

ORIGINAL ARTICLE

Colon Leakage Score and Preoperative Albumin for Predicting Anastomotic Leakage after Colorectal Cancer Resection in Indonesia: A Predictive Accuracy Study

Muhammad Rizqi Firyal^{1*}, Muhammad Hafidh Komar², Theodorus³

¹ Specialist Doctor Study Program, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

² Department of Digestive Surgery, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

³ Department of Pharmacology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

ARTICLE INFO

Article history:

Received: August 30, 2025

Revised: September 29, 2025

Accepted: October 26, 2025

Available: November 1, 2025

Published: November 3, 2025

Keywords:

Anastomotic leak; Colorectal neoplasms; Colon Leakage Score; Hypoalbuminemia; Sensitivity and specificity

Corresponding author:

Muhammad Rizqi Firyal

Email:

Rizqifiryal97@gmail.com

DOI:

<https://doi.org/10.37275/sjs.v8i2.161>

Access license:

Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Copyright:

© 2025 The Authors. Authors retain copyright and grant the journal the right of first publication. Published by HM Publisher.

ABSTRACT

Background: Anastomotic leakage (AL) is the most serious complication of colorectal cancer resection. The Colon Leakage Score (CLS) has no biochemical component and has not been tested in Indonesian patients, many of whom have hypoalbuminemia.

Objective: To measure how accurately CLS >11 combined with preoperative albumin <3.5 g/dL predicts AL, and to quantify what albumin adds to the CLS.

Methods: This retrospective STARD-guided study included 60 adults who underwent colorectal cancer resection with primary anastomosis and no diverting stoma at Dr. Mohammad Hoesin General Hospital, Palembang (January 2022–June 2024). Accuracy measures carry Wilson 95% confidence intervals (CIs). Albumin had not been cross-classified against AL. Every contingency table matching the observed data was therefore enumerated, with Firth regression across 19,977 admissible datasets.

Results: Thirteen patients (21.7%; 95% CI 13.1–33.6) developed AL, and 43 (71.7%) were hypoalbuminemic. Six of seven composite-positive patients leaked, as did 7 of 53 composite-negative patients (odds ratio 35.6; exact 95% CI 3.6–1850.2; $p < 0.001$). Sensitivity was 46.2% (23.2–70.9), below the 80% benchmark ($p = 0.007$). Specificity was 97.9% (88.9–99.6), positive predictive value 85.7% (48.7–97.4) and negative predictive value 86.8% (75.2–93.5). Seven of eight CLS-high patients were hypoalbuminemic; albumin reclassified one. CLS >11 was associated with AL in all 15 admissible tables (odds ratio 19.3–53.7). The albumin association (0.23–15.5) could not be identified.

Conclusion: The composite works as a high-specificity rule-in criterion, and the CLS carries its discrimination. It misses more than half of all leaks. Widespread hypoalbuminemia is a separate nutritional target that deserves prospective evaluation.

1. Introduction

Colorectal cancer made up 9.6% of all new cancers and 9.3% of cancer deaths worldwide in 2022. It ranked third for incidence and second for mortality¹. Asia carries half of the global caseload. There were 966,400 new cases in 2022, one in ten of them in younger adults, and cases are projected to reach 1.87 million by 2050². Early-onset disease is rising across the Asia-Pacific region, and its mortality has increased by 10.6% in Southeast Asia³. Indonesian registry data show the same trend. Incidence in Yogyakarta rose by 13.4% per year between 2008 and 2019⁴. Among hospital patients, 11.7% were younger than 50 years, and these patients were often underweight at presentation⁵. For localized disease, the curative treatment remains resection of the tumor-bearing segment with restoration of intestinal continuity. The integrity of the anastomosis therefore shapes both survival and quality of life.

Anastomotic leakage (AL) often turns a curative operation into a life-threatening one. In German national data on 690,690 resections, AL followed 6.7% of colon and 9.2% of rectal resections, and in-hospital mortality rose from 7.1% to 20.1% after colonic leakage⁶. Korean nationwide claims give a 30-day AL rate of 5.98%, with longer stays and higher costs⁷. In the binational Australian and New Zealand audit, AL complicated 5.0% of anastomoses yet preceded 21.4% of all postoperative deaths⁸. Rates are higher after mid and low rectal surgery (13.6%)⁹. A published Indonesian single-center series reports 25.9%¹⁰. The consequences reach beyond the index admission. AL independently shortens overall survival (hazard ratio

2.08)¹¹, and after right colectomy it halves five-year recurrence-free survival (43.6% vs 80.3%)¹². After rectal resection, only 43–45% of patients are stoma-free at one year¹³, and the odds of a permanent stoma rise eightfold¹⁴. First-year hospital costs roughly quadruple¹⁵. Comparison across settings is difficult. Only 7 of 38 countries keep national registries that capture leak outcomes, and the variables they record differ widely¹⁶.

Leak risk depends on patient, disease and operative factors. A meta-analysis of 115,462 colon cancer resections named male sex, diabetes, an American Society of Anesthesiologists (ASA) class of III or higher, open surgery and emergency surgery as independent predictors¹⁷. In a recent single-center series, emergency resection without diversion raised the leak rate from 5.3% to 19.7%¹⁸. Of all these factors, nutritional status is the easiest to modify. A meta-analysis of 33 studies (31,108 patients) linked lower preoperative albumin to AL (odds ratio [OR] 2.67; 95% CI 1.85–3.87), with an optimal risk threshold of 3.75 g/dL¹⁹. A second meta-analysis tied hypoalbuminemia to postoperative morbidity after colorectal cancer surgery (risk ratio 2.28)²⁰. Albumin, though, is also a negative acute-phase protein. Low levels follow systemic inflammation as closely as nutritional risk²¹, and albumin drops by about 5 g/L within three days of any major operation while C-reactive protein (CRP) climbs²². In one enhanced recovery after surgery (ERAS) program, preoperative albumin was similar in patients who leaked and those who did not (39 vs 38 g/L)²³. Whether albumin adds information to an established clinical score is thus an empirical question, not a physiological certainty.

The Colon Leakage Score (CLS) combines 11 patient and operative variables into a score from 0 to 43 points. In its Dutch test cohort of 121 patients it discriminated well (area under the curve [AUC] 0.95), with an OR of 1.74 per point²⁴. External validations have been smaller and less favorable. A Mexican series of 208 left-sided resections without diversion found an AUC of 0.898. At the conventional cut-off of 11, sensitivity was 53% and specificity 93%²⁵. An Indian prospective study preferred a cut-off above 9²⁶. In a Chinese cohort, 47.8% of patients were classified as CLS >11²⁷. Systematic reviews of 9 and 31 leak-prediction scores found that most had never been externally validated. They rated the CLS at high risk of bias, and albumin entered only one of nine published scores^{28,29}. Performance often falls on external testing. A random-forest model dropped from an AUC of 0.78 to 0.60³⁰, a gradient-boosting model from 0.984 to 0.703³¹, and a right-colectomy score from 0.64 to 0.59³². Nationwide models built from routine preoperative variables plateau near an AUC of 0.63–0.69^{33,34}. Albumin has entered several nomograms as an independent predictor^{35,36}. The only Indonesian study to examine albumin and the CLS together enrolled 32 patients with two leaks, and it detected no correlation with either³⁷.

Three gaps remain. First, nobody has reported the accuracy of the CLS against a defined leak outcome in an Indonesian population. Heavily weighted score items such as low anastomosis and neoadjuvant therapy may rarely apply there, whereas hypoalbuminemia is common. Second, adding albumin to a clinical score is intuitive, but no one has examined whether albumin changes any classification beyond the CLS. Third, retrospective series in this setting seldom record every joint distribution needed for full multivariable analysis, and the defensible inferential limits of such data are rarely stated. This study had three aims. The primary aim was to determine the predictive accuracy of a composite criterion (CLS >11 and preoperative serum albumin <3.5 g/dL) for AL after colorectal cancer resection with primary anastomosis at Dr. Mohammad Hoesin General Hospital, Palembang. The benchmark was a threshold of 80% for both sensitivity and specificity, taken from the literature before analysis. The secondary aims were to quantify the contribution of each component, using exact enumeration wherever the joint distribution had not been recorded, and to describe the cohort's risk profile against published populations.

2. Methods

Study design and setting

This retrospective, single-center study of predictive accuracy is reported according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD 2015)³⁸. The index test was a preoperative and intraoperative risk classification. The

reference standard was the later occurrence of AL, so the study estimates prognostic accuracy rather than concurrent diagnostic accuracy. It took place in the Department of Surgery of Dr. Mohammad Hoesin General Hospital, Palembang, the tertiary referral and academic hospital for South Sumatra Province, Indonesia. Inpatient and outpatient medical records from January 2022 to June 2024 were reviewed.

Participants and eligibility

All adults (≥18 years) with histologically confirmed primary colorectal adenocarcinoma (stage I–IV) who underwent resection with a primary anastomosis during the study period were eligible. Exclusions were non-adenocarcinoma histology, a known synchronous primary malignancy, a previous colorectal resection, and a record from which any of the 11 CLS items or the preoperative albumin value could not be abstracted. Patients with a protective (diverting) ileostomy or colostomy at the index operation were also excluded. This last criterion ensured that fecal diversion could not mask clinical leakage. Its consequences for the spectrum of included patients are addressed in the Discussion. Total (consecutive) sampling was used, so every patient who met the criteria entered the study.

Sample size

The planned sample size came from the single-proportion formula $n = Z^2 \alpha / 2 \times P(1 - P) / d^2$, with $Z_{\alpha/2} = 1.96$, an anticipated leak proportion $P = 0.217$ and an absolute precision $d = 0.10$. The minimum was 66 patients, and 60 eligible patients were available. The planning value equals the leak rate later observed in the cohort. The calculation is therefore reported as a statement of achieved precision, and the minimum of 66 patients was not reached. With 60 patients, the 95% Wilson interval for the leak rate has a half-width of 10.2 percentage points.

Variables and data collection

A standardized form was used to abstract data from inpatient and outpatient records. The CLS was calculated for each patient from its 11 items: age, sex, ASA physical status, body mass index (BMI), intoxication (smoking, alcohol, current steroid use), neoadjuvant therapy, emergency surgery, distance of the anastomosis from the anal verge, additional procedures, blood loss and transfusion, and operative duration. Emergency surgery meant an operation within 24 hours of admission for obstruction, perforation or uncontrolled hemorrhage. All emergency operations in this cohort were for obstruction. An additional procedure was any concurrent major intra-abdominal procedure beyond a standard colectomy, for example cholecystectomy, extensive adhesiolysis or small-bowel resection. Blood loss was the surgeon's intraoperative estimate, based on suction-canister volume and swab inspection.

Table 1. Colon Leakage Score items, point allocation and study definitions

Component	Categories (points)
Age, years	<60 (0); 60–69 (1); 70–79 (2); ≥80 (4)
Sex	Female (0); male (1)
ASA physical status	I (0); II (1); III (3); IV (6)
Body mass index, kg/m ²	19–24 (0); 25–30 (1); >30, <19 or weight loss >5 kg in 6 months (3)
Intoxication	None (0); smoking (1); alcohol >3 units/day (1); current steroids, excluding inhalers (4)
Neoadjuvant therapy	None (0); radiotherapy (1); chemoradiation (2)
Emergency surgery	None (0); bleeding (2); obstruction (3); perforation (4)
Distance of anastomosis from anal verge, cm	>10 (0); 5–10 (3); <5 (6)
Additional procedure	No (0); yes (1)
Blood loss, mL (and transfusion)	<500 (0); 500–1000 (1); 1001–2000 (3); >2000 (6)
Duration of operation, h:min	<2:00 (0); 2:00–2:59 (1); 3:00–3:59 (2); ≥4:00 (4)
CLS risk category	Total 0–43; high risk >11
Hypoalbuminemia	Serum albumin <3.5 g/dL, most recent value ≤7 days before surgery
Composite index test	Positive if CLS >11 and albumin <3.5 g/dL; negative otherwise
Reference standard: anastomotic leakage	≥1 of: clinical intra-abdominal sepsis; purulent or fecal drain/wound discharge; radiological leak (contrast extravasation or peri-anastomotic collection); defect seen at relaparotomy

Notes: ASA, American Society of Anesthesiologists; CLS, Colon Leakage Score.

Preoperative serum albumin was the latest value measured within seven days before surgery. Hypoalbuminemia meant a value below 3.5 g/dL. The index test was a composite. A patient was test-positive only when both criteria were met (CLS >11 and albumin <3.5 g/dL), and every other patient was test-negative. Both components were fixed before the outcome could occur: albumin before surgery, and the CLS at the end of the operation. The CLS cut-off, the albumin threshold and the 80% accuracy criterion all came from the published literature before analysis. Because the thresholds were taken from the literature and not selected in this cohort, optimism from threshold selection is limited. The albumin cut-off of 3.5 g/dL differs from the optimal threshold of 3.75 g/dL reported in a meta-analysis¹⁹.

The reference standard was clinical AL. It was recorded when at least one of the following was documented after surgery: (1) clinical signs of intra-abdominal sepsis (persistent fever, tachycardia, intractable abdominal pain); (2) purulent or fecal discharge from a drain or the wound; (3) unequivocal radiological evidence (contrast extravasation on computed tomography or enema, or a significant peri-anastomotic collection); or (4) direct visualization of an anastomotic defect at relaparotomy. The International Study Group of Rectal Cancer grade, the postoperative day of diagnosis and the confirming modality were not recorded. Abstraction was not blinded to outcome. Index-test and reference-standard data were complete for all 60 analyzed patients, so no imputation was needed.

