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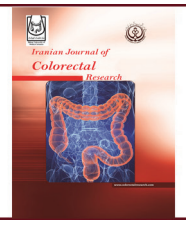

Role of Serum C-Reactive Protein, Interleukin-6, Leukocyte Indices, and Serum Albumin as Predictors of Anastomotic Leak in Colorectal Surgery: A Pilot Study from India

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Abstract

Background: Anastomotic leak (AL) following colorectal surgery can lead to significant morbidity and mortality, with an incidence ranging from 2% to 14%. Early diagnosis and management are crucial for improving patient outcomes. However, the clinical detection of leaks is often delayed, adversely affecting these outcomes. Therefore, there is a pressing need for serum markers that can serve as diagnostic tools prior to the onset of clinical manifestations. The objective of this study is to investigate the changes in serum C-reactive protein (CRP), albumin, leukocyte indices, and interleukin-6 (IL-6), and to access their association with AL in colorectal anastomosis.
Methods: This prospective observational pilot study included 30 patients undergoing elective colorectal resection and anastomosis for both benign and malignant conditions at the Department of Surgical Gastroenterology, SGPGIMS Lucknow, a tertiary care teaching hospital in northern India, from April 2021 to March 2022. Serum C-reactive protein (CRP), albumin, total leukocyte count (TLC), complete blood counts, platelet count, and IL-6 levels were measured preoperatively and postoperatively. Patients were divided into two groups: Group 1, which experienced anastomotic leaks, and Group 2, which did not. Changes in these markers were compared preoperatively and on postoperative days (POD) 1, 3, and 7. To compare the changes between groups, the Mann–Whitney U test was utilized, and multivariate analysis was conducted to identify predictors of anastomotic leaks using Firth logistic regression. A P value of <0.05 was considered statistically significant.
Results: Group 1 comprised 4 patients (13.3%), while Group 2 included 26 patients (86.7%). A statistically significant difference was observed in serum CRP levels (P=0.001), neutrophil-to-lymphocyte ratio (NLR) (P=0.009), and serum IL-6 levels (P=0.03) on POD 3 between group 1 and group 2. In the multivariate analysis utilizing Firth logistic regression, serum CRP exhibited OR=1.09 and NLR demonstrated OR=1.28.
Conclusion: A significant increase in serum CRP, NLR, and IL6 on POD 3 may serve as valuable markers for the early detection of AL.

Keywords: Colorectal surgery; Anastomotic leak; C-reactive protein; Colorectal neoplasms

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Introduction

The complication rate of colorectal surgery ranges from 26% to 35% (1-3). Complications may include bleeding, surgical site infections, intra-abdominal abscesses, anastomotic leaks (AL), ileus, urinary dysfunction, sexual dysfunction, intra-abdominal collections, anastomotic strictures, and stenosis, among others. AL is one of the major causes of morbidity and mortality associated with this type of surgery. The AL rate following colorectal surgery varies between 2% and 14%, while the mortality rate after AL ranges from 5% to 22% (4-10). Different authors have employed various criteria to define AL after colorectal surgery. Some have characterized it by clinical signs of peritonitis and/or clinical evidence of free fecal fluid within the abdomen or emerging from the drain site, which can be confirmed by contrast-enhanced computed tomography (CECT), or during re-exploration (11, 12). Garcia-Granero et al. classified AL as 'major' (requiring reoperation or percutaneous radiological drainage) or 'minor' (managed with conservative medical treatment) (13). AL may necessitate percutaneous intervention, re-exploration, or readmissions in up to 40% of cases, leading to increased costs and prolonged hospital stays (4, 5). Unfortunately, the clinical diagnosis of AL is often delayed due to various factors. Patient-related factors, such as immunocompromised status, clinician-related factors, including surgeons' lack of predictive accuracy for anastomotic leakage, and false-negative or non-specific radiological imaging contribute to this delay. Significant leaks can be diagnosed even after a patient has been discharged from the hospital (4, 5, 14). A delay in diagnosis may result in sepsis, multiple organ dysfunction, and even mortality. Research indicates that there is a 7.6% decrease in survival for each hour of delay in antibiotic administration (15). Early diagnosis of AL can reduce its clinical consequences through timely medical interventions, such as antibiotics, as well as radiological and surgical intervention (16).

