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Comparative Performance of Postoperative Day 3 Biomarkers for Predicting Anastomotic Leakage after Colorectal Cancer Surgery - A Retrospective Cohort Study

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Rezumat

Performanța comparativă a biomarkerilor din ziua a treia postoperatorie pentru predicția fistulei anastomotice după chirurgia cancerului colorectal – studiu retrospectiv de cohortă

Introducere: Fistula anastomotică (FA) reprezintă o complicație postoperatorie severă, în special în chirurgia oncologică digestivă, cu impact major atât asupra pacienților, cât şi asupra chirurgilor. Având în vedere severitatea consecințelor clinice, indentificarea precoce a pacienților cu risc de FA este esențială pentru îmbunătățirea rezultatelor postoperatorii. Studiul de față a avut ca scop evaluarea factorilor de risc clinici şi a biomarkerilor din ziua a 3-a postoperatorie (POD 3) în detectarea precoce a FA.
Material şi Metodă: A fost realizat un studiu retrospectiv observațional care a inclus 166 de pacienți supuşi rezecției cu anastomoză primară pentru cancer colorectal. Au fost colectate date privind caracteristicile pacienților, parametrii tumorali, factori operatori şi valori biologice din a 3-a zi postoperator. Performanța predictivă a fost evaluată utilizând curbe ROC şi modele de regresie logistică pentru identificarea factorilor de risc independenți.
Rezultate: FA a fost diagnosticată la 44 de pacienți (26.50%) şi a fost asociată cu spitalizare prelungită şi mortalitate postoperatorie crescută (25.00% vs 6.60%, p=0.002). Analiza multivariată a identificat intervenția chirurgicală în regim de urgență, localizarea tumorală rectală, necesarul de transfuzie intraoperatorie şi abordul chirurgical clasic ca factori de risc independenți pentru FA. Dintre biomarkerii evaluați postoperator, raportul proteină C reactivă/albumină (CAR) a prezentat cea mai mare acuratețe predictivă. După ajustarea în modelul multivariat, CAR a rămas predictor independent al FA (OR=1.91, p<0.001).
Concluzii: Fistula anastomotică după chirurgia neoplaziilor colorectale rămâne o complicație multifactorială, influențată de condițiile intraoperatorii, factorii locali tumorali şi răspunsul inflamator postoperator. În cohorta analizată, CAR determinat în ziua a 3-a postoperatorie a prezentat cea mai bună performanță discriminatorie dintre biomarkerii evaluați şi poate reprezenta un instrument accesibil pentru stratificarea precoce a riscului, atunci când este interpretat împreuna cu datele examinării clinice şi a factorilor operatori.

Cuvinte cheie: fistulă anastomotică, factori de risc, cancer colorectal, biomarkeri postoperatori, proteina C reactivă, CAR, LCR, NLR, albumina

Abstract

Background: Anastomotic leakage (AL) represents a serious postoperative complication after surgery, especially for digestive tract malignancies, concerning both patients and surgeons. Due to severe clinical repercussions, early identification of patients at risk is essential for improving postoperative outcomes. This study focused on assessing clinical risk factors and the postoperative day 3 (POD 3) biomarkers, in early detection of anastomotic leakage.

Materials and Methods: A retrospective observational study was conducted including 166 patients who underwent resection with primary anastomosis for colorectal cancer. Patient-related factors, tumor characteristics, operative factors and POD 3 laboratory data were collected. Receiver operating characteristics (ROC) curves and logistic regression models were used to assess predictive performance and identify independent risk factors.

Results: Anastomotic leakage occurred in 44 patients (26.50%) and was associated with prolonged hospitalization and higher postoperative mortality (25.00% vs 6.60%, p=0.002). Multivariable logistic regression identified emergency surgery, rectal tumor location, intraoperative transfusion and open surgical approach as independent risk factors. Among POD 3 biomarkers, C-reactive protein-to-albumin ratio (CAR) demonstrated the highest predictive accuracy for AL. After adjustment in the multivariable model, CAR remained an independent predictor of AL (OR=1.91, p<0.001).

