

Original Research Article

Serial postoperative C-reactive protein for early prediction of anastomotic leakage after colorectal surgery: a prospective observational study

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ABSTRACT

Background: Anastomotic leakage is a potentially life-threatening complication after colorectal surgery. Because clinical manifestations may be delayed or nonspecific, an accessible biochemical marker may facilitate earlier recognition and investigation. This study evaluated the association between serial postoperative serum C-reactive protein (CRP) levels and anastomotic leakage after colorectal surgery.

Methods: This prospective observational study was conducted in the Department of Colorectal Surgery, Shaheed Suhrawardy Medical College and Hospital, Dhaka, from July 2023 to June 2024. Forty patients undergoing colorectal surgery with anastomosis were included. Serum CRP was measured serially during the postoperative period, and patients were monitored clinically for anastomotic leakage, confirmed by clinical, radiological, endoscopic, or operative findings. Continuous variables were compared using the unpaired Student t test, and diagnostic performance was assessed using receiver operating characteristic (ROC) analysis.

Results: The mean age was 43.1 ± 12.1 years, and 26 (65.0%) patients were male. Diabetes mellitus and hypertension were present in 10 (25.0%) and 5 (12.5%) patients, respectively. Anastomotic leakage occurred in 3 (7.5%) patients. CRP did not differ significantly between leakage and non-leakage groups on postoperative day (POD) 1 but was significantly higher in the leakage group from POD 2 through POD 8. On POD 2, a CRP cutoff of 255.3 mg/L yielded an area under the ROC curve (AUC) of 0.934, with 100% sensitivity and 92.1% specificity. On POD 3, the AUC was 0.974, with 100% sensitivity and 94.7% specificity.

Conclusions: Serial postoperative CRP was associated with anastomotic leakage, with discriminatory performance evident from POD 2. CRP may complement clinical assessment in identifying patients requiring further evaluation. Larger multicentre studies are needed to validate these findings and establish generalizable thresholds.

Keywords: C-reactive protein, Anastomotic leakage, Colorectal surgery, Postoperative complications, Diagnostic accuracy

INTRODUCTION

Anastomotic leakage remains one of the most serious complications following colorectal surgery and may result in intra-abdominal sepsis, prolonged hospitalization, reoperation, impaired oncological outcomes and increased healthcare costs.¹⁻³ The reported incidence varies considerably according to the patient population, surgical procedure, anastomotic site and definition used for leakage.⁴

Early recognition of anastomotic leakage is clinically important because the initial manifestations may be nonspecific. Patients may initially have only persistent tachycardia, fever, abdominal discomfort or an abnormal inflammatory response before developing more obvious peritonitis or sepsis.⁵ Although computed tomography, endoscopy and other diagnostic modalities are useful, imaging may not always provide an immediate or definitive diagnosis.⁶ Consequently, postoperative biomarkers have been investigated as adjuncts for early detection.

C-reactive protein (CRP) is an acute-phase protein produced predominantly by hepatocytes in response to inflammatory cytokines, particularly interleukin-6. CRP rises after tissue injury and infection and has a relatively short biological half-life, making serial measurement potentially useful during the postoperative period.⁷⁻⁹ Because anastomotic leakage is associated with an inflammatory and infectious response, persistent or disproportionately elevated CRP concentrations may provide an early indication of an adverse postoperative process.

Several studies have evaluated CRP as a marker for colorectal anastomotic leakage. Almeida et al demonstrated an association between elevated postoperative CRP and anastomotic leakage, while García-Granero et al reported that CRP and procalcitonin could help predict leakage after colorectal surgery.^{10,11} Other prospective studies have demonstrated that the diagnostic value of CRP varies according to the postoperative day, with the most useful measurements generally occurring after the first postoperative day.¹² A systematic review and meta-analysis also supported the diagnostic utility of postoperative serum CRP, although substantial heterogeneity existed among studies.¹³

The usefulness of serial CRP measurement may be particularly relevant in settings where repeated advanced imaging is not always immediately available. However, the appropriate postoperative timing and cutoff value may differ according to the population, surgical approach and baseline inflammatory response. The present study therefore evaluated the relationship between serial postoperative CRP concentrations and anastomotic leakage following colorectal surgery and assessed the diagnostic performance of CRP at different postoperative time points.

