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Drainage Fluid Amylase as a Biomarker for the Detection of Anastomotic Leakage After Low Anterior Resection of Rectal Cancer: A Two-center Study

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Abstract. *Aim: This study aimed to investigate the utility of measuring amylase levels in drainage fluid (DFA) for early, non-invasive detection of anastomotic leakage (AL) in undergoing low anterior resection (LAR) for rectal cancer. Patients and Methods: This prospective observational cohort study analyzed drainage fluid samples from patients who underwent LAR for rectal cancer at two medical centers between February 2021 and December 2023. DFA levels were measured on postoperative days (PODs) 1, 3, and 5. AL was confirmed by clinical evidence and radiological imaging. Statistical analyses were performed to evaluate the diagnostic performance of DFA. Results: Of 120 LAR cases, AL occurred in five (4.16%). DFA levels on POD 3 and 5 were significantly higher in the AL than in the non-AL group (p<0.0001). DFA on POD 5 had the highest diagnostic accuracy for early AL detection, with an area under the curve of 0.99, achieving 100% sensitivity and 99.5% specificity at a cutoff of 846 U/l. A DFA >846 U/l predicted AL with negative predictive and positive predictive values of 83.3% and 100%, respectively, on POD 5. Conclusion: Measuring DFA is a non-invasive, simple and cost-effective method for early AL detection in patients with rectal cancer undergoing LAR. Our findings also suggested that drain placement may be useful for the early detection of AL through DFA measurement.*

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The incidence of anastomotic leakage after rectal anastomosis, as reported in a systematic review was 9.8% (1), and the associated overall mortality was 2-9% (2). From an economic perspective, anastomotic leakage incurs higher costs as a result of extended hospital stays, supplementary treatments, and additional surgical interventions (3).

Several treatments have been reported to reduce anastomotic leakage, such as evaluation of blood flow by indocyanine green fluorescence (4, 5) and placement of a transanal drainage tube (6). Furthermore, several studies have reported the diagnosis of anastomotic leakage in rectal cancer based on abdominal findings (7), abdominal computed tomography (CT) (8, 9), white blood cell count (10), C-reactive protein level (10, 11), and drainage fluid content (12). However, none of those tests have become established in clinical practice due to a lack of both specificity and positive predictive value (13, 14).

A previous report highlighted the presence of high amylase levels in stomal drainage (DFA) (15), and DFA measurement has been reported to be effective as a biomarker for early detection of anastomotic leakage after total colorectal resection for inflammatory bowel disease (15, 16).

We hypothesized that the DFA level in the drainage fluid might be a useful biomarker for early detection of anastomotic leakage in cases undergoing low anterior resection (LAR) for rectal cancer. Therefore, in this study, we compared DFA between patients with and without anastomotic leakage, with the aim of determining whether assessing DFA in the drainage fluid might be useful for early detection of anastomotic leakage.

Patients and Methods

This prospective observational cohort study analyzed samples of drainage fluid from who underwent LAR for rectal cancer at Saitama Medical University International Medical Center (Hidaka, Japan) and Kawasaki Saiwai Hospital (Kawasaki, Japan) between February 2021 and December 2023. Included were at least 18 years old and had undergone elective primary LAR for rectal cancer (adenocarcinoma). Exclusion criteria were creation of a covering stoma, emergency surgery, obstructive colorectal cancer, Mile's procedure, and Hartmann's operation. Additional clinical data were retrieved from medical records. Data regarding age, sex, body mass index, American Society of Anesthesiologists score, surgical outcomes, pathological findings, and TNM stage were also retrospectively collected from electronic medical records.

Research ethics. All study participants provided informed consent, and the study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (IRB number 2024-028).

Amylase measurements. The concentration of amylase in the drainage fluid was routinely measured on postoperative days (PODs) 1, 3, and 5. The amylase concentration was measured using a biochemical analyzer. Drainage fluid was collected from the drain tube each morning, with a volume of 5 ml retrieved.

