

Role of C-Reactive Protein (CRP) in the Prediction of Anastomotic Leakage Following Gastrointestinal Surgery

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Abstract: Anastomotic leak following gastrointestinal surgery is the most serious postoperative complication.¹ Anastomotic leakage was defined clinically by peritonitis resulting from the leakage, with signs of acute abdomen (fever, sepsis, pain abdomen), and suspicious quality or fecal discharge from drain wound is present.² Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery.³ Routine imaging is neither reliable nor cost-effective for the detection of leaks and it carries the drawback of radiation. A serum marker would have great advantages provided that it is cost-effective and sensitive enough to allow safe discharge of the patient.⁴ C-reactive protein (CRP) has been used for the diagnosis of intra-abdominal surgical infection, as a general marker of an unfavorable postoperative course including surgical and non surgical complication.⁵⁻⁷ Anastomotic leakage increases the duration of in-hospital stay, the risk of reoperation and also can lead to a fatal outcome. Systemic inflammation markers, including C-reactive protein (CRP) and white cell count, have been reported to provide early detection. However, their relative predictive value is unclear. The median normal concentration of CRP is 0.8mg/l, with 90% of apparently healthy individual having value less than 3mg/l and 99% less than 12mg/l. So, the reference range for CRP is: 0-10 mg/l.⁸ C-reactive protein greater than 14 mg/l is sensitive and specific marker for anastomotic leak. C-reactive protein (CRP) test is done to check for infection after surgery. CRP levels normally rise within 2 to 6 hours of surgery and then go down by the third day after surgery. If CRP levels stay elevated 3 days after surgery, an infection may be present. Normal CRP values vary from lab to lab. Generally, there is no CRP detectable in the blood or there is little CRP in blood serum. The normal level of CRP is less than 10 mg/dl, and patient who have elevation greater than 150 mg/dl, usually have severe disease. C-reactive protein (CRP) is an acute phase protein synthesized by the liver, which levels raise in response to inflammation.⁹ It is a member of the pentraxin family of proteins.¹⁰ Human serum contains two pentraxins, c-reactive protein (CRP) and serum amyloid p component (SAP), are located on the proximal long arm of chromosome 1.¹¹ C-reactive protein was the first pattern recognition receptor (PRR) to be identified.¹⁰ It has 224 amino acids,¹¹ has a monomer molecular mass of 25106 Da, The most striking difference between CRP and SAP is manifested during the acute phase response to inflammation. Whereas human SAP is expressed constitutively at relatively constant serum levels, C-reactive protein increases in concentration by up to 1000-fold in response to an inflammatory stimulus. C-reactive protein originally identified as a component present in the plasma of patients with acute infections, binds to the c-polysaccharide of streptococcus pneumoniae. Subsequently, it has been shown to have several immune related activities, for opsonisation of bacterial cell surfaces and activation of complement and to act as a scavenger for chromatin released by dead cells during inflammatory episodes. It plays a role in innate immunity as an early defense system against infections. CRP rises within two hours of the onset of inflammation, up to a 50,000-fold, and peaks at 48 hours. Its half-life of 48 hours is constant, and therefore its level is determined by the rate of production and hence the severity of the precipitating cause. CRP is thus a screen for inflammation. CRP is used mainly as a marker of inflammation. Apart from liver failure, there are few known factors that interfere with CRP production.² Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments. ELISA, immunoturbidimetry, rapid immunodiffusion and visual agglutination are all methods used to measure CRP. A high-sensitivity CRP (hs-CRP) test measures low levels of CRP using laser nephelometry. The test gives results in 25 minutes with sensitivity down to 0.04 mg/L. CRP is not diagnostic of any condition, but it can be used together with signs and symptoms and other tests to evaluate an individual for an acute or chronic inflammatory condition. CRP is a more sensitive and accurate reflection of the acute phase response than the ESR (Erythrocyte Sedimentation Rate).¹² ESR may be normal and CRP elevated. CRP returns to normal more quickly than ESR in response to therapy. Some medications - such as birth control pills; statins; nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (Advil, Motrin, others); and acetaminophen (Tylenol, others) — can affect your CRP level. Normal concentration in healthy human serum is usually lower than 10 mg/L, slightly increasing with aging. Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns(>200 mg/L).¹³ Due to its short half-life (19 h), CRP is a reliable marker of systemic inflammatory response secondary to the surgical procedure or even a marker of complications, tending to normalize rapidly with the patient's recovery.¹⁴⁻¹⁵

Keywords: Anastomotic leak, C-reactive protein, Systemic inflammation markers, pentraxin, serum amyloid p component, pattern recognition receptor, opsonisation, immunoturbidimetry, rapid immunodiffusion, visual agglutination

1. Aims and Objectives

1) To determine the reliability of C - reactive protein in predicting anastomotic leak following gastro-intestinal surgery.

