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Exclusion of Anastomosis Leakage after Colorectal Surgery using C-reactive protein: A Retrospective Study

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Abstract

Background: Anastomotic leakage (AL) is one of the common complications of colorectal surgeries. Shortening the hospitalization period due to the COVID-19 pandemic might be effective in the reduction of post-operative complications.

Objectives: This study aimed to define the role of serum CRP, WBC, and body temperature (BT) in the detection of AL and the value of postoperative CRP levels in excluding AL.

Methods: This study was a survey of laboratory tests. The patients with elective colorectal surgery were enrolled between 2017 and 2019. The symptoms of AL, such as high-level C-reactive protein, leukocytosis, body temperature, and ileus, were measured for five days after the surgery, and CRP levels were measured for five postoperative days to exclude anastomosis leakage.

Results: In total, 315 patients were enrolled in this study. The mean age of the patients was 56.2 years. Anastomotic leakage was detected in 26 patients. The CRP values for AL on days 2, 3, 4, and 5 after surgery were significant ($P<0.05$). The CPR values below 44 mg/L and 27.2 mg/L were found to be significant for the exclusion of anastomosis leakage on postoperative days 2 and 4.

Conclusion: Post-operative serum CRP, especially on postoperative days 2 and 4, with cut-off values of 44 mg/L and 27.2 mg/L, could be considered a highly sensitive marker to exclude AL and shorten the hospitalization period in the absence of ileus, fever, leukocytosis, and normal abdominal examination.

Keywords: Anastomotic leak, Body temperature, Colorectal surgery, C-reactive protein, White blood cells

1. Background

Cancer in old patients is the main cause of colorectal surgery with anastomosis. Readmission after surgery due to post-operative complications would consequently have negative impacts on the surgeon, health care system, and patients (1). The readmission due to complications within the first month after surgery has been noted in multiple studies (1-3). Anastomosis leakage is one of the most common complications of colorectal surgeries, which increases the risk of postoperative morbidity and mortality (4). C-reactive protein (CRP) is an acute-phase reactant protein that increases in some situations, such as inflammation and infection. Accordingly, in some previous studies, this has been implemented to predict AL (1, 3, 5-9). It should be noted that ileus can occur after surgery and may be associated with an AL; however, it is not a specific criterion (10). Prolonged hospitalization in post-operative patients has been proved to be one of the most important factors leading to many complications (11), especially during the COVID-19 pandemic.

2. Objectives

Therefore, shortening the hospitalization period seems to be effective in this regard. Therefore, this study aimed to determine the safest and shortest hospitalization period after colorectal surgeries.

3. Methods

The patients who have been nominated for elective colorectal surgery with anastomosis were listed initially. The study protocol was approved by the Ethics Committee of the School of Medicine, Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICINE.REC.1397.275) and the Sina hospital, Tehran, Iran. Informed consent was obtained from the participants. Patients who require emergency surgery due to high initial CRP, patients with mental disorders, and those who were unwilling to continue participation in the study were excluded from the study. The patients were given the necessary information about the surgery before the study, and the study was conducted following the ethical principles of Helsinki.

Afterward, the patients were visited before the surgery and checked for primary CRP and Complete Blood Count (CBC). Moreover, CBC and CRP were measured from day 1 to day 5 after surgery.

During the hospitalization period, the patients were monitored for any surgery complications. The standard surgical protocol, including prophylaxis administration of antibiotics, was performed half an hour before the surgery for all the patients.

Furthermore, antibiotics were discontinued 48 h after the surgery. Surgeries were performed by experienced surgeons in the field of colorectal surgery. The CRP level was checked once before and once after the surgery in a daily manner for up to five days. Moreover, the levels of white blood cells (WBC) were checked before and after the procedure for five consecutive days. We measured body temperature after surgical procedures every 8 h for 5 days and examined the abdomen and checked the bowel sounds and defecation daily for the evaluation of ileus.

3.1. Statistical analysis:

The collected data were analyzed in SPSS software (Version 20.0, SPSS Inc., Chicago, IL) using repeated measures analysis of variance (ANOVA). In addition, the Fisher exact test was used to evaluate the relationship between ileus and AL. The data were reported by such descriptive statistics as abundance, relative abundance, mean, and standard deviation. Afterward, the receiver operating characteristic curve (ROC) and the respective areas under the curve (AUC) were analyzed to evaluate the predictive value for the diagnosis of AL. Analysis of the obtained data was performed by logistic regression using a model for the prediction of the occurrence of AL. A p-value less than 0.05 (P<0.05) was considered statistically significant.

