ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 01 | January - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ROLE OF BIOMARKERS IN EARLY DIAGNOSIS OF ANASTOMOSIS LEAK FOLLOWING ELECTIVE AND EMERGENCY SURGERIES

General Surgery

Dr. Ankit Singh Lodhi Department of General Surgery, B.R.D Medical College, Gorakhpur.
Dr. Ashok Kumar MS, FLCS, FAIS, Professor and H.O.D Department of General Surgery, B.R.D Medical College, Gorakhpur.
Dr. Aquil Ahmad Assistant Professor Department of General Surgery, B.R.D Medical College, Gorakhpur.
Dr. Shaila Mitra Professor, Department of Pathology, B.R.D Medical College, Gorakhpur

ABSTRACT

Anastomotic leaks (AL) are serious complications following gastrointestinal surgery that are associated with a significant morbidity and death rate. Various biomarkers such as High-Sensitivity C-Reactive Protein, Procalcitonin, Interleukin-6, Total Leukocyte Count majorly use in diagnosis of the post-operative complication AL after elective and emergency surgeries. The present investigation is a prospective observational study done over a period of 1year at BRD Medical College, Gorakhpur. The study includes 48 patients for diagnosis. Biomarker assessments were obtained pre-operatively and on postoperative days (POD) 3, 5, and 7. The study results indicated that sensitivity and specificity of PCT and TLC levels were significantly higher than those of IL-6 and HS-CRP. Indeed, both PCT on postoperative days 5 and 7 were the most accurate predictors of AL. PCT, TLC showed a good early overall diagnostic performance for AL, and joint monitoring of these parameters with clinical evaluations and imaging would help with the management of patients.

KEYWORDS

Anastomotic leak, Procalcitonin, Interleukin-6, High-Sensitivity C-Reactive Protein, gastrointestinal surgery.

INTRODUCTION

Anastomotic leaks are one of the most common side effects of colorectal surgery.[1] A major consequence of colorectal surgery is anastomotic leakage (AL), which has a high risk of significant consequences like sepsis, the necessity for reoperation, the development of a stoma, and even death.[2] In patients with colorectal cancer, for example, AL is linked to a higher risk of local recurrence and a lower overall and long-term survival rate.[3] Anastomotic leakage is a defect on either end that allows intra- and extraluminal contents to communicate or extravasate.[4] Although the treatment of gastrointestinal cancer has advanced and multimodal therapies have become available, approximately 40% of AL events are reported post-surgical resection.[5 6] Several risk factors have been described for developing AL, such as blood loss, longer operative times, and perioperative weight loss.[7 8] Although the pathophysiology of AL has been studied extensively,[9] its precise nature is still not well understood. In fact, this is crucial for the early onset of AL patients to improve their quality of life and survival rate through early care.[10] Anastomotic leakage may occur with an extraperitoneal anastomosis (1%–30%)[11] (the most common reason), or other causes. The risk of leakage does not appear to be influenced by procedures such as spinal anesthesia, mechanical preparation of colon, and individualized hydration management.[12]

Computed tomography (CT), endoscopic examination, biomarkers, and study of abdominal drain output are the most often utilized modalities in clinical practice to identify anastomotic leakage.[13] Biomarkers are the naturally occurring symbols of healthy, vibrant life, while they may also be thought of as the pharmacological reactions to a treatment.[10] These biomarkers were originally investigated in 1996, which paved the way for further investigation. Examining the connection between intestinal cell damage indicators with AL and C-reactive protein (CRP) was of more interest to researchers.[9]

The majority of research on biomarkers in anastomotic leak has been focused mostly on colorectal malignancies. Nonetheless, oesophageal, stomach, small intestine, and large intestine procedures will all be addressed in this study. Thus, this study's goal was to investigate the function of biomarkers in early diagnosis of anastomosis leak following elective and emergency surgeries.