Statistical analysis

Descriptive statistics were produced in SPSS version 27.0. Python 3.14 with SciPy 1.18.1, statsmodels 0.15.0 and NumPy 2.4.4 was used for all other analyses. Categorical variables are given as counts and percentages with 95% Wilson score intervals. Continuous variables are given as printed medians, with interquartile range (IQR) where recorded. An exact binomial test compared the female proportion with parity. One-sample exact binomial tests compared cohort proportions with reference values from published populations: national and regional leak rates, hypoalbuminemia prevalence and the proportion of patients with CLS >11. Effect sizes are expressed as Cohen's *h*, and *p* values were adjusted with the Holm procedure across the eight comparisons. Sensitivity and specificity of CLS >11 were compared with the Mexican validation²⁵ by one-sample exact binomial tests against the published proportions (53% and 93%).

Accuracy of the composite was derived from the observed 2×2 table: sensitivity, specificity, positive and negative predictive values (PPV, NPV) and overall accuracy, with Wilson

intervals (Clopper–Pearson intervals served as a sensitivity check). Positive and negative likelihood ratios (LR+, LR–; log method), the diagnostic odds ratio, the Youden index *J* = sensitivity + specificity – 1 and the balanced accuracy are also reported. Balanced accuracy equals the AUC of a binary test. The conditional maximum-likelihood OR with an exact confidence interval, together with Fisher's exact test, summarized the association between test result and outcome. The risk ratio, the risk difference with a Newcombe hybrid-score interval, the phi coefficient and Cohen's *κ* are reported as well. One-sided exact binomial tests examined the criterion of good accuracy set before analysis (sensitivity and specificity both >80%), and the power of the sensitivity test was calculated for the observed number of leaks. A tipping-point analysis tested robustness to outcome misclassification by reclassifying false-negative leaks as non-leaks, one at a time. Bayes' theorem gave predictive values at other leak prevalences, with 95% bands from Jeffreys beta posteriors of sensitivity and specificity.

In the patient records, leakage was not cross-classified against albumin or against any covariate other than the composite. The analysis therefore had two pieces of observed joint information. First, by definition of the composite, all seven composite-positive patients belonged to the eight with CLS >11. The CLS × albumin cross-classification is thus fully determined. Second, the composite 2×2 fixes the leak count in the doubly positive stratum. The other seven leaks, found among the 53 composite-negative patients, can be spread over three strata: CLS >11 with normal albumin (*n* = 1, *b* leaks), CLS ≤11 with hypoalbuminemia (*n* = 36, *c* leaks) and CLS ≤11 with normal albumin (*n* = 16, *d* leaks). The only constraints are *b* + *c* + *d* = 7 and *b* ≤ 1. All 15 such tables were enumerated. This sensitivity analysis is labeled S1. For comparison, S0 enumerated every table that matches the printed margins alone.

Each admissible table yielded the OR for leakage by CLS >11 alone and by albumin <3.5 g/dL alone, with a Haldane–Anscombe correction for zero cells. Fisher's exact *p*, Cramér's *V*, the risk difference, sensitivity, specificity and AUC were computed as well. Firth-penalized logistic regression models were fitted with both components and with their interaction, and *p* values came from profile penalized-likelihood ratio tests. The Cochran–Armitage trend statistic and AUC for a 0–1–2 count of risk factors were also calculated, along with the net reclassification improvement (NRI) of the composite over CLS >11 alone. Results are given as the attainable minimum and maximum and as the percentage of admissible tables reaching *p* < 0.05. Each table was weighted by the number of patient-level arrangements it represents, which gives the percentage of

admissible datasets. This weighting is equivalent to assuming that leaks among composite-negative patients are exchangeable across the three strata, with no association within them. The weighted percentages therefore describe the null-centered part of the admissible space. They are not probabilities that an association exists. Margins-only (S0) bounds were also computed for sex, age ≥ 60 years, ASA III, stage III–IV and emergency surgery.

The multivariable layer used 20,000 admissible patient-level datasets. Each preserved every printed margin, the composite table and the CLS $\times$ albumin cross-classification. The remaining seven leaks were allocated at random among the composite-negative patients, and the label vectors for male sex, age ≥ 60 years, ASA III, stage III–IV and emergency surgery were permuted independently. A Firth model with all seven predictors was fitted to each dataset, with Wald p values from penalized standard errors. A fit was accepted only if the design matrix had full rank, the information matrix had a condition number below 10^8 , the penalized score was below 10^{-5} and every $|\beta|$ was below 15. Eight parameters and 13 events make this model a stress test rather than an estimate. A parsimonious model (CLS > 11 , albumin and emergency surgery) was therefore fitted across 20,000 further datasets. Wald and profile penalized-likelihood inference were compared for the two index-test components in 1,000 datasets. For each coefficient, two constructed and three random starting arrangements were each followed by 600 label swaps of hill-climbing towards the coefficient's extremes. The reported extremes are the most extreme values found, and they are lower bounds on the attainable range. Several covariates are themselves CLS items, so independent permutation admits some structurally impossible datasets. The admissible space is thus a superset of the feasible space. Its ranges are outer bounds, and its percentages are not probabilities. The interpretive rule was

fixed in advance, before any model was run. If an attainable range spans the null, the data cannot identify the association, and this is reported as a result. If a range lies wholly on one side of the null, the conclusion holds for every dataset that matches the observations. These analyses use only the space of datasets that match the observed counts. Patient-level values were not imputed or presented as measured. The 20,000 patient-level datasets were generated from the observed margins for the sensitivity analysis only and are not patient data. All tests were two-sided with $\alpha = 0.05$, and p values are reported to three decimals.

Ethics

The study protocol was approved by the CMHC Research Center Ethics Committee, Indonesia (approval No. 2024/8421) in 2024 for the retrospective analysis of anonymized medical records. The requirement for individual informed consent was waived because the study used existing, de-identified records only. The study was conducted in accordance with the Declaration of Helsinki.

3. Results

Participants and baseline characteristics

Sixty patients met the eligibility criteria and were analyzed. All had complete index-test and reference-standard data, and no index-test result was inconclusive (Figure 1). Table 2 and Figure 2 present the baseline characteristics. Women comprised 55.0% of the cohort (33/60; 95% CI 42.5–66.9), a proportion not different from parity (exact p = 0.519; h = 0.10). The median age was 58 years. Forty patients (66.7%; 54.1–77.3) were younger than 60 years, 15 (25.0%) were aged 60–69 years and 5 (8.3%) were 70 years or older. Most patients were ASA II (43; 71.7%); 12 (20.0%) were ASA I and 5 (8.3%) were ASA III. The median BMI was 22.5 kg/m² (IQR 20.8–25.0).

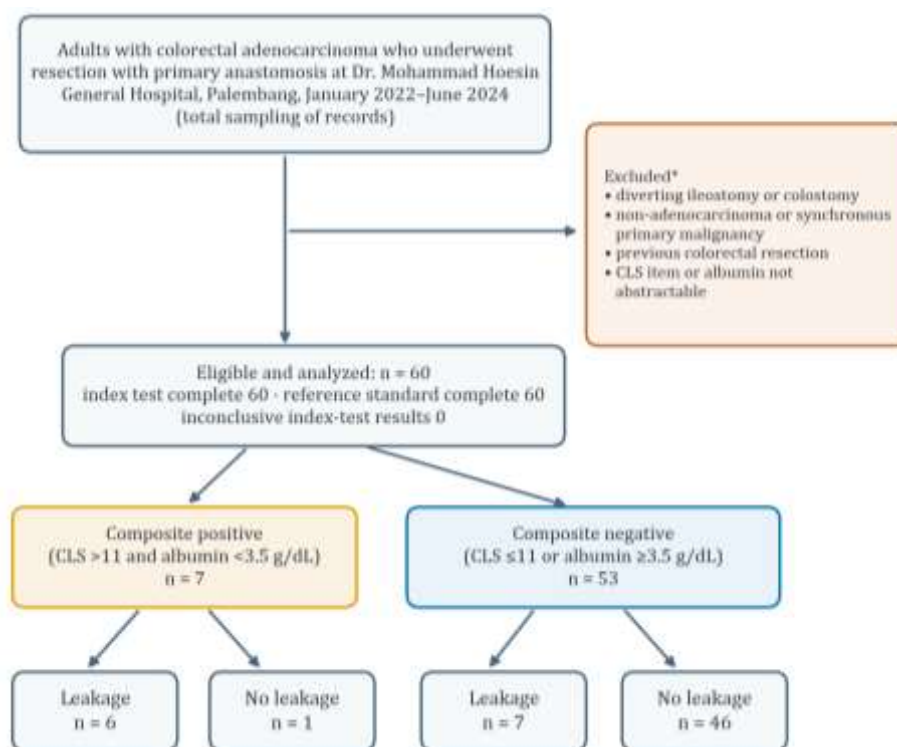


Figure 1. STARD participant flow. Adults with colorectal adenocarcinoma who underwent resection with primary anastomosis at Dr. Mohammad Hoesin General Hospital, Palembang (January 2022–June 2024). Diverted patients were excluded. All 60 analyzed patients had

complete index-test (Colon Leakage Score [CLS] and preoperative albumin) and reference-standard (anastomotic leakage) data. The number screened and excluded under each criterion was not retained.

Table 2. Baseline and clinical characteristics of the cohort (n = 60)

Characteristic	n (%) or median	95% Wilson CI, %
Sex		
Female	33 (55.0)	42.5–66.9
Male	27 (45.0)	33.1–57.5
Age		
Median age, years	58	—
<60 years	40 (66.7)	54.1–77.3
60–69 years	15 (25.0)	15.8–37.2
≥70 years	5 (8.3)	3.6–18.1
ASA physical status		
I	12 (20.0)	11.8–31.8
II	43 (71.7)	59.2–81.5
III	5 (8.3)	3.6–18.1
Median BMI, kg/m ² (IQR)	22.5 (20.8–25.0)	—
Pathological stage		
I	3 (5.0)	1.7–13.7
II	22 (36.7)	25.6–49.3
III	31 (51.7)	39.3–63.8
IV	4 (6.7)	2.6–15.9
Operative profile		
Neoadjuvant therapy	0 (0.0)	0.0–6.0
Emergency surgery (obstruction)	10 (16.7)	9.3–28.0
Anastomosis >10 cm from anal verge	58 (96.7)	88.6–99.1
Index-test components		
Albumin <3.5 g/dL	43 (71.7)	59.2–81.5
Albumin <3.5 g/dL, elective patients (lower bound)	≥33/50 (≥66.0)	52.2–77.6
CLS >11	8 (13.3)	6.9–24.2
Composite positive	7 (11.7)	5.8–22.2
Outcome		
Anastomotic leakage	13 (21.7)	13.1–33.6
Operative medians		
Blood loss, mL	700	—
Operative duration, min	195	—

Female proportion vs parity: exact binomial $p = 0.519$ (Cohen's $h = 0.10$). Medians are reported as recorded; interquartile ranges for age, blood loss and operative duration were not recorded. BMI, body mass index; CI, confidence interval; CLS, Colon Leakage Score.

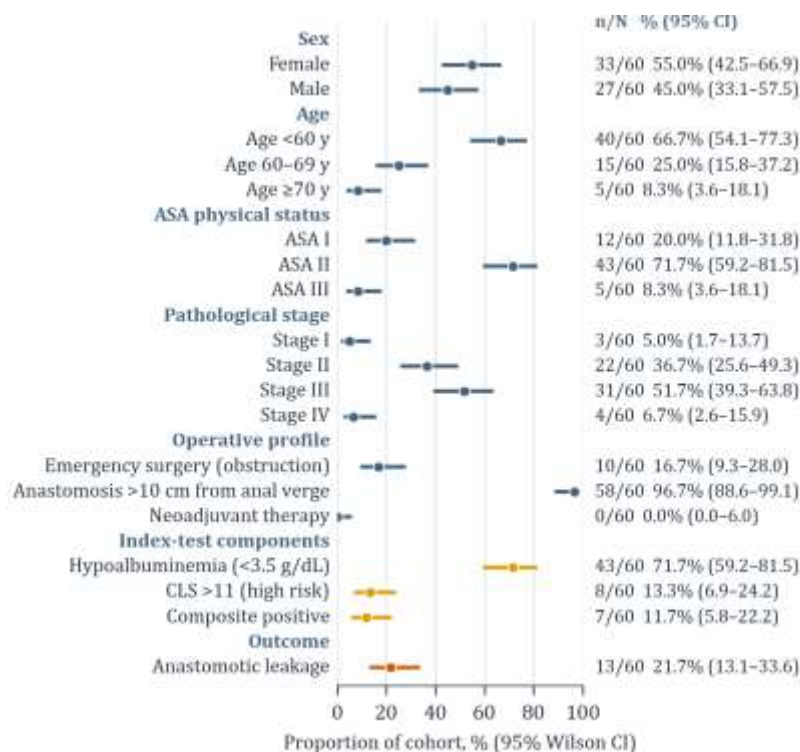


Figure 2. Cohort profile (n = 60). Points are proportions and horizontal bars 95% Wilson confidence intervals; values are given at right. Slate blue: patient, disease and operative characteristics; gold: index-test components; orange-red: outcome. ASA, American Society of Anesthesiologists; CLS, Colon Leakage Score.

Disease was predominantly locoregionally advanced. Thirty-one patients (51.7%; 39.3–63.8) had stage III and 22 (36.7%; 25.6–49.3) stage II disease, together 53 (88.3%; 77.8–94.2); 3 (5.0%) had stage I and 4 (6.7%) stage IV disease. No patient had received neoadjuvant therapy (0/60; 95% CI 0.0–6.0). Ten operations (16.7%; 9.3–28.0) were emergencies for malignant obstruction. The anastomosis lay more than 10 cm from the anal verge in 58 patients (96.7%; 88.6–99.1). The median intraoperative blood loss was 700 mL and the median operative duration 195 minutes.

Hypoalbuminemia was present in 43 patients (71.7%; 59.2–81.5). Eight patients (13.3%; 6.9–24.2) had CLS >11, and 7 (11.7%; 5.8–22.2) met the composite criterion. Anastomotic leakage occurred in 13 patients (21.7%; 13.1–33.6).

