

ORIGINAL RESEARCH ARTICLE

An early detector of anastomosis leakage following colorectal cancer surgery in intensive care

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Abstract

Colorectal cancer, comprising 10% of global cancer cases, often leads to anastomosis leakage (AL), a significant post-operative complication. Previous research on AL has highlighted the inflammatory response as a common risk factor and a potential diagnostic tool. This study aimed to investigate the inflammatory markers linked to AL and their prospective use as predictors of AL. This retrospective study was conducted in the intensive care unit of a state hospital in Ankara, Turkey. AL was detected through computed tomography and clinical evaluation (e.g., peritonitis and clinical deterioration). Inflammatory markers, including C-reactive protein and neutrophil-to-lymphocyte ratio (NLR), were examined in this study. A total of 410 patients were included in this study, among whom AL was observed in 26 cases (6.3%). The pre-operative levels of inflammatory markers did not differ between AL-positive and AL-negative groups, whereas the post-operative levels significantly differed between the groups ($P < 0.05$), particularly regarding post-operative NLR levels ($P < 0.001$). The predictive power of the difference in NLR was more prominent than the other inflammatory markers. In addition, the area under the curve of the NLR difference was sufficient to effectively predict AL. As the manifestation of AL signs and symptoms often occur in the later stages of inflammation, the early detection of inflammatory marker changes could signal the pre-emptive development of AL and enhance its management. In summation, the findings of this study further established the clinical potential of inflammatory markers for the early detection of AL, albeit requiring validation and support from additional prospective studies.

Keywords: Colorectal cancer; Surgery; Anastomosis leakage; Inflammatory marker; Prediction; Early detection

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1. Introduction

Colorectal cancer comprises approximately 10% of global cancer cases, with its incidence steadily increasing yearly. It is the second most diagnosed cancer in females and the third

in males.¹ Anastomosis remains a standard procedure in the treatment of colorectal cancer ideally to establish vascular perfusion without clinical complications.² Despite advancements in both surgery and perioperative care of colorectal cancer patients, anastomosis leakage (AL) remains one of the major complications in the post-operative period. AL has a mortality rate and is expensive to treat due to its delayed symptom manifestation (e.g., intra-abdominal abscess and sepsis) and subsequent diagnosis of approximately 2 – 4 days through clinical and laboratory assessments.^{3,4} Hence, the early detection of AL may decrease its incidence.

The early detection of AL can be performed intraoperatively using near-infrared fluorescence technology and postoperatively through computed tomography (CT) and other radiological evaluations with contrast enhancement. However, the post-operative evaluations are normally conducted at a later time due to the risk of iatrogenic contrast agent-induced dehiscence. This inevitable delay in detection could result in poorer AL prognosis and subsequent management.⁵ This limitation has prompted research efforts to identify risk factors and accurate predictors of AL. Several researchers have proposed different risk models and scoring systems to diagnose AL early and predict post-operative outcomes, but there is a lack of consensus or guidelines for their application in colorectal surgery.⁶ An inflammatory response is the common risk factor identified in AL-related studies and could potentially be an effective diagnostic tool for AL as the patients' inflammatory markers are routinely measured daily, including albumin, sodium, total lymphocyte count (TLC), C-reactive protein (CRP), and the neutrophil-to-lymphocyte ratio (NLR).⁷⁻⁹ Herein, this study aimed to evaluate the relationship between inflammatory markers (e.g., CRP, NLR, total neutrophil count [TNC], and TLC) and AL, as well as their prospective use for the early detection of AL. In addition, we compared the predictive power of these inflammatory markers.

2. Methods

2.1. Study population

This study was a case–control observational study that was designed retrospectively based on patients hospitalized in the intensive care unit (ICU) of a state hospital in Ankara, Turkey. The study population was composed of patients who underwent curative surgery with a confirmed diagnosis of colorectal cancer between March 1, 2016, and February 1, 2019. Patients (>18 years old) who had pathologically confirmed adenocarcinoma and underwent curative surgery were included in the study. The exclusion criteria were: (i) patients who underwent

surgery for benign pathologies such as inflammatory bowel disease (IBD), (ii) palliative and emergency surgeries, (iii) AL-positive (AL+) cases detected before day 6 or after day 28 in the post-operative period, (iv) pregnant and/or human immunodeficiency virus-positive (HIV+) patients, and (v) patients who developed infectious complications other than AL. Since the study was retrospective and observational, patient-signed informed consent and ethics committee approval were not necessary.

