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ORIGINAL ARTICLE

Prediction of Early Anastomotic Leakage Following Colorectal Cancer Surgery in Zagazig University Hospitals

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ABSTRACT

Background: Anastomotic leak (AL) is the most common unfavorable complication after colorectal surgery. Early discharge benefits the patient but carries a potential risk of developing AL. So the early diagnosis of AL is critical. The study aims **to** assess whether C-reactive protein (CRP) and Procalcitonin (PCT) will predict AL before early discharge. **Methods:** This study was carried out in Surgical-oncology Unit, General Surgery Department, Zagazig University Hospitals, during the period from May 2018 to November 2018. The study included 24 patients with Colorectal cancer undergoing elective open colorectal resection with anastomosis. CRP and PCT were measured pre-operatively, 8h after incision, and on the 3rd and 5th postoperative day (POD). 30-day readmissions, re-laparotomy, and mortality were recorded. **Results:** 5 patients had AL (20.8%). 5th day postoperative CRP and PCT were significantly lower in patients without AL than patients with AL. The present study revealed the diagnostic performance of CRP in the prediction of AL where 5th day CRP>198.23mg/mL had 100% sensitivity, 94.74% specificity, 83.3% positive predictive value, 100% negative predictive value and 95.8% accuracy in the prediction of AL. Also, the study revealed diagnostic performance of 5th day PCT in the prediction of AL where a cutoff of more than 1.212 ng/dl, 5th day PCT had 80% sensitivity, 100% specificity, 100% positive predictive value, 95% negative predictive value and 95.8% accuracy in prediction of AL. **Conclusion:** CRP and PCT measurements can positively identify patients at risk of AL with CRP being more accurate and a potentially powerful marker.

Keywords: colorectal cancer; anastomosis; leak; C-reactive protein; procalcitonin.

INTRODUCTION

Anastomotic leak (AL) is the most common major surgical complication after colorectal surgery **[1].**

AL is defined as a leak of luminal contents from a surgical join between two hollow viscera [**2].**

Early discharge benefits the patient but carries a potential risk of developing AL. So the early diagnosis of AL is critical [**3].**

Delayed diagnosis of AL is associated with increased morbidity, mortality as well as decreased long-term survival. So early diagnosis may also lead to improved long-term outcomes, such as decreasing the need for permanent stomas, as well as improving long-term survival **[4].**

Clinical signs of AL are generally unreliable and tend to occur late. A number of tools have been assessed in diagnosing AL at an early stage. Peritoneal cytokine levels, serum inflammatory biomarkers and diagnostic imaging such as CT scanning and water-soluble

contrast enema, have all been used in order to provide early detection of AL **[5].**

In this study, we will choose inflammatory serum biomarkers: CRP, PCT to assess their utility in predicting colorectal AL. In particular, we will determine whether the rate of change of these biomarkers is predictive of AL as defined by the need for radiological drainage or surgical intervention **[4].**

For many years, CRP and PCT were used to identify septic complications. They were used as markers in surgical departments to identify sepsis [**6].**

CRP is a liver - synthesized serum acute - phase reactant. Its production is in response to most forms of tissue damage, infection and malignant neoplasia. The median concentration of CRP in healthy young adults is about 0.8 mg / l, but after an acute phase stimulus, values may rise to over 500 mg / l **[7].**

PCT is another promising plasma marker for identifying sepsis. PCT is a protein made up of 116 amino acids, synthesized by the thyroid gland para-follicular C-cells. Bacterial endotoxins specifically induce the release of PCT, and its levels do not increase after non - infectious origin inflammation. Serum concentrations of PCT in healthy individuals are below 0.1 ng / ml. After surgery, PCT concentrations are commonly increased in patients on the 1st and 2nd postoperative days following major vascular and abdominal or thoracic operations and remain low in patients undergoing minor aseptic procedures [**8].**

PCT, therefore, appears to be a more specific marker for septic complications than CRP **[6].**

The Aim of work is the Prediction of early anastomotic leakage following open colorectal cancer surgery through estimation of C-reactive protein (CRP), and procalcitonin (PCT). The objective is Treatment of AL either by conservative treatment or surgical intervention or radiological drainage.

METHODS

The Site of study:

This study was conducted in Surgical-oncology Unit, General Surgery Department, Zagazig University Hospitals.

Sample size:

The study included 24 patients with Colorectal cancer undergoing elective open colorectal resection with anastomosis.

