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Original Research Article

Role of biomarkers in early detection of anastomotic leakage and follow up of patients with colorectal surgery managed by enhanced recovery protocol

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ABSTRACT

Background: Anastomotic leakage (AL) considered as the most feared complication after colorectal resection surgery increasing morbidity, mortality and risk of recurrence among these patients. Therefore, early detection of AL is crucial. Biomarkers as procalcitonin (PCT), C-reactive protein (CRP), white blood cell count (WCC) provide an easy, safe and efficient methods for early detection of AL and follow up of the patients after discharge.
Methods: This study included 130 patients presented with colonic or rectal cancer in the period from January 2018 to January 2021. This study was conducted in general surgery department, faculty of medicine, Benha university hospital. CRP, PCT and WBC count were measured pre-operatively, first, third, fifth and 7th day post-operative to detect the change in their levels when AL was diagnosed either by clinical, radiological or operative measures.
Results: Among 130 patients, only 10 patients had AL. On POD-3, CRP and WCC values were significantly increased in AL patients while PCT was significantly elevated only from POD-5. The best cut-off value for CRP on POD-3 was >30.1 mg/l, reaching 90% sensitivity and 100% specificity for detecting AL while for WCC was >7.1× 109 cell/l, with 90% sensitivity and 72% specificity. The best cut-off value for PCT was in POD-5 which was >1.7 ng/ml with 100% sensitivity and 84% specificity.
Conclusions: The analysis of CRP and WCC on POD-3 together with PCT serum concentrations on POD-5 is crucial for early detection of anastomotic leakage in either open or laparoscopic colorectal resection surgery.

Keywords: Anastomotic leakage, CRP, Procalcitonin, Colorectal

INTRODUCTION

One of the most serious complications of colorectal resection is Anastomotic leakage (AL), causing sepsis, increasing the rate of recurrences either locally or distally and increase mortality.[1] AL incidence varies from 2% to 10% with highest rates in coloanal anastomosis. Usually AL become apparent around the 5th and 7th postoperative day with most of AL occur after patient discharge as Enhanced recovery after surgery (ERAS) become the main protocol of management of the colorectal cancer patient.[2] The first international guidance published by the 'Surviving sepsis' campaign for the sepsis management and noted that each hour of delay in antibiotics administration from the onset of septic shock causes 7.6% decrease in survival rate.[3] Also, a delay in intervention in AL patients by 2.5 days increases mortality rate from 24% up to 39%.[4] So, early diagnosis is very important to minimize the devastating sequence of the AL.[5]

Biomarkers as CRP, WCC and PCT are usually used for identifying sepsis in surgical patients. The changes in their levels during the POD-3 and 5 have been shown to

provide a good prediction for detection of AL in early stage before clinical sign become evident.[6,7] For defining AL after gastrointestinal surgery, a more than 56 different definitions was described, however, we use the International Study Group of Rectal Cancer (ISREC) definition which entails (communication between the intra- and extraluminal compartments due to a defect of the integrity of the intestinal wall at the site of anastomosis between the colon and rectum or the anus).[8]

The aim of the study was to assess sensitivity and specificity of systemic biomarkers in early prediction of AL in patients who have undergone colorectal surgeries.

METHODS

Study design and setting

This prospective study was conducted at the general surgery department, Benha university hospital in the period between January 2018 to January 2021.

Inclusion criteria

Patients with resectable colorectal cancer undergoing elective resection of the affected part of the colon followed by colo-colic or colorectal anastomosis without covering ileostomy were included.

Exclusion criteria

Patients who were- (a) operation for recurrent tumor; (b) presented with colonic obstruction; (c) emergency surgery (due to fecal or septic peritonitis from colonic perforation); (d) on immunosuppressive drugs; and (e) with tumor causing pericolic abscess.

Approval of the ethical committee of the Faculty of Medicine, Benha University on the study was obtained (IRB: 4.11.2020). This study includes 130 patients with colorectal cancer undergoing elective resection of the affected part of the colon followed by colo-colic or colorectal anastomosis without covering ileostomy either by laparoscopic or open technique. Patients were informed about the nature of the study including the risks and benefits and an informed consent for participation in the study was obtained.

