ORIGINAL ARTICLE

High amylase concentration in drainage liquid can early predict proximal and distal intestinal anastomotic leakages: A prospective observational study

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Background: Anastomotic leak (AL) is a serious complication in digestive surgery. Early diagnosis might allow clinicians to anticipate appropriate management. The aim of this study was to assess the predictive value of amylase concentration in drain fluid for the early diagnosis of digestive tract AL. **Materials and Methods:** Hundred and fourteen consecutive patients "at risk" of AL, in whom a flexible drainage was placed by surgeon's choice after digestive anastomosis were included. Patients with eso-gastric, bilio-digestive, and pancreatic anastomoses were excluded. Drain amylase measurement (DAM) was routinely performed on postoperative day (POD) 1, 3, 5–7. DAM values were compared between patients with postoperative AL versus patients without AL. A receiver-operating curve (ROC) with calculation of the areas under the ROC curves area under curves was performed and a cutoff value of DAM was calculated. **Results:** AL occurred in 25 patients (AL group) and 89 patients did not present AL (C group). The mean DAM was significantly higher in AL group versus C Group on POD 1, 3, and 5. A cutoff value of 307 IU/L predicted the occurrence of AL with a sensitivity and specificity of 91% and 100%, respectively. Positive and negative predictive values were 100% and 97.5%, respectively. Patients with AL had an elevated DAM prior to the appearance of any clinical signs of AL. **Conclusion:** High level DAM could accurately predict AL for proximal and distal digestive tract anastomoses. This simple, noninvasive, and low-cost method can accurately predict early AL and help physicians to perform appropriate imaging and treatment.

Key words: Amylase, anastomotic leakage, digestive anastomosis, drain fluid

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INTRODUCTION

Despite improvements in surgical techniques and perioperative management, anastomotic leak (AL) still occurs and remains one of the most feared complication after gastrointestinal (GI) surgery.[1] Its incidence varies from 2% to 40% depending on the type of intervention, anastomotic site, and associated patient's comorbidities.[2,3] The occurrence of AL carries a significant degree of morbidity and mortality and impacts negatively the survival prognostic.[4]

The diagnosis of AL is usually based on the certain findings on computed tomography (CT)-scan like the presence of an intra-abdominal collection (s), extraluminal bubbles, and/or extravasation of contrast liquid.[5] It is often associated with certain nonspecific clinical signs such as fever, tachycardia, dyspnea, and abdominal pain. This is associated with biological

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markers modifications such as leukocytosis, lymphopenia, hyponatremia, and/or elevated C-reactive protein (CRP) levels. Den Dulk *et al*.[6] showed up to 15% increase in mortality rate in colorectal surgery alone. This emphasizes the importance of early diagnosis of AL in decreasing both morbidity and mortality rates. However, in clinical practice, the AL diagnosis is often late due to the lack of reliable early predictors.[2,7] Currently used biomarkers such as CRP and procalcitonin (PCT) have shown high sensitivity and negative predictive value in detecting major AL but lack both specificity and positive predictive value.[8,9]

Amylase is a digestive enzyme predominately secreted by the salivary glands and the pancreas. It has a low serum concentration (normal serum concentration <100 IU/L). Distal to the major duodenal papilla, the endoluminal amylase concentration is close to pancreatic main duct amylase concentration which varies from 20.000 IU/L in the fasting state to up to 250.000 IU/L in the fed state.[10,11] Along their enteric circulation, both salivary and pancreatic amylase are poorly reabsorbed. In fact, <10% of endoluminal amylase is reabsorbed or destroyed during the process of digestion. Therefore, the endoluminal concentration of amylase remains significantly elevated throughout its circulation from the duodenum to the rectum.[12,13]

Drain fluid amylase measurement (DAM) has been proven to predict AL after pharyngeal, esophageal, gastric and pancreatic surgery in several studies.[14-18] We hypothesized that high level amylase in any intra-abdominal drain next to a proximal or a distal GI surgery might predict the presence of AL. To our knowledge, the DAM has not been reported as an early predictor of AL in patients undergoing small bowel and/or colorectal surgeries.[3] For this purpose, a retrospective preliminary study, conducted in our center, showed a significant correlation between high DAM (between 3–4 fold normal serum level) and the presence of an AL, in patients with proximal and distal GI anastomoses.[19]

The aim of this study was to evaluate prospectively, the predictive and cutoff values of DAM for the diagnosis of AL.

