



Association between preoperative HALP score and anastomotic leakage following colorectal cancer resection: A retrospective cohort study

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ABSTRACT

Objective: Anastomotic leakage remains a major complication following colorectal surgery. This study aimed to evaluate the association between the preoperative hemoglobin, albumin, lymphocyte, and platelet (HALP) score and postoperative anastomotic leakage in patients undergoing colorectal cancer resection.

Material and Methods: This single-center retrospective cohort study included 505 patients who underwent colorectal resection with primary anastomosis for stage II-III colorectal cancer. The association between preoperative HALP score and anastomotic leakage was evaluated using univariable analyses and receiver operating characteristic (ROC) analysis. A multivariable logistic regression model adjusted for age and tumor location was fitted, and Firth's penalized likelihood estimation was used for the adjusted analysis because of the limited number of events. The study is reported in accordance with the strengthening the reporting of observational studies in epidemiology statement.

Results: Anastomotic leakage occurred in 18 patients (3.6%). Patients who developed leakage had significantly lower preoperative HALP scores than those without leakage [median 18.0 (10.8-33.3) vs. 34.5 (16.6-90.4); $p < 0.001$]. ROC analysis demonstrated good discriminative ability (area under the curve = 0.877; 95% confidence interval, 0.802-0.951; $p < 0.001$). The Youden-derived cut-off value of 22.1 yielded a sensitivity of 72.2% and a specificity of 85.0%. In the Firth penalized multivariable logistic regression model, a higher HALP score remained independently associated with lower odds of anastomotic leakage after adjustment for age and tumor location (adjusted odds ratio, 0.83 per 1-unit increase; 95% confidence interval, 0.76-0.91; $p < 0.001$). Given the limited number of leakage events, these findings should be interpreted as exploratory.

Conclusion: Lower preoperative HALP scores were associated with postoperative anastomotic leakage. Because of the retrospective study design, these findings should be interpreted as exploratory and require confirmation in larger prospective multicenter studies.

Keywords: Anastomotic leakage, HALP score, colorectal surgery, immunonutritional status, risk assessment

INTRODUCTION

Colorectal cancer continues to impose a substantial global disease burden and remains one of the leading causes of cancer-related mortality worldwide (1). Curative treatment primarily relies on oncological surgical resection with restoration of intestinal continuity whenever feasible (2). Despite continuous advances in surgical techniques and perioperative management, anastomotic leakage remains one of the most serious postoperative complications. It is associated with increased postoperative morbidity and mortality, prolonged hospital stay, higher reoperation rates, increased healthcare costs, and impaired oncological outcomes (3,4). Reported incidence rates vary between approximately 3% and 19% across different studies (5). Therefore, identifying patients at increased risk for anastomotic leakage remains an important objective in colorectal surgery.

Growing attention has recently been directed toward biomarkers reflecting patients' inflammatory and nutritional status because of their potential association with postoperative outcomes. Systemic inflammation adversely affects tissue healing, while adequate nutritional status is essential for wound repair and immune competence (6,7). Consequently, several composite inflammatory and nutritional indices have been proposed as prognostic biomarkers in surgical oncology.

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a composite immunonutritional index first introduced by Chen et al. (8) in 2015 as a prognostic marker in gastric cancer. It integrates four routinely available laboratory parameters

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reflecting oxygen-carrying capacity, nutritional status, immune function, and systemic inflammatory activity (9). Since its introduction, reduced HALP scores have been associated with poor survival and adverse postoperative outcomes in several malignancies, including gastric, prostate, bladder, and colorectal cancers (9,10).

In the surgical setting, HALP has also been associated with postoperative complications. Tarle et al. (11) demonstrated that the HALP score was associated with postoperative complications following head and neck microvascular free-flap reconstruction.

In colorectal cancer, Yalav et al. (12) identified HALP as an independent prognostic factor for overall survival in patients undergoing curative surgery. Likewise, Dagmura et al. (13) demonstrated that lower HALP scores were associated with poorer survival outcomes in colorectal cancer patients. However, evidence regarding the association between preoperative HALP score and anastomotic leakage remains limited.

