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ORIGINAL STUDY

High Amylase Level in Drain Fluid as an Early Predictive Biomarker for Gastrointestinal Tract Anastomotic Leakage

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Abstract

Objectives: **This study aimed to evaluate the value of drain fluid amylase (DAM) levels as a predictive biomarker for early detection of anastomotic leakage (AL) in proximal and distal gastrointestinal anastomosis.**

Background: **AL is a critical complication following bowel surgery, leading to significant morbidity and mortality. AL is defined as the leaking of luminal contents into the peritoneal cavity. Early detection greatly affects management.**

Patients and methods: **A prospective observational study was conducted on 33 of 300 patients who underwent gastrointestinal anastomosis at Menoufia University Hospitals from March 2023 to March 2024. The 33 patients have a relatively high suspicious to have AL. We included them to evaluate the level of amylase in drain fluid and confirm diagnosis clinically and radiologically. We used this technique to evaluate if we can use amylase level in drain fluid as an early predictor for AL.**

Results: **The study found that 63.6% of participants were males and 36.4% were females, with a mean age of 48.76 ± 12.52 years and a mean BMI of 26.70 ± 3.03 kg/m^2. Emergent surgeries accounted for 51.5% of cases, while elective surgeries made up 48.5%. The incidence of AL was 30.3%, with a higher incidence in emergent procedures (41.2%) compared to elective procedures (18.7%). DAM levels showed high sensitivity and specificity for predicting AL.**

Conclusions: **This study supports the use of DAM measurement as a simple, cost-effective, and reliable method to predict AL, allowing for early intervention.**

Keywords: Amylase, Anastomosis, Biomarker, Drain, Leak

1. Introduction

A leak of intestinal contents from the anastomotic line leading to a connection between intraluminal and extraluminal spaces is considered a serious complication following gastrointestinal tract (GIT) surgeries, especially in low rectal resection. It leads to morbidity and mortality and has a bad effect on oncologic outcomes. Early detection of this complication improves outcomes and avoids late consequences of sepsis and multiorgan failure [1]. According to management, there are three grades for anastomotic leakage (AL): grade A requires no active therapeutic intervention; grade B requires active therapeutic intervention without reoperation; and grade C requires a reoperation [2].

In most cases, diagnosis of intestinal content leakage is delayed to the fifth day and is suspected when the patient complains of abdominal pain and fever, which are nonspecific [3]. Manifestations such as prolonged ileus, fever, tachypnea, and abdominal pain may give the suspicion of AL but not give a sure diagnosis as it also may be due to infection [4]. Early diagnosis and treatment of leakage are the

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keys to the cure. Delay leads to prolonged contamination of the abdomen by the intestinal contents, leading to the development of severe sepsis and progression to multiorgan failure and death [5].

Serum biomarkers like elevated total leukocytic count (TLC), C-reactive protein (CRP), and fluid cytokine levels may be elevated due to AL; however, they are nonspecific. Pelvi-abdominal ultrasonography with ultrasound-guided aspiration from the intraperitoneal collection and computed tomography (CT) scan is the commonly used radiologic modalities for the detection of AL [6]. Dye extravasation in the abdominal cavity during a CT scan with oral contrast is used as a standard investigation to assure the presence of AL in suspected cases, which may demonstrate the presence of extravasation of contrast outside the bowel [7].

Several studies have been done to outline the risk factors for developing an AL. Some of these risk factors are rectal anastomosis, smoking, alcohol abuse, diabetes mellitus, obesity or malnutrition, the male sex, treatment with steroids, radiotherapy, and chemotherapy, a high American Society of Anesthesiologists score, cardiac and vascular diseases, peritoneal contamination, long intraoperative time, multiple anastomoses, and emergency surgery [8]. Due to morbidity and high rate of mortality caused by bowel AL, early predictive biomarkers for AL are needed [9]. Amylase is produced by pancreas and salivary glands. It is an enzyme that breaks down complex carbohydrates to simple sugars. Normally, its level in serum is less than less than 100 IU/l. Its concentration in the alimentary tract below the duodenal papilla is nearly the same as its concentration in the pancreatic duct. It ranges from 20 010 IU/l during fasting to up to 250 010 IU/l during feeding [10,11].