METHODS

We conducted a prospective observational study. From October 2017 to October 2019, patients who had GI anastomosis and peroperative drainage in our department were consecutively included. Patients who underwent proximal esophageal (Ivor-Lewis Santy), pancreatic, hepatic (bilio-enteric anastomosis), and/or splenic surgeries were excluded. The drains placed by surgeon's choice were flexible with one or more lumens, without size and/or suction limitations and could be removed at any time. Patients were followed-up from surgery until hospital discharge, drain removal, or AL occurrence.

DAM was routinely performed on postoperative days (PODs) 1, 3, 5 and 7 (if the drain was not removed before). For all patients, clinical symptoms such as fever and abdominal pain were assessed twice a day. Patients who had any suspicious clinical sign and/or elevated biological marker underwent an abdominopelvic CT-scan. The diagnosis of AL was established by the presence of one or more of these findings: (i) CT-scan presence of intra-abdominal collection, extraluminal bubbles, extraluminal contrast media and/or clear extravasation of contrast from the suture line, (ii) methylene blue recovered by adjacent drain after oral or rectal application, (iii) purulent or fecaloid output of the drain, and (iv) AL visualized at reoperation. Patients who were diagnosed with AL were considered in AL-Group, and the remaining served as control in C-Group. Patients were also stratified into proximal and distal digestive anastomoses. Proximal anastomoses included any anastomosis with small bowel such as distal esophago-jejunal, gastro-jejunal, jejuno-ileal, ileo-ileal, ileo-colic, Ileo-rectal, or ileo-anal anastomoses. Distal anastomoses included colo-colic, colo-rectal, or colo-anal anastomoses. Patients with stoma were classified based on the level of their principal anastomosis. If patient had two or more digestive anastomoses, the anastomosis that is close to the drain was considered as the principal one. Surgeons considered the presence of one or more comorbidities such as advanced age, morbid obesity, malnutrition, atherosclerosis, steroid or immune-suppressor therapies as risk factors of AL. In addition, patients with preoperative anemia (hemoglobin <8.5 g/dL), prolonged operative time (>4 h), intraperitoneal field major bacterial contamination, extended peritonectomy with hyperthermic intraperitoneal chemotherapy (HIPEC) and those who underwent more than 2 digestive anastomoses were considered at high risk of AL. The drains could be removed at any POD upon evolution by surgeon's prescription.

This study followed the precepts of the Declaration of Helsinki and French laws concerning biomedical research and was approved by Institutional Ethical Committee.

DAM was performed by enzymatic colorimetric test according to the international federation of clinical chemistry and laboratory medicine with Cobas Modular analyzer following the manufacturer's instruction and expressed in IU/L.[20]

Statistical analyses were performed using Statistical Package for the Social Science (SPSS) 20.0 (IBM, 2011, Chicago, IL, USA). Data were summarized as mean ± standard deviation or median (range) for the continuous variables and on

frequency (percentage) for the categorical variables. DAM levels were compared between AL group and C-group using nonparametric Mann–Whitney test. To assess the relationship between DAM level and AL, a logistic regression modeling taking into account location of the anastomosis as a covariable was used. Results were expressed on odds ratio (OR) and 95% confidence interval (95%CI). To assess the discriminatory performances of the cutoff value of DAM level for the diagnostic of AL, a receiver-operating curve (ROC) with the calculation of the areas under the ROC curves area under curves (AUCs) was performed. The sensitivity, specificity positive and negative predictive values, and likelihood ratio (sensitivity/[1.0-specificity]) were calculated. All *P* values were two-tailed, with significance indicated by a $P < 0.05$.

RESULTS

Out of all the patients undergoing GI anastomosis at our institution, <20% met the inclusion criteria. Out of 114 patients who were prospectively included, 71 patients (62.3%) had a proximal anastomosis and 43 patients (37.7%) had a distal anastomosis as previously defined. Population characteristics and details are summarized in Table 1. Median follow-up of hospitalized patients was 7 days.[2-16] AL- and C-groups included 25 (21.9%) and 89 (78.1%) patients, respectively. Among patients with proximal anastomosis, 12 patients presented an AL. Among patients with distal anastomosis, 13 patients presented an AL. DAM data were available for all patients on POD 1 and POD 3, 90% of patients on POD 5 and only 25% of patients on POD 7 mainly because of prior drain removal. Therefore, data on POD 7 were not reported.