Therefore, the present retrospective single-center cohort study aimed to evaluate the association between the preoperative HALP score and postoperative anastomotic leakage following colorectal cancer resection. We hypothesized that patients with lower preoperative HALP scores would have a higher likelihood of developing anastomotic leakage. If confirmed, the HALP score may represent a simple, inexpensive, and readily available adjunctive biomarker for preoperative risk assessment in colorectal surgery.

MATERIAL and METHODS

Study Design and Setting

This retrospective single-center cohort study is reported in accordance with the strengthening the reporting of observational studies in epidemiology statement for observational research (14). It was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of Zonguldak Bülent Ecevit University (approval no: 2025/16; date: 17 September 2025). Because of the retrospective study design, the requirement for informed consent was waived.

Participants

Medical records of 505 consecutive adult patients who underwent curative colorectal resection with primary anastomosis for histologically confirmed colorectal cancer at a tertiary referral center between January 2016 and December 2024 were retrospectively reviewed. Patients who did not undergo surgical treatment, had no histopathological confirmation of malignancy, had metachronous malignancies, had incomplete clinical records, had stage I disease treated by local excision, or had stage IV disease undergoing palliative surgery without curative intent were excluded. As a consequence of these predefined criteria, the final analytical cohort comprised exclusively patients with

pathological stage II or III disease; no stage I or stage IV patients remained after exclusion. This restriction was applied a priori to obtain a clinically homogeneous population undergoing resection with curative intent, in which restoration of intestinal continuity is the standard approach and anastomotic integrity is the relevant outcome. The potential impact of this restriction on generalizability is addressed in the limitations section. A patient selection flow diagram is presented in Figure 1.

Outcome Definition

Patients were classified into two groups according to the occurrence of postoperative anastomotic leakage. Anastomotic leakage was defined according to the criteria of the International Study Group of Rectal Cancer (ISREC) and diagnosed based on clinical findings, radiological evidence, or intraoperative confirmation. Leakage severity was graded according to the ISREC classification (Grades A-C). All leakage events were identified within the first 30 postoperative days or during the initial hospitalization. Although the ISREC definition was originally developed for rectal anastomoses, its constituent criteria—a defect of the intestinal wall at the anastomotic site resulting in communication between the intra- and extraluminal compartments, graded by the intensity of the required intervention—are anatomically generic and are not specific to the rectum. In the absence of a universally accepted colonic counterpart, the ISREC framework has been widely adopted for colonic anastomoses in both cohort studies and systematic reviews (5), and applying a single definition across both sites avoids differential outcome misclassification between the colonic and rectal subgroups. We therefore applied identical criteria to colonic and rectal anastomoses.

Mortality was defined as all-cause death occurring within 30 days of surgery or during the index hospitalization, whichever

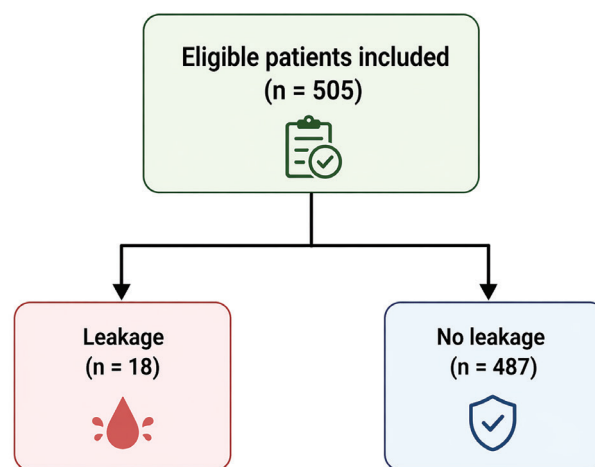


Figure 1. Flow diagram of patient selection according to predefined inclusion and exclusion criteria.

was longer. Because the present analysis was restricted to this fixed perioperative window, no longer-term or cause-specific (leakage-attributable) mortality was assessed, and survival beyond discharge was not analyzed.

