

CRP (C-Reactive Protein) In Colorectal Anastomatic Leak and Sepsis: A Prospective Study

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ABSTRACT

Background: Anastomotic leak is defined as the presence of pus or enteric contents in the drains or presence of abdominal or pelvic collection in the areas of anastomosis on postoperative CT scan or leakage of contrast at the anastomotic site during an enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis. Anastomotic leakage is one of the adverse events after colorectal surgery, which remains a significant burden for patients and surgeons. C-reactive protein (CRP) has proven to be a helpful parameter for detecting an anastomotic leak in colorectal surgeries.

Methods: This prospective observational study was done in the Department of General And Minimal Invasive Surgery, Colorectal Division, at Sher-i-Kashmir Institute of Medical Sciences (SKIMS) Soura, Srinagar. This study included all patients >14 years of age undergoing elective colorectal surgery with primary colorectal anastomosis. Abstracted data included age at the time of surgery, sex (male or female), medical comorbidities (hypertension, diabetes, Hypothyroidism), preoperative chemo radiotherapy (received or not received), relationship of CRP and anastomotic leak (AL) and management (reoperation, USG guided aspiration or CT showed pigtail drainage) of AL. CRP by latex-enhanced nephelometry was used in our study.

Results: A total of 130 patients were included in our study. There were 75 (57.7%) males and 55 (42.3%) females with a mean age of 52.2 years. In our study, 17 (13.1%) patients received preoperative chemo radiotherapy, and 7 (41%) among them developed an anastomotic leak. In comparison, 113 (86.9%) patients did not receive any preoperative chemotherapy or radiotherapy, and 17 (15%) among them developed a leak. Out of 24 patients having an anastomotic leak, 7 (29.1%) patients had an anastomotic leak on the 3rd day, 10 (41.6%) patients had an anastomotic leak on the 4th day, 5 (20.8%) patients had an anastomotic leak on the 5th day and 2 (8.3%) had an anastomotic leak on 6th day. Serum CRP level was significant in 26 cases and non-significant in 104 cases. Out of 26 patients with considerable serum CRP levels, 24 patients had an anastomotic leak. Among 24 patients who had an anastomotic leak, 5 (20.8%) patients were managed by reoperation in the form of peritoneal lavage and covering stoma (mostly ileostomy), and 19 (79.1%) were managed conservatively.

Key Words: Colorectal Surgery, Anastomotic Leak, C - reactive protein

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INTRODUCTION

Anastomotic leak is defined as the presence of one of the following criteria:-

- Presence of pus or enteric contents in the drains.
- Presence of abdominal or pelvic collection in the areas of anastomosis on postoperative CT scan.
- Leakage of contrast at the anastomotic site during an enema or evident anastomotic dehiscence at reoperation for postoperative peritonitis.

Anastomotic leakage may remain localized, causing peri-anastomotic inflammation or abscess formation or may progress to general peritonitis¹. Anastomotic leakage has a significant role in patient outcomes and hospital costs, and a timely diagnosis and intervention for the same are associated with a lower morbidity and mortality rate.

Gastrointestinal anastomotic leakage causes increased early

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mortality², and following potentially curative resection of colorectal cancer leads to higher recurrence rates and a poorer oncologic prognosis³. Anastomotic leaks (ALS) occur in 2% to 10% of patients undergoing gastrointestinal surgery⁴⁻⁷. In high-risk patients incidence rate increases to 18%⁸. Anastomotic leakage is one of the common adverse events after colorectal surgery, which remains a large burden for patients and surgeons⁹. Anastomotic leakage is associated with high morbidity¹⁰, mortality¹¹⁻¹³, re-operation¹⁴ and duration of hospitalization¹³.

Preoperative identification of patients who are at increased risk of AL is essential for patient optimization and selective proximal diversion^{15,16}, and its early detection reduces the incidence of generalized peritonitis and thus reoperations, intensive-care unit (ICU) stay and mortality^{17,18}. Short-term morbidity and mortality, as well as detrimental long-term effects, such as permanent stoma, might be reduced if AL is detected and treated in an early phase¹⁹. Many studies have focused on preoperative risk factors, such as age, sex, neoadjuvant therapy, emergency surgery and distance from the anal verge, and should enable estimation of risk of postoperative CAL²⁰⁻²³. Despite this caution, delay in diagnosis is expected and has been caused by false negative radiological investigation and intervening weekends²⁴. Anastomotic leakage is a significant challenge in colorectal surgery patients²⁵.