Regardless of the anastomosis location, mean DAM was significantly higher in AL-group compared to the C-group for POD 1, 3, and 5 (6789 ± 2248 vs. 277 ± 172 IU/L, respectively, $P = 0.0001$). As shown in Table 2, for proximal anastomoses, DAM was significantly higher in AL-group on POD 1. On the other hand, mean DAM showed significantly higher values on POD 3 and 5 in AL-group as compared to C-group in both proximal and distal GI anastomoses [Table 2]. In AL-group, when the median observance time of the first elevated DAM values was compared to the first median time of the positive diagnosis of AL, the difference was significant (1 [1–5] vs. 7 [2–16] days, respectively, $P = 0.0057$). In all of the patients included in AL-group, high amylase level in the drain was observed at least one and up to 14 days before positive diagnosis of AL.

Logistic regression modeling showed that DAM at POD 1, 3 and 5 were significantly correlated to occurrence of AL (OR = 1.015, 95%CI [1.006–1.025], $P = 0.002$). The AL was best predicted when using the decimal logarithmic conversion of DAM (OR = 308.2, 95%CI [6.266–15157.234], $P = 0.004$). As shown by the fit of the final model in Figure 1, the DAM was significantly associated with the probability of AL occurrence. The odds of positively predicting AL were increased by 1.5% for every extra 1.5 IU/L of DAM and by 573% for every extra unit of decimal logarithmic DAM, which points out significant changes of biomarker concentration in AL. On ROC curve

Table 1: Patient's characteristics

	n=114 (%)
Age median (range)	62 (17-87)
Sex (male)	63 (55.3)
Obese (BMI >25 kg/m^2)	25 (21.9)
Malnutrition	12 (10.5)
Benign disease	32 (28.1)
Crohn disease	6 (5.3)
Malignant disease	82 (71.9)
Preoperative chemotherapy	37 (32.7)
Resected organs	
Stomach (partial; total)	11 (9.6); (*n*=7; 4)
Small bowel (and duodenum)	17 (14.9); (*n*=2)
Colon (right; transverse; left; total)	81 (71.9); (*n*=32; 5; 36; 8)
Rectum (with preoperative radiotherapy)	4 (3.5)
CRS/HIPEC	19 (16.7)
Anastomotic level	
Proximal digestive tract	71 (62.3)
Distal digestive tract	43 (37.7)
Anastomoses features	
Oeso-jejunal	4 (3.5)
Gastro-jejunal	8 (7.0)
Small bowel	16 (14.0)
Ileo-colic	36 (31.6)
Ileo-rectal	6 (5.3)
Ileo-anal	1 (0.8)
Colo-colic	10 (8.8)
Colo-rectal	30 (26.3)
Colo-anal	3 (2.6)

BMI=Body mass index; CRS+HIPEC=Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy

Table 2: Comparison of drain amylase level between anastomotic leakage (anastomotic leak group) versus no anastomotic leakage (control group) according to digestive tract level

	AL group (*n*=25)	Control group (*n*=89)	*P*
Proximal digestive tract (*n*=71)			
POD 1	11831±10795	71±12	0.0126
POD 3	494±223	49±6	0.0056
POD 5	16965±8979	44±5	0.0356
Distal digestive tract (*n*=43)			
POD 1	2949±2881	39±4	0.2011
POD 3	918±508	42±9	0.0496
POD 5	1266±1156.5	43±8	0.081

Values are expressed in mean±SD (IU/L). POD=Postoperative day; SD=Standard deviation

analysis [Figure 2], the AL was associated with DAM values with an AUC = 0.982 (95%CI [0.959–1.000], $P < 0.0001$) and a "cut-off" point of 307 IU/L (almost 3 × normal serum level) characterized by a sensitivity of 91% (95%CI [78.8–97.5]) and a specificity of 100% (95%CI [93.4–100.0]) with the overall percentage of accurate prediction equal to 95% [Figure 3]. For this cutoff level, positive and negative predictive values for AL diagnosis were, respectively, 100% (77.0–100) and 97.5% (94.0–99.3). Patients with DAM higher than 307 U/L were 49 times more likely to have AL than patients with DAM below 307 IU/L ($P < 0.02$). Regarding true positive 21/25 patients (84%) who experienced an AL, they presented a high DAM value at any POD. Regarding true negative patients (C-group), all presented a low (<307 IU/L) DAM at any POD [Figure 3].

