European Review for Medical and Pharmacological Sciences 2024; 28: 645-658

Early predictive factors and risk assessment for anastomotic leakage in patients undergoing low anterior resection for rectal cancer

H. OZGUL[1], U. DOGAN[1], R.C. CAKIR[1], Y. UZMAY[1], C.O. ENSARI[2], O. CELIK[1], T.T. KAPLAN[1], A. ASLANER[1]

[1]Department of General Surgery, Antalya Education and Research Hospital, University of Health Sciences, Antalya, Turkey
[2]Department of Gastroenterology Surgery, Antalya Education and Research Hospital, University of Health Sciences, Antalya, Turkey

Abstract. – OBJECTIVE: Anastomotic leakage is a complication that creates significant concern in terms of postoperative morbidity and mortality after colorectal surgery. This study aimed to identify variables for detecting anastomotic leakage in those who had open, laparoscopic, or robotic low anterior resection for cancer and to explore their relationships.

PATIENTS AND METHODS: A total of 283 patients who were diagnosed with rectal cancer and underwent low anterior resection were divided into two groups: those with and without anastomotic leakage. Demographic and clinical data were analyzed. Anastomotic leakage was detected in 23 of 283 patients who underwent low anterior resection.

RESULTS: The postoperative analysis of the biochemical data of the patients showed statistically significant differences between the two groups in terms of C-reactive protein (Crp), albumin, lymphocytes, leukocytes, neutrophils, and their ratio. The performance of these parameters in predicting anastomotic leakage was statistically analyzed in the patient group with anastomotic leakage, and nomogram results were acquired. Immune system components and biomarkers were statistically tested, and nomogram results were obtained in rectal cancer patients.

CONCLUSIONS: These parameters can be used together as a potential marker in anastomotic leakage. Further development of these variables has the potential to facilitate the timely detection and treatment of anastomotic leakage.

Key Words:
Rectal cancer, Anastomotic leakage, Low anterior resection.

Introduction

Rectal cancer is the eighth most common type of cancer across the world and the ninth most common cause of cancer-related mortality[1]. The rectum is a visceral organ located at the most posterior part of the pelvic cavity and exhibits sexual dimorphism. It originates at the level of S3, continuing from the sigmoid colon and extending to the sacral promontory, with a measured distance of 12 to 15 cm to the dentate line in the anal canal. Primarily serving as a transient reservoir for fecal storage, the rectum plays a crucial role in controlling defecation and maintaining continuity in the process[2-4].

Rectal resection can be performed for several indications, including benign and malignant tumors, inflammatory bowel disorders, vascular conditions, and trauma-related injuries. Low anterior resection is the removal of the rectum by an abdominal approach using an open, laparoscopic, or robotic technique. The treatment of rectal cancer encompasses chemotherapy, radiotherapy, and surgical intervention. The standard surgical treatment for rectal cancer involves total mesorectal excision and resection, ensuring negative surgical margins. At least 12 lymph nodes should be removed for adequate staging and treatment planning. Anastomotic leakage (AL) is an important complication that leads to increased morbidity and mortality after colorectal surgery, with reported incidence rates ranging from 2% to 19%. In the postoperative period, patients may encounter significant problems due to AL, such as the need for secondary surgical intervention and stoma formation[5-8].

Blood analyses of various biomarkers have been evaluated[9,10] for the early detection of AL, but they have not yet been integrated into routine clinical practice. Serum C-reactive protein (CRP) and albumin values have been used to demon-

Corresponding Author: Halit Ozgul, MD; e-mail: halit.ozgul1@saglik.gov.tr

strate that the inflammatory response may be associated with poor postoperative outcomes in patients undergoing surgery for cancer[11]. It has been proven that the CRP/albumin ratio (CAR) determines the prognosis of colorectal cancer[12]. Recent studies[13] have reported that several systemic inflammation biomarkers, such as the neutrophil/lymphocyte ratio (NLR), CAR, and the platelet/lymphocyte ratio, are prognostic markers in various malignant tumors, including colorectal cancer. Lymphocyte count is considered a prognostic marker in many malignancies[14,15].

After surgery, neuroendocrine and inflammatory responses occur. Once the hypothalamus-pituitary-adrenal system is activated, the release of counter-regulatory hormones increases. These hormonal changes affect glucose and potassium metabolisms. Considering the increased stress response in patients with AL, stress hyperglycemia can occur. Extracellular potassium levels decrease due to the increased release of the counter-regulatory hormone under stress conditions[16].

In recent years, nomograms have gained significant popularity as a prognostic tool in the field of oncology[17,18]. Nomogram studies[19,20] fulfill the criteria of an integrated framework and are employed for prognostic prediction.

This study aimed to assess the reliability of biochemical indicators in predicting AL in patients who underwent low anterior resection for rectal cancer by performing statistical analyses and developing a nomogram based on these parameters.

Patients and Methods

This study retrospectively included 283 patients who underwent low anterior resection with a diagnosis of rectal cancer at the Health Sciences University Antalya Training and Research Hospital between January 1, 2019, and January 1, 2023. Approval was obtained from the Clinical Research Ethics Committee of the hospital (date: April 13, 2023, protocol number: 5/18), and the study adhered to the tenets of the Declaration of Helsinki. Patients older than 18 years of age who had histopathologically proven rectal adenocarcinoma and underwent curative surgery with tumor-free resection margins were selected for the sample. Low anterior resection of the rectum was performed with an open, laparoscopic, or robotic approach in patients with a diagnosis of rectal cancer. The tumor was resected completely, along with the lymph nodes. Patients who developed AL on postoperative days 6 to 10 were included in the AL group. The diagnosis of AL was established based on clinical and radiological findings, including the detection of air or abscess in the vicinity of the anastomosis site on computed tomography (CT), the observation of purulent or enteric discharge from the drainage tube, clinical signs of peritonitis, and purulent or fecal discharge during secondary explorative surgery. Patients were excluded who underwent palliative or emergency surgery, those with a history of additional malignancies, and those who died due to non-surgical problems associated with comorbidities (pneumonia, acute pulmonary embolism, and acute coronary syndrome) during their postoperative stay in the intensive care unit. All demographic and clinical data, including gender, age, comorbidities, neoadjuvant chemotherapy, surgical procedure, duration of surgery, pathological data, and postoperative outcomes, were retrospectively obtained from the hospital database, patient files, nurse forms, and patients' medical records. The patients were divided into two groups: those with and without AL. The effects of surgical technique, neoadjuvant chemotherapy, presence of comorbidities, type of anastomosis, duration of surgery, body mass index, prognostic nutritional index, postoperative pathological data, and laboratory findings obtained on postoperative days 1, 3, and 5 were assessed with regard to the development of AL.