The cohort against published populations

Table 3 and Figure 3 compare the cohort with reference populations. The leak rate of 21.7% was higher than the national colon rate in Germany (6.7%; $h = 0.44$; Holm-adjusted $p <$

0.001), the Korean nationwide rate (5.98%; $h = 0.47$; $p < 0.001$) and the rate in a Mexican CLS validation cohort without diversion (7.2%; $h = 0.43$; $p = 0.001$). It was similar to the 25.9% reported from Samarinda, Indonesia ($h = -0.10$; $p = 0.556$). Hypoalbuminemia was far more prevalent than in a Chinese series of 7,072 resections (15.2%; $h = 1.22$; $p < 0.001$), and in the range of reports from Pakistan (58.9%; unadjusted $p = 0.049$, Holm $p = 0.147$) and Syria (61.3%; Holm $p = 0.224$). The proportion with CLS >11 was much lower than in a Chinese cohort (13.3% vs 47.8%; $h = -0.78$; $p < 0.001$). Two-sample exact tests, which account for the comparators' own sampling error, gave the same conclusions: leakage vs the Mexican cohort OR 3.56 ($p = 0.003$) and vs Samarinda $p = 0.662$; hypoalbuminemia vs Pakistan $p = 0.105$; CLS >11 vs the Chinese cohort OR 0.17 ($p < 0.001$). The hypoalbuminemia excess was not explained by emergency presentations. Even if all ten emergency patients were hypoalbuminemic, at least 33 of the 50 elective patients (66.0%; 95% CI 52.2–77.6) were, still far above the Chinese reference ($p < 0.001$).

Table 3. Cohort proportions compared with previous studies.

Measure	Reference population	This cohort, % (95% CI)	Reference, %	Cohen's h	p	Holm p	Two-sample: comparator n/N ; p
Anastomotic leakage	Germany, national colon cancer resections ⁶	13/60: 21.7 (13.1–33.6)	6.7	0.44	<0.001	<0.001	—
Anastomotic leakage	Korea, nationwide colorectal resections ⁷	13/60: 21.7 (13.1–33.6)	5.98	0.47	<0.001	<0.001	—
Anastomotic leakage	Mexico, left-sided resections without stoma, CLS cohort ²⁵	13/60: 21.7 (13.1–33.6)	7.2	0.43	<0.001	0.001	15/208; OR 3.56; $p = 0.003$
Anastomotic leakage	Indonesia, Samarinda, elective primary anastomosis ¹⁰	13/60: 21.7 (13.1–33.6)	25.9	-0.10	0.556	0.556	14/54; OR 0.79; $p = 0.662$
Hypoalbuminemia <3.5 g/dL	China, 7,072 colorectal cancer resections ³⁹	43/60: 71.7 (59.2–81.5)	15.2	1.22	<0.001	<0.001	—
Hypoalbuminemia <3.5 g/dL	Pakistan, colorectal cancer surgical patients ⁴⁰	43/60: 71.7 (59.2–81.5)	58.9	0.27	0.049	0.147	73/124; OR 1.77; $p = 0.105$
Hypoalbuminemia <3.5 g/dL	Syria, elective sigmoid/rectal resections ⁴¹	43/60: 71.7 (59.2–81.5)	61.3	0.22	0.112	0.224	—
CLS >11	China, colorectal resections ²⁷	8/60: 13.3 (6.9–24.2)	47.8	-0.78	<0.001	<0.001	54/113; OR 0.17; $p < 0.001$

CLS, Colon Leakage Score.

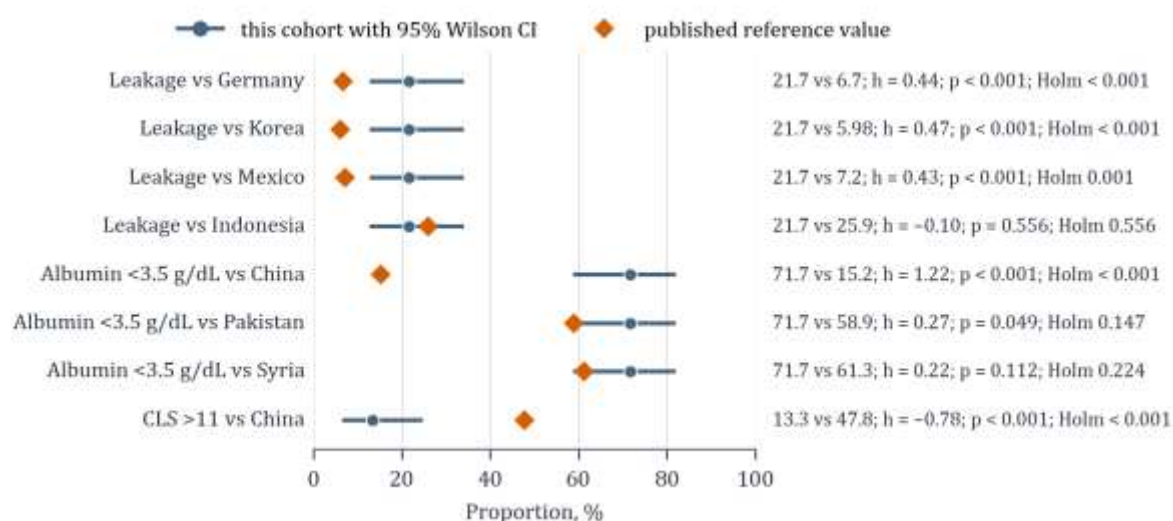


Figure 3. The cohort against previous studies. Circles with bars: this cohort with 95% Wilson confidence intervals; diamonds: published reference proportions. Text at right gives the reference value, Cohen's h and exact binomial p values (unadjusted and Holm-adjusted). CLS, Colon Leakage Score.

Accuracy of the composite criterion

Six of the seven composite-positive patients and 7 of the 53 composite-negative patients developed AL (Table 4; Figure 4). Sensitivity was 46.2% (6/13; 95% CI 23.2–70.9) and specificity 97.9% (46/47; 88.9–99.6). The PPV was 85.7% (6/7; 48.7–

97.4), the NPV 86.8% (46/53; 75.2–93.5) and the overall accuracy 86.7% (52/60; 75.8–93.1). The LR+ was 21.69 (2.86–164.51), an interval whose width reflects a single false-positive result, and the LR- 0.55 (0.33–0.91), giving a diagnostic odds ratio of 39.4 (4.1–378.4). A positive result was associated with

leakage: conditional OR 35.6 (exact 95% CI 3.6–1850.2), Fisher's exact $p < 0.001$, risk ratio 6.49 (3.05–13.79) and risk difference 72.5 percentage points (33.7–86.0). The Youden index was 0.44

(0.17–0.71), the balanced accuracy 0.720 (0.583–0.857), the phi coefficient 0.56 and Cohen's κ 0.53.

Table 4. Accuracy of the composite criterion (CLS >11 and albumin <3.5 g/dL) for anastomotic leakage

Index test	Leakage	No leakage	Total
Composite positive	6	1	7
Composite negative	7	46	53
Total	13	47	60

Measure	n/N	Estimate	95% CI (Wilson or stated)	95% CI (Clopper-Pearson)
Sensitivity	6/13	46.2	23.2–70.9	19.2–74.9
Specificity	46/47	97.9	88.9–99.6	88.7–99.9
Positive predictive value	6/7	85.7	48.7–97.4	42.1–99.6
Negative predictive value	46/53	86.8	75.2–93.5	74.7–94.5
Overall accuracy	52/60	86.7	75.8–93.1	75.4–94.1
Leakage among test-negative patients	7/53	13.2	6.5–24.8	5.5–25.3
Positive likelihood ratio	—	21.69	2.86–164.51	—
Negative likelihood ratio	—	0.55	0.33–0.91	—
Diagnostic odds ratio	—	39.4	4.1–378.4	—
Odds ratio (conditional MLE; exact CI)	—	35.6	3.6–1850.2	—
Risk ratio, positive vs negative	—	6.49	3.05–13.79	—
Risk difference, percentage points	—	72.5	33.7–86.0	—
Youden index	—	0.44	0.17–0.71	—
Balanced accuracy (AUC of a binary test)	—	0.720	0.583–0.857	—
Fisher's exact test	—	$p < 0.001$	—	—
Phi coefficient; Cohen's κ	—	0.56; 0.53	—	—
Sensitivity vs 80% (one-sided exact)	—	$p = 0.007$	—	—
Specificity vs 80% (one-sided exact)	—	$p < 0.001$	—	—
Power of the sensitivity test (13 leaks)	—	reject if ≤ 7 detected; $\alpha = 0.030$	power 80% at true Sn 46%; 71% at 50%	—

Estimates are percentages unless a ratio or index is stated. Likelihood ratios and diagnostic odds ratio: log-method CIs; risk difference: Newcombe hybrid-score CI. AUC, area under the curve; CLS, Colon Leakage Score; MLE, maximum-likelihood estimate.

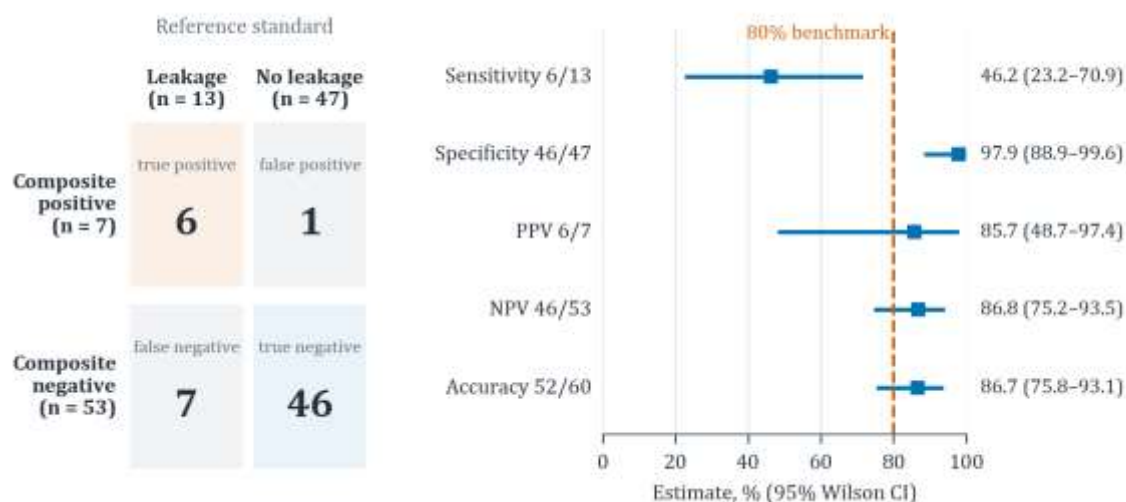


Figure 4. Accuracy of the composite criterion (Colon Leakage Score >11 and albumin <3.5 g/dL). Left: observed 2×2 table against the reference standard. Right: sensitivity, specificity, predictive values and accuracy with 95% Wilson confidence intervals; the dashed line marks the 80% benchmark. NPV, negative predictive value; PPV, positive predictive value.

The criterion of good accuracy set before analysis was not met. Sensitivity was significantly below 80% (one-sided exact $p = 0.007$) and indistinguishable from 50% ($p = 1.000$), whereas specificity exceeded 80% ($p < 0.001$). With 13 leaks, the exact test rejects a sensitivity of 80% when 7 or fewer leaks are detected (actual $\alpha = 0.030$). Its power is 80% if the true sensitivity is 46% and 71% if it is 50%, so the test was adequately powered only against the low sensitivity actually observed. Seven of the 13 leaks (53.8%) occurred in composite-negative patients, and 13.2% of test-negative patients leaked

(7/53; 95% CI 6.5–24.8). A positive result raised the probability of leakage from the pre-test 21.7% to 85.7%; a negative result lowered it only to 13.2%.

The shortfall in sensitivity was robust to outcome misclassification (Figure 5). If one of the seven missed leaks had been a false diagnosis, sensitivity would be 50.0% ($p = 0.019$ against 80%). The shortfall loses formal significance only if at least two of them were misdiagnosed (54.5%; $p = 0.050$).

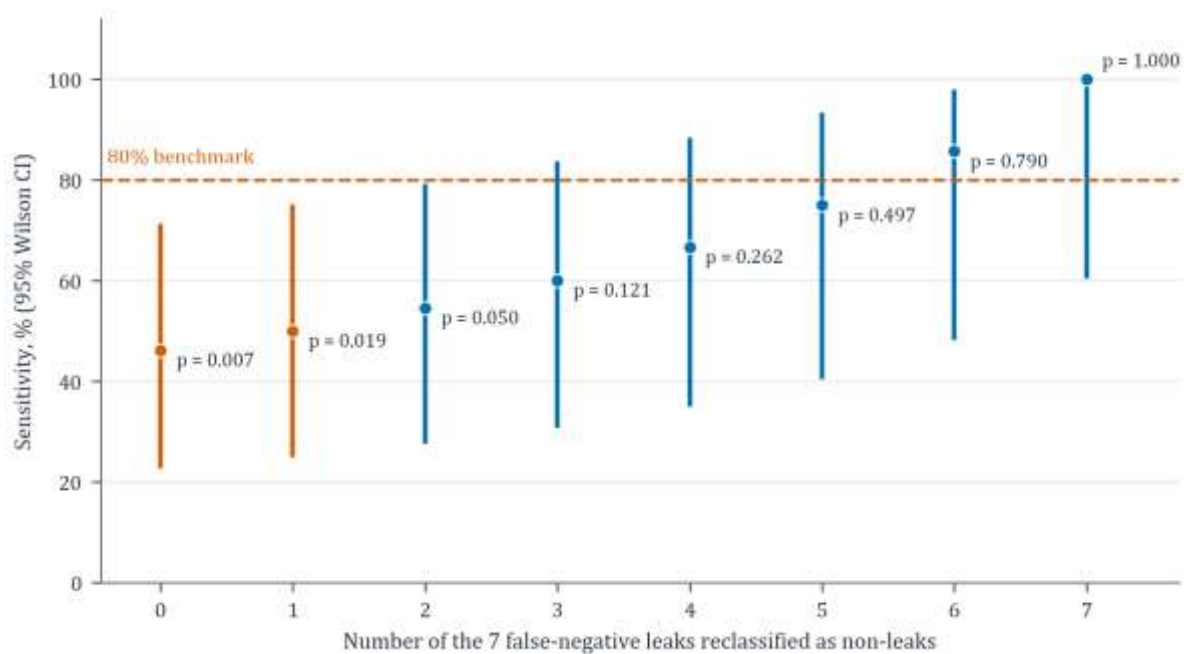


Figure 5. Tipping-point analysis for outcome misclassification. Sensitivity (points) and 95% Wilson confidence intervals (bars) when 0–7 of the seven false-negative leaks are reclassified as non-leaks. Labels give one-sided exact p values against the 80% benchmark (dashed line); orange marks $p < 0.05$.