DISCUSSION

In our study, we analyzed for the first time the diagnostic value of measuring the amylase level in the drain fluid of patients undergoing proximal or distal GI anastomosis. We found that an elevated amylase level on POD3 could strongly detect AL in both proximal and distal GI anastomoses. The cutoff value of 307 IU/L was an accurate predictor of leakage, up to 14 days prior to the confirmed diagnosis. Our data suggest that a DAM higher than 307 IU/L at any POD can be used as a diagnostic marker of digestive AL and thus allow early management and prevent further morbidity and mortality. The value of our study lies in the fact that DAM is a simple, low cost, and easily available biomarker.

AL is one of the most important life-threatening complications of digestive surgery.[5] Early postoperative diagnosis of AL is proven in many studies to be associated with lower morbidity and mortality. Therefore, the need for an accurate tool for the early diagnosis and treatment was the subject of many recent studies.[21] However, early and specific biomarkers are lacking. Postoperative increase of serum CRP, PCT or other inflammatory biomarkers such as interleukin (IL) 6, IL10, IL1, and tumor necrosis factor α (TNFα), has long been considered as indicators of postoperative infectious or necrotic complications, but have a low specificity to predict AL especially in colorectal surgery.[2,3,9] In addition, intraperitoneal biomarkers, such as IL6, CRP, PCT, *Escherichia coli*, IL10, and TNFα have been assessed to predict AL, mainly in colorectal surgery, were reported to be poor predictors.[2,8,9,22] Intraperitoneal lactate concentration during the first five PODs, versus other tested biomarkers (glucose, glycerol, and pyruvate), was the most significantly associated with diagnosis of AL, but with limited sensitivity (25%) and specificity (88%).[23] Moreover, many of these biomarkers are not routinely

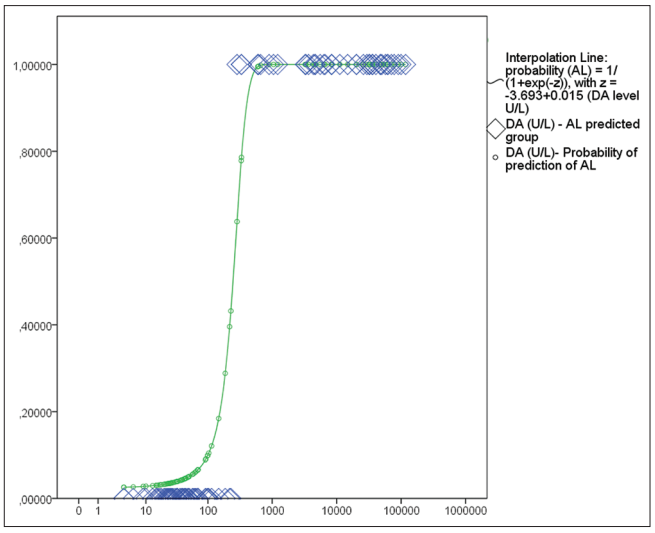

Figure 1: AL occurrence and predicted probability of AL (interpolation line) with respect to DA level (IU/L). AL=Anastomotic leak, DS=Drain amylase

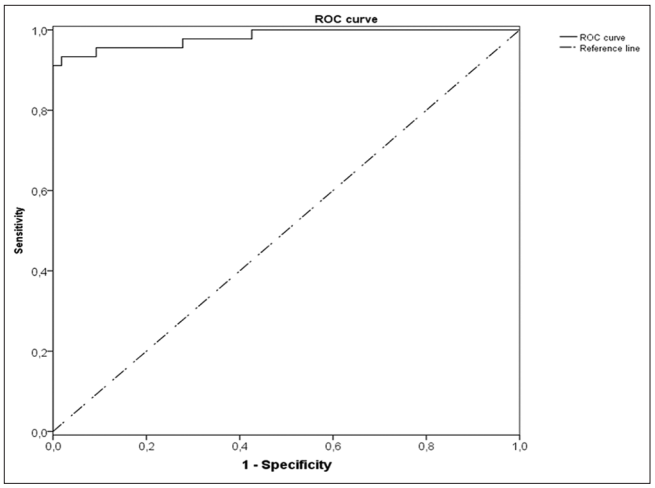

Figure 2: The ROC analysis with an AUC = 0.982 (95%CI [0.959 to 1.000], $P < 0.0001$). ROC = Receiver operator curve, AUC = Area under curve. CI = confidence interval

