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ORIGINAL ARTICLE

Predictors of Early Detection of Anastomotic Leakage After Gastrointestinal Surgery

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Abstract

Background: ***Intestinal anastomosis is a prevalent surgical operation that is performed both electively and in emergency situations. Anastomotic leakage is a catastrophic complication that occasionally arises after intestinal anastomosis (AL).***

Purpose: ***To evaluate early AL detection using biochemical markers (total leukocyte count (TLC), Procalcitonin (PCT), lactic dehydrogenase (LDH), and C-reactive protein (CRP)) for AL presence or absence.***

Patients and methods: ***Forty patients (16 years of age or older) who underwent elective open or laparoscopic gastrointestinal surgery with primary anastomosis were included in this prospective study. TLC, CRP, PCT, and LDH were measured in all patients. The levels of CRP, PCT, and LDH were assessed 8 hours following the incision, on the third and fifth days postoperatively, and daily if parameters were elevated until they returned to normal, and the patient was released.***

Results: ***Regarding the correlation between TLC, CRP, PCT, LDH, and the presence of leakage, a significant difference was reported regarding elevated TLC, CRP, PCT, and LDH with the presence of leakage.***

Conclusions: ***Monitoring levels of CRP, PCT, LDH, and white blood cell trends may have predictive value for detecting AL early after GI procedures with reestablished intestinal continuity.***

Keywords: Anastomotic Leakage; Intestinal anastomosis; Gastrointestinal Surgery

1. Introduction

One of the most often performed elective and emergency surgical operations is intestinal anastomosis .[1] Peritonitis is a severe complication caused by anastomotic leakage (AL) of intestinal anastomosis; it is characterized by a high incidence of morbidity and mortality .[2] AL is often detected in the late postoperative phase when patients exhibit symptoms of sepsis and peritonitis due to the absence of distinct and early symptoms .[3]

C-reactive protein (CRP) is classified as an acute-phase protein when its concentration in the bloodstream increases significantly and abruptly in response to inflammation or illness.[4] On postoperative day three (POD3), higher CRP levels were related to intra-abdominal infections .[5] Procalcitonin (PCT) is utilized as a prognostic biomarker to predict outcomes in septic patients. PCT is quickly released into the bloodstream in response to bacterial endotoxins that induce PCT production .[6]

Epithelial destruction is another consequence of intestinal ischemia and has been linked to an increased concentration of I-Intestinal Fatty Acid Binding Protein (FABP) in the plasma, a protein considered one of the potential indicators of enterocyte necrosis. I-FABP is restricted to mature enterocytes located in the large and small intestines .[7]

The following factors were proposed for an AL grading system: general variables as fever, respiratory rate, heart rate, mental status, production of urine and clinical condition. Local physical variables included fascial dehiscence, gastric retention, bowel obstruction, and abdominal pain. Laboratory assessment variables were white blood cells (WBC) count, creatinine, and urea. A further significant variable was nutritional status, which included total parenteral nutrition or tubal feeding .[8]

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One of the most used biomarkers to detect AL is serum lactic dehydrogenase (LDH). Numerous studies have hypothesized that early in AL, a significant increase in serum levels of LDH may serve as an indicator of the degree of tissue damage .[9] Leaking progression monitoring and early detection of the condition can be facilitated by measuring the LDH level in critically sick patients with suspected AL .[10]We aimed to evaluate early detection of AL using biochemical markers (TLC, PCT, LDH, CRP) for AL presence or absence.

2. Patients and methods

This prospective study was performed on 40 cases aged ≥ 16 years old, both sexes, who underwent elective open or laparoscopic gastrointestinal surgery with primary anastomosis at General Surgery Department at Al-Azhar university hospitals (Alhussain and Sayed Galal – Bab El-sheria) from March 2023 to April 2024.

Written informed consent was acquired from each subject. The study was done after approval from the Ethical Committee of Al-Azhar University Hospitals.

Exclusion criteria were age < 16 years, emergency surgery for colonic perforation, patients on immunosuppressive drugs, uncontrolled diabetes on high insulin doses, and IBD (as ulcerative colitis) or diverticulitis.

All cases underwent full history taking, clinical examination by general examination and local assessment for the presence of any palpable abdominal mass and Per Rectum (PR) evaluation, Pre-interventional investigations including laboratory investigations such as complete blood count (CBC), coagulation profile, and international normalized ratio, arterial blood gases, liver and kidney functions, PCT and CRP, abdominal and pelvic CT with oral and intravenous contrast, biopsies and pathology, lower endoscopy, metastatic workup, and lower endoscopy are all recommended for cases with colon cancer. Patients awaiting colostomy closure should have the following diagnostic procedures: biopsies, pathology, lower endoscopy, and CT enema from the anal canal and colostomy.

