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Role of Serum C-Reactive Protein in Predicting Early Anastomotic Leakage After Elective Gastrointestinal Cancer Surgeries

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ABSTRACT

Purpose: Anastomotic leakage (AL) is the most feared complication after gastrointestinal (GI) cancer surgeries. Early detection can improve patient outcomes. This study examines if C-reactive protein (CRP) can be used as an early predictor of AL in the preclinical stage of post-GI surgeries.

Methods: This study included 132 patients subjected to elective GI surgical resections. CRP and albumin levels were checked on POD1 and every other day until discharge or AL development. The diagnostic markers were serial CRP measurements, CRP/albumin ratio, and CRP ratio, which is the ratio between consecutive CRP measurements from POD3 onwards and that of POD1.

Results: Twenty patients (15.2%) developed AL. The frequency was 66.7% after pancreaticoduodenal surgery and 2.7 in colorectal tumors was 2.7%. From POD3 CRP, CRP/albumin ratio, and CRP ratio were significantly higher in the leakage patients. On POD3 at a cut-off level of 134.5 mg/L the sensitivity and specificity of CRP were 80% and 64.3%, respectively. The PPV and NPV were low. The CRP ratio was a superior predictor of AL with high specificity and NPV. On POD3, at a CRP ratio cut-off of 1.11, the specificity and NPV were 92.9% and 98.1%, respectively. The readings were 92.9% and 95.4% on POD5, respectively, at a ratio of 0.92.

Conclusion: The overall rate of AL after various GI cancer resections was 15.2%, highly influenced by the type of surgery. The low PPV and NPV limit CRP use as a sole predictor of AL. The CRP ratio is a significant tool for ruling out AL based on its high specificity and NPV.

Keywords: *CRP, Anastmotic leakage (AL), gastrointestinal (GI) cancer surgeries*

1. INTRODUCTION

Anastomotic leakage (AL) is a frequent complication of gastrointestinal (GI) cancer resections with different types of anastomoses. It is the primary cause of mortality following GI resections, with rates ranging from 14% to 20% [1,2]. The occurrence and implications of AL vary according to the anastomotic site. In esophagectomy, AL is a common complication reported in 12%−16% of cases [3]. The incidence of pancreatoenteric AL is notably elevated, ranging from 20% to 25% of all pancreatoduodenectomies [4]. The incidence of anastomotic failure in colorectal anastomoses varies from 5% to 20% [5].

In the short term, septic or hemorrhagic consequences can be life-threatening, especially in cases of proximal AL with elevated enzymatic activity. The long-term effects of AL are mostly characterized by anastomotic stricture, which adversely impacts patient quality of life. Ultimately, the start of AL serves as a prognostic indicator for diminished long-term overall survival [6].

Patient outcomes can be significantly impacted by early identification and prediction of AL [7]. However, because there is currently no reliable method for anticipating when AL may manifest, early detection of the condition remains challenging

due to the low specificity and sensitivity of the traditional basic clinical indicators such as fever, leukocytosis, and abdominal pain who have little predictive value for AL. the clinical state of AL can vary greatly From mild symptoms to serious outcomes like peritonitis and septic shock, sometimes requiring further surgical intervention [8].

C-reactive protein (CRP) has been shown to be an effective early predictor of AL in patients having colorectal resections. A strong negative predictive value (NPV) for AL has been detected using the measures of CRP on the third postoperative day (POD) [9]. Diagnosing AL at its early stage might lessen its effect on patient's health and hasten the start of needed treatment. As part of accelerated recovery after surgery (ERAS) programs, this marker may also help identify patients who are less likely to develop AL and potentially benefit from early discharge [10].

One important acute-phase reactant and a reliable indicator of tissue damage and inflammation is CRP [11]. Hepatocytes are the only cells that can produce plasma CRP, which is mostly controlled at the transcriptional level by IL-6. After a single stimulation, de novo hepatic synthesis starts quickly, with serum levels surpassing 5 mg/l around 6 hours later and peaking around 48 hours later. Elevated CRP levels in blood samples can be a happen due to of a variety of causes, such as infections, cardiovascular events, some autoimmune and neoplastic conditions, and a reaction to systemic inflammation or damage [12].

