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Early Detection of Anastomotic Leak via the Drain/Serum Amylase Ratio in Patients Undergoing Colorectal Surgery, Particularly in Ileal Anastomosis

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Purpose: A high index of suspicion is crucial for early anastomotic leak (AL) diagnosis, enabling timely intervention and conservative management. Although recent studies have highlighted the potential of drain amylase (dAmy) as a predictive marker for AL, its application in colorectal surgery remains underexplored.

Materials and Methods: A retrospective study was conducted among patients who underwent colorectal resection between March 2020 and November 2023. A total of 299 patients with at least one dAmy and serum amylase (sAmy) measurement between postoperative days 1 to 5 were included, after excluding patients with fecal diversion.

Results: Multiple logistic regression identified the drain/serum amylase ratio (d/s Amy) as an independent predictor of AL (odds ratio 1.032, 95% confidence interval 1.009–1.056; p=0.007). The receiver operating characteristic curve demonstrated significant diagnostic ability for AL [area under the curve (AUC)=0.691], with a cut-off value of 2.54, a sensitivity of 48.4%, and a specificity of 94.2%. Patients with d/s Amy ≥2.54 had a significantly higher incidence of AL with a faster diagnosis compared to conventional methods (3.5 days vs. 5 days, p=0.006). In patients who underwent ileal anastomosis, the d/s Amy ratio had an AUC of 0.936, with a sensitivity of 87.5% and a specificity of 96.6%.

Conclusion: The postoperative d/s Amy ratio is valuable for early AL detection in patients undergoing colorectal surgery, particularly in those with ileal anastomosis. This simple and noninvasive test can aid in timely diagnosis, offering earlier intervention compared with conventional methods.

Key Words: Amylase, anastomosis, surgical, postoperative complications, colon, rectum

INTRODUCTION

Anastomotic leak (AL), defined as the leakage of luminal contents from a surgical joining between two hollow viscera, has a reported incidence of 2.8%–30%.[1] AL is one of the most serious complications in colorectal surgery, often necessitating reoperation, significantly increasing the risk of mortality, and raising the likelihood of local recurrence in patients with rectal cancer, further complicating their prognosis.[2,3]

Despite the development of several predictive models to assess the risk of AL in patients with rectal cancer based on preoperative clinical factors, with reported accuracies ranging from 0.72–0.83, these models remain insufficiently reliable for guiding clinical decisions.[4,5] Although abdominal computed tomography (CT) scan is the most commonly used imaging modality for diagnosing AL, its limited ability to distinguish between normal postoperative changes and AL often leads to delayed diagnosis, typically occurring 5–7 days postoperatively, with recent studies indicating an average diagnosis time of 8.8 days.[6,7]

With the implementation of enhanced recovery after surgery protocols, which emphasize early recovery and discharge, there is an increasing need for earlier and more reliable methods to predict and diagnose AL before discharge.[8] Early diagnosis, fol-

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lowed by timely intervention, may increase the likelihood of successfully managing AL with conservative treatments rather than necessitating reoperation.

In pancreatic surgery, the concentration of drain amylase (dAmy) or its ratio to serum amylase (sAmy) activity is widely used to diagnose postoperative pancreatic fistula (POPF).[9-11] Although this method has demonstrated efficacy and continues to be investigated to improve its accuracy in pancreatic procedures, the use of dAmy for diagnosing AL in colorectal surgery remains underexplored. Recent studies suggest that elevated dAmy levels could be useful for the early detection of AL in patients undergoing restorative proctectomy with ileal J-pouch anastomosis.[12] However, the impact of these studies is limited due to the small sample sizes and their focus on only specific types of colorectal surgery. Based on our clinical observations of a relatively higher incidence of hyperamylasemia following colorectal surgery, with dAmy levels often correlating with sAmy concentrations, we hypothesized that an increase in dAmy concentration or its ratio to sAmy could serve as a predictor for the occurrence of AL in patients undergoing colorectal resection. This study aims to evaluate whether these markers can reliably predict AL. Early identification through a simple postoperative test is crucial, as it may help prevent emergency surgeries or the need for stomas.

MATERIALS AND METHODS

Study design, setting, and patients

Patients who underwent colon or colorectal resection for any cause at Yongin Severance Hospital, Yongin, Republic of Korea, between March 2020 and November 2023 were retrospectively reviewed. Patients were included if their dAmy and sAmy concentrations were measured at least once during the 1–5 days following their index surgery. We excluded patients who had fecal diversion. All patients who underwent colorectal resection at this institution had an intra-abdominal drain inserted during surgery, typically near the anastomosis site, and the timing of drain removal was determined based on the attending physician's medical judgment. The study protocol was approved by the Institutional Review Board of the Human Research Protection Center at Yongin Severance Hospital, Yongin, Republic of Korea (Project Number: 9-2024-0139). Informed consent was waived due to the retrospective nature of the study.