Inclusion criteria

All patients ≥ 16 years undergoing elective open colorectal cancer resection surgery with primary anastomosis, Sex: Both male and female.

Exclusion criteria

Patients < 16 years, Patients on immunosuppressive drugs, Emergency surgery for colonic perforation, uncontrolled diabetic patients on high insulin doses, Diverticulitis or colitis

Ethical Considerations:

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients were subjected to the following:

1. History taking:

We asked about: a) Personal History: name, age, sex and residency. b) Present history: we asked about a complaint. We analyzed complaint to know onset, course, duration, what increase, what decrease and associations. c) Past history. d) Family history.

2. Clinical Examination:

a) General examination: by inspection, palpation, to know if there were any organomegaly or lymphadenopathy, auscultation of abdomen to assess bowel movement. b) Local examination: if there is palpable mass in the abdomen and Per Rectum (PR) examination.

3. Pre-interventional investigations include: a)Laboratory investigations: such as Complete blood count (CBC), Liver and kidney functions, Coagulation profile (PT, PTT, and INR), Arterial blood gases (ABG), CRP and PCT. b) Imaging studies: Patients with cancer colon should have: CT abdomen and pelvis

with oral and intravenous contrast, lower endoscopy, biopsies and pathology, metastatic workup c) Patients prepared for the closure of colostomy should have: CT enema from colostomy and anal canal, lower endoscopy, biopsies, and pathology.

4. Preparation:

Patients fasting from solids started 6 hours before the operation. There was no need for colon preparation in right-sided colon surgery. In left-sided colon surgery, we prepared patients 2 days before operation with (laxatives, enema, Neomycin, and Flagyl tablets).

5. Procedure:

All patients entered the operation room, introduction of intravenous line Ryle, urinary catheter, epidural catheter. All patients had prophylactic Antibiotic. Start anesthesia, sterilization of abdomen. Midline exploration was done, dissection around the affected part, resection of the affected part, end to end anastomosis. Calculation of blood loss. Registration of blood transfusion, time of operation. Recovery of the patient and transferred to ICU.

6. Post-Operative:

Care at the day of operation:

Remove Ryle, urine catheter. All patients had good analgesia. Monitoring of vital data and random blood sugar. Patients encouraged to drink Sips of water when passing flatus and to move early as soon as possible. They encouraged to drink fluids in the 2nd day. They encouraged to eat semi-solid food on the 3rd day.

Investigations:

All patients had laboratory investigations such as Complete blood count, Bleeding profile PT, PTT, and INR, liver functions, kidney functions electrolytes. CRP and PCT measured 8 h after incision, and on the third and fifth postoperative days and daily in the case of elevated parameters until they become normal and patient discharged.

Follow up:

All patients were followed in the outpatient clinic 30-day after the operation. Registration of any complications and patient readmission.

7. Data collection:

- All data were collected then statistically analyzed and tabulated. AL was detected clinically, or by operative or radiological intervention. There was no need for radiological imaging to confirm the diagnosis in pronounced cases with clinically apparent leaks, but urgent re-laparotomy was done as an early intervention to avoid potential threatening effects. The number of clinical parameters suggestive of AL was determined. These parameters included tachycardia (heart rate >100 beats/minute), fever (body temperature >38°C), generalized or local peritoneal reaction during the physical examination, leukocytosis (>10×103 /ml), prolonged adynamic ileus (>2 days postoperatively), and delayed gastric emptying (nasogastric tube production of >200 ml/day or vomiting requiring reinsertion of the tube)
- A comparison was made between biomarkers (CRP, PCT) and clinical AL.

8. After completing all investigations 24 patients were divided into two groups:

- Group I: Anastomotic leak group (AL)
- Group II: Non-Anastomotic leak group (Non-AL)

Statistical analysis

All data were collected, tabulated and statistically analyzed using "SPSS 22.0" Statistical Package for the Social Sciences for Windows and Microsoft Office Excel 2010 for Windows. Continuous data are expressed as the mean ± SD & median (range), and the categorical data are expressed as a number (percentage). (Mann - Whitney U) test was used to compare non - normally distributed data groups with each other. Using (Friedman test) more than two related groups of non - normally distributed data were compared.

