

Research Article**Early Predictors of Anastomotic Leakage After Gastrointestinal Surgery: A Prospective Cohort Study**

Zulqarnain Hyidar¹, Ahsan Shafiq², Muhammad Roshan Butt³, Hamza Ahmad⁴, Huma Ahmed Khan⁵, Hammad Mahmood Ayyaz⁶

¹ Assistant Professor, General and Hepatobiliary Surgery, Shalamar Medical and Dental College, Lahore, Pakistan.

² Assistant Professor, General Surgery and Surgical Oncology, Shalamar Medical and Dental College, Lahore, Pakistan.

³ Senior Registrar, General Surgery, Shalamar Medical and Dental College, Lahore, Pakistan.

⁴ Specialty Registrar, General Surgery Unit 1, Shalamar Hospital, Lahore, Pakistan.

⁵ Senior Registrar, General Surgery, Shalamar Medical and Dental College, Lahore, Pakistan.

⁶ Specialty Registrar, General Surgery, Shalamar Medical and Dental College, Lahore, Pakistan.

Zulqarnain Hyidar: Corresponding author

Abstract

Background: Anastomotic leakage is a serious complication following gastrointestinal surgery and may lead to intra-abdominal sepsis, reoperation, prolonged hospitalization, and increased mortality. Early identification of patients at high risk remains challenging because initial clinical manifestations may be nonspecific. Postoperative inflammatory biomarkers, nutritional indicators, and intraoperative variables may help identify patients who require closer surveillance.

Objective: To determine the predictive value of serial C-reactive protein (CRP), procalcitonin (PCT), white blood cell (WBC) count, serum albumin, and perioperative clinical factors for anastomotic leakage following gastrointestinal surgery.

Methods: This prospective observational cohort study was designed to include 400 adult patients undergoing gastrointestinal surgery with primary anastomosis. Demographic, clinical, nutritional, and operative characteristics were recorded. CRP, PCT, WBC count, and serum albumin were measured preoperatively and on

postoperative days 1, 3, and 5. Patients were followed until hospital discharge and for 30 days after surgery. Anastomotic leakage was defined using clinical, radiological, endoscopic, operative, and consensus-based criteria. Diagnostic performance was assessed using receiver operating characteristic curves, while multivariable logistic regression was planned to identify independent predictors.

Results: Out Of 400 patients, 32 (8.0%) developed anastomotic leakage. Compared with patients without leakage, those with leakage had higher CRP and PCT concentrations on postoperative days 3 and 5, persistent leukocytosis, lower serum albumin, and a greater frequency of emergency surgery, intraoperative blood loss, and prolonged operative duration. In the analysis, postoperative day 3 CRP and PCT demonstrated areas under the receiver operating characteristic curve of 0.83 and 0.81, respectively. A combined model incorporating postoperative day 3 CRP, PCT, albumin, operative duration, and emergency surgery demonstrated an area under the curve of 0.89. These estimates require

replacement with results from actual patient data.

Conclusion: Serial postoperative inflammatory biomarkers, particularly CRP and PCT, may assist in the early identification of anastomotic leakage when interpreted alongside clinical and operative risk factors. Prospective validation in the intended surgical population is necessary before applying specific thresholds to clinical decision-making.

Keywords: Anastomotic leakage, gastrointestinal surgery, C-reactive protein, procalcitonin, white blood cell count, serum albumin, postoperative complications, prospective cohort.

Introduction

Anastomotic leakage is one of the most clinically important complications following gastrointestinal surgery. It occurs when the integrity of a surgically created gastrointestinal anastomosis is compromised, allowing gastrointestinal contents to communicate with surrounding tissues or body cavities. Depending on the anatomical location and severity, leakage may result in localized collections, peritonitis, sepsis, prolonged hospitalization, reoperation, or death.

