



## Research Article

# Is Peritoneal Drain pH an Indicator of Anastomotic Leakage in Colorectal Surgery?

Kornaropoulos Michail<sup>1\*</sup>, Chatzipetrou Maria<sup>1</sup>, Zevlas Andreas<sup>2</sup>, Politopoulos Christos<sup>1</sup>, Stavrou Effrosyni<sup>1</sup>, Tzanakis Nickolaos<sup>1</sup>, Gaitanarou Anna<sup>2</sup>, Patias Parmenion<sup>2</sup>, Evangelou Fani-Maria<sup>1</sup>, Vassiou Eirini<sup>1</sup>, Triantafillou Alexis<sup>1</sup>, Ralli Irw<sup>1</sup>, Sidiropoulos Theodoris<sup>3</sup>, Vassiliu Panteleimon<sup>3</sup>

<sup>1</sup>2<sup>nd</sup> Surgical Department, Askepieio General Hospital Voula, Voula, Greece

<sup>2</sup>1<sup>st</sup> Surgical Department, Gennimatas General Hospital, Athens, Greece

<sup>3</sup>4<sup>th</sup> Surgical Department, Attikon University Hospital, Athens, Greece

\*Corresponding author: Kornaropoulos Michail, 2<sup>nd</sup> Surgical Department, Askepieio General Hospital Voula, Voula, Greece

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### Abstract

**Introduction:** Early diagnosis of Anastomotic Leakage (AL) after Colorectal surgery is essential to reduce patient's morbidity and mortality. The current diagnostic strategy, consisting of clinical evaluation, blood tests and on-demand CT scanning, may fail to detect AL at an early stage. An innovative approach lies in evaluating biomarkers from the immediate environment of the anastomosis, such as pH value, lactate value and base deficit through peritoneal fluid sampling, that might offer the potential to achieve earlier and more specific AL detection than current methods.

**Methods:** In our study, peritoneal lactate, pH and base deficit, collected from the drain fluid for the first 5 postoperative days, were analyzed from 137 patients undergoing colectomy with a primary anastomosis for any colon or rectal pathology within 1 year.

**Results:** Mean pH values of drain fluid collected from patients developing AL had a statistically significant difference when compared to those without AL. Patients with AL demonstrated a consistent tendency to decrease, whereas patients without AL showed a stable and rising pattern. On the other hand, the results obtained from lactate and base deficit were not useful for prediction.

**Discussion:** Timing diagnosis of AL is of paramount importance in order to reduce morbidity and mortality. The goal is not necessarily to entirely prevent its occurrence, but rather to establish a cautious postoperative course. PH from the peritoneal drain sample seems able to predict AL in advance of its clinical presentation.

**Conclusion:** PH value of the perianastomotic drainage fluid after colorectal operations with anastomosis, may be a cheap, noninvasive and useful biomarker to identify AL early.

**Keywords:** Abdominal Drain pH; Anastomotic Leakage; Colorectal surgery; Predictive Biomarker

## Introduction

Anastomotic Leakage (AL) continues to pose a significant challenge in the field of colorectal surgery, resulting in substantial morbidity and mortality rates [1]. Patients with AL experience delayed recovery, prolonged hospital stays, higher morbidity, diminished quality of life, and higher risk of mortality [2,3]. Moreover, its implications extend into long-term outcomes, with studies pointing to inferior oncological results, heightened local recurrences, and compromised disease-free survival [4]. Despite the advancements in minimally invasive surgery, the development of sophisticated stapling devices, the optimization of preoperative patient preparation and the postoperative care, the occurrence of AL remains a complex and multifaceted issue, with reported incidences spanning a range from 1% to 30% [1,5]. The timing of AL diagnosis commonly occurs 5-8 days post-surgery. However, cases of delayed presentation extending beyond 30 days have been documented [6,7]. Typical clinical signs, suggestive of AL, such as fever, severe abdominal pain and surgical site infection while tends to arise after the fifth postoperative day (POD5), precluding an early diagnosis of leakage [7]. Up to 20% of AL is diagnosed after hospital discharge, with a mean time to diagnosis of 6-15 days [8]. To this regard, serum biomarkers such as White Blood Cells (WBC), C-Reactive protein (CRP) and Procalcitonin (PRL) are used as diagnostic or predictive tools for AL after colorectal resections [9,10]. Nevertheless, they lack specificity and positive predictive value (PPV) for AL, as their levels also rise due to other inflammatory complications [11].