4. Results

The patients who underwent elective colorectal surgery with primary anastomosis were enrolled in this study from 2017 to 2019. In total, 315 patients were statistically analyzed, of whom 190 (60.3%) cases were males and 125 (39.7%) cases were females. The mean age of participants was 56.2 years (age range: 23-84 years). Out of the total 315 anastomoses, 43 (13.7%), 119 (37.8%), 72 (22.9%), and 81 (25.7%) cases were colon to colon, colon to the rectum, ileum to the colon, and ileum to ileum, respectively. In total, there were 26 (8.3%) cases of AL, of whom 18 (69.2%) and 8 (30.8%) patients were male and female, respectively. The mean±SD age of the patients with AL was estimated at 58.96±13.28 years. Malignant and non-malignant lesions in the gastrointestinal tract accounted for 49.3% and 23.9% of the surgical procedures, respectively.

The monitoring of CRP before surgery and 1 to 5 days after surgery showed that the mean±SD serum level of CRP was 12.27±15.45 mg/L, which increased to 83.96±43.72 mg/L by the second day after surgery with a steep slope and then reduced further with a gentle slope (Table 1).

Furthermore, the WBC level in patients was lower before the surgery (7.31±2.59 10^9/L); however, it increased with a steep slope by the first day after surgery (11.63±3.8410^9/L) and then reduced to the normal range (9.39±3.94 10^9/L) at day 3 after the surgery (Table 1).

The body temperature of the patients was elevated with a steep slope from the normal level (36.57±0.18 ˚C) before surgery by the second day after surgery (37.28±0.50 °C) and then descended with a steep slope (36.95±0.51 ˚C) by the day 4 after surgery (Table 1). The maximum number (33 patients) of patients with ileus was found on days three and four after surgery.

The study showed that the maximum number of AL occurred in 7 (26.9%) cases on day 3 after surgery and in 5 (19.2%) cases on days 4 and 5 after the surgery. CRP levels were significant for the AL on the second day (105.53±57.5 mg/L, P=0.008), the third day (96.36±44.1 mg/L, P=0.001), fourth day (92.8038±50.99 mg/L, P<0.001), and the fifth day (88.79±61.7 mg/L, P<0.001) after surgery (Table 2).

There was no significant relationship between the anastomosis type and AL (P=0.9) (Table 3).

Table 1. Mean of variables in the study period

		Before surgery	POD 1	POD 2	POD 3	POD 4	POD 5	P-value
CRP, mg/L		12.27±15.45	64.39±41.12	83.96±43.72	76.32±33.58	64.67±34.88	57.63±37.89	<0.001*
WBC, 10^9/L		7.31±2.59	11.63±3.84	10.58±4.10	9.39±3.94	8.35±3.32	8.02±2.81	<0.001*
BT, °C		36.57±.18	37.06±.40	37.28±.50	37.19±.55	36.95±.51	36.73±.36	<0.001*
Ileus,	Y	-	10 (3.2%)	14 (4.4%)	33 (10.5%)	33 (10.5%)	22 (7%)	<0.001**
N (%)	N	-	305 (96.8%)	301 (95.6%)	282 (89.5%)	282 (89.5%)	293 (93%)	

CRP=C-reactive protein. WBC=White blood cells. BT=Body temperature. POD=Post-Operation Day. * Test: ANOVA. **Test: Chi-square

Table 2. Relationship of CRP to the anastomotic leak

	Anastomotic leak		P-value*
	No, n=289	Yes, n=26	
CRP, mg/L			
CRP before surgery	12.2329±15.73336	12.6962±12.17231	0.884
CRP POD 1	63.4875±41.21200	74.5077±39.53292	0.191
CRP POD 2	82.0242±41.84786	105.5346±57.50465	0.008
CRP POD 3	74.5263±31.95007	96.3615±44.17069	0.001
CRP POD 4	62.1436±31.99217	92.8038±50.99279	<0.001
CRP POD 5	54.8315±33.75139	88.7962±61.77461	<0.001

CRP=C-reactive protein. POD= Post-Operation Day.

Table 3. Anastomosis type and number of patients with anastomosis leakage

Anastomosis type	Leakage			
	No	Yes	Total	P-value
Colon to colon	39	4	43	0.928
Colon to rectum	108	11	119	
Ileum to colon	67	5	72	
Ileum to Ileum	75	6	81	
Total	289	26	315	

Test: chi square

As indicated in Table 4, the incidence of ileus on the third day (P=0.002), fourth day (P=0.04), and fifth day (P=0.02) after surgery was significantly associated with AL.

Based on the ROC curve analysis of CRP level, cut-off values of 72.4 mg/L and 66.5 mg/L were obtained at postoperative day 3 (POD3) and POD4, respectively. These values are considered the most important predictors and each are associated with AUC of 657 (sensitivity: 69.2%, specificity: 58%) and 0.707 (sensitivity 69.2%, specificity 64%), respectively (Figure 1).

