Serum C reactive Protein versus Total Leucocytic Count in Early Diagnosis of Leakage in Colonic Anastomosis

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Introduction: Anastomotic leakage (AL) is a major complication after intestinal and colorectal surgery due to its severity, high frequency and poor outcome.

Aim of work: The aim was to evaluate the role of serum C-reactive protein (CRP) and Total Leucocytic count (TLC) in detection of early anastomotic leakage in preclinical stage following open and laparoscopic colorectal and intestinal surgery.

Patients and methods: In the elective department of Kasr-Al Ainy hospital, Faculty of Medicine, Cairo University the study include a total of 115 patients who were indicated for colonic anastomosis as cancer colon patients, closure colostomy etc. Post-operative serum CRP & TLC were withdrawn and the patients were followed up for 5 days.

Results: Out of 115 patients 19.1% had leakage with mean time to leakage 5.1+1.2 days with range days 3-7 days, while 80.9% had no leakage. Comparison of TLC and CRP levels between patients who developed AL and those who did not showed that baseline TLC and CRP showed no statistically significant difference between groups, while Day 1, Day 2, Day 3 and Day 4 showed significantly higher among leakage group with p values <0.01 all. The highest difference was reported in Day 5 in terms of CRP and TLC with p values <0.001, and <0.001 respectively.

Conclusion: Patients undergoing elective colorectal surgery should routinely have their CRP levels measured. After the second postoperative day, persistently elevated CRP levels predict anastomotic leakage anastomosis.

Key words: CRP, TLC, anastomosis, leakage.

Introduction

Anastomotic leakage (AL) is the most frequent major adverse event after colorectal surgery and remains a large burden for patients and surgeons.[1]

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

Early discharge benefits the patient and cuts medical care costs but carries a potential risk of developing AL when a patient is already out of the hospital, so early diagnosis of AL is critical.[3]

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

In this study, we have chosed inflammatory serum biomarkers: Total leukocytic count (TLC), C-reactive protein (CRP) to assess their utility with respect to reliably predicting colorectal anastomotic leakage. In particular, we will determine whether the rate of change of these biomarkers is predictive of anastomotic leak as defined by the need for intervention with surgery or radiological drainage.[4]

C-reactive protein has been used for many years for identifying septic complications. They have been used as markers to identify sepsis in surgical departments.[5]

The aim was to evaluate the role of serum C-reactive protein (CRP) and Total Leucocytic count (TLC) in detection of early anastomotic leakage in preclinical stage following open and laparoscopic colorectal and intestinal surgery.

Patients and methods

We conducted an Observational analytical Cohort study which included 115 patients presenting to Kasr Al Ainy hospital who were indicated for any type of large bowel resection anastomosis, all patients were presented to general surgery outpatients' clinics then transferred to general surgery ward after baseline assessment and initial management.

Inclusion criteria: Candidates of large bowel anastomoses laparoscopic or open approach, patients who had anastomoses using hand sewn or stapling techniques in elective settings

Exclusion criteria: Patients on immunosuppressive drugs, uncontrolled diabetic patients on high insulin doses, severe bowel inflammatory disorders, patients below age of 14, patients refused to sign the consent, those who had no biomarkers withdrawn postoperatively (D 0, 1,2 ,3, 4 and 5) and patients in emergency setting.

Methodology:

All patients signed a written informed consent including all the steps of procedures, anticipated benefits and potential risks. All patients were assessed through the following steps.

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Preoperative: detailed history taking: Demographics: Age, gender, occupation, residence, and special habits of medical importance. Past history: chronic illnesses, regular treatment intake and previous abdominal surgeries. History of present illness: duration, course, and onset of abdominal symptoms, possible underlying causes (e.g., previous malignancies).

Thorough physical examination: General examination: vital signs and general features of the patients.

Local examination: Abdominal inspection, palpation, auscultation and Digital rectal examination Laboratory investigations: Complete blood picture (CBC), Kidney function test (creatinine, urea), Liver function test (ALT, AST, Bilirubin and Albumin, Coagulation profile (INR, PT, and PC), Serum electrolytes (sodium, potassium, chloride, and calcium), Arterial blood gases (ABG), C-reactive protein.