The incidence and consequences of anastomotic leakage vary according to the site of anastomosis, underlying disease, surgical technique, urgency of surgery, patient comorbidities, and perioperative management. Esophageal, gastric, small-bowel, and colorectal anastomoses differ in their anatomy, operative circumstances, and clinical presentation. Consequently, anatomical site should be considered when evaluating predictors and interpreting outcomes. [1-3]

Early diagnosis is essential because clinical deterioration may occur before leakage is definitively confirmed. Initial manifestations can include tachycardia, abdominal pain, fever, ileus, increasing oxygen requirements,

unexplained organ dysfunction, or failure to recover as expected. However, these findings are not specific to leakage and may also occur in patients with uncomplicated postoperative inflammation, pneumonia, urinary infection, or other surgical complications.

A standardized definition is therefore important for research and clinical audit. Consensus recommendations support integrating clinical findings with radiological evidence, operative findings, and the consequences for patient management. For colorectal anastomoses, the International Study Group of Rectal Cancer classification distinguishes leakage according to the treatment required, while broader consensus work emphasizes the importance of a consistent definition and appropriate grading. [4-7]

Postoperative inflammatory biomarkers have received substantial attention because they can provide measurable evidence of the systemic inflammatory response before the diagnosis becomes clinically obvious. CRP is a hepatic acute-phase protein whose concentration rises following tissue injury and inflammatory stimulation. Although postoperative elevation is expected, persistent or disproportionate increases may indicate an infectious complication, including anastomotic leakage.

PCT is another biomarker associated with bacterial infection and systemic inflammatory responses. It may complement CRP because the two markers reflect overlapping but different biological processes. [7-11]

WBC count is routinely available and inexpensive, but its predictive performance when used alone is limited. Serum albumin may provide additional information about nutritional status, inflammation, and physiological reserve. Neither marker should be interpreted in isolation. Leukocyte counts are affected by surgical stress, medications, and infection elsewhere, while albumin is

influenced by inflammation, fluid shifts, hepatic function, and nutritional status.

In addition to laboratory markers, patient and operative characteristics may contribute to leakage risk. Relevant factors include age, diabetes mellitus, smoking, anemia, malnutrition, emergency surgery, contamination, intraoperative blood loss, prolonged operative duration, and the anatomical site of anastomosis. Their contributions may differ between elective and emergency operations and between upper and lower gastrointestinal procedures.

Although CRP and PCT have been extensively studied after colorectal surgery, evidence cannot automatically be generalized to every gastrointestinal anastomosis. A prospective cohort that records both serial biomarkers and procedure-specific characteristics may help clarify their predictive value in a broader surgical population.

This study was therefore designed to evaluate the association of serial inflammatory biomarkers, serum albumin, and perioperative variables with anastomotic leakage following gastrointestinal surgery.

Objectives

Primary Objective

To determine the predictive value of CRP and PCT measured on postoperative day 3 for anastomotic leakage within 30 days of gastrointestinal surgery.

Secondary Objectives

1. To evaluate the association of postoperative WBC count and serum albumin with anastomotic leakage.
2. To assess the predictive value of changes in CRP and PCT between postoperative days 1 and 3.
3. To identify relevant patient-related and intraoperative predictors of leakage.
4. To evaluate the association between anastomotic leakage and reoperation,

length of hospital stay, and 30-day mortality.

5. To assess whether a combined clinical and biomarker model improves discrimination compared with individual biomarkers.

Materials and Methods

Study Design and Setting

A prospective observational cohort study was designed for adult patients undergoing gastrointestinal surgery at Shalamar Medical and Dental College, Lahore, Pakistan.

The study would not alter routine clinical care. Investigations, imaging, antibiotics, drainage, and reoperation would be undertaken by the treating team according to clinical indications.

Study Population

The target population would comprise patients undergoing elective or emergency gastrointestinal surgery involving an esophageal, gastric, small-intestinal, or colorectal anastomosis.

The anatomical site and surgical approach would be documented for every participant. Where feasible, upper gastrointestinal and colorectal anastomoses would be analyzed separately or included as a prespecified adjustment variable in the overall model.

Sample Size

The proposed sample size is 400 patients.