Therefore, the present study aimed to find out the significance of serum C-reactive protein in the prediction of anastomotic leakage in the preclinical stage following gastrointestinal surgeries.

2. Patients and Methods

This prospective study involved all patients who underwent elective gastrointestinal surgery, in the surgical oncology department, at the National Cancer Institute (NCI), Cairo University in the period from December 1st, 2022, to June 30th, 2023.

Inclusion criteria were any patient aged 18 or more, who had undergone an elective gastrointestinal (GI) surgical procedure (esophageal, gastric, pancreaticoduodenal, colorectal, small intestinal surgeries) with anastomosis. Patients with active infection (respiratory and urinary tract infection) before surgery or a defunctioning stoma were ruled out from the study.

Data of the included patients were retrieved from patients' files and computer systems at the surgery department. The following data were collected: age, sex, medical history, surgical history, diagnosis, preoperative labs (Hb, TLC, Albumin), and preoperative chemotherapy or radiotherapy.

Every patient got prophylactic antibiotics and underwent mechanical and chemical bowel preparation. Both the procedure type and the kind of intervention (open or laparoscopic) were noted. Following surgery, CRP, TLC, and albumin levels were assessed on POD1 and every other day until the patient was discharged or an AL developed. Every day, patients were monitored for leak symptoms and other postoperative problems, including as pulmonary embolism, DVT, cystitis, respiratory tract infections, and wound infections.

Clinical indications of leakage were used to define AL, and radiological investigation, endoscopy, or reoperation were used to confirm the diagnosis. If there was clinical evidence of leaks, such as peritoneal signs, faecal, gastric, bile, or pancreatic content in the drain, or if a contrast leak was visible on computed tomography or if guided aspiration of any fluid or localized collection revealed bile or faecal matter, the patient was diagnosed with AL.

The patients with confirmed leakage were compared to others to determine the clinicopathological attributes and the possible differences in postoperative laboratory variables, especially CRP. Three variables were tested as diagnostic markers of anastomotic leakage: a) Serial measurements of CRP. b) Serial measurements of CRP/albumin ratio, and c) CRP ratio, defined as the ratio between consecutive measurements of CRP on POD3 onwards and that of POD1.

Statistical Methods

IBM SPSS Advanced Statistics, version 27 (SPSS Inc., Chicago, IL), was used for data analysis. The mean and standard deviation or median and range were used to describe numerical data. Numbers and percentages were used to characterise categorical data. Using the Shapiro-Wilk and Kolmogorov-Smirnov tests, the data were examined for normality. The Mann-Whitney test was used for non-normally distributed numerical variables, while the student's t-test was used for comparisons between two groups for regularly distributed numerical data. The chi-square test, often known as Fisher's exact test, was used to compare categorical variables. The optimal cut-off and diagnostic performance of markers were found using ROC curve analysis. Every test had two tails. A p-value of less than 0.05 was deemed significant.

3. Results

This study comprised 132 participants who had elective gastrointestinal operations for various cancer types. AL occurred in 20 cases; therefore, the total incidence was 15.2%. The demographic, clinical, and laboratory features of the entire group under study are displayed in Table 1, along with a comparison of the leakage and non-leakage groups. There was no significant difference in comorbidities, smoking ($p=0.304$), sex ($p=0.553$), or age ($p=0.193$) between the leakage and non-leakage groups. Similarly, prior radiation or chemotherapy was similar for both groups.

There was a significant difference ($p<0.001$) in the tumor location between the leakage and non-leakage groups. Two-thirds

of pancreaticoduodenal tumors developed leakage, and one patient had cholangiocarcinoma and developed leakage. In contrast, AL did not occur in any of the small intestine cases, and it was only 2.7% in colorectal tumour resections. no leaks were observed during rectal cancer cases. All laboratory data, including baseline CRP levels, did not significantly vary among the two studied groups (p=0.489).