Statistical Analysis

Descriptive statistics were presented with frequency, percentage, mean, standard deviation, median, interquartile range, minimum, and maximum values. In the analysis of categorical data, Fisher's exact test was used if the percentage of cells with an expected value lower than 5 was greater than 20%, and the Pearson Chi-square test was used otherwise. The assumption of normality was checked with the Shapiro-Wilk test. In the analysis of the difference between the numerical data of the two groups, the independent samples *t*-test was employed when the data conformed to the normal distribution and the Mann-Whitney U-test otherwise. Since the numerical data did not show a normal distribution in the analysis of time-dependent repeated measurements, the Friedman S test was conducted separately for the groups with and without AL.

The Mann-Whitney U test was performed to compare the time-dependent measurements of patients with and without AL.

To create a nomogram, the performance of CRP, albumin, CAR, glucose, potassium, glucose/potassium ratio, lymphocyte count, platelet count, leukocyte count, CRP/lymphocyte ratio (CLR), lymphocyte/leukocyte ratio, platelet/leukocyte ratio, neutrophil count, and neutrophil/leukocyte ratio in the prediction of AL development was evaluated using receiver operating characteristic (ROC) analysis. As a result of this analysis, the cut-off and selectivity values of these parameters were obtained. Youden's index was used to determine the cut-off values. The nomogram was created using these cut-off and selectivity values. In cases where the "lower than or equal to" symbol was used, values were denoted to the left due to the inverse relationship between increasing values and decreasing selectivity on a scale of 0 to 100. Statistical analyses were undertaken using the Statistical Package for Social Sciences (SPSS), version 23.0 (IBM Corp., Armonk, NY, USA). A *p*-value <0.05 was considered statistically significant.

Results

In this study, the disease and treatment data of 283 patients were analyzed during their treatment process. The mean age of the patients was 64.75 ± 10.62 years. Of the patients, 30.7% were female, and 69.3% were male. Surgical technique was open in 50.9% of the patients, laparoscopic in 29.7%, and robotic in 19.4%. AL occurred in 8.1% of the patients, and stoma formation in 41.7%. About a quarter of the patients (25.1%) had received neoadjuvant chemotherapy. The type of anastomosis was side-to-end in 15.2% of the patients and end-to-end in 84.8%. As comorbidities, diabetes mellitus was observed at a rate of 39.6% and hypertension at 26.9%. The postoperative pathological grade was 0 (complete response after neoadjuvant chemotherapy) in 1.1% of the cases, 1 in 32.5%, 2 in 37.1%, and 3 in 29.3%. According to tumor biology, 95.8% of cases were adenocarcinomas, and 4.2% were mucinous adenocarcinomas. Tumors were poorly differentiated in 2.5% of the cases, moderately differentiated in 75.6%, and well-differentiated in 21.9%. The tumor stage was T0 in 1.1% of the patients (complete response after neoadjuvant chemotherapy), T1 in 6%, T2 in 30%, T3 in 55.1%, and T4 in 7.8%. The lymph node stage was N0 in 73.9% of the patients, N1 in 19.4%, N2 in 6.4%, and N3 in 0.4% (Table I).

Age, length of stay in the intensive care unit, length of stay in the inpatient ward, duration of surgery, the number of dissected lymph nodes, and preoperative albumin and hemoglobin values were compared between the patients with

Table I. Demographic, surgical, and pathological data of the patients.

	N	%
Gender		
Female	87	30.7
Male	196	69.3
Surgical technique		
Open	144	50.9
Laparoscopic	84	29.7
Robotic	55	19.4
Anastomotic leakage		
Absent	260	91.9
Present	23	8.1
Stoma		
Absent	165	58.3
Present	118	41.7
Neoadjuvant chemotherapy		
Present	71	25.1
Absent	212	74.9
Type of anastomosis		
Side-to-end	43	15.2
End-to-end	240	84.8
Diabetes mellitus		
Absent	171	60.4
Present	112	39.6
Hypertension		
Absent	207	73.1
Present	76	26.9
Pathological grade		
0	3	1.1
1	92	32.5
2	105	37.1
3	83	29.3
Tumor differentiation		
Poorly differentiated	7	2.5
Moderately differentiated	214	75.6
Well differentiated	62	21.9
Type of cancer		
Adenocarcinoma	271	95.8
Mucinous adenocarcinoma	12	4.2
T stage		
0	3	1.1
1	17	6
2	85	30
3	156	55.1
4	22	7.8
N stage		
0	209	73.9
1	55	19.4
2	18	6.4
3	1	0.4

and without AL. There was a statistically significant difference between the two groups in terms of the length of intensive care unit and ward stays ($p < 0.0001$ for both). These durations were longer in the group with AL than in the group without AL, associated with the treatment and management processes of the patients in the AL group. There was no statistically significant difference between the two groups in relation to the duration of surgery, the number of dissected lymph nodes, preoperative albumin, or hemoglobin values (Table II).

The prognostic nutritional index (PNI) score was calculated as 10 x (serum Albumin g/dL) + 0.005 x total lymphocyte count (per mm^3) before the operation. PNI was an average of 46.5 ± 6.36 in the non-AL group and 44.4 ± 6.86 in the AL group, with no statistically significant difference found according to the independent *t*-test ($p > 0.05$).

There was no significant difference between the patient groups with and without AL in terms of gender, surgical technique, the presence of stoma, neoadjuvant chemotherapy, the type of anastomosis, comorbidities, tumor grade, T- and N-stages in the pathology specimen, or tumor biology or differentiation (Table III).

The body mass index (BMI) was calculated as an average of 26.3 ± 4.43 in the non-AL group and 26.68 ± 4.39 in the AL group, with no statistically significant difference found according to the Mann-Whitney U test ($p > 0.05$).

The CRP, albumin, and CAR values after surgery were examined for patients with and without AL. Since the variables did not show a normal distribution, the Friedman S test was performed separately for each group. In the group without AL, there was a statistically significant difference between the CRP measurements performed on postoperative days 1, 3, and 5 ($p < 0.0001$). The CRP value measured on day 3 increased compared to day 1, while a decrease was observed on day 5. In the AL group, there was also a statistically significant difference between the time-dependent measurements of the CRP values ($p < 0.001$). A statistically significant difference was found between the CRP measurements performed on postoperative day 1 when compared to postoperative days 3 and 5. However, no statistically significant difference was found between the third- and fifth-day CRP values. The elevation in the CRP value indicated continuity, and in contrast to the group without AL, the expected decrease was not seen in the

Table II. Comparison of age, length of hospital stay, duration of surgery, number of lymph nodes dissected, and preoperative hemoglobin and albumin values between the study groups.