Amultidisciplinary team perform a preoperative assessment to all patients (includes at least one specialized representative from general surgery, radiology, pathology, radiotherapy, and medical oncology) to determine which patient will need a neoadjuvant treatment. Patients suspected to have nodal involvement, T3 or T4 tumors and those with a threatened circumferential resection margin received neoadjuvant treatment. All patients with rectal cancer received neoadjuvant chemoand radiotherapy. Cases who received neoadjuvant radiotherapy underwent a long-course radiotherapy (50.4 Gy over 6 weeks), with or without 5-fluorouracil-based chemotherapy. Surgery was scheduled after 6 weeks from the last of neoadjuvant course. All patients underwent the following: (1) full detailed history; (2) clinical examination, (3) laboratory investigations including complete blood picture (CBC), random blood glucose level, liver and renal function tests, CEA, CA 19-9, pre-operative level of CRP, WBC and procalcitonin and postoperative levels CRP, WBC count and procalcitonin at postoperative day 1, 3, 5 and 7, (4) full colonoscopy, (5) radiological investigations including- (a) MRI of the pelvis (in cases with rectal cancer), and (b) metastatic work up (Computerized tomography of the chest and abdomen); and (6) biopsy-by colonoscopy for histo-pathological diagnosis.

Pre-operative preparation

All the patients underwent bowel preparation using a polyethylene glycol solution over the day before surgery. A low-molecular-weight heparin was given as a thrombo-vascular prophylaxis at the night of surgery. An enterostomal therapist mark the site of probable ileostomy in case to be needed. Antibiotics were given during the induction of anaesthesia.

Operative plan

Mobilization of the descending colon was done with splenic flexure released to fully mobilize the descending colon. Identification and preservation of the pelvic nerves was done. Ligation of the inferior mesenteric artery at its origin from the aorta for proper harvesting of the draining lymph nodes. Ligation of the inferior mesenteric vein at the lower border of the pancreas. In rectal cancer cases, partial or total mesorectal excision (depending on the location of the tumor) was done through dissection at the holly plane. Restoration of the bowel continuity was done either via transanal double- stapling anastomosis or by hand- sewen anastomosis (single layer interrupted sutures using 3/0 vicryl suture). Air leak test was used to ensure the integrity of the anastomosis via transanal insufflation of the air. Intraabdominal pelvic drain was used.

Post-operative follow-up

ERAS protocol was applied for all patients with oral liquids intake (if the patient tolerate oral intake) started on POD-1, then a liquid and solid diet were allowed over the second and third postoperative days. Ambulation was advised on the day of surgery, and patients were discharged from the hospital when they can tolerate the normal diet and bowel function had returned.

All patients were examined clinically twice daily for clinical signs of AL. This includes an abdominal examination, observation of the contents of the drain and, checking of the vital signs. In cases where symptoms or signs of postoperative complication were suspected, the necessary investigations were requested.

Inflammatory biomarkers (CRP, WCC and PCT) were withdrawn at POD-1, 3, 5, and 7 and documented. CRP

was measured by immunonephelometry on an automated Dimension Vista analyzer (Siemens, Erlangen, Germany) while PCT was measured by the electrochemiluminescence immunoassay Elecsys BRAHMS PCT (Roche Diagnostics GmbH, D-68298 Mannheim, Germany).

Patients with AL were managed either conservatively or surgically as required. Reassessment of the patient was done in the outpatient clinic within 30 days from the day of the operation.

Diagnosis of AL

AL was recognized using different parameters including clinical signs (as fever, tachycardia, pain, peritonitis, purulent or intestinal content in the drain), radiologic (gas containing collections) and intra-operative findings (intestinal content spillage and disruption of the anastomosis).[9]

Statistical analysis

Data management and statistical analysis were done using SPSS vs 25 (IBM, Armonk, New York, United states). Numerical data was summarized as means and standard deviations or medians and ranges. Categorical data was summarized as numbers and percentages. Comparisons between both groups were done using Mann Whitney U test for numerical data. Categorical data was compared using Chi square test or Fisher's exact test if appropriate. Diagnostics indices for different markers were calculated at different time points. All p values were two sided. P values less than 0.05 were considered significant.

RESULTS

This study includes 130 consecutive patients underwent colorectal cancer resection. Seventy of these patients underwent an open resection and the remaining sixty patients had a laparoscopic resection, patient whom underwent conversion from laparoscopic to open procedures were included in the open group. The study included73 males and 57 females with mean age of 51.4 years and average Body mass index (BMI) of 26.4 kg/m^2. The mean length of hospital stay in anastomotic leakage group was significantly longer than the group with no leakage (14±3 days vs 4±1) with p value <0.001. The neoadjuvant chemo/radiotherapy has no significant effect on the rate of AL (p=0.215) (Table 1).