The final sample size should be justified using the expected incidence of leakage in the participating surgical population, the anticipated diagnostic performance of postoperative day 3 CRP or PCT, and the number of candidate predictors. If the expected leakage rate is approximately 8%, a cohort of 400 patients would yield around 32 leakage events. This may be insufficient for a large multivariable model. Predictor selection and model complexity must therefore be restricted, or a larger multicenter cohort should be considered.

Inclusion Criteria

Patients would be eligible if they:

1. Were aged 18 years or older.
2. Underwent gastrointestinal surgery with creation of a primary anastomosis.
3. Had an elective or emergency procedure.
4. Had baseline clinical and laboratory data available.
5. Could be followed for postoperative outcomes through 30 days.
6. Provided informed consent according to institutional ethics requirements.

Exclusion Criteria

Patients would be excluded if they:

1. Had a pre-existing anastomotic leak before the index operation.
2. Underwent surgery without creation of an anastomosis.
3. Had a planned staged procedure in which anastomotic integrity could not be assessed during the study period.
4. Had incomplete outcome ascertainment.
5. Were transferred to another facility before adequate outcome assessment, unless 30-day follow-up could be reliably obtained.

Patients with diabetes, anemia, malignancy, or emergency surgery would not automatically be excluded because these characteristics may be relevant predictors.

Data Collection

A structured case-report form would be used to record demographic, clinical, laboratory, operative, and outcome variables.

Patient-related variables:

- Age and sex.
- Body mass index.
- Smoking status.
- Diabetes mellitus.
- Hypertension and cardiovascular disease.
- Chronic kidney disease.
- Anemia.
- Preoperative albumin.
- Nutritional risk, where assessed.

- Preoperative CRP and WBC count.
- Elective or emergency presentation.
- Indication for surgery.
- Malignant or benign disease.
- Evidence of sepsis or contamination before surgery.

Operative variables:

- Anatomical site of anastomosis.
- Open, laparoscopic, or robotic approach.
- Elective or emergency surgery.
- Type of anastomosis.
- Hand-sewn or stapled technique.
- Duration of surgery.
- Estimated blood loss.
- Intraoperative transfusion.
- Degree of contamination.
- Intraoperative hemodynamic instability.
- Diversion or protective stoma.
- Surgeon and institutional factors, where appropriate and ethically approved.

Laboratory Measurements

CRP, PCT, WBC count, and serum albumin would be recorded preoperatively and on postoperative days 1, 3, and 5, where clinically and operationally feasible.

CRP would be reported in mg/L, PCT in ng/mL, WBC count in $\times 10^9/L$, and albumin in g/L.

Measurements would be performed using the hospital laboratory's standardized methods. The timing of blood collection would be recorded, and laboratory staff would follow routine quality-control procedures.

The primary biomarker time point would be postoperative day 3 because this timing is supported by existing colorectal surgery literature and may provide useful early risk stratification. However, the optimal threshold must be evaluated within the actual study population rather than assumed in advance.

Definition of Anastomotic Leakage

Anastomotic leakage would be defined as a defect in the integrity of the gastrointestinal

anastomosis that results in communication between the intraluminal and extraluminal compartments, confirmed through one or more appropriate clinical, radiological, endoscopic, or operative findings.

Confirmation could include:

- Contrast extravasation on imaging.
- A collection or abscess associated with the anastomosis and judged to represent leakage.
- Direct visualization of an anastomotic defect during endoscopy or surgery.
- Enteric contents from a drain or wound, where consistent with an anastomotic defect.
- Operative evidence of dehiscence or anastomotic breakdown.

A predefined adjudication process should be used to distinguish confirmed leakage from suspected leakage and from other postoperative infections. The definition and grading system should be selected before enrollment and applied consistently.

Follow-up

Patients would be monitored during hospitalization and followed for 30 days after surgery. Clinical observations would include temperature, heart rate, abdominal findings, gastrointestinal function, drain characteristics, hemodynamic status, and evidence of organ dysfunction.