2) To determine the efficacy of CRP in predicting early discharge and decreased length of hospital stay and hence overall cost.

2. Method

A study will be conducted on 54 patients admitted in Rajendra Institute of Medical Sciences (RIMS), Ranchi from October 2013 to October 2014 and underwent surgery with primary gastro-intestinal anastomosis for whatsoever cause, either as elective or emergency cases. Serum C-reactive protein was measured preoperatively to have a baseline value in all cases; and then measured postoperative on alternate day starting from day one, and onwards till 5th day. We assigned cases to one of two groups according to the presence or absence of anastomotic leakage: with anastomotic leakage (Group A, n = 6), without anastomotic leakage (Group B, n= 48). The two groups were compared according to the mean values of serum CRP in the pre and postoperative period.

Serums CRP up to 1.0 mg/L are considered normal value in our study.

Inclusion criteria- All surgical cases with primary gastro intestinal anastomosis (Elective and Emergency)

Exclusion criteria- Presence of a defunctioning stoma

The following Protocols was followed-

Post operative patients were monitored every day. Signs of peritonitis were looked for; pulse, BP, temperature and urine output was recorded. These data was correlated with C - reactive protein. A relationship with anastomotic leak, suggested by signs of peritonitis and deranged vitals was established.

If there were any signs suggestive of peritonitis and leakage found we did ultrasonography of the abdomen and correlated with them. A plan of further management decided upon presence or absence of leak

3. Observations

Case Details

CASE No.-
 anastomosis-
 Type of case -
 Name of patient-
 Reg. No & Add. -
 Age / Sex -

Pre-op

Temp(°C)	PR(min)	BP(mm Hg)	U/O(ml)	CRP(mg/Lt)

Clinical course -

Post-op Day 01-

Temp(°C)	PR(min)	BP(mm Hg)	U/O(ml)	CRP(mg/Lt)

Clinical course -

Post-op Day 03-

Temp(°C)	PR(min)	BP(mm Hg)	U/O(ml)	CRP(mg/Lt)

Clinical course -

Post-op Day 05-

Temp(°C)	PR(min)	BP(mm Hg)	U/O(ml)	CRP(mg/Lt)

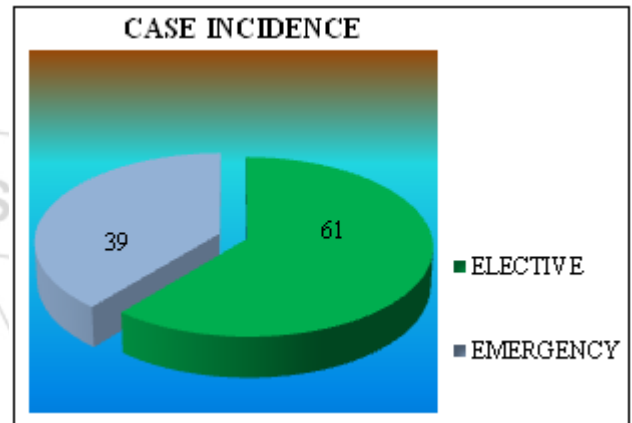
Clinical course -

USG Finding -

Plan of M/m -

Table 1: Case Incidence

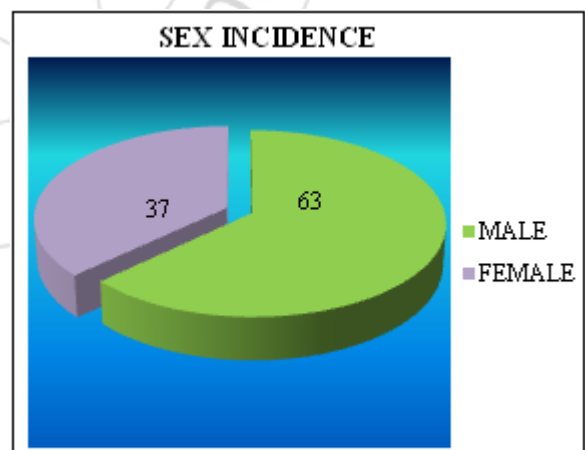
Type of Case	No. of Cases	Percentage (%)
Elective	33	61
Emergency	21	39
Total	54	100