Conclusions: Anastomotic leakage after colorectal cancer surgery remains a multifactorial complication influenced by operative conditions, local tumor-related factors, and the postoperative inflammatory response. In this retrospective cohort, POD 3 CAR showed the highest discriminatory performance among the evaluated biomarkers and may support early postoperative risk stratification when interpreted with clinical findings and operative risk factors.

Keywords: anastomotic leakage risk factors, colorectal cancer surgery, POD 3 biomarkers, C-reactive protein, CAR, LCR, NLR, albumin

Introduction

Anastomotic leakage (AL) represents a serious postoperative complication after surgery, especially for digestive tract malignancies, concerning both patients and surgeons (1). In spite of continuous improvements in diagnostics, surgical technique and postoperative management protocols, AL rates remain high. Reported incidence varies widely between 3% and 19% for colon cancer and up to 30% for rectal cancer (1,2).

The International Study Group of Rectal Cancer (ISREC) defines anastomotic leakage as a defect of intestinal wall integrity at the anastomotic site, resulting in a communication between intraluminal and extraluminal compartments. In addition, it emphasizes both clinical and radiological criteria in defining this complication and includes a severity grading system. Grade A leaks are subclinical and do not require intervention, Grade B leaks necessitate non-surgical management (antibiotic therapy, image-guided drainage), and Grade C leaks require surgical reintervention (3-5).

Anastomotic integrity is influenced by a range of factors that collectively determine the success of surgical intervention and postoperative outcomes. Patient-related factors such as comorbidities and physiological status, tumor-related characteristics including advanced stage and low rectal location, and operative variables such as emergency surgery, prolonged operative time, intraoperative transfusion and adverse events have all been associated with an increased risk of anastomotic leakage (6-10).

AL carries serious clinical repercussions. Patients who develop leakage require prolonged hospitalization, invasive interventions, and reoperations, often involving stoma formation. Moreover, AL is associated with increased mortality and may negatively influence long-term oncological outcomes (11,12).

Considering the importance of AL outcomes, alongside enhanced recovery after surgery protocols, increased attention has been directed toward early diagnosis and risk stratification (13). Recent studies have identified promising predictors of early anastomotic dehiscence. Nutritional factors such as albumin, inflammatory biomarkers, such as C-reactive protein (CRP), as well as composite indices, including the CRP-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-CRP ratio (LCR),

have demonstrated varying degrees of diagnostic accuracy for AL in patients who underwent surgical treatment for colorectal cancer (14-21).

Materials and Methods

Study Design and Patient Selection

This retrospective observational study was conducted at the First Surgery Clinic of Pius Brînzeu Timiş County Emergency Clinical Hospital, Timişoara, Romania, affiliated with the First Discipline of Surgery, Department X of Victor Babeş University of Medicine and Pharmacy Timişoara. Patients who underwent resection with primary anastomosis for colorectal cancer between January 2020 and December 2024 were included. From a total cohort of patients with digestive malignancies, 166 met eligibility criteria based upon colorectal tumor location and availability of postoperative day 3 laboratory data.

Inclusion and Exclusion Criteria

Inclusion criteria were:

- Adult patients with histopathologically confirmed colorectal malignancy who underwent resection with primary anastomosis.
- Availability of postoperative day 3 (POD 3) laboratory data, including complete blood count, albumin and C-reactive protein.

Exclusion criteria were:

- Patients without anastomosis.
- Patients with missing key laboratory parameters required for calculation of postoperative biomarkers.
- Patients with incomplete clinical or radiological data regarding anastomotic leakage.
- Patients with anastomotic leakage within the first three postoperative days, as these cases could not be reliably evaluated using POD 3 biomarkers.

All eligible patients were included consecutively according to the date of admission during the study period, provided that they met the predefined inclusion criteria. A complete case analysis was performed for variables included in regression models.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania, approval number 24/02.03.2026.

Definitions and Standardization of Procedures

Anastomotic leakage was defined as a defect in the integrity of the intestinal walls at the anastomotic site, leading to a communication between the intraluminal and extraluminal compartments, in accordance with the definitions proposed by the International Study Group of Rectal Cancer (5).