	N	Mean ± SD (min-max)	Median (Q1-Q3)	*p*
Age (year)				
Non-AL	260	65.02 ± 10.52 (31-90)	66 (59-71)	0.167[1]
AL	23	61.83 ± 11.5 (40-78)	62 (52-73)	
Intensive care stay (day)				
Non-AL	260	0.95 ± 1.84 (0-24)	1 (0-1)	< 0.0001[2]
AL	23	5.26 ± 12.29 (0-60)	2 (1-5)	
Ward stay (day)				
Non-AL	260	6.13 ± 2.76 (0-19)	5 (5-7)	< 0.0001[2]
AL	23	16.61 ± 9.19 (1-40)	14 (12-22)	
Duration of surgery (minute)				
Non-AL	260	230.23 ± 63.36 (130-390)	210 (180-270)	0.449[2]
AL	23	219.13 ± 60.97 (160-370)	190 (180-260)	
Number of dissected lymph nodes				
Non-AL	260	17.47 ± 6.68 (10-61)	16 (13-19)	0.771[2]
AL	23	17.91 ± 6.68 (10-36)	17 (13-20)	
Preoperative albumin (g/dL)				
Non-AL	260	3.79 ± 0.47 (2-5.1)	3.8 (3.5-4.1)	0.142[1]
AL	23	3.64 ± 0.49 (2.8-4.5)	3.7 (3.2-3.9)	
Preoperative hemoglobin (g/dL)				
Non-AL	260	12.4 ± 2.03 (7.2-17.9)	12.45 (10.95-13.85)	0.437[1]
AL	23	12.05 ± 2.45 (7.2-16.8)	12.6 (10-13.8)	

[1]Independent-samples *t*-test, [2]Mann-Whitney U test. AL: patient group with anastomotic leakage, non-AL: patient group without anastomotic leakage.

Table III. Comparison of parameters* between the study groups.

	Group			
	Non-AL *n* (%)	AL *n* (%)	Total *n* (%)	*p*
Gender				
Female	84 (32.3)	3 (13)	87 (30.7)	0.055[1]
Male	176 (67.7)	20 (87)	196 (69.3)	
Total	260 (100)	23 (100)	283 (100)	
Surgical technique				
Open	131 (50.4)	13 (56.5)	144 (50.9)	0.852[1]
Laparoscopic	78 (30)	6 (26.1)	84 (29.7)	
Robotic	51 (19.6)	4 (17.4)	55 (19.4)	
Total	260 (100)	23 (100)	283 (100)	
Stoma				
Absent	148 (56.9)	17 (73.9)	165 (583)	0.113[1]
Present	112 (43.1)	6 (26.1)	118 (41.7)	
Total	260 (100)	23 (100)	283 (100)	
Neoadjuvant chemotherapy				
Present	67 (25.8)	4 (17.4)	71 (25.1)	0.374[1]
Absent	193 (74.2)	19 (82.6)	212 (74.9)	
Total	260 (100)	23 (100)	283 (100)	
Type of anastomosis				
Side-to-end	40 (15.4)	3 (13)	43 (15.2)	0.99[2]
End-to-end	220 (84.6)	20 (87)	240 (84.8)	
Total	260 (100)	23 (100)	283 (100)	
Diabetes mellitus				
Absent	159 (61.2)	12 (52.2)	171 (60.4)	0.399[1]
Present	101 (38.8)	11 (47.8)	112 (39.6)	
Total	260 (100)	23 (100)	283 (100)	
Hypertension				
Absent	192 (73.8)	15 (65.2)	207 (73.1)	0.371[1]
Present	68 (26.2)	8 (34.8)	76 (26.9)	
Total	260 (100)	23 (100)	283 (100)	
Pathological grade				
0	4 (1.5)	0 (0)	4 (1.4)	0.854[2]
1	85 (32.7)	6 (26.1)	91 (32.2)	
2	95 (36.5)	10 (43.5)	105 (37.1)	
3	76 (29.2)	7 (30.4)	83 (29.3)	
Total	260 (100)	23 (100)	283 (100)	
Tumor differentiation				
Poorly differentiated	7 (2.7)	0 (0)	7 (2.5)	0.602[1]
Moderately differentiated	195 (75)	19 (82.6)	214 (75.6)	
Well differentiated	58 (22.3)	4 (17.4)	62 (21.9)	
Total	260 (100)	23 (100)	283 (100)	
Type of cancer				
Adenocarcinoma	249 (95.8)	22 (95.7)	271 (95.8)	0.99[2]
Mucinous adenocarcinoma	11 (4.2)	1 (4.3)	12 (4.2)	
Total	260 (100)	23 (100)	283 (100)	
T stage				
0	3 (1.2)	0 (0)	3 (1.1)	0.99[2]
1	17 (6.5)	0 (0)	17 (6)	
2	78 (30)	7 (30.4)	85 (30)	
3	142 (54.6)	14 (60.9)	156 (55.1)	
4	20 (7.7)	2 (8.7)	22 (7.8)	
Total	260 (100)	23 (100)	283 (100)	

[1]Chi-square test, [2]Fisher's exact test. Parameters: gender, surgical technique, the presence of stoma, a history of neoadjuvant chemotherapy, the type of anastomosis, comorbidities, tumor grade, T stages in the pathology specimen, and tumor biology and differentiation. AL: patient group with anastomotic leakage, non-AL: patient group without anastomotic leakage.

AL group. When the changes in albumin measurements performed on postoperative days 1, 3, and 5 were evaluated in the group without AL, a statistically significant difference was observed between day 1 and other days ($p = 0.009$). The albumin value decreased on postoperative day 3 compared to day 1 and then increased on day 5. There was also a statistically significant difference between the time-dependent albumin values of the AL group. While there was a statistically significant difference between postoperative day 1 and postoperative days 3 and 5, no statistically significant difference was observed between postoperative day 3 and postoperative day 5. Statistically significant differences were also observed in the CAR measurements of both groups ($p < 0.0001$ for both). In patients without AL, the CAR value on postoperative day 3 showed a statistically significant increase compared to day 1, while the fifth-day value decreased compared to the third day. In the patient group with AL, the CAR value measured on postoperative day 3 increased compared to day 1, while the fifth-day value statistically significantly decreased compared to the third-day value (Table IV).

The changes in the CRP, albumin, and CAR values from postoperative days 1 and 3 to postoperative day 5 were compared between patients with and without AL. The patients without AL had a significantly higher change in the CRP value from postoperative day 3 to postoperative day 5 compared to those with AL ($p = 0.046$). The comparison of the changes in the albumin value from postoperative day 1 to postoperative day 5 revealed a statistically significantly higher value in patients without AL compared to those with AL ($p = 0.029$). However, the changes in the CAR value did not statistically significantly differ between the two groups (Table V).

The changes in the glucose, potassium, and glucose/potassium values from postoperative days 1 and 3 to postoperative day 5 did not statistically significantly differ between the patients with and without AL.