The current diagnostic strategy, consisting of on-demand CT scanning, may fail to detect AL at an early stage because of a high false-negative rate. [12] Delayed reintervention after false-negative CT scanning is associated with increased mortality and prolonged hospital stay, [5] whereas another review suggested that a 2.5-day delay in therapeutic interventions could increase mortality rates from 24 to 39%. [13] Hence, early detection is of paramount importance to minimize postoperative morbidity and mortality. An innovative approach suggests evaluating biomarkers within the drain fluid to achieve early AL detection. The measurement of biomarkers in the immediate environment of the anastomosis, through peritoneal fluid sampling, presents a promising strategy and might offer the potential to achieve earlier and more specific AL detection than current methods. The acidic ischemic microenvironment that correlates to the develop AL and its detection in pelvic drainage, is the main theoretical foundation for the present study. Our aim is to evaluate the utility of postoperative pelvic drainage pH value, lactate value and base

deficit (B.D.) as an indicative tool for identifying the presence of an AL after colorectal anastomosis [14,15].

## Methods

### Study Design

This prospective study was conducted in three hospitals in Athens (Asklepieio Voula, Attikon Hospital Athens and G. Gennimatas General Hospital Athens). Patients were enrolled between November 2021 and November 2022. The study was approved by the Ethics Committee of each participating medical center, and informed consent was obtained from all patients. For the current study, data of all of the patients undergoing colectomy with a primary anastomosis for any colon or rectal pathology were analyzed. Patients who required resections in colon and rectum, with anastomosis either for benign or malignant disease, elective or emergency were considered eligible. Operations with anastomosis and the use of peritoneal drain such as Right Colectomy, Left Colectomy, Sigmoidectomy, Low Anterior Resection (LAR), Total Colectomy and Hartman's reversal were the inclusion criteria. Both open and laparoscopic approaches were included. Exclusion criteria were Hartmann procedures, abdominoperineal resection, surgery requiring temporary ileostomy and colectomies without placement of peritoneal drains were excluded from the analysis.

Collected data included patient demographics, symptoms at admission, TNM score, serum albumin, CEA, ASA score, BMI, comorbidities, indication for surgery, operative time, estimated blood loss, use of inotropes, postoperative day of bowel movement, postoperative day of feeding, leukocyte count and CRP on POD1 to POD5 were obtained. Postoperative course was documented in detail, including the occurrence of fever, bowel function restoration by means of flatus, bleeding, prolonged hospital stay, readmissions and Anastomotic Leakage (AL). The choice to drain, the type and placement of the drain tube were on surgeon's discretion. Type of drainage used included Penrose drain (corrugated silicone silastic drain), and Jackson-Pratt drain (silicone flat drain connecting to a vacuum ball). In our study, in Right Colectomies the drain was placed in the subhepatic space near the anastomosis, whereas in Left Colectomy, Sigmoidectomy, Total Colectomy and Hartman's Reversal the abdominal drain was placed at the paracolic gutter or at the pelvis near the anastomosis. Drain fluid was collected every day after the ward round respecting rules of sterility with a syringe. The contents of the first 24h (referred as POD 0) were evacuated (but not analyzed). POD 1 was considered the drain fluid obtained 24 h after surgery and this specimen included in the analysis. Similarly, drain fluid was collected and marked for the following days. Peritoneal lactate, pH and B.D. from the abdominal drain were analyzed immediately after collection using an ABL700 blood gas analyzer (Radiometer, Copenhagen, Denmark).