Despite evolutions in stapling techniques and operation modalities, the incidence of anastomotic leakage after colorectal surgery has not decreased over the last decade^{9,26}. Clinical signs of AL before the fifth postoperative day (POD) are uncommon, and most studies described a mean POD of eight for CAL to become clinically apparent. However, some studies even show that AL is diagnosed at mean POD 12^{27,28}.

Early clinical presentation is heterogeneous, and often nonspecific anastomotic leakage can present as peritonitis, localized fluid collections, or subclinical leakage detected by contrast radiology. In addition, nonspecific symptoms include fever, absence of bowel movements, and diarrhea only become apparent on postoperative days 4 to 7²⁹. Abdominal CT scan, the current standard for diagnosis of anastomotic leakage yield low sensitivity which can delay the diagnosis and appropriate treatment of anastomotic

leakage³⁰.

There is an urgent need for accurate diagnostic markers of anastomotic leakage early after colorectal surgery to decrease delayed diagnosis and its unfavorable sequel. C-reactive protein (CRP) was discovered in 1930 as a substance in the serum of patients having acute inflammation and named for its capacity to precipitate a non-protein somatic fraction (Fraction C) of *Streptococcus pneumoniae*. CRP is a sensitive systemic marker of tissue damage and inflammation but is not specific for infection³¹. C-reactive protein (CRP) is produced by liver cells in response to inflammation and has a short circulating half-life (4-6h). CRP is an acute-phase inflammatory reactant that increases a lot during the inflammatory response triggered by tissue injury or infections which peaks within 24-72 hours and then rapidly decreases after the resolution of the inflammatory process³². CRP reacts with the cell membrane components forming complexes that activate the complement system releasing opsonins, which induce phagocytosis and removal of such structures from the circulation. CRP plays an important role in the host's nonspecific defense by the removal of cell remnants produced from necrotic or damaged cells in the inflammation process, permitting tissue repair³⁴.

CRP levels significantly increase in the post-surgery period, so in the early postoperative period, its predictive value for the diagnosis of infection is reduced^{35,36}. Despite this, an interest in CRP as an infection monitoring tool in the perioperative setting has increased since it was reported that in values higher than 140 mg/L on a postoperative day (POD) 3-4, it would predict infectious complications after colorectal surgery³⁷.

CRP increases on the first day after surgery after the surgical procedure due to clinical phenomena like leucocytosis, fever and arrhythmias and rapidly drops at the end of the inflammatory response³⁸. In surgical site infections (SSI), CRP levels increase, and it has been used as a test for the early identification of SSI. Various studies demonstrate that preoperative CRP levels remained high in patients who developed a postoperative infection³⁸. Factors that can change CRP levels are infections, obesity, smoking, degenerative osteoarthritis, change in the acute phase and response to burns, post-traumatic stress, emotional disorders and menstrual cycle³⁹.

The acute phase protein CRP has shown to have a strong correlation with postoperative complications^{40,41}. CRP levels rise after surgery with a peak in 48-72 hours postoperatively and decrease thereafter⁴², and In patients with a complicated postoperative course, CRP levels remain elevated^{40,43}. Many studies aimed to establish a cut-off value for CRP as a predictor for postoperative complications, such as anastomotic leakage or septic complications^{41, 44-48}. Results are, however conflicting, postoperative complications are not stratified, and most studies merely aimed to set a cut-off for CRP as a marker for anastomotic leakage after colorectal surgery^{44, 47, and 48}.

MATERIAL AND METHODS

This prospective observational study was done at the Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Department of General And Minimal Invasive Surgery, Colorectal Division, Srinagar, after obtaining approval from the Institutional Ethical Committee.

Our study included all patients >14 years of age undergoing elective colorectal surgery with primary colorectal anastomosis.

CRP (C-reactive protein) by latex-enhanced nephelometry was used in our study. This is the qualitative and semi-quantitative estimation of CRP. The assay is performed by testing a suspension of latex particles coated with anti-human CRP antibodies against unknown serum. The presence of the visible agglutination indicates an increased level of CRP to a clinically significant level. The titre is expressed as reciprocal of the highest dilution showing macroscopic agglutination.

RESULTS

A total of 130 patients were included in our study. There were 75 (57.7%) males and 55 (42.3%) females with a mean age of 52.2 years. Most of the patients (68.4%) belonged to 40 to 69 years (Table 1).

Table 1: Showing Age Distribution		
Age group in years	Frequency	Percentage
14-19	4	3.07
20-29	8	6.1
30-39	13	10
40-49	24	18.4
50-59	34	26.1
60-69	31	23.8
70-79	15	11.5
80-89	1	0.8

82 (63.1%) of our patients had some underlying medical comorbidity. Hypertension was present in 30 (23.1%) patients, 16 (12.3%) patients were diabetic and 1 (0.8%) patient had COPD. CAD and Hypothyroidism were present in 10 (7.7%) and 16 (12.3%) patients, respectively.