Moreover, ROC analysis revealed that the WBC cut-off value of 7.95 10^9/L obtained in POD5 was the best predictor of AL with an AUC of 0.621 (sensitivity: 65.4%, specificity: 52.2%) (Figure 2).

A rule-in rule-out algorithm was used to evaluate the CRP value for the prediction of colorectal AL. Correspondingly, this approach involves consideration of CRP threshold levels with high sensitivity and negative predictive value (NPV), which rules out AL and shortens the hospitalization period. As demonstrated in Table 5, on postoperative days 2 and 4, CPR levels below 44 mg/L and 27.2 mg/L with a sensitivity of 96% and NPV of 62% can be used as a cut-off value to exclude AL. Patients were checked routinely for other causes of inflammation and those who developed these conditions (e.g., pneumonia, urinary tract infection) were excluded from the study.

Table 4. Association of ileus and the anastomotic leakage

			Anastomotic leakage		Total	*P-value
			No	Yes		
ILEUS, n	POD 2	Y	11	3	14	0.099
		N	278	23	301	
	POD 3	Y	25	8	33	0.002
		N	264	18	282	
	POD 4	Y	27	6	33	0.041
		N	262	20	282	
	POD 5	Y	17	5	22	.026
		N	272	21	293	
Total			289	26	315	

*Test: Fisher exact. POD=Post-Operation Day.

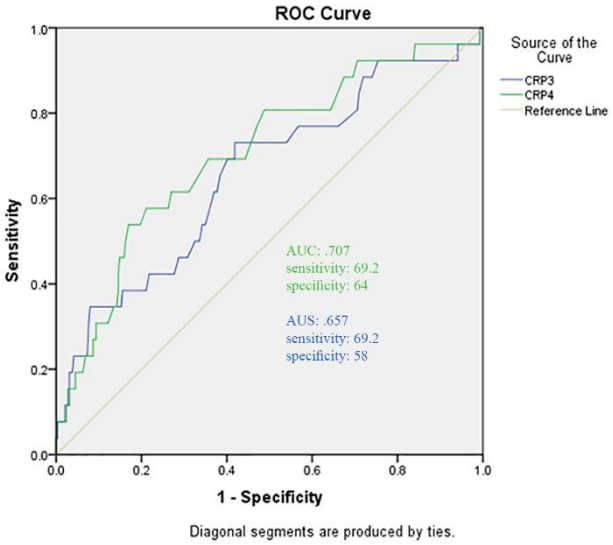

Figure 1. Receiver operating characteristic (ROC) curve of the C-reactive protein (CRP) level for the diagnosis of anastomotic leakage on post-operation day three and four; AUC=Area under the curve; CRP=C-reactive protein; CRP3=CRP at post-operation day three; CRP4=CRP at post-operation day four

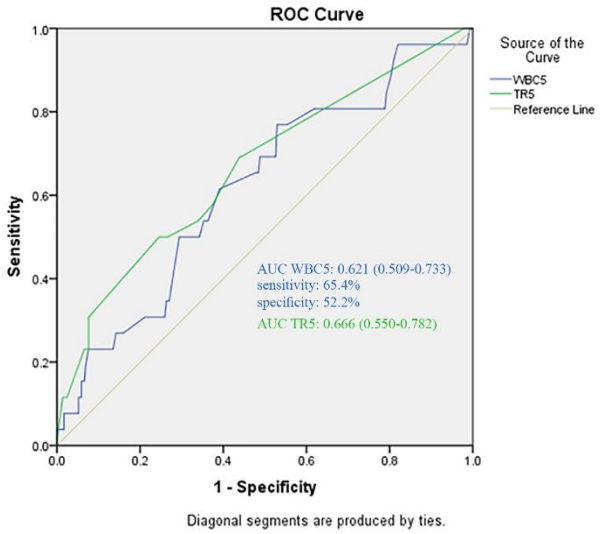

Figure 2. Receiver operating characteristic (ROC) curve of the white blood cell (WBC) level and body temperature for the diagnosis of anastomotic leakage on post-operating day five; AUC=Area under the curve; WBC5=WBC at post-operation day five; BT5=Body temperature at post-operation day five.

Table 5. CRP performance in detecting anastomosis leakage in this study

Post-operative day (POD)	Positive if greater than or equal to[a]	Sensitivity	Specificity	NPV
POD 1	39.5000	0.885	0.291	0.41455
POD 2	44.0000	0.962	0.173	0.679715
POD 3	54.5000	0.923	0.246	0.504094
POD 4	27.2000	0.962	0.159	0.625337
POD 5	29.5000	0.923	0.232	0.475694

a. The smallest cutoff value of the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values

5. Discussion

Anastomosis leakage after colorectal surgeries is a major clinical problem requiring revision surgeries and prolonged hospitalization. Although some leakages occurring early after surgery may occur with sepsis, other leakages can have a more insidious presentation, which is only clinically noticeable as late as postoperative days 8 to 12 (12-14). Post-operative mortality due to anastomosis complications is estimated to account for one-third of all deaths resulting from colorectal surgeries. Therefore, early detection of these complications is mandatory for decreasing postoperative morbidities.