Literature Survey

Anastomotic leak (AL) is a critical complication often seen after gastrointestinal surgeries. Over the years, various methods, including clinical assessments, imaging, and biomarker analysis, have been developed to detect AL. Biomarkers like (PCT), (IL-6), and (HS-CRP) are increasingly used for early diagnosis. These biomarkers help doctors detect complications sooner and guide better treatment decisions. This survey explores previous research on the role of these biomarkers, highlighting their effectiveness in diagnosing AL across different types of surgeries. Various similar studies have conducted like Cousin F et al (2016)[14] examined how well PCT and CRP predicted the development of IAIs after elective colorectal surgery. Su'a BU et al (2017)[15] evaluated biomarkers as possible diagnostic tools to find AL before it manifests. They observed that systemic biomarkers and peritoneal drain fluid are not very good indicators of AL after colorectal surgery. Their study proved that the predicted accuracy improved when these biomarkers were combined. Similar study by de Mooij CM et al (2019)[16] evaluated biomarkers for their potential use in the early stages of esophageal cancer surgery for the (pre)clinical identification of AL. After surgery for gastric cancer, they found that current biomarkers are not particularly good at predicting AL due to their limited sensitivity and positive predictive value.

MATERIAL AND METHOD

Study Design: The prospective observational study was carried out at BRD Medical College's General Surgery Department in Gorakhpur. The course lasted for a year.

Study Population: 48

Using a 72% predicted specificity and a 9.4% expected prevalence of AL, 48 samples were needed, with a 95% confidence range and a 10% relative precision.

Compared to CRP, PCT has less specificity. Therefore, sample size was determined using PCT's specificity.

When P was particular, the sample size was determined using the formula N = Z2 x P (1-P) / [d2 x (1-prevalence)]. The study's power was maintained at 80%.

Inclusion Criteria:

- All patients aged 18-70 years of age, who had undergone elective or emergency gastrointestinal surgery with an anastomosis of small and large intestine.

Exclusion Criteria:

- Patients not giving consent.
- Patients who had a fever or sepsis prior to surgery.
- Individuals who have undergone intraperitoneal chemotherapy.
- Patients in whom covering stoma was done with anastomosis.
- Patient above 70 years.
- Immunocompromised patients (Severe malnutrition, current steroid use, advance cancer not amenable to resection).

Study Procedure: Participants in this study were selected as part of a prospective, non-randomized study that examined inflammatory markers after bowel anastomosis and elective and emergency procedures. A physical examination, baseline blood tests, and a chest x-ray were all part of the preoperative workup. Perioperative and postoperative problems for patients were prospectively entered into the database up to 30 days following surgery.

Data Analysis:
Concentration of three biomarkers hs-crp, procalcitonin and IL-6 were measured at PRE-op, Post-op (Day3,5 and 7) HS-CRP was measured using the Multigent CRP Vario immunoturbidimetric test with the Architect 4100 Ci analyzer. By employing an ELISA kit and the immunofluorescence assay principle, PCT levels were measured. We used an immediate ELISA kit to test IL 6. The Sysmex Xt-2000i, which operates on the Coulter principle, was used to measure TLC. Patient information was collected, including age, sex, phone number, diagnosis, reason for operation, prior surgical experience, perioperative hemoglobin, total leucocyte counts (TLC), total protein, and albumin. Confounding factors were also be recorded, including surgical site infection and any further postoperative septic foci. Following surgery, patients were monitored for leak signs and symptoms as well as any other problems. To perform the statistical analysis, SPSS version 21 [IBM corporation: NY, USA] tools were used. 5% was chosen as the significance level.

Ethical Clearance
Study was approved in Institutional Ethics Committee Research Cell, BRD Medical College Gorakhpur.

RESULT
The study included 48 patients with a mean age of 37.77 ± 17.70 years, with 47.9% aged 18-30 years and 58.3% being male. The mean weight was 51.96 ± 9.80 kg, and the mean height was 151.67 ± 10.47 cm. Most patients (95.8%) had no comorbidities, while 16.7% consumed alcohol, 37.5% used tobacco, and 4.2% smoked. The presence of personal habits or comorbidities showed no significant correlation with anastomotic leaks.