The outcome of interest was AL within 30 days postoperatively. In our study AL was defined with clinical (gas, pus or fecal discharge from the drain, fecal discharge from the operative wound, peritonitis) or radiologic criteria (pelvic abscess, peri-anastomotic fistula, extravasation of contrast and peri-anastomotic liquid and air on CT scan). As AL were only considered cases confirmed either with CT scan or reoperation. Cases with minimal clinical presentation that were confirmed by CT scan were included. All the patients were assigned to one of two groups according to the presence or absence of AL: with AL (Group AL), without AL (Group n-AL). The two groups were compared according to peritoneal pH, lactate and base deficit (B.D.) levels on POD 1-5. AL was classified according to the system proposed by the International Study Group of Rectal Cancer (ISREC): Grade A can be left untreated, grade B requires medical management or minimally invasive therapeutic intervention (radiological drainage or other drainage) and grade C requiring revision surgery [8,16].

### Statistical Analysis

Data for pH values were analyzed within the methodological frame of General Mixed Models using the ANOVA method (36) according to the model that includes the effects (main and interaction) of one between subjects' factor with two levels (patients with an without AL) and one factor within subjects with five levels (the 5 post-operative days, treated as repeated measures). The ANOVA method was performed mainly for estimating the correct standard errors of the mean differences used for the clinically interesting comparisons of mean pH values. The mean values were compared with the protected Least Significant Difference (LSD) criterion. The model's assumptions relative to sphericity and homogeneity of error variances were fulfilled. Receiver Operating Characteristic (ROC) analysis was performed for post-operative days 2, 3 and 4, in order to assess the diagnostic performance of the pH taken from peritoneal drain for predicting AL. All statistical analyses were accomplished with the IBM SPSS Statistics v.23.0 software. In all hypothesis testing procedures, the significance level was predetermined at  $\alpha=0.05$  ( $P \leq 0.05$ ).

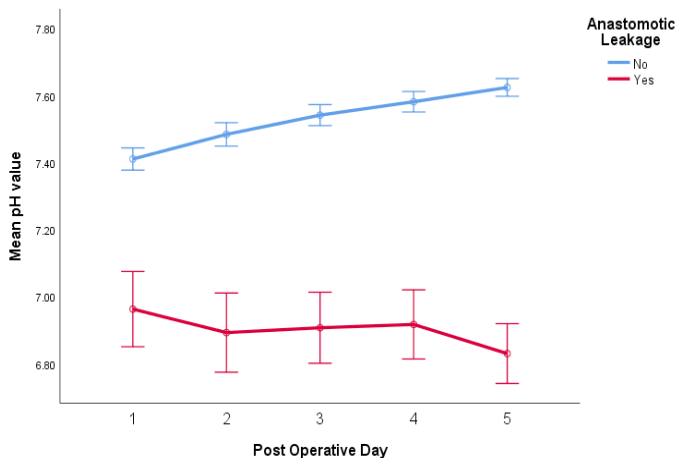
### Results

A total of 137 patients underwent colorectal resection during the study period (73 male patients, 64 female patients) were included. Median age was 71 (range 31-91) years. Most cases (73%,  $n=101$ ) underwent elective surgery, whereas 36 (27%) underwent emergency surgery. Fifty-seven cases (42%) underwent Right Colectomy, fourteen (10%) Left Colectomy, 34 (25%) Sigmoidectomy, 25 LAR (18%), 3 patients Total Colectomy and 4 Hartman's reversal procedure. Surgery was performed with