Predictive values depend on leak prevalence (Table 5; Figure 6). At the observed 21.7%, PPV and NPV were similar (85.7% and 86.8%). At the 6.7% national colon rate, the same sensitivity and specificity give a PPV of 60.9% and an NPV of 96.2%; at 5%

the values are 53.3% and 97.2%. The uncertainty band for PPV is wide at every prevalence because the specificity estimate rests on a single false-positive result.

Table 5. Predictive values of the composite criterion across anastomotic leakage prevalences

Leak prevalence, %	2	5	6.7	10	15	20	21.7	25	30
PPV, %	30.7	53.3	60.9	70.7	79.3	84.4	85.7	87.9	90.3
NPV, %	98.9	97.2	96.2	94.2	91.2	87.9	86.8	84.5	80.9
Post-test probability if positive, %	30.7	53.3	60.9	70.7	79.3	84.4	85.7	87.9	90.3
Post-test probability if negative, %	1.1	2.8	3.8	5.8	8.8	12.1	13.2	15.5	19.1

Bayes' theorem at the observed sensitivity (46.2%) and specificity (97.9%). 6.7% = national colon leak rate in Germany; 21.7% = this cohort. NPV, negative predictive value; PPV, positive predictive value.

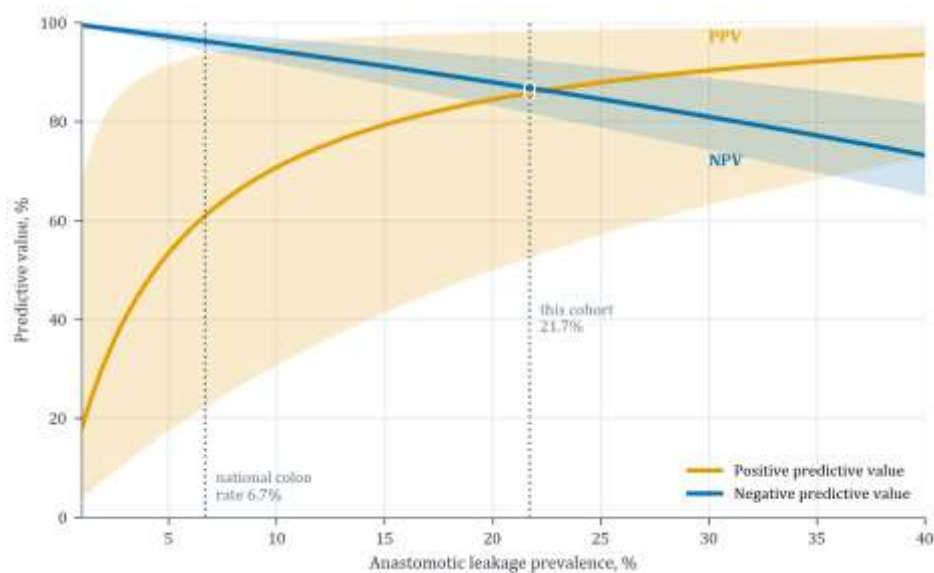


Figure 6. Positive (PPV) and negative (NPV) predictive values of the composite criterion as functions of leak prevalence. Lines: values at the observed sensitivity and specificity; shaded bands: 95% intervals from Jeffreys beta posteriors. Dotted lines mark the national colon leak rate (6.7%) and this cohort (21.7%).

Contribution of the two components

Hypoalbuminemia was present in 7 of 8 patients with CLS >11 (87.5%; 52.9–97.8) and 36 of 52 patients with CLS ≤11 (69.2%; 55.7–80.1); the two components were not detectably associated (OR 3.06; exact 95% CI 0.34–148.8; $p = 0.420$; $\phi = 0.14$) (Table 6). Albumin therefore changed the classification of exactly one patient relative to CLS >11 alone: the patient with CLS >11 and

normal albumin. In the doubly positive stratum, 6 of 7 patients leaked (85.7%; 48.7–97.4). The records do not show how the other seven leaks were distributed. The attainable leak rates were 0% or 100% for the single patient with CLS >11 and normal albumin, 0–19.4% for hypoalbuminemic patients with CLS ≤11 and 0–43.8% for normoalbuminemic patients with CLS ≤11 (Figure 7).

Table 6. Cross-classification of the two index-test components and leakage by stratum

Stratum	n	Leaks	Leak rate, % (95% CI or attainable range)	Basis
CLS >11 and albumin <3.5 g/dL	7	6	85.7 (48.7–97.4)	Observed
CLS >11 and albumin ≥3.5 g/dL	1	b = 0 or 1	0 or 100	Attainable
CLS ≤11 and albumin <3.5 g/dL	36	c = 0–7	0–19.4	Attainable
CLS ≤11 and albumin ≥3.5 g/dL	16	d = 0–7	0–43.8	Attainable
Composite negative (sum of last three strata)	53	7	13.2 (6.5–24.8)	Observed (b + c + d = 7)
Hypoalbuminemia among CLS >11	7/8	—	87.5 (52.9–97.8)	Observed
Hypoalbuminemia among CLS ≤11	36/52	—	69.2 (55.7–80.1)	Observed
Association CLS >11 × albumin <3.5 g/dL	—	—	OR 3.06 (exact 95% CI 0.34–148.8); $p = 0.420$	Observed

The cross-classification follows from the observed data: all seven composite-positive patients were among the eight with CLS >11. Attainable ranges cover every distribution of the seven composite-negative leaks consistent with the observations. CI, confidence interval; CLS, Colon Leakage Score; OR, odds ratio.

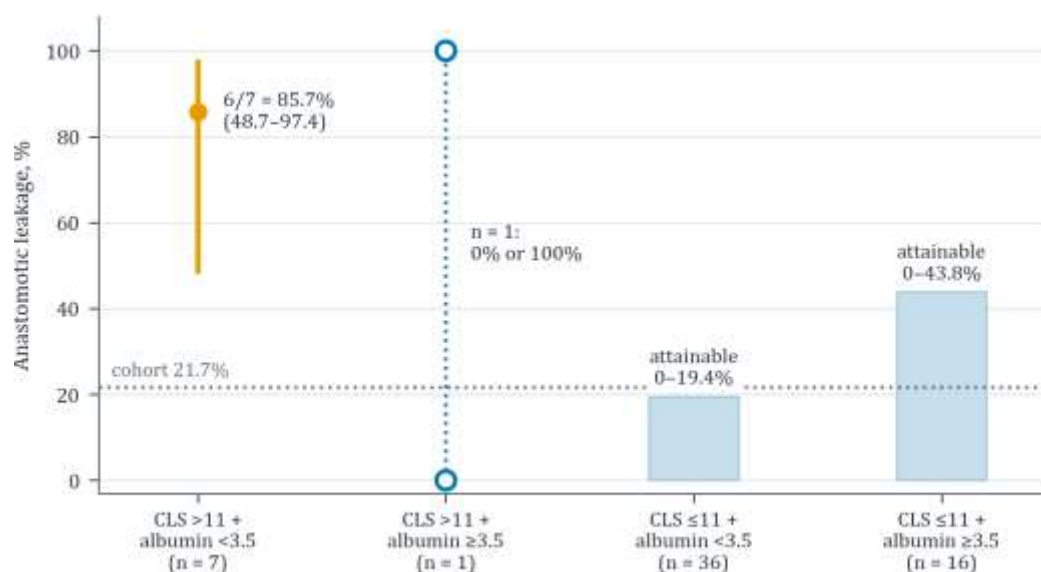


Figure 7. Anastomotic leakage by joint stratum of the two index-test components. Gold: the observed rate in the doubly positive stratum with its 95% Wilson confidence interval. Open circles and shaded bars: attainable rates in the other strata, among which the seven composite-negative leaks were distributed. Dotted line: overall cohort rate. CLS, Colon Leakage Score.

Sensitivity analysis over admissible tables

Table 7 summarizes the bivariate bounds, and Table 8 lists all 15 admissible tables. Using the printed margins alone (S0), the association of CLS >11 with leakage was not identifiable: the OR ranged from 0.17 to 146.8 across 9 tables, and 44.4% of tables reached significance. Margins alone also left every other covariate unidentified. The OR ranged from 0.03 to 62.4 for male sex, 0.05 to 145.8 for age ≥60 years, 0.29 to 61.5 for ASA III, 0.01

to 30.6 for stage III–IV and 0.13 to 285.0 for emergency surgery, with significance in 33.3–57.1% of tables. Adding the observed composite table and cross-classification (S1) confined the CLS OR to 19.3–53.7, with $p \leq 0.001$ in every table (Figure 8). CLS >11 alone therefore had a sensitivity of 46.2–53.8%, a specificity of 95.7–97.9% and an AUC of 0.709–0.759. Its association with leakage holds for every dataset consistent with the observations.

Table 7. Sensitivity analysis: attainable ranges of association measures across admissible tables

Measure	S0: printed margins only	S1: margins + observed composite table	% significant: tables / datasets	Interpretation
CLS >11 alone, OR	0.17–146.8 (9 tables; 44.4% significant)	19.3–53.7	100 / 100	Robust positive association
CLS >11 alone, sensitivity / specificity, %	—	46.2–53.8 / 95.7–97.9	—	Rule-in profile
CLS >11 alone, AUC	—	0.709–0.759	—	
Albumin <3.5 g/dL alone, OR	0.004–15.5 (14 tables; 57.1% significant)	0.23–15.49	20.0 / 5.4	Not identifiable (spans 1)
Albumin alone, sensitivity / specificity, %	—	46.2–100.0 / 21.3–36.2	—	Specificity ≤36.2% in every table
Albumin alone, AUC	—	0.337–0.681	—	
Firth model: adjusted OR, CLS >11	—	13.8–317.2	100 / 100	Robust
Firth model: adjusted OR, albumin	—	0.022–16.603	40.0 / 6.5	Not identifiable
Firth model: CLS × albumin interaction OR	—	0.21–220.44	20.0 / 2.0	Synergy not identifiable
0–1–2 count score: Cochran–Armitage χ^2	—	0.50–4.15	66.7 / 97.9	Positive trend in most datasets
0–1–2 count score: AUC	—	0.508–0.812	—	
NRI, composite vs CLS >11 alone	—	–0.077 to +0.021	—	Albumin changes one classification
Male sex (S0 only), OR	0.03–62.4 (14 tables; 50.0% significant)	—	50.0 / —	Not identifiable
Age ≥60 years (S0 only), OR	0.05–145.8 (14 tables; 57.1% significant)	—	57.1 / —	Not identifiable
ASA III (S0 only), OR	0.29–61.5 (6 tables; 33.3% significant)	—	33.3 / —	Not identifiable
Stage III–IV (S0 only), OR	0.01–30.6 (14 tables; 50.0% significant)	—	50.0 / —	Not identifiable
Emergency surgery (S0 only), OR	0.13–285.0 (11 tables; 54.5% significant)	—	54.5 / —	Not identifiable

S1 contains 15 admissible tables. Dataset percentages weight each table by the number of patient-level arrangements it represents. ORs use the Haldane–Anscombe correction for zero cells; Firth p values from profile penalized-likelihood ratio tests. AUC, area under the curve; CLS, Colon Leakage Score; NRI, net reclassification improvement; OR, odds ratio.

Table 8. The 15 admissible CLS × albumin × leakage tables

b/c/d	Leaks, CLS >11	OR, CLS alone (p)	Leaks, albumin <3.5	OR, albumin alone (95% CI); p	Firth aOR CLS / albumin	Interaction OR (p)	AUC, count score
0/0/7	6/8	19.3 (<0.001)	6/43	0.23 (0.06–0.8); 0.035	53.1 / 0.07	160.41 (0.003)	0.508
0/1/6	6/8	19.3 (<0.001)	7/43	0.36 (0.10–1.3); 0.163	31.5 / 0.15	54.60 (0.009)	0.552
0/2/5	6/8	19.3 (<0.001)	8/43	0.55 (0.15–2.0); 0.488	22.5 / 0.28	26.84 (0.025)	0.595
0/3/4	6/8	19.3 (<0.001)	9/43	0.86 (0.23–3.3); 1.000	17.8 / 0.50	10.94 (0.063)	0.638
0/4/3	6/8	19.3 (<0.001)	10/43	1.41 (0.34–5.9); 0.740	15.2 / 0.89	6.57 (0.136)	0.682
0/5/2	6/8	19.3 (<0.001)	11/43	2.58 (0.51–13.1); 0.314	13.9 / 1.68	3.95 (0.281)	0.725
0/6/1	6/8	19.3 (<0.001)	12/43	6.19 (0.74–52.0); 0.086	13.8 / 3.79	1.85 (0.665)	0.768
0/7/0	6/8	19.3 (<0.001)	13/43	15.49 (0.87–276.9); 0.012	16.3 / 16.60	0.45 (1.000)	0.812
1/0/6	7/8	53.7 (<0.001)	6/43	0.23 (0.06–0.8); 0.035	317.2 / 0.02	220.44 (0.180)	0.552
1/1/5	7/8	53.7 (<0.001)	7/43	0.36 (0.10–1.3); 0.163	103.8 / 0.09	28.42 (0.260)	0.595
1/2/4	7/8	53.7 (<0.001)	8/43	0.55 (0.15–2.0); 0.488	61.6 / 0.20	6.41 (0.378)	0.638
1/3/3	7/8	53.7 (<0.001)	9/43	0.86 (0.23–3.3); 1.000	44.0 / 0.39	1.62 (0.699)	0.682
1/4/2	7/8	53.7 (<0.001)	10/43	1.41 (0.34–5.9); 0.740	35.1 / 0.76	0.80 (1.000)	0.725
1/5/1	7/8	53.7 (<0.001)	11/43	2.58 (0.51–13.1); 0.314	31.0 / 1.59	0.37 (1.000)	0.768
1/6/0	7/8	53.7 (<0.001)	12/43	6.19 (0.74–52.0); 0.086	32.2 / 4.23	0.21 (0.488)	0.812

b, c, d = leaks among patients with CLS >11 and albumin ≥3.5 g/dL ($n = 1$), CLS ≤11 and albumin <3.5 g/dL ($n = 36$), and CLS ≤11 and albumin ≥3.5 g/dL ($n = 16$); $b + c + d = 7$. Fisher's exact p for bivariate ORs; profile penalized-likelihood p for Firth models. aOR, adjusted odds ratio; AUC, area under the curve; CLS, Colon Leakage Score; OR, odds ratio.