Patients with concerning clinical findings would undergo investigations according to the treating team's judgment. These could include abdominal CT with appropriate enteral contrast, other site-specific imaging, endoscopy, or operative assessment.

The study would record the date of first clinical suspicion, date of confirmation, anatomical site, severity, treatment, and outcome of leakage.

Outcome Measures

Primary outcome: Confirmed anastomotic leakage within 30 days of the index operation.

Secondary outcomes:

- Time from surgery to confirmed leakage.
- Severity or grade of leakage.
- Need for percutaneous drainage.
- Need for reoperation.
- Postoperative sepsis.
- ICU admission or readmission.
- Length of hospital stay.
- 30-day readmission.
- 30-day mortality.

Statistical Analysis

Data would be analyzed using SPSS or an equivalent statistical package.

Continuous variables would be assessed for distribution and summarized as mean and standard deviation or median with interquartile range. Categorical variables would be reported as frequencies and percentages.

Patients with and without leakage would be compared using the independent-samples t-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

ROC curves would be constructed for postoperative day 1, day 3, and day 5 CRP and PCT measurements. Areas under the curve with 95% confidence intervals would be reported. Sensitivity, specificity, positive predictive value, and negative predictive value would be calculated for prespecified or internally selected thresholds, with appropriate acknowledgment that predictive values depend on leakage prevalence.

A multivariable logistic regression model would be used to estimate independent associations with leakage. The model would be parsimonious because the number of leakage events limits the number of predictors that can be reliably estimated. Candidate predictors would be selected on clinical grounds and according to the prespecified analysis plan, rather than relying solely on univariable p-values.

Anatomical site, emergency surgery, and other major confounders would be

considered. Missing data, model calibration, and potential overfitting would be assessed. Internal validation using bootstrapping

would be preferable to reporting apparent model performance alone.

A two-sided p-value below 0.05 would be considered statistically significant.

Results

Baseline Characteristics

In the cohort of 400 patients, 32 (8.0%) developed anastomotic leakage within 30 days. The proportion of patients with leakage was higher among those undergoing emergency surgery and among those with greater intraoperative blood loss.

Table 1. Baseline and Operative Characteristics According to Anastomotic Leakage

Characteristic	Leakage (n = 32)	No leakage (n = 368)	p-value
Age, years	61.8 ± 13.6	57.9 ± 14.8	0.145
Male sex	21 (65.6%)	226 (61.4%)	0.643
Diabetes mellitus	13 (40.6%)	101 (27.4%)	0.116
Preoperative albumin, g/L	31.8 ± 5.4	36.2 ± 5.8	<0.001
Emergency surgery	15 (46.9%)	92 (25.0%)	0.008
Operative duration, minutes	228 ± 64	183 ± 57	<0.001
Estimated blood loss, mL	420 (250–650)	250 (150–400)	0.002
Intraoperative transfusion	8 (25.0%)	39 (10.6%)	0.019
Colorectal anastomosis	19 (59.4%)	180 (48.9%)	0.250

Table 2. Postoperative Laboratory Parameters According to Anastomotic Leakage

Characteristic	Postoperative day	Leakage (n = 32)	No leakage (n = 368)	p-value
CRP, mg/L	POD1	112 ± 39	91 ± 35	0.002
CRP, mg/L	POD3	218 ± 71	104 ± 48	<0.001
CRP, mg/L	POD5	196 ± 83	61 ± 36	<0.001
PCT, ng/mL	POD1	1.8 (0.9–3.4)	0.8 (0.4–1.6)	0.004
PCT, ng/mL	POD3	3.1 (1.5–6.8)	0.5 (0.2–1.1)	<0.001
PCT, ng/mL	POD5	2.7 (0.9–7.1)	0.3 (0.1–0.8)	<0.001

Characteristic	Postoperative day	Leakage (n = 32)	No leakage (n = 368)	p-value
WBC count, $\times 10^9/L$	POD3	14.2 ± 4.1	10.8 ± 3.6	<0.001
Albumin, g/L	POD3	27.9 ± 4.8	31.6 ± 5.1	<0.001

Note: CRP = C-reactive protein; PCT = procalcitonin; WBC = white blood cell count; POD = postoperative day.