Graph 1: Case Incidence

Table 2: Sex incidence

Sex	No. of Cases	Percentage (%)
Male	34	63
Female	20	37
Total	54	100

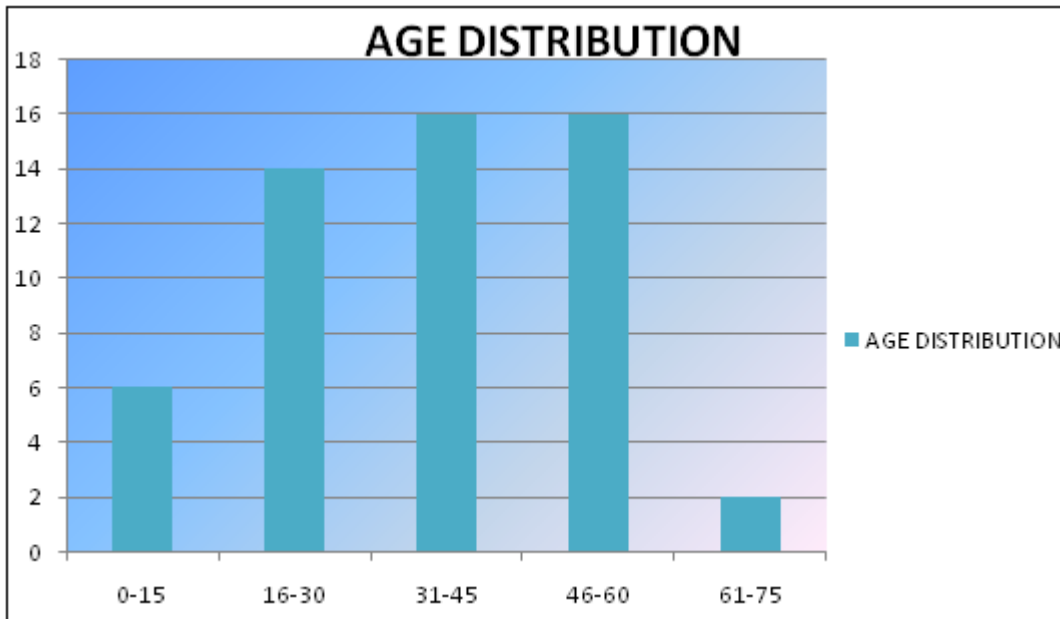


Graph 2: Sex incidence

Table 3: Age Distribution

Age Group	No. of Patients
0-15	6
16-30	14
31-45	16
46-60	16
61-75	2
TOTAL	54

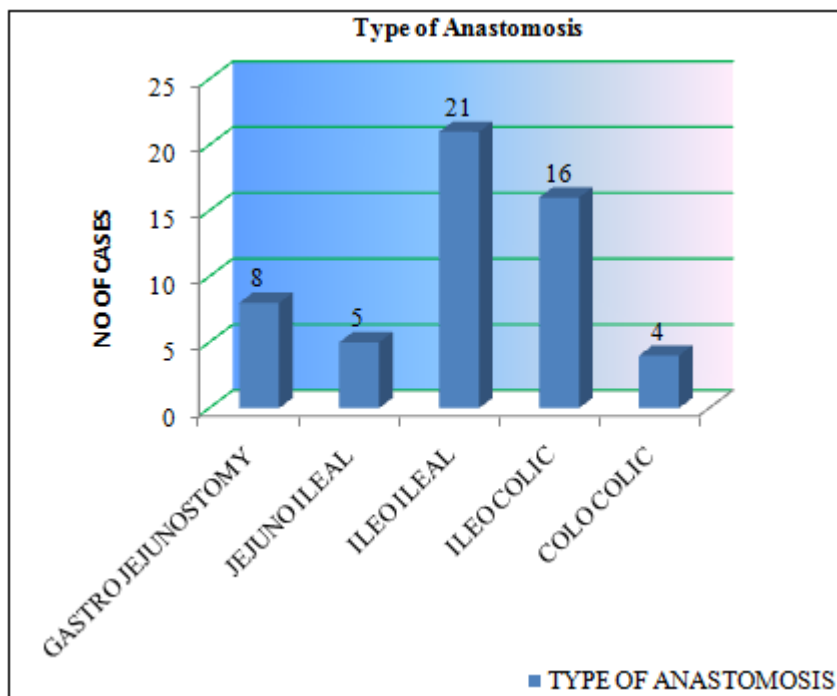
Mean age- 40 years



Graph 3: Age Distribution

Table 4: Type of Anastomosis

Type of Anastomosis	No. of Cases	Percentage
Gastro jejunostomy	08	15
Jejuno ileal	05	09
Ileo ileal	21	39
Ileo colic	16	30
Colo colic	04	07
Total	54	100