Definition and variables

AL is defined as the leakage of luminal contents from the surgical connection between two hollow viscera. This definition extends the concept of AL, which was originally proposed by the International Study Group of Rectal Cancer for colorectal or coloanal anastomoses, to encompass all types of colonic anastomoses.[13] Patients were considered to have an AL if the drain color changed significantly to brown or green, indicating bowel content leakage, or if bacterial cultures from the drain tested positive despite minimal or ambiguous color changes. All clinical and demographic data, including white blood cell (WBC) counts, C-reactive protein (CRP) levels, and sAmy and dAmy levels from postoperative days (PODs) 1–5, were collected. At our institution, the upper limit of normal sAmy activity is 115 IU/L; therefore, an activity level of 345 IU/L (i.e., three times the normal upper limit) was selected as a potential predictor for AL.[9] The drain/serum amylase ratio (d/s Amy) was calculated by dividing the dAmy concentration measured on PODs 1–5 by the corresponding sAmy value. If the sAmy level was not available for a particular day, the most recent previous sAmy value was used for the calculation. The highest d/s Amy ratio from PODs 1–5 was used as the representative value for each patient.

Statistical analysis

Data are presented as means±standard deviations for continuous, normally distributed variables or as medians (Q1–Q3) for nonparametric data, with differences between the two groups compared using Fisher's exact test or the χ^2 test for categorical variables and the Mann–Whitney U test for continuous variables. Variables with *p*-values <0.2 in the univariable analysis were included in a multivariable logistic regression analysis to identify predictors of AL. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values for continuous variables, defined by the Youden Index (J), and bootstrap resampling (1000 repetitions) was conducted. A *p*-value less than 0.05 was considered statistically significant; however, for multiple comparisons across PODs in laboratory measurements, Bonferroni correction was applied, and a threshold of 0.01 was applied. A generalized estimating equation (GEE) analysis was conducted for repeated measured outcomes without excluding cases with missing values. All statistical analyses were conducted using R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 299 patients who met the eligibility criteria were included in the final analysis. The median dAmy level peaked on POD 2 [37.5 (25.0–82.7) mg/dL] and reached its lowest value on POD 5 [30.0 (24.0–64.0) mg/dL]. Conversely, the median sAmy level was highest on POD 3 [69.0 (37.5–110.5) mg/dL] and lowest on POD 2 [52.0 (38.0–132.0) mg/dL]. Elevated dAmy levels (>115 mg/dL) at any time between PODs 1 and 5 were observed in 71 out of 299 patients (23.7%), whereas elevated sAmy levels (>115 mg/dL) were detected in 86 out of 299 patients (28.7%). Significant correlations were observed between these two markers on POD 3 (r=0.43; *p*<0.001) and POD 5 (r=0.43; *p*<0.001) (Fig. 1).