2.2. Data acquisition

The demographic data (e.g., patient age and gender) and disease severity scores (e.g., Charlson comorbidity index scores and acute physiologic assessment and chronic health evaluation II [APACHE II] scores) were obtained from the institutional database and nurse sheets. Likewise, the clinicopathological data (e.g., histopathological grade of the tumor, the location of the tumor, the clinical tumor-node-metastasis [TNM] stage, the surgical procedure, and the outcomes) were also collected from the institutional database. The TNM stage was determined using the TNM staging system of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC).¹⁰

AL was detected through CT (i.e., images of fluid or air deposits in the anastomotic region) and endoscopy or explorative surgery (i.e., peritonitis and clinical deterioration). The Clavien-Dindo (CD) classification was used to categorize post-operative complications (except AL) of colorectal cancer.¹¹ as independent variables: CD grade >2: Mild complications; CD grade >3: Complications that require surgical, endoscopic, or radiological intervention; CD grade >4: Life-threatening complications. The other outcomes that were appraised as discrete variables were the 30-day mortality rate, length of stay (LOS) in the hospital and ICU, and re-operation rate.

2.3. Inflammatory marker data

The inflammatory markers investigated in this study were CRP, total white cell count (TWC), TLC, TNC, platelet distribution width (PDW), and NLR. These markers were examined as a routine procedure in the pre-operative and post-operative periods daily. As the median time for AL complication was reported as 5 – 6 days in the post-operative period,¹² the levels of the inflammatory markers on post-operative day 6 (D6) were selected for comparison with the pre-operative levels (i.e., before surgery) (D₀). Other than the absolute values of these inflammatory markers that were mentioned above, we also calculated the differences and the delta values. The difference in inflammatory marker levels (X) was calculated as:

Difference in $X = X$ on post-operative day 6 (D6) – X in the pre-operative period (D0) (I)

The delta values of the inflammatory markers (X) were calculated with the formula:

$$\text{DeltaX} = \frac{X \text{ in the postoperative sixth day (D6)} - X \text{ in the preoperative period (D0)}}{X \text{ in the preoperative period (D0)}} \times 100 \quad (\text{II})$$

2.4. Statistical analysis

All data and variables were evaluated with the Kolmogorov–Smirnov test to determine the normality of the variables. As the derived data did not display a normal distribution, we utilized non-parametric tests for statistical analyses. Categorical variables were expressed as total number and percentage, whereas continuous variables were presented as mean and standard deviation (*SD*). Spearman's rho test was used to display the relationship between variables and the Mann–Whitney U test was used to elucidate the relationship between variables and inflammatory markers. In addition, receiver operating characteristic (ROC) curve analysis and its corresponding area under curves (AUC) were used to compare the predictive power of inflammatory markers for the detection of AL. The MedCalc v. 18.0.1 statistical software (MedCalc Software, Belgium) was used for statistical analyses, and the statistical significance was set at $P < 0.05$.

3. Results

During the study period, 536 patients underwent colorectal surgery in the state hospital. Among these, 122 were excluded due to benign pathologies (i.e., 68 patients with inflammatory bowel disease, 24 patients with mesenteric ischemia, and 30 patients with familial polyposis coli), and four were excluded for detected AL before the 6th day. The remaining 410 patients were included and analyzed in this

study. The study population is described in a flowchart in Figure 1.

The mean age of the patients was 61.1 ± 13.04 years old (18 – 96 years old), and 68% of the patients were male ($n = 279$). The descriptive and demographic variables of the patients ($n = 410$) are displayed in Table 1. The operation and post-operative parameters, including the mortality, LOS in the hospital, and other outcomes, are presented in Table 2. The median time to the clinical diagnosis of AL was 10 days (6 – 27 days). We identified 26 AL+ cases (6.3%). There was reportedly no significant correlation between the AL+ group and the variables sex and age.