Leakage occurrence was confirmed based on clinical evaluation and radiological results. Clinical diagnosis was established in the presence of abnormal drain output or wound discharge (e.g. purulent, enteric or feculent content), signs of abdominal sepsis or peritonitis or by means of surgical exploration in patients that required relaparotomy. Radiological confirmation was obtained using contrast-enhanced computed tomography, with or without oral or rectal contrast, illustrating extravasation of contrast, pneumoperitoneum or perianastomotic or intraperitoneal collections.

Anastomotic leakage severity was classified according to the ISREC grading system into (5):

- Grade A: asymptomatic, requiring no intervention.
- Grade B: clinically relevant leaks requiring active therapeutic intervention, but without reoperation.
- Grade C: clinically severe leaks requiring relaparotomy

Data Collection

Data were gathered retrospectively from electronic and paper medical records, patient charts, operative reports and discharge summaries. Laboratory parameters were obtained from the institutional laboratory information system.

All included cases were histopathologically confirmed colorectal malignancies based upon surgical specimens or preoperative biopsies.

The following variables were included in the analysis:

- Patient-related factors: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score.
- Tumor-related characteristics: tumor location and pathological tumor lymph node and metastasis (pTNM) T-stage.
- Operative variables: surgical approach (open or laparoscopic) and setting (emergency or elective), type of anastomosis (manual or stapled), intraoperative need for transfusion and intervention duration.
- Postoperative laboratory parameters: C-reactive protein (CRP), albumin, leukocyte count, neutrophil count, and lymphocyte count.
- Derived inflammatory indices: C-reactive protein-to-albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-CRP ratio (LCR).

Postoperative inflammatory biomarkers were calculated based on laboratory values obtained on postoperative day 3. CRP was recorded in mg/L and albumin in g/dL. For CAR calculation, CRP values were converted from mg/L to mg/dL by dividing by 10, in order to obtain a standardized CRP-to-albumin ratio. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. LCR was calculated by dividing the absolute lymphocyte count by CRP (mg/L).

The following indices were derived:

- C-Reactive-protein-to-albumin-ratio CAR= (CRP [mg/L]/10/albumin[g/dL].

$$CAR = \frac{CRP\ \left(\frac{mg}{L}\right)/10}{Albumin\ \left(\frac{g}{dL}\right)}$$

- Neutrophil-to-Lymphocytes-ratio: NLR = absolute neutrophil count/absolute lymphocyte count.

$$NLR = \frac{Neutrophils\ \left(*\frac{10^3}{\mu L}\right)}{Lymphocytes\ \left(*\frac{10^3}{\mu L}\right)}$$

- Lymphocyte-to-C-Reactive-protein-ratio: LCR = absolute lymphocyte count/CRP [mg/L]/

$$LCR = \frac{Lymphocytes\ \left(*\frac{10^3}{\mu L}\right)}{CRP\ (mg/L)}$$

Statistical Analysis

All data were entered into a secure database and statistical analysis was performed using JASP software (Version 0.96.0.0, JASP Team, University of Amsterdam, The Netherlands) (22). Continuous variables were summarized according to their distribution, being reported as mean ± standard deviation (SD) for normally distributed data, and as median with interquartile range (IQR) when normality was not assumed. Categorical variables were presented as absolute numbers and percentages.

Group comparisons were performed 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.

The predictive performance of postoperative inflammatory biomarkers was explored using receiver operating characteristic curve (ROC) analysis. The area under the curve (AUC) was calculated to evaluate diagnostic accuracy, and optimal cut-off values were determined using Youden's index. In addition, ROC curves were compared using DeLong's test.

To evaluate factors associated with anastomotic leakage, logistic regression analysis was carried out. Variables with potential clinical relevance or statistical significance in univariate analysis were included in multivariable models. Considering the 44 AL events, the number of variables included into the models was limited to reduce overfitting, resulting in an events-per-variable ratio ranging from 8.1 to 11 across the models. Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

The assumption of normality was assessed using the Shapiro-Wilk test. A p-value of <0.05 was considered statistically significant.

Results

Patient Characteristics and Baseline Risk Factors

A total of 166 patients undergoing colorectal cancer resection with primary anastomosis were included in the study. AL occurred in 44 patients (26.50%).

