic surgery between January 2004 and December 2013 were enrolled in this study. We collected data on surgical factors, perioperative levels of serum albumin and inflammatory markers, and perioperative factors affecting hypoalbuminemia from 196 CRC patients to assess the relation to anastomotic leakage.
Results: Anastomotic leakage occurred in 11 cases (5.6%) and the frequency was higher in rectal cancer patients ($p = 0.0044$). There was no significant difference of preoperative serum albumin level between the anastomotic leakage group (AL) and the nonanastomotic leakage group (NAL). Postoperative serum albumin levels in AL were significantly lower than in NAL [postoperative day (POD) 0, $p = 0.0004$; POD1, $p = 0.0001$; POD3, $p = 0.0004$; and POD7, $p = 0.0021$]. On multivariate analysis, lower average level of serum albumin on POD1 and POD3 {odds ratio (OR) [95% confidence interval (CI)] = 7.53 (1.60—55.80), $p = 0.0095$}, higher average level of serum white blood cells on POD1 and POD3 [OR (95% CI) = 7.24 (1.40—59.25), $p = 0.0165$], and surgery for rectal cancer [OR (95% CI) = 15.18 (3.26—93.99), $p = 0.0004$] were independent risk factors for anastomotic leakage.

Conflicts of interest: The authors have no conflicts of interest to disclose.

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http://dx.doi.org/10.1016/j.asjsur.2016.07.009

Conclusion: Lower early postoperative serum albumin levels are a potentially valuable indicator of anastomotic leakage in CRC patients undergoing curative surgery.

1. Introduction

Anastomotic leakage is a major complication after the curative resection of colorectal cancer (CRC) because it threatens patients' quality of life, increases the risk of local recurrence, and worsens cancer prognosis.[1–3] Several surgical procedures have been attempted to prevent anastomotic leakage; however, it can occur to a certain degree among those undergoing curative colorectal surgery. Indeed, recent reports demonstrated that the frequency of anastomotic leakage was between 3.6% and 15% after elective colorectal surgery.[4–6] In addition, anastomotic leakage rates are approximately the same between open and laparoscopic surgeries.[7] Therefore, it is important not only to evaluate the risk of anastomotic leakage, but also to diagnose anastomotic leakage early to prevent the patient's condition from worsening.

Although there is no precise consensus, a number of risk factors for anastomotic leakage after colorectal surgery have been proposed. For example, well-known risk factors are male sex, malnutrition, neoadjuvant therapy, rectal localization of tumor, length of surgery, and intraoperative blood transfusion.[5,8–11] Preoperative hypoalbuminemia, a well-known indicator for malnutrition, is one of the most prevalent risk factors associated with postoperative complications in colorectal surgery, including anastomotic leakage.[12–14] Although the serum albumin level often decreases after moderate to major gastrointestinal surgery because of increased vascular permeability, third space albumin loss with surgical stress, and perioperative fluid overload,[15–18] the association between perioperative serum albumin levels and anastomotic leakage has not been fully evaluated in CRC patients. In this study, we aimed to evaluate whether perioperative serum albumin levels can be monitoring markers for early diagnosis of anastomotic leakage in order to introduce an adequate procedure that can be useful to ameliorate the development of this troublesome complication after CRC surgery.

2. Methods

2.1. Patients

A total of 200 patients who underwent potentially curative laparoscopic surgery for CRC (Stage I—III) at the Department of Gastrointestinal and Pediatric Surgery of Mie University Graduate School of Medicine, Mie, Japan from January 2004 to December 2013 were included in this retrospective study. Staging was principally based on the Union for International Cancer Control (UICC) TNM classification of CRC. Curative resection was defined as the absence of any residual tumor from 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 no perioperative mortality was observed.

We usually performed colorectal contrast enema with water soluble gastrointestinal contrast medium (amidotrizoic acid), on postoperative day (POD) 3 in the case of colon cancer, and on POD6 in the case of rectal cancer. In this study, we diagnosed postoperative anastomotic leakage with this colorectal contrast enema.

One patient was excluded in this study because abdominal perineal resection with no anastomosis was performed. In addition, three patients who received hemodialysis were excluded from the analysis because their perioperative factors (e.g., perioperative fluid and albumin administration, urine output, etc.) were different from those of the patients who were not receiving hemodialysis.

The association between postoperative anastomotic leakage and clinicopathological factors, surgical factors, alteration of perioperative serum albumin levels, alteration of perioperative serum inflammation markers [white blood cells (WBC) and C-reactive protein (CRP) levels], perioperative in-out balance, and the amount of perioperative albumin administration was analyzed in 196 patients.

