

Postoperative C-reactive protein for detecting anastomotic leakage after elective laparoscopic colorectal resection: a prospective cohort study

Diego Gianetti Bahamonde

dgianettib@gmail.com

Hospital San Juan de Dios, Santiago, Chile <https://orcid.org/0009-0008-9282-0140>

Francisco Rivera Roa

Hospital San Juan de Dios, Santiago, Chile <https://orcid.org/0009-0005-0641-9632>

Fabio Paoletto

Hospital San Juan de Dios, Santiago, Chile

Manuel Lizana Corvera

Hospital San Juan de Dios, Santiago, Chile <https://orcid.org/0009-0001-5196-2897>

Research Article

Keywords: C-reactive protein, anastomotic leakage, laparoscopic colorectal surgery, postoperative complications, colorectal cancer

Posted Date: June 16th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10029864/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: The authors declare no competing interests.

Abstract

Purpose

Postoperative C-reactive protein (CRP) is widely used after colorectal surgery, but reported thresholds vary because of heterogeneous cohorts, outcome definitions, and perioperative pathways. This study evaluated CRP for detecting anastomotic leakage after elective laparoscopic colorectal resection and assessed whether diverting stoma status, empirical antibiotics, and CRP trajectory modify diagnostic performance.

Methods

We conducted a prospective observational cohort of consecutive adults undergoing elective laparoscopic colorectal resection with intestinal anastomosis between January 2017 and December 2025. Leakage was classified using a pragmatic modified ISREC-based grading system. The primary outcome was any anastomotic leakage. The predictive cohort excluded conversions, multivisceral resections, metastatic disease, and protective diverting stomas. CRP on postoperative days (POD) 2, 3, and 4 was evaluated using ROC analysis and Youden-derived thresholds.

Results

Among 367 patients, 347 formed the descriptive cohort and 260 the predictive cohort. In the predictive cohort, any leakage occurred in 28 patients (10.8%). POD4 CRP showed excellent discrimination, with an AUC of 0.930 and a threshold of 137.3 mg/L, yielding 92.9% sensitivity, 87.3% specificity, and 98.9% negative predictive value. POD4 CRP also performed well for invasive or surgical leakage. Absolute POD4 CRP outperformed trajectory-based metrics. Diagnostic performance was attenuated in diverted patients.

Conclusion

POD4 CRP provides a high-sensitivity, high-negative-predictive-value signal for excluding anastomotic leakage after elective laparoscopic colorectal resection. Its performance was superior to trajectory-based metrics but reduced in patients with protective diverting stomas, supporting context-specific interpretation and further evaluation of stoma-specific surveillance strategies. A reassuring POD4 CRP does not exclude delayed leakage; patients with post-discharge clinical deterioration warrant evaluation regardless of early CRP values. Because the threshold was derived and internally validated within a single cohort, external validation is required before clinical implementation.

INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide, accounting for approximately 1.9 million new cases annually and representing a leading cause of cancer-related mortality [1]. Its incidence continues to rise in countries undergoing epidemiological transition, including South America. In Chile, CRC is currently the second most frequently diagnosed cancer and the third leading cause of cancer-related death in both sexes, with an estimated incidence of 20.3 per 100,000 inhabitants [2].

Curative treatment of CRC relies primarily on resective surgery performed according to oncological principles, with minimally invasive approaches widely adopted in contemporary colorectal practice because of favourable short-term recovery and comparable oncological outcomes in selected patients [3–5]. Despite advances in surgical technique and perioperative management, postoperative complications remain common. Among these, anastomotic leakage (AL) is one of the most severe and clinically relevant complications following colorectal resection. The absence of a universally accepted definition and the heterogeneity in diagnostic criteria contribute to wide variability in reported incidence, ranging from 2% to 30% across published series [6, 7].

The occurrence of AL is associated with substantial short- and long-term consequences, including increased postoperative morbidity and mortality [6], impaired quality of life [8], higher healthcare costs [9], and adverse oncological outcomes, such as increased local recurrence and reduced overall, cancer-specific, and disease-free survival [10, 11].

Clinical diagnosis of AL is often delayed, typically occurring after the early postoperative period, when patients may already present with advanced sepsis or organ dysfunction [12–14]. In addition, AL risk is influenced by multiple patient- and surgery-related factors, including technical and anatomical variables [15]. Consequently, there is considerable interest in identifying reliable biomarkers that allow for earlier detection or safe exclusion of AL. C-reactive protein (CRP), an inexpensive and widely available inflammatory marker, has been extensively investigated as a postoperative biomarker for early detection of anastomotic leakage. Its principal value lies in its consistently high negative predictive value, reported in most series to exceed 95%, enabling clinicians to confidently rule out clinically relevant leakage and support early discharge or de-escalation of postoperative surveillance [12, 13]. Although CRP has limited specificity for confirming AL, its integration into

postoperative monitoring protocols may facilitate earlier intervention, potentially improving short-term outcomes and reducing length of hospital stay [16].

Despite extensive evidence supporting CRP-guided postoperative surveillance, reported cut-offs vary substantially across studies, reflecting differences in case mix, surgical approach, outcome definition, and institutional protocols. Most published series derive thresholds from open or mixed surgical cohorts and evaluate CRP against heterogeneous outcomes, limiting direct applicability to contemporary minimally invasive practice. Furthermore, empirical antibiotic treatment is frequently initiated in response to elevated early postoperative inflammatory markers, but its association with subsequent CRP values has not been well characterized. Similarly, whether a protective diverting stoma modifies CRP discriminatory ability remains incompletely defined. We therefore sought to address these gaps in a prospective laparoscopic cohort by evaluating CRP performance across multiple postoperative timepoints, analysing the effect of diverting stoma status, and describing CRP behaviour in patients exposed to empirical antibiotic treatment.

The primary objective of this study was to assess the diagnostic performance of C-reactive protein (CRP) measured on postoperative days (POD) 2, 3, and 4 for the detection of any anastomotic leakage after elective laparoscopic colorectal resection. Secondary objectives were to: (i) evaluate CRP performance for invasive or surgical leakage (ii) assess the influence of a protective diverting stoma on CRP discriminatory ability; (iii) compare absolute CRP values with trajectory-based metrics as predictors of anastomotic leakage; and (iv) characterize CRP patterns among patients who received empirical antibiotic treatment after elevated early postoperative CRP without confirmed leakage.

METHODS

Ethical aspects

This study was approved by the Scientific Ethics Committee of Hospital San Juan de Dios, Santiago, Chile. Owing to the observational nature of the study and the use of anonymized clinical data, the requirement for individual informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study design and population

We conducted a prospective observational cohort study including consecutive adult patients aged ≥ 18 years who underwent elective laparoscopic colorectal resection with construction of an intestinal anastomosis at our institution between January 2017 and December 2025.

Two analytic cohorts were defined. The descriptive cohort included all eligible patients with an intestinal anastomosis and was used to describe baseline characteristics, leakage incidence, leakage severity, and postoperative outcomes. Patients undergoing ileoanal or coloanal anastomosis were excluded from this cohort.

The predictive cohort was designed to evaluate the diagnostic performance of postoperative CRP under more homogeneous clinical conditions. For this analysis, patients were excluded if they underwent conversion to open surgery, multivisceral resection, resection in the setting of metastatic disease, or creation of a protective diverting stoma. Patients with diverting stomas were excluded from the primary diagnostic cohort because faecal diversion may modify the clinical presentation, severity grading, therapeutic management, and inflammatory expression of anastomotic leakage. These patients were retained in the descriptive cohort and evaluated separately in a stoma-stratified sensitivity analysis. The final cohort selection process is shown in Fig. 1.

Outcomes and follow-up

The primary outcome was anastomotic leakage of any grade occurring after elective laparoscopic colorectal resection with primary anastomosis. Anastomotic leakage was defined as a defect in the integrity of the intestinal wall at the anastomotic site, resulting in communication between the intraluminal and extraluminal compartments, according to the International Study Group of Rectal Cancer (ISREC) definition [17].

Leakage severity was classified using a pragmatic modified ISREC-based grading system. In contemporary postoperative practice, particularly within enhanced recovery pathways, clinical suspicion or radiological confirmation of a contained leak commonly triggers conservative medical measures. Because the original ISREC grade A definition requires no change in management, its rigid application may underrepresent medically managed contained leaks in non-diverted cohorts. Therefore, for the purposes of this study, modified grade A was defined as leakage requiring no intervention or strictly non-invasive conservative medical management, including transient fasting, observation, or empirical antibiotics. Modified grade B was defined as leakage requiring invasive non-surgical therapeutic intervention, such as percutaneous radiological drainage, endoscopic treatment, or transanal drainage. Modified grade C was defined as leakage requiring surgical reintervention.