In univariate analysis, ASA score (p=0.003), emergency surgery (p<0.001), open surgical approach (p<0.001), intraoperative transfusion (p<0.001), advanced tumor stage (pT3-pT4) (p=0.014) were significantly associated with an increased risk of developing AL. Operative duration was also significantly longer in patients with leakage (p<0.001).

No significant associations were observed for age (p=0.314), sex (p=0.918), tumor location (p=0.321), BMI (p=0.875), or between stapled versus manual anastomosis types (p=0.089). Baseline patient's characteristics and risk factors were summarized in *Table 1.*

Clinical Outcomes

Clinical outcomes were significantly worse in patients who developed anastomotic leakage compared to those that had a favorable postoperative course.

In this study the median time for diagnosis of AL was 6 days (IQR 5-8). Using a clinically relevant threshold, 68.2% of leaks were categorized as early (within 7 days postoperatively) and 31.8% were considered late leaks (after POD 7).

According to the ISREC severity classification patients who developed AL were graded as follows:

- Grade A: 7 patients (15.90%);
- Grade B: 19 patients (43.20%);
- Grade C: 18 patients (40.90%).

The majority of anastomotic leaks (84.10%) were clinically relevant (Grade B and C), requiring active intervention, as shown in *Table 2.*

Cumulative length of hospital stay (LOS) was

Table 1. Patient characteristics and baseline risk factors

Variable	No AL (n=122)	AL (n=44)	p-value
Age (years), mean ± SD	68.95 ± 10.54	67.05 ± 11.27	0.314
Sex (male), n (%)	58.20%	59.09%	0.918
BMI (kg/m^2), mean ± SD	27.84 ± 5.55	28.07 ± 5.59	0.819
ASA score ≥ 3, n (%)	38.98%	65.12%	0.003
Tumor location (rectum), n (%)	26.23%	34.09%	0.321
Tumor stage (pT3-pT4), n (%)	72.95%	90.91%	0.014
Emergency surgery, n (%)	18.85%	50.00%	<0.001
Open surgical approach, n (%)	63.11%	90.91%	<0.001
Intraoperative transfusion, n (%)	25.41%	61.36%	<0.001
Operative duration (min), mean ± SD	209.00 ± 83.00	262.50 ± 83.90	<0.001
Anastomosis type (stapled), n (%)	41.80%	27.27%	0.089

Note: Values are presented as mean ± standard deviation or n (%).
Abbreviations: AL, anastomotic leakage; ASA, American Society of Anesthesiologists score; BMI, body mass index.

prolonged in patients with AL compared to those without leakage (median 17 vs 9 days, p<0.001).

Postoperative mortality occurred in 19 patients (11.40%) and was significantly higher in the AL group compared to those without leakage (p=0.002). Clinical outcomes are detailed in *Table 3*.

Comparison of POD 3 Biomarkers

Postoperative day 3 inflammatory markers differed significantly between patients with and without anastomotic leakage.

AL group demonstrated higher CRP (p<0.001), CAR (p<0.001), NLR (p<0.001) and leukocyte count (p<0.001), while albumin was significantly lower (p<0.001) and LCR was decreased (p<0.001). A detailed comparison of POD 3 biomarkers is presented in *Table 4*.

Table 2. Anastomotic leakage characteristics

Variable	Value
Time to diagnosis (days), median (IQR)	6 (5-8)
Early leak (≤POD 7), n (%)	68.20%
Late leak (>POD 7), n (%)	31.80%
ISREC Grade A, n (%)	15.90%
ISREC Grade B, n (%)	43.20%
ISREC Grade C, n (%)	40.90%

Note: Values are presented as median (interquartile range) or n (%).
Abbreviations: POD, postoperative day; IQR, interquartile range; ISREC, International Study Group of Rectal Cancer.

Receiver Operating Characteristic (ROC) Curve Analysis of POD 3 Biomarkers

ROC analysis was performed in order to assess the predictive performance of each POD 3 biomarker.