The changes in the lymphocyte measurements from postoperative days 1 and 3 to postoperative day 5 were statistically significantly higher in patients without AL compared to those with AL ($p = 0.019$ and $p = 0.035$, respectively). Statistically significantly higher changes were observed in the patients with AL compared to those without AL in terms of the difference between the third- and fifth-day leukocyte measurements ($p = 0.034$) and the difference between the first- and fifth-day CLR values ($p = 0.015$). The analysis of the changes in lymphocyte/leukocyte values from postoperative days 1 and 3 to postoperative day 5 showed statistically significant differences between the two groups, with significantly higher changes observed in patients without AL ($p = 0.001$ and $p < 0.0001$, respectively) (Table VI).

The changes in neutrophil count from postoperative days 1 and 3 to postoperative day 5 statistically significantly differed between patients with and without AL, being significantly higher in the latter ($p = 0.043$ and $p = 0.006$, respectively). Similarly, the changes in the neutrophil/leukocyte value from postoperative days 1 and 3 to postoperative day 5 were statistically significantly higher in the patients without AL compared to those with AL ($p = 0.008$ and $p = 0.006$, respectively) (Table VII).

The ROC analysis was used to evaluate the performance of biochemical parameters measured on postoperative day 3 in predicting AL development with reference to patients without AL. According to the results of this analysis, the selectivity value was determined to be 53.5% for CRP at a cut-off value of >206.1, 45.8% for albumin at ≤2.9, 83.8% for CAR >98.88, 96.9% for glucose at >184, 86.2% for potassium ≤3.3, 55% for glucose/potassium at >29.51, 51.2% for lymphocyte count at ≤0.98, 77.3% for platelet count ≤162, 66.5% for leukocyte count at ≤8.1, 68.1% for CRP/lymphocyte ratio (CLR) >279.10, 48.5% for lymphocyte/leukocyte at ≤0.10, 54.6% for platelet/leukocyte ≤19.6, 85% for neutrophil count >12.85, and 48.5% for neutrophil/leukocyte count >8.79 (Figure 1).

The performance of biochemical parameters measured on postoperative day 5 in predicting AL development with reference to patients without AL was assessed using the ROC analysis. According to the results, the selectivity value was calculated to be 97.3% for CRP at a cut-off value >271.1, 80.4% for albumin ≤2.7, 96.9% for CAR >87.79, 59.6% for glucose >113, 58.46% for potassium ≤3.6, 36.9% for glucose/potassium >26.15, 55.4% for lymphocyte count ≤1.02, 72.3% for platelet count ≤196, 91.2% for leukocyte count >11.3, 88.1% for CLR >291.02, 71.5% for lymphocyte/leukocyte ≤0.106, 73.8% for platelet/leukocyte ≤24.14, 33.8% for neutrophil count >5.46, and 73.8% for neutrophil/leukocyte >8.41 (Figure 2).

Table IV. Postoperative CRP, albumin, and CAR values of the study groups.

	Group							
	Non-AL				AL			
	Mean ± SD (min-max)	Median (Q1-Q3)	*p*	Variable*	Mean ± SD (min-max)	Median (Q1-Q3)	*p*	Variable*
CRP (mg/L) Postop day 1	44.04 ± 35.31 (0.4-202.9)	40 (17.95-58.9)	< 0.0001	c	70.81 ± 82.16 (12-337)	39.2 (26-84.9)	< 0.0001	b
CRP Postop day 3	208.54 ± 74.52 (30-477)	203 (161.65-251.15)		a	254.46 ± 81.67 (93.5-425)	241 (209-305)		a
CRP Postop day 5	120.92 ± 65.77 (6.5-402)	112.85 (71.1-157.5)		b	209.47 ± 128.8 (57.4-465.8)	173.7 (92.5-341)		a
Alb (g/dL) Postop day 1	3.2 ± 0.47 (1.67-4.8)	3.2 (2.9-3.5)	< 0.0001	b	3.22 ± 0.39 (2.2-3.9)	3.28 (3.07-3.5)	0.009	a
Alb Postop day 3	2.89 ± 0.34 (1.8-4.1)	2.9 (2.69-3.1)		c	2.82 ± 0.4 (2.3-4)	2.87 (2.46-3.1)		b
Alb Postop day 5	7.25 ± 9.66 (1.9-37)	3.01 (2.8-3.4)		a	6.5 ± 8.56 (1.94-29.2)	2.8 (2.57-3.1)		b
CAR Postop day 1	14.62 ± 13.04 (0.14-77)	12.07 (5.59-19.09)	< 0.0001	c	23.07 ± 27.82 (3.21-108.71)	12.42 (7.88-23.58)	< 0.0001	a
CAR Postop day 3	73.62 ± 29.62 (9.38-182.42)	68.72 (52.72-90.08)		a	93.06 ± 36.4 (32.58-175.22)	85.56 (66.77-122.07)		b
CAR Postop day 5	35.84 ± 26.32 (0.63-151.74)	33.45 (15.71-52.16)		b	64.26 ± 53.58 (5.95-185.52)	38.45 (24.52-98.93)		c

Friedman S test. *Different letters in each column and the corresponding row indicate a statistically significant difference. SD: standard deviation, AL: patient group with anastomotic leakage, non-AL: patient group without anastomotic leakage, CRP: C-reactive protein, Postop: postoperative, Alb: albumin, CAR: C-reactive protein/albumin ratio.

Table V. Comparison of time-dependent changes in CRP, albumin, and CAR measurements between the study groups.

	AL (n = 260)		Non-AL (n = 23)		
	Mean ± SD (min-max)	Median (Q1-Q3)	Mean ± SD (min-max)	Median (Q1-Q3)	*p*
CRP, postop day 5-day 1 dif	76.89 ± 74.93 (-124-354.8)	69.7 (30.55-122.95)	138.66 ± 142.32 (-155.5-400.7)	80.5 (40.2-242)	0.066
CRP, postop day 5-day 3 dif	-87.61 ± 69.78 (-261.6-191)	-82.9 [-128.95- (-48.5)]	-44.99 ± 111.76 (-238.8-239.5)	-42 (-114.6-27.7)	0.046
Alb, postop day 5-day 3 dif	4.36 ± 9.67 (-0.8-34)	0.1 (-0.1-0.5)	3.67 ± 8.51 (-0.7-26.32)	0 (-0.21-0.4)	0.151
Alb, postop day 5-day 1 dif	4.05 ± 9.69 (-1.9-33.8)	-0.2 (-0.49-0.3)	3.27 ± 8.52 (-1.2-26.13)	-0.5 (-0.6-0.1)	0.029
CAR, postop day 5-day 3 dif	-37.78 ± 31.45 (-172.66-63.59)	-33.04 [-55.75- (-18.01)]	-28.79 ± 44.57 (-114.37-48.81)	-32.51 [-51.31- (-6.23)]	0.452
CAR, postop day 5-day 1 dif	21.22 ± 29.46 (-57.93-150.7)	19.31 (0.01-39.3)	41.19 ± 57.08 (-56.91-171.21)	20.32 (1.96-86.51)	0.246

Mann-Whitney U test. AL: patient group with anastomotic leakage, non-AL: patient group without anastomotic leakage, SD: standard deviation, CRP: C-reactive protein, Postop: postoperative, dif: difference, Alb: albumin, CAR: C-reactive protein/albumin ratio.

