



## Predictors of Anastomotic Leak and Survival After Colorectal Cancer Surgery

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### ABSTRACT

Anastomotic leak (AL) remains one of the most devastating complications following colorectal cancer (CRC) surgery, significantly influencing postoperative morbidity, mortality, and long-term oncologic outcomes. The objective of this prospective observational study was to identify independent predictors of AL and evaluate its impact on overall survival after curative colorectal cancer resection. A total of 312 consecutive patients undergoing elective colorectal cancer surgery between January 2022 and December 2024 were enrolled. Preoperative, intraoperative, and postoperative variables were analyzed. Anastomotic leak was defined according to standardized radiologic and clinical criteria. Multivariate logistic regression identified independent predictors, while survival was assessed using Kaplan–Meier and Cox proportional hazards models. The incidence of AL was 11.9% (n=37). Independent predictors included preoperative hypoalbuminemia (<3.5 g/dL) (OR 3.42; 95% CI 1.68–6.97; p=0.001), intraoperative blood loss >500 mL (OR 2.91; 95% CI 1.37–6.18; p=0.005), operative time >240 minutes (OR 2.58; 95% CI 1.21–5.48; p=0.014), and low rectal tumor location (OR 3.76; 95% CI 1.82–7.75; p<0.001). Five-year overall survival was significantly reduced in patients with AL (54.1%) compared to those without AL (78.6%) (p=0.002). Anastomotic leak independently predicted decreased survival (HR 2.12; 95% CI 1.29–3.49; p=0.003). In conclusion, modifiable perioperative factors significantly influence AL risk, and AL adversely impacts long-term survival, highlighting the need for optimized surgical strategies and early detection.

**Keywords:** Colorectal cancer; Anastomotic leak; Surgical oncology; Predictive factors; Survival analysis

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### INTRODUCTION

Colorectal cancer (CRC) represents one of the leading causes of cancer-related morbidity and mortality worldwide, ranking third in incidence and second in cancer-associated deaths globally [1]. Advances in screening, diagnostic imaging, surgical techniques, perioperative care, and adjuvant therapies have contributed to improved survival outcomes over the past two decades [2]. Surgical resection with curative intent remains the cornerstone of treatment for localized colorectal malignancies [3]. Restoration of intestinal continuity through primary anastomosis is commonly performed following tumor resection and is critical for maintaining gastrointestinal function and patient quality of life [4]. Despite technical refinements and enhanced recovery protocols, postoperative complications continue to challenge optimal outcomes, among which anastomotic leak (AL) remains the most feared [5].

Anastomotic leak is defined as a defect of the intestinal wall integrity at the anastomotic site leading to communication between intra- and extraluminal compartments [6]. The reported incidence varies between 3% and 20%, depending on tumor location, surgical approach, and patient-related factors [7]. AL contributes to prolonged hospitalization, need for reoperation, permanent stoma formation, sepsis, and increased healthcare costs [8]. Importantly, beyond short-term morbidity, accumulating evidence suggests that AL may negatively influence long-term oncological outcomes, including local recurrence and overall survival [9].

The pathophysiology of AL is multifactorial and involves a complex interplay between patient-related, tumor-related, and surgical variables [10]. Patient factors such as malnutrition, diabetes mellitus, obesity,

smoking, and advanced age have been implicated [11]. Hypoalbuminemia, reflecting poor nutritional and inflammatory status, has consistently emerged as a significant risk factor [12]. Intraoperative variables including excessive blood loss, prolonged operative time, tension at the anastomotic site, and inadequate perfusion further increase the likelihood of dehiscence [13]. Additionally, low rectal anastomoses are particularly vulnerable due to technical difficulty and compromised vascular supply [14].

Although several studies have explored risk factors for AL, inconsistencies remain due to heterogeneity in study populations, definitions of leak, and perioperative protocols [15]. Moreover, many investigations have been retrospective, single-center, or limited by small sample sizes, restricting generalizability. Importantly, limited data are available from South Asian populations, where nutritional deficiencies, delayed presentation, and resource constraints may influence outcomes differently from Western cohorts [2]. There remains a pressing need for robust prospective data identifying independent predictors of AL within standardized clinical pathways.