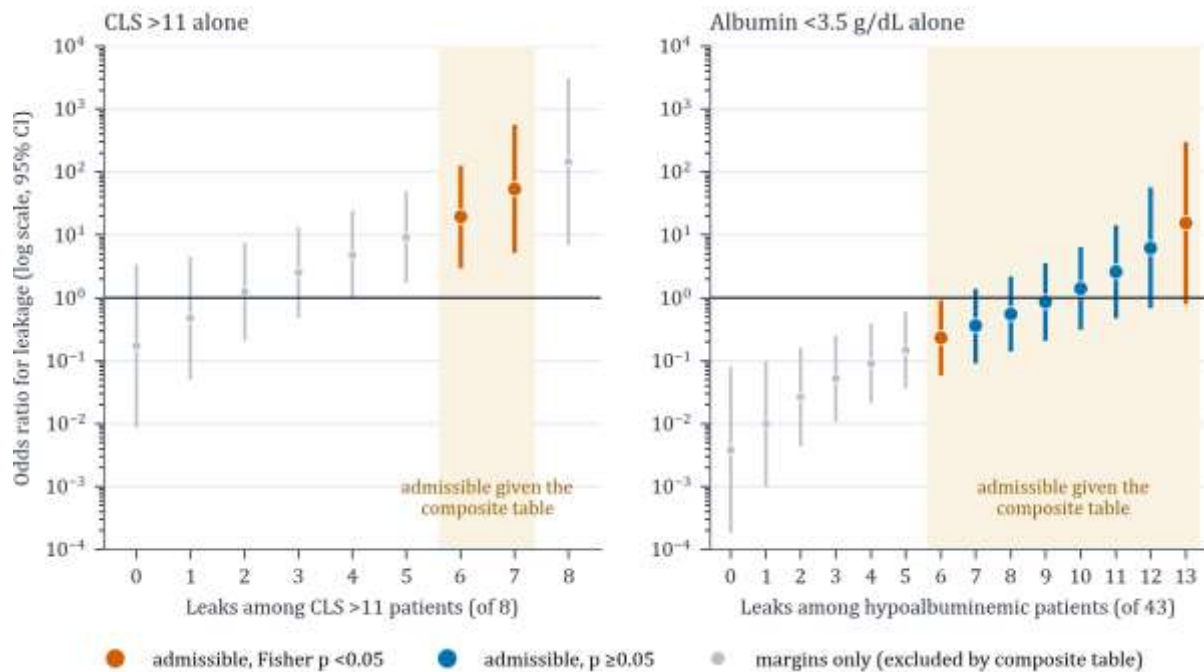


Figure 8. Identification of the associations of each component with leakage. Each point is the odds ratio (log scale; Haldane–Anscombe corrected, with 95% confidence interval) for one contingency table consistent with the printed margins (S0). Shaded region: tables also consistent with the observed composite table (S1), colored by Fisher's exact p . Left: Colon Leakage Score (CLS) >11 alone; right: albumin <3.5 g/dL alone.

Albumin alone was not identifiable. In S1 its OR ranged from 0.23 to 15.5 and spanned the null. It reached significance in 3 of 15 tables (20.0%): in two the association was inverse and in one positive. Weighted by patient-level arrangements, it reached significance in 5.4% of admissible datasets. Its sensitivity ranged from 46.2% to 100% but its specificity never exceeded 36.2% (range 21.3–36.2%), and its AUC lay between 0.337 and 0.681. With both components in Firth models, the adjusted OR for CLS >11 ranged from 13.8 to 317.2 and was significant in every table. The adjusted OR for albumin ranged from 0.022 to 16.6 and was significant in 40.0% of tables and 6.5% of datasets, in both directions. The CLS $\times$ albumin interaction OR ranged from 0.21 to 220.4 and was significant in 20.0% of tables and

2.0% of datasets, so synergy could be neither confirmed nor excluded.

A 0–1–2 count of risk factors showed a positive Cochran–Armitage trend ($z = 0.50$ – 4.15). The trend was significant in 66.7% of tables and 97.9% of datasets, with an attainable AUC of 0.508–0.812. In receiver operating characteristic (ROC) space (Figure 9), the composite (balanced accuracy 0.720) lay close to CLS >11 alone (0.709–0.759). The NRI of the composite over CLS >11 alone was -0.077 to $+0.021$: adding albumin either removed one false-positive classification or lost one true-positive classification.

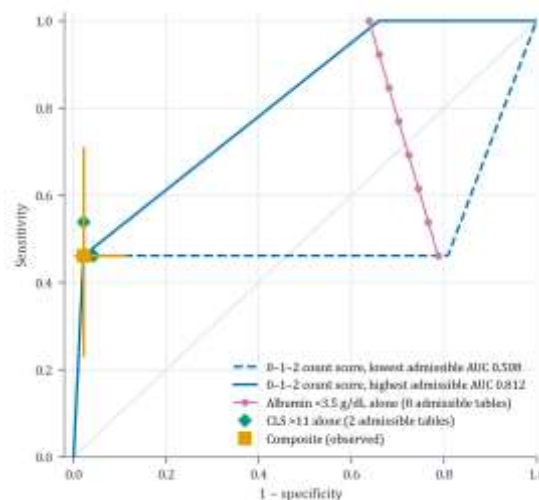


Figure 9. Receiver operating characteristic space. Square with bars: the composite criterion with 95% Wilson confidence intervals for sensitivity and $1 - \text{specificity}$. Diamonds: CLS >11 alone across its two admissible tables. Pink points: albumin <3.5 g/dL alone across its eight admissible tables. Blue lines: ROC curves of the 0–1–2 count score at its lowest (dashed) and highest (solid) admissible AUC. AUC, area under the curve; CLS, Colon Leakage Score.

Multivariable sensitivity analysis

Of 20,000 admissible datasets, 19,977 yielded converged Firth fits (Table 9; Figure 10). Adjusted for albumin, sex, age, ASA class, stage and emergency surgery, CLS >11 had a median OR of 15.88 (2.5–97.5 percentile band 8.44–85.23) and was significant in 99.4% of datasets. Albumin had a median adjusted OR of 1.45 (0.28–16.05) and was significant in 1.4% of datasets. Every other covariate had a median OR between 0.98 and 1.07 and reached significance in 1.7–2.8% of datasets, below the nominal 5%. Constructed arrangements produced quasi-complete separation, driving every coefficient, including that for CLS >11, to the numerical ceiling. With 13 events for 8 parameters, the attainable range in the full model is therefore effectively

unbounded. The adjusted association of CLS >11 is reversible only under contrived alignments of an unreported covariate with every leak. In the parsimonious model (CLS >11, albumin, emergency surgery; 20,000 converged fits), CLS >11 had a median adjusted OR of 14.74 (11.05–49.27) and was significant in all but one dataset. The adjusted OR was 1.60 (0.30–16.28) for albumin (significant in 0.4%) and 1.13 (0.09–5.60) for emergency surgery (2.5%). Profile penalized-likelihood inference agreed with Wald inference for CLS >11 in 99.7% of 1,000 datasets (significant in 99.9% vs 99.6%). For albumin, likelihood-based tests were more liberal (6.6% vs 0.5%; agreement 93.9%) but remained close to the 5% expected by chance.

Table 9. Multivariable sensitivity analysis: Firth-penalized logistic regression across admissible datasets

Predictor	Median adjusted OR	2.5–97.5 percentile band	% datasets with p < 0.05	% positive / % inverse
Seven-predictor model (19,977 datasets)				
CLS >11	15.88	8.44–85.23	99.4	99.4 / 0.0
Albumin <3.5 g/dL	1.45	0.28–16.05	1.4	0.8 / 0.6
Male sex	1.00	0.21–4.66	2.5	1.4 / 1.1
Age ≥60 y	1.01	0.17–4.78	2.4	1.7 / 0.6
ASA III	1.07	0.06–10.82	1.7	1.6 / 0.1
Stage III–IV	0.98	0.22–5.12	2.8	1.1 / 1.7
Emergency surgery	1.06	0.10–6.15	2.0	1.9 / 0.1
Parsimonious model (20,000 datasets)				
CLS >11	14.74	11.05–49.27	99.995	99.995 / 0.0
Albumin <3.5 g/dL	1.60	0.30–16.28	0.4	0.0 / 0.4
Emergency surgery	1.13	0.09–5.60	2.5	2.5 / 0.0

Each admissible dataset reproduces every printed margin, the composite 2×2 and the CLS × albumin cross-classification. Covariate labels were permuted independently because their joint distribution with leakage was not recorded. Wald p values from penalized standard errors. With 13 events and 8 parameters, contrived arrangements cause quasi-complete separation, so the attainable range of every coefficient is effectively unbounded (log-OR reached the ±15 numerical ceiling). Profile penalized-likelihood vs Wald inference in 1,000 datasets (seven-predictor model): CLS >11 significant in 99.9% vs 99.6% (agreement 99.7%); albumin 6.6% vs 0.5% (agreement 93.9%). The admissible space is a superset of the feasible space (several covariates are CLS items), so ranges are outer bounds and percentages are not probabilities. CLS, Colon Leakage Score; OR, odds ratio.

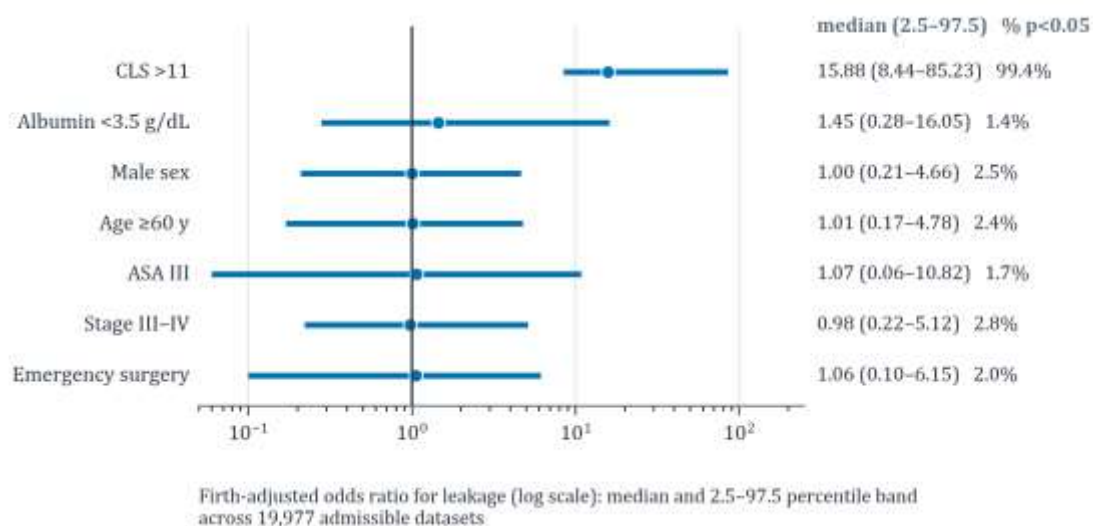


Figure 10. Multivariable sensitivity analysis. Firth-adjusted odds ratios (log scale) for seven predictors across 19,977 admissible patient-level datasets: points are medians and bars the 2.5–97.5 percentile bands. Text at right gives the median, band and percentage of datasets with p < 0.05. CLS, Colon Leakage Score.

4. Discussion

In this cohort from Dr. Mohammad Hoesin General Hospital, a composite of CLS >11 and preoperative hypoalbuminemia singled out a small group in whom leakage was very likely. Six of seven leaked, and the LR+ was 21.7. The composite nonetheless missed more than half of all leaks. It did not meet the criterion for good accuracy set before analysis. Two features of the data shape how the result should be read. First, almost every CLS-high patient was also hypoalbuminemic. The composite therefore reproduced CLS >11 alone, and albumin

altered a single classification. Second, the CLS association with leakage held in every dataset that matches the observations, while the association of albumin alone could not be identified. Apart from prediction, the cohort showed a leak rate two to four times international benchmarks and hypoalbuminemia in nearly three-quarters of patients. The study adds three things to the literature. It offers an external check of CLS >11 in an Indonesian population. It shows by exact enumeration that, at this prevalence, albumin adds at most one reclassification to the CLS. And it quantifies a hypoalbuminemia burden that remains after emergency presentations are set aside.