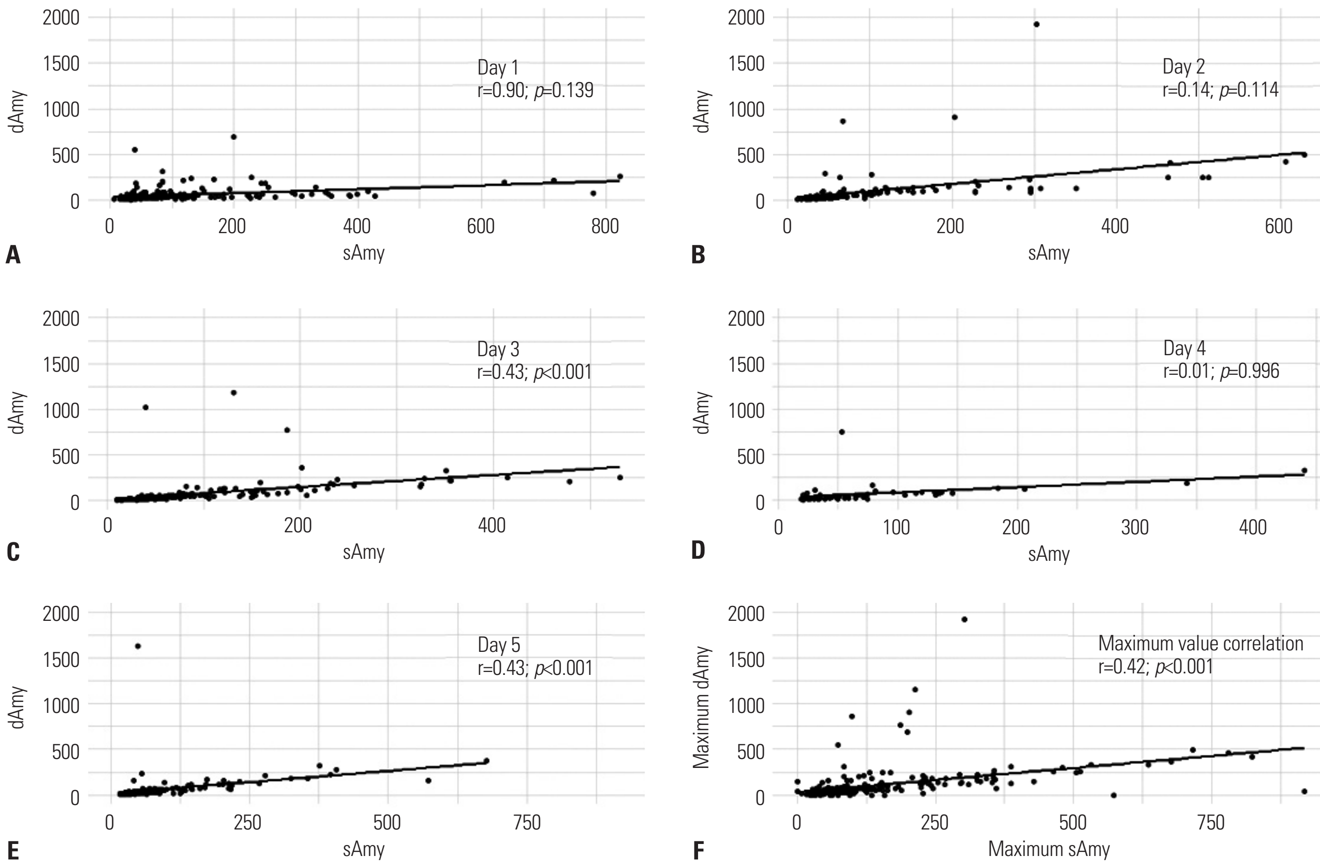

Fig. 1. Scatter plot of sAmy and dAmy levels during the postoperative period: (A) Day 1, (B) Day 2, (C) Day 3, (D) Day 4, (E) Day 5, and (F) correlations between the maximum values of sAmy and dAmy. dAmy, drain amylase; sAmy, serum amylase.

Table 1. Clinical Factors and Laboratory Values Associated with Anastomosis Leakage

	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age >70 years	0.564 (0.223–1.428)	0.227		
Male sex	0.698 (0.331–1.471)	0.345		
BMI >25 kg/m^2	0.698 (0.331–1.471)	0.345		
ASA score ≥3	0.523 (0.217–1.258)	0.147	0.497 (0.183–1.343)	0.171
Hemoglobin ≤10 g/dL	1.713 (0.691–4.245)	0.245		
Albumin ≤3.5 g/dL	3.244 (1.091–9.644)	0.034	0.463 (0.035–6.057)	0.557
Diagnosis				
Benign diseases	1 (ref)			
Colon cancer	0.672 (0.173–2.610)	0.566		
Rectal cancer	1.381 (0.378–5.038)	0.625		
Emergent surgery	1.471 (0.314–6.900)	0.624		
Anastomosis type				
Ileo-colic	1 (ref)			
Colo-colic	0.163 (0.397–6.702)	0.497		
Colo-rectal	0.135 (0.571–3.194)	0.493		
dAmy				
≤345 mg/dL	1 (ref)		1 (ref)	
>345 mg/dL	4.131 (1.924–8.871)	<0.001	3.431 (0.864–13.619)	0.080
d/s Amy	1.033 (1.013–1.053)	0.001	1.032 (1.009–1.056)	0.007

OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; dAmy, drain amylase; d/s Amy, drain/serum amylase ratio.

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Predictors of AL and cut-off value

The univariable analysis identified albumin ≤3.5 g/dL, dAmy >345 mg/dL, and d/s Amy as significant risk factors for AL. However, in the multivariate analysis, d/s Amy was the only variable significantly associated with AL (Table 1). The ROC curves were used to assess the discriminative value of the d/s Amy ratio for predicting AL (Fig. 2A), with the area under the curve (AUC) of 0.691. The cut-off value by Youden Index of d/s Amy for predicting AL was determined to be 2.54. At this threshold, the sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were 48.4%, 94.2%, 60.0%, and 96.3%, respectively. Bootstrapped median cutoff was 2.54 (1.64–5.01) (Supplementary Fig. 1, only online).

Group comparisons defined by the d/s Amy cut-off value

Using the obtained cut-off value, all patients were divided into two groups. Patients with hemoglobin ≤10 g/dL and albumin ≤3.5 g/dL were observed more frequently in the group with d/s Amy ≥2.54 (Group B) compared to those with d/s Amy <2.54 (Group A) (Table 2). Postoperative levels of dAmy, d/s Amy, WBC count, and CRP were higher in Group B, showing significant group differences from POD 2 to 5 after Bonferroni correction (Table 3) (Supplementary Fig. 2, only online). The subsequent GEE analysis revealed significant group effects in CRP, dAmy, WBC, and d/s Amy, indicating overall differences between the two groups regardless of time. However, significant interaction effects between time (POD) and group were observed in CRP (p<0.001) and dAmy (p=0.042), whereas no significant interaction effects were found in WBC (p=0.19) or d/s Amy (p=0.158). The incidence of all postoperative complications was higher in Group B than in Group A (84.0% vs. 40.9%; p<0.001) (Table 4). This included an increased rate of AL, with 60.0% of patients in Group B experiencing AL, compared to 5.8% in Group A (p<0.001).