Graph 4: Type of Anastomosis

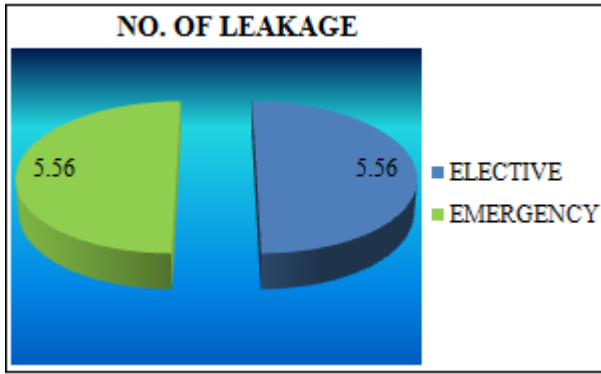
Table 5: No. of anastomotic leak in relation with site of anastomosis

Type of Anastomosis	Number of Leak
Gastrojejunostomy	0
Jejunoileal	1
Ileoileal	4
Ileocolic	1
Colocolic	0

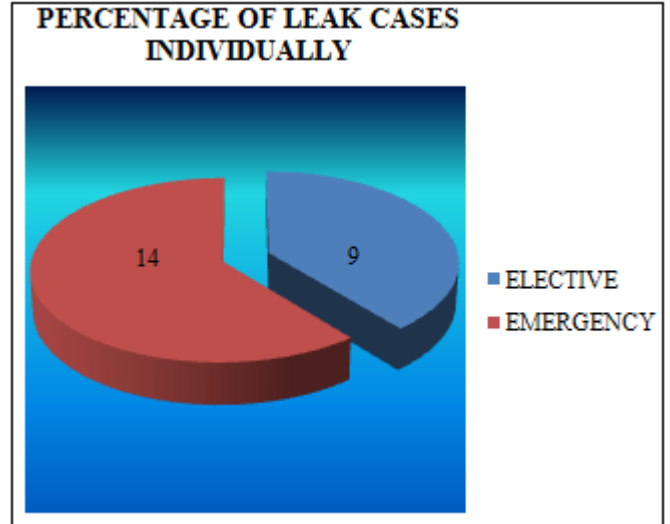
Male – 04, Female -02
 Mean age – 37 years

Table 6: No. of cases leak in total

Type of Case	No. of Cases Leak	Percentage (%)
Elective	03	5.56
Emergency	03	5.56
Total	06	11.12



Graph 5: No. of leak cases in total



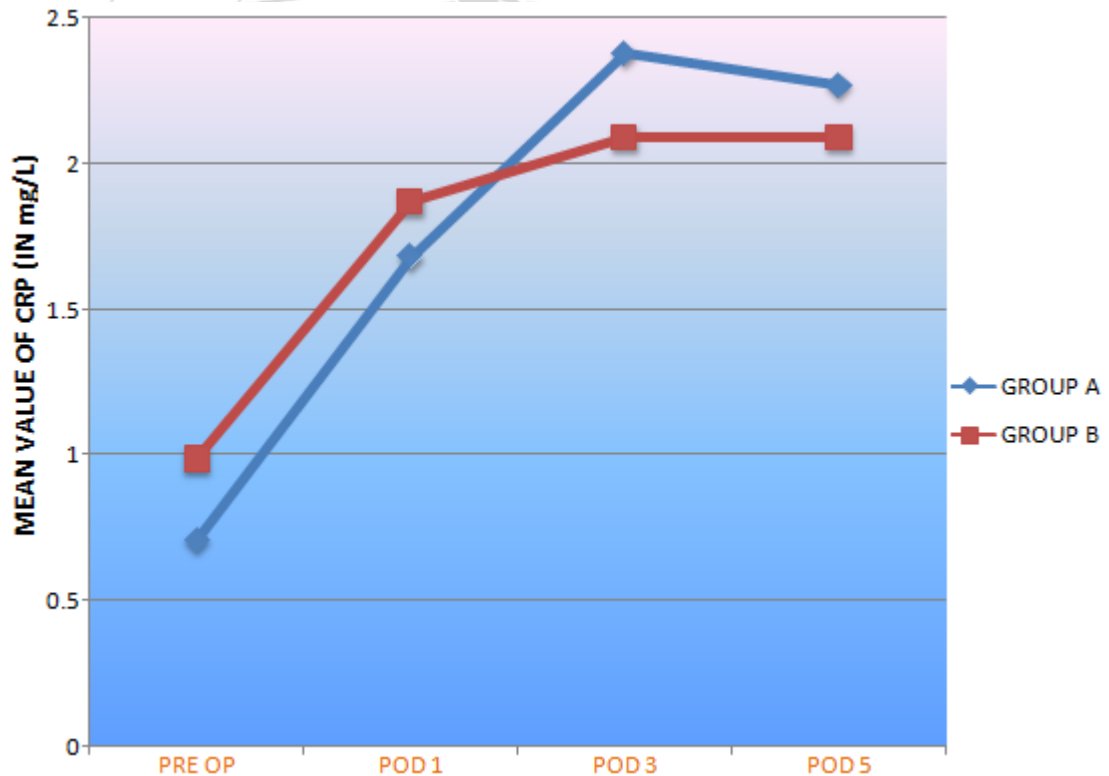
Graph 6: Percentage of leak cases individually