The right colon was the most common location of tumoral mass ($n=210$; 51.2%), while the right hemicolectomy was the most common surgical procedure performed ($n = 200$; 48.8%). A total of 210 cases (51.2%) had moderately differentiated histology, while 144 patients (35.1%) had Stage III tumors according to the TNM staging system. The mean APACHE II score of all patients calculated on the 1st day of admission to the ICU was 8 ± 3.7 . The APACHE II score was significantly different between the AL+ and AL- groups. The other demographic data and operation parameters were not significantly different ($P > 0.05$) between groups (Tables 1 and 2). Moreover, the metastasis rate and the length of operation time did not significantly differ between groups as well.

Notably, the LOS in the hospital and ICU, mortality rate, and CD grade (i.e., >2) were significantly different between the groups. The mortality (26.9% vs. 3.6%) and re-operation (46.2% vs. 2.6%) rates were higher and the LOS in the ICU (17.8 ± 17.6 days vs. 4.5 ± 9 days) and hospital (30 ± 17.9 days vs. 14 ± 12 days) were longer in AL+ group than in the AL- group.

In the second part of the study, we assessed the relationship between the inflammatory markers and AL by examining the absolute values, differences, and delta

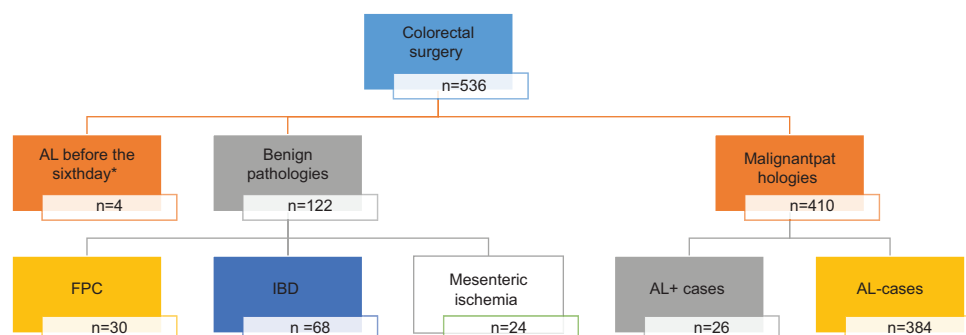


Figure 1. Flowchart of the study population after excluding the benign pathologies and AL before the 6th day in the post-operative period.

Note: *The cases in which anastomosis leakage were detected before 6th day in the postoperative period were excluded.

Abbreviations: AL+: Anastomoses leakage-positive; AL-: Anastomoses leakage-negative; FPC: Familial polyposis coli; IBD: Inflammatory bowel disease.

Table 1. Demographic data, disease severity classification, and clinicopathological variables of patients ($n=410$) in the AL+ ($n=26$) and AL- ($n=384$) groups

Parameter	All patients	AL+	AL-	P
Age (years)(mean \pm SD)	61.1 \pm 13.04	65.1 \pm 15.5	60.8 \pm 12.8	0.063
Sex (male) (n [%])	279 (68)	21 (80.8)	258 (67.2)	0.341
APACHE II (mean \pm SD)	8 \pm 3.7	10 \pm 7.6	7.9 \pm 3.4	0.022
Charlson comorbidity index (mean \pm SD)	5.7 \pm 3	7.3 \pm 4.2	5.6 \pm 2.9	0.097
Location of the tumor				0.086
Right colon (n [%])	210 (51.2)	8 (30.8)	202 (52.6)	
Left colon (n [%])	96 (23.4)	11 (42.3)	85 (22.1)	
Rectum (n [%])	104 (25.4)	7 (26.9)	97 (25.3)	
Histological grade				0.454
Well-differentiated (n [%])	105 (25.6)	7 (26.9)	98 (25.5)	
Moderately differentiated (n [%])	210 (51.2)	13 (50)	197 (51.3)	
Poorly differentiated (n [%])	95 (23.2)	6 (23.1)	89 (23.2)	
TNM stage				0.267
Stage I (n [%])	66 (16.1)	5 (19.2)	61 (15.9)	
Stage II (n [%])	132 (32.2)	3 (11.5)	129 (33.6)	
Stage III (n [%])	144 (35.1)	13 (50)	131 (34.1)	
Stage IV (n [%])	68 (16.6)	5 (19.2)	63 (16.4)	
Metastasis (n [%])	73 (17.8)	8 (30.8)	65 (16.9)	0.078

Note: The relationship between variables and groups was determined by utilizing either Spearman's rho test or the Mann-Whitney U test; the TNM staging was determined using the TNM staging system of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC).