Comparison with Colon Leakage Score studies

The rule-in profile of the composite is the profile of the CLS at its conventional cut-off. A Mexican validation of 208 left-sided resections without diversion gave a sensitivity of 53% and a specificity of 93% at CLS >11, although the continuous score had an AUC of 0.898²⁵. Across all admissible tables in our cohort, CLS >11 alone had a sensitivity of 46.2–53.8% and a specificity of 95.7–97.9%. These values cannot be statistically distinguished from the Mexican estimates (exact p 0.783–1.000 for sensitivity and 0.258–0.772 for specificity, one-sample exact binomial tests against 53% and 93%), and the original description reported an AUC of 0.95 in 121 patients with 10 leaks, but it did not test the dichotomized score²⁴. Others chose differently. An Indian prospective series chose a cut-off above 9 and reached a sensitivity of 83.3% with a specificity of 91.1%²⁶. In the Mexican data, a lower cut-off of 8.5 raised sensitivity to 93%²⁵. Taken together, these studies show that a threshold of 11 is specific but insensitive. The low sensitivity of our composite belongs to that threshold. It is no failure peculiar to this population.

Case mix explains why only 13.3% of our patients exceeded 11 points, against 47.8% in a Chinese colorectal cohort²⁷. Three of the most heavily weighted CLS items added little. Anastomotic distance can carry up to 6 points, yet 58 of 60 anastomoses lay more than 10 cm from the anal verge. Neoadjuvant therapy can carry up to 2 points, but no patient had received it. ASA class can carry up to 6 points. Only five patients were ASA III. Patients reached the high-risk band mainly through emergency surgery for obstruction (3 points), blood loss (up to 6) and operative duration (up to 4). A score designed for left-sided and rectal anastomoses loses dynamic range when applied to a mostly colonic population. At any fixed cut-off, that loss lowers sensitivity. Because the continuous CLS total was not recorded, the best local threshold could not be estimated; re-abstracting the existing records is the most direct way to close this gap.

The CLS is one of several dozen leak-prediction scores. Few have been externally validated, and most carry a high risk of bias^{28,29}. Performance drops on external testing. This is the rule. Machine-learning AUCs have fallen from 0.78 to 0.60³⁰ and from 0.984 to 0.703³¹. An institutional right-colectomy score dropped to a C-statistic of 0.59³². National models built from routine preoperative variables reach only 0.63 in Japan³³ and 0.69 in Denmark³⁴. Against that ceiling, a balanced accuracy of 0.720 for a two-item bedside composite is unremarkable but not inferior, and its value lies in its very high specificity and not in overall discrimination. In rectal cancer, multivariable predictors such as sex, BMI, tumor height and stapler cartridges dominate^{9,42,43}. They matter little in a cohort where 96.7% of anastomoses were colonic or high rectal, and this supports the use of a colon-oriented score.

Comparison with albumin studies

The albumin literature is heterogeneous, and our data fit almost all of it. The pooled OR of 2.67 for low albumin and AL¹⁹ lies inside our admissible range of 0.23–15.5, and so does the null. Two large single-cohort ORs, 16.25 for albumin <3 g/dL in an Egyptian multicenter series⁴⁴ and 22.2 in a Peruvian case-control study⁴⁵, come from intervals or designs that inflate apparent effects. Other cohorts differ. A Syrian cohort with a similar prevalence of hypoalbuminemia (61.3%) found it to be a significant risk factor⁴¹. An Australian ERAS cohort, by contrast, found no albumin difference between leakers and non-leakers²³. In a Glasgow cohort of 795 patients, hypoalbuminemia tracked inflammation and body composition but not complications²¹. The Bandung study, the only Indonesian precedent, could not detect any correlation³⁷. Our analysis adds a structural point that holds whatever the true joint distribution is. When 71.7%

of patients fall below the threshold, a binary cut-off at 3.5 g/dL cannot be specific. The arithmetic is simple. In every admissible table, albumin alone had a specificity of 36.2% or less.

This ceiling effect suggests better ways of using albumin. Discarding it is not one of them. A lower threshold may discriminate where 3.5 g/dL cannot, and the Egyptian association was seen at 3.0 g/dL⁴⁴. Composite inflammatory-nutritional indices usually do better than albumin alone. A high prognostic nutritional index (PNI) carried an adjusted OR for AL of 0.16 in 2,026 Taiwanese patients⁴⁶. The Onodera PNI combined with the neutrophil-lymphocyte ratio reached an AUC of 0.910 in rectal cancer⁴⁷. In a Japanese multicenter study, a PNI below 40 and a CRP/albumin ratio ≥ 0.07 were independent predictors⁴³. The postoperative CRP/albumin ratio reached AUCs of 0.825 and 0.91 for early leak detection^{48,49}. Albumin dynamics carry signal too. A relative postoperative decline of $\geq 27.2\%$ predicted AL in women⁵⁰, and day-3 albumin reached an AUC of 0.744⁵¹. Albumin was recorded as a binary value in our data, so none of these alternatives could be tested. They define the next analytic step.

The leak rate in regional context

A leak rate of 21.7% is high by international standards. It is roughly two to four times the national rates of 5.0–9.2% from Germany, Korea and Australia and New Zealand^{6–8}, and well above the falling Japanese low anterior resection rate of 7.1–9.8%⁵². It also far exceeds the 1.4% reported after elective right hemicolectomy in 52 Chinese centers⁵³. Regional comparators lie closer. A Thai stapler trial reported 5.1–13.2%⁵⁴, a Vietnamese series 7.9–8.3%⁵⁵, a Syrian cohort 15%⁴¹, an Egyptian multicenter cohort 6.9%⁴⁴ and a Samarinda series 25.9%¹⁰. Four features of our cohort probably contribute to its rate. The first is the exclusion of diverted patients, which leaves every leak clinically expressed. The second is the 16.7% of emergency operations for obstruction done without diversion, a setting in which leak rates of 19.7% have been reported (OR 4.35)¹⁸. The third is the burden of hypoalbuminemia and advanced disease. The fourth is an inclusive reference standard that accepts clinical sepsis alone. Definitions of leakage differ across institutions and registries¹⁶, and some of our 13 leaks may have been sepsis from other sources. The tipping-point analysis shows that the central conclusion, sensitivity below 80%, holds unless at least two of the seven missed leaks were misdiagnosed. Misclassification can also run the other way. Imaging was requested on clinical suspicion, so subclinical leaks in asymptomatic patients would have been recorded as no leak. A missed leak in a composite-negative patient would lower sensitivity further. A missed leak in the single false-positive patient would raise sensitivity only to 50.0% (7/14) while making specificity 100%. Neither direction would weaken the conclusion of low sensitivity. These rate comparisons are contextual and not causal. The national comparators include rectal resections and a different case mix, although two-sample tests that allow for the smaller comparators' sampling error gave the same answers.

Emergency resection for obstruction needs separate attention here. In a Dutch national audit of right-sided colon cancer, emergency resection doubled mortality (9.4% vs 4.2%) without increasing leakage⁵⁶. After resection of obstructive left-sided cancer, 37% of patients ended with a permanent stoma⁵⁷. One in six of our operations was an emergency for obstruction. Such patients make up much of the CLS-high group and probably account for some of the leaks among composite-negative patients. They are also the group for whom the choice between primary anastomosis and diversion matters most.

Spectrum of included patients

Excluding patients who received a diverting stoma made leakage clinically detectable, yet it changed the spectrum of included patients. Surgeons divert the patients they judge to be at highest risk, so the excluded group was probably enriched for high CLS values, low anastomoses and intraoperative difficulty. Accuracy in the remaining patients describes the decision that is left after the surgeon has declined to divert. That is the relevant population for a tool meant to guide the decision, but it is not the full surgical population. Diversion also alters what a leak looks like. In a French series of CLS-defined high-risk left colectomies, a defunctioning stoma did not reduce the leak rate (21.6% vs 16.4%), although it changed management⁵⁸. A Swedish multicenter study found that a stoma halved early leaks (hazard ratio 0.47), but late leaks were more frequent after diversion (7.5% vs 1.9%)⁵⁹. In Vietnamese patients, a transanal drainage tube gave leak rates similar to a diverting stoma⁵⁵. Including diverted patients would call for active ascertainment of late and subclinical leaks and not reliance on clinical presentation. The number of diverted patients was not retained, so the size of spectrum bias cannot be quantified. Its direction can still be reasoned. Excluding the patients that surgeons judged at highest risk most likely removed CLS-high patients. This depletes the test-positive group, which helps explain why only 13.3% exceeded 11 points, and it makes the observed PPV specific to undiverted patients. Specificity is the measure least affected, because almost all patients who did not leak were retained. The effect on sensitivity is unclear. The leaks that diverted patients would have had are fewer and later, so they would have entered the reference standard differently.

Mechanistic interpretation

Figure 11 organizes the findings around two streams of risk that meet at the healing anastomosis. The first is the burden of

operative and patient stressors captured by the CLS: prolonged operation, blood loss, emergency surgery on obstructed and contaminated bowel, male sex and comorbidity. Each may impair perfusion or raise tension and contamination, although none was measured here. Technical determinants outside the score also count. Three or more stapler firings raised the odds of leakage 2.7-fold after minimally invasive rectal resection⁶⁰. Indocyanine green perfusion assessment reduced leakage in a Japanese phase 3 trial⁶¹, but not significantly in a European trial⁶². In a porcine model, single-layer extramucosal and double-layer anastomoses differed in bursting pressure without a significant difference in leaks⁶³. A preoperative score measures none of these factors. They probably account for many of the seven leaks among composite-negative patients.

The second stream is physiological reserve, and albumin is an imperfect proxy for it. In malnourished rats, nutritional repletion restored anastomotic perfusion and bursting pressure, whereas exercise alone did not⁶⁴. Collagen content of the bowel wall independently predicted leakage after chemoradiotherapy³⁶. Both observations support a nutritional pathway to anastomotic failure. Yet albumin falls with surgical inflammation and endothelial leak²², and in cancer it reflects systemic inflammation as much as protein status²¹. A low albumin in a patient with advanced, obstructing cancer may signal inflammation that impairs healing, nutritional depletion, or both. Each pathway in Figure 11 is a hypothesis and not a demonstrated mechanism. Our data cannot separate them, and CRP was not available. Figure 11 is therefore only a hypothesis about how the two streams interact. The bounds analysis shows that the data identify the first stream (CLS) but not the second (albumin) or their interaction.

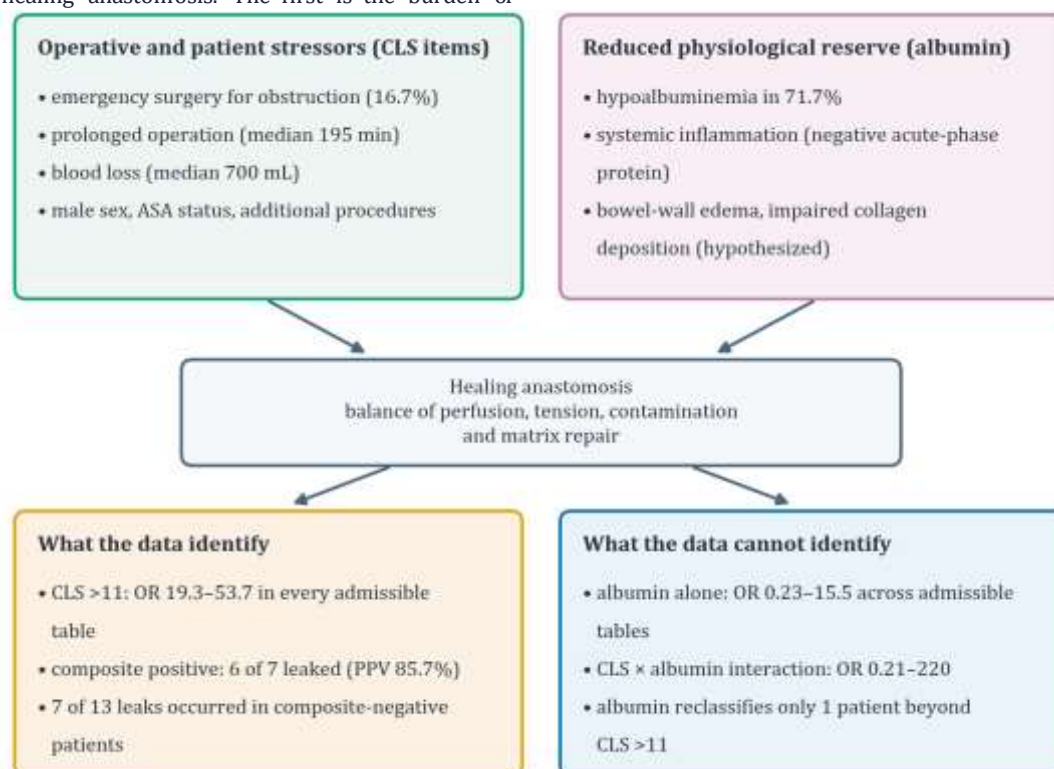


Figure 11. Conceptual framework. Operative and patient stressors captured by the Colon Leakage Score (CLS) and reduced physiological reserve (indexed by albumin) converge on the healing anastomosis. Lower panels separate what the data identify from what they cannot identify. The mechanistic links are hypotheses, not demonstrated associations.

Clinical implications

A rule-in test helps when a positive result changes management. With an LR+ of 21.7, a positive composite raised the probability of leakage in this cohort from 21.7% to 85.7%. Even at the lower 6.7% prevalence of national colon series, the PPV would be about 61%. A positive result could prompt a discussion with the patient about protective strategies, a suggestion that needs prospective testing. These include diversion, an alternative reconstruction, or at least closer postoperative surveillance. Evidence that diversion lowers the incidence of leakage in high-risk colonic anastomoses is weak⁵⁸. Its benefit lies mainly in softening the consequences of a leak, and part of its effect is to delay diagnosis⁵⁹. The composite must not be used to reassure. A negative result left a 13.2% probability of leakage, and more than half of all leaks occurred in test-negative patients. Postoperative markers complement it well. CRP on the fourth postoperative day had an NPV of 97% in 2,501 Spanish patients⁶⁵, and a CRP rise of more than 50 mg/L between consecutive days had an NPV of 0.99⁶⁶. In CLS-high patients, day-3 procalcitonin and CRP reached AUCs of 0.78 and 0.71²⁷. A sequenced strategy follows naturally. A preoperative composite would rule in high risk, and postoperative CRP would then rule out leakage before discharge.