In addition, we performed univariate and multivariate analyses for detecting the demographic, tumor specific, surgical, and blood laboratory factors affecting anastomotic leakage. In regard to postoperative serum albumin and serum inflammatory markers (WBC and CRP), we selected the average of each serum levels on POD1 and POD3 as a candidate predictor because we wanted to identify monitoring markers to diagnose anastomotic leakage earlier during the postoperative period. The cut off value of the average serum albumin on POD1 and POD3 was defined using Receiver Operating Characteristic (ROC) analysis for anastomotic leakage. The cut off values of the average serum WBC and CRP on POD1 and POD3 were, respectively, were defined according to the median serum levels in our study cohort.

Moreover, we analyzed the correlation between the average amount of drained pelvic fluid per day (mL/d) and the occurrence of anastomotic leakage and early postoperative serum albumin levels in 20 rectal cancer patients who underwent pelvic drain insertion at the end of surgery. (In our institution, no drains are inserted for colon cancer patients or rectosigmoid cancer patients.)

Peripheral blood samples were collected from patients at the perioperative period. Written informed consent was obtained from all participants according to the local ethics guidelines and all participants stated their willingness to donate blood for research. Blood collection and subsequent analyses were approved by the Institutional Review Boards of Mie University Hospital (protocol number, 2216).

2.2. Statistical analysis

The data are presented as median (range). Correlations were evaluated using the Mann–Whitney *U* test or Fisher's exact test. Univariate and multivariate analyses were performed using logistic regression analysis to determine the factors affecting anastomotic leakage. Parameters with $p < 0.05$ in the univariate analysis were used for the multivariate analysis. All statistical analyses were carried out using JMP version 10 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient characteristics, association between anastomotic leakage and demographic, tumor specific, surgical factors

The study group comprised 95 males and 101 females aged from 37 years to 89 years (median, 69 years). Of the 196 registered patients, 135 (68.9%) had colon tumors and 61 (31.1%) had rectal tumors. Sixteen patients (8.2%) had Stage 0 disease, 58 (29.6%) had Stage I, 69 (35.2%) had Stage II, and 53 (27.0%) had Stage III. Anastomotic leakage occurred in 11 patients (5.6%). The frequency of anastomotic leakage was higher in cases of rectal cancer including rectosigmoid cancer (13.1%) than that of colon cancer (2.2%; $p = 0.0044$, shown in Table 1).

Table 1 Association between anastomotic leakage and clinicopathological variables.

Variables		*N*	Group		*p**
			NAL ($n = 185$)	AL ($n = 11$)	
Gender	Male	95	91	4	
	Female	101	94	7	0.539
Age (y)			69 (37–89)	71 (52–80)	0.932
Tumor size (mm)			30 (3–85)	48 (18–65)	**0.030**
Rectal cancer	Yes	61	53	8	
	No	135	132	3	**0.0044**
T stage	T0, T1	65	63	2	
	T2, T3, T4	131	122	9	0.343
Lymph node metastasis	Negative	143	134	9	
	Positive	53	51	2	0.730
UICC TNM stage	0, 1	74	71	3	
	2, 3	122	114	8	0.539

Data are presented as median (range).
* Bold font indicates statistical significance.
AL = anastomotic Leakage; NAL = nonanastomotic leakage; UICC = Union for International Cancer Control.

Tumor size in the anastomotic leakage group (AL) was larger than that in the nonanastomotic leakage group (NAL; $p = 0.030$). Gender, age, T stage, existence of lymph node metastasis, and UICC TNM stage were not statistically different between AL and NAL (Table 1).

Operation time ranged from 101 minutes to 561 minutes (median, 220 minutes), and operative blood loss was ranged from 0 mL to 640 mL (median, 30 mL). Although the amount of operative blood loss in AL was not larger than that in NAL ($p = 0.863$), the operation time in AL was significantly longer than that in NAL ($p = 0.029$; Table 2).

Neither the amount of perioperative fluid administration nor the amount of perioperative urine output was statistically different between AL and NAL (Table 2).

Three patients received red cell concentrate blood transfusions intraoperatively because of preoperative anemia; while no patient was administered albumin intraoperatively (data not shown).

Three patients (1.5%) were converted to open surgery. Two cases were converted because of difficulty in rectal mobilization due to tumor progression, and the other was converted because of dense adhesion after gynecologic surgery (data not shown).

3.2. Postoperative hypoalbuminemia was correlated with anastomotic leakage

Preoperative serum albumin levels in AL were not lower than that in NAL ($p = 0.474$). In the meanwhile, postoperative serum albumin levels in AL were significantly lower than that in NAL on POD0 ($p = 0.0004$), POD1 ($p = 0.0001$), POD3 ($p = 0.0004$), and POD7 ($p = 0.0021$; Figure 1A). Average of serum albumin levels on POD1 and POD3 in AL were significantly lower than that in NAL ($p < 0.0001$; Table 2).