Secondary outcomes included: (i) invasive or surgical anastomotic leakage, defined as modified grades B + C; (ii) diagnostic performance of CRP stratified by protective diverting stoma status; (iii) diagnostic performance of absolute CRP values compared with trajectory-based metrics, including absolute delta and ratio between postoperative timepoints; (iv) POD4 CRP patterns among patients who received empirical antibiotics without confirmed anastomotic leakage; and (v) postoperative outcomes, including major postoperative complications, length of hospital stay, 30-day reintervention, and 30-day mortality.

Postoperative serum CRP levels were routinely measured on POD2 and POD4. POD3 CRP measurement was incorporated into institutional postoperative surveillance in later years of the study period and was therefore available only in a subset of patients. Analyses involving POD3 were considered exploratory.

Diagnosis of anastomotic leakage

The diagnosis of anastomotic leakage was confirmed by one or more of the following criteria [18]: (i) direct visualization of leakage during surgical reintervention; (ii) drainage of purulent, enteric, or faecal material through a perianastomotic drain; (iii) identification of a perianastomotic fluid or air collection on postoperative computed tomography (CT); and/or (iv) extravasation of contrast medium outside the intestinal lumen on CT imaging.

CT imaging was requested based on clinical suspicion, including fever, abdominal pain, ileus, tachycardia, leukocytosis, abnormal drain output, or unfavourable postoperative course. CRP values were not used as a sole trigger for imaging; however, because they formed part of the overall clinical assessment, potential verification bias was acknowledged.

Data collection

Demographic characteristics, comorbidities, intraoperative variables, postoperative outcomes, empirical antibiotic treatment, and serum CRP values were collected prospectively from institutional clinical databases. Outcomes were assessed during the index hospitalization and through the 30-day postoperative period for reintervention and mortality.

Statistical analysis

Statistical analyses were performed using R statistical software (version 4.6.0; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as mean $\pm$ standard deviation or median with interquartile range, according to their distribution. Categorical variables were reported as absolute frequencies and percentages. Comparisons between groups were conducted using Student's t-test or the Mann–Whitney U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

No formal sample size calculation was performed, as this was a prospective observational cohort including all consecutive eligible patients treated during the study period.

The diagnostic performance of CRP was assessed using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC) and 95% confidence intervals. Youden's index was used to identify optimal cohort-derived thresholds. Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios were calculated for each threshold. To assess optimism arising from deriving and evaluating the POD4 CRP threshold in the same cohort, internal validation was performed using Harrell's enhanced bootstrap (2000 resamples, fixed random seed). In each replicate the Youden-optimal threshold was re-derived and its operating characteristics were evaluated in both the bootstrap sample and the original cohort; the mean difference (optimism) was subtracted from the apparent estimates. Discrimination (AUC) was internally validated using the same procedure.

Trajectory-based metrics were calculated as absolute differences and ratios between postoperative CRP measurements. The primary trajectory metrics were POD4–POD2 delta and POD4/POD2 ratio. POD3-dependent trajectory metrics were analysed only in the subset with available POD3 measurements and were considered exploratory.

To evaluate whether empirical antibiotic treatment influenced subsequent CRP interpretation, patients who received empirical antibiotics after POD2 CRP assessment but had no confirmed anastomotic leakage were described as a separate group. In this subgroup, empirical antibiotics had been initiated by the treating team in response to elevated POD2 CRP rather than for microbiologically or radiologically confirmed infection. A sensitivity analysis excluding this group was performed to assess the robustness of the POD4 CRP threshold.

Missing data were not imputed. All analyses were performed using complete cases for each specific analysis. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Cohort characteristics

Between January 2017 and December 2025, 367 patients underwent elective laparoscopic colorectal resection with construction of an intestinal anastomosis. After exclusion of 20 patients with ileoanal or coloanal anastomosis, the descriptive cohort included 347 patients. No colo-colonic anastomoses were performed, as this is not part of our institutional practice; lesions that might otherwise require one (e.g., splenic flexure tumours) were managed by extended resection with an ileocolic or colorectal anastomosis. For diagnostic performance analyses, the predictive cohort included 260 patients after exclusion of patients with conversion to open surgery, multivisceral resection, metastatic disease, or protective diverting stoma (Fig. 1).

In the descriptive cohort, the median age was 66 years (IQR 57–73), and 173 patients were male (49.9%). Colorectal cancer was the indication for surgery in 298 patients (85.9%). Colorectal anastomoses accounted for 186 procedures (53.6%) and were predominantly mechanical, whereas ileocolic anastomoses were more frequently hand-sewn (Table 1).

Table 1
Baseline characteristics of the descriptive cohort stratified by AL status

Variable	No AL (n = 297)	Any AL (n = 50)	p-value
Demographic and preoperative data			
Age, years	66.0 (56.0–74.0)	65.0 (60.0–71.0)	0.705
Male sex	137 (46.1%)	36 (72.0%)	< 0.001
BMI, kg/m ²	26.6 (24.3–29.8)	26.3 (24.5–29.9)	0.691
Obesity (BMI ≥ 30 kg/m ²)	74 (24.9%)	13 (26.0%)	0.861
Charlson Comorbidity Index	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.100
Arterial hypertension	153 (51.5%)	23 (46.0%)	0.542
Type 2 diabetes mellitus	71 (23.9%)	11 (22.0%)	0.858
History of heart disease	31 (10.4%)	5 (10.0%)	1.000
History of lung disease	22 (7.4%)	2 (4.0%)	0.551
History of inflammatory bowel disease	3 (1.0%)	0 (0.0%)	1.000
Active smoking	33 (11.1%)	7 (14.0%)	0.631
Neoadjuvant radiotherapy	26 (8.8%)	10 (20.0%)	0.023
Chronic systemic corticosteroid use	5 (1.7%)	2 (4.0%)	0.266
Intraoperative data			
Oncologic surgery	253 (85.2%)	45 (90.0%)	0.510
Conversion to open surgery	24 (8.1%)	8 (16.0%)	0.107
Type of anastomosis			0.360
Ileocolic	141 (47.5%)	20 (40.0%)	
Colorectal	156 (52.5%)	30 (60.0%)	
Anastomosis technique			0.587
Handsewn	125 (42.1%)	19 (38.0%)	
Mechanical	172 (57.9%)	31 (62.0%)	
Duration of surgery, minutes	210.0 (165.0–263.0)	197.5 (135.2–244.5)	0.491
Blood loss, mL	100.0 (50.0–200.0)	200.0 (50.0–300.0)	0.021
Drain usage	199 (67.0%)	40 (80.0%)	0.071
Diverting stoma	38 (12.8%)	14 (28.0%)	0.009
Multivisceral resection	6 (2.0%)	3 (6.0%)	0.126
Values are presented as median (interquartile range) or n (%). Anastomotic leakage includes modified ISREC-based grades A, B, and C. BMI = body mass index; ISREC = International Study Group of Rectal Cancer.			

Incidence of anastomotic leakage and postoperative outcomes

In the descriptive cohort, anastomotic leakage of any grade occurred in 50 patients (14.4%). According to the modified ISREC-based grading system, 19 leaks were classified as modified grade A (5.5%), six as modified grade B (1.7%), and 25 as modified grade C (7.2%). Invasive or surgical anastomotic leakage, defined as modified grades B + C, occurred in 31 patients (8.9%) (Table 2).

Table 2
Postoperative outcomes according to anastomotic leakage status

A. Incidence and characteristics of anastomotic leakage in the descriptive cohort (n = 347)			
	Total AL (n = 50)		
Any anastomotic leakage, modified grades A + B+C	50/347 (14.4%)		
Modified grade A	19/347 (5.5%)		
Modified grade B	6/347 (1.7%)		
Modified grade C	25/347 (7.2%)		
Invasive or surgical leakage (modified grades B + C)	31/347 (8.9%)		
Anastomotic leakage by anastomosis type			
Ileocolic (Any AL)	20/161 (12.4%)		
Ileocolic (modified grades B + C)	11/161 (6.8%)		
Colorectal (Any AL)	30/186 (16.1%)		
Colorectal (modified grades B + C)	20/186 (10.8%)		
Day of leakage diagnosis	4 (3–5)		
AL Diagnosis supported by CT	41/50 (82.0%)		
Anastomotic takedown due to leakage	13/50 (26.0%)		
Anastomotic preservation at day 30	37/50 (74.0%)		
Ostomy creation due to leakage	9/50 (18.0%)		
B. Postoperative outcomes according to anastomotic leakage status in the predictive cohort (n = 260)			
	No AL (n = 232)	Any AL (n = 28)	p-value
Hospital Stay (days)	5.0 (4.0–7.0)	16.5 (7.8–24.2)	< 0.001
Mortality at 30 days	1 (0.4%)	3 (10.7%)	0.004
Values are presented as n/N (%), n (%), or median (interquartile range). Anastomotic leakage severity was classified according to a modified ISREC-based grading system: modified grade A = no intervention or non-invasive conservative medical management; modified grade B = invasive non-surgical intervention; modified grade C = surgical reintervention. CT = computed tomography; ISREC = International Study Group of Rectal Cancer.			