Abbreviations: AL+: Anastomosis leakage-positive; AL-: Anastomosis leakage-negative; SD: Standard deviation; APACHE II: Acute Physiologic Assessment And Chronic Health Evaluation II; TNM: Tumor, node, metastasis.

Table 2. Operative and post-operative variables and outcomes of patients ($n=410$) in the AL+ ($n=26$) and AL- ($n=384$) groups

Parameter	All patients	AL+	AL-	P
Surgical procedure				0.066
Right hemicolectomy (n [%])	200 (48.8)	8 (30.8)	192 (50)	
Left hemicolectomy (n [%])	80 (19.5)	7 (26.9)	73 (19)	
Total colectomy (n [%])	33 (8)	4 (15.4)	31 (8.1)	
Low anterior resection (n [%])	97 (23.7)	7 (26.9)	88 (22.9)	
Colostomy rate (n [%])	132 (32.2)	13 (50)	119 (31)	0.066
Duration of surgery (h) (mean \pm SD)	3.2 \pm 1.4	3.2 \pm 1.3	3.3 \pm 1.4	0.728
Reoperation rate (n [%])	22 (5.4)	12 (46.2)	10 (2.6)	<0.001
Mortality (n [%])	21 (5.19)	7 (26.9)	14 (3.6)	<0.001
Clavien-Dindo grade >2 (n [%])	48 (11.7)	26 (100)	22 (5.7)	<0.001
LOS in hospital (days) (mean \pm SD)	15 \pm 13	30 \pm 17.9	14 \pm 12	<0.001
LOS ICU (days) (mean \pm SD)	5.3 \pm 10.3	17.8 \pm 17.6	4.5 \pm 9	<0.001

Note: The relationship between variables and groups was determined by utilizing either Spearman's rho test or the Mann-Whitney U test.

Abbreviations: AL+: Anastomosis leakage-positive; AL-: Anastomosis leakage-negative; SD: Standard deviation; LOS: Length of stay; ICU: Intensive care unit.

values of the inflammatory markers of all patients, as well as the AL+ and AL- groups (Table 3). The pre-operative

levels of inflammatory markers (i.e., CRP, TNC, TLC, TWC, NLR, and PDW) were not significantly different

Table 3. Pre-operative and post-operative levels of inflammatory markers in the AL+ (n=26) and AL- (n=384) groups

Inflammatory marker	Condition	All patients	AL+o	AL-	P
CRP (mg/L)	Pre-operative	27.7±35	31.7±30	27.4±36.2	0.105
	Post-operative	117.4±80	176.1±100	113.4±77.2	0.001
	Difference	89.6±79	144.4±106	85.9±76.2	0.005
	Delta	1731±4621	2015.3±4803	1712±4615	0.438
TNC (×10 ⁹ /L)	Pre-operative	6.4±4	6.5±2.6	6.4±4.1	0.284
	Post-operative	7.6±4	10.1±5.8	7.5±3.8	0.008
	Difference	1.2±4.5	272.2±309	144.5±239.1	0.028
	Delta	46.5±105	77.6±113	44.4±104.6	0.124
TLC (×10 ⁹ /L)	Pre-operative	1.7±0.8	1.7±0.6	1.7±0.8	0.751
	Post-operative	1.2±1.3	0.9±0.5	1.3±1.4	0.037
	Difference	-0.5±1.4	-0.7±0.6	-0.4±1.4	0.073
	Delta	-21.2±75	-34.6±43.9	-20.3±77.2	0.028
PDW (%)	Pre-operative	17.7±14	17.9±8.1	17.8±14	0.088
	Post-operative	16.6±7	15.6±2.6	16.7±7.6	0.380
	Difference	-1.1±13	-2.2±7.8	-1±13.4	0.185
	Delta	-0.8±18	-0.5±22.4	-0.5±18.2	0.212
TWC (×10 ⁹ /L)	Pre-operative	9±4	9±2.5	8.9±4.1	0.279
	Post-operative	9.7±4.2	11.9±6.4	9.6±4	0.045
	Difference	0.7±4	2.9±7	0.6±4.4	0.219
	Delta	18.7±53	41.3±81.4	17.2±50.5	0.225
NLR	Pre-operative	4.9±5.5	5±4.9	4.9±5.6	0.655
	Post-operative	8.2±7.2	11.8±6.8	7.9±7.1	<0.001
	Difference	3.2±8.1	6.7±8.6	3±8	0.013
	Delta	152.6±245.7	272±309	144±239	0.028