Preparation:

Patients began fasting from solid foods six hours before the procedure. Right-sided colon surgery did not require any form of colon preparation. The patients were prepared for left-sided colon surgery two days prior to the procedure using (Neomycin, Flagyl tablets, enema, and laxatives).

Procedure:

All patients were brought into the operating room, where an intravenous line, epidural catheter, urine catheter, and Ryle were inserted. Prophylactic antibiotics were administered to all patients. Initiate anesthesia and abdominal sterilization. Anastomosis was performed open through Midline exploration for most patients and laparoscopic dissection around the affected area, resection with end-to-end anastomosis or side to side anastomosis of the affected part.

Methods of anastomosis in our cases:

Surgical staplers:

Staplers are used in open and laparoscopic anastomosis. There are two types of staplers used: linear and circular. For side-to-side anastomosis, linear staplers are used, whereas for end-to-end anastomosis, circular staplers are utilized.

Hand-sewn anastomoses:

Done in end to side and open end to end anastomosis.

Postoperative:

Day of procedure care: The urinary catheter and Ryle were removed. Good analgesia was given to every patient. Random blood sugar levels and vital data are monitored. It was advised that patients who had flatulence consume little amounts of water and walk about as quickly as possible. They were instructed to consume fluids on day two and semi-solid foods on day three.

Investigations:

CBC, TLC, and electrolyte analysis were performed on every subject. The levels of PCT, CRP, and LDH were assessed 8 hours after the incision, on the third and fifth days postoperatively, and daily if parameters were elevated until they returned to normal and the patient was released. All patients underwent a 30-day follow-up in the outpatient clinic after the procedure. Any complications and patient readmission were registered.

Statistical analysis:

SPSS (Statistical Package for the Social Sciences) version 25 (IBM Inc., Chicago, IL, USA) was utilized for the statistical analysis. Histograms and the Shapiro-Wilks test for normality were utilized to examine the distribution of quantitative data and determine whether parametric or nonparametric statistical testing was appropriate. Means and standard deviations (SD) were utilized to compare parametric variables across the three groups using the F test; for each pair of groups, the post hoc (Tukey) test was applied. Paired T-tests were utilized to compare two variables of the same group. For nonparametric variables, the median and interquartile range (IQR) were utilized for analysis using the Kruskal-Wallis's test. To compare each two groups, further analysis was conducted using the Mann–Whitney (U) test. The Wilcoxon test was utilized to compare two variables that were from the same group. Statistical analysis was conducted using the chi-square test on categorical variables, which were represented as

frequencies and percentages. A two-tailed P value ≤ 0.05 was deemed statistically significant.

3. Results

The mean age of studied patients was 53.2±7.2 years and ranged from 42 – 68 years. 40% of patients were males compared to 60% of females of studied patients. 80% of patients had no leakage after anastomotic surgeries compared to 20% of patients had AL. Type of procedure performed are represented in Table 1.

Table 1. Demographics and prevalence of leakage in the studied cases

		(N = 40)
AGE (YEARS)	Mean ± SD	53.2± 7.2
	Min – Max	42 – 68
SEX	Male	16 (40%)
	Female	24(60%)
LEAKAGE	No	32(80%)
	Yes	8(20%)
TYPE OF PROCEDURE	Colonic anastomosis after sigmoid cancer resection	6(15%)
	Colonic resection with anastomosis	1(2.5%)
	Esophagectomy with anastomosis	1(2.5%)
	Gastric resection with anastomosis	7(17.5%)
	Hepatic resection with anastomosis	1(2.5%)
	Ileocecal resection with anastomosis	1(2.5%)
	Jejunal resection with anastomosis	1(2.5%)
	Leakage after sleeve gastrectomy	3(7.5%)
	Pancreaticoduodenectomy with anastomosis	1(2.5%)
	Rectal resection with anastomosis	1(2.5%)
	Sigmoid resection and anastomosis for Dolichocolon	4(10%)
	Small bowel resection with anastomosis	1(2.5%)
	Small intestinal anastomosis after GIST resection	10(25%)
	Small intestinal anastomosis after Iatrogenic injury during a gynecological procedure	1(2.5%)
	Splenic resection with anastomosis	1(2.5%)

Data are presented as mean ± SD, Min – Max, or frequency (%).