Surgical procedure. Double- or single-stapling techniques were performed after LAR. Specifically, in the case of transanal total mesorectal excision (taTME), we choose the single-stapling techniques. The surgeon routinely placed a pelvic drain at the dorsal anastomosis and inserted a transanal tube into the anal canal.

Anastomotic leakage is generally defined as developing within 2 weeks after surgery (17-19), while late anastomotic leakage is defined as occurring after POD 6 (20). Therefore, the transanal tube was removed on POD 2, while the pelvic drain was removed on POD 5.

Peri- and postoperative care. Fluid intake was started from POD 1 and oral intake from POD 3. When postoperative peritoneal irritation symptoms developed, abdominal CT was performed to identify the etiology. When the CT scan showed perianastomotic air or abscess formation around the anastomosis, the patient was considered to have anastomotic leakage; when no peritoneal irritation symptoms were found, conservative treatment was indicated.

Definition of anastomotic leakage. Anastomotic leakage was assessed according to clinical evidence and was confirmed by radiological imaging. Clinical evidence was defined as the presence of peritonitis, purulent or fecal discharge from the abdominal drain, or free air around the anastomosis area revealed by CT or an enema contrast X-ray.

Anastomotic leakage was diagnosed and categorized into grades in line with the International Study Group in Rectal Cancer recommendations (22). Grade A (anastomotic leakage confirmed solely by diagnostic imaging of the anastomosis site, despite the absence of clinical symptoms) did not require any active therapeutic intervention. Grade B (anastomotic leakage with clinical symptoms, requiring therapeutic intervention other than surgery) was managed with percutaneous or transanal drainage and antibiotic treatments. Grade C (anastomotic leakage with clinical symptoms, necessitating surgical intervention) was treated surgically. This study included all grades. Patients were followed-up for 30 days after surgery.

Statistical analysis. Statistical analyses were performed using JMP Pro 16 software (SAS Institute, Cary, NC, USA). Results are presented as medians and ranges for continuous variables, and as numbers and frequencies for categorical variables. Comparisons of median or mean values between groups were conducted using the Mann–Whitney test and the chi-square test, respectively. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

Furthermore, receiver operating characteristic curve analysis was performed, and the respective areas under the curve (AUC) were calculated to evaluate the predictive value for anastomotic leakage diagnosis, only for variables with statistically significant differences in the univariate analysis. The greater the AUC, the more accurate the test was, with 0.90-1.0 representing excellent accuracy, 0.8-0.9 good accuracy, 0.7-0.8 fair accuracy, and 0.6-0.7 poor accuracy. Sensitivity, specificity, positive-predictive value (PPV), and negative-predictive value (NPV) were calculated for DFA on PODs 1, 3, and 5. The best cutoff was determined as the value that maximized the Youden index (*i.e.* sensitivity + specificity – 1).

Results

Overall, at our two centers, 120 cases of LAR for rectal cancer in whom postoperative DFA was measured were included. The anastomotic leakage group of five cases (4.16%) was compared with the non-leakage group of 115 cases (95.8%).

Patients' characteristics. Age, body mass index, American Society of Anesthesiologists score, tumor location and preoperative treatment were not significantly different between the two groups (Table I).

Surgical outcomes. Robotic surgery was significantly more prevalent in the non-leakage group compared to the leakage group. (0% *vs*. 41%, p=0.02). Postoperative hospital stay was longer in the anastomotic leakage group than in the non-leakage group (23 *vs*. 9 days, p<0.001) (Table II).

The other parameters studied were not significantly different between the two groups (Table II). Two cases of postoperative small bowel perforation and one case of acute pancreatitis occurred in the non-leakage group.

Patients with anastomotic leakage. Five patients suffered from anastomotic leakage, and four of these underwent laparoscopic peritoneal lavage with creation of a loop ileostomy, while the remaining patient improved with conservative treatment. The onset of anastomotic leakage was POD 3 in two cases and POD 5 in three cases (Table III). These cases included four grade C and one grade B.