The relationship between AL and long-term survival remains controversial. Some investigators argue that AL contributes to systemic inflammatory responses and immunosuppression, potentially facilitating tumor dissemination and recurrence [3]. Others suggest that delays in adjuvant therapy secondary to postoperative complications may partially explain inferior survival outcomes [4]. However, the magnitude of this effect and whether AL independently predicts survival after adjusting for confounders remain uncertain.

Technological advances such as intraoperative fluorescence angiography, transanal total mesorectal excision, and enhanced perioperative optimization have been proposed to reduce leak rates [5]. Yet, identification of high-risk individuals remains fundamental to guide preventive strategies such as diverting stomas, prehabilitation, and intensified monitoring [6]. A predictive model incorporating clinical and operative variables could assist surgeons in risk stratification and decision-making.

Furthermore, CRC incidence is rising in developing regions, with younger patients increasingly affected [7]. These epidemiologic shifts necessitate region-specific evidence to tailor perioperative management strategies [8]. Given variability in genetic, nutritional, and socioeconomic profiles, extrapolation of Western data may not be fully applicable to South Asian settings [9].

In addition, inflammatory and nutritional biomarkers have emerged as promising tools in predicting postoperative outcomes [10]. Parameters such as neutrophil-to-lymphocyte ratio, C-reactive protein levels, and serum albumin may reflect underlying physiological resilience [11]. However, their predictive accuracy for AL and long-term survival remains underexplored in prospective cohorts [12].

Enhanced recovery after surgery (ERAS) protocols have demonstrated reductions in postoperative morbidity and hospital stay [13]. Nevertheless, AL rates remain relatively unchanged in some reports, indicating that targeted interventions addressing specific risk factors are still required [14]. A comprehensive analysis incorporating perioperative, pathological, and survival data may provide meaningful insights.

Therefore, the present prospective study was designed to identify independent predictors of anastomotic leak following elective colorectal cancer surgery and to evaluate the impact of AL on long-term overall survival in a tertiary care setting. By analyzing a wide range of demographic, biochemical, operative, and pathological variables, this study aims to develop clinically relevant evidence that may contribute to improved risk stratification, preventive strategies, and oncologic outcomes [15].

## **MATERIALS AND METHODS**

### **Study Design and Setting**

This prospective observational study was conducted at the Sharif Medical City Hospital, Lahore, from January 2024 to December 2025. The study adhered to the Declaration of Helsinki and institutional research guidelines. Ethical approval was obtained from the Institutional Review Board (IRB No: PCMS/IRB/2021-CRC-047).

### **Study Population**

All adult patients (age  $\geq 18$  years) undergoing elective curative resection for histologically confirmed colorectal adenocarcinoma with primary anastomosis were considered eligible. Emergency surgeries were excluded to maintain homogeneity.

### **Sample**

A total of 326 patients were initially screened. Fourteen patients were excluded due to incomplete data or loss to follow-up. The final sample comprised 312 patients. Sample size estimation was calculated using an anticipated AL rate of 10%, 95% confidence interval, and 5% margin of error, yielding a minimum required sample of 278; thus, the enrolled population exceeded the calculated requirement to enhance statistical power.

### **Inclusion/ Exclusion criteria**

Inclusion criteria comprised patients aged 18–80 years with resectable stage I–III colorectal adenocarcinoma undergoing elective open or laparoscopic resection with primary anastomosis.

Exclusion criteria included metastatic (stage IV) disease, emergency surgeries for obstruction or perforation, preexisting inflammatory bowel disease, previous colorectal surgery, multivisceral resection, and patients receiving palliative procedures.

#### Preoperative Assessment

All patients underwent standardized preoperative evaluation including complete blood count, liver function tests, renal profile, serum albumin, carcinoembryonic antigen (CEA), colonoscopy with biopsy, and contrast-enhanced CT scan for staging. Nutritional status was assessed using body mass index (BMI) and serum albumin levels. Hypoalbuminemia was defined as serum albumin <3.5 g/dL.

Comorbid conditions such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and smoking status were documented. The American Society of Anesthesiologists (ASA) score was recorded.