Variables

Collected variables included age, sex, family history of malignancy, tumor location, pathological TNM stage, preoperative HALP score, and mortality. Tumor staging was performed according to the 2016 TNM classification system. The HALP score was calculated from the most recent preoperative laboratory values as:

$\text{HALP} = \text{Hemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocyte count (/L)} / \text{platelet count (/L)}$

Because of the retrospective nature of the study, several important perioperative and comorbidity-related variables—including American Society of Anesthesiologists (ASA) score, body mass index, diabetes mellitus, smoking status, steroid use, neoadjuvant therapy, diverting ileostomy, type of resection, anastomotic level, operative approach, surgeon experience, and transfusion data—were not consistently recorded in the institutional database and therefore could not be included in the analyses. The consequences of this omission for causal interpretation are discussed in the limitations section.

Pre-specified and Post-hoc Analyses

The primary exposure variable was the preoperative HALP score and the primary outcome was postoperative anastomotic leakage. Age and tumor location (colon vs. rectum) were pre-specified as clinically relevant covariates for the adjusted model. One subgroup analysis—stratification by tumor location (colon vs. rectum)—was pre-specified. All other subgroup analyses, including the comparison of HALP scores between patients aged ≥ 80 years and younger patients, were performed post-hoc and are explicitly labeled as such in the results. No adjustment for multiple comparisons was applied; given the number of subgroup and outcome comparisons performed, nominal p-values from these analyses should be regarded as descriptive rather than inferential.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA); Firth's penalized likelihood logistic regression was performed in R version 4.3.1 using the *logistf* package, because this estimator is not implemented in SPSS. Two-sided p-values < 0.05 were considered statistically significant.

Continuous variables were summarized as mean $\pm$ standard deviation or median (minimum-maximum), depending on data distribution, whereas categorical variables were presented as frequencies and percentages. Normality was assessed using the

Shapiro-Wilk test. Comparisons between groups were performed using the independent-samples t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Receiver operating characteristic (ROC) analysis was performed to assess the ability of the preoperative HALP score to discriminate between patients with and without anastomotic leakage. The area under the curve (AUC) was reported with a 95% confidence interval derived from the nonparametric (DeLong) method. The optimal cut-off was determined by maximizing the Youden index (sensitivity + specificity - 1), and the corresponding sensitivity, specificity, positive and negative predictive values, and likelihood ratios were calculated with 95% Wilson confidence intervals. Because the cut-off was derived and evaluated in the same dataset, internal validation was performed using 1000 bootstrap resamples to estimate optimism in the AUC.

A multivariable binary logistic regression model was specified with anastomotic leakage as the dependent variable and HALP score, age, and tumor location as covariates. The conventional maximum likelihood model demonstrated complete separation and failed to produce finite, reliable coefficient estimates. Therefore, Firth's penalized likelihood logistic regression was used as the primary adjusted analysis. This bias-reduction method provides finite estimates in the presence of sparse data and separation. Adjusted odds ratios with 95% confidence intervals and two-sided p-values are reported. Because only 18 leakage events occurred, the adjusted results should be considered exploratory.

Because of the limited number of events, the multivariable and ROC analyses are considered exploratory and hypothesis-generating rather than confirmatory; no clinical decision threshold is proposed on the basis of these data. This caveat is not repeated elsewhere in the manuscript and applies to all model-based results reported below.

Cases with missing key variables were excluded from the relevant analyses; no imputation was performed. Since this was a retrospective cohort study, no a priori sample size calculation was performed, and the study population consisted of all eligible patients treated during the study period.

RESULTS

The analysis included 505 patients, of whom 18 (3.6%) developed anastomotic leakage and 487 (96.4%) did not. All included patients had pathological stage II ($n=262$, 51.9%) or stage III ($n=243$, 48.1%) disease; no patients with stage I or stage IV disease remained in the cohort after application of the exclusion criteria. Table 1 summarizes the demographic and

clinical characteristics of the study population according to the occurrence of anastomotic leakage. The median age of the entire cohort was 59 years (range, 32-86 years).