Table 1: Distribution Based On Bio-markers At Different Time Intervals:

Biomarkers		N	Minimum	Maximum	Mean	S. D
HS-CRP (Reference range 0.52-200 mg/L)	Pre-op	48	10.0	350.0	58.54	53.16
	Post op Day 3	48	11.0	400.0	60.10	60.99
	Post op Day 5	48	8.0	350.0	51.52	58.54
	Post op Day 7	48	6.0	320.0	54.85	48.71
Procalcitonin (Reference range 0.1-0.5 ng/ml)	Pre-op	48	.01	6.00	0.77	1.31
	Post op Day 3	48	.05	21.00	2.29	4.61
	Post op Day 5	48	.02	17.00	1.88	3.65
	Post op Day 7	48	.02	22.00	2.42	5.34
IL-6 (Reference range <7-pg/ml)	Pre-op	48	.11	80.00	8.48	11.89
	Post op Day 3	48	.15	92.00	11.04	14.18
	Post op Day 5	48	.30	70.00	9.79	11.61
	Post op Day 7	48	.6	78.0	9.35	12.42
TLC (Reference range 4000-10000 cells/mm^3)	Pre-op	48	4000.0	14000.0	7485.42	2425.84
	Post op Day 3	48	3400.0	19000.0	7797.92	2981.68
	Post op Day 5	48	3000.0	14000.0	7529.17	2502.34
	Post op Day 7	48	3000.0	13700.0	7000.00	2141.78

The table presents the distribution of biomarkers (HS-CRP, Procalcitonin, IL-6, and TLC) at different time intervals (Pre-op, Post-op Day 3, 5, and 7) for 48 patients. Mean HS-CRP and Procalcitonin levels increased post-operatively, peaking on Day 3, while IL-6 levels gradually decreased. TLC levels rose on Day 3 before declining by Day 7. Standard deviations indicate variability in biomarker levels, with reference ranges provided for clinical interpretation.

Table 2: Association of presence or absence of leak with type surgery

Type of surgery		Leak		Total
		NO	YES	
Gastrojejunosto	Count	1	0	1
	%	2.4%	0.0%	2.1%
Hartman reversal	Count	1	0	1
	%	2.4%	0.0%	2.1%
Loop closure	Count	37	7	44
	%	90.2%	100.0%	91.7%
RA	Count	2	0	2
	%	4.9%	0.0%	4.2%
Total	Count	41	7	48
	%	100.0%	100.0%	100.0%
Chi-square value- 0.745				
p value-0.863				

The table 2 shows the association between the presence or absence of anastomotic leaks and different types of surgeries. Among the 48 patients, leaks occurred in 7 cases, all from loop closure surgeries (100% of leaks). Other surgeries, including gastrojejunostomy, Hartman reversal, and RA, showed no leaks. The chi-square value of 0.745 and p-value of 0.863 indicate no statistically significant association between surgery type and leak occurrence.

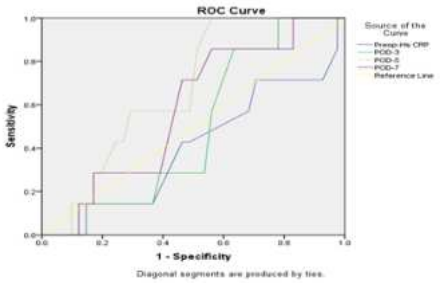

Figure 1: ROC Curve to predict the leak with biochemical marker HS-CRP at different time intervals (PRE-OP, POST -OP DAY 3, 5 AND 7)