No mortality was recorded in the study group. AL occurred in only 10 cases (7.7 %) which start to be clinically symptomatic between the POD-3 and POD-12, and all these cases required a reoperation to control the leakage. There was an increase in the mean value of CRP on POD-1 and POD-3 in all patients. However, the peak of CRP become significantly higher in the AL group only on the third POD. On the POD-3, the mean values of CRP were 22.3 ±3.3 mg/l in non-AL patients and 39.7±7.5 mg/l in AL patients (p value <0.001). Likewise, the mean WCC increased on POD-1 and 3 in all patients but it was significantly higher in the AL group only on the third POD than in non-AL group (8.4±1.1 vs 6.9±0.8) with p value <0.001 (Table 2).

On the other hand, the mean PCT value increased in the POD-1 and POD-3 but this increase was not significant until the fifth POD where the rise in the mean value in AL group was significantly higher than the non-AL group (2.05±0.21 vs 1.39±0.26 with p value <0.001) (Table 3).

The analysis of ROC curves revealed that CRP on POD-3 had AUC of 0.972 (0.915-1), while WCC on POD-3 had AUC of 0.886 (0.775-0.997).

However, the PCT had AUC of 0.971 (0.924-1) only on the fifth POD. The beast cut-off value for CRP on POD-3 was >30.1 mg/l, with 90% sensitivity and 100% specificity of AL. While for the WCC, the best cut-off value was >7.1×109 cell/l on the third POD with a sensitivity of 90% and specificity of 72% for AL. The best cut-off value for PCT on POD-5 was >1.7 ng/ml with sensitivity of 100% and specificity of 84% for AL (Table 4) (Figure 1).

Table 1: Difference in hospital stay length between the two groups and the effect of neoadjuvant chemo/radiotherapy.

Variables		Anastomotic leakage		P value
		Yes (n=10)	No (n=120)	
Length of hospital stay (days)	Mean±SD	14±3	4±1	<0.001
Neoadjuvant chemo/radiotherapy	Yes N (%)	5 (50.0)	42 (35.0)	0.215

Note: Mann Whitney U test was used for length of stay. Chi square test was used for neoadjuvant therapy.

Table 2: CRP, WCC and PCT at day 3 post-operative.

Variables		Anastomotic leakage		P value
		Yes (n=10)	No (n=120)	
CRP	Mean±SD	39.7±7.5	22.3±3.3	<0.001
WCC	Mean±SD	8.4±1.1	6.9±0.8	<0.001
PCT	Mean ±SD	1.54±0.21	1.49±0.38	0.653

Note: Mann Whitney U test was used.

Table 3: CRP, WCC and PCT at day 5 post-operative.

Variables		Anastomotic leakage		P value
		Yes (n=10)	No (n=120)	
CRP	Mean±SD	104±6.4	29.4±2.1	<0.001
WCC	Mean±SD	9.9±2.7	6.6±1.8	<0.001
PCT	Mean±SD	2.05±0.21	1.39±0.26	<0.001

Note: Mann Whitney U test was used.

Table 4: ROC analysis for markers in prediction of anastomotic leakage at different time points.

Variables	AUC (95% CI)	Best cut-off	Sensitivity (%)	Specificity (%)	P value
At day 3					
CRP	0.972 (0.915-1)	>30.1	90	100	<0.001
WCC	0.886 (0.775-0.997)	>7.1	90	72	<0.001
At day 5					
CRP	0.896 (0.789-1.0)	>31.1	90.0	72.0	<0.001
WCC	0.904 (0.806-1.0)	>6.5	90.0	80.0	<0.001
PCT	0.971 (0.924-1)	>1.7	100	84	<0.001
At day 7					
CRP	0.972 (0.926-1.0)	>56.1	90	92	<0.001
WCC	0.958 (0.897-1.0)	>6.3	100	88	<0.001
PCT	0.960 (0.902-1.0)	>0.81	100	80	<0.001

Note: AUC: Area under curve, 95% CI: 95% Confidence interval.