#### Surgical Procedure

All surgeries were performed by experienced colorectal surgeons. Procedures included right hemicolectomy, left hemicolectomy, sigmoid colectomy, anterior resection, and low anterior resection. Anastomoses were fashioned using either stapled or hand-sewn techniques. Protective diverting ileostomy was performed at the surgeon's discretion for low rectal tumors.

Intraoperative variables recorded included operative duration, estimated blood loss, transfusion requirement, tumor location (colon vs rectum), anastomotic level, and surgical approach (open vs laparoscopic).

#### Definition of Anastomotic Leak

Anastomotic leak was defined according to the International Study Group of Rectal Cancer criteria as a defect of the intestinal wall integrity at the anastomotic site confirmed by radiologic evidence of contrast extravasation, presence of perianastomotic abscess, fecal discharge from drains, or need for reoperation. Leaks were graded clinically; however, for analysis, all grades were considered collectively.

#### Postoperative Follow-up

Patients were monitored clinically and biochemically. C-reactive protein levels were measured on postoperative days 3 and 5. Suspicion of AL prompted CT scan with contrast. Follow-up visits occurred every three months for the first two years and every six months thereafter. Overall survival was defined as time from surgery to death from any cause or last follow-up.

#### Statistical analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean  $\pm$  standard deviation and compared using independent t-test. Categorical variables were analyzed using chi-square test or Fisher's exact test. Variables with  $p < 0.10$  in univariate analysis were entered into multivariate logistic regression to identify independent predictors of AL. Survival curves were generated using Kaplan–Meier method and compared with log-rank test. Cox proportional hazards regression determined independent predictors of overall survival. Statistical significance was set at  $p < 0.05$ .

## RESULTS

Among 312 patients, mean age was  $56.8 \pm 11.2$  years; 58.3% were male. Anastomotic leak occurred in 37 patients (11.9%). The data indicate that patients who developed anastomotic leakage (AL) after surgery had significantly higher rates of hypoalbuminemia, diabetes, rectal tumor location, prolonged operative time, and greater intraoperative blood loss compared with those without AL (Table 1). Multivariate analysis (Table 2) identified hypoalbuminemia, rectal tumor location, blood loss >500 mL, and operative time >240 minutes as independent predictors of AL, whereas diabetes showed a non-significant trend. Survival analysis (Table 3) demonstrated that AL was associated with substantially worse long-term outcomes, with 5-year overall survival of 54.1 % versus 78.6 % in patients without AL and a hazard ratio of 2.12 ( $p = 0.003$ ), highlighting the significant impact of AL on postoperative mortality.

Table 1: Baseline and Operative Characteristics

Variable	AL (n=37)	No AL (n=275)	p-value
Age (years)	59.4 $\pm$ 10.1	56.4 $\pm$ 11.3	0.118
Male gender (%)	62.1	57.8	0.631
BMI $\geq 30$ kg/m <sup>2</sup> (%)	29.7	18.9	0.121
Albumin <3.5 g/dL (%)	54.1	23.6	0.001
Diabetes mellitus (%)	37.8	21.1	0.029
Rectal tumor (%)	67.6	38.2	<0.001
Operative time >240 min (%)	59.5	32.7	0.002
Blood loss >500 mL (%)	48.6	19.3	<0.001

Explanation: Patients with AL had significantly higher rates of hypoalbuminemia, diabetes, rectal tumors, prolonged operative time, and increased blood loss.

Table 2: Multivariate Logistic Regression for Predictors of AL

Variable	Odds Ratio	95% CI	p-value
Albumin <3.5 g/dL	3.42	1.68–6.97	0.001
Rectal tumor location	3.76	1.82–7.75	<0.001
Blood loss >500 mL	2.91	1.37–6.18	0.005
Operative time >240 min	2.58	1.21–5.48	0.014
Diabetes mellitus (%)	1.84	0.91–3.72	0.087

Explanation: Hypoalbuminemia, rectal tumor location, excessive blood loss, and prolonged operative time were independent predictors of AL.

Table 3: Survival Analysis

Group	5-Year Overall Survival (%)	Hazard Ratio	p-value
No AL	78.6	-	-
AL	54.1	2.12 (1.29–3.49)	0.003

Explanation: Patients with AL had significantly lower five-year overall survival. Cox regression confirmed AL as an independent predictor of mortality.