In our study, 17 (13.1%) patients received preoperative chemoradiotherapy, and 7 (41%) among them developed an anastomotic leak. In comparison, 113 (86.9%) patients did not receive any preoperative chemotherapy or radiotherapy, and 17 (15%) among them developed a leak.

Out of 24 patients having an anastomotic leak, 7 (29.1%) patients had an anastomotic leak on the 3rd day, 10 (41.6%) patients had an anastomotic leak on the 4th day, 5 (20.8%) patients had an anastomotic leak on 5th day and 2 (8.3%) had an anastomotic leak on 6th day.

Serum CRP level was measured in the postoperative period from day 2 to day 6. Serum CRP level was significant in 26 cases and non-significant in 104 cases. Out of 26 patients with considerable serum CRP levels, 24 patients had an anastomotic leak (Table 2).

Table 2 Relationship between CRP and Leak		Significant CRP	Non-Significant CRP
Anastomotic leak	Present 24 (true positive)	26 (positive) 24	104 (negative) 0 (false negative)
	Absent 106 (true negative)	2 (false positive)	104

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive} + \text{False negative}} \times 100 = \frac{24}{24+0} \times 100 = 100\%$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative} + \text{False positive}} \times 100 = \frac{106}{106+2} \times 100 = 98.15\%$$

Among 24 patients who had an anastomotic leak, 5 (20.8%) patients were managed by reoperation in the form of peritoneal lavage and covering stoma (mostly ileostomy), and 19 (79.1%) were managed conservatively, as shown in table 3.

Re-operation was done in those cases having signs and symptoms of peritonitis (Free anastomotic leaks).

Out of 24 patients who had anastomotic leaks, 7 (29.1%) were managed by USG (ultrasonography) guided aspiration of collection and 12 (50%) patients were managed by pigtail

catheter drainage of collection. USG guided aspiration and CT guided pigtail catheter drainage was done in those cases that had contained collection and no symptoms and signs of peritonitis.

Table 3. Relationship between Re-operation and CRP is shown in

Table 3		CRP	
		Significant	Non-Significant
Re operation	No	19 79.1%	106 100.0%
	Yes	5 20.8%	0 0.0%
Total		24 18.4%	106 81.6%

DISCUSSION

C-reactive protein has proven to be a useful parameter used for detecting an anastomotic leak in colorectal surgeries. The aim of the study was to evaluate the efficiency of CRP in predicting and diagnosing anastomotic leak after colorectal surgery. The total numbers of patients included in our study were 130, including 75 (57.7%) males and 55 (42.3%) females. This is comparable with the study of Dana et al.⁴⁹. In their study, 49% were males, and 51% were females, while in the study done by Reisinger et al.⁵⁰, 64.3% were males and 35.7% were females.

In our study mean age was 52.2 years ranging from 14 years to 80 years, which closely matches with a mean age of [55.6 years] as reported by Dana et al.⁴⁹.

In our study, comorbidity was present in 82 (63.1%), while 48 (36.9%) patients had no comorbidity. Hypertension was present in 30 (23.1%) patients, 16 (12.3%) patients were diabetic and 1(0.8%) patient had COPD. CAD and Hypothyroidism were present in 10 (7.7%) and 16 (12.3%) patients, respectively. 114 (87.7%) of our patients were euthyroid, and no one had hyperthyroidism. In relation to various comorbidities, our study is consistent with the study by Dana et al.⁴⁹.

17(13.1%) of our patients had received preoperative chemoradiotherapy, and 7 (41%) among them developed a leak, while 113 (86.9%) patients had not received any preoperative chemotherapy or radiotherapy and 17 (9.7%) among them developed a leak. Thus preoperative chemoradiotherapy increases the chances of anastomotic leak. Dana et al.⁴⁹ has also mentioned a high leak incidence in patients who had received chemoradiotherapy.

In our study 26 (20%) patients had significant postoperative level of CRP (>30mg/dl) while as remaining 104 (80%) patient had non-significant level of CRP (<30mg/dl). This figure is comparable with the study carried by Reisinger et al.⁵⁰.

Out of 130 patients who underwent primary colorectal anastomosis, twenty-four (18.4%) patients had an anastomotic leak (AL), while 106 (81.5%) patients had no anastomotic leak. Karliczek et al.⁵¹ reported an anastomotic leak in 13.6%, while Reisinger et al.⁵⁰, in 9.2% and Pablo Ortega-Deballan et al.⁵², shows the overall incidence of anastomotic leaks was 15.5% in their study.