Patients who developed anastomotic leakage were significantly older than those without leakage [median 70.5 (52-85) vs. 58 (32-86) years; $p=0.001$]. Sex distribution was comparable between the two groups ($p=0.13$).

Tumor location differed significantly between groups. Rectal tumors were more frequent among patients with leakage than among those without leakage (66.7% vs. 30.0%; $p=0.003$); the leakage rate was 7.6% (12/158) after rectal resection compared with 1.7% (6/347) after colonic resection. Pathological stage III disease was also more frequent in the leakage group (77.8% vs. 47.0%; $p=0.014$).

Patients who developed anastomotic leakage had significantly lower preoperative HALP scores than those without leakage [median 18.0 (10.8-33.3) vs. 34.5 (16.6-90.4); $p<0.001$]. Perioperative mortality occurred in 14 patients (2.8%) overall. Mortality was numerically higher among patients who developed anastomotic leakage than among those who did not (11.1% vs. 2.5%), but this difference did not reach statistical significance ($p=0.08$, Fisher's exact test). No other demographic or clinical variables differed significantly between the groups.

ROC analysis demonstrated good discriminatory performance of the preoperative HALP score for anastomotic leakage [AUC = 0.877; 95% confidence interval (CI), 0.802-0.951; $p<0.001$] (Figure 2). The optimal cut-off identified by the Youden index was a HALP score of 22.1, corresponding to a sensitivity of 72.2% (95% CI, 49.1-87.5), a specificity of 85.0% (95% CI, 81.6-87.9), a positive predictive value of 15.1%, a negative predictive value of 98.8%, and positive and negative likelihood ratios of 4.82 and 0.33, respectively. Anastomotic leakage occurred in 13 of 86 patients (15.1%) with a HALP score ≤ 22.1 compared with 5 of 419 patients (1.2%) above this threshold ($p<0.001$). Internal validation using 1000 bootstrap resamples yielded a negligible

optimism estimate for the AUC (<0.005), which is expected for a single continuous predictor evaluated without model fitting; the bootstrap percentile confidence interval (0.800-0.945) was closely concordant with the DeLong interval.

In univariable logistic regression, each one-unit increase in the preoperative HALP score was associated with lower odds of anastomotic leakage [odds ratio (OR) 0.79; 95% CI, 0.71-0.89; $p<0.001$], corresponding to an approximately threefold increase in odds for every 5-unit decrease in HALP score (OR 3.18; 95% CI, 1.81-5.57).

Because complete separation was detected and the conventional maximum likelihood logistic regression model failed to converge, Firth's penalized likelihood logistic regression was used for the adjusted analysis. After adjustment for age and tumor location, each 1-unit increase in the preoperative HALP score was independently associated with a 16.8% reduction in the odds of anastomotic leakage (adjusted OR 0.83; 95% CI, 0.76-0.91; $p<0.001$). Expressed on a more clinically interpretable scale,

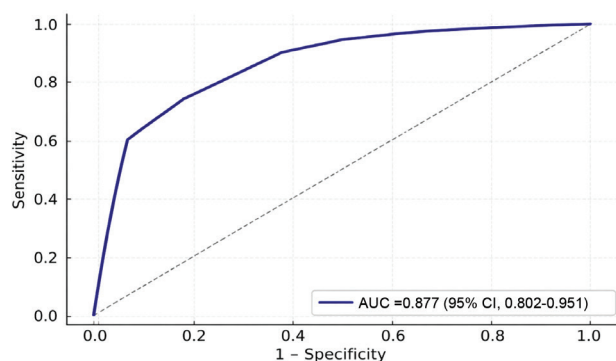


Figure 2. Receiver operating characteristic curve of the preoperative HALP score for postoperative anastomotic leakage (AUC = 0.877; 95% CI, 0.802-0.951). The marked point corresponds to the Youden-derived cut-off of 22.1 (sensitivity 72.2%, specificity 85.0%).

HALP: Hemoglobin, albumin, lymphocyte, and platelet, AUC: Area under the curve, CI: Confidence interval.