Group B was associated with a significantly prolonged median time to first flatus (6 days vs. 3 days; p<0.001), delayed initiation of a liquid diet (2 days vs. 2 days; p=0.002), and a longer median hospital stay (19 days vs. 8 days in Group A; p<0.001) (Table 4).

Time to diagnosis of AL: d/s Amy ≥2.54 vs. conventional clinical methods

A comparison of the time to diagnose an AL among 31 patients with confirmed leaks was performed using conventional clinical methods (e.g., clinical signs such as drain color change, CT scan, endoscopy, and reoperation) versus the first day when d/s Amy exceeded 2.54. The median time to diagnosis using the d/s Amy >2.54 criterion was significantly shorter than that using the clinical methods (3.5 days vs. 5 days; p=0.006).

Diagnostic performance of d/s Amy for AL by anastomosis types

Based on clinical observations, ROC curve analysis was conducted for subgroups defined by anastomosis types. Patients were categorized into those with ileal anastomosis (ileo-colic,

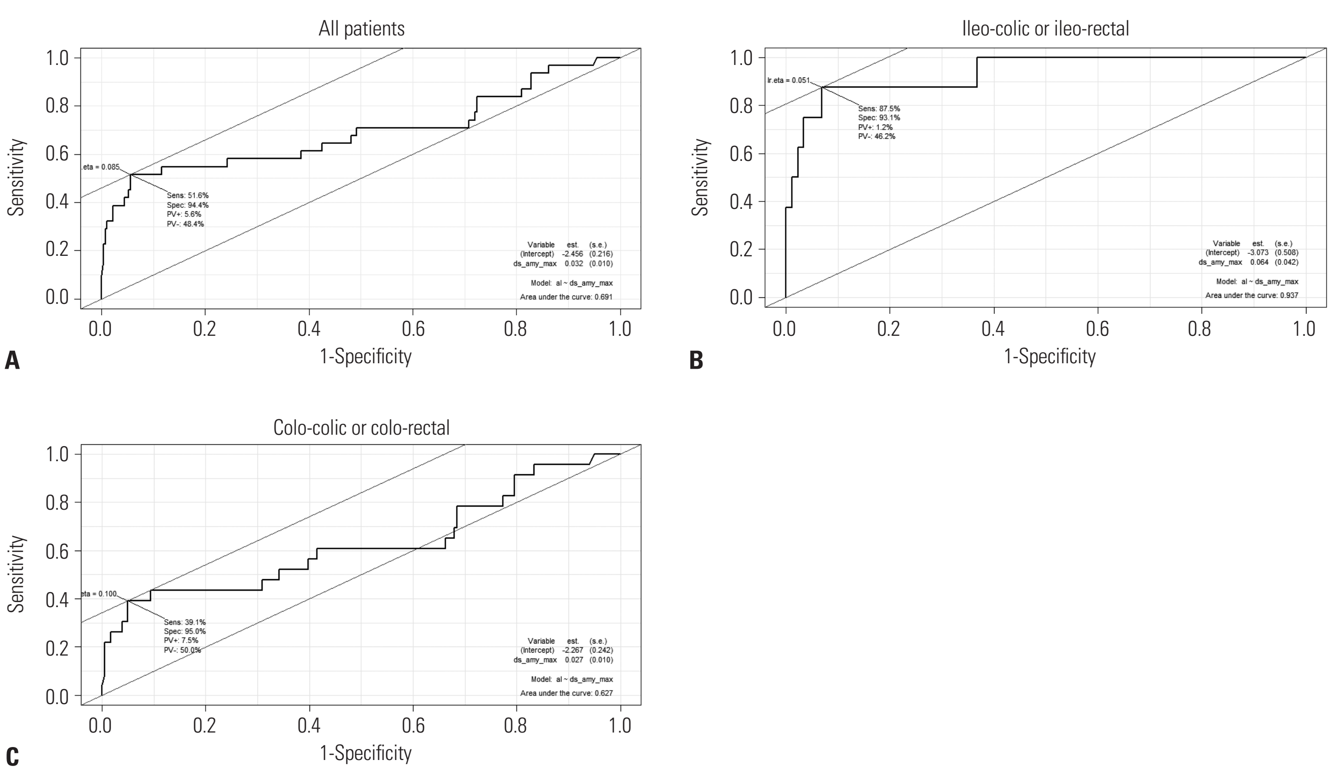

Fig. 2. ROC curves of the d/s Amy ratio for detecting AL: (A) all patients, (B) ileal group, and (C) non-ileal group. ROC, receiver operating characteristic; d/s Amy, drain/serum amylase ratio; AL, anastomotic leak.