Imaging and endoscopy: Patient with cancer colon should had computed tomography (CT) scan on abdomen and pelvis with oral and intravenous (IV) contrast. Lower endoscope biopsies and pathology metastatic work-up

Operative procedures: Usually, patients in open approach were operated through midline exploratory incision. Laparoscopic approach was applied for most patients in elective setting, the sites of ports were chosen according to the site of the resection.

Tips in bowel anastomoses: Variable techniques: End to end: This technique connects the two open ends of the intestines together. End to side: This technique connects the end of the proximal loop of intestine with the side of the distal loop. Side to side: This technique connects the sides of each part of the bowel together rather than the two ends. The ends are stapled or sewn closed. SSA anastomoses are at less risk of having narrowing complications in the future. Hand-sewn anastomosis: Intestinal anastomosis can be performed by a hand-sewn technique using absorbable or non-absorbable sutures. Hand-sewn anastomosis can be simple interrupted one-layer or two-layer technique and can be continuous single layer technique **(Fig. 1)**.

Stapling anastomosis: Three types of suturing devices have been developed: non-cutting linear suturing forceps, cutting linear suturing forceps and circular suturing forceps. Staplers are appealing because they are easy to use and may be quicker than some sutured anastomoses **(Figs. 2,3)**.

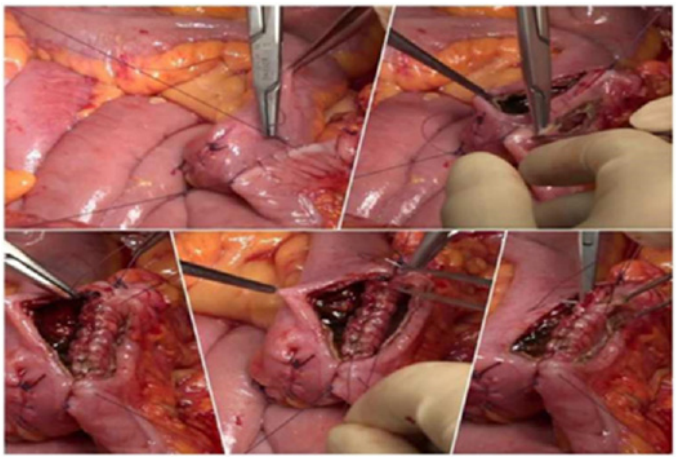

Fig 1: Side to side ileo-colic anastomosis; continuous first layer and simple interrupted second layer.

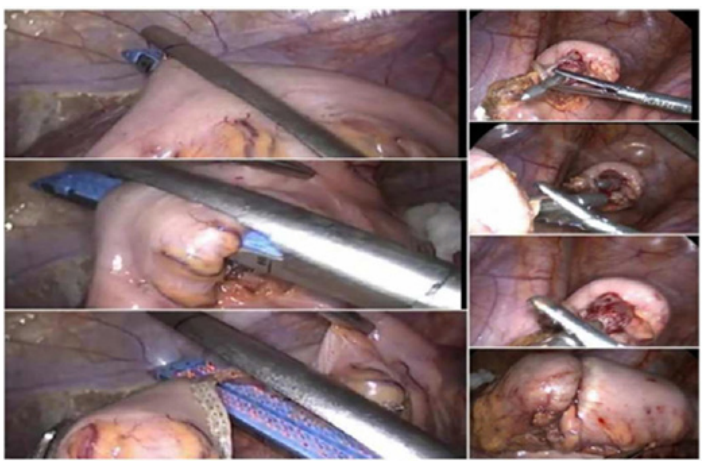

Fig 2: Sigmoidectomy with colo rectal (End to end) anastomosis using both linear and circular stapler.