Out of 24 patients having an anastomotic leak, 7 (29.1%) patients had an anastomotic leak on the 3rd day, 10 (41.6%) patients had an anastomotic leak on the 4th day, 5 (20.8%) patients had an anastomotic leak on the 5th day, and 2 (8.3%) had an anastomotic leak on the 6th day. So in our study, high chances of AL were on the 3rd, 4th and 5th days. Pablo Ortega-Deballan et al.⁵² also reported an increased incidence of AL on the 3rd, 4th and 5th day while as MarekZawadzki et al.⁵³ reported that in most instances, AL occurs around the 5th-7th postoperative day (POD), but it might develop any time from the day of index surgery to the third postoperative week. The average day of AL in our study was the 4th postoperative day. Dagmar et al.⁵⁴ had also reported an average of AL as the 4th postoperative day, and Reisinger et al.⁵⁰ reported the average day of AL as the 6th postoperative day.

Serum CRP level was measured in the postoperative period in 130 patients who underwent anastomosis after resectioning the colonic or rectal tumour. Serum CRP level was significant in 26 cases and non-significant in 104 cases. Out of 26 patients with considerable serum CRP levels, 24 (92.3%) patients had an anastomotic leak. In our study, sensitivity was 100%, and specificity was 98.15%. Thus C-reactive protein in the postoperative period was a good predictor of anastomotic leak.

Reisinger K Wet al⁵⁰ reported sensitivity of 100%, specificity of 89% in their study, and P. Waterland et al.⁵⁵ reported sensitivity of 94 % and specificity 60%.

Among 24 patients who had an anastomotic leak, 5 (20.8%) patients were managed by reoperation in peritoneal lavage and covering stoma, and 19 (79.1%) were managed

conservatively. Out of 24 patients who had anastomotic leaks, 7 (29.1%) of them were managed by USG (ultrasonography) guided aspiration of collection and 12 (50%) patients were managed by CT (computerized tomography) guided Pigtail catheter drainage of collection.

Reoperation with peritoneal lavage and covering loop ileostomy was done in those cases having signs and symptoms of peritonitis (Free anastomotic leaks). Conservative management included: stopping orals, giving intravenous fluids, intravenous antibiotics, total parental nutrition, drainage of contained collection by USG (ultrasonography) guided aspiration or CT (computerized tomography) guided Pigtail drainage. The assessment of anastomotic leak and collection was done by serial ultrasonography and computerized tomography. USG guided aspiration and CT guided Pigtail drainage was done in those cases that had contained collection and no symptoms and signs of peritonitis

Management of AL in other studies matched our study as; Karliczek et al.⁵¹ studied dramatic clinical consequences of anastomotic leakage in gastrointestinal surgery can be reduced by a diverting stoma. MarekZawadzki et al.⁵³ showed anastomotic leaks became clinically symptomatic between the 3rd and 12th postoperative days, and all required reoperation. Giuseppe Pappalardo et al.⁵⁶, they had 15 (6.8%) AL with 5 (2.3%) major and 10 (4.4%) minor. In the five major AL, an immediate colostomy was performed with one death. Esin Kabul Gürbulark et al.⁵⁷ studied the gold standard of surgical treatment of colorectal anastomotic leak is abdominal drainage of collected fluid and stoma formation.

Mark A. Boccol et al.⁵⁸ observed Level I evidence to support the use of drain tube insertion in the correct settings, including those associated with the poor patient, disease and/or operative factors. Esin Kabul Gürbulak et al.⁵⁷ studied the gold standard of minimally invasive management of colorectal anastomotic leak is abdominal drainage of collected fluid. W.M. Chambers et al.⁵⁹ studied postoperative leakage and abscess formation after colorectal surgery. AL may be grouped into clinically significant and those which are not significant. AL occurs in 3.46% of all colorectal cases, but rectal anastomoses have clinically significant AL in 2.915.3% of cases. Mortality following a leak maybe 6.039.3%. There is no evidence for

the use of drains when an anastomosis has been made outside the pelvis, but pelvic drainage may be important after anterior resection. Intra-abdominal abscesses, in most cases, can be treated by radiologically guided drainage. Roland Kiss et al.⁶⁰ showed 7.3% of 341 patients developed AL, (80%) underwent reoperation, 20% of AL patients were treated conservatively. The high mortality in patients with AL (8%) is caused by sepsis.

Conflict of Interest: None

Financial Sources: None

Consent: Taken

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