There is a growing interest in identifying useful serum markers for the early detection of AL. Serum C-reactive protein (CRP), a negative acute phase reactant, has been identified as an early predictor of anastomotic leaks following elective colorectal procedures (17-19). It demonstrates comparable diagnostic accuracy on postoperative days (POD) 3, 4, and 5 exhibiting a useful negative predictive value; however, it is not a strong positive predictor of AL (20). Recently, some authors have demonstrated that interleukin-6 (IL-6) serves as a reliable independent early marker for postoperative sepsis or septic shock after major oncological surgery. In contrast, other studies have indicated that IL-6 is not effective in the detection of AL (21-23). Leukocyte indices, such as the neutrophil-lymphocyte ratio (NLR), are independent predictors of major surgical complications (24). Cook et al. were the first to report an association between an elevated postoperative NLR and the occurrence of surgical complications (25). A higher lymphocyte-to-monocyte ratio (LMR) may indicate a reduced likelihood of postoperative infection, thereby facilitating patient discharge. In contrast, lower LMRs may serve as an early warning for clinicians to reassess and modify the patient's management (26). The association between a decreased Platelet-to-lymphocyte ratio (PLR) and postoperative infectious complications is probably complex and remains unclear (27). Serum albumin, a negative acute phase reactant, can predict postoperative complications (28). It remains unclear whether the combination of various laboratory markers improves the accuracy of early diagnosis for postoperative complications in colorectal surgery (29, 30). This study aimed to investigate the role of serum CRP, serum albumin, leukocyte indices, and changes in serum IL-6 levels in predicting AL following colorectal surgery.

Patients and Methods

Study Design

This was a prospective observational pilot study that included 30 consecutive patients with colorectal diseases who underwent elective resectional surgery for both benign and malignant conditions in the Department of Surgical Gastroenterology, SGPGIMS Lucknow, a tertiary care teaching hospital in northern India, from April 2021 to March 2022.

After obtaining written informed consent, all patients underwent routine investigations, including complete blood counts, liver function tests, renal function tests, coagulation profiles, chest X-rays, and electrocardiogram (ECG). Serum samples for CRP and serum albumin were collected preoperatively and on POD 1, 3, and 7 as part of standard protocol. Serum samples for IL-6 were obtained preoperatively, one day before surgery, and on POD 3, and were analyzed in the Department of Clinical Immunology. All relevant clinical data—including age, sex, occupation, medical history, and family history—along with laboratory markers, radiological studies, surgical parameters, and clinical outcomes, were recorded on a predefined pro forma in a computerized database. Patients younger than 18 years, those undergoing emergency surgery, individuals with ongoing preoperative infections, inflammatory bowel disease, Koch's abdomen, or those unwilling to provide consent were excluded from the study.

An anastomotic leak is defined as the presence of feculent fluid draining from abdominal wound or drain, radiological evidence of a leak on imaging, or, in the case of laparotomy or reoperation, evidence of anatomical disruption accompanied by feculent material in the peritoneal cavity.

For analysis, patients were divided into two groups: Group 1 consisted of patients with an anastomotic leak, while group 2 included patients without an anastomotic leak. The changes in CRP, albumin

levels, leukocyte indices, and IL-6 were compared between these two groups during the preoperative period and on postoperative days 1, 3, and 7. All patients were included in both study groups and there were no dropouts.