3.3. The association between perioperative serum inflammatory markers and anastomotic leakage

Serum WBC levels in AL were significantly higher than that in NAL on POD3 ($p = 0.013$). In the meanwhile, serum WBC levels between AL and NAL did not show statistical difference in the preoperative period ($p = 0.403$), POD1 ($p = 0.066$), and POD7 ($p = 0.216$) (Figure 1B). The averages of serum WBC levels on POD1 and POD33 in AL were significantly higher than that in NAL ($p = 0.012$; Table 2).

Serum CRP levels in AL were significantly higher than in NAL on POD3 ($p = 0.019$), and POD7 ($p = 0.0027$). In the meanwhile, serum CRP levels between AL and NAL did not show statistical differences in the preoperative period ($p = 0.547$) and POD1 ($p = 0.447$; Figure 1C). The averages of serum CRP levels on POD1 and POD3 in AL were significantly higher than that in NAL ($p = 0.043$; Table 2).

3.4. Early postoperative hypoalbuminemia is an independent predictor for anastomotic leakage

We identified the predictors for anastomotic leakage using logistic regression analysis. In regard to early postoperative serum candidate predictors, the cut off value of the average serum albumin on POD1 and POD3 was defined as

Please cite this article in press as: Shimura T, et al., Monitoring perioperative serum albumin can identify anastomotic leakage in colorectal cancer patients with curative intent, Asian Journal of Surgery (2016), http://dx.doi.org/10.1016/j.asjsur.2016.07.009

Table 2 Association between anastomotic leakage and perioperative variables.

Variables	Group		p
	NAL (n = 185)	AL (n = 11)	
Operation time (min)	217 (101–514)	248 (187–561)	**0.029**
Operative blood loss (mL)	30 (0–640)	27.5 (0–350)	0.863
Amount of intraoperative fluid administration (mL/kg/h)	9.18 (1.36–20.14)	8.18 (4.67–19.16)	0.747
Amount of intraoperative urine output (mL/kg/h)	1.39 (0.25–11.38)	1.26 (0.40–4.90)	0.962
Amount of fluid administration on POD1 (mL/kg/h)	1.64 (0.96–3.13)	1.77 (1.43–2.55)	0.316
Amount of urine output on POD1 (mL/kg/h)	1.11 (0.24–2.73)	0.78 (0.41–2.50)	0.771
Average amount of fluid administration on POD1–POD3 (mL/kg/h)	1.58 (0.97–2.62)	1.77 (1.39–2.47)	0.224
Average amount of urine output on POD1–POD3 (mL/kg/h)	1.35 (0.47–2.74)	1.48 (0.79–2.25)	0.741
Average of serum Alb on POD1 & POD3 (g/dL)	3.3 (2.05–4.05)	2.9 (2.65–3.2)	**< 0.0001**
Average of serum CRP on POD1 & POD3 (mg/dL)	6.65 (1.53–17.89)	10.52 (1.9–16.21)	**0.043**
Average of serum WBC on POD1 & POD3 (/uL)	7660 (3440–16,600)	9090 (6770–12070)	**0.012**

Data are presented as median (range).
* Bold indicates statistical significance.
Alb = albumin; AL = anastomotic leakage; NAL = nonanastomotic leakage; POD = postoperative day.

3.2 g/dL using ROC analysis for anastomotic leakage (sensitivity was 1.00 and specificity was 0.64), and the cut off values of the average serum WBC and CRP on POD1 and POD3 were 7750/uL and 6.88 mg/dL, respectively, according to the median level in our study cohort.

Univariate analysis showed that lower average levels of serum albumin on POD1 and POD3 (p = 0.0006), higher average levels of serum WBC and CRP on POD1 and POD3 (WBC, p = 0.0227; CRP, p = 0.0227), and surgery for rectal cancer (p = 0.0034) were significant predictors affecting anastomotic leakage. Multivariate analysis using these four predictors revealed that lower average levels of serum albumin on POD1 and POD3 (OR = 7.53, 95% CI = 1.60–55.80; p = 0.0095), higher average levels of serum WBC on POD1 and POD3 (HR = 7.24, 95% CI = 1.40–59.25; p = 0.0165), and surgery for rectal cancer (HR = 15.18, 95% CI = 3.26–93.99; p = 0.0004) were identified as independent risk factors for anastomotic leakage for CRC patients with curative laparoscopic surgery (Table 3).

Operation time ranged from 151 minutes to 561minutes (median, 246 minutes), and operative blood loss ranged from 0 mL to 640 mL (median, 25 mL). Although the amount of operative blood loss between AL and NAL did not show statistical difference (p = 0.347), the operation time in AL was significantly longer than that in NAL (p = 0.0089; Table 4).

We investigated the location of anastomosis (distance from anal verge) using postoperative contrast colorectal enema, and we revealed that location of anastomosis in AL was more shorter from anal verge than that of NAL (p = 0.041). In regard to the other surgical factors, the type of surgery and the number of linear staplers for rectal resection were not statistically different between AL and NAL (Table 4).