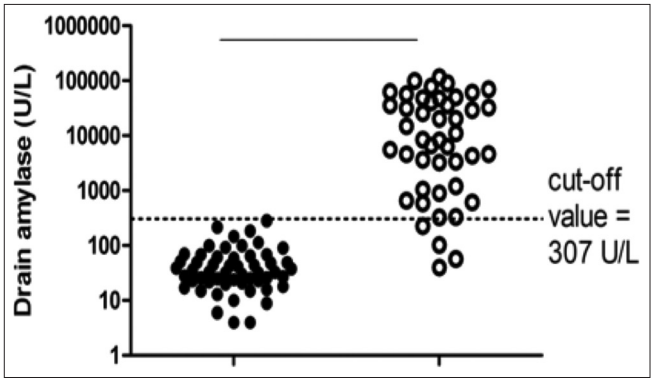

Figure 3: Comparison of drain amylase concentrations between patients with and without AL (median [min-max]: 9808 [40 – 117361] vs. 33 [4–283] respectively, $P < 0.0001$). Cut-off value of drain amylase level of 307 IU/L (almost 3 times normal serum level) is highly correlated to the presence of AL in proximal and distal digestive anastomosis. AL = Anastomotic leak

used, mainly because of their cost and the complexity to perform their dosage.

Amylase measurement in intraperitoneal fluid has been used as diagnostic and predictive biomarker of AL after esophageal,[17] Roux-en-Y gastric bypass (measuring salivary amylase)[16,24] or after ileal pouch surgery (measuring pancreatic amylase).[25] Remarkably, the "cutoff" amylase level in our study was close to the levels reported in the previous studies which were between 250 and 400 IU/L with a sensitivity and a specificity rates of 94.1% and 90%, respectively. To our knowledge, DAM was never used for other GI surgeries including small bowel and colorectal anastomoses. Given amylase concentration in GI endoluminal fluid remains elevated up until the rectum due to low reabsorption, it seems logical to extrapolate the results from previous studies to other lower tract anastomoses including colorectal surgeries. Interestingly, the DA dosage is cheap (5.4 euros, 6 US dollars), and can be performed rapidly and easily in all worldwide hospitals.[2,16,26] As for urine tests, one could imagine a semi-quantitative strip test for the immediate detection of elevated DAM after per-operative microdialysis catheter positioning.[3]

Our current study confirmed the clinical utility of DAM in the diagnosis of AL. An amylase level of more than 307 U/L (almost 3 fold normal serum level) in a drain liquid could accurately predict early AL for proximal as well as distal GI tract anastomoses. Interestingly, DAM was more sensitive in patients with proximal GI tract anastomosis and was able to detect AL as early as POD 1 and on POD 3 in patients with distal GI tract anastomosis. In addition, the prediction of AL by high DAM preceded the clinical or imaging diagnosis by at least 1 day (and up to 14 days in some patients). This is a major point as it may allow appropriate management and avoid postoperative mortality related to a delayed diagnosis of AL.[6]

Limitations to the present study have to be mentioned. First, <20% of patients undergoing GI surgery and anastomosis were drained at our institution. Routine drainage is no longer recommended in most GI surgeries and is not part of the enhanced recovery after surgery protocol.[27] However, patients included in this study were considered at high risk given age, comorbidities, and type of procedure and thus were drained as per surgeons' preference. This explains the high rate of AL in this selected population. Given the results of this study, if DAM is low, the drain can be safely removed on early POD, as recommended for pancreatic surgery.[28] Second, although postoperative complications were prospectively registered, the DAM were retrospectively collected occasionally resulting in incomplete data, mostly due to the early removal of the drains. Finally, this is a single center experience and further validation in multicenter studies with larger sample size is still needed.

CONCLUSION

In conclusion, the DAM higher than 3-fold normal level has shown the ability to predict early proximal and distal AL with a sensitivity of 91% and a specificity of 100%. We hope that, this could help clinicians to manage AL promptly.

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Conflicts of interest
There are no conflicts of interest.

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