The concentration of amylase in intestinal fluid remains high from the duodenum to the rectum. Only a small fraction, less than 10%, is degraded in the enteric circulation, while most amylase remains unabsorbed. So, the amylase level in intestinal content is high as it passes from the duodenum to the rectum [12,13]. Some studies predicted leakage after pharyngeal, esophageal, gastric, and pancreatic surgery by measuring amylase in drain fluid [14–18].

This study aimed to evaluate the sensitivity of raised amylase level in the drain fluid as a predictive biomarker for early detection of AL in both GIT anastomosis. The definitive management varies regarding the type of leak, whether low output or high output, and also the general condition of the patient. Low output leaks (<200 ml/day) may be managed conservatively (NPO and TPN − i.v. antibiotics − minimal invasive percutaneous drainage). In cases of high output fistula (>500 ml/day), mostly laparotomy is needed especially when there is progressive deterioration in general condition (tachycardia, tachypnea, fever, abdominal pain), severe sepsis (rising TLC, CRP, erythrocyte sedimentation rate), multiple collections, or conservative and medical therapy has failed [19,20]. This study aimed to evaluate the value of drain fluid amylase (DAM) levels as a predictive biomarker for early detection of AL in proximal and distal gastrointestinal anastomosis.

2. Patient and methods

The data collected were analyzed using SPSS Inc. released 2018. IBM SPSS statistics for windows, version 26.0, Armnock, NY: IBM Corp., version 26. Descriptive statistics included numbers and percentages for qualitative data and mean with SD for quantitative data. Analytic statistics comprised several tests: Fisher exact test for associations between two qualitative variables in 2×2 tables with expected counts less than five, Student *t* test for associations between two normally distributed quantitative variables, and Mann−Whitney *U* test for associations between two nonnormally distributed quantitative variables. Repeated measures one-way analysis of variance analyzed dependent variables measured repeatedly, while the Friedman test compared quantitative variables across more than two measures in the same group for nonnormally distributed data. The receiver operating characteristic curve assessed biomarker performance, with area under the receiver operating characteristic values indicating test accuracy from excellent (0.90−1) to fail (0.50−0.60). Sensitivity and specificity calculations were also performed, and a *P* value less than 0.05 was deemed statistically significant. This study was approved by the Menoufia Faculty of Medicine Hospital Research Committee on Ethics. Written permission was obtained from the patients included in the study.

This study is a prospective observational study conducted on 33 patients of 300 patients who underwent gastrointestinal anastomosis at Menoufia University Hospitals from March 2023 to March 2024. The 33 patients have a relatively high suspicious to have AL. We included them to evaluate the level of amylase in drain fluid and confirm diagnosis clinically and radiologically. We used this technique to evaluate if we can use amylase level in drain fluid as an early predictor for intestinal leak. The inclusion criteria encompassed all patients in the General Surgery Department who underwent GIT anastomosis with relatively high suspicious of having anastomotic leakage. Exclusion criteria included immunocompromised patients, those without intraperitoneal drains, patients who refused participation, those with preoperative elevated serum amylase (pancreatitis), patients with protective diversions (ileostomy or colostomy), and those who underwent pancreatic or hepatic surgeries.