In regard to early postoperative serum markers, the average serum albumin levels on POD1 and POD3 in AL were significantly lower than that in NAL (p = 0.0005). Both of the average serum WBC and CRP levels on POD1 and POD3 in AL were also significantly higher than that in NAL (p = 0.0044 and p = 0.0018, respectively; Table 4).

3.5. Patient characteristics, association between anastomotic leakage and each variable in rectal cancer patients

In addition, we performed subgroup analysis in 61 rectal cancer patients (including rectosigmoid cancer patients) because the frequency of anastomotic leakage was higher than that of colon cancer patients in our study. The study subgroup comprised 29 males and 32 females aged from 37 years to 89 years (median, 68 years). Of the 61 registered patients, four (6.6%) had Stage 0 disease, 20 (32.8%) had Stage I, 19 (31.1%) had Stage II, and 18 (29.5%) had Stage III. Anastomotic leakage occurred in eight patients (13.1%).

In regard to demographic and tumor specific factors, gender, age, tumor size, location of tumor, T stage, existence of lymph node metastasis, and UICC TNM stage were not statistically different between AL and NAL (Table 4).

3.6. Early postoperative hypoalbuminemia tended to be a significant predictor for anastomotic leakage in rectal cancer patients

We identified the predictors for anastomotic leakage using logistic regression analysis in 61 rectal cancer patients. In regard to early postoperative serum candidate predictors, the cut off value of the average serum albumin on POD1 and POD3 was defined as 3.1 g/dL using ROC analysis for anastomotic leakage (sensitivity was 0.88 and specificity was 0.78), and the cut off value of the average serum WBC and CRP on POD1 and POD3 was 7337/uL and 5.63mg/dL, respectively according to the median level in our subgroup study cohort.

Univariate analysis showed that lower average levels of serum albumin on POD1 and POD3 (p = 0.0074) and higher average levels of serum WBC and CRP on POD1 and POD3 (WBC; p = 0.0159, CRP; p = 0.0159) were also significant predictors affecting anastomotic leakage. Multivariate