Nutritional burden and public health

The prevalence of hypoalbuminemia, 71.7%, is a principal finding in itself. It is nearly five times the 15.2% in 7,072 Chinese resections³⁹, and similar to the 58.9% in Pakistan⁴⁰ and 61.3% in Syria⁴¹. It also agrees with GLIM-defined malnutrition rates of 30.7–45.5% in colorectal cancer surgery^{67,68} and with the independent role of nutritional risk scores in leak nomograms⁶⁹. Hypoalbuminemia is linked to postoperative morbidity even where its contribution to leak prediction is uncertain^{20,39}. The burden was not an artifact of acute presentation, since at least 66.0% of elective patients were hypoalbuminemic. Whether patients received albumin infusion or nutritional support before surgery was not recorded. Either would weaken any association between preoperative albumin and leakage. The cohort was also fairly young. Two-thirds of patients were younger than 60 years, and the median age was 58 years. A Peruvian multicenter series, by contrast, had two-thirds aged 65 years or older⁴⁵. This age profile fits the rising early-onset incidence across Asia and Indonesia^{2,3,5}. Taken with stage II–III disease in 88.3% and no neoadjuvant therapy, the profile is compatible with late presentation of younger patients with depleted reserves, although symptom duration and nutritional assessment were not recorded.

Interventions exist, and some have been tested. In a randomized trial, a four-week multimodal prehabilitation program of exercise, nutrition and psychological support reduced severe complications from 29.7% to 17.1%⁷⁰. Seven days of preoperative immunonutrition alone did not reduce infectious complications⁷¹. After Syria introduced a nutritional and anemia-correction guideline, both hypoalbuminemia and leakage fell⁴¹. For South Sumatra, these results support considering routine nutritional screening at referral, using GLIM criteria together with albumin and CRP, and a structured preoperative window for nutritional optimization in elective cases. That case rests on the prevalence of hypoalbuminemia and its link with morbidity, whether or not albumin improves leak prediction.

Research agenda

Four studies would settle the questions these data leave open. First, re-abstraction of the existing records should capture the continuous CLS total, its 11 item scores, continuous albumin,

and the cross-classification of each with leakage. This would turn the bounds analysis into exact estimates, yield ROC curves with DeLong intervals, and allow a local CLS threshold to be chosen. With 13 leaks, an AUC near 0.80 would be estimated within about ± 0.15 . Second, a prospective multicenter validation across South Sumatra and other Indonesian referral hospitals should include diverted patients and grade every leak by the International Study Group of Rectal Cancer criteria with radiological confirmation. Estimating a sensitivity near 50% within ± 15 percentage points needs about 43 leaks, which means roughly 199 patients at a 21.7% leak rate or 430 at 10%. A precision of ± 10 points needs 97 leaks, or about 448 patients. Third, that cohort should compare CLS cut-offs of 9 and 11, continuous albumin, PNI, the CRP/albumin ratio and GLIM malnutrition as rival or additive predictors. The comparison should use calibration as well as discrimination, and it should follow prediction-model reporting standards. Fourth, a practical randomized trial of preoperative nutritional prehabilitation in hypoalbuminemic patients undergoing elective resection should be considered. Halving the leak rate from 21.7% to 10.9% with 80% power at two-sided $\alpha = 0.05$ would take 177 patients per arm, and a reduction to 13% would take 294 per arm [Author query: state the sample-size formula; the standard two-proportion formula gives about 180 and 293 per arm]. These targets matter because sensitivity estimated from few reference-positive cases is unstable. Even when a test meets its target in 30 positives, the probability that its real-world sensitivity falls short is 10.7–13.5%⁷².

Strengths and limitations

The study has four strengths. Every analyzed patient had complete index-test and reference-standard data. The internally consistent 2x2 table was set before analysis, and every derived statistic can be reproduced from the reported counts. Joint distributions that were not recorded were handled by exhaustive enumeration and penalized regression over every consistent dataset, not by imputation. The conclusions therefore state exactly what the data can and cannot support. Finally, the cohort was benchmarked against named populations, which places a single-center Indonesian series in an international frame.

The limitations are considerable. The design was retrospective and single-center, and only 13 leaks occurred, so every accuracy estimate is imprecise. The confidence interval for sensitivity spans 23.2–70.9%. Leakage was not cross-classified against albumin alone, the continuous CLS, its item scores, sex, age, ASA class, stage, emergency status, blood loss or operative time. Every association involving these variables is therefore a bound and not an estimate. The number of excluded patients, in particular those diverted, was not retained, so spectrum bias cannot be quantified. The reference standard admitted clinical sepsis alone, without leak grading, time of diagnosis or a defined observation window beyond the recorded inpatient and outpatient follow-up. Abstraction was not blinded to outcome. Albumin was measured up to seven days before surgery without a concurrent CRP. Tumor site, operative approach and anastomotic technique were not recorded. The flow counts and the interval between index test and reference standard required by STARD could not be reported. The findings apply to colonic and high rectal anastomoses in patients who were not diverted at a single Indonesian referral center. Only two anastomoses lay 10 cm or less from the anal verge, and no patient received neoadjuvant therapy. The results should not be extrapolated to low rectal or diverted populations.

5. Conclusion

At Dr. Mohammad Hoesin General Hospital, a composite of CLS >11 and preoperative albumin <3.5 g/dL identified patients at very high risk of AL. Six of seven leaked (PPV 85.7%; LR+ 21.7). Sensitivity was 46.2% (95% CI 23.2–70.9) and failed the criterion set before analysis. By the point estimate the composite missed more than half of all leaks, and at best it detected about seven in ten. The CLS carries its discrimination, and the CLS association with leakage holds in every dataset that matches the observations. Albumin reclassified only one patient, and its own association could not be identified. In practice, a positive composite should prompt consideration of diversion or closer surveillance. A negative result should not reassure, and postoperative CRP monitoring should follow it. Hypoalbuminemia in 71.7% of patients (at least 66.0% of elective patients), together with a leak rate of 21.7%, suggests a nutritional target for South Sumatran colorectal surgery that merits prospective evaluation. These conclusions apply to colonic and high rectal anastomoses without diversion. Prospective multicenter validation should test continuous CLS and albumin, lower CLS cut-offs and inflammatory–nutritional indices in a cohort that includes diverted patients and graded leaks.

6. Declarations

Ethics Approval and Consent to Participate

The study was approved by the CMHC Research Center Ethics Committee, Indonesia (approval No. 2024/8421) for the retrospective analysis of anonymized medical records. The requirement for individual informed consent was waived because only existing, de-identified records were used. The study was conducted in accordance with the Declaration of Helsinki.

Consent for Publication

Not applicable. The article reports aggregate data only and contains no individually identifiable patient information, images or clinical details.

Availability of Data and Materials

All aggregate counts analyzed are reported in the article. Patient-level records are held by Dr. Mohammad Hoesin General Hospital and are not publicly available because of patient-confidentiality regulations; de-identified data may be requested from the corresponding author, subject to institutional approval.

Artificial Intelligence Use Statement

None.

Author Contribution Statement

M.R.F.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. M.H.K.: Conceptualization, Supervision, Validation, Writing – review & editing. T.: Methodology, Formal analysis, Supervision, Writing – review & editing. All authors reviewed and approved the final manuscript.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest / Competing Interests

The authors declare that they have no competing interests.

Acknowledgements

None.

7. References

- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–63. doi:10.3322/caac.21834
- Fu M, Li Y, Wang J. Incidence and Mortality of Colorectal Cancer in Asia in 2022 and Projections for 2050. *J Gastroenterol Hepatol.* 2025;40(5):1143–56. doi:10.1111/jgh.16910
- Danpanichkul P, Moolkaew P, Kanjanakot Y, et al. Rising incidence and impact of early-onset colorectal cancer in the Asia-Pacific with higher mortality in females from Southeast Asia: a global burden analysis from 2010 to 2019. *J Gastroenterol Hepatol.* 2023;38(12):2053–60. doi:10.1111/jgh.16331
- Wiranata JA, Puspitaningtyas H, Hutajulu SH, et al. Temporal and spatial analyses of colorectal cancer incidence in Yogyakarta, Indonesia: a cross-sectional study. *Geospat Health.* 2023;18(1). doi:10.4081/gh.2023.1186
- Hutajulu SH, Howdon D, Putra YR, et al. Clinicopathologic Characteristics Influencing Overall Survival of Patients With Early-Versus Average-Onset Colorectal Cancer at a Tertiary Care Center in Indonesia. *JCO Glob Oncol.* 2024;10:e2400188. doi:10.1200/GO.24.00188
- Weber MC, Berlet M, Stoess C, et al. A nationwide population-based study on the clinical and economic burden of anastomotic leakage in colorectal surgery. *Langenbecks Arch Surg.* 2023;408(1):55. doi:10.1007/s00423-023-02809-4
- Kang J, Kim H, Park H, et al. Risk factors and economic burden of postoperative anastomotic leakage related events in patients who underwent surgeries for colorectal cancer. *PLoS One.* 2022;17(5):e0267950. doi:10.1371/journal.pone.0267950
- Wells CI, Baraza W, O'Grady G, et al. 'Failure to rescue' from anastomotic leak following colorectal cancer resection: An observational study from a binational registry. *Colorectal Dis.* 2025;27(10):e70262. doi:10.1111/codi.70262
- Ochiai K, Hida K, Yamaguchi T, et al. Risk Factors for and Oncologic Impact of Anastomotic Leakage After Sphincter-Preserving Proctectomy for Mid/Low Rectal Cancer: A Multi-institutional Cohort Study in Japan. *Ann Surg Oncol.* 2025;32(10):7315–25. doi:10.1245/s10434-025-17763-2
- Yuliandar AA, Iwan Dani M, Suprpto B, et al. Relationship of Neutrophil-to-Lymphocyte Ratio with Anastomosis Leakage as Complication of Colorectal Surgery in Colorectal Cancer Patients. *Int J Curr Res Rev.* 2020;12(22):2–7. doi:10.31782/ijcrr.2020.122213
- Brito da Silva F, Lopes P, Cavadas D, et al. The impact of anastomotic leakage after curative colon cancer resection on long-term survival: A retrospective cohort study. *Cir Esp (Engl Ed).* 2024;102(1):3–10. doi:10.1016/j.cireng.2023.05.011
- Ono R, Tominaga T, Nonaka T, et al. Risk factors for anastomotic leakage and long-term outcomes after laparoscopic right colectomy: a multicenter study in a Japanese rural area. *Surg Today.* 2025;55(11):1609–20. doi:10.1007/s00595-025-03066-2
- Grijdanus NG, Wienholts K, Ubels S, et al. Stoma-free Survival After Rectal Cancer Resection With Anastomotic Leakage: Development and Validation of a Prediction Model in a Large International Cohort. *Ann Surg.* 2023;278(5):772–80. doi:10.1097/SLA.0000000000006043
- Eriksen JD, Emmertsen KJ, Madsen AH, et al. Anastomotic leakage following restorative rectal cancer resection: treatment and impact on stoma presence 1 year after surgery—a population-based study. *Int J Colorectal Dis.* 2022;37(5):1161–72. doi:10.1007/s00384-022-04164-0
- Nijssen DJ, Wienholts K, Postma MJ, et al. Hospital costs of different treatment strategies for anastomotic leakage after total mesorectal excision: a multicentre cost analysis. *Tech Coloproctol.* 2025;29(1):173. doi:10.1007/s10151-025-03215-2
- de Wit A, Daams F, Lam K, et al. Reporting of colorectal anastomotic leakage: Worldwide audit of national databases. *Colorectal Dis.* 2026;28(9):e70619. doi:10.1111/codi.70619
- He J, He M, Tang JH, et al. Anastomotic leak risk factors following colon cancer resection: a systematic review and meta-analysis.