a laparoscopic approach in 50 patients (37%). The diagnosis of AL (confirmed with CT) occurred in 10 patients (7%) becoming clinically evident after a mean time of 8 days (6-12) from surgery (Table 1). Of these patients, 50% ( $n=5$ ) developed grade B AL, whereas 30% ( $n=3$ ) developed grade C AL. Patients developing AL showed a significantly lower pH value even from POD1 with mean pH value 6.89 whereas the n-AL group had mean  $pH=7.42$  (T-value 4.678,  $p < 0.05$ ) and were consistent every postoperative day (POD2 AL 6.81 vs n-AL 7.51, POD3 6.86 vs 7.57) (Table 2). In the postoperative period, it was clear that in the group AL the mean pH values demonstrated a consistent tendency to decrease, whereas the n-AL group mean pH values showed a stable and rising pattern (Figure 1). The measurement from lactate and B.D. from the abdominal drain were not useful for prediction. Neither lactate nor base deficit levels exhibited stability and showed significant fluctuant changes in anastomotic leakage. Moreover, in our study, they demonstrated inadequate sensitivity and specificity. We conducted Receiver Operating Characteristic (ROC) analysis to assess the diagnostic performance of the pH of peritoneal drain for predicting AL. The Area Under the Curve (AUC) value obtained on POD2 was 0.918, for POD3 the AUC was 0.918, whereas for POD4 was 0.957 (Figure 2). These results indicate that pH value from peritoneal drain may be a promising biomarker to distinguish patients with AL and without AL.

	Total no of patients	No-Anastomotic Leakage	Anastomotic Leakage
<b>Operation</b>	137	127 (93%)	10 (7%)
Right colectomy	58	52	6
Left colectomy	14	14	0
Sigmoidectomy	34	32	2
Low anterior resection	25	22	4
Total colectomy	3	33	0
Hartman reversal	4	0	0
Elective	101	94	6
Emergency	36	32	4
Open	50	47	3
Laparoscopic	87	80	7

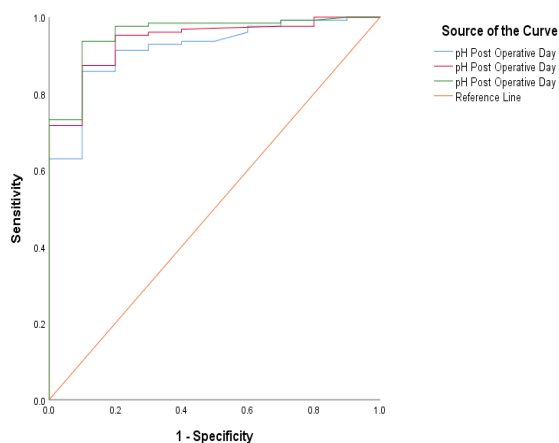
**Table 1:** Type of Operations and Presence of Anastomotic Leakage.



**Figure 1:** Evolution of mean pH values in the postoperative period in patients with and without Anastomotic Leakage. The error bars correspond to the standard errors of mean values.

Post Operative Day	AL (n=10)			n-AL (n=127)			LSD P-value
	min pH	Mean pH	max pH	min pH	Mean pH	max pH	
Day 1	7.42	6.89	6.50	6.50	7.42	7.90	<0.001
Day 2	7.51	6.81	6.05	6.50	7.51	7.90	<0.001
Day 3	7.57	6.86	6.50	6.62	7.57	7.90	<0.001
Day 4	7.60	6.84	6.50	6.70	7.60	7.90	<0.001
Day 5	7.64	6.77	6.50	6.79	7.64	7.90	<0.001

**Table 2:** Comparisons of mean pH values between patients with (AL) and without (n-AL) Anastomotic Leakage (AL) within the five Post-Operative Days. Mean values were compared with the protected Least Significance Difference Criterion – LSD at significance level  $\alpha=0.05$ .



**Figure 2:** Plot of the receiver operating characteristic (ROC) curve of peritoneal pH for Post-Operative Day 2,3 and 4 in predicting Anastomotic Leakage.