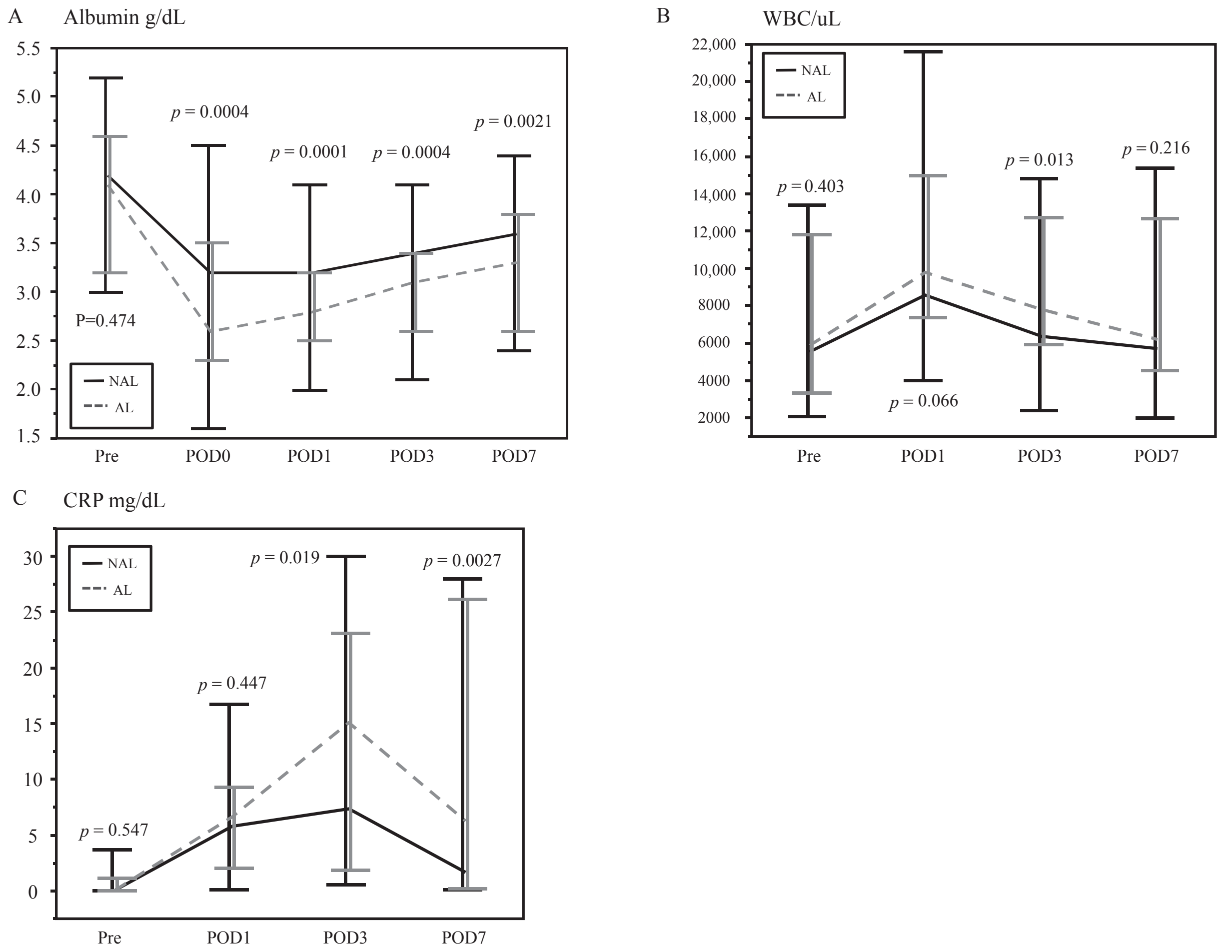

Figure 1 The alteration of perioperative serum levels of albumin and inflammatory markers [white blood cells (WBC) and C-reactive protein (CRP)] in anastomotic leakage group (AL) and nonanastomotic leakage group (NAL). (A) Preoperative serum albumin levels in AL (median, 4.1 g/dL; range, 3.2–4.6 g/dL) were not lower than in NAL (median, 4.2 g/dL; range, 3.0–5.2 g/dL; $p = 0.474$). In the meanwhile, postoperative serum albumin levels in AL were significantly lower than in NAL on postoperative day (POD) 0 (AL: median, 2.6 g/dL and range, 2.3–3.5 g/dL; NAL: median, 3.2 g/dL and range, 1.6–4.5 g/dL; $p = 0.0004$), POD1 (AL: median, 2.8 g/dL and range, 2.5–3.2 g/dL; NAL: median, 3.2 g/dL and range, 2.0–4.1 g/dL; $p = 0.0001$), POD3 (AL: median, 3.1 g/dL and range, 2.6–3.4 g/dL; NAL: median, 3.4 g/dL and range, 2.1–4.1 g/dL; $p = 0.0004$), and POD7 (AL: median, 3.3 g/dL and range, 2.6–3.8 g/dL; NAL: median, 3.6 g/dL and range, 2.4–4.4 g/dL; $p = 0.0021$). (B) Serum WBC levels in AL were significantly higher than in NAL on POD3 (AL: median, 7820/uL and range, 5920–12,740/uL; NAL: median, 6390/uL and range, 2380–14,830/uL; $p = 0.013$). In the meanwhile, serum WBC levels between AL and NAL did not show statistical difference in the preoperative period (AL: median, 5845/uL and range, 3350–11,830/uL; NAL: median, 5540/uL and range, 2070–13,370/uL; $p = 0.403$), POD1 (AL: median, 9790/uL and range, 7340–15,000/uL; NAL: median, 8570/uL and range, 3970–21,590/uL; $p = 0.066$), and POD7 (AL: median, 6190/uL and range, 4550–12,660/uL; NAL: median, 5720/uL and range, 2020–15,380/uL; $p = 0.216$). (C) Serum CRP levels in AL were significantly higher than in NAL on POD3 (AL: median, 15.12 mg/dL and range, 1.81–23.14 mg/dL; NAL: median, 7.46 mg/dL and range, 0.56–30.05 mg/dL; $p = 0.019$), and POD7 (AL: median, 6.22 mg/dL and range, 0.19–26.17 mg/dL; NAL: median, 1.64 mg/dL and range, 0.13–27.98 mg/dL; $p = 0.0027$). In the meanwhile, serum CRP levels between AL and NAL did not show statistical difference in the preoperative period (AL: median, 0.10 mg/dL and range, 0.01–1.06 mg/dL; NAL: median, 0.07 mg/dL and range, 0.01–3.65 mg/dL; $p = 0.547$), and POD1 (AL: median, 6.66 mg/dL and range, 1.99–9.27 mg/dL; NAL: median, 5.94 mg/dL and range, 0.11–16.71 mg/dL; $p = 0.447$).

analysis using these three predictors revealed that lower average levels of serum albumin on POD1 and POD3 (HR = 4.49, 95% CI = 0.77–29.58; $p = 0.0955$) and higher average levels of serum WBC on POD1 and POD3 (HR = 5.62, 95% CI = 0.76–115.34; $p = 0.0952$) tended to be a significant predictor for anastomotic leakage for rectal cancer patients with curative laparoscopic surgery (Table 5).

3.7. Larger amount of drainage fluid was associated with anastomotic leakage and early postoperative hypoalbuminemia in rectal cancer patients

We investigated the association of the amount of drainage fluid in rectal cancer patients treated by laparoscopic low anterior resection (data were available in 20 cases out of a

Table 3 Univariate and multivariate analysis of risk factors influencing anastomotic leakage.