Table 7: No. of cases leak individually (elective and emergency)

Type of Case	No. of Cases	No. of Leak Cases	Percentage (%)
Elective	33	3	9
Emergency	21	3	14
Total	54	6	11

Table 8: Mean values of CRP (mg/l) in the pre- and postoperative periods in total cases. (Group A – with leakage; Group B – without leakage)

CRP (mg/L)	No of Cases	Pre	POD 1	POD 3	POD 5
Group A	6	0.71	1.68	2.38	2.27
Group B	48	0.99	1.87	2.09	2.09
Total	54				

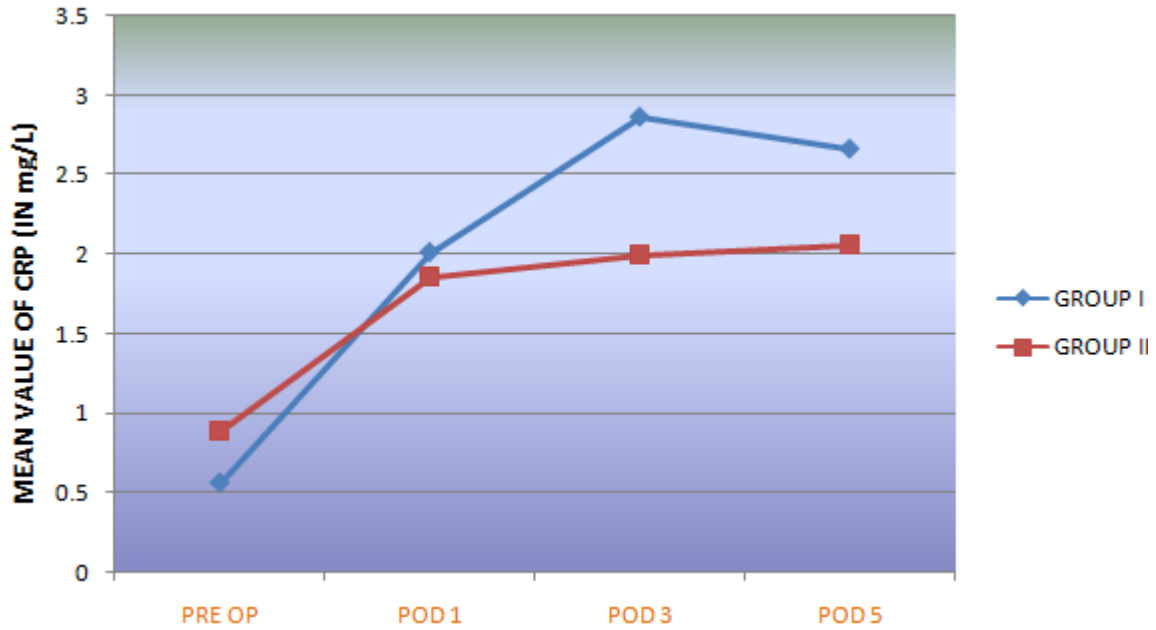


Graph 7: Mean value of CRP in (mg/l) in Total cases

Table 9: Mean values of CRP (mg/l) in the pre- and postoperative periods in Elective cases (Group I – with leakage; Group II – without leakage)

Group	No. of Cases	PRE OP	POD 1	POD 3	POD 5
Group I	03	0.56	2.01	2.86	2.66
Group II	30	0.89	1.86	2.0	2.06
Total	33				