**Discussion**

Anastomotic Leak (AL) is still one of the most dreaded surgical complications in colorectal surgery. Surprisingly, the precise definition of what constitutes an AL remains a subject of debate. A review conducted by Bruce et al., encompassing 97 papers, highlighted the lack of uniformity in defining AL, revealing the identification of 56 distinct terms to describe the phenomenon. [15] Maintaining uniform definitions is crucial to understand risk factors for AL, document incidence, and compare therapeutic outcomes. Risk factors for AL have been studied in-depth in the literature. Among these factors are male sex, older age, malignancy, high ASA score, prolonged operation time, emergency operation, preoperative radiotherapy, anastomotic height and perioperative blood loss or transfusion [5,6]. Unfortunately, diagnosis remains challenging as there are no pathognomonic signs which can be specifically attributed to an AL. Typically during 5<sup>th</sup> to 8<sup>th</sup> POP wide-ranging clinical symptoms (abdominal pain, fever, ileus) can sometimes be difficult to distinguish from those caused by normal postoperative inflammatory and physiological responses. Based on clinical assessments, one study demonstrated that 69% of AL patients had a delayed diagnosis, of which the majority of patients presented with only cardiovascular symptoms. [17] Clinical evaluation, irrespective of one’s expertise and training, is thus considered an inadequate method for detecting high-risk AL patients or its timely diagnosis [18].

A variety of blood tests are used to help the early detection of AL. CRP, PRL and blood cells indexes like neutrophil to lymphocyte (NLR), lymphocyte to monocyte (LMR), and platelet to lymphocyte (PLR) ratio have been evaluated in predicting Anastomotic Leakage (AL) in colorectal cases with relatively good results. [11,19] Unfortunately, these markers are again non-specific, with raised levels commonly occurring secondary to various post-operative complications, including chest, urinary and surgical site infections [9,11]. Scoring systems have also been designed to predict AL risk. Using known AL risk factors (pre-operative, intra-operative) the Colon Leakage Score (CLS) can predict the risk of anastomotic leakage after left-sided colorectal surgery, yet they are mostly used to help the surgeon decide whether to perform an anastomosis or make a (nonfunctional) stoma in operating room [20,21]. Current clinical practices for AL diagnosis rely on contrast-enhanced CT scan. However, studies have shown that CT has variable sensitivity and specificity [22-23]. Pathognomonic CT sign of an AL like extravasation of contrast may not always be present, while peri-anastomotic liquid and air can be misinterpreted with normal postoperative inflammatory findings. These indicate that an experienced radiologist is required, and that clinical judgment and correlation with other diagnostic information are crucial for accurate diagnosis [24,25]. What is more, the wishful thinking of the surgeon or a possible reluctance

to perform multiple scans due to cost, miscommunication between doctors and patient inconvenience, may delay CT scan and AL diagnosis.

Given these limitations, new strategies to detect AL are required. One of those is the measurement of local biomarkers in the immediate environment of the anastomosis. Biomarkers, indicative of physiological, pathogenic, or pharmacological processes, were initially outlined by Komen et al. in 2008, establishing criteria for biomarkers of AL in peritoneal fluid [26] (Table 3).

Significant change in biomarker concentration in anastomotic leakage
Structural stability of the biomarker in the peritoneal environment and drain fluid
Biomarker level not influenced by the primary disease.
Biomarker with sufficient sensitivity and specificity for anastomotic leakage
Biomarker allowing for easy, fast and cheap real-time testing