We obtained written consent from each patient after explaining the aims and benefits of this study. Complete history taking, physical examinations, and preparing patients for surgery with nasogastric tubes and urinary catheters. Mechanical bowel preparation was given before elective colorectal anastomosis. An intra-abdominal tube drain was put close to the anastomosis. We collected samples from drained fluid every other day starting from postoperative day 1. Antibiotics such as cefotaxime were administered for 2−7 days postsurgery. The fluid of the drain near anastomosis was collected every other day from day 1 postoperative in a plain vacutainer tube under complete aseptic condition. Samples were labeled and sample left to coagulate for about 10−20 min. Serum was obtained after centrifugation of the sample. The method used was a kinetic method (definitive substrate method), the used pamphlet was AGAPPE, 1 ml (1000 micron) of reagent was added to 25 micron of serum and analyzed by analyzer called Bio systems AGAPPE DIAGNOSTICS LTD Kerala, India-683 562.

Postoperative follow-up for any abnormal clinical manifestation such as fever, abdominal pain, tachycardia, tachypnea, localized, or generalized tenderness. Analysis of drain fluid (amount, odor, color, amylase level). Laboratory investigations included CBC, CRP, erythrocyte sedimentation rate, and serum amylase levels. Diagnosis of an intestinal leak in the case of elevated amylase level in the drain was confirmed with radiological studies as ultrasound-guided aspiration of abdominal collection and CT abdomen with contrast.

*The principle of AGAPPE pamphlet was:

SCNPG3 ———— 3CNP+2CNPG2+3Maltotriose +2 Glucose

CNP − 2-chloro-4-nitrophenol

CNP-G2-2-chloro-4-nitrophenol-a-maltotriose

*The reference of the test was:

Serum/plasma: 25−86 IU/l

Data collection included demographic data (age, BMI, sex, comorbidity), level of anastomosis, postoperative complications (wound infection, bleeding), and follow-up data. Serum and drain amylase levels were measured every other day until the seventh postoperative day. Patients with elevated drain-to-serum amylase ratios up to threefold were considered to have AL. These patients were subjected to further investigations such as abdominal ultrasound with aspiration from the intraperitoneal collection and CT abdomen with oral and i.v. contrast. Patients with certain intestinal leaked were managed based on their condition and the severity of the case, either through urgent exploration or conservative treatment.

High drain fluid amylase levels up to threefold the normal serum level prompted further investigations for AL. On the postoperative day of diagnosis, the exact site of anastomosis, diagnostic approach, and treatment were documented.

3. Results

The data showed that 63.6% of the studied participants were males and 36.4% were females, with a mean age of 48.76 ± 12.52 years and a mean BMI of 26.70 ± 3.03 kg/m^2. Among the participants, 39.4% had no medical comorbidities, while diabetes mellitus was the most prevalent comorbidity at 39.4% (Table 1).

51.5% of the surgical indications were emergent, and 48.5% were elective. The most common site of

Table 1. Demographic characteristics of studied patients (N = 33).

Variables	No. of studied patients = 33 [*n* (%)]
Sex	
Male	21 (63.6)
Female	12 (36.4)
Age (years)	
Mean ± SD	48.76 ± 12.52
Range	17−72
Age groups	
<40 years	8 (24.2)
40−50 years	8 (24.2)
50−60 years	13 (39.4)
>60 years	4 (12.1)
BMI (kg/m^2)	
Mean ± SD	26.70 ± 3.03
Range	20−34
BMI classification	
Normal	0
Overweight	0
Obesity I	7 (21.2)
Obesity II	21 (63.6)
Obesity III	5 (15.2)
Medical comorbidities	
Nil	13 (39.4)
Hypertension	12 (36.4)
Diabetes mellitus	13 (39.4)
Chemotherapy	4 (12.1)
Cardiac	4 (12.1)
Bronchial asthma	1 (3)

BMI (underweight<18.5, normal: 18.5−24.9, overweight: 25−29.9, obesity I: 30−34.9, obesity II: 35−39.9, obesity III >40).

anastomosis was ileo-ileal (27.3%), the most common type of anastomosis was end-to-end (84.8%), and the most common technique was hand-sewn (72.7%).

There was a statistically significant difference in postoperative systolic blood pressure measurements ($P < 0.05$) but no significant difference in postoperative temperature, diastolic blood pressure, respiratory rate, or heart rate measurements ($P > 0.05$) (Table 2).