Table 3. Clinical outcomes

Outcome	No AL (n=122)	AL (n=44)	p-value
LOS (days), median (IQR)	9 (7-12)	17 (14-25)	<0.001
Mortality, n (%)	8 (6.60%)	11 (25.00%)	0.002

Note: Values are presented as median (inter quartile range) or n (%)
Abbreviations: AL: anastomotic leakage; LOS, length of stay; IQR, interquartile range

Table 4. Postoperative day 3 biomarkers

Biomarker	No AL	AL	p-value
CRP (mg/L)	103.00 ± 57.00	251.10 ± 70.20	<0.001
Albumin (g/dL)	3.07 ± 0.64	2.50 ± 0.63	<0.001
Leukocytes (x10^9/L)	8.58 ± 3.13	11.74 ± 6.55	<0.001
NLR	6.75 ± 4.89	11.81 ± 11.93	<0.001
LCR	0.016 ± 0.013	0.006 ± 0.006	<0.001
CAR	3.60 ± 2.44	10.85 ± 4.37	<0.001

Note: Values are presented as mean ± standard deviation.
Abbreviations: AL, anastomotic leakage; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-CRP ratio; CAR, C-reactive protein-to-albumin ratio

Albumin and LCR were inverted because lower values were associated with a higher risk of AL.

CAR showed the highest discriminatory ability (AUC=0.963), followed by CRP (AUC=0.942). LCR demonstrated good predictive performance (AUC = 0.855), while albumin showed moderate discrimination (AUC=0.824). NLR (AUC=0.680) and Leukocyte count (AUC=0.664) showed limited predictive value. The ROC curves are presented in *Fig. 1.*

Pairwise comparisons of ROC curves were performed using DeLong's test, that showed higher discriminatory performance of CAR than the other evaluated biomarkers. Optimal cut-off values were determined using Youden's index. The performance hierarchy of POD 3 biomarkers is presented in *Table 5.*

An exploratory sensitivity ROC analysis was performed for clinically relevant leaks, defined as Grade B or C according to the ISREC classification. For this analysis, patients with Grade B/C leaks were considered positive events, while those without anastomotic leakage and Grade A leaks were considered negative events. In this analysis, CAR maintained a high discriminatory performance (AUC=0.962, p <0.001), an optimal cut-off value of 5.76 was determined using the Youden index. These findings were consistent with the main ROC analysis and support the robustness of CAR for identifying clinically relevant anastomotic leakage.

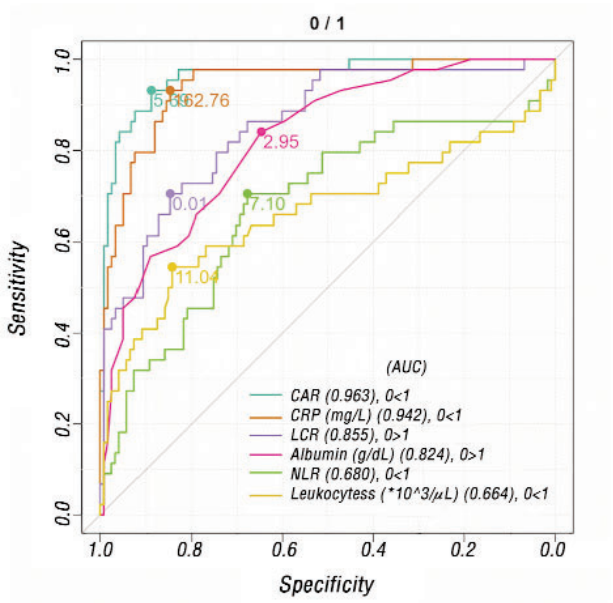

Figure 1. Receiver operating characteristic curves for POD3 biomarkers in predicting anastomotic leakage after colorectal cancer surgery. Abbreviations: AUC, area under the curve; CAR, C-reactive protein-to-albumin ratio; CRP, C reactive protein; LCR, lymphocyte-to-C reactive protein ratio; NLR, neutrophil-to-lymphocyte ratio.

Logistic Regression Analysis

In univariate logistic regression analysis, POD 3 CAR composite biomarker was strongly associated with anastomotic leakage (OR=2.17, p<0.001) with excellent model performance at the optimal threshold of 5.69.