Statistical Analysis

Data were maintained prospectively in a spreadsheet and analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM, Armonk, NY, USA). The normality of the data was assessed using the Shapiro-Wilk test. Continuous data are presented as the median and interquartile range (IQR), while categorical data are reported as frequency and percentage. The two groups were compared using the Mann–Whitney U test. The association of the categorical variable was examined using the chi-square test. Changes in markers over different time points were assessed using the Friedman test. The Wilcoxon test, with Bonferroni correction, was applied to analyze changes in inflammatory markers. Subsequently, multivariate analysis was conducted to identify significant predictors of anastomotic leaks using Firth logistic regression, as the sample size was small. Firth logistic regression reduces bias associated with small sample sizes and improves the reliability of parameter estimates by modifying the likelihood function. Statistical significance was set at a P-value of less than 0.05.

Ethical Considerations

This study was approved by the Institutional Ethical Committee, SGPGIMS Lucknow, India (IEC Code: 2021-340-MCh-EXP-44).

Results

Demographic and Clinicopathological Characteristics

Among the 30 patients, 27 (90%) were men and 3 (10%) were women. Of the patients, 27 (90%) had malignant diseases, while 3 (10%) had benign diseases. The details are illustrated in Table 1. Ten (33.3%) of the patients had associated comorbidities, which included diabetes mellitus in 5 (16.6%), hypertension in 7 (23.3%), cardiac disease in 4 (13.3%), and one patient each with chronic obstructive pulmonary disease (COPD) and hypothyroidism. The median body mass index (BMI) of the patients was 22.7 kg/m^2. The median preoperative values of hemoglobin (Hb) and albumin were 10.5 g/dL and 4.1 g/dL, respectively (Table 1).

Analysis of Inflammatory Markers

The median CRP level in the preoperative period for 30 patients was 1.03 (0.26, 2) mg/dL. This level significantly changed on POD 1 to 12.15 (9.53, 17.6) mg/dL, and on POD 3 to 13.05 (9.28, 17.8) mg/dL, and on POD 7 to 4.36 (1.87, 7.57) mg/dL. The median serum albumin level of all patients during the preoperative period was 4.15 (3.7, 4.5) g/dL, which significantly decreased in the postoperative period. The median TLC level during the preoperative period was 7.85 (5.6, 9.4) (×1000/ul). This level changed significantly only on POD 1, increasing to 9.55 (7.9, 11.4) (×1000/ul). There were no significant changes observed on POD 3, and 7. The median NLR during the preoperative period was 3.65 (2.5, 5) ul/ul and changed significantly on POD 1 to 5.3 (3.9, 7.8) ul/ul, and on POD 3 to 4.4 (3.9, 5.3) ul/ul but did not changed significantly on POD 7. LMR and PLR did not change significantly during the postoperative period among all patients. The median serum IL-6 level in the preoperative period was 9.37 (9.37, 62.5) pg/ml and increased significantly on POD 3 to 167.25 (20.5, 654) pg/ml (Tables 2 and 3).

An anastomotic leak was observed in 4 patients (13.3%) in group 1, while 26 patients (86.7%) in group 2 did not experience any anastomotic leaks.

Table 1: Demographic and Clinicopathological characteristics of the patients

Factors		Total (n=30)	No Anastomotic leak (n=26)	Anastomotic leak (n=4)	P value
Age (yrs)*		60(40,65)	62.5(41,66)	48.5(28.5,57.5)	0.099
Sex	Male	27	23(88.5%)	4(100%)	0.998
	Female	3	3(11.5%)	0(0%)	
BMI (kg/m^2)*		22.7(21,24.5)	22.7(21,24.5)	22.8(20.9,27.3)	0.625
Preop Hb (g/dl)*		10.5(9.1,12.3)	10.4(9,12)	12.3(10.5,16.9)	0.132
Preop Alb (g/dl)*		4.15(3.7,4.5)	4.1(3.6,4.5)	4.3(3.9,4.85)	0.417
Diagnosis Malignant Pathology (n=27)					
Ca Cecum		3	3(11.5%)	0(0%)	
Ca Ascending colon		8	8(30.7%)	0(0%)	
Ca Hepatic flexure		3	3(11.5%)	0(0%)	
Ca Transverse colon		1	1(3.8%)	0(0%)	
Ca Sigmoid colon**		3	2(7.7%)	1(25%)	0.291
Ca Rectum		9	9(34.6%)	0(0%)	
Benign (n=3)					
Inflammatory stricture	Ascending colon**	2	0(0%)	2(50%)	
SRUS**		1	0(0%)	1(25%)	

*Median values (Interquartile range), ** Anastomotic leak pathology, Preop Hb: Preoperative Hemoglobin, Preop Alb: Preoperative Albumin, BMI: Body Mass Index, Ca: Carcinoma, SRUS: Solitary rectal ulcer syndrome.

