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C-Reactive Protein Trajectory Predicts Anastomotic Leak In Gastro Intestinal Surgery

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ABSTRACT

Objective: To determine c-reactive protein (CRP) trajectory prediction anastomotic leak in gastrointestinal surgery.
Study Design: Cross Sectional Study
Place and Duration of Study: Surgical department of Combined Military Hospital and Pak Emirates Military Hospital, Rawalpindi, from April 2022 to September 2022.
Methodology: A sample size of a minimum of 281 was calculated using a WHO calculator, keeping a 5% margin of error,95% confidence level, and a prevalence of anastomotic leak of 24%. 308 patients who were undergoing elective or semi-urgent gastrointestinal surgery of both genders aged 18 to 65 years and willing to participate in the study were included.
Results: Our study included 308 patients who underwent elective abdominal surgery. 184(59.7%) were males and 124(40.3%) were females. The mean age of study participants was 47.09±11.90 years. The rise of >50mg/dl in CRP levels as an indicator of postoperative anastomotic leaks in gastrointestinal surgeries had a sensitivity of 100.0% but a specificity of only 46.6% with a 7.1% positive predictive value.
Conclusions Rise in CRP levels of 50mg/dl or more between any two consecutive days post-operatively following gastrointestinal surgeries is a good indicator of the probability of anastomotic leakage having high sensitivity.

Keywords: Anastomosis, CRP, Colorectal, Gastrointestinal, Leak

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INTRODUCTION

The number of major surgical procedures performed around the globe each year is estimated to be in the millions. Postoperative complications and deaths are rare in general, but patients undergoing gastrointestinal surgery are typically among those at high risk. Anastomosis leakage is a major complication in the gastrointestinal tract, with frequencies varying depending on the site.[1] As the surgical technique and clinical management have improved during preoperative and postoperative periods, the frequency of this complication has gradually decreased.[2] Even so, it remains a fearsome complication that prolongs hospital stays, impairs patient quality of life, increases the risk of local recurrences, and negatively impacts cancer prognosis.[3] After surgery, AL is typically diagnosed between six and 15 days later. The dehiscence of various gastrointestinal anastomoses is associated with local recurrence rates of malignant tumors and higher mortality rates caused by peritonitis and septicaemia in the absence of a valid diagnostic test to detect AL early in the postoperative period. The clinical manifestation of AL typically occurs after discharge in 20% of cases.[4]

In addition to prolonged hospital stays, delayed diagnosis is associated with higher mortality rates. AL can be difficult to diagnose in the early stages because of non-specific signs and symptoms. The results of these investigations have led to the discovery of many predictors of AL. Systemic inflammation response biomarkers have also proven useful as potential clinical predictors of AL.[5,6] AL development involves an active systematic inflammatory response. Several methods have been proposed for detecting anastomotic leakage early, including imaging, peritoneal cytokine levels, and serum biomarkers of inflammation. It was found that postoperative C-reactive protein (CRP) levels and albumin levels were particularly relevant.[5] Postoperative complications following gastrointestinal surgery can be predicted with greater accuracy by the CRP-Alb ratio (CAR) than by CRP or Alb alone.[3]

Several previous studies have attempted to find biomarkers that can help diagnose anastomotic leakage early. These studies identify changes in CRP,

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WBC, and procalcitonin (PCT) as potential markers of anastomotic leakage following gastrointestinal surgery and emphasize that CRP trajectory is highly accurate when diagnosing anastomotic leakage.[7] One of the most widely studied biomarkers is C-reactive protein (CRP). An increase in individual CRP levels of 50 mg/l per day postoperatively should be considered.[8] There was good diagnostic accuracy at the cut-off levels above certain points on postoperative days 3, 4, and 5.[9] Anastomotic leakages in gastrointestinal tissues could be predicted accurately with these trajectory measurements.[10] Before incorporating this into routine clinical practice, it is necessary to seek further validation. This study aimed to determine whether CRP-trajectory is an accurate predictor of AL after gastrointestinal surgery.

METHODOLOGY

This cross-sectional study was conducted at the Surgical department of Combined Military Hospital and Pak Emirates Military Hospital, Rawalpindi, for a period of 1 year (Jan 2022 to Dec 2022). We obtained ethical approval from the institutional review board (IRB) vide reference number 318. After a thorough literature search, a sample size of a minimum of 281 was calculated using a WHO calculator, keeping a 5% margin of error,95% confidence level, and a prevalence of anastomotic leak of 24%.[11] Sampling was done using the nonprobability consecutive sampling technique. A maximum number of available participants (308) during the study period were recruited.

Inclusion Criteria: Diagnosed cases undergoing elective or semi-urgent gastrointestinal surgery of both genders aged 18 to 65 years and willing to participate in the study were included. Patients undergoing reversal of colostomy, reversal of ileostomy, gastrojejunostomy, anterior resection, right hemicolectomy, and sigoid resection were included in the study.