Among patients with anastomotic leakage, the median day of diagnosis was postoperative day 4 (IQR 3–5). Diagnosis was supported by computed tomography in 41 patients (82.0%). Anastomotic takedown was required in 13 patients (26.0%), and ostomy creation due to leakage occurred in nine patients (18.0%) (Table 2).

In the predictive cohort (n = 260), anastomotic leakage of any grade occurred in 28 patients (10.8%), including 10 modified grade A leaks, one modified grade B leak, and 17 modified grade C leaks. Invasive or surgical leakage occurred in 18 patients (6.9%). Patients with anastomotic leakage had a significantly longer postoperative hospital stay than those without leakage (median 16.5 vs. 5.0 days; $p < 0.001$) and higher 30-day mortality (10.7% vs. 0.4%; $p = 0.004$) (Table 2).

Postoperative CRP levels and diagnostic performance

Postoperative CRP concentrations increased according to modified leakage grade (Table 3, Fig. 2). In the predictive cohort, median POD2 CRP was 72.6 mg/L (IQR 48.2–110.3) in patients without leakage, 101.1 mg/L (IQR 86.2–151.0) in modified grade A leakage, and 158.9 mg/L (IQR 72.0–216.7) in modified grades B + C ($p = 0.002$). On POD3, median CRP values were 70.1 mg/L (IQR 39.9–126.0), 372.1 mg/L (IQR 259.5–433.1), and 267.9 mg/L (IQR 196.2–327.8), respectively ($p < 0.001$). On POD4, median CRP values were 48.0 mg/L (IQR 28.3–84.3), 312.1 mg/L (IQR 219.4–398.1), and 317.1 mg/L (IQR 236.9–375.6), respectively ($p < 0.001$).

Table 3
Postoperative C-reactive protein levels

A. Postoperative CRP levels according to modified ISREC-based leakage grade in the predictive cohort				
Postoperative day	No anastomotic leakage	Modified grade A	Modified grades B + C	p-value
POD2 CRP, mg/L	72.6 (48.2–110.3)	101.1 (86.2–151.0)	158.9 (72.0–216.7)	0.002
POD3 CRP, mg/L	70.1 (39.9–126.0)	372.1 (259.5–433.1)	267.9 (196.2–327.8)	< 0.001
POD4 CRP, mg/L	48.0 (28.3–84.3)	312.1 (219.4–398.1)	317.1 (236.9–375.6)	< 0.001
B. POD4 CRP according to empirical antibiotic treatment status in the predictive cohort				
Group			POD4 CRP, mg/L	p-value
No empirical antibiotics, no leakage			43.4 (26.1–71.4)	Ref.
Empirical antibiotics, no confirmed leakage			100.8 (80.6–201.2)	< 0.001
Confirmed anastomotic leakage			317.1 (225.4–392.4)	< 0.001
Values are presented as median (interquartile range). Leakage severity was classified according to a modified ISREC-based grading system. p-values in panel A were calculated using the Kruskal–Wallis test across groups. p-values in panel B compare each group with the reference group using the Mann–Whitney U test. CRP = C-reactive protein; ISREC = International Study Group of Rectal Cancer; POD = postoperative day.				

ROC analysis showed fair discrimination on POD2, good discrimination on POD3, and excellent discrimination on POD4 (Table 4, Fig. 4). For any anastomotic leakage, POD4 CRP had an AUC of 0.930 (95% CI 0.861–0.981). The Youden-derived POD4 threshold was 137.3 mg/L, yielding 92.9% sensitivity, 87.3% specificity, 49.1% positive predictive value, and 98.9% negative predictive value. Internal bootstrap validation (2000 resamples) confirmed negligible optimism for POD4 discrimination (apparent AUC 0.930; optimism < 0.001; optimism-corrected AUC 0.930; bootstrap 95% CI 0.861–0.981), and at the Youden-derived threshold the optimism-corrected operating characteristics were 89.6% sensitivity, 87.1% specificity, 47.5% positive predictive value, and 98.5% negative predictive value; the bootstrap-derived threshold remained close to the apparent value (median 141.7 mg/L, IQR 137.3–189.1). POD3 CRP showed good exploratory discrimination, with an AUC of 0.874 (95% CI 0.725–0.977) and a Youden-derived threshold of 184.0 mg/L. However, this analysis was restricted to 79 patients and should be interpreted cautiously because POD3 sampling was not available throughout the entire study period.

Table 4
Diagnostic performance of postoperative C-reactive protein for anastomotic leakage detection

A. Any anastomotic leakage (A + B+C)									
Day	Cutoff (mg/L)	n	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR-
POD2	150.2	239	0.726 (0.608–0.841)	47.6 (28.3–67.6)	91.3 (86.8–94.3)	34.5 (19.9–52.7)	94.8 (90.9–97.1)	5.46	0.57
POD3 [†]	184.0	79	0.874 (0.725–0.977)	81.8 (52.3–94.9)	86.8 (76.7–92.9)	50.0 (29.0–71.0)	96.7 (88.8–99.1)	6.18	0.21
POD4	137.3	240	0.930 (0.861–0.981)	92.9 (77.4–98.0)	87.3 (82.1–91.1)	49.1 (36.1–62.1)	98.9 (96.2–99.7)	7.29	0.08
B. Invasive or surgical anastomotic leakage, modified grades B + C									
Day	Cutoff, mg/L	n	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR-
POD2	150.2	239	0.752 (0.592–0.901)	58.3 (32.0–80.7)	90.3 (85.8–93.5)	24.1 (12.2–42.1)	97.6 (94.5–99.0)	6.02	0.46
POD3 [†]	120.5	79	0.868 (0.753–0.956)	100 (61.0–100.0)	69.9 (58.6–79.2)	21.4 (10.2–39.5)	100 (93.0–100)	3.32	–
POD4	137.3	240	0.928 (0.873–0.972)	94.4 (74.2–99.0)	83.8 (78.4–88.1)	32.1 (21.1–45.5)	99.5 (97.0–99.9)	5.82	0.07
C. Trajectory-based metrics vs absolute POD4 – Any anastomotic leakage, modified grades A + B+C									
Metric	Cutoff / threshold	n	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR-
POD4 absolute	137.3 mg/L	240	0.930 (0.861–0.981)	92.9 (77.4–98.0)	87.3 (82.1–91.1)	49.1 (36.1–62.1)	98.9 (96.2–99.7)	7.29	0.08
Delta POD4 – POD2	+ 14.7 mg/L	219	0.869 (0.756–0.961)	85.7 (65.4–95.0)	81.8 (75.9–86.6)	33.3 (22.2–46.6)	98.2 (94.8–99.4)	4.71	0.17
Ratio POD4/POD2	1.06	219	0.865 (0.757–0.944)	85.7 (65.4–95.0)	78.3 (72.0–83.5)	29.5 (19.6–41.9)	98.1 (94.6–99.4)	3.95	0.18
Delta POD3 – POD2 [†]	+ 91.5 mg/L	73	0.800 (0.548–0.990)	75.0 (40.9–92.9)	90.8 (81.3–95.7)	50.0 (25.4–74.6)	96.7 (88.8–99.1)	8.13	0.28
Delta POD4 – POD3 [†]	+ 13.1 mg/L	61	0.536 (0.264–0.803)	45.5 (21.3–72.0)	92.0 (81.2–96.8)	55.6 (26.7–81.1)	88.5 (77.0–94.6)	5.68	0.59
Values correspond to complete-case analyses. All thresholds were calculated using the Youden index. Leakage severity was classified according to a modified ISREC-based grading system.									
† POD3-dependent analyses were restricted to the available subset and should be considered exploratory.									

A. Any anastomotic leakage (A + B+C)									
Day	Cutoff (mg/L)	n	AUC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+	LR-
AUC = area under the curve; CI = confidence interval; CRP = C-reactive protein; ISREC = International Study Group of Rectal Cancer; LR = likelihood ratio; NPV = negative predictive value; POD = postoperative day; PPV = positive predictive value.									

