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Original Article

Predictive Value of Postoperative C-Reactive Protein in Anastomotic Leakage After Colon Cancer Surgery

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ABSTRACT

Background. *Anastomotic leakage (AL) following colon surgery is a serious complication. Early diagnosis permits timely intervention and improvement in the clinical outcomes of the leak. C-reactive protein (CRP) has been shown to be a valuable marker of AL in several prospective studies. However, most of the recent studies include colon and rectum patients concurrently. The aim of this study was to evaluate the diagnostic accuracy of post-operative CRP measurement specifically in colon cancer surgery as its role in this setting is less well established.* ***Methods.*** *Patients who underwent elective colon resection for cancer with immediate anastomosis between January 2018 and December 2020 at Habib Bourguiba Hospital were included in this retrospective study.* ***Results.*** *Of the 59 patients involved in this study, the majority underwent sigmoidectomy (n=24) and right colectomy (n=23). Eight patients underwent left colectomy, three patients had segmental splenic flexure resection and one patient had a total colectomy. The median time for operation was 156 min [90 min-340 min]. Overall morbidity was 32,2%. Nine patients (15,3%) developed AL and the median time to diagnosis was POD 6 (range 4–10). On POD 3, a cut-off value of 170 mg/L was associated with the diagnosis of AL, with 85.71% sensitivity, 64.44% specificity and with a negative predictive value (NPV) of 96.67%. Using a cut-off value of 150 mg/L on POD 5, the sensitivity was 77.78%, the specificity was 85.19%, and the NPV was 92%.* ***Conclusion.*** *Patients with signs of sepsis and elevated CRP levels during the first 5 postoperative days should be closely monitored and considered for radiological exploration and possibly reoperation.*

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INTRODUCTION

Anastomotic leakage (AL) following colon surgery is a serious complication. It is responsible for an increase in mortality, morbidity and length of hospitalization (1). This results in a significant impact on the patient's quality of life and on the overall cost of treatment (2). Some authors even suggest a deterioration of the long-term oncological prognosis (3). Early diagnosis permits timely intervention and improvement in the clinical outcomes of the leak. During the early post-operative period, it can be difficult to distinguish sepsis associated with AL from the systemic inflammatory response to surgical stress (4). Currently, there is a tendency towards earlier discharge of patients having colonic surgery as part of an Enhanced Recovery After Surgery protocol. In this context, C-reactive protein (CRP) has been shown to be a valuable marker of AL in several prospective studies (5–7). CRP is an acute-phase protein produced by hepatocytes in response to pro-inflammatory cytokines (8). It increases rapidly in response to infection, tissue damage and ischaemia and falls just as rapidly with

resolution of such conditions due to its short half-life of 19 h (9). However, most of the recent studies include colon and rectum patients concurrently. Still, several authors suggest that clinicians should consider colon and rectal cancer as different entities (10,11). The aim of this study was to evaluate the diagnostic accuracy of post-operative CRP measurement specifically in colon cancer surgery as its role in this setting is less well established.

METHODS

Study design, setting and population

A retrospective study was carried out from January 2018 until December 2020 in the Department of Surgery at Habib Bourguiba Hospital in Sfax, Tunisa. Patients who underwent elective colon resection for cancer with immediate anastomosis were included.

Data collection

Data were collected using data collection form designed as per the objective of the study. Patient demographics, operative details, final pathology and postoperative complications were recorded, as were the CRP levels on post-operative days (POD) 3 and 5.

Exclusion criteria

Exclusion criteria were acute resection, resection not involving an immediate anastomosis (e.g., Bouilly-Volkman or Hartman procedures) and resection involving the rectosigmoid junction. Patients who did not have post-operative CRP levels measured were also excluded.

Definition

AL was defined as recommended by the 2020 consensus published in the "World Journal of Surgery"[10]. Therefore, it was defined by the presence of at least one of the following criteria:

- Discharge from abdominal drainage
- Abscess around the anastomosis on a CT-scan
- Extravasation of endoluminal administrated contrast on a CT-scan
- Dehiscence of the anastomosis discovered during a reoperation for postoperative peritonitis

Statistical analysis

Analyses were performed using SPSS® version 22.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were reported as mean and standard deviation and were analysed by two-tailed student t test. Whereas, qualitative variables were reported as number of patients and percentage. Receiver operating characteristic (ROC) analysis was performed to allow the diagnostic accuracy of CRP in the presence of post-operative AL. Cut-off values for CRP were selected based on those values that gave the best combination of high sensitivity and high specificity. In all cases, a P value of <0.05 was considered to be statistically significant.

Ethical considerations

In order to guarantee the confidentiality of patients' personal information, data were collected on anonymized forms throughout this study.

RESULTS

A total of 120 patients were identified. Sixty-one patients were excluded as they did not have CRP measurements. Of the 59 patients in this study, the majority underwent sigmoidectomy (n = 24) and right colectomy (n=23). 8 patients underwent left colectomy, three patients had segmental splenic flexure resection and one patient had a total colectomy. Fifty-five anastomoses in the study population were stapled and 5 patients had a handsewn anastomosis. Patient characteristics, surgical procedures and pathology of the study population are summarized in Table 1.