Table 1: Baseline and clinical characteristics and laboratory variables in the whole studied group and in relation to leakage incident

	All (n=132)	Leakage (n=20)	Non-Leakage (n=112)	p-value
Age (years)	53.9±14.4	50.1±12.5	54.6±14.7	0.193
Sex				
Male	74 (56.1%)	10 (13.5%)	64 (86.5%)	0.553
Female	58 (43.9%)	10 (17.2%)	48 (82.8%)	
Diabetes mellitus	26 (19.7%)	4 (20.0%)	22 (19.6%)	1.000
Hypertension	36 (27.3%)	6 (30.0%)	30 (26.8%)	0.766
Smoking	19 (14.4%)	1 (5.0%)	18 (16.1%)	0.304
Previous Chemotherapy	39 (29.5%)	6 (30.0%)	33 (29.5%)	0.961
Previous Radiotherapy	6 (4.5%)	0 (0.0%)	6 (5.4%)	0.590
Type of Surgery				< 0.001
Colonic	70 (53.0%)	2 (2.9%)	68 (97.1%)	
Hepatobiliary surgeries	22 (16.7%)	15 (68.2%)	7 (31.8%)	
Gastric	21 (15.9%)	1 (4.8%)	20 (95.2%)	
Gastro-esophageal	7 (5.3%)	2 (28.6%)	5 (71.4%)	
Small intestinal	7 (5.3%)	0 (0.0%)	7 (100.0%)	
Rectal	5 (3.8%)	0 (0.0%)	5 (100.0%)	
Hb concentration (gm/dL)	11.4±2.3	12.1±1.9	11.2±2.3	0.096
TLC (x103/ml)	7.81±2.68	7.3±2.5	7.9±2.7	0.351
Serum Albumin (gm/dL)	3.81±0.52	3.9±0.6	3.8±0.5	0.654
C-reactive protein (mg/L)	9.0 (0.1-127.3)	4.3 (0.1-127.3)	9.3 (0.2-98.7)	0.489

Figures are displayed as mean±SD, number (%), median (range)
Hb: Hemoglobin, TLC: Total leucocytic count

Whipple pancreaticoduodenectomy was done in 21 patients, 14 of whom (66.7%) developed leakage. Other specific surgical procedures are shown in Table 2. All procedures except one were open surgery. The median time of leakage development was on POD6 (range: 2-12). Early leakage between POD2 and 5 was observed in the pancreaticoduodenal procedures (n=9).

Table 2: Specific surgery in patients with leakage and timing of leakage diagnosis

	Number (%)
Surgical Procedure	
Whipple	14/21 (66.7%)
Ivor-Lewis Esophagectomy	2/7 (28.6%)
Pancreatectomy + jejuno-jejunostomy	1/1 (100.0%)
Distal gastrectomy	1/4 (25.0%)
Left hemicolectomy	1/5 (20.0%)
Right hemicolectomy (extended)	1/17 (5.9%)
Day of diagnosis (median)	6 (2-12)
POD2	1 (5.0%)
POD3	3 (15.0%)
POD4	3 (15.0%)
POD5	2 (10.0%)
POD6	6 (30.0%)
POD7	1 (5.0%)

POD8	1 (5.0%)
POD10	1 (5.0%)
POD11	1 (5.0%)
POD12	1 (5.0%)

The median levels of CRP in the leakage and non-leakage groups increased after surgery, with no significant difference between the two groups on POD1 (p=0.376). Afterward starting from POD3 CRP levels were significantly higher in the leakage group (Table 3). The same pattern was observed in the CRP/albumin ratio. The CRP ratio was significantly higher in the leakage group. The median CRP ratio shows almost a rising pattern in the leakage group and a decreasing pattern in the non-leakage group (Figure 1).