Table 3. Diagnostic Performance of Biomarkers for Anastomotic Leakage

Biomarker or prediction model	AUC	95% confidence interval
POD1 CRP	0.66	0.56–0.76
POD3 CRP	0.83	0.76–0.90
POD5 CRP	0.87	0.80–0.94
POD3 PCT	0.81	0.72–0.90
POD5 PCT	0.84	0.76–0.92
POD3 WBC count	0.69	0.59–0.79
POD3 CRP and PCT	0.87	0.80–0.94
Combined clinical and biomarker model	0.89	0.83–0.95

Note: All AUCs and confidence intervals are . AUC = area under the receiver operating characteristic curve.

Table 4. Multivariable Logistic Regression for Anastomotic Leakage

Predictor	Adjusted odds ratio	95% confidence interval	p-value
POD3 CRP, per 50 mg/L increase	1.42	1.16–1.74	0.001
POD3 PCT, per 1 ng/mL increase	1.28	1.08–1.51	0.004
Preoperative albumin, per 5 g/L decrease	1.51	1.10–2.07	0.011
Emergency surgery	1.82	0.86–3.86	0.118
Operative duration, per 30-minute increase	1.19	1.01–1.40	0.036

OR = odds ratio; CRP = C-reactive protein; PCT = procalcitonin. The model requires appropriate validation and may be too complex for the proposed number of leakage events.

Table 5. Postoperative Outcomes According to Anastomotic Leakage

Outcome	Leakage (n = 32)	No leakage (n = 368)
Reoperation	15 (46.9%)	8 (2.2%)
Percutaneous drainage	10 (31.3%)	5 (1.4%)
ICU admission or readmission	17 (53.1%)	38 (10.3%)
Length of hospital stay, days	19 (13–28)	7 (5–10)
30-day mortality	4 (12.5%)	7 (1.9%)

Discussion

This prospective cohort study is designed to investigate whether routinely available inflammatory biomarkers, nutritional indicators, and operative factors can identify patients at increased risk of anastomotic leakage following gastrointestinal surgery.

The principal hypothesis is that persistent postoperative inflammatory activation, particularly an elevated CRP or PCT concentration on postoperative day 3, may identify patients who require further clinical assessment. The value of these markers is likely to be greatest when they are interpreted alongside the patient's clinical trajectory, surgical procedure, and baseline risk.

CRP as an Early Predictor

CRP is widely available and relatively inexpensive, making it a practical candidate for postoperative surveillance. Surgical tissue injury causes an expected inflammatory response; therefore, a single elevated value immediately after surgery is not sufficient to diagnose leakage.

The postoperative trajectory may be more informative than the absolute concentration at one time point. A persistently elevated or rising CRP on postoperative days 3–5 may increase suspicion of a complication,

especially when accompanied by tachycardia, abdominal pain, ileus, fever, or clinical deterioration. [11-13]

A systematic review and meta-analysis of colorectal surgery studies found that CRP measured on postoperative days 3–5 may help identify patients at low risk when concentrations remain below suitable thresholds. Its strongest practical role may be to support exclusion of leakage in clinically stable patients rather than to establish the diagnosis by itself.

The thresholds reported in previous studies should not automatically be applied to every gastrointestinal procedure. The expected inflammatory response, prevalence of leakage, and consequences of a false-negative result differ across surgical settings. A threshold developed in colorectal surgery may not have equivalent performance after esophagectomy or gastric surgery. [14-16]

Procalcitonin and Bacterial Complications

PCT may complement CRP by providing additional information about systemic bacterial infection and inflammatory complications. In the proposed study, serial PCT measurements would be examined to determine whether they improve discrimination beyond CRP alone.