According to the presence or absence of AL, there was a statistically significant difference in POD3, POD5 temperature, systolic blood pressure at POD5, diastolic blood pressure at POD3 and POD5, respiratory rate at POD3 and POD5, and heart rate at POD3 and POD5 ($P < 0.05$). For cases with and without AL, significant differences were observed in postoperative measurements at POD1, POD3, and POD5 for temperature, systolic blood pressure, diastolic blood pressure, respiratory rate, and heart rate ($P < 0.05$) (Table 2).

There was a statistically significant difference in postoperative TLC, CRP, and drain amylase levels ($P < 0.05$), but not in postoperative serum amylase levels and drain/serum amylase levels ($P > 0.05$).

For cases with AL, significant differences were observed in postoperative measurements at POD1, POD3, and POD5 for TLC, CRP, serum amylase, drain amylase levels, and drain/serum amylase ratio ($P < 0.05$). For cases without AL, significant differences were found in TLR and CRP ($P < 0.05$) (Table 3).

Table 2. Vital signs measurements in studied patients.

	Mean ± SD	Range (minimum–maximum)	P value
Vital	Temperature (C°)		
POD1	37.27 ± 0.33	36.5–38	0.393 (NS)
POD3	37.26 ± 0.38	36.5–38.2	
POD5	37.38 ± 0.63	36.7–38.7	
	Systolic blood pressure (mmHg)		
POD1	127.73 ± 10.39	110–160	<0.001[a]
POD3	123.64 ± 9.94	90–140	
POD5	117.27 ± 11.26	80–140	
	Diastolic blood pressure (mmHg)		
POD1	80.00 ± 7.91	60–90	0.114 (NS)
POD3	77.88 ± 9.60	60–90	
POD5	76.67 ± 10.51	50–90	
	Respiratory rate (breath/min)		
POD1	20.42 ± 2.09	16–26	0.364 (NS)
POD3	19.64 ± 2.13	16–24	
POD5	20.12 ± 3.62	16–30	
	Heart rate (beat/min)		
POD1	82.39 ± 6.61	68–90	0.171 (NS)
POD3	84.48 ± 9.30	68–110	
POD5	86.09 ± 15.20	70–130	

[a] significant value.

Table 3. Laboratory data in studied patients.

Laboratory data	Mean ± SD	Range (minimum–maximum)	P value[a]
TLC (× $10^3/mm^3$)			
POD1	14.03 ± 3.02	7–18	0.026[b]
POD3	12.42 ± 2.68	7–19	
POD5	11.89 ± 5.11	6–24	
CRP			
POD1	30.91 ± 18.92	12–96	0.010[b]
POD3	27.09 ± 17.88	6–96	
POD5	26.36 ± 31.89	6–96	
Serum amylase level (IU/l)			
POD1	41.97 ± 26.66	12–117	0.477 (NS)
POD3	40.85 ± 22.96	12–108	
POD5	43.73 ± 27.95	17–116	
Drain amylase level (IU/l)			
POD1	47.39 ± 51.93	7–210	0.044[b]
POD3	3883.24 ± 14387.25	9–80335	
POD5	4638.73 ± 13717.95	9–65578	
Drain/serum amylase ratio			
POD1	1.06 ± 0.67	0.24–3.09	0.152 (NS)
POD3	45.87 ± 139.88	0.19–743.84	
POD5	48.49 ± 132.03	0.22–570.24	

CRP, C-reactive protein; NS, nonsignificant; POD, postoperative day; TLC, total leukocytic count.
[a] Friedman test.
[b] Statistically significant.

The mean time of leakage diagnosis was 1.7 ± 2.74 days, ranging from the third day postoperative to the seventh day postoperative. In emergent procedures, the mean leakage time was 2.29 ± 2.95 days, ranging between the third day postoperatives to the seventh day postoperative, while the mean leakage time in the elective procedures was 1.06 ± 2.43 days, ranging from the third day postoperative to the seventh day postoperative.