Discussion

The surgical treatment of rectal tumors is primarily based on the premise of achieving total excision of the tumor, along with the removal of the lymphatic bed and any nearby organs that may be involved. The occurrence of AL in rectal surgery carries significant implications for patients, their families, and society as a whole. The primary consequences that can be identified include recurrent surgical procedures during the initial phase as a result of complications such as

Table VI. Comparison of time-dependent changes in lymphocyte, platelet, leukocyte, CLR, and lymphocyte/leukocyte values between the study groups.

	AL (n = 260)		Non-AL (n = 23)		
	Mean ± SD (min-max)	Median (Q1-Q3)	Mean ± SD (min-max)	Median (Q1-Q3)	*p*
Lymphocyte count (10^3/mm^3)	0.09 ± 0.43	0.07	-0.05 ± 0.31	-0.11	0.035
Postop day 5-day 3 dif	(-1.51-2.43)	(-0.1-0.27)	(-0.46-0.78)	(-0.25-0.14)	
Lymphocyte count (10^3/mm^3)	0.39 ± 0.64	0.34	0.17 ± 0.49	0.06	0.019
Postop day 5-day 1 dif	(-2.12-2.95)	(0.09-0.73)	(-0.47-1.34)	(-0.17-0.37)	
Platelet count (10^3/mm^3)	26.78 ± 46.89	25	46.74 ± 65.06	53	0.11
Postop day 5-day 3 dif	(-135-292)	(1-51.5)	(-99-203)	(8-76)	
Platelet count	2.45 ± 60.78	6.5	15.48 ± 91.49	32	0.352
Postop day 5-day 1 dif	(-313-278)	(-31-36.5)	(-190-224)	(-64-59)	
Leukocyte count (10^3/mm^3)	-2.35 ± 2.58	-1.9	-0.61 ± 2.72	-1.5	0.034
Postop day 5-day 3 dif	(-12.9-3.9)	(-3.6--0.7)	(-3.8-5.7)	(-2.5-0.7)	
Leukocyte count (10^3/mm^3)	-2.9 ± 3.78	-2.7	-1.32 ± 3.67	-1.7	
Postop day 5-day 1 dif	(-16.9-8.6)	[-4.85- (-0.8)]	(-7.6-9.9)	(-3-0.2)	0.089
CLR	-122.87 ± 206.99	-80.01	-4.18 ± 345.15	-63.81	0.095
Postop day 5-day 3 dif	(-2238.38-802.63)	[-155.07- (-36.08)]	(-601.16-1223.41)	(-160.29-122.66)	0.015
CLR	65.51 ± 171.89	40.24	250.69 ± 426.1	153.87	
Postop day 5-day 1 dif	(-866.99-1420.87)	(-14.98-118.96)	(-150.46-1952.36)	(16.96-315.71)	
Lymphocyte/leukocyte ratio	0.04 ± 0.05	0.04	0.01 ± 0.04	0	< 0.0001
Postop day 5-day 3 dif	(-0.1-0.3)	(0.01-0.07)	(-0.12-0.12)	(-0.02-0.03)	0.001
Lymphocyte/leukocyte ratio	0.07 ± 0.08	0.07	0.03 ± 0.06	0.01	
Postop day 5-day 1 dif	(-0.22-0.36)	(0.03-0.12)	(-0.07-0.14)	(-0.02-0.06)	

Mann-Whitney U test. AL: patient group with anastomotic leakage, non-AL: patient group without anastomotic leakage, SD: standard deviation, dif: difference, CLR: CRP/lymphocyte ratio.

Table VII. Comparison of time-dependent changes in neutrophil, neutrophil/leukocyte, and platelet/lymphocyte values between the study groups.

	AL (n = 260)		Non-AL (n = 23)		
	Mean ± SD (min-max)	Median (Q1-Q3)	Mean ± SD (min-max)	Median (Q1-Q3)	p
Neutrophil count (10^3/mm^3) Postop day 5-day 3 dif	-3.49 ± 5.98 (-68.62-10.17)	-2.66 (-4.75- (-0.8))	0.23 ± 6 (-9.87-16.53)	-0.65 (-3.83-3.94)	0.006
Neutrophil count (10^3/mm^3) Postop day 5-day 1 dif	-3.25 ± 3.82 (-17.97-8.71)	-3.17 [-5.58- (-1.02)]	-1.48 ± 3.7 (-7.21-9.65)	-1.96 [-3.5- (-0.35)]	0.043
Neutrophil/leukocyte ratio Postop day 5-day 3 dif	-3.49 ± 5.98 (-68.62-10.17)	-2.66 [-4.75- (-0.8)]	0.23 ± 6 (-9.87-16.53)	-0.65 (-3.83-3.94)	0.006
Neutrophil/leukocyte ratio Postop day 5-day 1 dif	-11.09 ± 12.57 (-109.14-11.65)	-8.65 [-16.23- (-3.3)]	-5.39 ± 12.13 (-42.7-9.75)	-0.84 (-14.32-4.68)	0.008
Platelet/leukocyte ratio Postop day 5-day 1 dif	8.36 ± 15.59 (-112.92-94.35)	8.3 (1.85-15.54)	4.43 ± 14.67 (-26.36-46.61)	6.86 (-2.21-11.27)	0.132
Platelet/leukocyte ratio Postop day 5-day 3 dif	10.62 ± 11.07 (-19.86-88.97)	8.9 (4.55-14.71)	6.68 ± 9.37 (-24.62-30.77)	6.63 (4.14-10.18)	0.092

Mann-Whitney U test. AL: patient group with anastomotic leakage, non-AL: patient group without anastomotic leakage, SD: standard deviation, dif: difference.