Table 3: Serial measurements of CRP, CRP/albumin ratio, and ratio of CRP ratio in patients with confirmed leakage and those with no leak

	n	Leakage	n	No Leakage	p-value
CRP					
POD1	20	136 (20.6-391)	112	157.1 (32-533)	0.376
POD3	20	195 (30.9-479)	112	88.3 (12.7-398.6)	< 0.001
POD5	18	213.1 (56-507)	112	48.7 (7-393.4)	< 0.001
POD7	12	164.9 (26.5-475.8)	38	70.5 (11-461)	0.012
POD9	9	155 (86.1-410.3)	24	72 (10-422)	0.011
POD11	8	265 (69.4-473.9)	18	60.5 (13.6-283)	0.003
CRP/Albumin					
POD1	20	44.5 (7.4-119)	112	54.0 (8.8-177.7)	0.713
POD3	20	67.8 (10.7-201.1)	112	30.8 (3.7-188.0)	< 0.001
POD5	18	53.6 (0.0-190.9)	112	15.8 (1.9-158.2)	< 0.001
POD7	12	36.7 (0-183)	38	24.3 (3.8-159)	0.197
POD9	9	51.3 (0-152)	24	24.5 (3.3-145.5)	0.046
POD11	8	86.7 (0-182.3)	18	18.4 (3.8-113.2)	0.046
CRP Ratio					
POD3/1	20	1.48 (0.5-3.86)	112	0.58 (0.13-2.49)	< 0.001
POD5/1	20	1.35 (0.7-3.44)	112	0.33 (0.11-2.14)	< 0.001
POD7/1	18	1.83 (0.27-5.29)	38	0.45 (0.12-1.92)	0.001
POD9/1	12	1.92 (0.48-7.52)	24	0.49 (0.11-1.85)	0.002
POD11/1	8	2.04 (0.35-13.57)	18	0.47 (0.14-1.93)	0.003

Figures are displayed as median (range)

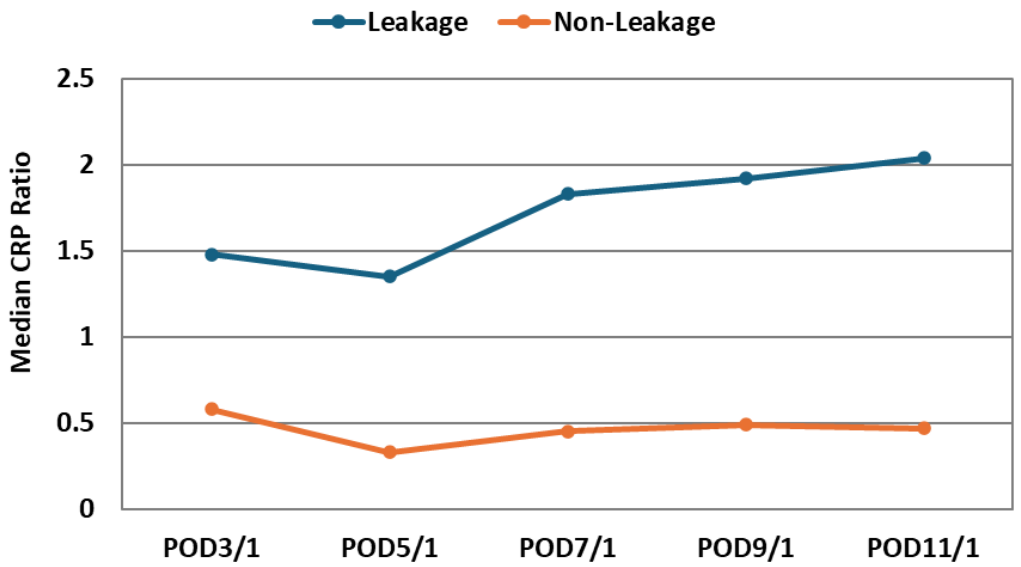

Figure 1: Change of the median CRP ratio in the postoperative period in the leakage and non-leakage groups

Table 4: Results of ROC curve analysis for serial CRP and CRP ratio for prediction of anastomotic leakage