However, PCT may also rise in severe noninfectious illness, major surgery, and organ dysfunction. Renal impairment and other clinical factors can influence its concentration. Consequently, elevated PCT should prompt contextual clinical assessment rather than automatically trigger antibiotics or invasive investigations.

The most useful question is not whether PCT is elevated in patients with leakage, but whether it adds meaningful predictive information after accounting for CRP, operative factors, and clinical status. [17-18]

White Blood Cell Count and Albumin

WBC count is readily available but nonspecific. Leukocytosis may occur after uncomplicated surgery, while some patients with serious infection may not develop marked leukocytosis. Its role is therefore likely to be complementary rather than independent.

Albumin may reflect nutritional reserve, systemic inflammation, and illness severity. Low preoperative albumin may be associated with poor healing and adverse surgical outcomes, but postoperative albumin changes can also result from fluid shifts and the acute inflammatory response. A prospective study should distinguish preoperative albumin, which may help characterize baseline risk, from postoperative albumin, which is affected by events after surgery.

Importance of Operative and Patient-Related Factors

Biomarkers should not replace assessment of established clinical and operative risk factors. Emergency procedures, contamination, intraoperative blood loss, prolonged surgery, and the anatomical site of the anastomosis may all influence risk. [19-20]

These factors can also confound biomarker associations. For example, patients undergoing emergency surgery may have higher inflammatory markers before the procedure and a greater risk of postoperative complications. A multivariable model should

therefore include a carefully selected set of clinically justified covariates.

The proposed sample size also deserves attention. With an expected leakage incidence of 8%, 400 patients would yield approximately 32 events. This is useful for estimating incidence and comparing a limited number of prespecified markers, but it does not support an unrestricted model containing many independent predictors. A larger multicenter cohort may be required for reliable model development and validation.

Implications for Postoperative Management

If validated, serial CRP and PCT measurements could help identify patients who need closer surveillance, repeat examination, or targeted imaging. Conversely, low inflammatory-marker concentrations may support early discharge in selected clinically stable patients when the overall clinical assessment is reassuring.

Biomarkers should never override concerning clinical findings. A patient with peritonitis, hemodynamic instability, or clear evidence of leakage requires prompt surgical assessment regardless of CRP or PCT results. Similarly, a high CRP alone does not establish an anastomotic defect.

The clinical utility of a prediction model depends on whether it improves decisions and patient outcomes, not simply whether it achieves a high AUC. Future validation should assess calibration, false-negative rates, decision thresholds, and whether implementation reduces delayed diagnosis without increasing unnecessary CT examinations, antibiotics, or reoperations.

Strengths

1. Prospective data collection.
2. Evaluation of serial biomarkers rather than a single postoperative measurement.
3. Inclusion of patient-related and operative risk factors.
4. Assessment of clinically important outcomes through 30 days.

5. Potential application to a broad gastrointestinal surgical population.
6. Use of a standardized leakage definition and predefined follow-up.

Limitations

First, the incidence and predictors of leakage vary substantially by anatomical site and procedure. Combining different gastrointestinal anastomoses may obscure procedure-specific effects.

Second, CRP and PCT are nonspecific and may rise due to postoperative inflammation or infections unrelated to leakage.

Third, the proposed sample size may yield too few leakage events for a complex prediction model.

Fourth, biomarkers measured only on selected postoperative days may miss changes occurring between samples.

Fifth, decisions to perform imaging or reoperation may be influenced by clinicians' knowledge of laboratory results, potentially introducing ascertainment bias.

Sixth, thresholds selected within the same cohort may overestimate diagnostic performance unless internally and externally validated.

Finally, the numerical results in this manuscript are and cannot be interpreted as evidence of actual associations.

Conclusion

Serial postoperative CRP and PCT, interpreted alongside serum albumin, patient characteristics, operative variables, and clinical findings, represent a practical approach to investigating early predictors of anastomotic leakage after gastrointestinal surgery.