Using the (Chi - square test), categorical data were compared. Changes in the distribution of relative frequencies among ordinal data were compared. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of CRP and PCT with maximum sensitivity and specificity for prediction of AL. Area Under Curve (AUROC)

was also calculated: 0.90 – 1 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair; 0.60-0.70 = poor; and 0.50-0.6 = fail. The optimal cutoff point was established at the point of maximum accuracy. All tests were two-sided. P - Value <0.05 was considered statistically significant (S), P - value <0.001 was considered highly statistically significant (HS), and P - value ≥0.05 was considered statistically insignificant (NS).

RESULTS

In the present study, 17 (70.8%) was male. Mean age was 60.91 years, mean body mass index was 25.45 kg/m2 and 5 (20.8%) was obese and 8 (33.3%) was overweight. The most frequent site was sigmoid colon carcinoma where seven (29.2%) had sigmoid colon carcinoma, six (25%) patients had ascending colon carcinoma and five (20.8%) patients had descending colon carcinomas (**Table 1)**.

Table (2) demonstrated the operative data where seven (29.2%) patients underwent sigmoidectomy. Six (25%) patients underwent right hemicolectomy. Six (25%) patients underwent left hemicolectomy. Mean duration of operation was 156.25 minutes. Average amount of blood loss was 418.75 cc. Sixteen (66.7%) had need transfusion. Average amount of transfused plasma was 2.26 units and average amount of transfused blood was 794.11 cc. Twelve (50%) patients had Colocolic anastomosis and eight (33.3%) patients had ileocolic anastomosis.

There was significant increase in CRP, PCT preoperatively versus postoperatively.

Five (20.8%) patients had developed AL, one patient underwent conservative management and the other four underwent surgical management. Four (16.7%) patients had bad surgical recovery. Twenty (83.3%) patients were admitted to ICU. Average duration of ICU admission was 2.25 days. Sixteen (66.7%) patients had early discharge. But, eight (33.3%) patients had complications, three (12.5%) patients had wound infection, two (8.3%) patients had wound seroma and two (8.3%) patients had wound dehiscence **(Table 3).**

In our study, there were insignificant differences between patients without AL and patients with AL regarding preoperative and 8 hour postoperative CRP, PCT.

Table (4) showed the relation between laboratory findings at 3rd day and 5th day postoperatively and AL. Where the 3rd day postoperative CRP was significantly lower in patients without AL than patients with AL. But, there was an insignificant difference between patients without AL and patients with AL regarding 3rd day postoperative PCT.

The 5th day postoperative CRP and PCT were significantly lower in patients without AL than patients with AL.

When ROC curves were applied **(Figure 1)**, the present study revealed diagnostic performance of 5th day PCT in predication of AL **(Table 5)** where at cutoff of more than 1.212 ng/dl, 5th day PCT had 80%sensitivity, 100%specificity, 100%positive predictive value, 95%negative predictive value and 95.8%accuracy in prediction of AL.

Also, the study revealed diagnostic performance of CRP and PCT in predication of AL **(Table 5)** where 3rd day CRP>123.32mg/mL had 80% sensitivity, 89.47% specificity, 66.7% positive predictive value, 94.4% negative predictive value and 89.6% accuracy in prediction of AL, 5th day CRP>198.23mg/mL had 100% sensitivity, 94.74% specificity, 83.3% positive predictive value, 100% negative predictive value and 95.8% accuracy in prediction of AL, and 5th day PCT>1.212 had 80% sensitivity, 100% specificity, 100% positive predictive value, 95% negative predictive value and 95.8% accuracy in prediction of AL.

Table (1): Basic characteristics

Basic characteristics	All (N=24)	
	No.	%
Sex		
Male	17	70.8%
Female	7	29.2%
Age (years)		
Mean ± SD	60.91 ± 10.62	
Median (Range)	62.60 (33 – 75)	
BMI (kg/m^2)		
Mean ± SD	25.45 ± 4.76	
Median (Range)	26 (17 – 35)	
Underweight <18.5	2	8.3%
Average = 18.5–24.9	9	37.5%
Overweight = 25–29.9	8	33.3%
Obese= 30 or greater	5	20.8%
Diagnosis		
Ascending	6	25%
Hepatic flexure	2	8.3%
Splenic flexure	1	4.2%
Descending	5	20.8%
Sigmoid	7	29.2%
Rectum	3	12.5%