A multivariable analysis including tumor characteristics and operative variables (Model 1) identified emergency surgery (OR=2.61, p=0.048), open approach (OR=3.81, p=0.025), intraoperative transfusion (OR=3.15, p=0.007) and rectal tumor location (OR=2.67, p=0.035) as independent predictors of AL. Advanced tumor TNM T-stage did not reach statistical significance. When CAR was introduced into the model (Model 2), it remained a strong independent predictor of AL (OR=1.91, p<0.001), indicating a substantial increase in the odds of leakage with increasing CAR values. In this adjusted model, only tumors located in the rectum and intraoperative transfusion retained statistical significance, while emergency setting and open approach were no longer significant. Both multivariate regressions are presented in *Table 6.*

Subgroup Analysis: Colon vs Rectum Tumor Location

Although rectal tumors showed a greater prevalence of AL rates (31.90%) than colonic tumors (24.40%), this difference did not reach statistical significance (p=0.321).

Table 5. Diagnostic performance of postoperative day 3 biomarkers

Biomarker	AUC	95% CI	Cut-off	Sensitivity	Specificity	p-value
CAR	0.963	0.932-0.993	5.69	93.18%	88.89%	<0.001
CRP	0.942	0.903-0.981	162.80	93.18%	84.75%	<0.001
LCR	0.855	0.789-0.920	0.0055	70.45%	84.75%	<0.001
Albumin	0.824	0.755-0.894	2.95	84.09%	64.71%	<0.001
NLR	0.680	0.579-0.781	7.10	70.45%	67.77%	<0.001
Leukocytes	0.664	0.552-0.776	11 x 103/µL	54.55%	84.30%	0.004

Note: ROC curves were generated for postoperative day 3 values.
Abbreviations: AUC, area under the curve; CI, confidence interval: CAR, C-reactive protein-to-albumin ratio; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LCR, lymphocyte-to-CRP ratio.

Table 6. Multivariable logistic regression analysis of risk factors for anastomotic leakage

Variable	OR (Model 1)	95% CI	p-value	OR (Model 2)	95 % CI	p-value
Emergency surgery	2.61	1.009 – 6.749	0.048	0.52	0.107 – 2.492	0.410
Rectal tumor location	2.67	1.072 – 6.652	0.035	4.87	1.278 – 18.558	0.020
Intraoperative transfusion	3.15	1.376 – 7.209	0.007	5.07	1.303 – 19.755	0.019
Open approach	3.81	1.179 – 12.325	0.025	1.50	0.335 – 6.748	0.595
CAR	-	-	-	1.91	1.520 – 2.408	<0.001

Note: Model 1 includes only clinical and operative variables. Model 2 includes CAR in addition to clinical and operative variables.
Abbreviations: OR, odds ratio; CAR, C-reactive protein-to-albumin ratio

CAR maintained a strong predictive performance in both subgroups, supporting its applicability across colorectal cancer resections.

Operative Duration Analysis

An operative duration ROC analysis was conducted that demonstrated a modest predictive ability for AL (AUC=0.689, p<0.001). The optimal cut-off value was identified at 285 minutes, with a 51.20% sensitivity and 82.40% specificity, suggesting that prolonged surgical procedures are associated with an increased risk of AL.

Discussion

Anastomotic leakage remains a major postoperative complication for patients who undergo surgical treatment for colorectal cancer. In the present cohort, AL occurred in 26.50% of patients, which is higher than the rates reported in many published series. The relatively high incidence rate observed in our cohort should be interpreted in the context of several factors. First, the definition used included both clinically manifest and radiologically detected events, capturing a broader spectrum of this complication. Second, the cohort included both colon and rectal cancer resection, with rectal tumors being associated with higher technical complexity and a greater risk of anastomotic failure. Third, the study period encompassed the COVID-19 pandemic, during which delayed presentation, more advanced-stage disease, increased comorbidity burden and a higher proportion of emergency surgical procedures were observed. This interval was also marked by a significant reallocation of healthcare resources toward the management of SARS-CoV-2 patients, with changes in surgical team composition, perioperative staffing, and operating room logistics. In addition, supply chain disruptions and inconsistent availability of surgical devices may have influenced surgical decision-making. In our study, patients with AL experienced worse clinical postoperative evolution, including prolonged hospital stay and significantly higher mortality. These findings are consistent with numerous previous studies showing the severe impact of this complication on short-term recovery and overall prognosis(23–26).