Exclusion Criteria: Patients with Ileoanal (pouch) anastomoses and unwillingness to participate in the study were excluded.

Before enrolling all patients, we obtained their written consent, and the confidentiality of the patients was ensured at all levels. Detailed history and complete physical examination were done. A series of demographic, fitness, BMI, co-morbidities, surgery, postoperative complications, hospital stay duration, as well as anastomosis leakage data were collected prospectively. In addition to investigating and managing anastomosis leaks, and assessing readiness for discharge, all clinical management was done at the discretion of the treating teams. Using mechanical or oral antibiotic bowel preparations and diverting stomas was completely dictated by the treating surgeon's preferences in this pragmatic observational study. The CRP results were not hidden from clinicians. After surgery, the CRP level was measured daily for patients discharged earlier than this date. The trajectory of CRP was analysed prospectively concerning their accuracy in the prediction of anastomotic leakage. Surgical or radiological interventions were required to repair anastomotic leaks in the intestinal wall. Anastomotic leaks, including those managed medically, were analyzed as part of a secondary analysis. During the study, leakage was compared with a CRP trajectory of 50 mg/l per day as well as Singh and colleagues' cut-off points.

Data were entered in Microsoft excel and later analyzed using Statistical Package for Social Sciences (SPSS) 23.0. Quantitative data was represented using mean ± standard deviation and qualitative data was represented by using percentage and frequency. 2×2 contingency table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.

RESULTS

Our study included 308 patients who underwent elective abdominal surgery. 184(59.7%) were males and 124 (40.3%) were females. The mean age of study participants was 47.09±11.90 years. A maximum number of cases dealt with were of reversal of colostomy (72) and reversal of ileostomy (84) whereas sigmoid resection was done in only 20 cases out of the total 308 patients included in the study. Patient characteristics are given in the table-I below.

Table-I: Demographic Characteristics of Study Participants(n=308)

Parameters		Frequency (%)
BMI (Kg/m2)	18-24	52(16.9%)
	25-30	137(44.5%)
	>30	119(38.6%)
Smoking	Smokers	96(31.2%)
	Non-smokers	212(68.8%)
Diabetes	Diabetic	72(23.4%)
	Non-Diabetic	236(76.6%)
Hospital Stay	<5 days	120(39.0%)
	≥5days	188(61.0%)

Among 308 patients, 170(55.2%) had a CRP increase of more than 50 mg/dL. CRP elevation was

more frequent in patients with a hospital stay of ≥5 days (77.7%) compared with those staying less than 5 days (20.0%). Regarding surgical procedures, CRP elevation was observed in all patients undergoing gastrojejunostomy and sigmoid resection (100.0%) followed by anterior resection (71.4%), right hemicolectomy (70.0%), reversal of colostomy (50.0%) and reversal of ileostomy (14.3%) shown in Table. These findings indicate that increased CRP levels were more common among patients with prolonged hospital stays and varied across surgical procedures.

Table-II Crosstabulation of C - Reactive Protein levels with Hospital Stay and Surgical Intervention (n=308)

Parameters		C - Reactive Protein Increase n (%)		Total 308 (100.0%)
		>50mg/dl 170 (55.2%)	≤50mg/dl 138 (44.8%)	
Hospital stay	<5 days	24(20.0%)	96(80.0%)	120(38.9%)
	≥5days	146(77.7%)	42(22.3%)	188(61.1%)
Surgical Procedure	Reversal of colostomy	36(50.0%)	36(50.0%)	72(23.4%)
	Reversal of ileostomy	12(14.3%)	72(85.7%)	84(27.3%)
	Right hemicolectomy	42(70.0%)	18(30.0%)	60(19.5%)
	Anterior resection	30(71.4%)	12(28.6%)	42(13.6%)
	Gastrojejunostomy	30(100.0%)	0(0.0%)	30(9.7%)
	Sigmoid Resection	20(100.0%)	0(0.0%)	20(6.5%)

Table-III below shows the sensitivity and specificity along with positive and negative predictive values of the rise in CRP levels in detecting the leak postoperatively. As can be seen from the table below, a total of 170 participants had a rise in CRP value of >50mg/dl in two consecutive days, out of which only 12 (True Positives) participants suffered an anastomotic leak postoperatively, the remaining 158 (false positives) did not have postoperative anastomotic leakage. Out of the total 138 (True Negatives) participants with ≤50mg/dl rise in CRP values, there was no incidence of leak post-operatively. There were no False Negatives. Therefore, using a rise of >50mg/dl in CRP levels as an indicator of postoperative anastomotic leaks in gastrointestinal surgeries had a sensitivity of 100% but a specificity of only 46.6% with a 7.1% positive predictive value.