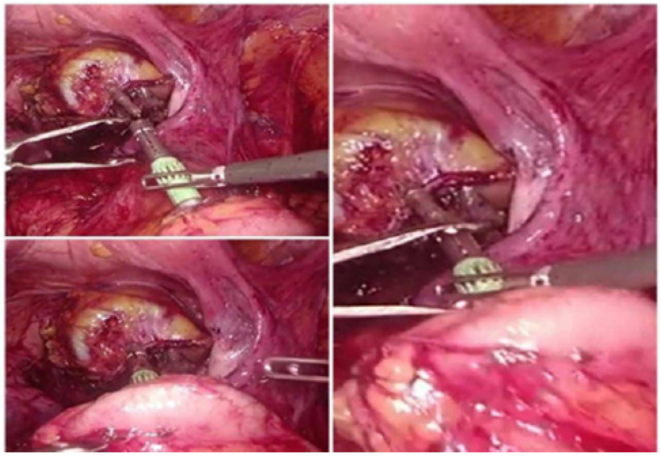

Fig 3: Left hemicolectomy with colo-rectal anastomosis.

Postoperative care: Monitoring of vital data and random blood sugar. Patients were under Enhanced Recovery after Surgery (ERAS) pathways, they were encouraged to start sips of water or clear fluids during the 1st postoperative day, followed by larger amount on the second day then the oral intake was increased gradually according to patients' tolerance. Patients underwent further postoperative diagnostic tests or treatment only in the event of symptoms or signs of a complication.

Postoperative investigations: For the purpose of the study, all laboratory tests were measured 8 hours after incision (day 0), and first five days postoperative days.

Complete blood picture, C- reactive protein, TLC (Total leucocytic count).

Anastomotic leak was defined as a defect within the anastomosis requiring operative intervention, or a collection adjacent to the anastomosis requiring radiological intervention. Usually, anastomotic leakage was diagnosed by signs of peritonitis, imaging studies or discharge of gastrointestinal content through the wound or drain.

Data collection: All data were collected then statistically analyzed and tabulated Anastomotic leakage detected clinically is treated by operative or radiological intervention. In pronounced cases with clinically apparent leaks, there was no need for radiological imaging to confirm the diagnosis, but urgent relaparotomy performed as early intervention in order to avert potential threatening consequences. Radiological examination of the anastomosis was not performed on a routine basis, but only when leakage was suspected on clinical grounds. The number of clinical parameters suggestive of anastomotic leakage was determined. These parameters included tachycardia (Heart rate >100 beats per minute), fever (Body temperature>38°C), local or generalized peritoneal reaction during physical examination, leukocytosis (>10×103/ml), prolonged a dynamic ileus (>2 days postoperatively), and delayed gastric emptying (Nasogastric tube production of more than 200ml per day or vomiting necessitating tube reinsertion) according to Doeksen et al.[6]

Comparison was made between biomarkers (TLC and CRP) and clinical anastomotic leakage.

Follow up: All patients were instructed to follow up in the general surgery outpatient clinics every week; they were instructed about alarming symptoms and possible complications during the rehabilitation period. Any reported complications were documented.

Sample size: Sample size has been calculated: based on assumptions from previous research on AUC of serum C Reactive Protein in predicting leakage in Colonic anastomosis at 4th day post-operative using Med calc.[7] for sample size based on AUC value of study parameter where: two-sided alpha of 0.05, power of 0.8 and AUC were 0.743 and null hypothesis AUC 0.5 The minimum required number was 42 patients with at least 21 patients with positive leakage.

Study outcomes: Primary outcome: Preclinical detection of early anastomotic dehiscence depending on the level of biomarkers post operatively. Secondary outcomes: Risk factors of anastomotic disruption (Age, gender, type of operation, surgery situation, anastomosis type and anastomosis technique)

Statistical analysis: Statistical analysis was conducted using SPSS 22nd edition, categorical variables were presented in frequency and percentage, and compared using Chi2 test. Quantitative variables were presented in mean, standard deviation (SD), and range. It was compared between study groups using student T test. Sensitivity analysis was conducted to estimate the predictive ability of CRP and TLC levels for postoperative anastomotic leakage, any p value <0.05 was considered significant.