Table 2: Preoperative and postoperative absolute median values (IQR) of inflammatory serum markers (n=30)

Markers (n=30)	Preoperative (a)	POD 1 (b)	POD 3 (c)	POD 7 (d)	P value
CRP (mg/dl)	1.03(0.26,2)	12.15(9.53,17.6)	13.05(9.28,17.8)	4.36(1.87,7.57)	<0.001
ALB(g/dl)	4.15(3.7,4.5)	3.15(2.9,3.6)	3.3(3,3.4)	3.5(3.1,3.6)	Non-significant
TLC(×1000/ul)	7.85(5.6,9.4)	9.55(7.9,11.4)	8.35(6.4,10.7)	8.4(6.4,9.45)	0.001
NLR (ul/ul)	3.65(2.5,5)	5.3(3.9,7.8)	4.4(3.9,5.3)	4.2(3.3,5.9)	0.003
LMR (ul/ul)	9.5(7.7,12.7)	7.5(4,11)	8.5(5,10)	6.7(4,14)	0.08
PLR (cmm/ul)	175.88 (103.42,204.4)	163.69 (106.38,313.54)	177.26 (117.45,229.79)	223.96 (166.34,320.51)	0.062
IL6 (pg/ml)	9.37 (9.37,62.5)		167.25(20.5,654)		0.003

Friedman test; CRP: C-reactive protein, TLC: Total leucocyte count, NLR: Neutrophil Lymphocyte ratio, LMR: Lymphocyte monocyte ratio, PLR: Platelet Lymphocyte ratio, IL-6: Interleukin -6, ALB: Albumin, Sig: Significant change

Table 3: Post-hoc analysis: Wilcoxon test to compare changes of inflammatory markers at different time points

Marker	Preop (0)-POD	No Anastomosis leak (median (IQR))	Anastomosis leak present (median (IQR))	P value	P value*
CRP	0-1	10.96(7.67,14.83)	19.03(6.25,27.52)	0.359	<0.001
	0-3	10.05(7.61,14.11)	28.82(22.54,35.66)	<0.001	
	0-7	2.9(0.64,4.31)	14.1(11.27,34.66)	0.009	
ALB	0-1	-0.9(-1.3,-0.7)	-0.6(-1.15,-0.35)	0.392	0.489
	0-3	-0.9(-1.2,-0.6)	-0.75(-1.65,-0.55)	0.826	
	0-7	-0.6(-0.8,-0.4)	-1.1(-2.5,-0.3)	0.284	
TLC	0-1	1.9(-0.1,3.7)	3.45(2.25,6.45)	0.172	0.109
	0-3	0.7(-0.5,1.9)	1.45(-2.45,8.15)	0.735	
	0-7	0.2(-1.5,1.8)	2.4(1.3,5.7)	0.108	
NLR	0-1	1.35(0.7,3.8)	0.5(0.25,14.9)	0.545	0.014
	0-3	0.45(-0.4,1.7)	6.15(3.9,6.8)	0.007	
	0-7	0.6(-1.8,2.5)	1.8(0.5,4.3)	0.435	
LMR	0-1	-4(-7.5,1)	0.65(-3.15,5.65)	0.265	0.528
	0-3	-2.1(-4,2.6)	-1.35(-4.85,0.35)	0.967	
	0-7	-0.5(-7.8,8)	-4.8(-5.7,-2.6)	0.462	
PLR	0-1	12.69(-54.65,100.06)	3.23(-126.67,178.33)	0.93	0.049
	0-3	-17.08(-61.9,21.52)	134.57(-32.62,172.6)	0.177	
	0-7	67.22(19.05,135.32)	-39.65(-188.47,-21.79)	0.045	
IL-6	0-3	34.57(0,470)	877.57(509.82,930.57)	0.021	0.016