Note: Data are presented as mean±SD; the relationship between variables and groups was determined by utilizing either Spearman's rho test or the Mann-Whitney U test.

Abbreviations: AL+: Anastomosis leakage-positive; AL-: Anastomosis leakage-negative; CRP: C-reactive protein; TNC: Total neutrophil count; TLC: Total lymphocyte count; PDW: Platelet distribution width; TWC: Total leucocyte count; NLR: Neutrophil-to-lymphocyte ratio; SD: Standard deviation.

between groups, while the post-operative levels of CRP, TNC, TLC, TWC, and NLR significantly differed between the groups ($P < 0.05$), particularly the post-operative level of NLR ($P < 0.001$). The (pre-operative vs. post-operative) differences in CRP, TNC, and NLR levels were significant between groups, whereas the (pre-operative vs. post-operative) differences in TWC, PDW, and TLC levels were not statistically significant between the groups. In addition, the delta NLR and TLC values differed significantly between the groups ($P < 0.05$).

We also compared the predictive power of the inflammatory markers for AL. In most of the studies, the absolute pre-operative or post-operative value was studied as prognostic markers instead of the difference in the values.^{6,8} Hence, we compared the pre-operative and post-operative levels of the inflammatory markers with ROC curves (Figure 2) and their corresponding AUCs

(Table 4). It was demonstrated that the predictive power of the difference in NLR levels was greater than that of the other inflammatory markers.

The AUC of the ROC curve (Figure 3) for the difference in NLR was 0.751 with a cutoff point of 7.62, sensitivity of 66.67, specificity of 78.51, significance of $P < 0.001$, and a satisfactory 95% confidence interval (CI) of 0.694 – 0.802 (Table 5).

We further evaluated the outcomes and AL (using You den's J index) based on the identified cutoff point of the NLR difference (i.e., 7.62) (Table 6). Only 71 patients (17.3%) had an NLR difference >7.62 . The post-operative outcomes were worse in the group with an NLR difference >7.62 than in the group with an NLR difference ≤ 7.62 . The mortality (14.1% vs. 3.5%) and reoperation rates (15.5% vs. 3.2%) were higher in the NLR difference > 7.62 group

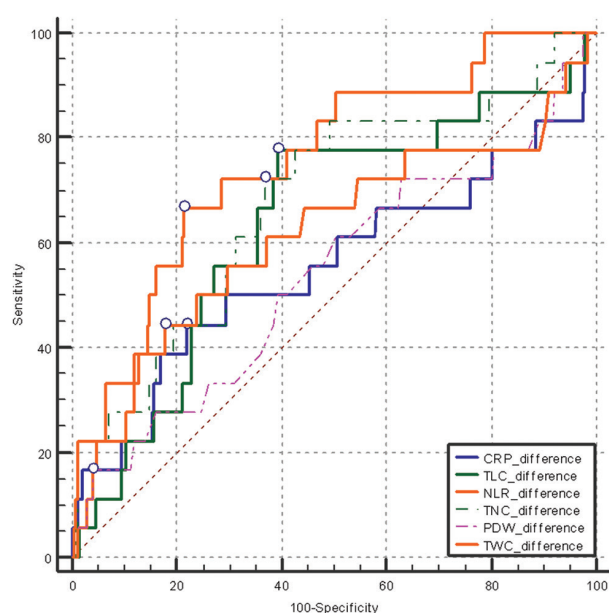


Figure 2. ROC curves of the different inflammatory marker levels between the AL+ and AL- groups.