ileo-rectal, or ileo-anal, n=95) and those without ileal anastomosis (colo-colic, colo-rectal, or colo-anal, n=204). The AUC for d/s Amy was significantly higher in the ileal group compared with the non-ileal group (0.936 vs. 0.626; $p<0.001$), as determined by DeLong's test (Fig. 2B and C). In the non-ileal group, the Se, Sp, PPV, and NPV at the optimal threshold of 2.54 were 74.1%, 82.9%, 56.3%, and 91.5%, respectively. For the ileal group, these values at the optimal threshold of 2.57 were

Table 2. Comparisons of Baseline Characteristics between Groups Defined by the d/s Amy Cut-Off Value

	Total (n=299)	Group A (d/s Amy <2.54, n=274)	Group B (d/s Amy ≥2.54, n=25)	*p* value
Age >70 years	86 (28.8)	82 (29.9)	4 (16.0)	0.141
Male	178 (59.5)	166 (60.6)	12 (48.0)	0.220
BMI >25 kg/m^2	109 (36.5)	102 (37.2)	7 (28.0)	0.359
ASA class ≥3	103 (34.4)	96 (35.0)	7 (28.0)	0.478
Hemoglobin ≤10 g/dL	46 (15.4)	38 (13.9)	8 (32.0)	0.016
Albumin ≤3.5 g/dL	20 (6.7)	12 (4.4)	8 (32.0)	<0.001
Diagnosis				0.364
Benign diseases	29 (9.7)	27 (9.9)	2 (8.0)	
Colon cancer	139 (46.5)	124 (45.3)	15 (60.0)	
Rectal cancer	131 (43.8)	123 (44.9)	8 (32.0)	
Emergent surgery	14 (4.7)	11 (4.0)	3 (12.0)	0.070
Anastomosis type				0.262
Ileo-colic or ileo-rectal	95 (31.8)	85 (31.0)	10 (40.0)	
Colo-colic	23 (7.7)	23 (8.4)	0 (0.0)	
Colo-rectal or colo-anal	181 (60.5)	166 (60.6)	15 (60.0)	

d/s Amy, drain/serum amylase ratio; BMI, body mass index; ASA, American Society of Anesthesiologists.
Data are presented as n (%).

Table 3. Comparisons of Postoperative Laboratory Results between Groups Defined by the d/s Amy Cut-Off Value

	Total	Group A (d/s Amy <2.54)	Group B (d/s Amy ≥2.54)	*p* value*
dAmy (mg/dL)				
Day 1	32.5 (24.0–58.0)	32.0 (24.0–56.0)	47.0 (22.0–117.0)	0.211
Day 2	37.5 (25.0–82.7)	36.0 (25.0–75.0)	85.0 (29.0–291.0)	0.010
Day 3	34.5 (24.0–64.0)	33.0 (24.0–59.0)	96.0 (31.0–257.0)	<0.001
Day 4	33.0 (23.0–62.0)	32.0 (22.0–52.0)	149.0 (65.0–747.0)	<0.001
Day 5	30.0 (21.0–52.0)	29.0 (20.0–47.0)	73.0 (42.0–274.0)	<0.001
d/s Amy				
Day 1	0.60 (0.39–0.84)	0.59 (0.37–0.82)	0.69 (0.46–1.76)	0.057
Day 2	0.65 (0.51–0.84)	0.65 (0.50–0.80)	1.25 (0.51–6.44)	0.004
Day 3	0.61 (0.42–0.87)	0.60 (0.40–0.84)	1.50 (0.55–5.16)	<0.001
Day 4	0.59 (0.36–0.87)	0.56 (0.34–0.81)	3.04 (0.98–5.85)	<0.001
Day 5	0.56 (0.32–0.86)	0.54 (0.30–0.82)	1.67 (0.67–4.02)	<0.001
WBC count (10^3/μL)				
Day 1	9.8 (8.2–12.7)	9.7 (8.2–12.4)	11.3 (8.2–15.3)	0.354
Day 2	8.8 (7.3–11.2)	8.8 (7.1–10.5)	10.7 (8.5–15.6)	0.005
Day 3	7.9 (6.2–10.6)	7.8 (6.0–9.8)	9.4 (6.9–13.4)	0.015
Day 4	7.3 (5.5–9.1)	6.6 (5.4–8.5)	8.9 (7.7–13.1)	0.004
Day 5	6.6 (5.4–8.3)	6.5 (5.2–8.1)	8.3 (6.8–13.6)	0.001
CRP (mg/L)				
Day 1	41.5 (23.0–60.0)	40.9 (23.4–60.4)	40.9 (7.3–369.9)	0.248
Day 2	114.7 (83.1–155.3)	115.2 (83.1–154.6)	108.3 (80.9–162.3)	0.083
Day 3	116.4 (76.6–175.5)	115.9 (71.9–169.2)	123.7 (96.7–195.0)	0.001
Day 4	83.7 (53.3–136.3)	72.5 (49.5–129.1)	136.9 (100.4–186.4)	0.003
Day 5	65.7 (34.6–102.8)	56.4 (31.5–88.8)	150.5 (96.2–228.9)	<0.001