METHODS

Study design and setting

This prospective observational study was conducted in the Department of Colorectal Surgery, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh, from July 2023 to June 2024. The study included patients undergoing colorectal surgery requiring intestinal resection and anastomosis. The study protocol received ethical approval from the ethical review committee of Shaheed Suhrawardy Medical College Hospital. Written informed consent was obtained from participants before enrollment.

Participants

Patients undergoing colorectal surgery with anastomosis were considered for inclusion. The protocol specified adults aged ≥ 18 years. Patients with metastatic rectal cancer, those younger than 18 years, patients who did not provide consent, and patients undergoing simple stoma closure or having anastomoses protected by proximal diversion were excluded from the primary analysis.

A total of 40 patients were included in the final dataset. The sample size in the protocol was based on an anticipated anastomotic leakage rate of 2.4%, with a target sample size of 40 patients.

Perioperative management

Patients underwent standard perioperative management according to departmental practice. Mechanical bowel preparation and oral antibiotic preparation were used for the relevant colorectal procedures. Prophylactic antibiotics consisting of a third-generation cephalosporin and metronidazole were administered at induction and subsequently according to the institutional protocol. A standardized anesthetic approach was used. Abdominal drains were routinely placed for postoperative monitoring.

The operations included right hemicolectomy, extended right hemicolectomy, left hemicolectomy, high anterior resection, low anterior resection and proctocolectomy with ileal pouch-anal anastomosis, in addition to cases recorded as stoma closure. The most frequently reported procedure was low anterior resection.

Measurement of CRP

Postoperative serum CRP was measured serially during the postoperative period. The study dataset included CRP measurements from POD 1 through POD 8. CRP values were expressed in mg/l. Patients were monitored clinically throughout the postoperative period, and suspected anastomotic leakage was evaluated using clinical and appropriate diagnostic investigations.

Definition and diagnosis of anastomotic leakage

Anastomotic leakage was defined as a defect of the intestinal wall at the anastomotic site, including the suture or staple line, resulting in communication between the intra- and extraluminal compartments. The definition was based on the established concept of colorectal anastomotic leakage.¹⁶

Leakage was identified using clinical findings such as fever, tachycardia, hypotension, peritonitis, abnormal bowel sounds and fecal drainage, together with digital rectal examination, computed tomography, endoscopy or operative findings when indicated.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 22.0. Continuous variables were summarized as mean±standard deviation, whereas categorical variables were summarized as frequency and percentage. The unpaired Student t test was used for comparison of continuous variables between groups. A $p < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) analysis was performed to assess the ability of CRP measured on individual postoperative days to discriminate patients with and without anastomotic leakage. Sensitivity, specificity, positive predictive value, negative predictive value and area under the ROC curve (AUC) were calculated.

RESULTS

Forty patients were included in the analysis. The mean age was 43.1 ± 12.1 years. Twenty-one patients (52.5%) were aged 36–50 years. There were 26 (65.0%) male and 14 (35.0%) female patients, giving a male-to-female ratio of 1.86:1. Diabetes mellitus was present in 10 (25.0%) patients and hypertension in 5 (12.5%).

Table 1: Baseline characteristics of the study population (N=40).

Characteristics	N (%)
Age group, years	
17–35	9 (22.5)
36–50	21 (52.5)
51–65	10 (25.0)
Mean age, years	43.1 ± 12.1
Sex	
Male	26 (65.0)
Female	14 (35.0)
Comorbidities	
Diabetes mellitus	10 (25.0)
Hypertension	5 (12.5)

Open surgery was recorded in 22 (55.0%) patients and laparoscopic surgery in 18 (45.0%). The source dataset

also recorded nine conversions among the laparoscopic procedures; this variable should be verified against the operative records before submission. Low anterior resection was the most frequently recorded procedure, accounting for 11 (27.5%) cases, followed by right hemicolectomy and stoma closure.

Table 2: Operative characteristics of study population.