Drainage fluid amylase (DFA). The DFA level on PODs 3 and 5 was significantly higher in the anastomotic leakage than in the non-leakage group (p<0.0001) (Table IV).

Table I. *Patient characteristics (whole cohort).*

		AL (n=5)	Non AL (n=115)	*p*-Value
Age, years	Median (range)	62 (50-85)	68 (42-92)	0.36
Sex, n (%)	Male	5 (83.3%)	72 (62.6%)	0.4
	Female	1 (16.7%)	43 (37.4%)	
BMI, kg/m^2	Median (range)	21.2 (18.9-28.9)	22 (16-33.3)	0.61
ASA score, n (%)	1	2 (40%)	36 (31.3%)	0.73
	2	3 (60%)	73 (63.5%)	
	3	0	5 (5.2%)	
Tumor location, n (%)	Mid rectum (AV 6-10 cm)	5 (100%)	95 (82.6%)	0.17
	Lower rectum (AV 0-5 cm)	0	20 (17.4%)	
CRT, n (%)	Yes	0	7 (6.1%)	0.4

AL: Anastomotic leakage; ASA: American Society of Anesthesiologists; AV: anal verge; BMI: body mass index; CRT: chemoradiotherapy.

Table II. *Surgical outcomes and pathological findings in patients undergoing low anterior resection (LAR) for rectal cancer.*

		AL (n=5)	Non AL (n=115)	*p*-Value
Surgical approach, n (%)	Robotic	0	47 (41%)	0.02
	Laparoscopic	5 (100%)	68 (59%)	
	Open	0	0	
Surgical procedure, n (%)	LAR	5 (100%)	114 (99%)	0.91
	ISR	0	1 (0.87%)	
	taTME	0	20 (17.4%)	
Anastomosis procedure, n (%)	SST	0	21 (17.4%)	0.17
	DST	5 (100%)	94 (82.6%)	
Operative time, min	Median (range)	267 (175-287)	228 (95-495)	0.71
Bleedings, ml	Median (range)	0 (0-70)	5 (0-494)	0.68
Postoperative stay, days	Median (range)	23 (14-25)	9 (6-36)	<0.001
Pathological findings				
T	0	0	5 (4.4%)	0.56
	1	2 (20%)	34 (29.5%)	
	2	0	22 (19%)	
	3	2 (20%)	44 (38.3%)	
	4	1 (10%)	10 (8.7%)	
N	0	4 (80%)	70 (60.9%)	0.65
	1	1 (20%)	32 (27.8%)	
	2	0	10 (8.7%)	
	3	0	3 (2.61%)	
M	0	4 (80%)	110 (95.6%)	0.21
	1	1 (20%)	5 (4.4%)	

DST: Double stapling technique; ISR: intersphincteric resection; SST: single stapling technique; taTME: transanal total mesorectal excision.

The DFA on POD 5 (AUC=0.99) had the highest diagnostic accuracy for detection of anastomotic leakage (Figure 1), with a cutoff of 846 U/l, sensitivity of 100%, and specificity of 99.05%. A DFA >846 U/l on POD 5 predicted anastomotic leakage with an PPV and NPV of 83.3% and 100%, respectively (Table V).

The false-positive cases with high DFA levels included two cases of small intestinal perforation and one case of acute pancreatitis, indicating that this test is also useful for diagnosing intra-abdominal complications other than anastomotic leakage. Two cases developed postoperative small bowel perforation, and showed elevated DFA levels of 10,210 U/l and 13,120 U/l. The patient with acute pancreatitis had a DFA level of 5,680 U/l.

Discussion

In this study, we measured DFA after rectal cancer surgery and examined whether it was useful as a biomarker for early detection of anastomotic leakage. The anastomotic leakage

Table III. *Drainage fluid amylase (DFA) levels on postoperative day (POD) 1, 3, and 5 in patients with anastomotic leakage (AL).*

	Patient A	Patient B	Patient C	Patient D	Patient E
DFA, U/l					
POD 1	38	81	38	17	112
POD 3	29	63,500	33	14,191	66
POD 5	14,600	294,576	54,243	846	24,456
Day of clinical AL	5	3	5	3	5
AL grade	B	C	C	C	C

AL: Anastomosis leakage; DFA: drain fluid amylase; POD: postoperative day.