Abbreviations: AL+: Anastomoses leakage-positive; AL-: Anastomoses leakage-negative; CRP: C-reactive protein; TNC: Total neutrophil count; TLC: Total lymphocyte count; PDW: Platelet distribution width; TWC: Total leucocyte count; NLR: Neutrophil-to-lymphocyte ratio; ROC: Receiver operating characteristic.

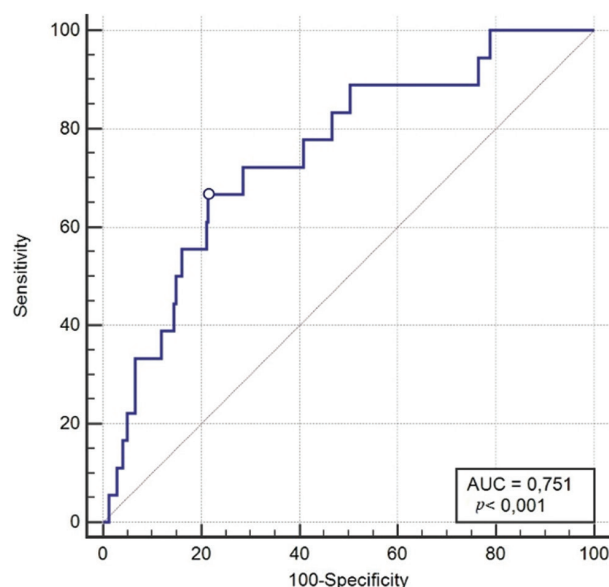


Figure 3. ROC curve of the different NLR levels between the AL+ and AL- groups.

Abbreviations: AL+: anastomoses leakage-positive; AL-: anastomoses leakage-negative; AUC: Area under the curve; NLR: Neutrophil-to-lymphocyte ratio; ROC: Receiver operating characteristic.

than in the NLR difference ≤ 7.62 . The other outcomes of the patients (e.g., AL, LOS in the hospital, LOS in the ICU,

Table 4. Difference in inflammatory marker levels between the AL+ and AL- groups

Inflammatory marker	AUC	SE	95% CI	PPV	NPV
CRP	0.553	0.0878	0.490 – 0.615	13.1	95
TLC	0.639	0.0721	0.577 – 0.698	12.8	97.4
NLR	0.751	0.0594	0.694 – 0.802	18.8	96.9
TNC	0.679	0.0712	0.619 – 0.736	12.7	96.8
PDW	0.538	0.0803	0.475 – 0.600	23.1	93.9
TWC	0.621	0.0849	0.559 – 0.680	15.7	95.2

Abbreviations: AL+: Anastomosis leakage-positive; AL-: Anastomosis leakage-negative; AUC: Area under the curve; CI: Confidence interval; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; NPV: Negative predictive value; PDW: Platelet distribution width; PPV: Positive predictive value; SE: Standard error; TLC: Total lymphocyte count; TNC: Total neutrophil count; TWC: Total leucocyte count.

Table 5. Difference in NLR between the AL+ and AL- groups

Parameter	Value
Area under the ROC curve	0.751
Standard error	0.0594
95% confidence interval	0.694 – 0.802
z-score	4.225
P	<0.0001
You den's J index	0.4518
Criterion	>7.62
Sensitivity	66.67
Specificity	78.51

Abbreviations: AL+: Anastomosis leakage-positive; AL-: Anastomosis leakage-negative; NLR: Neutrophil-to-lymphocyte ratio; ROC: Receiver operating characteristic.

and CD grade >2) also differed significantly between the groups ($P < 0.001$).

Similarly, the APACHE II score (9.6 vs. 7.7) and metastasis rate (26.8% vs. 15.9%) were higher in the NLR difference >7.62 group than in the NLR difference ≤ 7.62 group. The other pre-operative variables did not differ significantly between groups ($P > 0.05$). The AL, reoperation, and mortality rates differed significantly between the groups ($P < 0.001$). Patients with NLR difference >7.62 also stayed longer in the hospital and ICU.