Table (2): Operative data

Operative data	All (N=24)	
	No.	%
Operation		
Rt hemicolectomy	6	25%
Rt extended hemicolectomy	2	8.3%
Lt hemicolectomy	6	25%
Sigmoidectomy	7	29.2%
LAR	3	12.5%
Durations (min)		
Mean ± SD	156.25 ± 34.23	
Median (Range)	150 (120 – 240)	
Blood loss (cc)		

Mean ± SD	418.75 ± 266.95	
Median (Range)	400 (200 – 1500)	
Transfusion		
No	8	33.3%
Yes	16	66.7%
Blood (cc)		
Mean ± SD	794.11 ± 309.17	
Median (Range)	1000 (500 – 1500)	
Plasma (unit)		
Mean ± SD	2.26 ± 0.70	
Median (Range)	2 (2 – 4)	
Level of anastomosis		
Ileocolic	8	33.3%
Colocolic	12	50%
>6cm from verge	4	16.7%

Table (3): Outcome of surgery.

Outcome of surgery	**All (N=24)**	
	No.	%
Anastomotic leak		
No	19	79.2%
Yes	5	20.8%
Leak treatment	(N=5)	
Conservative	1	20%
Surgical	4	80%
Recovery		
Good	20	83.3%
Bad	4	16.7%
ICU admission		
No	4	16.7%
Yes	20	83.3%
Duration of ICU admission (days)		
Mean ± SD	2.25 ± 1.01	
Median (Range)	2 (1 – 4)	
Patient discharge		
Early	16	66.7%
Late	8	33.3%

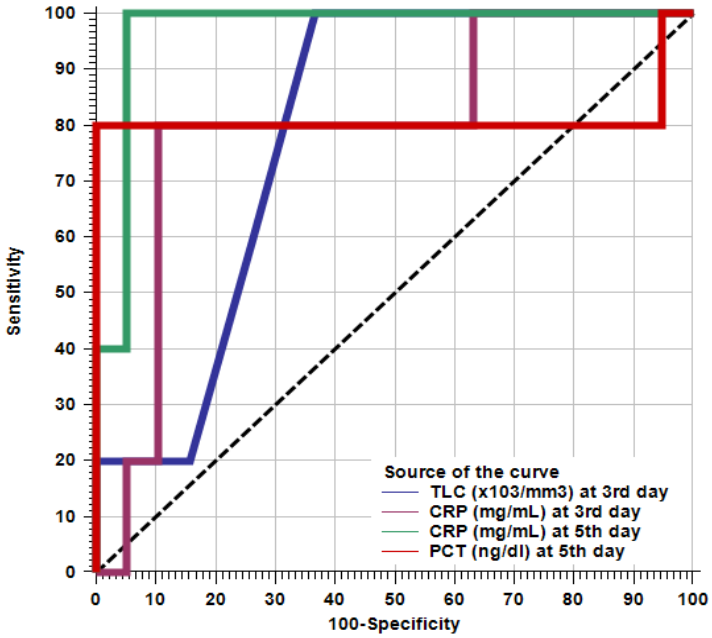
Table (4): Relation between laboratory findings at 3rd day and 5th day postoperatively and anastomotic leak.

laboratory findings	All (N=24)	Anastomotic leak		Test•	p-value (Sig.)
		Absent (N=19)	Present (N=5)		
3rd day postoperative					
TLC ($x10^3/mm^3$)				-2.002	0.045 (S)
Mean ± SD	13.38 ± 3.56	12.64 ± 3.19	16.20 ± 3.83		
Median (Range)	13 (9.10 – 23)	11 (9.10 – 21)	15 (14 – 23)		
CRP (mg/mL)					
Mean ± SD	107.30 ± 46.95	98.98 ± 47.20	138.90 ± 32.76	-2.026	0.043 (S)
Median (Range)	106.40 (0.18 – 201.32)	102.98 (0.18 – 201.32)	132.50 (101 – 191)		
PCT (ng/dl)					0.303
Mean ± SD	14.159 ± 42.914	16.879 ± 48.080	3.823 ± 4.244	-1.031	(NS)
Median (Range)	0.830 (0.010 – 178.230)	0.730 (0.010 – 178.230)	3.290 (0.060 – 10.889)		
5th day postoperative					
TLC ($x10^3/mm^3$)					
Mean ± SD	13.62 ± 3.09	13 ± 2.72	16 ± 3.53	-1.827	0.068 (NS)
Median (Range)	13 (8 – 21)	13 (8 – 18)	15 (12 – 21)		
CRP (mg/mL)					
Mean ± SD	147.11 ± 113.25	101.11 ± 65.80	321.93 ± 77.53	-3.163	0.002 (S)
Median (Range)	107.67 (4.71 – 432)	97.23 (4.71 – 302.65)	298.69 (224 – 432)		
PCT (ng/dl)					
Mean ± SD	2.464 ± 7.365	0.356 ± 0.334	10.476 ± 14.493	-2.097	0.036 (S)
Median (Range)	0.285 (0.010 – 35.878)	0.220 (0.010 – 1.212)	4.870 (0.012 – 35.878)		