dAmy, drain amylase; d/s Amy, drain/serum amylase ratio; WBC, white blood cell; CRP, C-reactive protein.
*$p<0.01$ was considered significant due to Bonferroni correction for multiple comparisons.

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Table 4. Comparisons of Postoperative Outcomes between Groups Defined by the d/s Amy Cut-Off Value

	Total (n=299)	Group A (d/s Amy <2.54, n=274)	Group B (d/s Amy ≥2.54, n=25)	*p* value
All complications	133 (44.5)	112 (40.9)	21 (84.0)	<0.001
Ileus	20 (6.7)	19 (6.9)	1 (4.0)	0.574
Wound infection	10 (3.3)	10 (3.6)	0 (0.0)	0.331
IAI, except AL	17 (5.7)	16 (5.8)	1 (4.0)	0.704
AL	31 (10.4)	16 (5.8)	15 (60.0)	<0.001
Surgical others	34 (11.4)	32 (11.7)	2 (8.0)	0.579
Medical	32 (10.7)	28 (10.2)	4 (16.0)	0.371
Time to flatus	3 (3–4)	3 (3–4)	6 (3–8)	<0.001
Time to liquid diet	2 (2–2)	2 (2–2)	2 (2–7)	0.002
Time to soft diet	3 (3–4)	3 (3–4)	3 (3–13.5)	0.064
Length of stay	8 (7–11)	8 (7–11)	19 (10–33)	<0.001
Re-admission	9 (3.0)	9 (3.3)	0 (0.0)	0.358

d/s Amy, drain/serum amylase ratio; IAI, intra-abdominal infection; AL, anastomosis leakage.
Data are presented as n (%) or median (Interquartile range, Q1-Q3).