*P value after Bonferroni correction

All 4 patients in group 1 required re-exploration. There were no statistically significant differences in the preoperative absolute median values of serum CRP levels, serum albumin levels, total leukocyte count, NLR, LMR, PLR, and serum IL-6 levels between the anastomotic leak group and the no anastomotic leak group. Serum CRP levels were significantly elevated on POD 3 (29.9 (24.05, 35.75)) (P=0.001) and on POD 7 (15.1 (13.3, 34.7)) (P=0.009) in patients with an anastomotic leak compared to those without an anastomotic leak. The TLC increased significantly on POD 7, with a median value of 10.2 (9.2, 10.4) (P=0.047) in the anastomotic leak group. The NLR significantly increased on POD 3, with a median value of 9.8 (7.55, 9.9) (P=0.009) in the anastomotic leak group, but did not show significant changes on POD 1 and 7. There was no significant change in LMR between the groups. However, PLR significantly decreased on POD 7, reaching a median value of 86.51 (69.02, 182.69) (P=0.029) in the anastomotic leak group. Serum IL-6 levels significantly increased in the anastomotic leak group on POD 3, with a median value of 904 (536.25, 950.75) (P=0.03) (Table 4, Figure 1). In a multivariate analysis using Firth logistic regression, serum CRP on POD 3 showed an 8% increase (OR=1.085, 95% CI=0.81-1.44), while the NLR on POD3 demonstrated a 28% increase (OR=1.284, 95% CI=0.85-3.60) in group 1 patients and POD3 IL-6 levels showed no significant effect (Table 5). The presentation, investigation, and management of group 1 patients are detailed in Table 6.

Discussion

In our study, we prospectively analyzed various serum markers for their role in predicting anastomotic leaks during the early postoperative period. Our findings revealed a statistically significant change in the absolute median values of serum CRP, serum albumin, TLC, NLR and serum IL-6 in the postoperative period compared to preoperative values after colorectal resection and anastomosis in all patients. The anastomotic leak rate in our study was 13.3%, which is comparable to the rates reported in the literature (6, 7).

Table 4: Comparison of inflammatory markers between anastomotic leak group and non-anastomotic leak group

Inflammatory Markers	Anastomotic leak		P value
	No (median (IQR))	Yes (median (IQR))	
Preop CRP	1.17(0.29,2)	0.57(0.09,1.52)	0.324
POD1 CRP	11.95(9.53,16.8)	19.6(6.77,28.6)	0.355
POD3 CRP	11.5(8.66,15.4)	29.9(24.05,35.75)	0.001
POD7 CRP	3.97(1.84,5.36)	15.1(13.3,34.7)	0.009
Preop ALB	4.1(3.6,4.5)	4.3(3.9,4.85)	0.417
POD1 ALB	3.1(2.9,3.3)	3.6(3.55,3.7)	0.027
POD 3 ALB	3.3(3,3.4)	3.35(2.95,3.6)	0.598
POD 7 ALB	3.5(3.1,3.7)	3(2.7,3.4)	0.074
PREOP TLC	7.8(5.6,9.9)	7.85(6.25,8.55)	0.736
POD1 TLC	9.45(7.8,11.2)	11.3(10.8,12.7)	0.059
POD 3 TLC	8.35(6.4,10.6)	9.3(6.05,14.45)	0.488
POD7 TLC	8.2(6.3,9.3)	10.2(9.2,10.4)	0.047
PREOP NLR	3.8(2.5,6.5)	3.2(3,3.75)	0.714
POD1 NLR	5.35(4.3,7.8)	4.1(3.7,18.2)	0.565
POD3 NLR	4.3(3.8,5.3)	9.8(7.55,9.9)	0.009
POD7 NLR	4.2(3.2,5.9)	4.6(3.7,8.6)	0.646
PREOP LMR	10(7,13)	8.65(8,10.25)	0.695
POD1 LMR	7.4(4,11)	10.25(6.5,14.25)	0.527
POD3 LMR	8.5(5,15)	7(4.75,9)	0.274
POD 7 LMR	7.75(4,17)	5.7(3.3,6.7)	0.381
PREOP PLR	182.2(110.27,204.42)	113.41(95.74,248.66)	0.498
POD 1 PLR	195.2(108.16,313.54)	113.81(98.97,297.09)	0.498
POD 3 PLR	161.8(112.13,207.89)	243.05(198.37,286.01)	0.061
POD 7 PLR	243.02(171.4,344.32)	86.51(69.02,182.69)	0.029
PREOP IL 6	9.37(9.37,80)	20.18(9.37,37.25)	0.866
POD 3 IL6	109.75(9.37,532)	904(536.25,950.75)	0.03