For invasive or surgical anastomotic leakage, defined as modified grades B + C, POD4 CRP also showed excellent discrimination, with an AUC of 0.928 (95% CI 0.873–0.972). The Youden-derived POD4 threshold was 137.3 mg/L, yielding 94.4% sensitivity, 83.8% specificity, 32.1% positive predictive value, and 99.5% negative predictive value (Table 4, Fig. 4).

Among patients with anastomotic leakage and available POD4 CRP, two false-negative cases were observed using the 137.3 mg/L threshold. Both corresponded to delayed leaks diagnosed on POD13 and had low early CRP values. Thus, false-negative POD4 results occurred in delayed rather than early inflammatory leaks.

Trajectory analysis

Trajectory-based metrics did not outperform absolute POD4 CRP values (Table 4). For prediction of any anastomotic leakage, the AUC was 0.869 for the absolute delta between POD4 and POD2 and 0.865 for the POD4/POD2 ratio, compared with 0.930 for absolute POD4 CRP. POD3-dependent trajectory metrics were less stable: the AUC was 0.800 for the POD3–POD2 delta and 0.536 for the POD4–POD3 delta (Table 4).

Empirical antibiotic treatment

Data on empirical antibiotic treatment initiated after POD2 CRP assessment were available in 237 patients in the predictive cohort. Of these, 39 patients (16.5%) received empirical antibiotic treatment. Ten of these patients had confirmed anastomotic leakage, whereas 29 received empirical antibiotics without confirmed leakage.

Among patients without confirmed leakage who received empirical antibiotics, POD4 CRP values were intermediate between uncomplicated patients and those with confirmed leakage (Table 3, Fig. 3). Median POD4 CRP was 100.8 mg/L (IQR 80.6–201.2) in patients receiving empirical antibiotics without confirmed leakage, compared with 43.4 mg/L (IQR 26.1–71.4) in patients without antibiotics and without leakage, and 317.1 mg/L (IQR 225.4–392.4) in patients with confirmed leakage. Among patients receiving empirical antibiotics without confirmed leakage and available POD4 CRP, 17 of 28 patients (60.7%) had POD4 CRP values below 150 mg/L (Fig. 3).

A sensitivity analysis excluding patients who received empirical antibiotics without confirmed leakage showed a marginally higher POD4 AUC for any anastomotic leakage (0.945 vs. 0.930), while the Youden-derived threshold remained unchanged at 137.3 mg/L.

Diverting stoma-stratified analysis

In the sensitivity cohort used to evaluate the effect of protective diverting stoma, patients with conversion to open surgery, multivisceral resection, or metastatic disease were excluded, while patients with diverting stomas were retained. This cohort included 301 patients, of whom 41 had a protective diverting stoma.

Compared with patients without a diverting stoma, CRP discrimination was attenuated among diverted patients (Fig. 5, Supplementary Table 1). In the diverting stoma subgroup, AUC values for any anastomotic leakage were 0.621 on POD2, 0.575 on POD3, and 0.810 on POD4. In contrast, among patients without a diverting stoma, AUC values were 0.726 on POD2, 0.874 on POD3, and 0.930 on POD4. The 95% confidence intervals for POD2 (0.348–0.860) and POD3 (0.248–0.904) included 0.5, indicating discrimination not significantly better than chance, and the diverting-stoma POD4 threshold (186.7 mg/L) differed substantially from that of the overall cohort (137.3 mg/L). Given the small subgroup size and the limited number of events, these findings are hypothesis-generating only and insufficient to support reliable threshold derivation or clinical recommendations in diverted patients.

DISCUSSION

This study demonstrates that postoperative C-reactive protein (CRP) has high diagnostic accuracy for detecting anastomotic leakage (AL) in a prospective cohort of patients undergoing elective laparoscopic colorectal resection. By restricting the primary diagnostic analysis to a more homogeneous minimally invasive population—excluding open conversions, multivisceral resections, metastatic disease, and protective diverting stomas—we aimed to reduce clinical heterogeneity and address a major limitation of prior evidence derived from mixed surgical cohorts. POD4 CRP showed excellent discriminatory performance for any AL, with an AUC of 0.930 and a Youden-derived threshold of 137.3 mg/L. These findings support absolute POD4 CRP as a pragmatic and clinically useful biomarker for postoperative risk stratification in contemporary minimally invasive colorectal practice.

Our derived POD4 threshold of 137.3 mg/L lies within the range reported in meta-analyses evaluating CRP for postoperative infectious complications and anastomotic leakage after colorectal surgery [12, 13, 19]. However, direct comparability remains limited, because previous cohorts frequently combined open and minimally invasive approaches, right- and left-sided resections, different anastomotic techniques, and heterogeneous outcome definitions [12, 13, 19]. Regional evidence remains limited, and available Chilean data have focused mainly on elective colon surgery with specific biomarker protocols, further limiting direct transferability across settings [20]. In the present study, the same POD4 threshold was also selected by the Youden index for invasive or surgical leakage, defined as modified ISREC-based grades B + C, although with a different diagnostic profile: higher negative predictive value but lower positive predictive value. This reinforces that CRP is more useful as a rule-out and risk-stratification biomarker than as a definitive diagnostic test. The relatively low positive predictive value at this threshold (49.1% for any leakage) implies that approximately half of the patients exceeding it will not have an anastomotic leak. False-positive results carry tangible costs, including unnecessary cross-sectional imaging, prolonged hospitalization, empirical antibiotic exposure, and patient anxiety. An elevated POD4 CRP should therefore be interpreted as a trigger for structured clinical reassessment and further diagnostic evaluation rather than as an indication for direct therapeutic intervention. The observed inflammatory gradient across modified leakage grades was mainly supported by our own data and is consistent with previous reports showing higher CRP values among patients with anastomotic leakage [21]. Early landmark studies [22] proposed lower cut-offs because they aimed to rule out a broad spectrum of postoperative infectious complications. More recent laparoscopic or enhanced-recovery cohorts have advocated for thresholds in the range of approximately 150–163 mg/L [23, 24]. In contrast, studies designed to capture any postoperative complication or broader morbidity endpoints continue to propose lower cut-offs [25, 26]. Collectively, these discrepancies underscore that CRP thresholds are context-dependent and should be interpreted according to surgical approach, anastomotic configuration, perioperative management, and the clinical definition of the target outcome.

An additional source of heterogeneity that deserves attention is anastomotic technique. In our cohort, both hand-sewn and mechanical anastomoses were included, whereas some comparative series include predominantly or exclusively stapled anastomoses. This may influence postoperative inflammatory behaviour and leakage presentation, although our sample size was insufficient to build stable technique-specific diagnostic models. Future studies should evaluate whether CRP thresholds require stratification by anastomotic site and construction technique. Descriptive leakage rates and median POD4 CRP values according to anastomosis type and construction technique are summarized in Supplementary Table 2.

Despite growing interest in dynamic CRP models [27], their clinical superiority remains unproven. The multicentre PREDICT trial failed to confirm the superiority of trajectory-based approaches over absolute values [28], and while some recent models advocate for trend analysis, they still lack robust external validation [29]. In our cohort, neither the POD4–POD2 delta nor the POD4/POD2 ratio outperformed absolute POD4 CRP. The Youden-derived delta threshold reflected failure of CRP to decline between POD2 and POD4 rather than a clinically intuitive absolute increase. POD3-dependent analyses were less stable because POD3 measurements were available only in a subset of patients. Although same-day diagnosis does not necessarily invalidate CRP as a clinically useful diagnostic signal, the available dataset did not consistently allow determination of whether POD3 blood sampling preceded diagnostic imaging or clinical confirmation. Therefore, POD3-derived thresholds should not be interpreted as validated discharge cutoffs. Consequently, absolute POD4 CRP remains the most pragmatic monitoring tool in this dataset.

The imperative for early AL detection is well established, with large international registries reporting reoperation rates exceeding 80% and frequent ostomy creation [30]. In our cohort, the proportion of patients requiring anastomotic takedown or stoma formation was lower. While the observational design precludes causal inference, systematic CRP monitoring may have contributed to earlier clinical suspicion, closer surveillance, and timely diagnostic escalation [16]. Although procalcitonin and composite clinical scores have shown diagnostic value in selected settings [31], their cost, availability, and implementation requirements limit their widespread use as first-line tools compared with CRP.