Table (5): Diagnostic performance of TLC, CRP and PCT in predication of anastomotic leak: ROC curve analysis.

Cut-off values	SN % (95% CI)	SP % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy (95% CI)	AUROC (95% CI)	p-value (Sig.)
TLC 3rd day >12x10^3/mm^3	100% (47.8-100)	63.16% (38.4-83.7)	41.7% (15.2-72.3)	100% (71.5-100)	70.8% (40.4-87.1)	0.789 (0.576-0.927)	0.025 (S)
CRP 3rd day >123.32mg/mL	80% (28.4-99.5)	89.47% (66.9-98.7)	66.7% (22.3-95.7)	94.4% (71.8-99.9)	89.6% (58.9-98.9)	0.800 (0.588-0.934)	0.018 (S)
CRP 5th day >198.23mg/mL	100% (47.8-100)	94.74% (74-99.9)	83.3% (35.9-99.6)	100% (81.5-100)	95.8% (68.6-99.9)	0.968 (0.804-1.000)	<0.001 (HS)
PCT 5th day >1.212ng/dl	80% (28.4-99.5)	100% (82.4-100)	100% (39.8-100)	95% (74.4-99.9)	95.8% (71.2-99.9)	0.811 (0.600-0.940)	0.013 (S)

Figure (1): Receiver operating characteristic (ROC) curve of TLC, CRP and PCT in predication of anastomotic leak.



DISCUSSION

AL is the most common major surgical complication following colorectal surgery, with reported rates ranging from 2% to 14%. The clinical significance of AL should not be underestimated due to increased morbidity, mortality and reduced long - term survival **[9].**

AL clinical signs are generally unreliable and tend to occur late [**10].**

AL occurs around the 5th–7th postoperative day (POD), but from the day of the index of surgery to the 3rd postoperative week it may develop at any time. Patients are usually hospitalized with the standard postoperative protocols on POD 7 and clinical symptoms announce the leakage **[11].**

The aim of the present study was to predict early AL following open colorectal cancer surgery through estimation of CRP, PCT. This prospective study involved 24 patients with colorectal cancer undergoing elective resection with anastomosis.

CRP and PCT were measured pre-operatively, eight hours after incision, and on the 3rd and 5th postoperative days and daily in the case of elevated parameters until they become normal and patient discharge. AL was detected clinically by operative or radiological intervention.

Our study revealed that five (20.8%) patients had developed an AL, one patient

underwent conservative management and the other four underwent surgical management.

Smith et al. **[4]** chose CRP and PCT to evaluate their utility in predicting colorectal AL. 197 patients underwent colectomy, 11 (5.6%) of whom had an AL. Age, sex, BMI, preoperative chemotherapy and/or radiotherapy and anastomotic location did not seem to have a change on AL.

Our study revealed that 3rd day postoperative CRP and 5th day postoperative CRP, PCT were significantly lower in patients without AL than patients with AL.

Zawadzki et al. **[12]** enrolled 55 patients undergoing colorectal cancer resections. 26 patients had an open resection and 29 patients underwent a robotic procedure. Zawadzki et al. **[12]** found that 5 resections (9.1%) were complicated by AL. AL became clinically symptomatic between the 3rd and 12th postoperative day, and all required re-laparotomy.

With respect to the postoperative course, Zawadzki et al. **[12]** observed differences in the CRP and PCT values within POD 0–3. The mean value of CRP increased on POD1 and POD3 in all patients. The peak of CRP was significantly higher in the AL group only on POD3. The mean values of CRP On the 3rd postoperative day were 114 mg/l in non-AL patients and 321 mg/L in Al patients (p = 0.0001). Similarly, the mean PCT increased on POD 1 and 3 in all patients, but the rise of PCT was significantly higher among the patients with AL only on POD 3. The mean PCT on POD 1 was 2.0 ng / ml in non-AL and 3.8 ng / ml in AL patients (p=0.36), In contrast, on POD 3 it was 0.56 ng / ml and 10.4 ng / ml, respectively (p = 0.017).