Results

In the current study we included a total of 115 patients who were indicated for GI surgeries, they showed a mean age of 48.9± 14.2 years, males outnumbered females and accounted for 60% of the included patients. 39.1% of the included patients reported positive medical history, with hypertension being the commonest accounting for 27% followed by diabetes 13.9% and cardiovascular diseases conditions in 3 patients only **(Table 1).**

Regarding operative details, Right Hemicolectomy was the most performed operation accounting for 31.3% of the included patients, followed by Left Hemicolectomy in 20.9%, then Sigmoidectomy in 15.7% of the included patients. Twenty-two (19.1%) patients developed postoperative anastomotic leakage (AL) with mean time to leakage 5.1±1.2 days, with range 3-7 days **(Table 2).**

Laboratory findings

Table 3 is showing a descending pattern of TLC Levels versus ascending pattern for CRP levels across study period while **(Figs. 4,5)** show TLC & CRP trends during hospital stay in both leakage and no- leakage group.

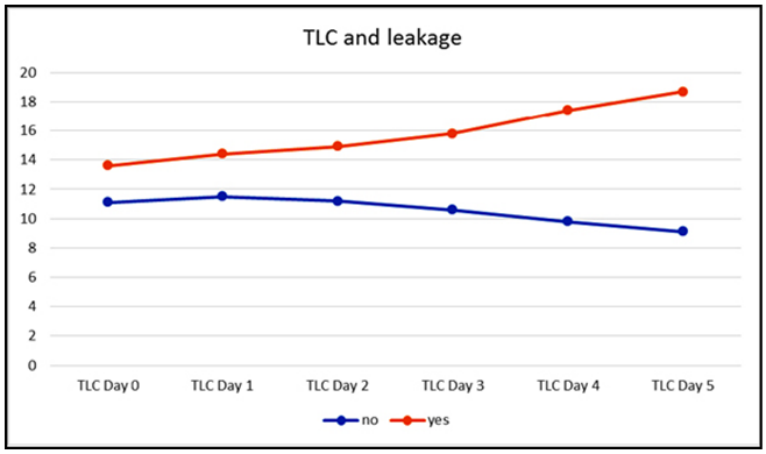

Fig 4: Line graph showing TLC levels across hospital stay according to incidence of AL.

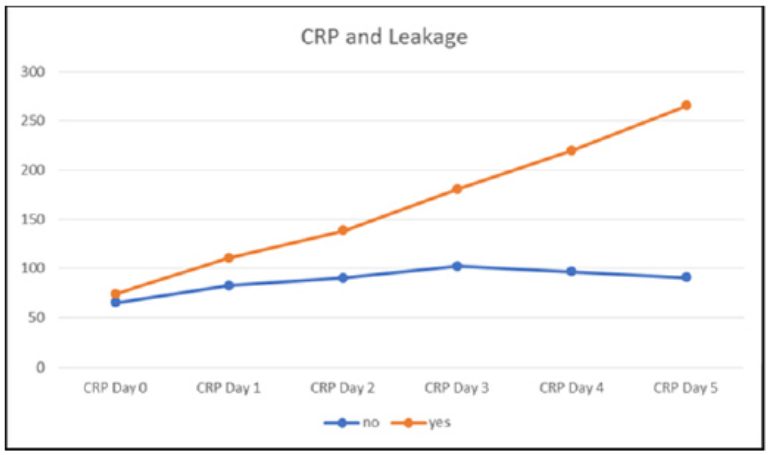

Fig 5: Line graph showing CRP levels across hospital stay according to incidence of AL.

There was no statically significant difference between patients who developed leakage and those who don't in terms of demographics, medical history, operative procedure, type and mode of anastomosis with p values >0.05 all **(Table 4).**

Sensitivity analysis

Sensitivity analysis for CRP showed that CRP levels on Day 1, 2, 3, 4 and 5 can significantly predict AL using cutoff 70, 100, 118, 151, and 160 respectively, with sensitivity 86.5% to 91% and specificity 42-98% **(Fig. 6).**

Sensitivity analysis for TLC showed that TLC levels on Day 1, 2, 3, 4 and 5 can significantly predict AL using cutoff 12, 11.5, 12.1, 12, and 12.7 respectively, with sensitivity 59.1% to 81.8% and specificity 64.4-95% **(Fig. 7).**