Table 1. General characteristics of the study population

Items	All patients (n= 59)	Patients with AL (n=9)
Age, mean (SD)	62(14,6)	62 (9,5)
Sex, n (%)		
Male	35 (59%)	7 (78%)
Female	24 (41%)	2(23%)
ASA, n (%)		
1	47 (80%)	7(78%)
2	9 (15%)	1(11%)
3	3 (5%)	1(11%)
Type of surgery, n (%)		
Sigmoidectomy	24 (40,6%)	3 (33,3%)
Left Colectomy	8 (13,6%)	3 (33,3%)
Segmental Splenic Flexure Resection	3 (5,1%)	0
Right Colectomy	23 (39%)	3 (33,3%)
Total Colectomy	1 (1,7%)	0
TNM stage		
I	4 (6,8%)	0
II	24 (40,7%)	2 (22%)
III	25 (42,3%)	7 (78%)
IV	6 (10,2%)	0
Time of operation in minutes (SD)	156(54)	171 (56)
AL, anastomotic leak; ASA, American Society of Anaesthesiologists score; SD, standard deviation		

The median time for operation was 156 min [90 min-340 min]. Overall morbidity was 32,2%. Nine patients (15,3%) developed AL and the median time to diagnosis was POD 6 (range 4–10). four patients were managed by return to theatre (Clavien-Dindo grade IIIb–IVb), of whom two died in the postoperative course. Two patients had radiological drainage (Clavien-Dindo IIIa). The remaining three patients had contained leaks and were managed with intravenous antibiotics only (Clavien-Dindo II). The median length for hospital stay was 10 days [4 days-60 days]. The mean CRP level on POD 3 and POD 5 for patients who developed AL compared to those who did not are shown in Table 2.

Table 2. Comparison of CRP means between patients with or without AL (t-test)

Category	AL	Mean	Std. Deviation	Std. Error Mean
CRP POD 3	no	139,89	88,80	13,23
	yes	221,00	58,48	22,10
CRP POD 5	no	88,64	63,96	12,31
	yes	207,11	92,39	30,80
AL: Anastomotic Leakage				

The mean CRP levels were significantly higher in the AL group compared to those who did not leak (Figure 1 and Table2). Using receiver operating characteristic analysis, the AUC of the CRP level on POD 3 was 0.71, while it was 0,88 for POD 5. On POD 3, a cut-off value of 170 mg/L was associated with the diagnosis of AL, with 85.71% sensitivity, 64.44% specificity and with a positive predictive value (PPV) of 27.27% and a negative predictive value (NPV) of 96.67%. Using a cut-off value of 150 mg/L on POD 5, the sensitivity was 77.78%, the specificity was 85.19%, the PPV was 63.64% and the NPV was 92% (Figure 2).

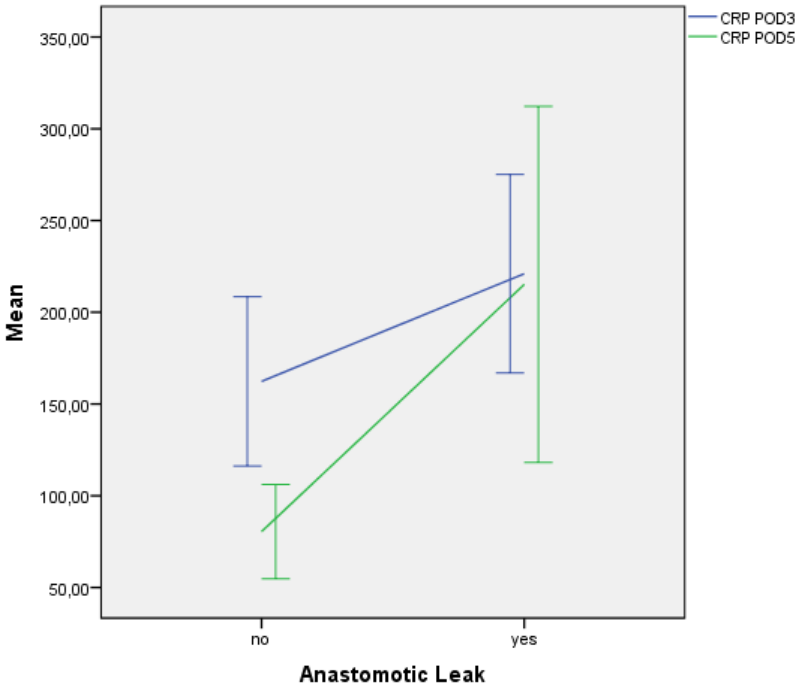

Figure 1. Change in C-reactive protein (CRP) in patients with no major complications compared to whom with anastomotic leak. Data are presented as mean (error bars 95% confidence interval)