Table IV. *Drainage fluid amylase (DFA) levels in patients with anastomotic leakage (AL) at different postoperative days (POD).*

	DFA, U/L		
POD	AL (n=5)	Non AL (n=115)	*p*-Value
1	38 (17-112)	64 (12-10,210)	0.65
3	66 (29-63,500)	43 (3-13,120)	<0.001
5	5243 (846-29,576)	36 (7-2,115)	<0.001

Data are the median (range).

Table V. *Diagnostic performance of different cutoff drainage fluid amylase levels (DFA) on postoperative day 5.*

DFA at AL diagnosis (U/l)	Sensitivity	Specificity	PPV	NPV
846	100%	99.5%	83.3%	100%
<500	100%	96.2%	62.5%	100%
<250	100%	90.5%	31.3%	100%

NPV: Negative-predictive value; PPV: positive-predictive value.

group had significantly higher DFA levels than the non-leakage group. The cutoff value of DFA on POD 5 was 846 U/l, which yielded a sensitivity of 100%, specificity of 99.47%, NPV of 100%, and PPV of 83.3%, suggesting that this test is a useful method for diagnosing and particularly for ruling out anastomotic leakage. The median DFA of the non-leakage group was 60 U/l, whereas in the patients with anastomotic leakage, on the day of onset, it was 5,234 (1,191-63,500) U/l, which was 87 times that in the non-leakage group.

Komen *et al*. (23) reported that increased concentrations of lipopolysaccharide-binding protein in drainage fluid are associated with colorectal anastomotic leakage. Lipopolysaccharide-binding protein, C-reactive protein, and procalcitonin were all significantly higher in the anastomotic leakage group at PODs 2, 3 and 4, and the possibility of anastomotic leakage was reported to be 1.6 times higher than normal when lipopolysaccharide-binding protein was increased. A review on drainage fluid analysis focused mainly on interleukins 6 and 10, and tumor necrosis factor-α; however, some cytokines were not related to anastomotic leakage, and this approach is not yet clinically applicable (24). Tujinaka *et al*. (12) reported that 71.4% of patients with anastomotic leakage had a change in drainage fluid content. In our study, the NPV was as high as 99.5%, which indicates that DFA is reliable and useful as an objective test for excluding anastomotic leakage. Previous studies investigating DFA and anastomotic leakage reported an NPV of 97.5%, which our finding is consistent with (25).

Previous studies have reported that DFA is useful for the diagnosis of anastomotic leakage in who have undergone total colorectal resection for inflammatory bowel disease (16, 17). In those studies, the mean transanal amylase levels were reported to be 65,968 U/l (range=6,343-176,480 U/l) (16). However, in the present study, the DFA was as high as 5,234 (range=1,191-63,500 U/l) in anastomotic leakage cases, even in who had undergone LAR and had residual colon, which is a useful new finding. Previous reports have indicated a cut-off value of 307 U/l, studied across multiple organs. Furthermore, Clark *et al*. (17) focused on total colectomy cases, underscoring the significance of our rectum-focused study.

Whether or not to place a pelvic drain is controversial. Although Tsujinaka *et al*. have stated that placing a drain reduces anastomotic leakage (12), a meta-analysis indicated that whether a drain is placed or not does not contribute to the incidence and mortality of anastomotic leakage (26). Tominaga *et al*. reported the efficacy of drainage fluid culture and Gram staining for early detection of occult anastomotic leakage (27). Furthermore, our study also suggested that drain placement may be useful for early detection of anastomotic leakage, by measurement of DFA. Moreover, measuring DFA is inexpensive, minimally invasive, and simple (16, 17). Previous reports indicated that measuring DFA costs approximately 5.4 euros or 6 US dollars, and it does not necessitate specialized expertise (13, 27).