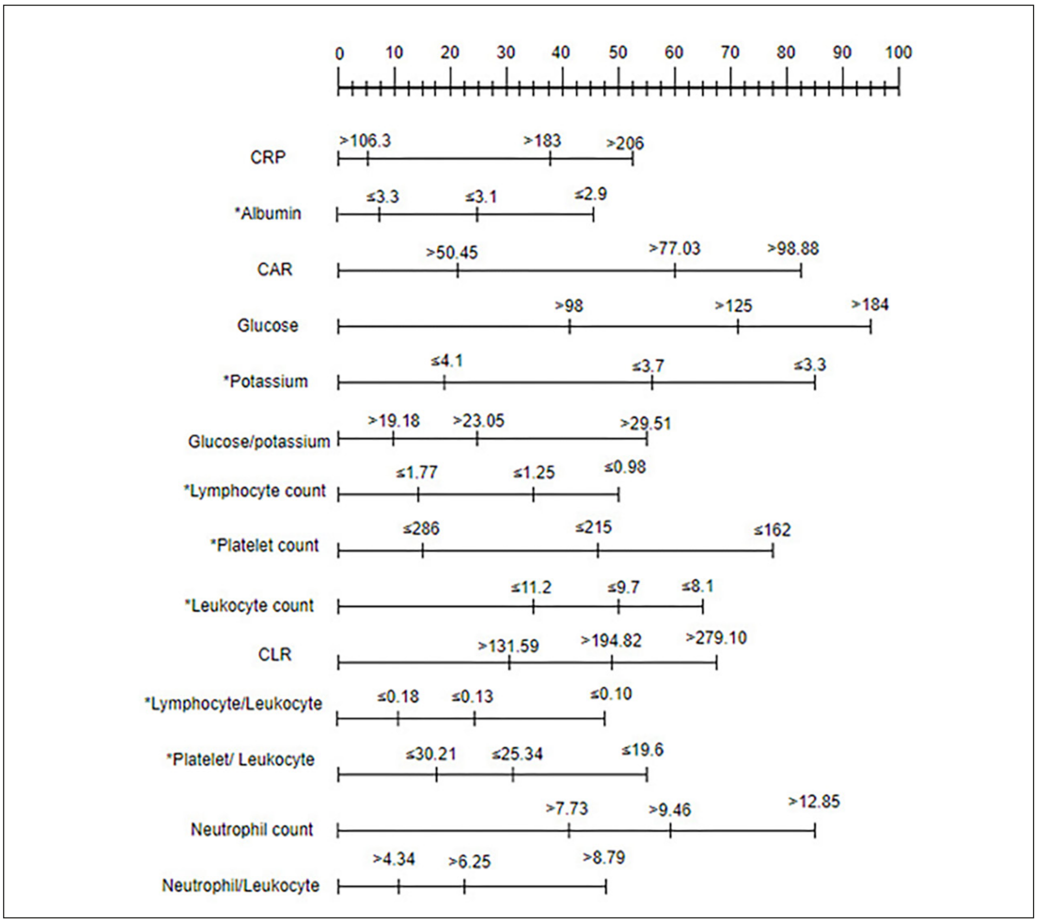

Figure 1. Nomogram created using the postoperative third-day measurements of parameters. In cases where the less than or equal to (≤) symbol is used, values are denoted to the left due to the inverse relationship between increasing values and decreasing selectivity on a scale of 0 to 100. CRP: C- reactive protein CLR: CRP/lymphocyte ratio CAR: C-reactive protein/albumin ratio.

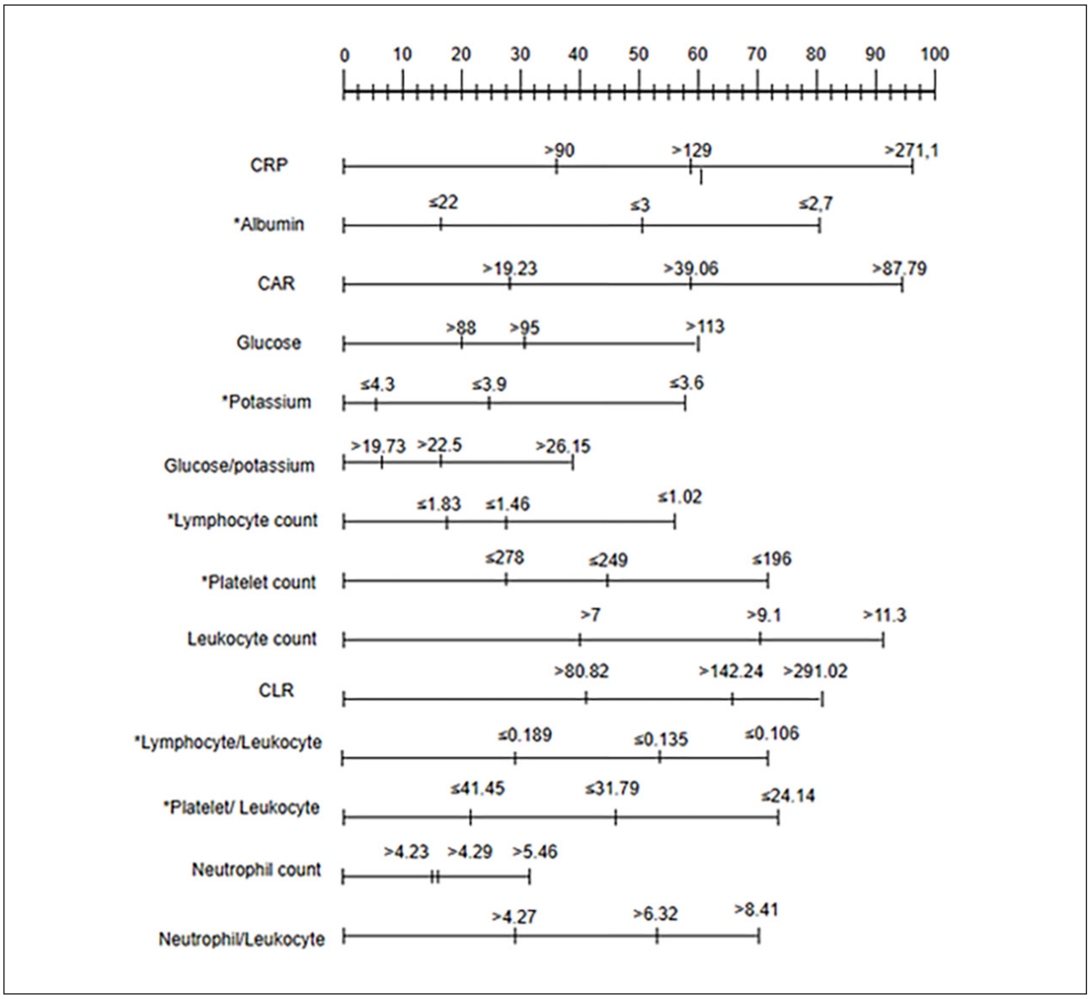

Figure 2. Nomogram created using the postoperative fifth-day measurements of parameters. In cases where the "lower than or equal to" (≤) symbol is used, values are denoted to the left due to the inverse relationship between increasing values and decreasing selectivity on a scale of 0 to 100. CRP: C- reactive protein CLR: CRP/lymphocyte ratio CAR: C-reactive protein/ albumin ratio.