Table 1. Baseline demographic and clinical characteristics of patients with and without anastomotic leakage

Variable	Anastomotic leakage (n=18)	No leakage (n=487)	Test	p
Age, years, median (min-max)	70.5 (52-85)	58 (32-86)	Mann-Whitney U	0.001
Sex, female/male, n (%)	9 (50.0)/9 (50.0)	155 (31.8)/332 (68.2)	Fisher's exact	0.13
First-degree family history of cancer, yes/no, n (%)	4 (22.2)/14 (77.8)	85 (17.4)/402 (82.6)	Fisher's exact	0.54
Tumor location, rectum/colon, n (%)	12 (66.7)/6 (33.3)	146 (30.0)/341 (70.0)	Fisher's exact	0.003
Pathological TNM stage, II/III, n (%)	4 (22.2)/14 (77.8)	258 (53.0)/229 (47.0)	Fisher's exact	0.014
Preoperative HALP score, median (min-max)	18.0 (10.8-33.3)	34.5 (16.6-90.4)	Mann-Whitney U	<0.001
Perioperative mortality, yes/no, n (%)	2 (11.1)/16 (88.9)	12 (2.5)/475 (97.5)	Fisher's exact	0.08

HALP: Hemoglobin, albumin, lymphocyte, and platelet. Data are presented as median (minimum-maximum) or number (percentage). Continuous variables were compared using the Mann-Whitney U test and categorical variables using Fisher's exact test; two-sided $p<0.05$ was considered statistically significant. Perioperative and comorbidity-related variables (American Society of Anesthesiologists score, body mass index, diabetes mellitus, smoking status, neoadjuvant therapy, diverting stoma, anastomotic level, operative approach, transfusion, surgeon experience) were not consistently available because of the retrospective design and are therefore not shown.

each 5-unit decrease in the HALP score was associated with approximately 2.5-fold higher odds of leakage (adjusted OR 2.51; 95% CI, 1.62-3.89; $p < 0.001$).

Each 10-year increase in age was independently associated with higher odds of anastomotic leakage (adjusted OR 1.49; 95% CI, 1.22-1.81; $p < 0.001$). Rectal tumor location showed a positive but highly imprecise association with leakage (adjusted OR 160.75; 95% CI, 0.64-40,499.54; $p = 0.072$). The extreme effect estimate and wide confidence interval for tumor location likely reflect sparse outcome data and residual separation despite penalization and therefore should not be interpreted as a reliable estimate of the true effect size.

In the pre-specified subgroup analysis by tumor location, the association between a lower HALP score and anastomotic leakage was more evident among patients with rectal cancer, whereas a similar direction of effect was observed in patients with colon cancer without reaching statistical significance. In a post-hoc analysis, patients aged ≥ 80 years had lower HALP scores than younger patients, consistent with an age-related decline in immunonutritional status. Because this analysis was not pre-specified and no correction for multiplicity was applied, it should be regarded as descriptive.

DISCUSSION

In this retrospective single-center cohort study, lower preoperative HALP scores were associated with the occurrence of postoperative anastomotic leakage following colorectal cancer resection. Patients who developed leakage had significantly lower HALP values than those without leakage, the HALP score discriminated between the two groups with an AUC of 0.877, and the association persisted after adjustment for age and tumor location. Consistent estimates obtained with Firth's penalized likelihood method suggest that these findings are not an artifact of the limited number of events.

Nevertheless, several established risk factors for anastomotic leakage were unavailable for adjustment. Therefore, the observed association may partly reflect residual confounding rather than an independent biological effect of the HALP score itself. Furthermore, the identified HALP threshold requires external validation before clinical implementation.

Subgroup analyses suggested that the association between lower HALP score and anastomotic leakage was more evident among patients with rectal cancer than among those with colon cancer. This observation is biologically plausible because rectal surgery is technically more demanding, the anastomosis is typically lower and less well vascularized, and rectal resection is generally associated with a higher baseline risk of anastomotic leakage—a pattern also reflected in the present cohort, in which

the leakage rate after rectal resection was more than four times that after colonic resection.