Mann Whitney U test; CRP: C-reactive protein, ALB: Albumin, TLC: Total leucocyte count, NLR: Neutrophil Lymphocyte ratio, LMR: Lymphocyte Monocyte ratio, PLR: Platelet Lymphocyte ratio, IL-6: Interleukin-6

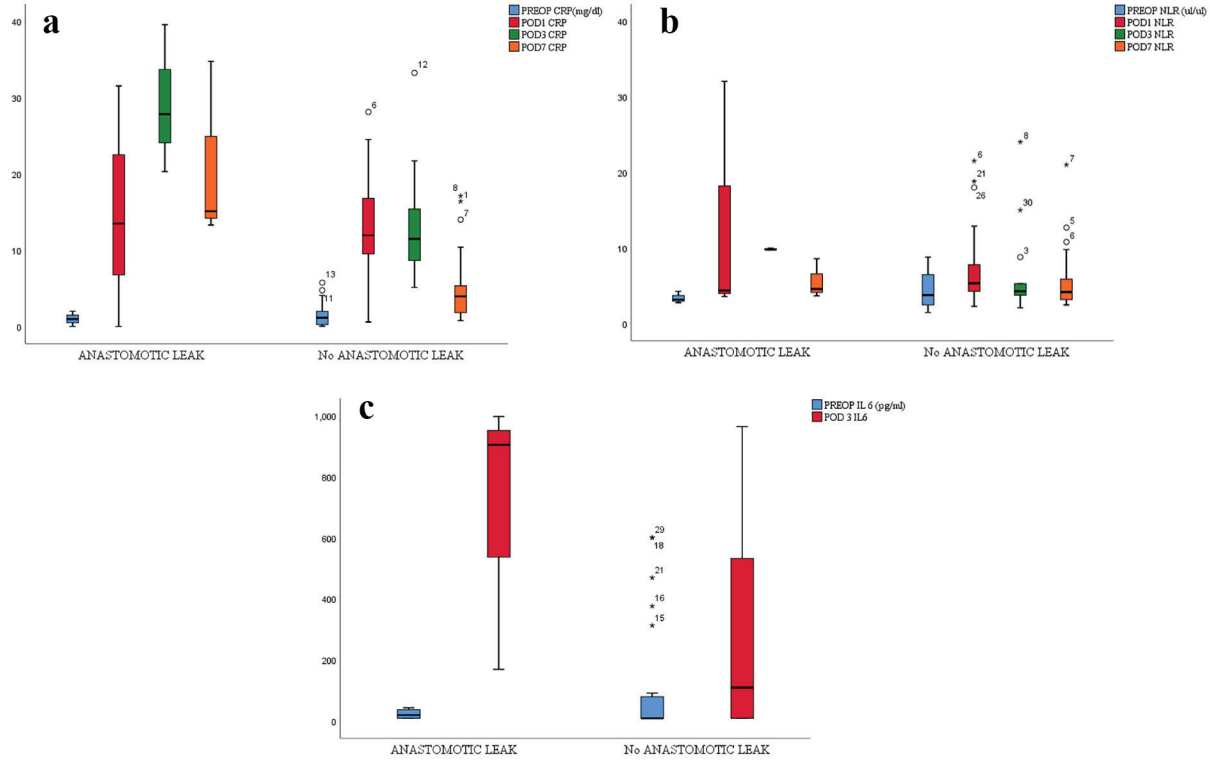

Figure 1: Box and Whiskers plot comparing inflammatory markers between the anastomotic leak group and the non-anastomotic leak group, which showed significant differences (P<0.05) on POD 3: (a) C-Reactive Protein (CRP), (b) neutrophil-to-lymphocyte ratio (NLR), and (c) Interleukin (IL-6)

Table 5: Comparison of inflammatory markers between anastomotic leak and no Leak adjusting demographic factors.

Variable	OR	95% C.I.		P value
		Lower	Upper	
POD3CRP	1.085	0.814	1.442	0.428
POD7CRP	0.986	0.675	1.455	0.927
POD7TLC	1.288	0.571	3.099	0.318
POD3NLR	1.284	0.855	3.600	0.231
POD7NLR	1.175	0.602	3.456	0.609
POD7PLR	0.997	0.973	1.011	0.633
POD3IL6	1.000	0.993	1.006	0.997

Multivariate analysis: Firth logistic regression; CRP: C-reactive protein, ALB: Albumin, TLC: Total leucocyte count, NLR: Neutrophil Lymphocyte ratio, PLR: Platelet Lymphocyte ratio, IL-6: Interleukin-6

Table 6: Details of patients with anastomotic leak, presentation and management

No.	Diagnosis	Surgery	Clinical Presentation	Imaging	Treatment	Outcome
1.	Sigmoid Colon Adenocarcinoma	Laparoscopic-Assisted sigmoidectomy with colorectal anastomosis	POD 4: Feculent content in drain. Tachycardia, Tachypnoea, fever, Leukocytosis	CECT Abdomen	Re-exploration, Repair anastomotic site disruption Diversion ileostomy	Recovered
2.	SRUS	Open Ultra Low anterior resection with Covering loop Ileostomy	POD 5: Turbid and haemorrhagic output in drain. Tachycardia, Tachypnoea, fever, Leukocytosis	CECT Abdomen	Percutaneous drainage of pelvic collection, Re-exploration and lavage, Per rectal catheter drainage	Recovered