Variables		Univariate analysis			Multivariate analysis		
		OR	95% CI	*p*	OR	95% CI	*p*
Average of serum Alb on POD1 & POD3 (g/dL)	(< 3.2 vs. ≥ 3.2)	10.33	2.56–69.27	**0.0006**	7.53	1.60–55.80	**0.0095**
Preoperative serum Alb (g/dL)	(< 3.5 vs. ≥ 3.5)	2.54	0.13–16.43	0.450			
Average of serum CRP on POD1 & POD3 (mg/dL)	(> 6.88 vs. ≤ 6.88)	4.95	1.23–33.11	**0.0227**	5.27	0.98–42.84	0.053
Average of serum WBC on POD1 & POD3 (/uL)	(> 7750 vs. ≤ 7750)	4.94	1.23–33.06	**0.0227**	7.24	1.40–59.25	**0.0165**
Gender	(Male vs. female)	0.59	0.15–2.02	0.405			
Age (y)	(≥ 70 vs. ≤ 69)	1.35	0.39–4.84	0.628			
Tumor size (mm)	(> 30 vs. ≤ 30)	2.20	0.64–8.63	0.211			
Surgery for rectal cancer	(Yes vs. no)	6.64	1.84–31.20	**0.0034**	15.18	3.26–93.99	**0.0004**
Operation time (min)	(> 220 vs. ≤ 220)	2.88	0.80–13.44	0.107			
Operative blood loss (mL)	(> 30 vs. ≤ 30)	0.84	0.24–2.89	0.783			
T stage	(T 2, 3, 4 vs. T 0, 1)	2.32	0.58–15.54	0.254			
Lymph node metastasis	(Positive vs. negative)	0.58	0.09–2.36	0.479			
UICC TNM stage	(2, 3 vs. 0, 1)	1.66	0.46–7.77	0.451			

* Bold indicates statistical significance.
Alb = albumin; CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; POD = postoperative day; UICC = Union for International Cancer Control.

Table 4 Association between anastomotic leakage and each variables in rectal cancer.

Variables		Number	Group		*p*
			NAL (*n* = 53)	AL (*n* = 8)	
Gender	Male	29	25	4	
	Female	32	28	4	0.881
Age (y)			65 (37–89)	73 (52–80)	0.315
Tumor size (mm)			35 (10–80)	45 (25–65)	0.142
Average of serum Alb on POD1 & POD3 (g/dL)			3.35 (2.35–4.05)	2.85 (2.65–3.2)	**0.0005**
Average of serum CRP on POD1 & POD3 (mg/dL)			5.38 (1.53–14.6)	10.92 (3.83–16.21)	**0.0018**
Average of serum WBC on POD1 & POD3 (/uL)			7155 (3790–11605)	9220 (6770–12070)	**0.0044**
Location of tumor	RS	27	25	2	
	Ra	18	15	3	
	Rb	16	13	3	0.476
Type of surgery	HAR	29	27	2	
	LAR	32	26	6	0.260
Operation time (min)			225 (151–426)	293 (245–561)	**0.0089**
Operative blood loss (mL)			25 (0–640)	70 (0–350)	0.347
No. of linear staplers using rectal resection	1	15	13	2	
(except the cases with no data)	≥ 2	42	37	5	0.886
Location of anastomosis (mm from anal verge)			67 (33–113)	47 (36–85)	**0.041**
T stage	T0, T1	20	19	1	
	T2, T3, T4	41	34	7	0.253
Lymph node metastasis	negative	43	36	7	
	positive	18	17	1	0.417
UICC TNM stage	0,1	24	22	2	
	2, 3	37	31	6	0.462

Data are presented as median (range).
* Bold indicates statistical significance.
Alb = albumin; AL = anastomotic leakage; CRP = C-reactive protein; HAR = high anterior resection; LAR = low anterior resection; NAL = nonanastomotic leakage; POD = postoperative day; UICC, Union for International Cancer Control; WBC = white blood cells.

Table 5 Univariate and multivariate analysis of risk factors influencing anastomotic leakage in rectal cancer.