When ROC curves were applied **(Figure 1)**, the present study revealed diagnostic performance of CRP in prediction of AL where 3rd day CRP>123.32mg/mL had 80% sensitivity, 89.47% specificity, 66.7% positive predictive value, 94.4% negative predictive value and 89.6% accuracy in prediction of AL, 5th day CRP>198.23mg/mL had 100% sensitivity, 94.74% specificity, 83.3% positive predictive value, 100% negative predictive value and 95.8% accuracy in prediction of AL.

Also, the study revealed diagnostic performance of 5th day PCT in the prediction of AL where a cutoff of more than 1.212 ng/dl, 5th day PCT had 80% sensitivity, 100% specificity, 100% positive predictive value, 95% negative predictive value and 95.8% accuracy in prediction of AL.

Considering the value of CRP as a biomarker for leakage, Platt et al. **[13]** showed that it has excellent negative predictive value, at best showing to have the only reasonable discriminatory capability with respect to AL, with AUROC values ranging from 0.69 to 0.87.

Garcia-Granero et al. **[14]** suggested a cut-off value of 0.64 ng/ml for PCT and 172 mg / l for CRP and on POD 3.

A meta-analysis showing the predictive value of CRP for infectious complications after colorectal surgery was published in 2012 by Warschkow et al. **[15]** They found that CRP testing on POD4 was satisfactory to predict AL and suggested a cut-off value of 135 mg / l with a negative predictive value of 89 %.

After colorectal resection, Lagoutte et al. **[16]** described PCT kinetics. They evaluated a group of 100 patients, and PCT levels in non - AL patients increased at POD1 to reach a peak on POD2 and gradually declined. Patients with a leak had a higher peak of PCT on POD1, followed by a subsequent decline. PCT showed the best accuracy of AL prognosis in POD 4, but its correlation with leakage was weaker than for CRP.

Garcia-Granero et al. **[17]** evaluate CRP and PCT levels between POD 1 and 5 in 205 colorectal patients with 11 major AL. PCT was a satisfactory predictor of AL on POD 3, 4 and 5 (AUC >0.80), reaching its peak on the 5th postoperative day (AUC 0.867). PCT on POD 5 had the best accuracy in the prognosis of AL. Among analyzed variables (PCT, CRP, neutrophils on POD 3, 4, 5). They proposed a PCT cut-off value of 0.31 ng / ml on POD 5.

Zawadzki et al. **[12]** showed that PCT on POD 3 had AUC of 0.85 and CRP on POD 3 had AUC of 0.996. A cut-off CRP value on

POD 3 was calculated at the level of 245.64 mg/l, resulting in 100% sensitivity and 98% specificity of AL. A PCT cut-off value on POD 3 was calculated at the level of 3.83 ng/ml with 75% sensitivity and 100% specificity for AL.

Zawadzki et al. **[12]** concluded that CRP and PCT single measurement on the 3rd postoperative day following colorectal cancer resection allows identification of patients at low risk of AL.

Smith et al. **[4]** found that the AUROC was 0.961 using CRP and 0.763 using PCT. The optimum CRP cutoff value was 53. Sensitivity was 90.9% and specificity was 95.7%. They identified changes in CRP and PCT as potential markers of AL following colorectal surgery and in particular CRP trajectory as extremely accurate in diagnosing AL requiring intervention.

In AL prediction, we found no advantage of PCT over CRP. The cost of additional testing must be taken into account in the global trend of reducing healthcare expenses. The cost of the PCT test is higher than the cost of the CRP test. Because of the low cost of the test, it is advisable to recommend CRP as a routine test on POD 3 and use PCT as a second line test, verifying the abnormal results of CRP. Secondly, an additional investigation is necessary to determine whether such routine testing on POD 3 should be recommended for all colorectal resections or selectively for patients at higher risk of AL (left-sided or rectal resections, elderly patients, obese, etc.).

CONCLUSION

We concluded that estimation of C-reactive protein (CRP), and procalcitonin (PCT) in the first 5 days after surgery can positively predict early Anastomotic leak (AL) following open colorectal cancer surgery with CRP being more accurate and a potentially powerful marker.

Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
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