A relevant finding of this study is the attenuation of CRP discriminatory ability in patients with a protective diverting stoma. Diagnostic performance in this subgroup was lower than in non-diverted patients, particularly on POD2 and POD3, and only partially recovered by POD4. This is consistent with findings from the MIRECA multicentre cohort [32], which reported significantly lower diagnostic accuracy of CRP in patients with a primary diverting stoma after minimally invasive rectal resection. Biologically, faecal diversion may reduce pelvic contamination and attenuate the systemic inflammatory response during a leak [33]. This provides a plausible explanation for the divergent CRP trajectories observed between diverted and non-diverted patients. Consequently, standard CRP-based surveillance appears less reliable in diverted patients and should probably be complemented by lower clinical thresholds for imaging or alternative diagnostic strategies.

We also evaluated the subgroup of patients who received empirical antibiotics after elevated early postoperative CRP without confirmed AL. These patients showed intermediate POD4 CRP values: higher than uncomplicated patients without antibiotics, but substantially lower than patients with confirmed AL. This pattern suggests that empirical antibiotic treatment may modify subsequent CRP trajectories or identify patients with postoperative inflammatory states that do not meet criteria for confirmed leakage [34]. However, because antibiotic initiation was not standardized or randomized, causality cannot be inferred. Importantly, the sensitivity analysis excluding patients who received empirical antibiotics without confirmed AL yielded a marginally higher POD4 AUC while the Youden-derived threshold remained unchanged at 137.3 mg/L, supporting the robustness of the primary finding.

This study has limitations. First, although data were collected prospectively, the observational design introduces potential verification bias, because CRP values formed part of the overall clinical assessment and may have influenced the decision to obtain CT imaging. CT was not performed systematically in all patients; therefore, minimally symptomatic or radiological leaks may have been underdetected. Because imaging was performed only on clinical suspicion rather than as a screening test, a formal comparison between imaged and non-imaged patients is constrained, because the two groups are defined by the clinical-suspicion criterion under study; the principal consequence is potential overestimation of the negative predictive value (98.9%) and, to a lesser extent, specificity, as clinically silent leaks in patients with low CRP and no symptoms may have gone undetected and been classified as true negatives. Such occult leaks, by definition not prompting symptoms, CRP elevation, or intervention, are of limited clinical relevance for a biomarker intended to trigger further assessment rather than to detect radiologically silent disease. Moreover, false-negative cases observed with the POD4 threshold corresponded to delayed leaks diagnosed after the first postoperative week, highlighting that low early CRP values cannot fully exclude delayed post-discharge anastomotic failure. Second, we used a pragmatic modified ISREC-based grading system to distinguish non-invasive conservative management from invasive non-surgical procedures and surgical reintervention. Although this reflects contemporary practice in non-diverted enhanced recovery pathways, it may limit direct comparability with studies applying the original ISREC grading system rigidly. Third, POD3 CRP was incorporated later in the study period, resulting in missing POD3 data and limiting the strength of POD3 and trajectory-based analyses. Finally, empirical antibiotic treatment was not protocolized. The single-centre design also requires external validation before routine implementation of these thresholds; until externally validated, this cohort-derived cutoff should be regarded as hypothesis-generating.

These limitations are balanced by several strengths. The study was based on a prospectively maintained cohort of consecutive patients undergoing elective laparoscopic colorectal resection. By showing that absolute POD4 CRP outperformed trajectory-based metrics and by characterizing the limitations of CRP in diverted and delayed-leak scenarios, this study provides a clinically pragmatic framework for interpreting postoperative CRP in laparoscopic colorectal surgery.

CONCLUSION

In this prospective cohort of patients undergoing elective laparoscopic colorectal resection, postoperative CRP demonstrated excellent diagnostic performance for the detection of anastomotic leakage, particularly on POD4. The cohort-derived POD4 threshold of 137.3 mg/L showed high sensitivity and negative predictive value for both any anastomotic leakage and invasive or surgical leakage, supporting its role as an adjunct for early postoperative leakage risk stratification rather than as a standalone diagnostic tool. A reassuring early CRP, however, does not exclude delayed anastomotic leakage: two leaks presented on postoperative day 13, underscoring that patients with clinical deterioration after discharge require evaluation irrespective of their POD4 CRP.

Absolute POD4 CRP outperformed trajectory-based metrics, while POD3 analyses remained exploratory because of limited data availability.

Overall, these findings support the use of POD4 CRP as a pragmatic biomarker within contemporary laparoscopic colorectal surgery pathways. External validation is required before routine implementation of these cohort-derived thresholds.

Declarations

Funding:

No funding was received for conducting this study.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Scientific Ethics Committee of Hospital San Juan de Dios, Santiago, Chile.

Consent to participate: The requirement for individual informed consent was waived by the Scientific Ethics Committee of Hospital San Juan de Dios owing to the observational nature of the study and the use of anonymized clinical data.

Consent to publish: Not applicable.

Author Contributions

(CRediT): Conceptualization: DGB, MLC; Data curation: DGB, FRR, MLC; Formal analysis: DGB; Investigation: DGB; Methodology: DGB, MLC; Software: DGB; Supervision: MLC; Visualization: DGB; Writing—original draft: DGB; Writing—review and editing: DGB, FRR, MLC.

Acknowledgments:

The authors gratefully acknowledge the Coloproctology Unit and the General Surgery residents of the University of Chile for their daily dedication to patient care, which made this prospective cohort possible, and for their valuable contribution to the prospective completion of the clinical database.

Data availability:

The datasets generated and/or analysed during the current study are not publicly available because they contain sensitive clinical information. Anonymized data may be available from the corresponding author on reasonable request and subject to institutional approval.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I et al (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74:229–263. <https://doi.org/10.3322/caac.21834>
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L et al (2024) Chile: GLOBOCAN 2022 fact sheet. International Agency for Research on Cancer, Lyon. <https://gco.iarc.who.int/media/globocan/factsheets/populations/152-chile-fact-sheet.pdf>. Accessed 2 May 2026
3. Romano G, Gagliardi G, Bianco F, Parker MC, Corcione F (2008) Laparoscopic colorectal surgery: why it is still not the gold standard and why it should be. *Tech Coloproctol* 12:185–188. <https://doi.org/10.1007/s10151-008-0416-8>
4. Liang Y, Li G, Chen P, Yu J (2008) Laparoscopic versus open colorectal resection for cancer: a meta-analysis of results of randomized controlled trials on recurrence. *Eur J Surg Oncol* 34:1217–1224. <https://doi.org/10.1016/j.ejso.2007.11.004>
5. Safiejko K, Tarkowski R, Koselak M, Juchimiuk M, Tarasik A, Pruc M et al (2022) Robotic-assisted versus standard laparoscopic surgery for rectal cancer resection: a systematic review and meta-analysis of 19,731 patients. *Cancers (Basel)* 14:180. <https://doi.org/10.3390/cancers14010180>
6. Rennie O, Sharma M, Helwa N (2024) Colorectal anastomotic leakage: a narrative review of definitions, grading systems, and consequences of leaks. *Front Surg* 11:1371567. <https://doi.org/10.3389/fsurg.2024.1371567>
7. He J, He M, Tang JH, Wang XH (2023) Anastomotic leak risk factors following colon cancer resection: a systematic review and meta-analysis. *Langenbecks Arch Surg* 408:252. <https://doi.org/10.1007/s00423-023-02989-z>
8. Gielen AHC, Heuvelings DJI, Sylla P, van Loon YT, Melenhorst J, Bouvy ND et al (2025) Impact of anastomotic leakage after colorectal cancer surgery on quality of life: a systematic review. *Dis Colon Rectum* 68:154–170. <https://doi.org/10.1097/DCR.0000000000003478>
9. Nijssen DJ, Wienholts K, Postma MJ et al (2024) The economic impact of anastomotic leakage after colorectal surgery: a systematic review. *Tech Coloproctol* 28:55. <https://doi.org/10.1007/s10151-024-02932-4>
10. Koedam TWA, Bootsma BT, Deijen CL, van de Brug T, Kazemier G, Cuesta MA et al (2022) Oncological outcomes after anastomotic leakage after surgery for colon or rectal cancer: increased risk of local recurrence. *Ann Surg* 275:e420–e427. <https://doi.org/10.1097/SLA.0000000000003889>
11. Ha GW, Kim JH, Lee MR (2017) Oncologic impact of anastomotic leakage following colorectal cancer surgery: a systematic review and meta-analysis. *Ann Surg Oncol* 24:3289–3299. <https://doi.org/10.1245/s10434-017-5881-8>
12. Singh PP, Zeng IS, Srinivasa S, Lemanu DP, Connolly AB, Hill AG (2014) Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. *Br J Surg* 101:339–346. <https://doi.org/10.1002/bjs.9354>
13. Yeung DE, Peterknecht E, Hajibandeh S, Hajibandeh S, Torrance AW (2021) C-reactive protein can predict anastomotic leak in colorectal surgery: a systematic review and meta-analysis. *Int J Colorectal Dis* 36:1147–1162. <https://doi.org/10.1007/s00384-021-03854-5>
14. Facy O, Paquette B, Orry D, Binquet C, Masson D, Bouvier A et al (2016) Diagnostic accuracy of inflammatory markers as early predictors of infection after elective colorectal surgery: results from the IMACORS study. *Ann Surg* 263:961–966. <https://doi.org/10.1097/SLA.0000000000001303>
15. Frasson M, Flor-Lorente B, Ramos Rodríguez JL, Granero-Castro P, Hervás D, Alvarez Rico MA et al (2015) Risk factors for anastomotic leak after colon resection for cancer: multivariate analysis and nomogram from a multicentric, prospective, national study with 3193 patients. *Ann Surg* 262:321–330. <https://doi.org/10.1097/SLA.0000000000000973>
16. Gozalichvili D, Binquet C, Boisson C, Guiraud A, Facy O, Ortega-Deballon P et al (2023) Early detection of anastomotic leak with C-reactive protein increases the chances of anastomotic salvage. *Colorectal Dis* 25:728–737. <https://doi.org/10.1111/codi.16399>
17. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A et al (2010) Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery* 147:339–351. <https://doi.org/10.1016/j.surg.2009.10.012>
18. Chiarello MM, Fransvea P, Cariati M, Adams NJ, Bianchi V, Brisinda G (2022) Anastomotic leakage in colorectal cancer surgery. *Surg Oncol* 40:101708. <https://doi.org/10.1016/j.suronc.2022.101708>