No significant difference was reported regarding presence of AL regarding gender, as 6 females experienced leakage in comparison to 2 males. Table 2

Table 2. Distribution of the studied cases based on the presence of anastomotic leakage in relation to gender.

		LEAKAGE		TOTAL	P-VALUE
		No leakage	Leakage		
GENDER	Female	18	6	24	0.433
	Male	14	2	16	

Data are presented as frequency.

Table 3 showed that no significant difference was reported regarding presence of AL regarding age.

Table 3. Distribution of the studied cases based on the relation of age and presence of AL

	N	MEAN	SD	95% CI		MIN	MAX	P-VALUE
				LB	UB			
NO LEAKAGE	32	53.48	7.293	50.90	56.07	42	68	0.672
LEAKAGE	8	52.25	7.536	45.95	58.55	42	65	

Data are presented as mean ± SD, Min – Max, or frequency. CI: Confidence interval, SD: Standard deviation, LB:lower border, UB: upper letter

Table 4 showed that no significant difference was reported regarding presence of AL in relation to type of procedure.

Table 4. Correlation between type of procedures and presence of leakage

TYPE OF PROCEDURE	LEAKAGE		P-VALUE
	No leakage	Leakage	
COLONIC ANASTOMOSIS AFTER SIGMOID CANCER RESECTION	6	0	0.233
COLONIC RESECTION WITH ANASTOMOSIS	0	1	
ESOPHAGECTOMY WITH ANASTOMOSIS	1	0	
GASTRIC RESECTION WITH ANASTOMOSIS	6	1	
HEPATIC RESECTION WITH ANASTOMOSIS	0	1	
ILEOCECAL RESECTION WITH ANASTOMOSIS	0	1	
JEJUNAL RESECTION WITH ANASTOMOSIS	0	1	
LEAKAGE AFTER SLEEVE GASTRECTOMY	3	0	
PANCREATICODUODENECTOMY WITH ANASTOMOSIS	1	0	
RECTAL RESECTION WITH ANASTOMOSIS	0	1	
SIGMOID RESECTION AND ANASTOMOSIS FOR DOLICHOCOLON	4	0	
SMALL BOWEL RESECTION WITH ANASTOMOSIS	0	1	
SMALL INTESTINAL ANASTOMOSIS AFTER GIST RESECTION	10	0	
SMALL INTESTINAL ANASTOMOSIS AFTER IATROGENIC INJURY DURING A GYNECOLOGICAL PROCEDURE	1	0	
SPLENIC RESECTION WITH ANASTOMOSIS	0	1	

Data are presented as frequency.

Table 5 shows the descriptive analysis of TLC, CRP, PCT, and LDH among studied patients.

Regarding the correlation between TLC, CRP, PCT, LDH and presence of leakage, we found a significant difference regrading elevated TLC, CRP, PCT, and LDH with the presence of leakage.

Table 5. Descriptive analysis of TLC, CRP, PCT, and LDH among studied patients (N=40)

		MEAN	MEDIAN	STD. DEVIATION	RANGE	MINIMUM	MAXIMUM
TLC	8 hours post-operative TLC ($x10^3/mm^3$)	11.5634	11	1.67164	6.7	9.2	15.9
	2nd day TLC ($x10^3/mm^3$)	12.2756	11.7	1.55785	6.3	10.5	16.8
	3rd day TLC ($x10^3/mm^3$)	12.5878	12.2	1.97727	7.5	9.7	17.2
	5th day TLC ($x10^3/mm^3$)	12.8634	11.6	2.81991	10.6	10.2	20.8

CRP	8 hours post operative CRP mg/ml	83.323	82.67	9.4225	37.5	63.8	101.2
	2nd day CRP mg/ml	68.7173	60.91	24.5088	80.96	40.95	121.91
	3rd day CRP mg/ml	56.68	40.28	40.004	124	21	144
	5th day CRP mg/ml	88.19	38.61	108.906	355	20	375
PCT	8 hours post-operative PCT ng/ml	0.7761	0.578	0.50545	1.99	0.54	2.53
	2nd day PCT ng/ml	1.0252	0.542	1.29675	5.64	0.5	6.14
	3rd day PCT ng/ml	1.3465	0.517	2.32956	10.01	0.48	10.49
	5th day PCT ng/ml	2.2856	0.262	6.49701	35	0.14	35.13
LDH	8 hours post-operative LDH IU/L	191.146	173	42.4721	156	135	291
	2nd day LDH IU/L	183.098	153	70.4787	240	124	364
	3rd day LDH IU/L	189.781	147	102.357	349	109	458
	5th day LDH IU/L	226.537	172	128.285	420	129	549

TLC: Total leukocyte count, PCT: Procalcitonin, CRP: C-reactive protein, LDH: Lactate dehydrogenase.