The figure 1 shows the predictive value of High-Sensitivity C-Reactive Protein for detecting leaks at various time points, revealing that none of the measurements (pre-op, post-op days 3, 5, and 7) were statistically significant. Pre-op HS-CRP had an AUC of 0.402 (p=0.413) with a cutoff of 42, showing 57.1% sensitivity and 32% specificity. Post-op Day 3 had an AUC of 0.490 (p=0.93) with a cutoff of 40.5, yielding 57.1% sensitivity and 43.9% specificity. Day 5 showed an AUC of 0.671 (p=0.086) with a cutoff of 44.5, providing 57.1% sensitivity and 70.7% specificity. Day 7 had an AUC of 0.58 (p=0.502) with a cutoff of 46, showing 71.4% sensitivity and 53.7% specificity.

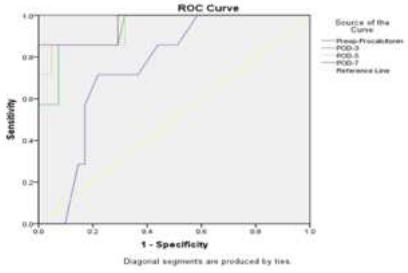

Figure 2: ROC curve to predict the leak with biochemical marker procalcitonin at different time intervals (PRE-OP, POST -OP DAY 3, 5 AND 7)

The figure 2 shows procalcitonin levels for predicting leaks at various time points, showing statistically significant results. Pre-op Procalcitonin had an AUC of 0.753 (p=0.034) with a cutoff of 0.775, 71.4% sensitivity, and 78% specificity. Post-op Day 3 showed an AUC of 0.936 (p=0.001) with a cutoff of 2.75, 85.7% sensitivity, and 92.7% specificity. Day 5 had an AUC of 0.948 (p=0.001) with a cutoff of 2.95, 85.7% sensitivity, and 95.1% specificity. Day 7 had an AUC of 0.958 (p=0.001) with a cutoff of 1.15, 85.7% sensitivity, and 85.4% specificity.

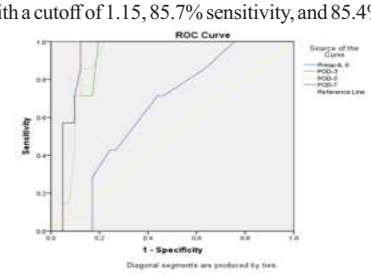

Figure 3: ROC curve to predict the leak with biochemical marker IL-6 at different time intervals (PRE-OP, POST -OP DAY 3, 5 AND 7)

In figure 3 Interleukin-6 (IL-6) levels shows the predicting leaks at various time points, with mixed results. Pre-op IL-6 had an AUC of 0.643 (p=0.231) and a cutoff of 6.9, showing 71.4% sensitivity and 56.1% specificity, which was not statistically significant. Post-op Day 3 showed an AUC of 0.906 (p=0.001) with a cutoff of 11.5, 71.4% sensitivity, and 82.9% specificity. Day 5 had an AUC of 0.895 (p=0.001) with a cutoff of 9.5, 85.7% sensitivity, and 82.9% specificity. Day 7 had an AUC of 0.925 (p=0.001) with a cutoff of 10.5, 85.7% sensitivity, and 87.8% specificity.

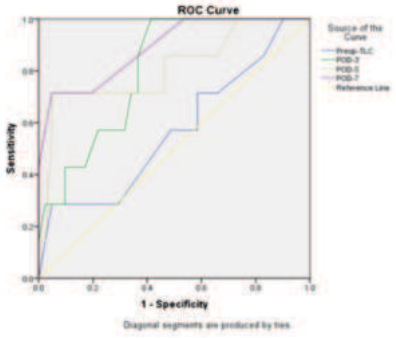

Figure 4: ROC curve to predict the leak with biochemical marker TLC at different time intervals (PRE-OP, POST -OP DAY 3, 5 AND 7)

The figure 4 demonstrate the Total Leukocyte Count (TLC) levels for predicting leaks at various time points. Pre-op TLC had an AUC of 0.568 (p=0.569) with a cutoff of 6900, showing 57.1% sensitivity and 51.2% specificity, which was not statistically significant. Post-op Day 3 had an AUC of 0.801 (p=0.012) with a cutoff of 7300, 85.7% sensitivity, and 63.4% specificity. Day 5 showed an AUC of 0.812 (p=0.009) with a cutoff of 6950, 85.7% sensitivity, and 53.7% specificity. Day 7 had an AUC of 0.889 (p=0.001) with a cutoff of 7500, 71.4% sensitivity, and 80.5% specificity.