3.	Ascending Colon Ischemic Stricture	Laparoscopic-assisted right hemicolectomy and Ileo-transverse anastomosis	POD 3: Enteric content in drain. Fever, hemodynamic instability. Leukocytosis	CECT Abdomen	Re-exploration, repair of staple line and diversion loop ileostomy	Mortality (septic shock, MODS, Atrial Fibrillation)
4.	Ascending Colon Inflammatory Stricture	Laparoscopic-assisted right hemicolectomy and ileo-transverse anastomosis	POD 6: Purulent content in drain. Fever, Tachycardia, leukocytosis	CECT Abdomen	Re-exploration, repair of staple line and diversion loop ileostomy	Recovered

SRUS: Solitary rectal ulcer syndrome, POD: postoperative day, MODS: multiple organ dysfunction syndrome, CECT: contrast-enhanced computed tomography

Table 7: Serum markers and their significance in anastomotic leaks: a review of published studies

Studies	Sample Size	Type of Study	Markers	POD	P value
Facy et al.[29] 2016	501	Prospective	CRP	4	<0.0001
Paliogiannis et al.[33] 2020	1432	Retrospective	NLR PLR	4 4	<0.0001 <0.0001
Kuru et al.[35] 2021.	40	Retrospective	Albumin	3 4	0.028 0.045
Slavin et al.[36] 2022	92	Retrospective	CRP	3 4 5	0.000 0.001 0.004
Present Study	30	Prospective	CRP NLR IL-6	3 3 3	0.001 0.009 0.03

CRP: C-reactive protein, NLR: neutrophil-to-lymphocyte ratio, PLR: Platelet Lymphocyte ratio, IL-6: Interleukin -6, CECT: contrast-enhanced computed tomography

The various biological markers investigated for predicting an anastomotic leak are not included in the recommendations or guidelines for routine measurement in colorectal surgery. Furthermore, most of the earlier studies were retrospective (Table 7).