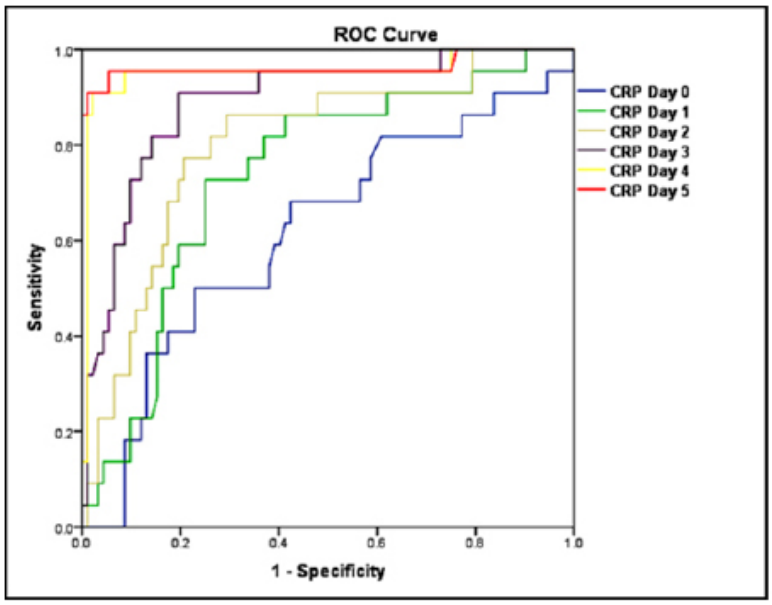

Fig 6: ROC curve showing predictability of CRP.

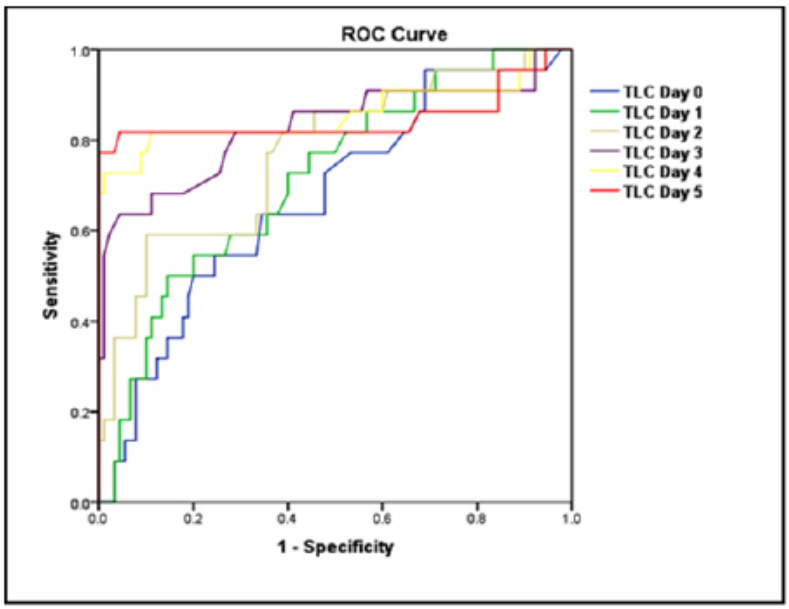

Fig 7: ROC curve showing predictability of TLC for AL.

Table 1: Demographics and medical history of included patients

		N = 115	
Age	Years	48.9± 14.2	14-75
Gender	Female	46	40.0%
	Male	69	60.0%
Co-Morbidities	No	70	60.9%
	Yes	45	39.1%
Hypertension	No	84	73.0%
	Yes	31	27.0%
Diabetes	No	99	86.1%
	Yes	16	13.9%
Cardiac	No	112	97.4%
	Yes	3	2.6%