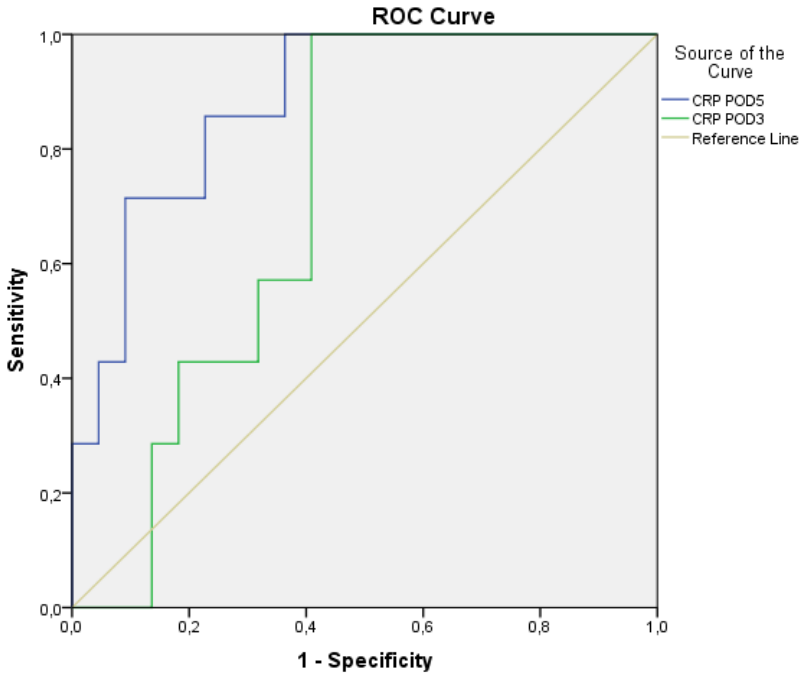

Figure 2. ROC curve on post-operative days 3 and 5

DISCUSSION

Monitoring inflammatory markers after colon surgery is a reliable mean of postoperative surveillance. This is particularly relevant in the era of Enhanced Recovery After Surgery protocols. This study found that serum CRP concentration measured on POD 3 and 5 after colon resection for cancer is a useful negative predictive test for the development of leakage after surgery. It is, however, not a good positive predictor.

CRP is an acute-phase protein produced by hepatocytes in response to pro-inflammatory cytokines (8). It is the most commonly used markers of postoperative inflammation and infection. The CRP level has been used successfully as an indicator of AL in colorectal surgery. Several other authors have shown, as in our work, the value of postoperative CRP measurement for the early diagnosis of anastomotic leakage. But its threshold value differs from a study to another and most of the studies included colon and rectum cancer patients. Therefore, accurate cut-off values of CRP are not well established specifically for colon surgery.

A study of 129 patients found this was not a good way to distinguish between AF and other septic complications. However, a level greater than 200 mg/l was the most sensitive on POD3 (sensitivity 68%, specificity 74%) (12). A meta-analysis of 2483 patients (7 studies) demonstrated that the median day of diagnosis was between day 6 and 9 and that CRP levels above 172, 124 and 144 mg/l were the "cut-off" values for POD 3, 4 and 5 respectively (negative predictive value 97%) (13).

The recent study by Paliogiannis et al (14), published in 2021, demonstrated the value of calculating the postoperative CRP/albuminemia ratio (CAL) to predict AL in patients undergoing elective surgery for colorectal cancer. Merging CRP and albumin into a single index might be more accurate than CRP and albumin alone. A CAL ratio > 46 showed good AL sensitivity, superior to that of CRP and albumin separately; with a sensitivity and specificity of 79.6% and 87.2%, respectively. The same study reported that CAL is also very interesting for predicting early postoperative mortality with a sensitivity of 100% and a specificity of 91%.

Limitations

Our study is retrospective and 61 patients were excluded due to lack of serial post-operative CRP levels. Actually, surgeons' preferences determinates patients who had CRP measurements. Therefore, the more high-risk patients may have had CRP measured while those with minimal co-morbidities did not. This explains the hight incidence of AL in our study. A prospective study including systematic CRP measurements would lead to a more efficient study. Another consideration is that, the inclusion of other risk factors like nutritional state indicators such as preoperative albuminemia would be more accurate to estimate the real value of CRP in predicting AL. Finally, it is possible that some patients may have had subclinical AL as CT scan was not always performed.

CONCLUSION

The results of our study suggest that post-operative CRP levels can identify patients who are at risk of developing AL following resection for colon cancer. We recommend having a low threshold for early investigation of these patients. Although the specificity of CRP in this study was not high, the NPV of 90% indicates a good accuracy for ruling out AL and allows to select patients suitable for earlier discharge. However, patients with signs of sepsis and elevated CRP levels during the first 5 postoperative days should be closely monitored and considered for radiological exploration.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Competing interest

There are no financial, personal, or professional conflicts of interest to declare.

Data Availability Statement

Personal data of the patient were respected. No data is available for this submission.

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