DISCUSSION

The purpose of this study was to investigate the function of biomarkers in the early detection of anastomosis leak after both elective and urgent procedures. In the current investigation, the average age of the patients was 37.77 ± 17.70 years. The majority (58.3%) of the participants were men. These findings are similar with the study of Sirois-Giguère et al. noted that men made up 95% of the patient population.[17] High incidence of anastomotic leak has been linked to an American Society of Anesthesiologists score of at least 3.[1218] In the current study, the most prevalent diagnosis was perforation with loop ileostomy, which affected 17 patients (35.4%). Similar study by Gessler et al., 18.8% had rectal resection and 8.6% had a sigmoid colectomy seven patients (14.6%) in the current investigation had an anastomotic leak.[19] When diagnosing anastomotic leak, which usually happens on post-operative days (POD) 5-7, a number of clinical, biochemical, and radiological indicators are evaluated. Henderson et al. reported that fever, tachycardia, peritonitis, delayed ileus, nausea, and vomiting are common symptoms and indicators of anastomotic leak.[20]

C-Reactive Protein, leukocytes, and procalcitonin are important tools for diagnosing anastomotic leaks (AL). CRP and leukocytes are widely and regularly used but unfortunately, the results are nonspecific for the differentiation of AL and other complications, whereas CRP shows high negative predictive value (NPV) for early postoperative days. PCT is more sensitive and specific, but its usage is limited by cost and availability. Studies demonstrate the usefulness of these markers in detecting early AL, such as seen with CRP >50 mg/L on POD 3 which showed 96% specificity for AL. TLC, IL-6 and PCT were revealed to be a better risk factor of anastomotic leakage and sequelae on POD 3, POD 5 and POD 7 compared with to Hs-CRP.

CONCLUSION

The study concluded that TLC, IL-6 and PCT were found to be a more accurate indicator of anastomotic leaks and sequelae on POD 3, POD 5 and POD 7 compared to Hs-CRP. Elevated PCT values might indicate a particular mix of surgical and infectious problems, with AL being the most common. High-quality prospective trials with exact definitions of AL are needed to identify a near-perfect biomarker reflecting the perianastomotic environment for predicting AL in the early postoperative period prior to discharge. A surgeon's understanding of the potential risk factors, diagnostic techniques, and accessible treatment options following colorectal anastomosis may improve patient outcomes.

Recommendation

The investigation recommends measuring PCT, IL-6 and TLC levels as a routine postoperative marker to identify patients at increased risk for AL. These levels could also guide antibiotic therapy and predict complications. These biomarkers must be assessed at different time points, i.e. at 24,48 and 72 hours to capture the dynamics of their level and enhance predictive accuracy. Moreover, these biomarkers must be interpreted in conjunction with clinical findings and imaging studies.