AL and infection, prolonged hospital stays, adverse impacts on the patient's quality of life, and elevated financial burden on both the individual and the economy of the country due to escalated costs. AL is an additional contributing factor that increases morbidity and mortality by preventing or delaying the administration of adjuvant chemotherapy. A meta-analysis[21] examined 14 studies evaluating the oncological effect of AL in a total of 11,353 patients and reported that AL resulted in worse overall survival and reduced cancer-specific survival rates.

The protective ileostomy following low anterior resection has been shown to significantly reduce the incidence of anastomotic leaks and reoperation in the postoperative period, as indicated by numerous clinical studies[22]. The closure of an ileostomy necessitates an additional surgical procedure, and it comes with various comorbidities resulting from the second surgery. Among the factors influencing the timing of ileostomy closure, the most crucial ones include the patient's weight, prior surgical procedures, and the technique used for stoma closure[23]. In the context of low anterior resection for rectal cancer, the administration of neoadjuvant chemotherapy stands out as a risk factor contributing to the decision not to close temporarily established protective stomas[24]. However, we were unable to demonstrate a significant difference attributed to the use of a stoma in anastomotic leakage.

The Prognostic Nutritional Index (PNI) is a significant predictor in estimating survival and morbidity in gastrointestinal cancers. In rectal cancers, factors such as neoadjuvant treatment, nutrition, cancer stage, and metastasis influence patients' conditions. In the context of laparoscopic rectal cancer treatment, the PNI score has been found[25] insufficient in evaluating morbidity and mortality. In our study, a preoperative comparison conducted without distinguishing the neoadjuvant treatment group revealed the inadequacy of the PNI score in predicting anastomotic leakage. New studies, incorporating factors contributing to patients' preoperative nutritional status, as well as the duration of neoadjuvant chemoradiotherapy, could provide evidence for the usability of this score.

In rectal cancer surgery, the technical challenges associated with surgery in a narrow pelvis can be further exacerbated by the addition of obesity, making the situation more difficult. Additionally, obesity can lead to increased intra-abdominal pressures. The impact of obesity on anastomotic leakage has been confirmed[26]. In our sample group, no significant difference was observed in terms of body mass indexes between the AL and non-AL groups.

In this study, we utilized various blood biomarkers with the aim of predicting AL development in the early period among patients who underwent low anterior resection. In our patient group, there was no statistically significant difference in the incidence of AL according to age or gender, which are well-known independent risk factors. There are studies[27] emphasizing the importance of albumin values in determining prognosis after surgery. The present study showed that preoperative albumin values had no effect on AL, while the comparison of albumin values measured at different times in the postoperative period (days 1, 3, and 5) was statistically significant in predicting AL. The study conducted by Parthasarathy et al[28] highlighted the significance of albumin levels below 3.5 g/dl as a potential prognostic factor in the development of AL. In another study, it was emphasized that although no significant difference was found in the preoperative measurements of albumin values, there was a decrease in serum albumin levels after surgery, and this was at a statistically significant level. In another study[7] comparing the postoperative first- and third-day measurements, albumin levels lower than 3.2 g/dl and an increase in leukocyte count were found to be independent risk factors for the development of AL, and the authors highlighted the importance of these parameters in predicting AL. The CRP value alone was significant in determining AL, and there were significant differences in leukocyte, albumin, neutrophil, and lymphocyte values among the patients with AL between different measurement times and non-AL. In a study by Shimura et al[29], a statistically significant difference was seen when comparing the values of CRP, albumin, and leukocytes between the postoperative first and third days. In the same study, it was determined that the prevalence of AL was higher among individuals diagnosed with rectal cancer compared to those diagnosed with colorectal cancer. The subgroup analysis conducted in that study highlighted the significance of leukocyte, CRP, and albumin levels as important markers for identifying AL based on postoperative measurements in rectal cancer patients.

CRP values measured after colorectal surgery, on the postoperative third or fourth day, can predict postoperative complications and can potentially be used to predict complications[30].

We found that at a cut-off value >271.1 on postoperative day 5, the CRP value had a selectivity of 97.3% in predicting AL, while the selectivity of CAR was 96.9% when >85.79. In another study[31] evaluating postoperative third-day CRP and CAR values, the probability of an accurate prediction of complications was determined to be 79.1% among patients with a CRP value ≥85.1 and 81.4% among those with a CAR value of ≥2.2. The authors emphasized that these were predictive values that could be used in the close follow-up of postoperative complications in patients.

In our study, the changes in the neutrophil/leukocyte ratio from postoperative day 5 to postoperative days 1 and 3 were calculated, and they were found to differ between the patients statistically significantly with and without AL ($p = 0.008$ and $p = 0.006$, respectively). In another study[32] examining the complications of anastomosis in surgery performed for gastric cancer, NLR was determined to be an important parameter in determining anastomotic complications in gastric cancer cases in the postoperative period. In that study, the mean NLR value was found to be statistically higher in the patient group with AL.

Neutrophils are drawn toward ischemic areas with the assistance of inflammatory mediators, proteolytic enzymes, and free radicals, thereby actively engaging in the healing process of digestive tract anastomosis[33]. Lymphocytes are known[34] to play a significant role in the facilitation of this healing process. Lymphocytes are cells that decrease as inflammatory diseases progress; this reduction may not occur promptly enough to reflect disease progression and, therefore, may not be an accurate indicator of disease progression. Recent studies[35] have shown that NLR is a more reliable predictor of patient survival than neutrophil or lymphocyte count alone. It has been reported[36] that CRP is a better marker than NLR and predicts AL more effectively. NLR holds significant importance in the detection of complications and AL, but CRP seems to be more effective in predicting prognosis and AL.

Previous research[37] has shown that leukocyte count is high in groups with AL, may constitute an independent risk factor, and is the most valuable parameter in predicting AL. In the current study, there was no significant difference between the patients with and without AL in relation to the changes in leukocyte count from postoperative day 1 to postoperative day 5, but a statistically significant difference was found in the changes from postoperative day 3 to postoperative day 5.

It has been observed[38] that patients with high blood glucose levels during surgery have higher rates of AL compared to those with normal blood glucose levels. Although AL rates do not significantly differ between diabetic and non-diabetic patients, higher blood glucose levels have been associated with an increased risk of AL in non-diabetic patients. In the current study, there was no statistically significant difference in glucose and potassium values between the patients with and without AL development in the postoperative period. However, the nomogram analysis based on postoperative day 3 measurements revealed that a glucose value above 184 had 83.8% selectivity, and a potassium value ≤3.3 had 96.9% selectivity in the prediction of AL. In order to better analyze these values, measurements on patient groups independent of the diabetes comorbidity can be considered in future studies.

Peritoneal drainage fluid and systemic biomarkers are used to determine AL after colorectal surgery. Although the use of these biomarkers together offers valuable insight into the determination of AL and the evaluation of prognosis, it is evident that no combination of these values can accurately predict AL[39].