Our findings are consistent with previous reports evaluating the clinical relevance of HALP in surgical oncology. Tarle et al. (11) reported similar associations with postoperative complications following head and neck microvascular reconstruction. Likewise, studies in colorectal cancer have primarily focused on the prognostic value of HALP for long-term survival rather than postoperative morbidity (12,13). Our findings extend these observations by suggesting that lower preoperative HALP scores may also be associated with an increased likelihood of anastomotic leakage.

The HALP score is increasingly recognized as a composite biomarker reflecting both nutritional and immunological status in patients with solid malignancies. Hemoglobin and albumin reflect oxygen-carrying capacity and nutritional reserve, whereas lymphocyte and platelet counts represent immune competence and systemic inflammatory activity. Consequently, a reduced HALP score may indicate impaired wound healing potential and diminished physiological reserve. Previous studies have consistently demonstrated that hypoalbuminemia, anemia, and lymphopenia are individually associated with increased postoperative complications, whereas the HALP score combines these parameters into a single immunonutritional index that may better reflect overall patient vulnerability (15-20).

Preoperative nutritional optimization may represent one potential strategy for reducing postoperative complications in patients with poor immunonutritional status. Jie et al. (21) demonstrated that perioperative nutritional support shortened postoperative hospital stay in patients undergoing abdominal surgery. Although our study was not designed to evaluate nutritional interventions, these findings support the concept that optimization of preoperative nutritional status may contribute to improved postoperative recovery. Whether preoperative correction of a low HALP score translates into a lower leakage rate remains an untested hypothesis that would require a prospective interventional design.

Study Limitations

Several limitations should be acknowledged. First, the retrospective single-center design may have introduced selection bias and limits generalizability; because stage I and stage IV patients were excluded by design, the findings apply only to patients undergoing resection with curative intent for stage II-III disease.

Second, only 18 leakage events occurred, yielding an events-per-variable ratio of 6 in the multivariable model. Although Firth's penalized estimation and bootstrap internal validation

were used to mitigate small-sample bias and optimism, the confidence intervals remain wide, external validation was not possible, and the model should not be used for individual risk prediction. Multiple subgroup and outcome comparisons were performed without correction for multiplicity, which further increases the probability of chance findings.

Third, several clinically relevant perioperative and comorbidity-related variables—ASA score, body mass index, diabetes mellitus, smoking status, steroid use, neoadjuvant therapy, diverting stoma, anastomotic level, operative approach, transfusion data, and surgeon experience—were not available. Because these are among the strongest recognized determinants of anastomotic leakage, residual confounding cannot be excluded and the observed association must not be interpreted as causal.

Fourth, HALP was measured at a single preoperative time point, so longitudinal changes in immunonutritional status could not be evaluated. Fifth, mortality was assessed only within a fixed perioperative window and was all-cause; leakage-attributable deaths could not be distinguished. With only 14 deaths, the study was underpowered to detect a difference in perioperative mortality between the groups, and the numerically higher mortality observed after anastomotic leakage should not be interpreted as evidence of absence of an effect. Finally, detailed information regarding leakage severity grade, management strategy, and time to diagnosis was not consistently recorded.

CONCLUSION

In conclusion, lower preoperative HALP scores were associated with postoperative anastomotic leakage in patients undergoing resection for stage II-III colorectal cancer. Given its low cost and routine availability, the HALP score may serve as a simple adjunctive marker of preoperative physiological vulnerability. Further prospective multicenter studies with comprehensive perioperative data are warranted to validate these findings before clinical implementation.

Ethics

Ethics Committee Approval: It was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of Zonguldak Bülent Ecevit University (approval no: 2025/16; date: 17 September 2025).

Informed Consent: Because of the retrospective study design, the requirement for informed consent was waived.

Acknowledgments

For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized for language assistance and linguistic refinement. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Author Contributions

Surgical and Medical Practices - U.T.; Concept - U.T.; Design - U.T.; Data Collection or Processing - U.T.; Analysis or Interpretation - U.T., A.I.B., B.S.; Literature Search - U.T.; Writing - U.T.

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