Variables		Univariate analysis			Multivariate analysis		
		OR	95% CI	*p*	OR	95% CI	*p*
Average of serum Alb on POD1 & POD3 (g/dL)	(< 3.1 vs. ≥ 3.1)	8.75	1.80–50.30	**0.0074**	4.49	0.77–29.58	0.0955
Preoperative serum Alb (g/dL)	(< 3.5 vs. ≥ 3.5)	3.64	0.16–43.27	0.353			
Average of serum CRP on POD1 & POD3 (mg/dL)	(> 5.63 vs. ≤ 5.63)	9.00	1.44–175.06	**0.0159**	4.57	0.57–95.44	0.1597
Average of serum WBC on POD1 & POD3 (/uL)	(> 7337 vs. ≤ 7337)	9.00	1.44–175.06	**0.0159**	5.62	0.76–115.34	0.0952
Gender	(Male vs. female)	1.12	0.24–5.19	0.881			
Age (y)	(≥ 69 vs. ≤ 68)	2.35	0.52–12.42	0.266			
Tumor size (mm)	(>35 vs. ≤35)	2.35	0.52–12.43	0.266			
Location of tumor	(Rb vs. RS & Ra)	1.85	0.12–2.93	0.451			
Type of surgery	(LAR vs. HAR)	3.12	0.65–22.60	0.161			
Operation time (min)	(> 246 vs. ≤ 246)	4.57	0.95–33.26	0.058			
Operative blood loss (mL)	(> 25 vs. ≤ 25)	2.01	0.45–10.64	0.362			
Number of linear stapler using rectal resection	(1 vs. ≥ 2)	1.14	0.15–6.03	0.886			
Location of anastomosis (mm from anal verge)	(< 63 vs. ≥ 63)	3.75	0.77–27.53	0.105			
T stage	(T 2,3,4 vs. T 0,1)	3.91	0.63–75.97	0.169			
Lymph node metastasis	(positive vs. negative)	0.30	0.016–1.90	0.225			
UICC TNM stage	(2,3 vs. 0,1)	2.13	0.44–15.46	0.360			

Alb = albumin; CI = confidence interval; CRP = C-reactive protein; OR = odds ratio; POD = postoperative day; UICC = Union for International Cancer Control.
Bold indicates statistical significance.

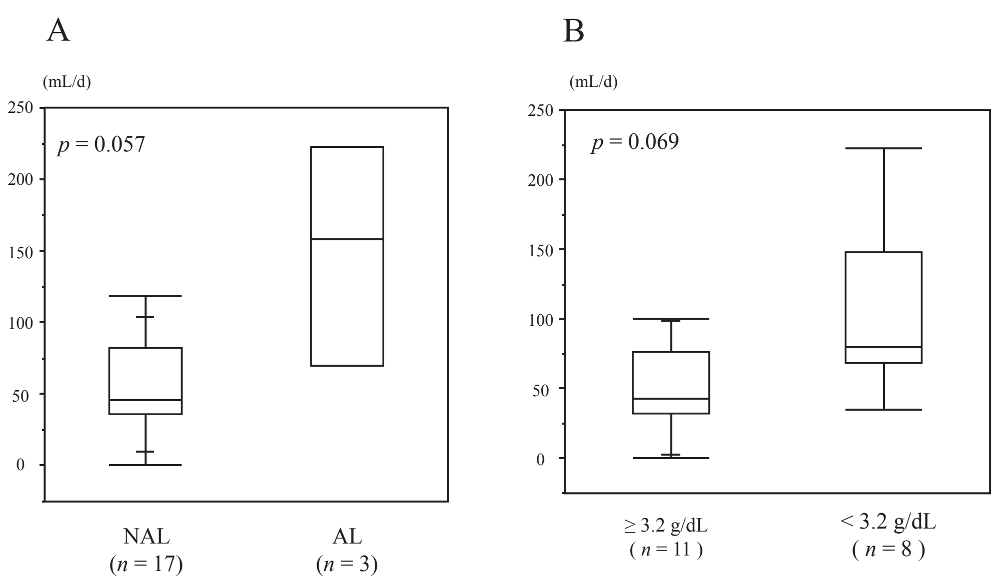

Figure 2 The association of the amount of drainage fluid in rectal cancer patients treated by laparoscopic low anterior resection (LAR). (A) The average amount of drainage fluid (mL/d) in anastomotic leakage group (AL; $n = 3$; median, 158.3 mL/d; range, 70–222.5 mL/d) tended to be larger than that in nonanastomotic leakage group (NAL; $n = 17$; median, 46.3 mL/d; range, 0–118.3 mL/d; $p = 0.057$). (B) The average amount of drainage fluid in the group of early postoperative hypoalbuminemia (average serum albumin levels on POD1 and POD3 were lower than 3.2 mg/dL, $n = 8$; median, 80 mL/d, range, 35–222.5 mL/d) tended to be larger than that in the group of non-early postoperative hypoalbuminemia ($n = 11$; median, 42.8 mL/d; range, 0–100 mL/d; $p = 0.069$; 1 patient in NAL was excluded because blood samples were not taken on POD3).

Please cite this article in press as: Shimura T, et al., Monitoring perioperative serum albumin can identify anastomotic leakage in colorectal cancer patients with curative intent, Asian Journal of Surgery (2016), http://dx.doi.org/10.1016/j.asjsur.2016.07.009

total of 32 patients treated by low anterior resection). The average amount of drainage fluid (mL/d) in AL ($n = 3$) tended to be larger than that in NAL ($n = 17$; $p = 0.057$; Figure 2A).