4. Discussion

A delayed diagnosis of AL is correlated with heightened morbidity and death, in addition to a worse prognosis in the long term. Consequently, early detection may also result in enhanced long-term consequences and increased survival rates.[11]

In our study, 80.5% of patients had no leakage after anastomotic surgeries compared to 19.5% of patients who had AL.

Anwar et al.[12] who sought to determine whether PCT and CRP might be used to predict AL prior to early discharge. Five cases (20%) were found to have developed an AL; four required surgical intervention while one was treated conservatively.

Smith et al.[11] selected CRP and PCT in order to assess their predictive value for colorectal AL. Eleven (5.6%) of the 197 individuals who had colectomy developed AL, which is also less than our AL incidence rate.

Our research reported no significant difference regarding the presence of AL regarding gender, as six females experienced leakage in comparison to 2 males. No significant difference was reported regarding the presence of AL regarding age.

This agrees with Smith et al.[11] who reported that age and sex did not seem to have a change on AL. On the other hand, El-Badawy[13] discovered a statistically significant rise in the incidence of AL in individuals aged 65 and older. 6/21 as opposed to 11/89 among individuals younger than 65 years (P< 0.001). In accordance with our findings, they discovered an increase in AL among male patients, although it did not reach statistical significance.

In contrast to our findings, another research concluded that age more than 60 years remains an independent variable for AL .[14]

Male gender is widely acknowledged as a risk factor for AL among patient-related variables.[14, 15] This also disagrees with Kirchhoff et al.,[16] who showed that there is an elevated risk of complications in both open and laparoscopic surgery for male patients.

Our study showed no significant difference regarding the presence of AL in relation to the type of procedure.

This disagrees with El-Badawy[13] who reported that independent risk variables for AL were the bowel preparation and type of operation. They discovered that the incidence of AL is higher in patients who underwent emergency surgery (8/37) as opposed to elective cases (9/73) and in individuals who do not have intestinal preparation as opposed to those who do.

Nevertheless, several randomized trials have documented significant disparities in results between mechanical preparation and the administration of oral antibacterial medicines. Irvin and Goligher[17] documented a significant reduction in anastomotic dehiscence when mechanical bowel preparation was utilized as opposed to the absence of such preparation.

In our study regarding the correlation between TLC and the presence of leakage, we found a significant difference between elevated TLC and the presence of leakage.

This was consistent with a subsequent study's findings that elevated WBC count (WBCC) did not manifest until six days postoperatively among patients who developed an AL .[18]

Evaluation of WBCC was conducted in a smaller study of 129 patients undergoing laparoscopic colorectal surgery. The second day WBCC cutoff value of >12 × 109 demonstrated a specificity of 62% and a sensitivity of 90%. In conclusion, WBCC was an inadequate early diagnostic indicator for predicting postoperative septic complications, according to the authors (including AL) .[19]

While, a subsequent study, conducted by Cikot

et al.[20] they investigated cases who developed AL post-surgery. This study found that no changes in WBCC were seen in these individuals on the first, third, and fifth days after the procedure. Contrary to our results, Awad et al.[21] reported that four days of postoperative follow-up did not reveal a statistically significant variation in the number of WBCs.

One of the classical acute-phase proteins is CRP. After an inflammatory stimulation, CRP levels normally increase within 6 to 12 hours and peak around 48 hours later. In general, this increase is proportionate to the extent of tissue injury. In our study, regarding the correlation between CRP and the presence of leakage, we found a significant difference between elevated CRP and the presence of leakage .[22]

This is in agreement with Jin and Chen[3] who reported that, in all groups, CRP levels were elevated following surgery. After the third postoperative day, CRP decreased in patients without AL, even those with infection complications, as a result of the administration of anti-infective medications or decreased tissue damage. AL, on the other hand, is a critical tissue damage characterized by significant pathophysiologic responses. Thus, individuals with AL exhibited persistently elevated CRP levels beyond the third postoperative day. Upon making additional comparisons, it was observed that the mean CRP level varied significantly ($P < 0.05$) in relation to the postoperative outcome from day three to day seven. On postoperative day six, there was a significant difference ($P < 0.05$) in the mean CRP readings between the AL group and the other groups.

This is also in accordance with Anwar et al.[12] who reported that Patients without AL had significantly lower CRP levels on the third and fifth postoperative days compared to those with AL.