The distribution according to the ISREC severity classification demonstrated that most leaks (84.10%) required active intervention or relaparotomy, emphasizing the significant burden of this complication (5,27,28). Furthermore, the consequences of anastomotic failure underline the importance of early diagnosis and risk stratification to prevent progression to sepsis and higher mortality (29,30).

From a surgical perspective, anastomotic integrity is primarily dependent on adequate perfusion of bowel stumps, absence of tension in the anastomosis, meticulous technique and appropriate patient selection for primary anastomosis(31). Local factors such as peritumoral inflammation, obstruction, distal rectal location, narrow pelvic anatomy and neoadjuvant therapy may further increase the risk of dehiscence(31). In this context, postoperative biomarkers should not be interpreted as isolated determinants of AL, but rather as an early warning signal for attentive monitoring.

Multiple factors are responsible for anastomotic leakage, involving complex interrelationships between patient-related factors, tumor characteristics, operative factors and postoperative inflammatory response. In our cohort, single variable analysis showed that ASA score ≥ 3, emergency surgery, open approach, intraoperative transfusion, advanced tumor stage and prolonged surgical procedures were associated with this complication. After adjustment in a multivariable analysis, emergency setting, tumors located in the rectum, the need for intraoperative transfusion and open approach remained independent risk factors for leakage. These findings are consistent with the technical difficulty of rectal resections, the adverse conditions associated with emergency surgery, and the impact of intraoperative physiological stress (32,33). In contrast with our findings, patient-related factors such as advanced age and male-sex, were non-negligible risk factors for anastomotic failure (34,35).

Operative duration analysis demonstrated a modest predictive ability for AL, with an optimal cut-off value of 285 minutes. This finding suggests that procedures lasting less than 285 minutes carry a lower risk of developing leakage (82.40% specificity). In concordance with our results, multiples studies concluded that operative times longer than 4 hours were associated with increased risk of developing anastomotic insufficiency, among other postoperative complications (32,33).

Although preoperative and operative factors provide valuable information in constructing a baseline risk assessment, they do not fully account for the dynamic postoperative evolution that determines anastomotic healing. Thus, postoperative inflammatory and metabolic alterations may offer additional insight into early pathological processes, that ultimately lead to anastomotic dehiscence (12).

The present study aimed to assess the potential role of postoperative day 3 biomarkers in the early prediction of impaired anastomotic healing. Among available POD 3 laboratory biomarkers, CAR showed the highest discriminatory performance, with an AUC of 0.963, followed by CRP, LCR, albumin, NLR, and leukocyte count. In addition, CAR remained an independent predictor after inclusion in a multivariable analysis that encompassed clinical and operative risk factors. Furthermore, CAR maintained a high discriminatory performance (AUC=0.962) in the sensitivity analysis performed for clinically relevant leakage (ISREC Grade B/C). However, given the retrospective design and the limited number of events, this analysis should be interpreted with caution and requires external validation.

CRP is an acute-phase protein produced by hepatocytes after inflammatory stimulation, that has been widely shown to be an effective and sensitive predictor of AL (36,37). Albumin represents a marker for nutritional index and systemic metabolic reserve, with lower serum concentrations being associated with impaired wound healing and an increased risk of dehiscence. Nevertheless, disagreement among CRP and albumin concentrations are not uncommon, with a wide variation in threshold values being reported (36,38-40).

Recent studies proposed derived inflammatory biomarkers such as NLR, LCR and CAR as more refined indicators for immunological and inflammatory response. In our study, all composite biomarkers were associated with a higher risk of anastomotic failure. To assess which postoperative biomarker showed the greatest predictive value for AL, an ROC curve analysis was performed. Pairwise comparisons showed that CAR had the highest discriminatory ability, followed by CRP. LCR and albumin revealed good predictive performance, while absolute leukocyte count and NLR showed limited predictive ability. In concordance with our findings, several articles revealed the utility of composite biomarkers in early prediction of AL. However, literature is divergent regarding optimal plasmatic concentration ranges and the ideal postoperative day for blood sample collection that offers the highest accuracy for this complication (41-43).