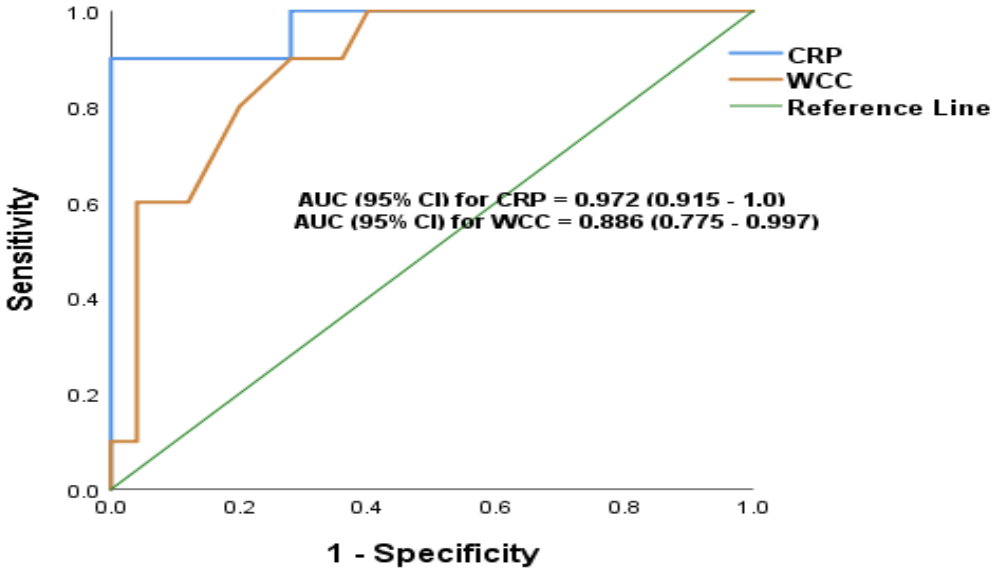

Figure 1: ROC analysis of CRP and WCC at day 3 post-operative.

DISCUSSION

CRP, PCT and WCC are usually used to detect septic condition.[10] Therefore, they may have a role in detection of anastomotic complications at an early stage and ensuring safe early discharge of patients with intestinal anastomoses, according to the ERAS protocol (maximum of four postoperative-day stay).[11] CRP is one of the acute-phase reactants, primarily synthesized in the liver, as a result to stimulation by proinflammatory cytokines. The median value of CRP is 0.8 mg/l and it increases up to 500 mg/l after an acute-phase stimulus. De novo synthesis of CRP starts rapidly after the stimulus and reaches its peak within 48 h, with plasma half-life about 19 hours.[12] PCT is formed by para follicular C-cells of thyroid with normal blood concentration <0.1 ng/ml. This level increases in presence of bacterial endotoxins in the blood, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns, which leads to a high increase in its blood concentrations.[13]

Our study major findings showed that CRP, PCT, WCC are all statistically significant regarding early leak detection of anastomotic dehiscence at POD-5 with sensitivity 90.0%, 100% and 90% respectively and specificity 72.0%, 84% and 80% respectively. The best cut off value in our study was >31.1 mg/l for CRP, >1.7 ng/ml for PCT and >6.5×109 cell/l for WCC. On the other hand, CRP and WCC appear to be more beneficial in early leak detection of anastomotic leakage at POD-3 with sensitivity 90% for both and specificity 100% and 72% respectivelywith the best cut-off value was >30.1 mg/l for CRP and >7.1× 109 cell/l for WCC.

A meta-analysis done in 2012 by Warschkowet al found that measurement of CRP on POD-4 provide an accurate predictive marker for infectious complications of AL.[14] The cut-off value for CRP was 135 mg/l and a negative predictive value of 89%. Afterwards, another recent meta-analysis (N=2483) done by Singh et al they measured CRP as an AL predictor on POD-3, 4 and 5.[15] They demonstrated a similar benefit of CRP in leakage detection at the three days with 21-23% positive predictive value and 97% negative predictive value. Thus, the CRP level is a good negative test but not a useful positive test for prediction of anastomotic dehiscence. More recently, Zawadzki et al demonstrated that CRP was significantly high on POD-3 in the AL group. The best cut-off value for CRP on POD 3 was 245.64 mg/l, on analysis of ROC and AUC curves, with 100% sensitivity and 98% specificity for AL. However, elevation of CRP might not be due to AL. It may be due to presence of another source of infection as respiratory or urinary tract infection or even wound.[16]

However, PCT levels are usually raised after major abdominal and thoracic operations in POD-1 and POD-2 but not in minor aseptic procedures as its production are induced by bacterial infection or translocation during surgery or even during preparation of intestinal anastomosis. It has also been suggested that PCT level was higher in patients who suffered from postoperative complications than patients with normal post-operative course.[17,18] Therefore, PCT appears to be a better predictive marker of septic complications than CRP.