- Langenbecks Arch Surg. 2023;408(1):252. doi:10.1007/s00423-023-02989-z
18. Horváth RS, Moca AE, Gozman-Pop A, et al. Emergency Surgery and the Risk of Anastomotic Leakage After Colorectal Resection with Primary Anastomosis for Benign and Malignant Disease: A Single-Center Retrospective Study. *J Clin Med*. 2026;15(14):5551. doi:10.3390/jcm15145551
 19. Tang XY, Chen Y, Liu YC, et al. Relationship between preoperative albumin level and risk of site-specific anastomotic leakage in digestive tract surgery: a systematic review and meta-analysis. *Int J Surg*. 2026;112(2):5111-9. doi:10.1097/JS9.0000000000003884
 20. Christina NM, Tjahyanto T, Lie JG, et al. Hypoalbuminemia and colorectal cancer patients: Any correlation?: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2023;102(8):e32938. doi:10.1097/MD.00000000000032938
 21. Almasaudi AS, Dolan RD, Edwards CA, et al. Hypoalbuminemia Reflects Nutritional Risk, Body Composition and Systemic Inflammation and Is Independently Associated with Survival in Patients with Colorectal Cancer. *Cancers (Basel)*. 2020;12(7):1986. doi:10.3390/cancers12071986
 22. Grogan A, Barclay K, Colville D, et al. Retinal small vessel dilatation in the systemic inflammatory response to surgery. *Sci Rep*. 2022;12(1):13291. doi:10.1038/s41598-022-17467-7
 23. Do Woong Choi J, Kwik C, Vivekanandamoorthy N, et al. Is preoperative hypoalbuminemia or hypoproteinemia a reliable marker for anastomotic leakage risk in patients undergoing elective colorectal surgery in an enhanced recovery after surgery (ERAS) program? *Int J Colorectal Dis*. 2023;38(1):152. doi:10.1007/s00384-023-04450-5
 24. Dekker JW, Liefers GJ, de Mol van Otterloo JC, et al. Predicting the risk of anastomotic leakage in left-sided colorectal surgery using a colon leakage score. *J Surg Res*. 2011;166(1):e27-34. doi:10.1016/j.jss.2010.11.004
 25. De Los Santos-Lopez AG, Martínez-Mier G, Reyes-Ruiz J, et al. Application of colon leakage score in the left-sided colorectal surgery. *Cir Cir*. 2024;92(3):388-94. doi:10.24875/CIRU.22000507
 26. Ganayee MA, Parrray FQ, Fazlulhaq M, et al. Predicting Anastomotic Leak in Left-sided Colorectal Cancer Surgery: A Prospective Study Using the Colon Leakage Score. *Indian J Surg Oncol*. 2026;17(2):430-5. doi:10.1007/s13193-025-02331-7
 27. Hu Y, Ren J, Lv Z, et al. Procalcitonin and C-reactive protein as early predictors in patients at high risk of colorectal anastomotic leakage. *J Int Med Res*. 2024;52(6):3000605241258160. doi:10.1177/03000605241258160
 28. Litchinko A, Buchs N, Balaphas A, et al. Score prediction of anastomotic leak in colorectal surgery: a systematic review. *Surg Endosc*. 2024;38(4):1723-30. doi:10.1007/s00464-024-10705-1
 29. Venn ML, Hooper RL, Pampiglione T, et al. Systematic review of preoperative and intraoperative colorectal Anastomotic Leak Prediction Scores (ALPS). *BMJ Open*. 2023;13(7):e073085. doi:10.1136/bmjopen-2023-073085
 30. Taha-Mehlitz S, Wentzler L, Angehrn F, et al. Machine learning-based preoperative analytics for the prediction of anastomotic leakage in colorectal surgery: a swiss pilot study. *Surg Endosc*. 2024;38(7):3672-83. doi:10.1007/s00464-024-10926-4
 31. Kang BY, Qiao YH, Zhu J, et al. Serum calcium-based interpretable machine learning model for predicting anastomotic leakage after rectal cancer resection: A multi-center study. *World J Gastroenterol*. 2025;31(19):105283. doi:10.3748/wjg.v31.i19.105283
 32. Sassun R, Bews KA, Sileo A, et al. Application of a Right-Sided Colectomy Anastomotic Leak Score to a Multi-institutional Cohort. *J Surg Res*. 2025;315:930-6. doi:10.1016/j.jss.2025.10.016
 33. Sakamoto T, Endo H, Yamamoto H, et al. Machine learning prediction of anastomotic leak after low anterior resection: Nationwide database analysis. *Medicine (Baltimore)*. 2025;104(34):e43977. doi:10.1097/MD.00000000000043977
 34. Lin V, Tsouchnika A, Allakhverdiiev E, et al. Training prediction models for individual risk assessment of postoperative complications after surgery for colorectal cancer. *Tech Coloproctol*. 2022;26(8):665-75. doi:10.1007/s10151-022-02624-x
 35. Zhang Z, Sun W, Wang J, et al. A nomogram to predict the risk of colorectal anastomotic leakage combining inflammatory-nutritional and abdominal aorta calcium index. *Front Surg*. 2022;9:1008448. doi:10.3389/fsurg.2022.1008448
 36. Jiang W, Feng M, Zheng J, et al. Association of the collagen score with anastomotic leakage in rectal cancer patients after neoadjuvant chemoradiotherapy. *Surgery*. 2021;170(5):1331-41. doi:10.1016/j.surg.2021.05.023
 37. Rudiman R, Hapsari P, Indrajaya NC. Correlation between Albumin, Colon Leakage Score (CLS), and Anastomotic Leakage after Colorectal Cancer Resection. *Majalah Kedokteran Bandung*. 2022;54(4):228-34. doi:10.15395/mkb.v54n4.2666
 38. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527. doi:10.1136/bmj.h5527
 39. Kang B, Zhao ZQ, Liu XY, et al. Effect of hypoalbuminemia on short-term outcomes after colorectal cancer surgery: A propensity score matching analysis. *Front Nutr*. 2022;9:925086. doi:10.3389/fnut.2022.925086
 40. Naz T, Naz S, Bhatti AM, et al. Frequency and Clinical Correlates of Hypoalbuminemia in Colorectal Cancer Patients at A Tertiary Care Hospital. *Pak J Health Sci*. 2024;5(12):34-9. doi:10.54393/pjhs.v5i12.2493
 41. Bitar E, Al-Karad D, Sahlieh H, et al. Anastomotic leakage in colorectal cancer surgery in Syria: risk factors and improvements following guideline implementation - a retrospective cohort study. *Ann Med Surg (Lond)*. 2026;88(4):2501-8. doi:10.1097/MS9.0000000000004810
 42. Degiuli M, Elmore U, De Luca R, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer (RALAR study): A nationwide retrospective study of the Italian Society of Surgical Oncology Colorectal Cancer Network Collaborative Group. *Colorectal Dis*. 2022;24(3):264-76. doi:10.1111/codi.15997
 43. Bekki T, Shimomura M, Adachi T, et al. Predictive factors associated with anastomotic leakage after resection of rectal cancer: a multicenter study with the Hiroshima Surgical study group of Clinical Oncology. *Langenbecks Arch Surg*. 2023;408(1):199. doi:10.1007/s00423-023-02931-3
 44. Habeeb TAAM, Hussain A, Chiaretti M, et al. Updates in surgery for colorectal cancer: incidence and risk factors for acute anastomotic leak-a retrospective study. *Updates Surg*. 2026;78(1):127-38. doi:10.1007/s13304-025-02411-x
 45. Rodriguez SLR, Montoro DFS, De la Cruz Ku G, et al. Risk factors of anastomotic leak in colorectal cancer: a multicentric study in a Latin American country. *Ecanmedicalscience*. 2024;18:1696. doi:10.3332/ecancer.2024.1696
 46. Kor CT, Tsai TJ, Chuang T, et al. Preoperative Prognostic Nutritional Index Predicts Postoperative Outcomes in Colorectal Cancer: A Propensity Score-Matched Cohort Study. *Cancer Manag Res*. 2026;18:558639. doi:10.2147/CMAR.S558639
 47. Zhang ZY, Li KJ, Zeng XY, et al. Early prediction of anastomotic leakage after rectal cancer surgery: Onodera prognostic nutritional index combined with inflammation-related biomarkers. *World J Gastrointest Surg*. 2025;17(4):102862. doi:10.4240/wjgs.v17.i4.102862
 48. Paliogiannis P, Deidda S, Maslyankov S, et al. C reactive protein to albumin ratio (CAR) as predictor of anastomotic leakage in colorectal surgery. *Surg Oncol*. 2021;38:101621. doi:10.1016/j.suronc.2021.101621
 49. Subaşı İE, Topcu A, Saydın F. Postoperative C-Reactive Protein-to-Albumin Ratio Predicts Anastomotic Leakage After Elective Right Hemicolectomy for Colon Cancer. *Ann Ital Chir*. 2026;97(9):1701-7. doi:10.62713/aic.4761
 50. Hu K, Tan K, Shang Q, et al. Relative decline in serum albumin help to predict anastomotic leakage for female patients following sphincter-preserving rectal surgery. *BMC Surg*. 2023;23(1):38. doi:10.1186/s12893-023-01923-w
 51. Guo K, Jin T, Pian G. Postoperative day 3 geriatric nutritional risk index as an early warning marker for anastomotic leakage after colorectal cancer surgery: A retrospective cohort study. *Medicine (Baltimore)*. 2026;105(31):e49985. doi:10.1097/MD.00000000000049985

52. Seishima R, Endo H, Maeda H, et al. Nationwide Trends in Short-Term Outcomes After Low Anterior Resection for Rectal Cancer: A Pre- and Post-COVID-19 Analysis From the Japanese National Clinical Database, 2018-2023. *Ann Gastroenterol Surg.* 2025;9(5):1029-35. doi:10.1002/ags3.70031
53. Gao J, Gu X, Pang M, et al. Risk factors for anastomotic leak and postoperative morbidity after right hemicolectomy for colon cancer: results from a prospective, multi-centre, snapshot study in China. *Br J Surg.* 2024;111(1):znad316. doi:10.1093/bjs/znad316
54. Sirikurnpiboon S. Randomized Controlled Trial Comparative Study in Powered and Manual Stapler in Low Anterior Resection of Rectal Cancer. *Asian J Endosc Surg.* 2025;18(1):e70132. doi:10.1111/ases.70132
55. Ho HA, Trieu TD, Nguyen MD. Anastomotic leakage following rectal cancer laparoscopic surgery: can a transanal drainage tube be an alternative to diverting stoma? *Eur Rev Med Pharmacol Sci.* 2024;28(10):3642-9. doi:10.26355/eurrev_202405_36301
56. Kertzman BAJ, Amelung FJ, Burghgraef TA, et al. Outcomes After Elective Versus Emergency Resection for Right-Sided Colon Cancer: A Propensity Score-Matched Analysis. *Dis Colon Rectum.* 2025;68(6):753-63. doi:10.1097/DCR.00000000000003680
57. Zamaray B, Veld JV, Burghgraef TA, et al. Risk factors for a permanent stoma after resection of left-sided obstructive colon cancer - A prediction model. *Eur J Surg Oncol.* 2023;49(4):738-46. doi:10.1016/j.ejso.2022.12.008
58. Bouland T, Sabbagh C, Allart K, et al. Is a Defunctioning Stoma Necessary After Left Colectomy in High-risk Patients for Anastomotic Leak? *Surg Laparosc Endosc Percutan Tech.* 2022;32(6):677-82. doi:10.1097/SLE.0000000000001109
59. Rutegård M, Svensson J, Segelman J, et al. Anastomotic Leakage in Relation to Type of Mesorectal Excision and Defunctioning Stoma Use in Anterior Resection for Rectal Cancer. *Dis Colon Rectum.* 2024;67(3):398-405. doi:10.1097/DCR.0000000000003050
60. Damgaard Eriksen J, Emmertsen KJ, Madsen AH, et al. The impact of multiple firings on the risk of anastomotic leakage after minimally invasive restorative rectal cancer resection and the impact of anastomotic leakage on long-term survival: a population-based study. *Int J Colorectal Dis.* 2022;37(6):1335-48. doi:10.1007/s00384-022-04171-1
61. Watanabe J, Takemasa I, Kotake M, et al. Blood Perfusion Assessment by Indocyanine Green Fluorescence Imaging for Minimally Invasive Rectal Cancer Surgery (Essential trial): A Randomized Clinical Trial. *Ann Surg.* 2023;278(4):e688-e694. doi:10.1097/SLA.0000000000005907
62. Jayne D, Croft J, Corrigan N, et al. Intraoperative fluorescence angiography with indocyanine green to prevent anastomotic leak in rectal cancer surgery (IntAct): an unblinded randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2025;10(9):806-17. doi:10.1016/S2468-1253(25)00101-3
63. Warsinggih, Akil F, Lusikooy RE, et al. The comparison of anastomosis strength and leakage between double-layer full-thickness and single-layer extramucosal intestine anastomosis. *Ann Med Surg (Lond).* 2023;85(8):3912-5. doi:10.1097/MS9.0000000000001072
64. Lévy K, Kovács S, Budai A, et al. Physical prehabilitation improves colonic anastomosis healing in a malnourished rat model only if attached to effective nutritional prehabilitation - Experimental study. *Surgery.* 2025;188:109677. doi:10.1016/j.surg.2025.109677
65. Sala Hernandez A, Frasson M, García-Granero A, et al. Diagnostic accuracy of C-reactive protein, procalcitonin and neutrophils for the early detection of anastomotic leakage after colorectal resection: a multicentric, prospective study. *Colorectal Dis.* 2021;23(10):2723-30. doi:10.1111/codi.15845
66. Stephensen BD, Reid F, Shaikh S, et al. C-reactive protein trajectory to predict colorectal anastomotic leak: PREDICT Study. *Br J Surg.* 2020;107(13):1832-7. doi:10.1002/bjs.11812
67. Shen N, Wen J, Chen C, et al. The relationship between GLIM-malnutrition, post-operative complications and long-term prognosis in elderly patients undergoing colorectal cancer surgery. *J Gastrointest Oncol.* 2023;14(5):2134-45. doi:10.21037/jgo-23-543
68. Fisunoglu M, Yildiz Kopuz TN, Yildiz HF, et al. Preoperative nutritional factors as predictors of postoperative early outcomes in colorectal cancer - A prospective cohort study. *Nutr Hosp.* 2024;41(5):1032-43. doi:10.20960/nh.05331
69. Xiang S, Yang YK, Wang TY, et al. Development and validation of a nomogram to predict anastomotic leakage in colorectal cancer based on CT body composition. *Front Nutr.* 2022;9:974903. doi:10.3389/fnut.2022.974903
70. Molenaar CJL, Minnella EM, Coca-Martinez M, et al. Effect of Multimodal Prehabilitation on Reducing Postoperative Complications and Enhancing Functional Capacity Following Colorectal Cancer Surgery: The PREHAB Randomized Clinical Trial. *JAMA Surg.* 2023;158(6):572-81. doi:10.1001/jamasurg.2023.0198
71. Lee SY, Lee J, Park HM, et al. Impact of Preoperative Immunonutrition on the Outcomes of Colon Cancer Surgery: Results from a Randomized Controlled Trial. *Ann Surg.* 2023;277(3):381-6. doi:10.1097/SLA.0000000000005140
72. Sammut-Powell C, Reynard C, Allen J, et al. Examining the effect of evaluation sample size on the sensitivity and specificity of COVID-19 diagnostic tests in practice: a simulation study. *Diagn Progn Res.* 2022;6(1):12. doi:10.1186/s41512-021-00116-4