4. Discussion

While surgery remains the main treatment option for colorectal cancer, the incidence of AL reportedly occurs in 1.5 – 23% of cases.¹³ Diagnosis of AL relies on clinical evaluation, but more accurate diagnosis is achieved through biochemical and radiological assessments, as non-specific symptoms may mask the occurrence

Table 6. Pre-operative and post-operative variables and outcomes of patients (n=410) based on the cutoff point of the NLR difference (i.e., 7.62)

Variables	All patients (n=410)	NLR difference >7.62 (n=71)	NLR difference ≤7.62 (n=339)	P
Age (years) (mean±standard deviation [SD])	61.1±13.04	63.3±13.7	60.6±12.8	0.095
Sex (male) (n [%])	279 (68)	55 (77.5)	224 (66.1)	0.062
Metastasis rate (n [%])	73 (17.8)	19 (26.8)	54 (15.9)	0.030
Poorly differentiated histology (n [%])	95 (23.2)	17 (23.9)	78 (23)	0.454
APACHE II (mean±SD)	8±3.7	9.6±5.5	7.7±3.2	0.013
Charlson comorbidity index (mean±SD)	5.7±3	6±3.2	5.6±2.9	0.442
Reoperation rate (n [%])	22 (5.4)	11 (15.5)	11 (3.2)	<0.001
Anastomotic leakage	26 (6.3)	12 (16.9)	14 (4.1)	<0.001
Clavien-Dindo grade>2 (n [%])	48 (11.7)	25 (35.2)	23 (6.8)	<0.001
LOS in hospital (days) (mean±SD)	15±13	21.2±21.8	13.8±10	<0.001
LOS ICU (days) (mean±SD)	5.3±10.3	8.5±15.6	4.6±8.6	<0.001
Mortality rate (n [%])	21 (5.1)	10 (14.1)	11 (3.2)	<0.001

Note: The relationship between variables and groups was determined by utilizing either Spearman's rho test or the Mann-Whitney U test.

Abbreviations: APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; NLR: Neutrophil-to-lymphocyte ratio; LOS: Length of stay; ICU: Intensive care unit.

of early-stage AL. Delayed diagnosis of AL affects the perioperative period, the post-operative period of surveillance, and the tumor recurrence rate.^{7,14,15} It was reported that delayed diagnosis could be reduced to 1.5 days after detecting the first symptom with standard paraclinical and clinical parameters. However, the reduction of delayed diagnostic time from 4 to 1.5 days did not affect the mortality rate.^{4,16}

Although the pathogenesis of AL is still not fully understood, local ischemia and/or inflammation are considered key factors in the pathogenesis of AL.¹⁷ Hence, we evaluated the potential role of systemic inflammatory markers as predictive factors of AL after colorectal cancer surgery. Notably, various medical centers have recommended different scores, indices, and laboratory parameters (e.g., albumin, lymphocytes, CRP, NLR, and platelet-related indicators) to detect AL earlier by assessing a patient's inflammatory status after colorectal surgery.^{3,6,8,14}

In a recent study, a microdialysis catheter was used to measure intraperitoneal lactate concentration and detect early-stage AL.⁴ Moreover, radiologic tests, such as psoas density measurements, were proposed as a predictor of AL after colorectal cancer surgery but were not considered for cost-effectiveness.¹⁸ Our retrospective study involved data on inflammatory markers that were readily available from the institutional database. These data were obtained from peripheral blood analytics in the pre-operative and the post-operative stages as a routine procedure, reinstating their validity and cost-effectiveness for predicting AL. Furthermore, inflammatory markers have been widely

discussed for their prognostic power of morbidity and mortality in cases of oncological surgery.^{8,19}

Bailon-Cuadrado *et al.* reported the rates of AL and reoperation as 7.4% and 6%, respectively,³ whereas this study reported the rates of AL and reoperation were slightly lower at 6.3% and 5.4%, respectively.^{8,13} The median time post-operation was identified as 10 days, which was similar to previous studies. Meanwhile, several studies have reported an AL-induced mortality rate of 6 – 22%, while this study reported a higher AL-induced mortality rate of 26.9%.²⁰