Preoperative absolute median serum CRP levels were similar between both groups; however, levels were significantly higher in the anastomotic leak group on POD 3 and 7. Pablo et al. also demonstrated a significant change in serum CRP levels on POD

4 in patients with an anastomotic leak. In contrast, Messias et al. did not observe any statistically significant change in serum CRP levels on POD 3 (18, 30). Our study demonstrated that a serum CRP value greater than 19.15 mg/dL on POD 3 is significant. Similarly, Zaher et al. found that a serum CRP value exceeding 11.41 mg/dL on POD 3 exhibited 85.2% specificity with a negative predictive value (NPV) of 97.5% (31). The higher CRP value of significance observed in our study may be attributed to the smaller sample size (30 patients compared to 205 patients in Zaher et al.'s study).

Serum albumin levels typically decrease following major surgery. This decline is attributed to increased vascular permeability and the redistribution of albumin into extravascular compartments as a result of surgical stress, protein loss due to hemorrhage during the procedure, and perioperative fluid overload. We also found that serum albumin levels significantly decreased in the postoperative period following colorectal resection and anastomosis. However, on POD 3 and 7, there was no significant reduction in serum albumin levels in the anastomotic leak group in our study. This contrasts with most studies in the literature, which have reported a significant decrease in the postoperative period for patients with anastomotic leaks (32). We attribute this finding to the smaller sample size of patients in the anastomotic leak group (n=4) in our study.

Leukocyte indices, such as NLR, significantly increased on POD 3 in patients with anastomotic leaks, while the LMR and PLR showed no change during the early postoperative period. An NLR greater than 9.5 on POD 3 was observed. Paliogiannis et al. showed that NLR significantly increased on POD 1 and POD 4 in patients with anastomotic leaks (33). The NLR can be routinely assessed in the early postoperative days to predict anastomotic leaks.

Serum IL-6 levels changed significantly during the postoperative period, with a significant increase observed on POD 3 in patients with anastomotic leaks. However, Zawadzki et al. reported a specificity of 74% for serum IL-6 levels on POD 3 in relation to anastomotic leaks (P=0.024) (34).

Earlier published studies (Table 7) have reported the significance of various serological markers; however, they typically focused on only one, two, or three markers, and most were retrospective in nature. Our study had a small sample size due to the COVID-19 waves that occurred during the research period, which resulted in a reduced number of patients presenting to the hospital. Despite being a prospective study evaluating seven markers, the limited sample size may affect the generalizability of our findings. In contrast, a prospective study by Facy et al. (Table 7) had a larger sample size, as it was a multicenter observational study; however, it only examined two markers (CRP and procalcitonin) and found CRP to be more accurate (29).

Conclusion

There was a significant change observed in the serum levels of CRP, albumin, TLC, NLR, and IL-6 in the postoperative period compared to preoperative values in all patients. Serum levels of CRP, NLR, and IL-6 on POD 3, were significantly associated with anastomotic leaks and may serve as early predictive serum markers for this complication. Despite the widespread adoption of fast-track protocols for colorectal surgery, there remains a potential disadvantage: the delayed diagnosis of anastomotic leaks. Serum markers may assist in ruling out an anastomotic leak during the early postoperative period, thereby facilitating the timely discharge of the patient from the hospital. This pilot study conducted in India suggests the need for further research in a clinical trial setting with a larger sample size to evaluate various inflammatory markers and identify their definitive roles in the postoperative period following colorectal anastomosis. The ultimate goal would be to incorporate these markers into routine investigations during the postoperative period at various time points.

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Authors' Contribution

Conceptualization: A.K.; Writing of the original draft: R.B.; Writing, reviewing, and editing: A.K., V.A. All authors participated in data acquisition, data analysis, and data interpretation. All authors approved the final version.

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