At a cut-off point of 34 in POD1, the sensitivity and specificity of serum amylase level for predicting AL were 80 and 78%, respectively. At POD3, the sensitivity and specificity were 80 and 100%, and at POD5, they were 80 and 100%. For drain amylase level, at a cut-off point of 34.5 in POD1, sensitivity and specificity were 80 and 78%, respectively; at POD3, they were 100 and 96%; and at POD5, they were 100 and 91% (Table 4).

At a cut-off point of 1.10 in POD1, the sensitivity and specificity of the drain-to-serum amylase ratio for predicting AL were 80 and 83%, respectively. At POD3, with a cut-off point of 2.39, the sensitivity and specificity were 100 and 100%; and at POD5, with a cut-off point of 2.81, they were 100 and 87% (Table 5 and Figs. 1 and 2).

4. Discussion

Intestinal anastomosis is the main aim after GIT resection to regain continuity of GIT. Intestinal leakage is a serious complication that leads to

Table 4. Laboratory measurements in relation to anastomotic leakage.

Laboratory data	Anastomotic leakage		Test of significance	P value
	Present ($N = 10$)	Absent ($N = 23$)		
	Mean ± SD	Mean ± SD		
TLC (× 10^3/mm^3)				
POD1	11.70 ± 3.43	15.04 ± 2.21	$t = 3.37$	0.002[c]
POD3	13.90 ± 3.57	11.78 ± 1.95	$t = 2.21$	0.035[c]
POD5	17.90 ± 4.07	9.28 ± 2.79	$t = 7.08$	<0.001[c]
P value[a]	<0.001[c]	<0.001[c]		
CRP				
POD1	20.40 ± 9.88	35.48 ± 20.22	$U = 2.30$	0.021[c]
POD3	37.80 ± 24.67	22.43 ± 11.89	$U = 1.98$	0.048[c]
POD5	66.00 ± 32.62	9.13 ± 4.38	$U = 4.67$	<0.001[c]
P value[b]	0.001[c]	<0.001[c]		
Serum amylase level (IU/l)				
POD1	61.70 ± 28.65	33.39 ± 21.07	$U = 2.59$	0.009[c]
POD3	59.30 ± 27.58	32.83 ± 15.28	$U = 2.75$	0.006[c]
POD5	73.90 ± 29.82	30.61 ± 13.36	$U = 3.80$	<0.001[c]
P value[b]	0.061	0.989		
Drain amylase level (IU/l)				
POD1	97.20 ± 70.17	25.74 ± 17.06	$U = 2.98$	0.003[c]
POD3	12761.10 ± 24704.76	23.30 ± 14.53	$U = 3.80$	<0.001[c]
POD5	15245.70 ± 22129.84	27.00 ± 24.39	$U = 2.98$	0.003[c]
P value[b]	0.001[c]	0.738		
Drain/serum amylase ratio				
POD1	1.60 ± 0.88	0.83 ± 0.38	$U = 2.51$	0.012[c]
POD3	149.56 ± 228.97	0.79 ± 0.40	$U = 4.51$	<0.001[c]
POD5	157.88 ± 207.13	0.94 ± 0.75	$U = 4.39$	<0.001[c]
P value[b]	0.001[c]	0.926		

CRP, C-reactive protein; POD, postoperative day; TLC, total leukocytic count.

[a] Repeated measures analysis of variance.

[b] Friedman test.

[c] Statistically significant.

Table 5. Diagnostic accuracy of serum amylase level, drain amylase, and drain-to-serum amylase ratio in prediction of anastomotic leakage.