In addition, the average amount of drainage fluid in the group of early postoperative hypoalbuminemia (average serum albumin levels on POD1 and POD3 were lower than 3.2 mg/dL, $n = 8$) tended to be larger than that in the group of non-early postoperative hypoalbuminemia ($n = 11$; $p = 0.069$; 1 patient in NAL was excluded because blood samples were not taken on POD3; Figure 2B).

4. Discussion

In this study, we first found out that CRC patients complicated with anastomotic leakage (AL) presented significantly decreased early postoperative serum albumin levels compared with those without anastomotic leakage (NAL) after curative laparoscopic surgery. Moreover, multivariate analysis revealed that early postoperative hypoalbuminemia was an independent risk factor of anastomotic leakage in 196 CRC patients. In the meanwhile, multivariate analysis revealed that early postoperative hypoalbuminemia tended to be a significant indicator of anastomotic leakage in 61 rectal cancer patients. Collectively, early postoperative hypoalbuminemia might be a useful indicator for anastomotic leakage as well as serum inflammatory markers (WBC and CRP) in patients with CRC.

Malnutrition commonly encountered in patients with different types of cancer is a crucial problem that affects postoperative outcome.[19] Thus, several researches have focused on determining the best methods to assess malnutrition in patients with CRC.[20] Serum albumin is considered the most important parameter in correlation with the degree of malnutrition that can contribute to the development of postoperative complications.[21–23] Likewise, preoperative hypoalbuminemia in CRC patients is an important risk factor for postoperative outcome.[12–14] In their large retrospective study, Lai et al[13] demonstrated that patients with preoperative hypoalbuminemia had a higher rate of postoperative complications, including anastomotic leakage.

However, in our study, preoperative serum albumin levels between AL and NAL were not statistically different (although serum levels in AL were slightly lower than that in NAL, $p = 0.474$). A possible explanation for this finding may be that our cohort was not afflicted with advanced CRC with distant metastasis or cancer cachexia, which result in hypoalbuminemia. The majority of our patients had tumors at earlier stages (over 70% of patients in this cohort were node negative).

Serum albumin levels often decrease after moderate to major gastrointestinal surgery because of increased vascular permeability, third space albumin loss with surgical stress, weakened liver ability to synthesize albumin, direct albumin loss due to intraoperative blood loss, and dilution of serum albumin due to perioperative fluid overload.[15–18] It is well known that perioperative volume overload increases surgical morbidity in colorectal surgery,[24] but the effect of postoperative hypoalbuminemia on postoperative complications in CRC patients, in particular, anastomotic leakage, has not been reported previously. Our current study demonstrated that early postoperative hypoalbuminemia (in particular the average level for POD1 and POD3) was a useful predictor of anastomotic leakage in CRC patients with curative intent. Collectively, measuring albumin levels early during the postoperative period can help to determine whether it is adequate to introduce intensive antiseptic therapy for the prevention of severe sepsis secondary to anastomotic leakage.

However, why were the postoperative serum albumin levels significantly lower in AL than in NAL? In this study, intraoperative blood loss, intraoperative fluid overload, and lower perioperative urine output did not affect postoperative hypoalbuminemia. It has been reported that the distribution of albumin from intravascular to extravascular space is remarkably increased during stress, such as in severe sepsis.[25,26] In other words, inflammation secondary to leaked digestive fluid might accelerate extravascular albumin permeability into the nearby leakage site in the abdominal cavity.

Accumulating evidence is consistent with our results, which indicate that increased pelvic fluid drainage in rectal cancer patients was associated with anastomotic leakage and early postoperative hypoalbuminemia. This hypothesis should be proved, for example, by measuring albumin levels on pelvic drainage fluid from now on.

Our study has some limitations. Because the number of patients were small in the subgroup of rectal cancer patients, well-known risk factors for anastomotic leakage such as male sex, length of surgery, and rectal localization of tumor (which were mentioned in the introduction section) were not identified as significant indicators in univariate analysis for anastomotic leakage. Therefore, we need to conduct further study using a larger number of patients with rectal cancer.

In conclusion, although our retrospective study has the limitations mentioned before, our findings showed that early postoperative hypoalbuminemia among CRC patients treated with curative surgery might be a potent indicator of anastomotic leakage. Even though clinical symptoms are not present, postoperative hypoalbuminemia might be a useful decision-making tool to determine whether starvation cure should be continued, strengthening intensive antiseptic therapy, and determining surgical interventions to prevent progression of potentially severe septic conditions.

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Please cite this article in press as: Shimura T, et al., Monitoring perioperative serum albumin can identify anastomotic leakage in colorectal cancer patients with curative intent, Asian Journal of Surgery (2016), http://dx.doi.org/10.1016/j.asjsur.2016.07.009