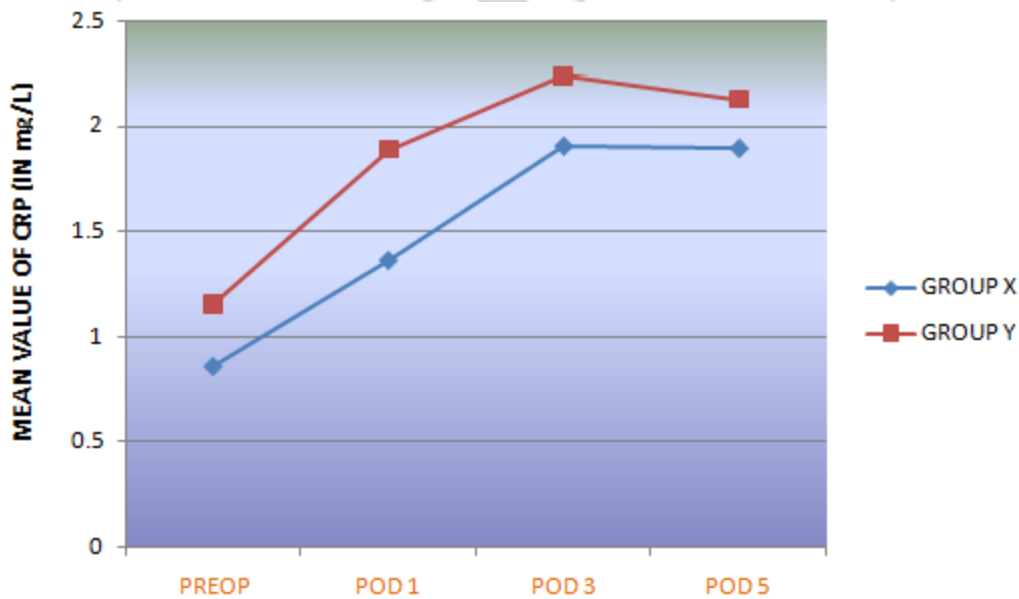
CRP (mg/L)	No. of Cases	PRE OP	POD 1	POD 3	POD 5
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Graph 8: Mean value of CRP in (mg/l) in Elective case

Table 10: Mean values of CRP (mg/l) in the postoperative periods in Emergency cases (Group X – with leakage; Group Y – without leakage)

CRP (mg/L)	No. of Cases	PREOP	POD 1	POD 3	POD 5
Group X	03	0.86	1.36	1.90	1.89
Group Y	18	1.15	1.89	2.24	2.13
Total	21				



Graph 9: Mean value of CRP in (mg/l) in Emergency cases

Table 10: Various Ultrasonography finding in leak cases

S. No.	Usg Finding	No. of Cases
1	Interseptate collection	1
2	Pelvic collection	2
3	Interseptate collection with pelvic collection	1
4	Ascitis	2

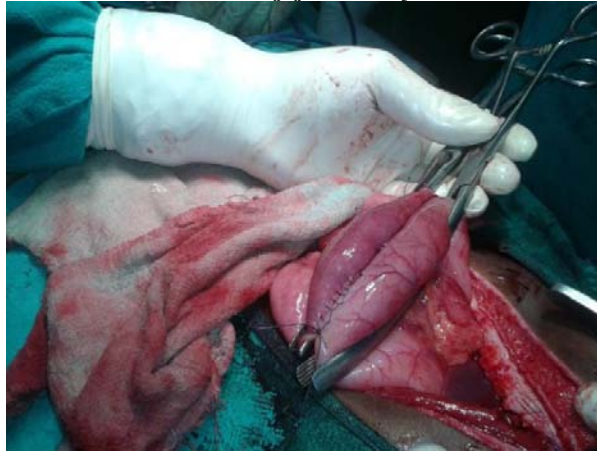
Mean hospital stay of patients without leak- 7 days
 Mean hospital stay of patients with leak- 11 days