REFERENCES

1. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Annals of surgery. 2007 Feb 1;245(2):254-8.
2. Rajabaleyan P, Jootun R, Möller S, Deding U, Ellebæk MB, Al-Najami I, Lindsey I. Early warning model to detect anastomotic leakage following colon surgery: a clinical observational study. Annals of Coloproctology. 2024 Oct 8;40(5):431.
3. Litchinko A, Buchs N, Balaphas A, Toso C, Liot E, Meurette G, Ris F, Meyer J. Score prediction of anastomotic leak in colorectal surgery: a systematic review. Surgical Endoscopy. 2024 Apr;38(4):1723-30.
4. Carboni F, Valle M, Federici O, Sandri GB, Camperchioli I, Lapenta R, Assisi D, Garofalo A. Esophagojejunal anastomosis leakage after total gastrectomy for esophagogastric junction adenocarcinoma: options of treatment. Journal of gastrointestinal oncology. 2016 Aug;7(4):515.
5. Sauvanet A, Mariette C, Thomas P, Lozac'h P, Segol P, Tiret E, Delpero JR, Collet D, Leborgne J, Pradère B, Bourgeon A. Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. Journal of the American College of Surgeons. 2005 Aug 1;201(2):253-62.
6. Bruce J, Krukowski ZH, Al.Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. British Journal of Surgery. 2001 Sep;88(9):1157-68.
7. Deguchi Y, Fukagawa T, Morita S, Ohashi M, Saka M, Katai H. Identification of risk factors for esophagojejunal anastomotic leakage after gastric surgery. World journal of surgery. 2012 Jul;36:1617-22.
8. Kim SH, Son SY, Park YS, Ahn SH, Park DJ, Kim HH. Risk factors for anastomotic leakage: a retrospective cohort study in a single gastric surgical unit. Journal of gastric cancer. 2015 Sep 1;15(3):167-75.
9. Oshi M, Kunisaki C, Miyamoto H, Kosaka T, Akiyama H, Endo I. Risk factors for anastomotic leakage of esophagojejunostomy after laparoscopy-assisted total gastrectomy for gastric cancer. Digestive surgery. 2017 Dec 12;35(1):28-34.
10. Markar S, Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, Lefevre JH, Brigand C, Vaillant JC, Adham M, Msika S. The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Annals of surgery. 2015 Dec 1;262(6):972-80.
11. Neutzling CB, Lustosa SA, Proenca IM, da Silva EM, Matos D. Stapled versus handsewn methods for colorectal anastomosis surgery. Cochrane Database of Systematic Reviews. 2012(2).
12. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Journal of British Surgery. 2015 Apr;102(5):462-79.
13. Kornmann VN, Treskes N, Hoonhout LH, Bollen TL, van Ramshorst B, Boerma D. Systematic review on the value of CT scanning in the diagnosis of anastomotic leakage after colorectal surgery. International journal of colorectal disease. 2013 Apr; 28:437-45.
14. Cousin F, Ortega-Deballon P, Bourredjem A, Doussot A, Giaccaglia V, Fournel I. Diagnostic accuracy of procalcitonin and C-reactive protein for the early diagnosis of intra-abdominal infection after elective colorectal surgery: a meta-analysis. Annals of surgery. 2016 Aug 1;264(2):252-6.
15. Su'a BU, Mikaere HL, Rahiri JL, Bissett IB, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. Journal of British Surgery. 2017 Apr;104(5):503-12.
16. de Mooij CM, Maassen van den Brink M, Merry A, Tweed T, Stoot J. Systematic review of the role of biomarkers in predicting anastomotic leakage following gastroesophageal cancer surgery. Journal of Clinical Medicine. 2019 Nov 17;8(11):2005.
17. Chiarello MM, Fransvea P, Cariati M, Adams NJ, Bianchi V, Brisinda G. Anastomotic leakage in colorectal cancer surgery. Surgical oncology. 2022 Mar 1; 40:101708.
18. He J, He M, Tang JH, Wang XH. Anastomotic leak risk factors following colon cancer resection: a systematic review and meta-analysis. Langenbeck's Archives of Surgery. 2023 Jun 29;408(1):252.
19. Gessler B, Eriksson O, Angenete E. Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. International Journal of colorectal disease. 2017 Apr; 32:549-56.
20. Hernandez PT, Paspulati RM, Shanmugan S. Diagnosis of anastomotic leak. Clinics in colon and rectal surgery. 2021 Nov;34(06):391-9.