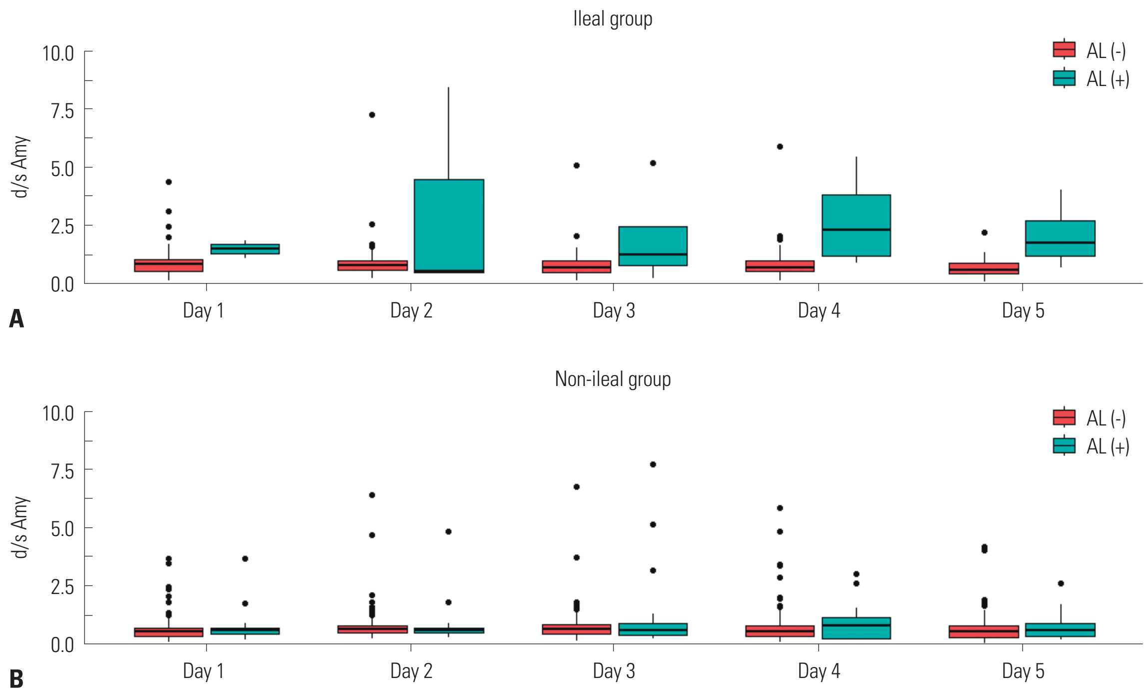

Fig. 3. Box plot comparison of the d/s Amy ratios between patients with and without AL from PODs 1–5: ileal anastomosis (A) vs. non-ileal anastomosis (B) groups. In the non-ileal group, the d/s Amy ratio was significantly higher in the AL+ group compared to the AL- group on POD 5 [0.71 (0.33–1.69) vs. 0.54 (0.28–0.82); *p*=0.037], with no significant differences on other days. In the ileal group, a trend was observed toward higher d/s Amy ratios in AL+ patients on PODs 1–3 compared to AL– patients [POD 1: 1.46 (1.07–1.84) vs. 0.81 (0.46–1.08); *p*=0.061, POD 2: 4.42 (0.41–8.42) vs. 0.76 (0.57–0.97); *p*=0.101, POD 3: 2.70 (0.23–5.16) vs. 0.65 (0.46–1.01); *p*=0.065]. On PODs 4–5, AL+ patients demonstrated significantly higher d/s Amy ratios compared to AL– patients [POD 4: 2.08 (0.88–3.27) vs. 0.63 (0.38–0.96); *p*=0.006, POD 5: 1.69 (0.68–2.70) vs. 0.60 (0.41–0.88); *p*<0.001]. AL, anastomotic leak; d/s Amy, drain/serum amylase ratio; PODs, postoperative days.

87.5%, 96.6%, 70.0%, and 98.8%, respectively.

Additionally, we examined whether d/s Amy levels differed based on the presence or absence of an AL within subgroups defined by anastomotic type (Fig. 3). In the non-ileal group, no statistically significant differences in d/s Amy were observed between patients with AL (AL+) and those without (AL-) from PODs 1–4. However, on POD 5, AL+ patients exhibited higher d/s Amy ratios compared to AL- patients [0.71 (0.33–1.69) vs. 0.54 (0.28–0.82); *p*=0.037]. In the ileal group, the d/s Amy ratio tended to be consistently elevated in AL+ patients across all days in comparison with AL- patients. On POD 4, AL+ patients had significantly higher d/s Amy ratios compared to AL- patients [2.08 (0.88–3.27) vs. 0.63 (0.38–0.96); *p*=0.006], with the most pronounced difference occurring on POD 5, where AL+ patients demonstrated significantly elevated d/s Amy ratios compared to AL-patients [1.69 (0.68–2.70) vs. 0.60

(0.41–0.88); $p<0.001$].

DISCUSSION

This study demonstrated that the postoperative d/s Amy ratio could be a valuable tool for the early detection of AL following colorectal surgery. The method showed greater diagnostic value in patients who underwent ileal anastomosis than those who did not. Notably, the d/s Amy ratio exceeded 2.54 by approximately 3.5 days postoperatively, which was 1.5 days earlier than when evaluating using conventional clinical diagnostic methods. This research represents the largest patient cohort to date investigating the utility of dAmy for diagnosing AL in colorectal surgery. Furthermore, to our knowledge, it is the first study to explore the ratio between dAmy and sAmy rather than focusing on the absolute value of dAmy, underscoring its potential for improved clinical application.

Although the International Study Group on Pancreatic Fistula defines POPF as drain output on or after POD 3 with an amylase concentration more than three times the sAmy activity, research to establish a definitive gold standard for diagnosing POPF is ongoing. Fukada, et al.[14] proposed that the postoperative d/s Amy ratio may be a more reliable marker for diagnosing POPF compared with the total drained amylase amount (volume×concentration). In contrast, other studies suggested that elevation of the sAmy level is the predictor for POPF.[15-17] These findings may be partially explained by the hypothesis that pancreatic enzymes enter the systemic circulation via the splanchnic circulation in cases of pancreatitis or pancreatic injury during surgery.[18]

Studies investigating the elevation of sAmy or dAmy levels following colorectal surgery are limited. Chun and Yoon[19] observed this phenomenon in 25 out of 72 patients (34.7%) undergoing elective colorectal resection. The identified risk factors for hyperamylasemia include pancreatic manipulation and the intraoperative use of volume expanders, with the suggestion that unintentional excessive traction or accidental pancreatic injury may contribute to elevated sAmy levels. Our study noted a positive correlation between dAmy and sAmy levels. This finding is supported by several studies demonstrating that surgery can cause plasma protein leakage. Fleck, et al.[20] reported a 100% increase in the transcapillary escape rate of albumin within 7 hours post-surgery in cardiac patients, and Norberg, et al.[21] observed a shift of albumin from the bloodstream to the peritoneum within 1 hour following major abdominal surgery. The increased vascular permeability, possibly due to damage-associated molecular patterns released during surgery, might explain these phenomena.[22-24] In our view, elevated dAmy concentrations should be interpreted in conjunction with sAmy levels to assess their clinical significance.