4. Photographs Showing Various Types Of Anastomosis

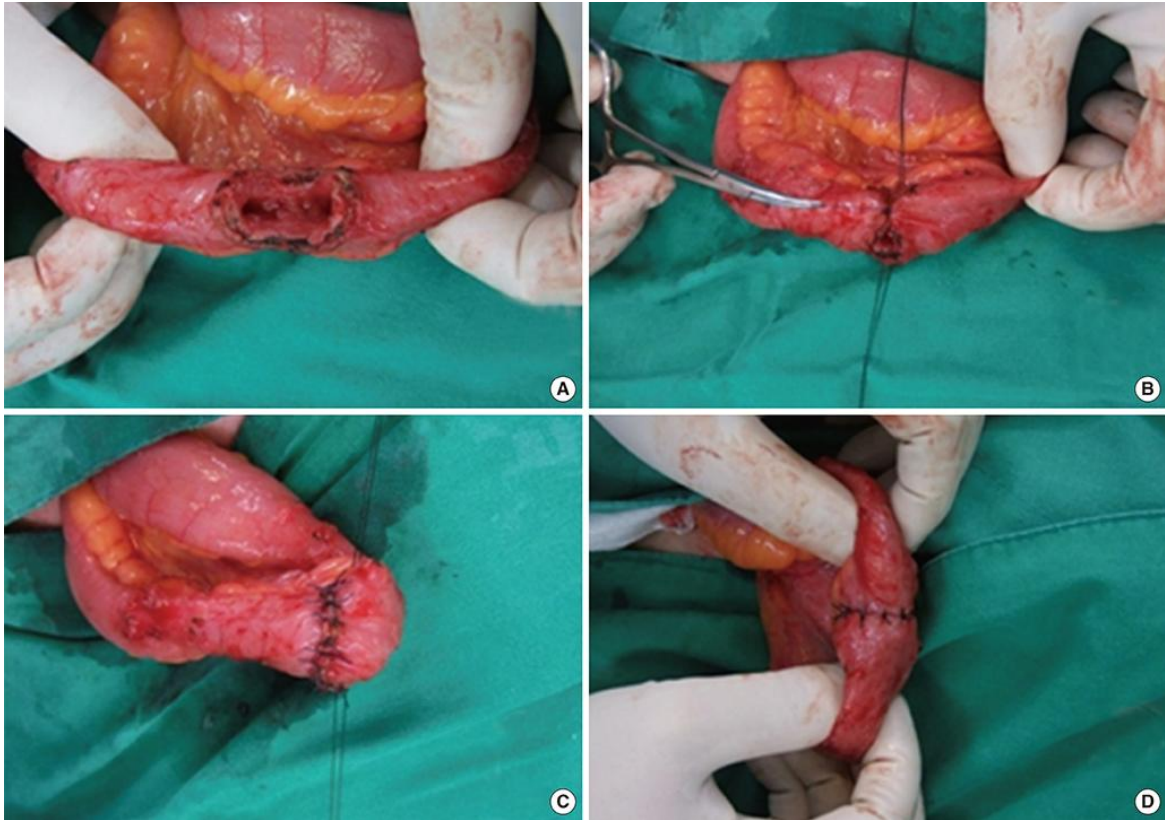
Table 11: Management given in leak cases