Variables	N (%)
Initial surgical approach	
Open	22 (55.0)
Laparoscopic	18 (45.0)
Procedure	
Right hemicolectomy	9 (22.5)
Extended right hemicolectomy	3 (7.5)
Left hemicolectomy	3 (7.5)
High anterior resection	3 (7.5)
Low anterior resection	11 (27.5)
Proctocolectomy with IPAA	1 (2.5)
Stoma closure	10 (25.0)

Three of the 40 patients developed anastomotic leakage, giving an overall incidence of 7.5%, whereas 37 (92.5%) patients did not develop leakage. On POD 1, the mean CRP concentration was 128.41 ± 47.84 mg/l among patients recorded as having laparoscopic surgery and 137.05 ± 48.86 mg/l among those recorded as having open surgery. The difference was not statistically significant ($p = 0.595$). There was no statistically significant difference in CRP concentration between patients with and without anastomotic leakage on POD 1. From POD 2 onward, CRP was significantly higher in the leakage group. The mean CRP in the leakage group increased from 147.50 ± 71.42 mg/l on POD 1 to 258.65 ± 2.33 mg/l on POD 2 and 301.35 ± 17.47 mg/l on POD 3. It reached 324.00 ± 36.77 mg/l on POD 4 before declining thereafter. In contrast, the mean CRP in the non-leakage group declined progressively after POD 3. The difference between groups was statistically significant from POD 2 through POD 8.

Table 3: Serial postoperative CRP concentrations according to anastomotic leakage status.

Post operative day	Leakage group, mean±SD (mg/l)	Non-leakage group, mean±SD (mg/l)	P value
POD 1	147.50 ± 71.42	131.76 ± 46.57	0.650
POD 2	258.65 ± 2.33	156.17 ± 49.25	0.006
POD 3	301.35 ± 17.47	123.60 ± 58.09	<0.001
POD 4	324.00 ± 36.77	78.84 ± 43.84	<0.001
POD 5	226.10 ± 0.14	52.62 ± 27.59	<0.001
POD 6	208.70 ± 3.54	49.99 ± 26.21	<0.001
POD 7	206.30 ± 3.96	47.49 ± 24.90	<0.001
POD 8	202.80 ± 6.08	45.11 ± 23.66	<0.001

The trajectory demonstrated an important difference between the two groups. CRP increased during the early postoperative period in both groups, but subsequently declined in patients without leakage. In patients with leakage, CRP remained substantially elevated.

ROC analysis demonstrated poor discrimination on POD 1, with an AUC of 0.526. On POD 2, the AUC increased to 0.934, with a CRP cutoff of 255.3 mg/l providing 100% sensitivity and 92.1% specificity. On POD 3, the AUC was 0.974, with a cutoff of 273.5 mg/l providing 100% sensitivity and 94.7% specificity.

The study dataset demonstrated an AUC of 1.00 from POD 4 through POD 8, with 100% sensitivity and specificity at the corresponding cutoffs. These estimates should be interpreted cautiously because only three patients developed leakage.

Table 4: Diagnostic performance of postoperative CRP for anastomotic leakage.

POD	CRP cutoff (mg/l)	AUC	Sensitivity (%)	Specificity (%)
1	196.5	0.526	50.0	92.1
2	255.3	0.934	100.0	92.1
3	273.5	0.974	100.0	94.7
4	269.5	1.000	100.0	100.0
5	173.5	1.000	100.0	100.0
6	160.5	1.000	100.0	100.0
7	156.3	1.000	100.0	100.0
8	151.1	1.000	100.0	100.0

DISCUSSION

Anastomotic leakage remains an important complication after colorectal surgery because delayed recognition may result in intra-abdominal sepsis, reoperation, prolonged hospitalization, and increased morbidity.¹⁴ In the present prospective observational study, 3 of 40 patients developed anastomotic leakage, giving an incidence of 7.5%. The principal finding was that postoperative serum C-reactive protein (CRP) concentrations were significantly higher in patients who developed leakage from postoperative day (POD) 2 onward, whereas no significant difference was observed on POD 1. This temporal pattern suggests that serial postoperative CRP measurements may provide more clinically useful information than a single early postoperative value.

The observed leakage rate was within the range reported in previous colorectal surgical series. Hyman et al. emphasized that anastomotic leakage may become clinically apparent later than initially expected, supporting continued postoperative surveillance.¹⁵ Reported leakage rates vary according to the type of

colorectal procedure, anastomotic location, patient characteristics, and surgical approach.¹⁶ Therefore, the 7.5% incidence observed in this study should be interpreted cautiously because of the small sample size and inclusion of heterogeneous colorectal procedures.