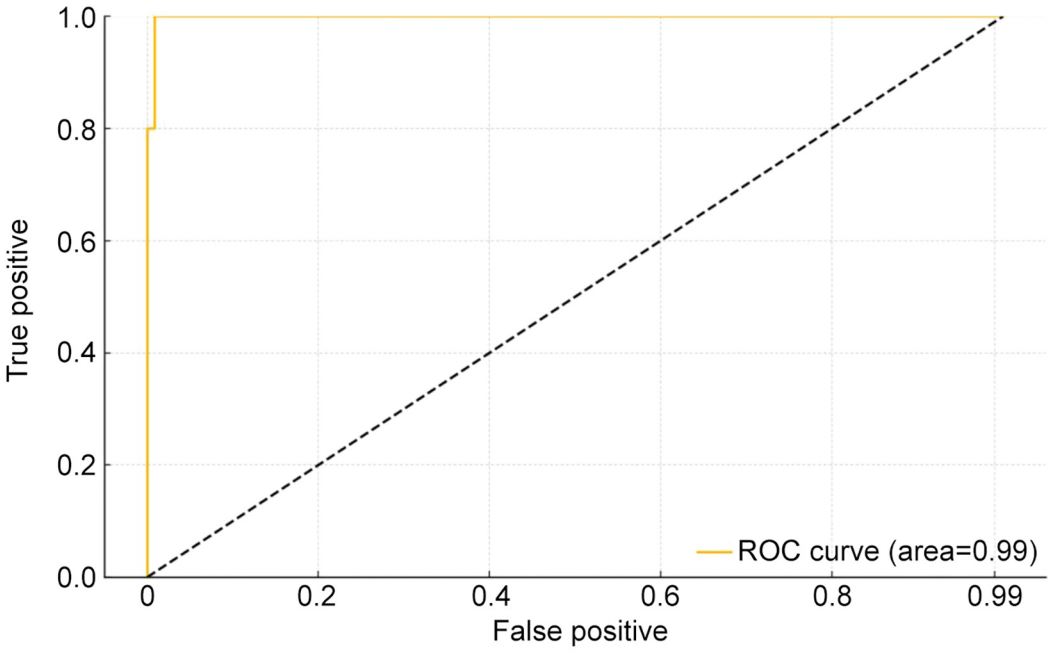

Figure 1. *Receiver operating characteristic curve of the predictive capability of drainage fluid amylase level on postoperative day 5 for anastomotic leakage. Using a cutoff of 846 U/l gave an area under the curve of 0.99, with sensitivity of 100% and specificity of 99.05%.*

Study limitations. Firstly, if the drainage position was poor and drainage aspiration was poor, the DFA tests may have yielded false-negative results. Secondly, DFA may be affected by serum amylase levels. In the non-leakage group, DFA was >500 U/l in 10 and all of them had abnormal levels of serum amylase (mean=1,179 U/l, range=463-2,633 U/l). Finally, the sample size was small, with only five cases of anastomotic leakage, while the median sample size was 26 in previous reports of biomarkers for anastomotic leakage (24). The small number of patients with anastomotic leakage makes statistical analysis difficult, and further studies with larger sample sizes are needed.

Conclusion

The present study examined DFA level and showed that it is useful for early detection of anastomotic leakage in patients who have undergone colorectal anastomosis. DFA measurement is a non-invasive test, allowing prediction and early diagnosis of anastomotic leakage. Furthermore, our results indicate that even asymptomatic anastomotic leakage may be diagnosed by using DFA. Measuring DFA may contribute to the early detection of anastomotic leakage, potentially preventing the development of severe complications.

Conflicts of Interest

None declared.

Authors' Contributions

YI, and YH designed the study and performed the experiments. YI, YM, TF, SA and NO wrote the article. YH, CH and SS drafted the original article. YH and SS supervised the conduct of this study. All Authors approved the final version of the article to be published.

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