In patients who do not have complications, the CRP serum levels tends to return to normal by day three postoperatively, as demonstrated by several publications. Persistent rises in CRP following rectal resection are indicative of AL, according to Matthiessen et al.[15]. Assessing CRP levels in the postoperative phase may prove beneficial in the early detection of AL. A cutoff value was not, nonetheless, determined in their research.

Furthermore, prior research has demonstrated that CRP levels were significantly increased in the days preceding AL in patients who underwent colorectal surgery, as opposed to those who experienced a typical postoperative course .[18, 23]

Recent studies have demonstrated that blood CRP levels might dramatically increase days prior to the clinical diagnosis of AL in contrast to patients who experience a smooth postoperative recovery .[11, 24]

AL is predominantly caused by bacterial contamination during anastomotic suture, which results in elevated levels of CRP. Furthermore, leakage may occur as a consequence of chronic anastomosis infection. CRP levels, therefore, are elevated prior to the clinical manifestation of AL. Conversely, the levels of CRP are elevated concurrently with infections devoid of AL and other infectious complications. Other indicators of inflammation include elevated WBCC or body temperature, as well as infections of the urinary system, lungs, incision, and so forth. However, their specificity is inferior to that of CRP, which serves as an AL indicator .[25]

Monitoring postoperative levels of CRP might thereby minimize morbidity and death associated with delayed AL detection .[26]

In our study regarding the correlation between PCT and the presence of leakage, we found a significant difference between elevated PCT and the presence of leakage.

This agrees with Anwar et al.[12] who revealed that cases without AL had a significantly reduced 5-day postoperative PCT than those with AL.

These findings were similar to more recent investigation which indicated that individuals who later developed an AL had elevated levels of PCT on days one through three following surgeries. Early release of patients with a low chance of acquiring an AL might be facilitated, according to the authors, using this marker .[27]

Five resections (9.1%) were complicated by AL in Zawadzki et al.'s[28] study. From day three to today, twelve postoperatively, AL developed clinical symptoms that necessitated the relaparotomy. Zawadzki et al.[28] identified variations in PCT levels during POD 0–3 with respect to the postoperative course. The average PCT was elevated on PODs 1 and 3 for all patients, although the increase was significantly greater for those who developed AL-only on POD 3. On POD 1, the average PCT for non-AL cases was 2.0 ng/ml, and for AL cases, it was 3.8 ng/ml ($p=0.36$). On POD 3, the PCT was 0.56 ng/ml and 10.4 ng/ml, respectively ($p=0.017$).

Lagoutte et al.[29] studied PCT kinetics after to gastrointestinal resection. PCT levels in non-AL patients was elevated at POD1 and peaked at POD2 before declining gradually, according to an analysis of one hundred individuals. The PCT of patients with a leak peaked at a greater value on POD1, then declined. PCT demonstrated the highest prognostic accuracy for AL in POD 4.

On the first day after surgery, blood PCT levels between 1.42 and 4.62 ng/mL indicated which gastrointestinal and anastomotic resection cases will develop an AL, according to one research including 157 cases. The observed values in this

group were much greater than those in individuals who experienced a smooth recovery (0.09–0.44 ng/mL). The authors hypothesized that PCT might be utilized to identify high-risk individuals at this early postoperative duration.[30]

A PCT cutoff value of 2.7 ng/mL exhibited specificity of 91.7% and a negative predictive value (NPV) of 96.9% on the third day post-surgery in the PREDICS study, conversely, a cutoff value of 2.3 ng/mL on day five demonstrated specificity of 93% and a NPV of 98.3% for AL detection .[31]

In our study regarding the correlation between LDH and the presence of leakage, we found a significant difference between elevated LDH and the presence of leakage.

In accordance, Agnello et al.[32] enrolled 187 patients. At POD3 and POD5, LDH concentrations in serum and drainage fluid were significantly elevated. At a cutoff of 2,186 U/L, drainage fluid LDH had the highest diagnostic performance for AL, with an area under the curve (AUC) of 0.921 (0.849–0.993), 90% specificity and 82% sensitivity. They reached the conclusion that LDH in drainage fluid and serum might be promising indicators of AL.

4. Conclusion

Our study found an AL rate of 19.5%. There were statistically significant elevations in several laboratory parameters in cases that developed a leak in comparison to those that did not - including higher levels of total leukocyte count, CRP, PCT, and lactate dehydrogenase. Given these consistent biomarkers indicating a correlation with AL postoperatively, monitoring levels of CRP, PCT, LDH, and WBC trends may have predictive value for early AL detection after open GI procedures with reestablished intestinal continuity.

Disclosure

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