	AUC	Cutoff level	Sensitivity	Specificity	PPV	NPV	Accuracy
Serial CRP (mg/L)							
POD3	0.444	134.5	80.0%	64.3%	28.6%	20.0%	66.7%
POD5	0.625	135.5	66.7%	83.9%	40.0%	33.3%	81.5%
POD7	0.854	106.5	66.7%	71.1%	42.1%	33.3%	70.0%
POD9	0.792	97.9	77.8%	62.5%	43.8%	88.2%	66.7%
POD11	0.854	70.5	87.5%	66.7%	53.8%	92.3%	73.1%
CRP ratio							
POD3/1	0.872	1.11	90.0%	92.9%	69.2%	98.1%	92.4%
POD5/1	0.903	0.92	72.2%	92.9%	61.9%	95.4%	90.0%
POD7/1	0.958	1.09	66.7%	89.5%	66.7%	89.5%	84.0%
POD9/1	0.854	1.07	66.7%	83.3%	60.0%	87.0%	78.8%
POD11/1	0.854	0.85	75.0%	83.3%	66.7%	88.2%	80.8%

AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value

Using ROC curve analysis, serial CRP measurements revealed a rising area under the curve (AUC), however, the positive predictive value (PPV) and negative predictive value (NPV) tend to be low on days 3 to 7, but NPV is reasonable during late measurements (Table 4). On the other hand, the CRP ratio on consecutive measurements relative to POD1 levels showed better predictive capacity, especially the high specificity and NPV.

4.Discussion

In this study, the overall rate of AL was 15.2%. The results demonstrated a significant difference in the median CRP levels between the leakage and non-leakage groups starting from POD3 onwards. The same pattern was noticed in the CRP/albumin and CRP ratios. Using ROC curve analysis, serial CRP measurements showed a growing area under the curve (AUC). On POD3 at a cut-off level of 134.5 mg/L the sensitivity and specificity of CRP were 80% and 64.3%, respectively. On POD5, the results were 66.7% and 83.9% at a concentration of 135.5 mg/L, respectively. The PPV and NPV were quite low. The CRP ratio was a superior predictor of AL, exhibiting sufficiently high specificity and NPV, hence supporting its application in ruling out the likelihood of AL. On POD3, at a CRP ratio cut-off of 1.11, the specificity and negative predictive value were 92.9% and 98.1%, respectively. The readings were 92.9% and 95.4% on POD5, respectively, at a ratio of 0.92.

The effectiveness of CRP as a biological marker for early identification of AL is still being studied, despite its widespread use for diagnosis, tracking the course of the illness, and assessing the effectiveness of therapy [13]. Higher CRP levels and the incidence of AL were found to be significantly correlated in several researches, especially after colorectal procedures

[13–15]. High CRP level may indicate postoperative problems like AL, whereas a persistently low level after the second postoperative day suggests straightforward recovery following surgery [16–20]. From postoperative days 3 to 6, the recorded cut-off values for CRP were in the range from 77 to 180 mg/L [21]. The present study suggested cut-off is around 135 mg/L which is located almost exactly in the middle of this wide range.

Using CRP as a diagnostic marker for AL is significantly hampered by the cuto-ff variability shown in many investigations. One research found that CRP levels ≤ 172 mg/L at POD3 were linked to early recovery in 80% of patients and the absence of significant issues in 95% of cases [17]. In contrast, another study found that a lower POD3 result of 118 mg/L was suggestive of AL [22]. Therefore, to determine the ideal CRP cutoff levels, sensitivity and specificity must be carefully balanced. Whilst lower levels may increase sensitivity but decrease specificity, higher cutoff values may increase specificity at the price of sensitivity [23].

This issue prompted an examination of the CRP to albumin ratio and the ratio of successive CRP levels to the level of POD1 in the present study. However, we failed to find an added value of the CRP/albumin ratio. This was discordant with Paliogiannis et al. [24] who identified the CRP/albumin ratio as a significantly more effective predictor of AL than CRP alone. On the other hand, the CRP ratio was a better predictor of AL, at least as a relatively accurate indicator to exclude AL due to the high specificity and NVP. In a previous study of 1278 patients who underwent laparoscopic rectal surgery [25], the ratio of CRP of POD4 to that of POD2 of 1.007 had a sensitivity, specificity, and NPV of 92.0%, 96.5%, and 99.5, respectively. These values are comparable to 90%, 92.9%, and 98.1%, respectively in the current study at a ratio of 1.11.