Time	AUC	SE	P value	95% CI	Cut off point	Sensitivity	Specificity
POD1	0.787	0.088	0.010[a]	0.614–0.960	46	80%	78%
POD3	0.804	0.096	0.006[a]	0.615–0.993	46	80%	83%
POD5	0.922	0.047	<0.001[a]	0.831–1.000	41	80%	83%
Time	AUC	SE	P value	95% CI	Cut off point	Sensitivity	Specificity
POD1	0.830	0.085	0.003[a]	0.663–0.997	34.5	80%	78%
POD3	0.996	0.007	<0.001[a]	0.982–1.000	485	80%	100%
POD5	0.983	0.018	<0.001[a]	0.948–1.000	758.5	80%	100%
Time	AUC	SE	P value	95% CI	Cut off point	Sensitivity	Specificity
POD1	0.778	0.113	0.012[a]	0.558–0.999	1.10	70%	91%
POD3	1.000	0.00	<0.001[a]	1.000–1.000	2.39	90%	100%
POD5	0.987	0.014	<0.001[a]	0.959–1.000	2.81	80%	100%

AUC, area under curve; CI, confidence interval.

[a] Statistically significant.

morbidity and mortality; many studies have been done to label out patients at risk.

Many approaches have emerged for the early detection of AL as systemic biomarkers, but they have low sensitivity. They have low positive predictive value but with high negative predictive value and are good indicators of patients with no AL, so they can be used to decide patient discharge after surgery [21]. In some cases, intestinal leak is diagnosed late with complications that affect the general condition. Drain fluid biomarkers were introduced to give a better idea about the fluid near the anastomotic line, but it has low specificity and cutoff values [22]. Amylase is a carbohydrates digestive enzyme mainly secreted by the pancreas and salivary gland. Studies proved a higher level of amylase in the terminal ileum than in circulation [23]. And this is the backbone of our study.

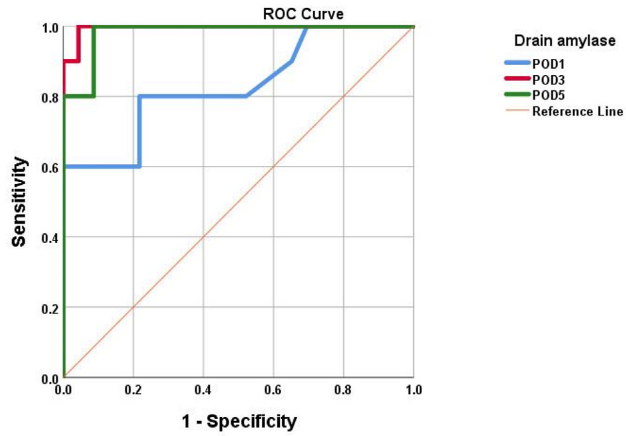

Fig. 1. ROC curve of drain amylase as a predictor of anastomotic leakage. ROC, receiver operating characteristic.

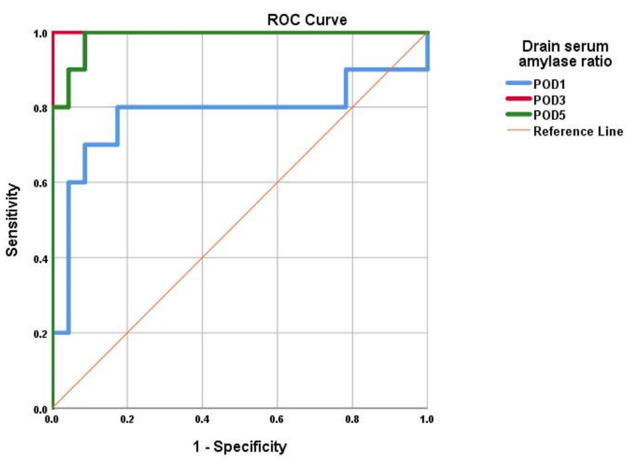

Fig. 2. ROC curve of drain-to-serum amylase ratio as a predictor of anastomotic leakage. ROC, receiver operating characteristic.