**Table 3:** Suggested criteria for a biomarker of AL in peritoneal fluid.

Potential biomarkers can be divided into four categories: immune parameters [Cytokines such as interleukin (IL)-1, 6, 10 and tumor necrosis factor-a (TNF-a)], tissue-repair matrix metalloproteinases (MMPs), ischemia-related parameters (pH, lactate), and microbiological parameters (lipopolysaccharides, a marker of bacteria). Although promising, most of these biomarkers are expensive, labor-intensive, require technically challenging sophisticated methods to measure them [27]. In contrast, measurement of ischemia related pH and lactate from peritoneal drain fluid may provide a quick, easy and inexpensive alternative. The principle of this approach is that inadequate blood supply to the anastomosis increases the risk of a leak as well as the acidity in the vicinity of the anastomosis. [28,29]. Four studies have assessed pH and lactate levels via peritoneal drain sample as a predictive factor of AL. In 2013, Yang et al. in a retrospective study of 753 patients after low anterior resection first noted a significant decrease in pH among patients who leaked (pH <6.978 on POD3) with excellent sensitivity (98.7%) and specificity (94.7%). [30,31] Similarly, in 2014, Bini et al. evaluate lactate via peritoneal drain fluid in 88 patients after abdominal surgery, concluding that peritoneal/serum lactate level >4.5 or a peritoneal lactate level >9.1 were associated with post-operative complications requiring intervention (including AL). [32] Molinary et al. evaluate drain fluid pH after studying 173 elective colorectal operations with excellent results (pH < 7.53 on POD1 and pH <7.21 on POD3 showed 93.75% sensitivity and 97% specificity respectively). [33] In 1994, Simmen et al. correlated low pH (< 7.1) and pO<sub>2</sub> (< 6.5 kPa) and high pCO<sub>2</sub> (> 8 kPa) in the peritoneal fluid with the



presence of intra-abdominal infection on POD4 [34].

Our study is the first to evaluate pH, Lactate and B.D. in every colorectal operation, regardless of the underlying reason. Interestingly, no significant difference in the rate of AL was detected among the different types of colorectal resection, even among elective and emergency cases, probably due to the limited sample size. Given our results, pH from the peritoneal drain fluid correlates with AL earlier than its clinical presentation. The mean peritoneal pH values in the AL group were significant lower when compared to those in the n-AL group. Even from POD2 pH assessment performed well in ruling out AL, whereas on POD3 and POD4 performed even safer.

Conversely, peritoneal lactate and peritoneal base deficit measurements did not relate with AL. There was no statistically significant distinction between the two groups (AL and n-AL). These biomarkers did not exhibit satisfactory levels of sensitivity and specificity in detecting AL and they lacked stability, likely because of the constrained sample size.

Major limitation of the study is the trend to avoid placement of drains in the current surgical practice, as the benefit of drains has been challenged [35]. In the current study the decision, the position, and the type of the drain was exclusively surgeon's preference, which may influence the composition of the drained fluid. The study's population is heterogeneous including different types of resections of large bowel. However, it's worth noting that the role of ischemia in the development of AL remains the same and the acid microenvironment is present in every AL. It is possible that certain patients in n-AL group might have had a subclinical anastomotic leakage. On the other hand, AL group cases were confirmed with a CT or reoperation, a very austere definition that could impact study results. Finally, larger-scale studies involving a substantial number of patients are necessary in order to clarify the stability of these factors in peritoneal fluid and conduct meaningful comparisons of sensitivity and specificity across different studies. As already mentioned, early AL diagnosis is essential to reduce patient morbidity and mortality. The goal is not necessarily to entirely prevent its occurrence, but rather to establish a safe outcome. Measures such as delaying the initiation of feeding for the patient, avoiding early discharge, modification of antibiotic use but most importantly being alert for the potential need for re-operation could reduce further complications. What is more, the exclusion of AL enables the identification of candidates for Enhanced Recovery After Surgery (ERAS), an approach that has gained momentum in the management of patients with colorectal surgery, which reduces morbidity and shortens the hospital stay [14,36].

## Conclusion

In summary, pH value of the perianastomotic drainage fluid after colorectal operations with anastomosis, has shown in the current study to identify AL early. It is a safe, simple, non-expensive, noninvasive biomarker that may be useful in identifying those patients requiring clinical reassessment and possibly imaging to confirm or exclude AL, and offer early treatment to those with AL.

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