S. No.	Management	No. of Cases
1	Conservative	5
2	Temporary stoma	1

Gastrojejunostomy

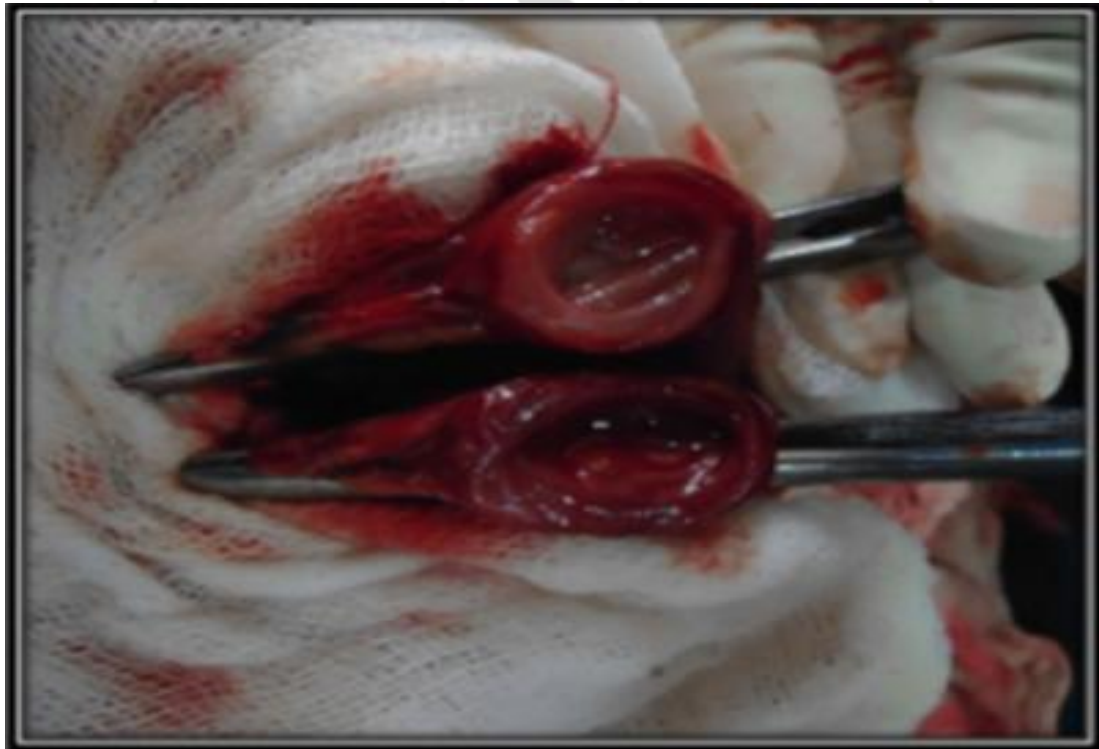


Jejunoleal Anastomosis



Ileostomy Closure

Ileileal Anastomosis





Ileocolic Anastomosis



Colocolic Anastomosis

5. Results

A total of 54 patients underwent resection and anastomosis during the study period (oct.2013-oct.2014). Mean age was 40 years. Among 54 patients 34 (63%) are male and 20 (37%) are female. In this study we included 33 cases as elective and 21 cases as emergency. Leaks developed in 6 patients (11%), including 4 males and 2 females. The mean age of patients with a leak was 37 years. The leak percentage was high in emergency cases (14) than in elective cases (9). The leak rate was markedly increased in ileoileal anastomosis (4 cases).

Mean values of CRP (mg/l) in the pre- and postoperative periods was higher in patients with leakage than in patients without leakage. Mean CRP was markedly increased from Preop to POD 1 and onwards (POD 3 and POD 5) in leaked cases, whereas mean CRP is moderately increased from Preop to POD 3 and then onwards POD (POD 5), CRP was either static or decreased in without leak cases.

After diagnosed by clinical suspicion and ultrasonography, 1 patient required fecal diversion by ileostomy, whereas 5 patients were managed non operatively.

Patients without leak were discharged earlier from hospital than patients with leak.

Mean hospital stay was longer for leaked patients (11 days) as compared to patients without leak (7 days).

6. Discussion

Some medications - such as birth control pills; statins; nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (Advil, Motrin, others); and acetaminophen (Tylenol, others) — can affect your CRP level.

Normal concentration in healthy human serum is usually lower than 10 mg/L, slightly increasing with aging. Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns(>200 mg/L).

Due to its short half-life (19 h), CRP is a reliable marker of systemic inflammatory response secondary to the surgical procedure or even a marker of complications, tending to normalize rapidly with the patient's recovery. Together with clinical signs and other inflammatory markers, CRP has been evaluated as an indicator of an unfavorable postoperative course, including surgical and non-surgical complications.

C-reactive protein (CRP) test is done to check for infection after surgery. CRP levels normally rise within 2 to 6 hours of surgery and then go down by the third day after surgery. If CRP levels stay elevated 3 days after surgery, an infection may be present.

In this series, we observed that from the first postoperative day onwards, mean serum CRP was significantly higher in the group who developed leakage, and this marker remained elevated until the diagnosis of the complication. These results are consistent with others recently published and seem to suggest that the early and sustained elevation of postoperative serum CRP may be used as a predictor of anastomotic leakage in patients in whom other infectious complications (respiratory, urinary tract and surgical wound infections) could be excluded.

C-reactive protein at postoperative days 3 and 5 was a good predictor of anastomotic leak and other postoperative septic complications, showing the highest accuracy among clinical and laboratory data.

The changes observed in postoperative CRP levels in patients who developed leakage demonstrate the presence of an inflammatory process and the activation of hepatic synthesis of CRP immediately after the surgical procedure (and before the occurrence of clinical manifestations). As the synthesis of this inflammatory marker is dependent only on the liver function and not compromised by any other organ failure, the rate of CRP production actually reflects the intensity of the inflammatory process.

In this study, CRP increases in both type of cases (elective and emergency) from their preoperative value to onwards postoperative days 3 and then decreases gradually.

The increase of CRP was marked in leak cases than in cases without leak upto 3rd POD then there was nothing significant difference in value of CRP in both group of cases (cases with leak and cases without leak).

7. Conclusion

This study shows that C-reactive protein does increase in cases of anastomotic leakage, but not marked difference was found in mean value of CRP in both group of cases (patients with anastomotic leak and patients without anastomotic

leak). Hence, it is not a reliable predictor/indicator of impending anastomotic leak. Therefore only on the basis of value of CRP we can't decide management of patient and also early discharge or further hospital stay. CRP value can be used in conjunction with other clinical parameters for management of patient.

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