The biological behavior of CRP provides a plausible explanation for the observed postoperative pattern. CRP is an acute-phase protein synthesized by hepatocytes in response to inflammatory cytokines and increases following tissue injury and infection.¹⁷ Following surgery, CRP normally rises as part of the inflammatory response and reaches relatively high concentrations during the early postoperative period.¹⁸ Consequently, an elevated CRP concentration on POD 1 may reflect surgical trauma rather than anastomotic failure. In the present study, CRP did not significantly distinguish patients with and without leakage on POD 1. From POD 2 onward, however, patients with leakage demonstrated substantially higher CRP concentrations, while CRP tended to decline in patients without leakage. This finding supports the potential clinical value of monitoring the postoperative trajectory rather than relying on an isolated measurement.

The results are broadly consistent with previous studies evaluating CRP as a marker of colorectal anastomotic leakage. Komen et al identified postoperative CRP elevation as a potentially useful marker of leakage, while Smith et al. demonstrated that postoperative inflammatory biomarkers may provide early evidence of anastomotic complications.^{19,20} Facy reported useful predictive information from postoperative CRP, particularly during the later early postoperative period, and Alves et al. similarly found CRP to be useful for identifying patients at risk of leakage following anterior resection.^{21,22}

In the present study, the area under the receiver operating characteristic curve (AUC) was 0.934 on POD 2 and 0.974 on POD 3. A CRP cutoff of 255.3 mg/L on POD 2 yielded 100% sensitivity and 92.1% specificity, while a cutoff of 273.5 mg/l on POD 3 yielded 100% sensitivity and 94.7% specificity. Although these findings indicate strong discrimination within this dataset, the relatively high thresholds compared with those reported elsewhere require cautious interpretation.

Fernández et al reported pooled diagnostic performance with useful thresholds of approximately 172 mg/l on POD 3 and 124 mg/l on POD 4, while Ortega-Deballon et al reported a POD 4 threshold of approximately 125 mg/l for predicting septic complications.^{23,24} Differences in patient populations, operative procedures, surgical approaches, sampling times, laboratory methods, and definitions of leakage may contribute to variation in reported thresholds.^{25,26}

The AUC of 1.00 observed from POD 4 onward should be interpreted particularly cautiously. Only three patients

developed leakage, and therefore a small number of observations can produce apparently perfect diagnostic performance. These estimates are likely to be imprecise and may not be reproducible in larger cohorts. Accordingly, the present findings should be regarded as preliminary evidence of an association between postoperative CRP patterns and anastomotic leakage rather than evidence of perfect diagnostic accuracy.

This study has several limitations. The sample size was small, with only three leakage events, substantially limiting the precision of diagnostic estimates and making the high AUC values vulnerable to overestimation. The study was conducted at a single hospital, limiting generalizability. Inclusion of different colorectal procedures and both open and laparoscopic approaches may also have introduced variability in postoperative inflammatory responses. No multivariable analysis was performed; therefore, the observed association between CRP and leakage cannot be interpreted as evidence of independent predictive ability after adjustment for clinical or operative factors.

In addition, the source dataset contains one patient below the stated minimum inclusion age and an internally inconsistent record regarding conversion from laparoscopic to open surgery. These records should be verified against the original clinical documentation before submission. Finally, the limited follow-up restricts assessment of longer-term outcomes associated with anastomotic leakage. Larger, multicenter prospective studies are required to establish reproducible CRP thresholds and determine their incremental value alongside clinical assessment and imaging.

CONCLUSION

Serial postoperative CRP was significantly associated with anastomotic leakage after colorectal surgery, with meaningful discrimination emerging from POD 2 rather than POD 1. In this cohort, CRP thresholds of 255.3 mg/L on POD 2 and 273.5 mg/L on POD 3 demonstrated high sensitivity and specificity. Given its low cost, wide availability, and suitability for serial monitoring, CRP may serve as a useful adjunct to clinical surveillance and guide further evaluation when leakage is suspected. However, the apparently high diagnostic performance should be interpreted cautiously because only three leakage events occurred. Larger prospective multicenter studies are required to validate these findings and establish reliable, generalizable postoperative CRP thresholds.

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