Another study evaluated PCT and CRP levels between POD-1 and POD-5 in 205 patients, eleven of whom showed significant anastomotic dehiscence.[18] PCT was a reliable predictor of AL on POD-3, 4 and 5 with its maximal AUC value on POD-5 (AUC=0.867) with 100% sensitivity and 72% specificity. The authors concluded that PCT had the best accuracy in early detection of AL on POD-5. The study obtained a PCT best cut-off value of 0.31 ng/ml on POD-5. Giaccaglia et al recently showed similar results and conclusion.[7] These previous results are consistent with ours. In our study, PCT was significantly high on POD-5 with 100% sensitivity and 84% specificity and AUC of 0.971 whereas CRP showed 90% sensitivity and 72% specificity. This indicates that PCT has the best accuracy and more superior than CRP.

On the other hand, a study done by Zawadzki et al demonstrated higher accuracy of CRP. Authors had 55 patients, 29 of whom underwent robotic resections and 25 underwent open resections. Only 5 patients had anastomotic dehiscence. The mean PCT and CRP elevated on POD-1 and POD-3 in all patients. Results of ROC and AUC curves, showed 245.64 mg/l cut-off value for CRP on POD-3 with 100% sensitivity and 98% specificity for anastomotic dehiscence group, PCT on POD-3 showed a cut off value of 3.83 ng/ml, with sensitivity of 75% and specificity of 100% for anastomotic dehiscence group.[16] Furthermore, Benoit et al reported 522 patients underwent colorectal resection, majority of patients underwent colorectal (31%) and coloanal anastomoisis (29%). The incidence of overall complications was 29.3%. CRP was significantly high in patients with intra-abdominal complications at an earlier stage (POD-1-2), (164.6 vs 136.2; p=0.0028) and late stage (POD-3-4) (209.4 vs 132.1; p<0.0001), in multivariate analysis, early CRP was associated with BMI while late CRP was affected by BMI and associated extra-colonic procedures. Sensitivity, specificity, negative predictive values (NPV), and positive predictive values (PPV) for intra-abdominal complication were 85.9%, 33.6%, 89.3%, and 27.1% for an early CRP 100 mg/l versus 6% with CRP.[20]

Hence, some studies- including our study- apparently demonstrated more accuracy of PCT analysis than CRP analysis as well as the benefits of the combined analysis of the CRP and PCT level.[7,15] However, other literature demonstrated the superiority of the CRP levels over the PCT levels.[21,23,24] Interestingly, financial issues may settle these variations in the results between literatures. As the global efforts are more directed towards lowering health care expenses, adding cost of additional tests should be taken with caution. PCT analysis costs €21, which is eight times higher than the cost of the CRP test. For this reason, the literature in support of CRP higher accuracy might be favored.

Therefore, CRP might be recommended as a routine test on postoperative days and seeking PCT will be as a confirmatory test or a second line test. In addition, further investigations are urgently needed to specify whether this routine test must be performed to all patients underwent colorectal cancer resections or specifically to patients who are at high risk of anastomotic leakage such as left sided rectal resections, elderly or obese patients. The best biochemical markers are the ones, which have the ability to detect individuals at high risk of developing anastomotic leakage before appearance of clinical symptoms. Our current data confirmed the significance of both PCT and CRP levels in early detection of postoperative complications. Those biomarkers can precede the clinical and radiological diagnosis. Low CRP and PCT serum levels have a good negative predictive value, which in turn can guarantee early safe discharge and exclude septic complications. This seems to be crucial in reducing morbidity and mortality rates as well

as costs due to prolonged hospitalization.[22,24] Nevertheless, positive predictive value of both CRP and PCT determine the decision of re-intervention.

Limitations of our study could obviously be the small sample size. As of the 130 patients, who joined the study, only 10 cases developed anastomotic leakage. Furthermore, the surgical team were not the same for all patients. The variability in the surgeons' experience and skills may have influenced or biased our results as well. The differences in best cut-off value of the markers between our study and others could be referred to different laboratory reference range and different methods of markers measuring.

CONCLUSION

In conclusion, the current study together with previous literature suggests that the analysis of CRP and WCC on the POD-3 as well as PCT serum concentrations on POD-5 is crucial for early detection of anastomotic leakage in either open or laparoscopic colorectal resection surgery.

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