In this study, we analyzed the predictive value of amylase level in drain fluid in patients with GIT anastomosis. In most cases, there was an elevated amylase level on the third postoperative day in cases with AL. The cut-off point of 485 IU/l was a good marker of intestinal leak before clinical and radiological diagnosis. This study postulates that an amylase level in drained fluid of more than 485 IU/l at any postoperative day is a predictor of the leak from the anastomosis. This helps for early control of leaks and their complications. This test is simple, noninvasive, cheap, and easily performed.

This matches with studies by Su'a *et al.* [22] and Giglio *et al.* [23] that have shown that measuring amylase level in the intraperitoneal fluid can predict AL in esophageal Roux-en-Y gastric bypass, or after ileal pouch surgery [24,25]. The “cutoff” value of amylase concentration in this study was near to the concentrations recorded in the study by Singh *et al.* [26], which was between 250 and 400 IU/l with sensitivity and specificity rates of 94.1 and 90%, respectively. However, amylase level in drained fluid is not widely used to detect leakage in gastrointestinal surgeries like small bowel and colorectal anastomoses. Intestinal amylase level remains high till the rectum as it is poorly reabsorbed through enteric circulation. So in this study, we evaluated its level in drained fluid as a marker to detect leaks [9,27,28].

We proposed that when anastomosis is at risk for leak, a small amount of amylase leaks around the anastomosis so it can be detected in drained intraperitoneal fluid before the clinical manifestations of leak appear on the patient.

In agreement with Luo *et al.* [29] results, there is a statistically significant difference between vital signs, including (BP–RR–TEMP–HR) between the intestinal leak group and nonintestinal leak group.

In agreement with Almeida *et al.* [30] data, there is a statistically significant difference between CRP and TLC levels between the intestinal leak group and the nonintestinal leak group.

In the present study, we found that in patients with AL there is a significant rise in serum amylase, drain amylase, and drain-to-serum amylase ratio observed from POD 1 to POD5. On the other hand, patients without leakage did not demonstrate significant changes in serum amylase, drain amylase, and drain-to-serum amylase ratio from POD 1 to POD5.

In agreement with Amroun *et al.* [25] results in the sensitivity and specificity of drain amylase level in detecting AL was 91 and 100%, respectively. The results of our study show high sensitivity and specificity of drain amylase level and drain-to-serum amylase ratio in early detection of GIT AL as follow: POD 1 (sensitivity 80% − specificity 78%), POD 3 (sensitivity 100% − specificity 96%), POD5 (sensitivity 100% − specificity 91%).

Also, in agreement with our results, Paasch *et al.* [9] performed a monocentric nonrandomized prospective clinical study on 100 patients with left hemicolectomy, high anterior resection, sigmoid resection, and reversal of Hartmann's procedure or low anterior resection from June 2015 to October 2017. They measured the concentration of bilirubin, amylase, and bile acid in the drain fluid in the first four postoperative days. They revealed that the level of these markers is significantly increased in the anastomotic leak group than in patients of the nonleak group on the first postoperative day and on the third postoperative day.

In the present study, regarding drain amylase level analysis, the results showed that drain amylase level was found to be an excellent predictive test on

POD 1–5, with a sensitivity range (80–100%) and specificity range (78–96%).

4.1. Conclusion

This study demonstrated that (drain/serum ratio), drain amylase, and serum amylase in the first 5 days postoperatively could serve as potential biomarkers for bowel AL, with drain/serum ratio and drain amylase showing superior predictive value. Early detection of anastomotic leaks through this biomarker, along with physiological changes, blood test values, and observational markers, allows early intervention in anastomosis leaks and reduces morbidity and mortality. Further research with larger samples is necessary to validate these findings.

Ethics information

This study was approved by the Menoufia Faculty of Medicine Hospital Research Committee on Ethics. Written permission was obtained from the patients included in the study.

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Authors themselves and Menofia University.

Conflicts of interest

There are no conflicts of interest.

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