Table 2: Operative details and postoperative outcomes

		N = 115	
Operative Procedure	Closure Of Colostomy	19	16.5%
	Closure Of Hartman's	10	8.7%
	Extended left Hemicolectomy	3	2.6%
	High Anterior Resection	1	0.9%
	Left Hemicolectomy	24	20.9%
	Low Anterior Resection	3	2.6%
	Right Hemicolectomy	36	31.3%
	Sigmoidectomy	18	15.7%
	Subtotal Colectomy	1	0.9%
Type of Anastomosis	End to End	87	75.7%
	End to Side	3	2.6%
	Side to Side	25	21.7%
Mode of Anastomosis	Hand Sewn	55	47.8%
	Stapler	60	52.2%
Leakage	No	93	80.9%
	Yes	22	19.1%
Time of Leakage	Day	5.1±1.2	3-7

Table 3: Laboratory series of TLC and CRP levels during hospital stay among the included patients

		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
TLC	Mean ± SD	11.6 ± 4.7	12 ± 4	11.9 ± 3.5	11.6 ± 3.8	11.2 ± 4.5	10.9 ± 5.3
	Min-Max	4-27.6	4.6-23.7	4.4-23.6	4-26	4.2-29.2	4.4-32.3
CRP	Mean ± SD	66.8 ± 37	88 ± 41.8	99.4 ± 47.3	117.3 ± 54.7	120.3 ± 63.5	124 ± 80.5
	Min-Max	4.9-218.1	30.8-290	34-311.9	31.6-370	40-375	19-380

Discussion

Total leukocytic count had been used for prediction of infection, or inflammation postoperatively; studies had showed that high TLC was associated with higher risk of AL.[8]

Thus, we conducted a prospective cross section study including patients presenting to Kasr AlAiny hospital who were indicated for bowel resection and anastomosis, aiming to assess sensitivity of serum CRP and TLC as a predictor for leakage post colonic anastomosis.

In the current study we included a total of 115 patients who were indicated for major GI surgeries, they showed a mean age of 48.9±14.2 years, males outnumbered females and accounted for 60% of the included patients. 39.1% of the included patients reported positive medical history, with hypertension being the commonest accounting for 27% followed by diabetes 13.9% and cardiac conditions in 3 patients only.

Our data showed that the incidence of AL was 19.1% with mean time to leakage 5.1±1.2 days, with range 3 -7 days. There was no statically significant difference between patients who developed leakage and those who don't in terms of demographics, medical history, operative procedure, type, and mode of anastomosis with p values >0.05 all.

Our findings were comparable with the rate of AL reported by Jina et al.,[8] who conducted a prospective cross section study including 156 patients who were indicated for intestinal resection and anastomosis, they reported the rate of AL to be 16.02%, they also reported no significant difference in the incidence of AL according to the age, gender, and socioeconomic status.

Messias et al.,[7] reported slightly lower rate of AL among their cohort of 90 patients with incidence of anastomotic leakage 12.2%, which was diagnosed between 3 – 24 postoperative days.

In the present study, comparison of TLC and CRP levels between patients who developed AL and those who did not showed that baseline TLC and CRP showed no statistically significant difference

Table 4: Risk factors associated with incidence of postoperative anastomotic leakage

		Leakage				P Value
		No		Yes		
		Mean/ Count	SD/ %	Mean/ Count	SD/ %	
Age	Years	48.6	13.9	50.2	16	
Gender	Female	37	39.80%	9	40.90%	0.923
	Male	56	60.20%	13	59.10%	
Co-Morbidities	No	56	60.20%	14	63.60%	0.767
	Yes	37	39.80%	8	36.40%	
Hypertension	No	69	74.20%	15	68.20%	0.568
	Yes	24	25.80%	7	31.80%	
Diabetes	No	81	87.10%	18	81.80%	0.52
	Yes	12	12.90%	4	18.20%	
Cardiac	No	90	96.80%	22	100.00%	0.393
	Yes	3	3.20%	0	0.00%	
Operative Procedure	Closure Of Colostomy	15	16.10%	4	18.20%	0.381
	Closure Of Hartman's	9	9.70%	1	4.50%	
	Extended Left Hemicolectomy	1	1.10%	2	9.10%	
	High Anterior Resection	1	1.10%	0	0.00%	
	Left Hemicolectomy	20	21.50%	4	18.20%	
	Low Anterior Resection	3	3.20%	0	0.00%	
	Right Hemicolectomy	31	33.30%	5	22.70%	
	Sigmoidectomy	12	12.90%	6	27.30%	
	Subtotal Colectomy	1	1.10%	0	0.00%	
Type Of Anastomosis	End To End	70	75.30%	17	77.30%	0.694
	End To Side	3	3.20%	0	0.00%	
	Side To Side	20	21.50%	5	22.70%	
Mode Of Anastomosis	Hand Sewn	41	44.10%	14	63.60%	0.099
	Stapler	52	55.90%	8	36.40%	