Postoperative day 3 inflammatory markers are particularly relevant candidates, but their diagnostic performance should be assessed separately by anatomical site where possible. A parsimonious, validated prediction model may improve postoperative risk stratification. However, no biomarker should replace

clinical examination, appropriate imaging, or timely surgical assessment.

A sufficiently powered prospective cohort using standardized outcome definitions and real patient data is required to establish reliable thresholds and demonstrate clinical utility.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287.
2. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010;147(3):339–351. doi:10.1016/j.surg.2009.10.012.
3. Consensus on the definition of colorectal anastomotic leakage: a modified Delphi study. *World Journal of Gastroenterology*. 2020;26(23):3293–3303. PMID:32684743.
4. Aiolfi A, et al. C-reactive protein and procalcitonin levels to predict anastomotic leak after colorectal surgery: systematic review and meta-analysis. *Journal of Gastrointestinal Surgery*. 2023;27(1):166–179. PMID:36175720.
5. Predictive biomarkers for the early detection of anastomotic leaks in colorectal surgeries: a systematic review. 2024. PMID:39735081.
6. McKechnie T, Cloutier Z, et al. Using preoperative C-reactive protein levels to predict anastomotic leaks and other complications after elective colorectal surgery: a systematic review and meta-analysis. *Colorectal Disease*. 2024;26(6):1114–1130. doi:10.1111/codi.17017.
7. Italian multi-society modified Delphi consensus on the definition and management of anastomotic leakage in colorectal surgery. 2020. PMID:32613380.

8. Diagnosis and definition of anastomotic leakage from the surgeon's perspective. 2010. PMID:21107971.
9. Early postoperative systemic inflammatory response as predictor of anastomotic leakage after esophagectomy: a systematic review and meta-analysis. *Journal of Gastrointestinal Surgery*. 2024;28(5):757–765. doi:10.1016/j.gassur.2024.02.003.
10. Additional procedure-specific literature on postoperative CRP and PCT thresholds should be selected and bibliographically verified before journal submission.
11. Aiolfi A, et al. C-reactive protein and procalcitonin levels to predict anastomotic leak after colorectal surgery: systematic review and meta-analysis. *Journal of Gastrointestinal Surgery*. 2023;27(1):166–179. Available from: <https://pubmed.ncbi.nlm.nih.gov/36175720/>.
12. Yeung DE, Peterknecht E, Hajibandeh S, Hajibandeh S, Torrance AW. C-reactive protein can predict anastomotic leak in colorectal surgery: a systematic review and meta-analysis. *International Journal of Colorectal Disease*. 2021;36(6):1147–1162. doi:10.1007/s00384-021-03854-5.
13. McKechnie T, Cloutier Z, Archer V, et al. Using preoperative C-reactive protein levels to predict anastomotic leaks and other complications after elective colorectal surgery: a systematic review and meta-analysis. *Colorectal Disease*. 2024;26(6):1114–1130. doi:10.1111/codi.17017.
14. Almutairi et al. Role of biomarkers in the diagnosis of anastomotic leakage after colorectal surgery: a systematic review and meta-analysis. 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39011204/>.
15. Predictive biomarkers for the early detection of anastomotic leaks in colorectal surgeries: a systematic review. 2024. Available from: <https://pubmed.ncbi.nlm.nih.gov/39735081/>.
16. CRP in drain fluid as a predictive marker of anastomotic leak in colorectal surgery: a systematic review of the literature. 2023. Available from: <https://pubmed.ncbi.nlm.nih.gov/37369500/>.
17. Predictors that identify complications such as anastomotic leak in colorectal surgery: a systematic review. *Cureus*. 2022. doi:10.7759/cureus.28894.
18. 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. *British Journal of Surgery*. 2015;102(5):462–479.
19. van Rooijen SJ, Huisman D, Stuijvenberg M, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together. *International Journal of Surgery*. 2016;36(Pt A):183–200.
20. Risk and protective factors for postoperative anastomotic leakage in esophageal and gastrointestinal surgery: an umbrella review of meta-analyses and systematic reviews. 2025. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12825836/>.