This study aimed to define the role of serum CRP, WBC, and body temperature (BT) in the detection of AL and the value of postoperative CRP levels in excluding AL.

The CRP is an acute-phase reactant protein induced by the IL-6 in the acute phase of an inflammatory or infectious process. The CRP level rises and falls rapidly with the onset of inflammation (15). Concerning postoperative complications, T Welsch et al. in their study demonstrated that CRP elevation in complicated cases occurs before clinical manifestations (e.g., fever) and almost immediately after operation. This could be of value in the early diagnosis of postoperative complications, such as AL. However, the elevated CRP may occur in a patient without AL, which may be related to other factors, such as blood loss and duration of the operation (16).

Regarding the predictive value of CRP specific to AL after colorectal surgery, Waterland et al. reported that the CRP levels are higher in open colorectal surgeries compared to laparoscopic surgeries. The CRP levels on POD 3 and 4 were found to be the most important predictors of leakage in an open group with CRP cut-off values of 209 mg/L and 123.5 mg/L (sensitivity of 80% and specificity of 80%). Moreover, the CRP level on POD 2 was also reported to be significant with a cut-off CRP value of 146.5 mg/L for the laparoscopic group (sensitivity of 75% and specificity of 70%) (17).

Catarci et al. in their study reported that DLS has better performance for AL on POD 2 and 3 compared to CRP and PTC, using Dutch leakage score (DLS), serum CRP, and serum procalcitonin, whereas CRP level had better sensitivity and specificity curves on POD 6. Considering the cut-off value of 81.54 mg/L, CRP was found to be associated with 80% sensitivity and 75% specificity in POD 6 (18). The obtained results demonstrated that CRP increment in patients with AL was significant in the first five postoperative

days, ranging from 74.5 mg/L to 105.5 mg/L. Cut-off values of 72.4 mg/L and 66.5 mg/L on POD 3 and POD 4 were also found to be the most important predictors of AL.

One of the main goals of this study was to shorten the hospitalisation period through evaluation of the CRP levels to exclude AL. It was found that CRP levels on POD 2 and POD 4 with cut-off values of 44 mg/L and 27.2 mg/L with 96% sensitivity and 67% and 62% NPV, respectively were significant in excluding AL.

Messias et al. reported that a CRP level of 180 mg/L on POD 4 was the most sensitive and specific level to exclude AL. In this study, decreased CRP levels were also observed on POD2 in patients without AL (19). The obtained results were in agreement with those in a study conducted by Woeste et al. who showed that although CRP level increased in patients with or without AL around POD 2, it decreased gradually after an uneventful course of hospitalisation. Moreover, higher CRP levels were not observed after POD 2 in the patients who did not develop AL (20).

However, it is difficult to compare studies in the literature due to non-standard definitions for anastomosis leakage, time of CRP testing, patient selection, and surgical approaches.

Some studies have indicated that many cases of AL occur within seven days after surgery and that late AL is considered to be a rare event (21). Accordingly, careful evaluation of patients, including close observation of body temperature and level of white blood cells along with the decreased CRP levels, could provide a margin of safety for being discharged after colorectal surgeries, as indicated by the study results.

This was a single-center study with relatively small sample size. Further studies with a larger sample size are needed to confirm the obtained findings and extend them to clinical practice.

6. Conclusion

Serum CRP levels can be analyzed to evaluate the probability of AL in patients undergoing elective or emergency colorectal surgeries. Post-operative serum CRP, especially on POD 2 and 4, with cut off values of 44 mg/L and 27.2 mg/L, respectively, may be considered a good predictor for the exclusion of AL and shortened hospitalization period in the absence of ileus, fever, leukocytosis, and normal abdominal examination

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Footnotes

Conflicts of Interest: The authors declare that they have no conflict of interest regarding the publication of this study.

Authors' contributions: HA and ER conceived and designed the study. MK and SG collected the clinical data and RH carried out the data gathering. ER, FV, and MK performed the statistical analysis. SG and MK drafted the manuscript and provided logistic support. HA, FV, and RH edited and prepared the final version of the article. All authors proofread and approved the final version of the manuscript.

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Ethics approval: The study protocol was approved by the Ethics Committee of the School of Medicine, Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICINE.REC.1397.275), on July 25, 2018. Permission to carry out the study and access patients' records was sought from the respective administrative divisions at Tehran University of Medical Sciences, Tehran, Iran.

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