In earlier researches, the concept of evaluating the CRP curve over different PODs—was proposed. It was noted that early patient discharge would be possible if there was no increase in CRP levels of more than 50 mg/L during any 24-hour postoperative period [26]. Instead of using a 24-hour period, some researchers have assessed the change in CRP between two different PODs [27, 28]. For instance, an increase in CRP-level of 50 mg/l during POD1-2 showed an NPV of 92% and specificity of 71% in a study of 271 patients having rectal cancer surgery, and was 94% and 76%, respectively, for the alterations between POD1-3 [28].

Changes in postoperative CRP levels seen in leaking patients suggest an inflammatory response and the start of hepatic CRP production right after surgery, prior to the development of clinical symptoms [29]. A rapid and severe inflammatory response that results in increased production of CRP appears to be caused by tissue ischemia close to the suture line of leaking anastomosis [30].

The postoperative time-point at which AL is detected is one of the basic elements for the classification of AL in addition to grading systems, clinical manifestations, radiographic observations, serum indicators [31,32]. In the current study, we observed that Al occurred in 9 patients (45%) within the first 5 days after surgery, all of them had pancreaticoduodenal procedures. The current study's median time for AL incidence (6 days) is comparable to the median time for AL occurrence identified in several investigations, which was 7 days [8, 33].

Early AL is linked to severe peritonitis and requires surgical re-exploration. In general, surgical issues including technical difficulties in anastomosis are frequently linked to extremely early leaks. This might explain why we had a correlation between extremely early AL especially in Whipple surgery which is well known to be technically demanding. Inadequate wound healing ability, poor baseline health, or patient illness may all be associated with more delayed AL [34, 35].

Like many other earlier studies, we recommend using CRP as a helpful prognostic biomarker for AL. However, because it can be impacted by a many factors, including as surgical stress, postoperative infection, and other systemic inflammatory comorbidities, CRP shows inadequate specificity for AL [36]. As a result, false-positive diagnoses may arise [37]. The modest positive predictive value of CRP levels on days three and five makes this noteworthy in the current research.

In the current study, we measured CRP levels every other day starting from POD1. Conducting measurements too soon post-surgery may result in false-negative outcomes. This stresses the need to select the optimal time point for evaluating CRP to enhance diagnostic precision. The cut-off values on days 3 to 11 in the current study were 134.5, 135.5, 106.5, 97.9, and 70.5 mg/L. This wide variability across different PODs highlights the absence of standard levels in CRP thresholds for AL diagnosis, complicating clinicians' ability to establish and utilize a uniform criterion [16,17,38,39,22,19].

The present study included patients who underwent heterogeneous types of elective GI surgery for cancer treatment, involving esophageal, gastric, pancreaticoduodenal, colorectal, and small intestinal procedures. The overall rate of AL was 15.2%. However, we observed an exceedingly high rate of AL in cases of the Whipple procedure (66.7%). This may be explained by the intricacy of this kind of surgery, which requires resection of the pancreatic head and biliary ducts, duodenum, the first jejunal loop, and excision of the gastric antrum [40,41]. Pancreatico-jejunal AL and the resulting pancreatic fistula are the main issues related to the pancreatic remnant [42, 43]. Reoperation is necessary in cases with severe AL and depends on the clinical state of the patient [44].

A principal strength of this study lies in its utilization of the CRP ratio of consecutive measurements relative to the level at POD1 as an indicator of AL. Additionally, the sample size is adequate, and the relatively high incidence of cases with AL permits robust statistical analysis. However, the study had limitations; including being a single-center study with a diverse group of patients and various types of surgeries and anastomoses. CRP was measured every other day, which means some variations could have been missed on the days when measurements were not taken.

5.Conclusion

The overall rate of anastomotic leakage (AL) in patients with various GI cancers undergoing different types of resection was 15.2%. The type of surgery influenced the AL rate; the Whipple procedure had the highest rate at 66.7% due to its complexity, while colorectal surgery had a rate of 2.7%. Serial postoperative measurements are necessary for using CRP to detect AL early. The CRP/albumin ratio does not improve the predictive value beyond CRP alone. The low PPV and NPV limit CRP's use as a sole predictor of AL. The CRP ratio showed better predictive power, with high specificity and NPV (92.9% and 98.1%), making it a significant tool for ruling out AL.

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