There is indirect evidence that may explain the higher diagnostic performance of the d/s Amy ratio, particularly in the ileal anastomosis group. Studies investigating amylase concentrations across different tissues in animal models, such as rats and dogs, have shown that the average amylase concentration in the pancreas is significantly higher—275000 and 496000 units/100 mL or 100 g, respectively—compared with 63600 and 2190 in the duodenum and 3500 and 356 in the colon.[25] Although similar data in humans are limited, one study measured amylase concentrations in ileal effluent following ileostomy, reporting a median concentration of 23000 U/L on POD 3.[26] Additionally, a study involving 43 patients who underwent restorative proctectomy with ileal J-pouch anal anastomosis without loop ileostomy found that four patients with suspected leakage had median dAmy levels of 21897 U/L.[27] In contrast, patients with AL after rectal resection had a median dAmy concentration of 1373.5 U/L.[28] These findings suggest that amylase concentrations decrease as they move distally through the gastrointestinal tract, which may explain why the d/s Amy ratio has a lower predictive value in non-ileal anastomosis groups compared with ileal anastomosis groups.

Although a d/s Amy >2.54 demonstrated good diagnostic performance in the ileal anastomosis group, caution should be exercised due to the potential for false positives, such as those resulting from pancreatic injury. Among the 10 patients with a d/s Amy >2.54 who did not have an AL, 3 were from the ileal anastomosis group and had undergone laparoscopic right hemicolectomy for ascending colon cancer. One patient developed a fever of 38.8°C on POD 4 and exhibited turbid, milky drain fluid. The d/s Amy ratios on PODs 1 and 2 were 13.7 and 7.2, respectively. Abdominal CT imaging revealed focal perfusion defects in the pancreatic head, with surrounding air bubbles and fluid collection, suggesting possible pancreatic injury. The patient was managed conservatively with fasting and was discharged on POD 22. The other two patients exhibited temperatures of 37.7°C and 36.9°C on POD 3. Their d/s Amy ratios on POD 3 were 5.0 and 5.8, with corresponding CRP levels of 190 and 102, respectively. However, there were minimal changes in the appearance of the drain fluid, and bacterial cultures of the drain fluid were negative for all of these patients.

Many biomarkers in drain fluid have been proposed as innovative strategies for the early detection of AL. These biomarkers are categorized into those related to ischemic changes at the anastomotic site (lactate/pyruvate ratio, pH), bacterial infection (Escherichia coli, Enterococcus faecalis, lipopolysaccharide-binding protein), inflammation [tumor necrosis factor-α, interleukin (IL) -6, IL-10], and wound healing (metalloproteinases).[29,30] Although several studies have shown positive results in the early diagnosis of AL using these biomarkers, they were often limited by small sample sizes and did not adequately assess predictive accuracy. Moreover, the assessments for many of these markers are expensive, technically challenging, and labor-intensive, limiting their widespread clinical application. In contrast, measuring dAmy offers several advantages: it is fast, cost-effective, and can be easily implemented in most hospi-

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tals, making it a more practical option for clinical use.

This study inherently carries the limitations associated with retrospective analyses. One key limitation is the presence of missing data for dAmy or sAmy levels, which are critical for diagnosing AL. Consequently, instead of using the d/s Amy ratio from specific PODs, the highest value recorded between PODs 1 and 5 was used as a predictor. This approach may result in the time point at which the d/s Amy exceeding 2.54 being assessed later than it actually occurred in some patients. While bootstrap analysis confirmed that the Youden Index-based cutoff aligned with the bootstrap median, the wide 95% confidence interval indicates substantial variability across different datasets. This result suggests that the same analysis in larger cohorts might yield a different cutoff value. Furthermore, the generated model has not undergone internal or external validation, leaving its generalizability unconfirmed.

In conclusion, the postoperative d/s Amy ratio may serve as an effective biomarker for the early detection of AL in patients undergoing colorectal surgery. This marker should be considered a valuable tool to complement earlier diagnosis and intervention compared to conventional methods, particularly in patients with ileal anastomosis. Although a cutoff of 2.54 provides a useful reference, its variability across datasets suggests the need for further research to establish optimal thresholds and assess its clinical applicability. Multicenter studies will be necessary to validate these findings and confirm the utility of the d/s Amy ratio in broader clinical applications.

AUTHOR CONTRIBUTIONS

Conceptualization: Jong Min Lee and Nam Kyu Kim. Data curation: Jong Min Lee. Formal analysis: Jong Min Lee. Investigation: Jong Min Lee. Methodology: Jong Min Lee. Project administration: Nam Kyu Kim. Supervision: Nam Kyu Kim. Validation: Nam Kyu Kim. Visualization: Jong Min Lee. Writing—original draft: Jong Min Lee. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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