19. Warschkow R, Beutner U, Steffen T, Müller SA, Schmied BM, Güller U, Tarantino I (2012) Safe and early discharge after colorectal surgery due to C-reactive protein: a diagnostic meta-analysis of 1832 patients. *Ann Surg* 256:245–250. <https://doi.org/10.1097/SLA.0b013e31825b60f0>
20. Díaz Gasaly F, Mansilla Espinosa J, Troncoso Trujillo A, Muñoz Pérez N, Soto Fuentes A, Navarro Cáceres P (2024) Procalcitonina y proteína C reactiva como predictores precoces de fuga anastomótica en pacientes sometidos a cirugía resectiva de colon con anastomosis primaria electiva. *Rev Cir* 76:313–320. <https://doi.org/10.35687/s2452-454920240042030>
21. Guevara-Morales GR, Regalado-Torres MA, Cantarell-Castillo E, Castro-Salas R, Maldonado-Barrón R, Castellanos-Juárez JC (2018) Utilidad de la proteína C reactiva en el diagnóstico oportuno de fuga de anastomosis en cirugía colorrectal. *Cir Cir* 86:432–436. <https://doi.org/10.24875/CIRU.18000261>
22. Adamina M, Warschkow R, Näf F, Hummel B, Rduch T, Lange J et al (2014) Monitoring C-reactive protein after laparoscopic colorectal surgery excludes infectious complications and allows for safe and early discharge. *Surg Endosc* 28:2939–2948. <https://doi.org/10.1007/s00464-014-3556-0>
23. Muñoz JL, Alvarez MO, Cuquerella V, Miranda E, Picó C, Flores R et al (2018) Procalcitonin and C-reactive protein as early markers of anastomotic leak after laparoscopic colorectal surgery within an enhanced recovery after surgery program. *Surg Endosc* 32:4003–4010. <https://doi.org/10.1007/s00464-018-6144-x>
24. Fukada M, Matsuhashi N, Takahashi T, Imai H, Tanaka Y, Yamaguchi K et al (2019) Risk and early predictive factors of anastomotic leakage in laparoscopic low anterior resection for rectal cancer. *World J Surg Oncol* 17:184. <https://doi.org/10.1186/s12957-019-1726-3>
25. Smit C, Janssen-Heijnen ML, van Osch F, Rops J, Gielen AHC, van Heinsbergen M et al (2025) The optimal cut-off value of postoperative day three C-reactive protein to predict for major complications in colorectal cancer patients. *Langenbecks Arch Surg* 410:85. <https://doi.org/10.1007/s00423-025-03655-2>
26. Dos Santos BDN, Beruti C, Azevedo J, Herrando I, Vieira P, Domingos H et al (2025) Using inflammatory parameters for safe and early discharge after minimally invasive colorectal surgery for colorectal cancer. *Tech Coloproctol* 29:97. <https://doi.org/10.1007/s10151-025-03134-2>
27. Smith SR, Pockney P, Holmes R, Doig F, Attia J, Holliday E et al (2018) Biomarkers and anastomotic leakage in colorectal surgery: C-reactive protein trajectory is the gold standard. *ANZ J Surg* 88:440–444. <https://doi.org/10.1111/ans.13937>
28. Stephensen BD, Reid F, Shaikh S, Carroll R, Smith SR, Pockney P (2020) C-reactive protein trajectory to predict colorectal anastomotic leak: PREDICT study. *Br J Surg* 107:1832–1837. <https://doi.org/10.1002/bjs.11812>
29. Niemann BR, Murthy J, Breinholt C, Swords J, Stevens A, Garland-Kledzik M et al (2025) Postoperative C-reactive protein trend is a more accurate predictor of anastomotic leak than absolute values alone. *J Clin Med* 14:2931. <https://doi.org/10.3390/jcm14092931>
30. Warps AK, Dekker JWT, Tanis PJ, Tollenaar RAEM (2022) An evaluation of short-term outcomes after reoperations for anastomotic leakage in colon cancer patients. *Int J Colorectal Dis* 37:113–122. <https://doi.org/10.1007/s00384-021-03996-6>
31. Catarci M, Ruffo G, Borghi F, Patriiti A, Delrio P, Scatizzi M et al (2020) Anastomotic leakage after elective colorectal surgery: a prospective multicentre observational study on use of the Dutch leakage score, serum procalcitonin and serum C-reactive protein for diagnosis. *BJS Open* 4:499–507. <https://doi.org/10.1002/bjs5.50269>
32. Nijssen DJ, Broekman M, Rensink F, Stuart G, Geitenbeek RTJ, Stael J et al (2026) Diagnostic accuracy of C-reactive protein in detecting anastomotic leakage after minimally invasive rectal cancer surgery. *Surg Endosc* 40:2178–2188. <https://doi.org/10.1007/s00464-025-12428-3>
33. Wu Y, Zheng H, Guo T, Keranmu A, Liu F, Xu Y (2017) Temporary diverting stoma improves recovery of anastomotic leakage after anterior resection for rectal cancer. *Sci Rep* 7:15930. <https://doi.org/10.1038/s41598-017-16311-7>
34. Najdawi A, Rao A, Razzaq H, Dworkin M (2021) Impact of enteral prophylactic antibiotics on the trends of inflammatory markers following laparoscopic colorectal cancer surgery: a retrospective and prospective cohort study. *Ann Med Surg* 70:102752. <https://doi.org/10.1016/j.amsu.2021.102752>