We evaluated the inflammatory marker scores and their predictive power of AL in this retrospective study as compared to previous studies that evaluated the relationship between inflammatory scores and AL morbidity in cancer patients.^{8,19} We utilized only the predictive power of the difference in inflammatory markers rather than the pre-operative, post-operative, and delta values because the pre-operative levels of the inflammatory markers were not significantly different between the AL+ and AL- groups. Moreover, we aimed to compare the predictive power of the changes in inflammatory marker status after surgery and before AL, rather than pre-operative inflammatory status.

Notably, the operation conditions of patients may affect the post-operative outcomes and their inflammatory status.^{3,17} The localization and stage of the tumor, comorbidities, type of surgery, and duration of the operation were evaluated in the first part of the study to validate the aforementioned claim.

The variables (e.g., Charlson comorbidity index, TNM stage, histopathological grade and location of the tumor, metastasis rate, surgery type, duration of surgery, and the colostomy rate) were assessed against NLR difference (strongest predictive power in this study), and the findings revealed no significant differences for these variables between the AL+ and AL- groups, except for metastasis rate which was higher in the NLR difference >7.62 group.

Josse *et al.*²¹ reported that NLR was related to morbidity but AL, discouraging the use of NLR as a predictive factor of AL. On the contrary, our study revealed that NLR difference had the highest predictive power for AL with an AUC of 0.751 (sensitivity = 66.67; specificity = 78.51). NLR was also reportedly implicated in the post-operative complications of major abdominal surgeries more than the other inflammatory markers, like CRP.²² Another study investigated the diagnostic power of CRP in the post-operative period to predict infectious complications after colon cancer surgery and concluded that CRP levels significantly differed between the groups.²³ The change in CRP values post-operation was reportedly due to infectious complications, including AL, and the AUC was the highest on post-operative day 5 (AUC= 0.657).²³ In our study, the AUC of the CRP difference was 0.553, which was lower than the AUC reported by Oberhofer *et al.*²³ Besides that, we only evaluated AL and not other infectious complications, such as wound infection, intra-abdominal collection, and abscesses. Lyu *et al.*²⁴ claimed that CRP level at post-operative day 3 had a better predictive power (AUC = 0.93) and concluded that CRP was effective in excluding AL rather than predicting AL occurrence.

Platelet-related indicators, such as PDW, were also used as inflammatory markers and prognostic indicators for colorectal cancer. Qian *et al.*²⁵ reported a decrease in PDW after curative surgery, while we observed this decline in both the AL+ and AL- groups. The consistent findings with previous studies encouraged us to utilize platelet-related indicators for colorectal surgery. In a recent study, a scoring system was developed to predict the risk of AL in rectal cancer patients. The scoring system assessed the patient's age, body mass index, albumin value, and anastomosis distance to the anal verge. The AUC of this system (AUC = 0.656)⁵ was smaller than the AUC of the NLR difference reported in the present study (AUC= 0.751).

Nonetheless, the present study had several limitations: (i) the retrospective nature of the study; (ii) the small sample size; and (iii) the single-center-based study. These limitations could have affected the reliability of our findings, warranting further validation in a multicenter prospective study with a larger population group. Notably, these factors were also considered limiting in previous studies.

5. Conclusion

The symptoms and signs of AL are typically manifested in its later stages, triggering inflammatory responses in the process. Hence, measuring the changes in the levels of inflammatory markers may detect AL before its full development. In our study, the AUC of the NLR difference was 0.751 (sensitivity = 66.67 and specificity = 78.51), which was sufficient to predict AL in the early stages. Hence, the findings of this study further established the clinical potential of inflammatory markers for the early detection of AL but should be validated and supported with additional prospective studies.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

As our study was retrospective and non-interventional, ethics committee approval was unnecessary. Therefore, additional informed consent beyond that obtained during admission was not required from patients. This study complies with the principles outlined in the Declaration of Helsinki (1975), as revised in 2008.

Consent for publication

Not applicable.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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