between groups (0.260, and 0.322 respectively), while Day 1, Day 2, Day 3 and Day 4 showed significantly higher among leakage group with p values <0.01 all. The highest difference was reported in Day 5 in terms of CRP and TLC with p values <0.001, and <0.001 respectively.

When ROC curves were applied, our data showed that sensitivity analysis showed that TLC levels on Day 1, 2, 3, 4 and 5 can significantly predict AL using cutoff 12, 11.5, 12.1, 12, and 12.7 respectively, with sensitivity 59.1% to 81.8% and specificity 64.4-95%.

These findings were consistent with Nabil et al., who assessed the association between TLC and anastomotic leakage, results showed that there was a statistically significant difference in the levels of serum TLC in the first and third postoperative days p value 0.04 and 0.03.[9]

However, our findings disagree with Scepanovic et al., and Vaziri- Moghadam et al., who reported no significant rise or difference in TLC among patients who developed postoperative anastomotic leakage.[10]

Our findings agree with a cross section study conducted in Zgazig University, Egypt, their results showed that TLC was significantly higher among AL group on the 3rd postoperative day while same difference was not significant in the 5th day. Sensitivity analysis showed that using a cutoff >12x103/mm3 can significantly predict AL on the 3rd postoperative day with sensitivity 100%, specificity 63% and diagnostic accuracy 70.8%.[11]

Aaron et al., conducted a prospective cross section study and assessed serial CRP and TLC in the perioperative period, they found that TLC count can significantly predict AL using a cutoff point 9.5 103/

mm3, the sensitivity was 72.7% and the specificity was 56.5%.[12] This cutoff was lower than reported in the present cohort.

Also, Our study showed that sensitivity analysis showed that CRP levels on Day 1, 2, 3, 4 and 5 can significantly predict AL using cutoff 70, 100, 118, 151, and 160 respectively, with sensitivity 86.5% to 91% and specificity 42-98%.

Our findings were consistent with ones reported by Su'a et al. who systematically reviewed 11 studies on anastomotic leakage and identified a wide variation in CRP cutoff values, ranging from 94 to 190 mg/L in the postoperative day.[13]

Similar findings were reported by Waterland et al., reported that a level of 123.5 mg/L on Day 4 after conventional surgery was the most predictive of anastomotic leakage, their study was similar to ours in terms of including elective colorectal surgeries only.[14]

In another study, Muñoz et al.,[15] evaluated only patients who underwent elective laparoscopic colorectal cancer resection using the enhanced recovery after surgery (ERAS) protocol. In their study, CRP on Day 3 with a cutoff level of 163mg/L.

Anwar et al.,[11] have shown that 3rd and 5th postoperative level of CRP can significantly predict AL using cutoff point >123.32mg/mL and >198.23mg/mL respectively with sensitivity 80%, 100%, specificity 90%, 95% and diagnostic accuracy 89.6% and 95.8% respectively.

In the present study we faced the limitations of short postoperative follow up period, none of the included patients was subjected to emergency intestinal resection and anastomosis, only few patients were revealed to have intestinal malignancy and this may prevent our findings from being generalized over patients who are undergoing emergency operations and those with GI malignancy.

Conclusion

Patients undergoing elective or emergency colorectal surgery should routinely have their CRP levels measured. After the second postoperative day, persistently elevated CRP levels predicts anastomotic leakage because they are unaffected by individual inflammatory response, or type of surgical approach. A cutoff level of 160 mg/L on Day 5 can indicate anastomotic leakage with sufficient accuracy to warrant additional monitoring and hospitalization.

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