Figures

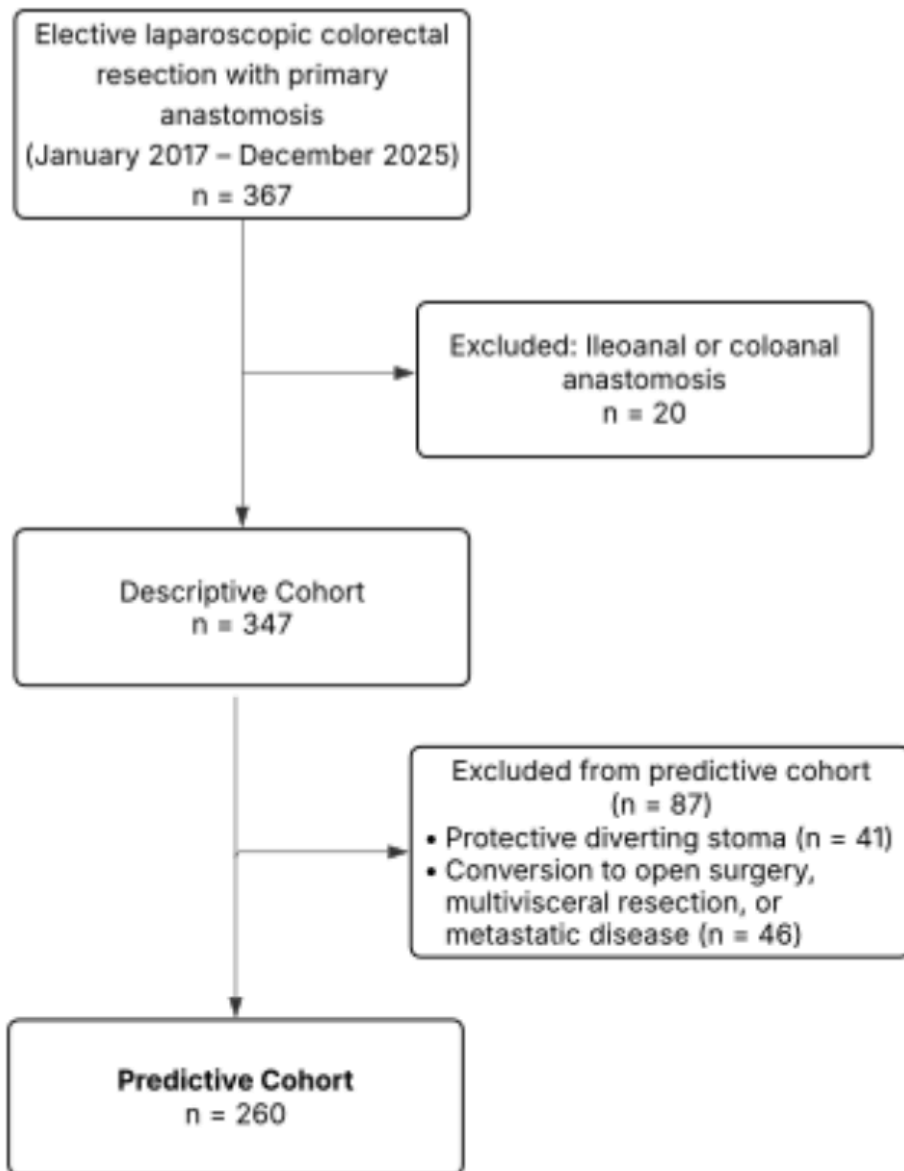


Figure 1

Flow diagram of the study cohort selection process.

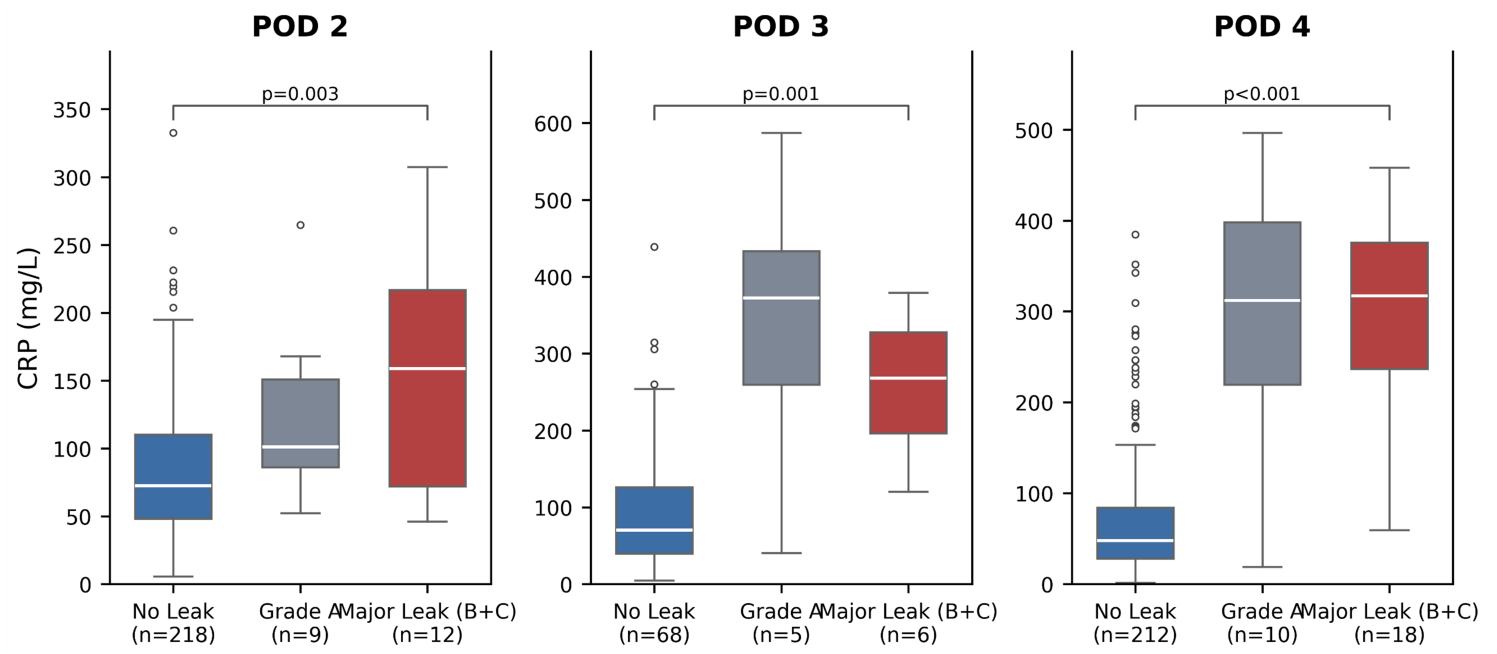


Figure 2

Postoperative C-reactive protein (CRP) levels on POD2, POD3, and POD4 according to modified ISREC-based leakage grade.

Boxes show the interquartile range, central lines the median, whiskers the range excluding outliers, and circles outliers. p-values compare no leakage versus modified grades B+C. CRP = C-reactive protein; ISREC = International Study Group of Rectal Cancer; POD = postoperative day.

*POD3 results are exploratory (POD3 CRP available in 79 patients).

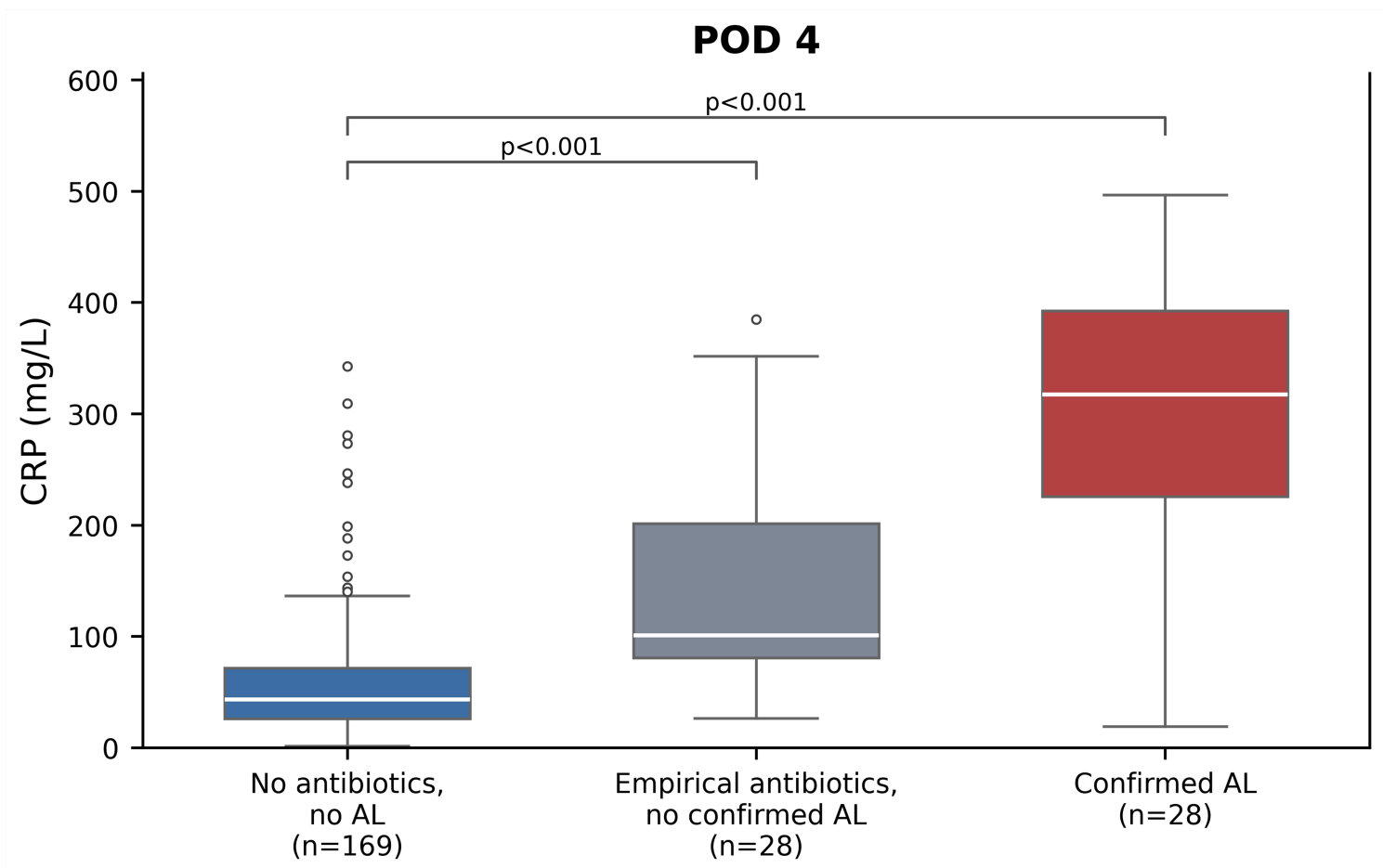


Figure 3

POD4 C-reactive protein (CRP) levels according to empirical antibiotic treatment and anastomotic leakage status.