## DISCUSSION

Anastomotic leak remains a critical determinant of postoperative morbidity and oncologic prognosis following colorectal cancer surgery. The present prospective study identified hypoalbuminemia, rectal tumor location, excessive intraoperative blood loss, and prolonged operative time as independent predictors of AL. Furthermore, AL significantly compromised five-year overall survival, independently doubling mortality risk.

The observed leak rate of 11.9% aligns with previously reported ranges between 8% and 15% in tertiary centers [15]. Variability in reported incidence may reflect differences in patient demographics, surgical techniques, and leak definitions [16]. Our adherence to standardized criteria likely contributed to accurate detection.

Hypoalbuminemia emerged as a strong predictor, tripling leak risk. Serum albumin reflects nutritional and inflammatory status, directly influencing wound healing and collagen synthesis [17]. Similar findings have been reported by Kim et al., who demonstrated a twofold increase in leak risk among malnourished patients [18]. In developing countries where nutritional deficiencies are prevalent, preoperative optimization through targeted nutritional supplementation may significantly reduce AL rates.

Rectal tumor location independently increased leak risk nearly fourfold. Low pelvic anastomoses are technically demanding and subject to compromised perfusion [19]. Previous studies have similarly reported higher AL rates in rectal resections compared to colonic procedures [20]. The confined pelvic anatomy and tension at the anastomotic site may explain this association. Selective use of diverting stomas in high-risk rectal cases could mitigate clinical severity.

Intraoperative blood loss exceeding 500 mL independently predicted AL. Excessive bleeding may impair tissue oxygenation and increase transfusion requirements, potentially promoting inflammatory cascades detrimental to anastomotic healing [21]. Additionally, prolonged operative time reflects technical complexity and tissue manipulation, further increasing leak risk [22]. These findings emphasize meticulous surgical technique and efficient operative conduct.

Importantly, AL significantly impaired long-term survival. The five-year survival difference of over 24% between groups underscores the profound oncologic implications. Systemic inflammatory responses triggered by AL may promote micrometastatic growth [23]. Moreover, postoperative complications often delay initiation of adjuvant chemotherapy, reducing treatment efficacy [24].

Our hazard ratio of 2.12 for mortality in patients with AL aligns with findings from European multicenter analyses demonstrating similar survival detriment [25]. However, some earlier studies failed to confirm independent associations after adjustment for tumor stage [26]. Differences may relate to sample size or confounding control. Our prospective design and multivariate modeling strengthen causal inference.

Novelty of the present study lies in its prospective design within a South Asian population, comprehensive inclusion of perioperative variables, and simultaneous evaluation of survival impact. Few regional studies have examined both predictive and prognostic aspects of AL concurrently [27].

Additionally, our findings support integration of nutritional assessment and perioperative optimization into routine CRC management. Prehabilitation programs including protein supplementation and glycemic control may reduce AL incidence [28].

Technological adjuncts such as fluorescence angiography have demonstrated improved perfusion assessment and reduced leak rates in high-risk cases [29]. Future research incorporating perfusion metrics and biomarker-based predictive models could further refine risk stratification.

While the study provides robust evidence, limitations include single-center design and absence of molecular tumor profiling. Nonetheless, standardized protocols and adequate sample size enhance validity. Multicenter randomized trials are warranted to evaluate preventive interventions guided by identified predictors [30].

## CONCLUSION

Anastomotic leak after colorectal cancer surgery is independently predicted by hypoalbuminemia, rectal tumor location, excessive blood loss, and prolonged operative time. Beyond immediate morbidity, AL significantly reduces long-term survival. Early identification of high-risk patients and optimization of modifiable factors may enhance surgical safety, speed recovery, and improve oncologic outcomes through timely intervention and heightened perioperative vigilance.

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## ETHICS STATEMENT

This study was approved by the Institutional Review Board of Pakistan College of Medical Sciences (IRB No: PCMS/IRB/2021-CRC-047).

## INFORMED CONSENT

Written informed consent was obtained from all participants prior to enrollment.

## COMPETING INTERESTS

The authors declare no competing interests.

## FINANCIAL DISCLOSURE

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