DISCUSSION

CRP is an acute-phase reactant that along with other APRs is synthesized in the liver and released in circulation in response to cytokines. It is produced as a result of a nonspecific acute phase response to tissue damage that can be due to reasons such as infection, inflammation, and malignancy.[12] Interleukin-6 is the regulator for the synthesis of CRP, which is produced mostly from macrophages in the pathological tissue. CRP causes complement activation after binding with macromolecular ligands on the surface of dead cells.[13]

Table-III Diagnosists Parameters of C - Reactive Protein levels rise in predicting anastomotic leak (n=308)

		C - Reactive Protein Increase		Total 308 (100%)
		>50mg/dl	≤50mg/dl	
Leak	No	158 (53.4%)	138 (46.6%)	296 (96.1%)
	Yes	12 (100.0%)	0 (0.0%)	12 (3.9%)
Total		170 (55.2%)	138 (44.8%)	308 (100.0%)

Sensitivity= TP/(TP+FN)= 12/(12+0)*100=100.0%
Specificity= TN/(TN+FP)= 138/(138+158)*100=46.6%
Positive Predictive Value= TP/(TP+FP)*100= 12/(12+158)= 7.0%
Negative Predictive Value= TN/(TN+FN)*100=138/(138+0)= 100.0%
Diagnostic Accuracy=(TP+TN)/All patients*100 = (12+138)/308=48.7%

Our study has analyzed the use of a rise in CRP levels in the timely diagnosis of anastomotic leakage post gastrointestinal surgeries, even though the testing CRP levels have shown high sensitivity (100%) in detecting anastomotic leaks in such patients but it lacks specificity (46.6%) owing to the fact that CRP is an acute phase reactant. This was in accordance with the study conducted by B.D Stephensen et al, in which it was shown that specificity in early days postoperatively was low due to false-positives as a result of CRP level increased due to other sources of infection and surgical trauma.[14] Anastomotic Leak rate was only 3.9% in our study which was significantly lower than a study by Awad et al, where the rate of anastomosis leakage was 8.57%11 P.waterland et al, carried out a study that showed a sensitivity of 75% and specificity of 70% using CRP levels as an indicator of anastomotic leakage in open and laparoscopic abdominal surgeries. Our results showed a significantly greater sensitivity of 100% however with a lower specificity of 46.7%.[15] In another similar study conducted by Lucas F. Leisenfeld *et al*, the sensitivity ranged from 44 to 68%,(much lower as compared to our results) while the specificity ranged from 51 to 75%.[12] A meta-analysis was carried out on 23 comparative studies to determine the accuracy of CRP levels postoperatively in predicting anastomotic leaks in colorectal surgeries. This meta-analysis showed sensitivity and specificity of 95% which was higher as

compared to our results.[17] In a study carried out by Zawadzki M *et al,* it was shown that anastomotic leakage was observed in patients who had undergone low anterior resection whereas in our study anastomotic leakage occurred in cases of anterior resection as well as a gastrojejunostomy.18 Alexandra C. Gordon *et al*, in their study performed on patients who underwent gastroesophageal resection showed that CRP levels predicted leak in anastomosis postoperatively with 100% sensitivity, 61% specificity, and a positive predictive value (PPV) of 21% and a negative predictive value (NPV) of 100%. These results were quite similar to our study analysis.[19] Our study results showed a significant association between postoperative CRP levels and anastomotic leak. However, as indicated by high sensitivity and lower specificity, CRP values are more useful as a screening marker for the probability of anastomotic leak after elective gastrointestinal surgeries rather than being used as a diagnostic marker. Therefore, to facilitate and expedite the safe recovery of patients post-gastrointestinal surgery, CRP can be used in conjunction with other radiological and biochemical investigations for ruling out the incidence of anastomotic leakage. It is worth mentioning that biochemical markers like CRP no matter how accurate a study predicts them to be, can never replace clinical investigation carried out by doctors and should only be used in combination with clinical evaluation.

LIMITATION OF STUDY

Our study included only people from Pakistan, consisting of a population belonging to the south Asian ethnicity. Also, only cases being carried out in CMH Rawalpindi were included in the study. The patients included in our study underwent open surgery so the results may not apply to laparoscopic surgery because reduced inflammatory response is observed in laparoscopic procedures.

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CONCLUSIONS

The rise in CRP levels of 50mg/dl or more between any two consecutive days post-operatively following gastrointestinal surgeries is a good indicator of the probability of anastomotic leakage having high sensitivity. However, due to other causes of the rise in CRP levels, it should not be used as a sole diagnostic marker and should be validated with clinical and radiological investigations.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AZUA & NMW: Data acquisition, data analysis, critical review, approval of the final version to be published.

TK & WAK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AAM & KSB: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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