Despite multiple authors evaluating the usefulness of postoperative biological predictors, literature remains heterogeneous, and no single biomarker has been universally accepted as superior (43-45). Systematic analyses have demonstrated variability in the predictive value of CRP, NLR, LCR and other indices across different patient populations and clinical settings. In this context, our findings support the role of CAR as a highly informative marker, while also emphasizing the need for further standardization and validation of biomarker-based prediction strategies.

From a clinical perspective, the integration of biomarker assessment with established risk factors may enhance early postoperative monitoring. The use of CAR as a simple, inexpensive, and widely available parameter may support early identification of high-risk patients, prompting closer surveillance and timely imaging. This approach may be particularly valuable in the context of enhanced recovery protocols, where early discharge decisions must be balanced against the risk of undetected complications. However, surgical decision-making in suspected anastomotic leakage remains based upon clinical examination, hemodynamic status, drain output, imaging results and the surgeon's judgement, therefore the value of CAR lies in supporting, rather than replacing clinical management.

Study Limitations

Several limitations of this study should be acknowledged. The retrospective design and inclusion criteria restricted to patients with available postoperative day 3 laboratory data, may introduce selection bias and limits causal interpretation. The research was conducted in a single center, which may affect generalizability. The inclusion of both colon and rectal cancers reflects real-world clinical practice but introduces important heterogeneity, as rectal resections are technically more demanding and are influenced by additional factors such as pelvic anatomy, low anastomotic level and neoadjuvant therapy. To address this limitation a subgroup analysis according to tumor location was performed, but the sample size may have limited the

statistical power to fully explore the differences between colon and rectal cancer patients.

Important variables, such as the use of diverting ileostomy, the exact level of rectal anastomosis, detailed preoperative nutritional assessment beyond albumin values or neoadjuvant therapy, that may influence anastomotic healing were not consistently available in the retrospective records and could not be included in the analysis. Furthermore, the study period encompassed the COVID-19 pandemic, which may have influenced patient presentation and perioperative management. An additional consideration is the very high diagnostic performance of CAR in this study. While this finding highlights its potential utility, such excellent discriminatory ability may be reflected by the relatively high incidence of AL and study population characteristics included in this cohort. In addition, postoperative biomarkers were assessed at a fixed time point (POD 3), which may capture established inflammatory responses rather than early predictive changes, affecting the statistical analysis accuracy. Therefore, the performance of CAR should be interpreted with caution and requires external validation in larger, multicenter cohorts.

Overall, the present study highlights the multifactorial nature of anastomotic leakage, in which clinical risk factors and postoperative biological response are closely interconnected. While surgical and patient-related factors define baseline risk, postoperative inflammatory and metabolic alterations may play a role in determining clinical decision-making. In this context, CAR emerges as a clinically relevant biomarker that integrates these processes and may improve early detection of anastomotic leakage following colorectal surgery.

Conclusions

Anastomotic leakage remains a multifactorial and clinically significant complication, after colorectal cancer surgery, associated with prolonged hospitalization and increased postoperative mortality. In the present study, operative factors such as emergency surgery setting, open approach, rectal tumor location and intraoperative transfusion were associated with an increased risk of anastomotic failure.

Among the analyzed postoperative biomarkers, CAR demonstrated the highest predictive performance and remained a statistically significant risk factor after adjustment for operative risk factors. In the sensitivity analysis restricted to clinically relevant ISREC Grade B/C leaks, CAR also maintained high discriminatory performance, supporting its potential role in early postoperative risk stratification.

However, given the retrospective, single-center design and the high diagnostic performance of CAR, these findings should be interpreted cautiously. CAR should not be considered an isolated decision-making tool or an indication for reintervention. Instead, it may support closer monitoring, timely imaging and individualized surgical management when integrated with clinical assessment and operative findings. Further prospective multicenter studies are required to validate the role of composite biomarkers and to establish standardized thresholds for clinical implementation.

Conflicts of Interest

The authors declare no conflicts of interest.

Institutional Review Board Statement

The study was conducted in accordance with the latest version of the Declaration of Helsinki and was approved by the Ethics Committee of Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania, approval number 24/02.03.2026. Given the retrospective observational design of the study and the use of anonymized data collected from medical records, the requirement for individual informed consent was waived by the Ethics Committee. All patient data were collected confidentially and anonymized before analysis.

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