Boxes show the interquartile range, central lines the median, whiskers the range excluding outliers, and circles outliers. p-values compare each group with patients without empirical antibiotics and without leakage. AL = anastomotic leakage; CRP = C-reactive protein; POD = postoperative day.

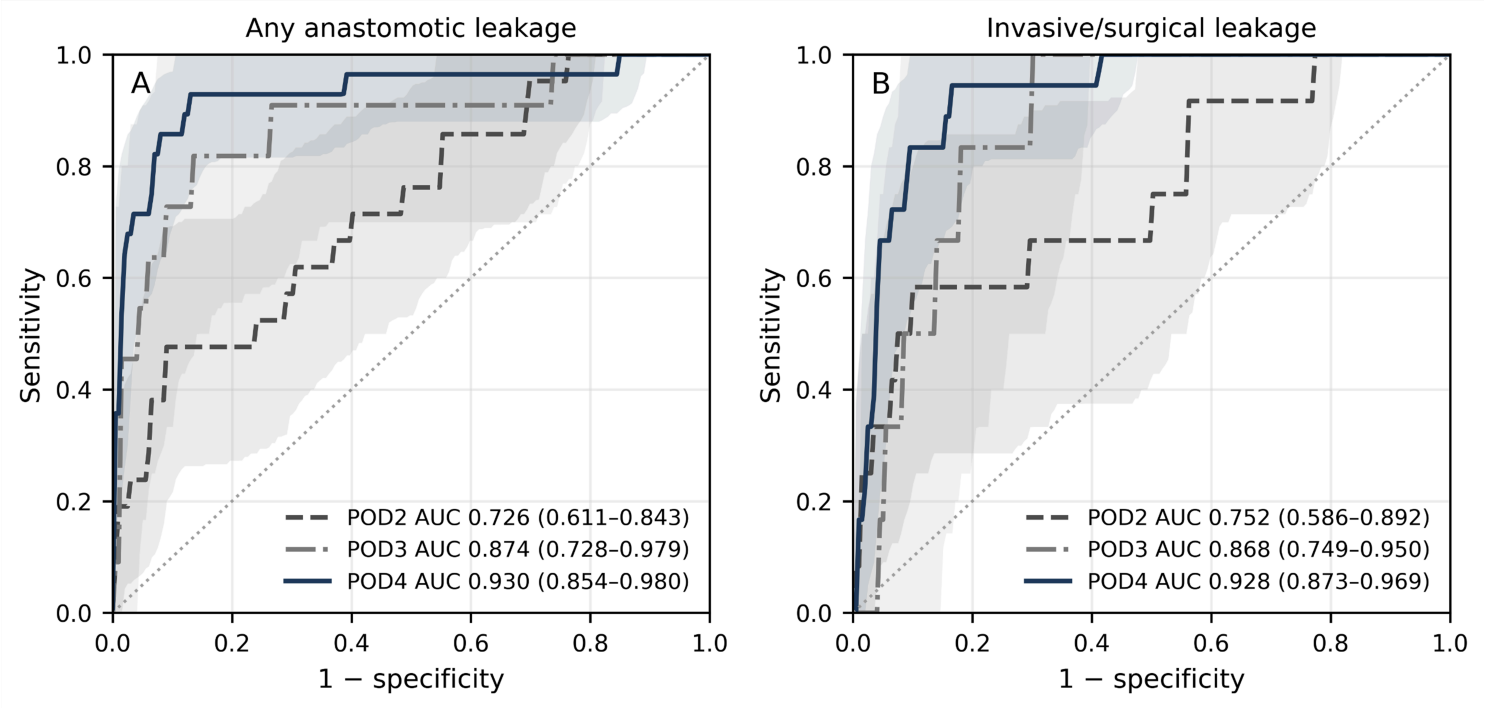


Figure 4

Receiver operating characteristic (ROC) curves for postoperative C-reactive protein on postoperative days 2, 3, and 4.

Panel A shows any anastomotic leakage, defined as modified grades A+B+C. Panel B shows invasive or surgical leakage, defined as modified grades B+C. Shaded areas represent bootstrapped 95% confidence intervals. AUC = area under the curve; CRP = C-reactive protein; POD = postoperative day. *POD3 results are exploratory (POD3 CRP available in 79 patients).

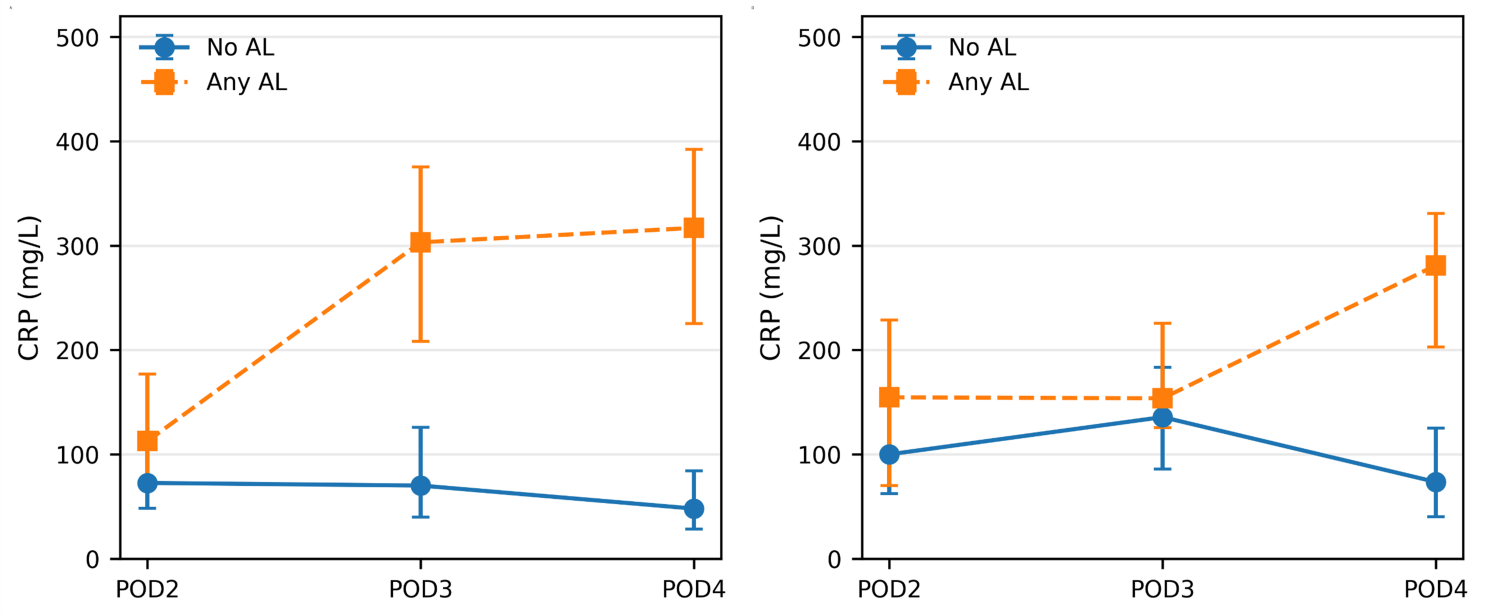


Figure 5

Postoperative CRP trajectory by anastomotic leakage status and protective diverting stoma.

Panel A shows patients without a diverting stoma; Panel B shows patients with a diverting stoma. Points show medians and error bars show interquartile ranges. AL = anastomotic leakage; CRP = C-reactive protein; POD = postoperative day.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterial.docx](#)