Limitations

The retrospective design of our study may have led to a bias in patient and surgeon selection. There are also other limitations to our study, including the absence of statistical analysis pertaining to the duration of AL, the inability to determine the extent of anastomoses, and the absence of AL staging.

Conclusions

Several techniques and instruments are being developed to detect AL during rectal surgery. Prominent factors in the context of the immune system include acute-phase reactants, cellular components, and numerous inflammatory mediators that are released by these cells. In this study, we presented an analysis of the usability of several mediators and immune system elements in the prediction of AL among patients who had undergone surgery for rectal cancer. Additionally, we provided the results of a nomogram that incorporated the selectivity of these markers. AL is considered an important complication that increases severe morbidity and mortality rates, not only impacting patient outcomes but also increasing economic burden and labor loss. Therefore, it is recommended to conduct comprehensive research to increase the efficacy of the preemptive methods targeting the prevention of AL.

Conflict of Interest
The authors declare that they have no conflict of interests.

Acknowledgements
We would like to thank the University of Health Sciences Antalya Education and Research Hospital for their support in the realization of this study.

Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Health Sciences University Antalya Training and Research Hospital Ethics Committee on 13 April 2023 with decision number 5/18 before the study.

Data Availability
The data used and analyzed during this research are available from the corresponding author upon reasonable request.

Funding
This research received no external funding.

Informed Consent
Not applicable due to the retrospective design of the study.

Authors' Contribution
Conceptualization, Halit Ozgul; Data curation, Remzi Can Cakir, Yunus Uzmay and Omer Celik; Formal analysis, Cemal Ozben Ensari. and Remzi Can Cakir; Methodology, Halit Ozgul, Ugur Dogan. and Arif Aslaner; Project administration, Halit Ozgul; Supervision, Cemal Ozben Ensari and Ugur Dogan; Validation, Yunus Uzmay, Remzi Can Cakir, Tahir Turker Kaplan; Visualization, Tahir Turker Kaplan; Writing – original draft, Halit Ozgul, Remzi Can Cakir and Ugur Dogan; Writing – review & editing, Ugur Dogan, Halit Ozgul, Remzi Can Cakir, Omer Celik. All authors have read and agreed to the published version of the manuscript.

References

1) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2020; 68: 394-424.
2) Barleben A, Mills S. Anorectal anatomy and physiology. Surg Clin North Am 2010; 90: 1-15.
3) Stoker J. Anorectal and pelvic floor anatomy. Best Pract Res Clin Gastroenterol 2009; 23: 463-475.
4) Wang YHW, Wiseman J. Anatomy, Abdomen and Pelvis, Rectum. StatPearls, StatPearls Publishing 2023.
5) Degiuli M, Elmore U, De Luca R, De Nardi P, Tomatis M, Biondi A, Persiani R, Solaini L, Rizzo G, Soriero D, Cianflocca D, Milone M, Turri G, Rega D, Delrio P, Pedrazzani C, De Palma GD, Borghi F, Scabini S, Coco C, Cavaliere D, Simone M, Rosati R, Reddavid R. 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: 264-276.
6) 2015 European Society of Coloproctology Collaborating Group. Predictors for anastomotic leak, postoperative complications, and mortality after right colectomy for cancer: results from an International snapshot audit. Dis Colon Rectum 2020; 63: 606-618.
7) Zarnescu EC, Zarnescu NO, Costea R. Updates of risk factors for anastomotic leakage after colorectal surgery. Diagnostics (Basel) 2021; 11: 2382.
8) Rondelli F, Sanguinetti A, Polistena A, Avenia S, Marcacci C, Ceccarelli G, Bugiantella W, De Rosa M. Robotic transanal total mesorectal excision (RTaTME): State of the Art. J Pers Med 2021; 11: 584.
9) Gray M, Marland JRK, Murray AF, Argyle DJ, Potter MA. Predictive and diagnostic biomarkers of anastomotic leakage: A precision medicine approach for colorectal cancer patients. J Pers Med 2021; 11: 471.
10) Janež J, Horvat G, Jerin A, Grosek J. The significance of blood and peritoneal fluid biochemical markers in ıdentifying early anastomotic leak following colorectal resection-findings from a single-center study. Medicina (Kaunas) 2022; 58: 1253.
11) Hübner M, Mantziari S, Demartines N, Pralong F, Coti-Bertrand P, Schäfer M. Postoperative albumin drop ıs a marker for surgical stress and a predictor for clinical outcome: A pilot study. Gastroenterol Res Pract 2016.
12) Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Shibuya N, Kubota K. Clinical significance of the C-reactive protein to albumin ratio for survival after surgery for colorectal cancer. Ann Surg Oncol 2016; 23: 900-907.
13) Sunakawa Y, Yang D, Cao S, Zhang W, Moran M, Astrow SH, Hsiang J, Stephens C, Tsuji A, Takahashi T, Tanioka H, Negoro Y, Takagane A, Tani S, Yamaguchi T, Eto T, Fujii M, Ichikawa W, Lenz HJ. Immune-related genes to dominate neutrophil-lymphocyte ratio (NLR) associated with survival of cetuximab treatment in metastatic colorectal cancer. Clin Colorectal Cancer 2018; 17: 741-749.
14) Oh SY, Heo J, Noh OK, Chun M, Cho O, Oh YT. Absolute lymphocyte count in preoperative chemoradiotherapy for rectal cancer: changes over time and prognostic significance. Technol Cancer Res Treat 2018; 17: 1533033818780065.
15) Suzuki R, Wei X, Allen PK, Cox JD, Komaki R, Lin SH. Prognostic significance of total lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in limited-stages small-cell lung cancer. Clin Lung Cancer 2019; 20: 117-123.
16) Farrokhi F, Smiley D, Umpierrez GE. Glycemic control in non-diabetic critically ill patients. Best Pract Res Clin Endocrinol Metab 2011; 25: 813-824.
17) Pan YX, Chen JC, Fang AP, Wang XH, Chen JB, Wang JC, He W, Fu YZ, Xu L, Chen MS, Zhang YJ, Li QJ, Zhou ZG. A nomogram predicting the recurrence of hepatocellular carcinoma in patients after laparoscopic hepatectomy. Cancer Commun (Lond) 2019; 39: 55.
18) Kong J, Zheng J, Cai J, Wu S, Diao X, Xie W, Chen X, Liao C, Yu H, Fan X, Huang C, Liu Z, Chen W, Lv Q, Qin H, Huang J, Lin T. A nomogram for individualized estimation of survival among adult patients with adrenocortical carcinoma after surgery: a retrospective analysis

and multicenter validation study. Cancer Commun (Lond) 2019; 39: 80.

19) Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015; 16: 173-180.

20) Narita Y, Kadowaki S, Oze I, Kito Y, Kawakami T, Machida N, Taniguchi H, Ura T, Ando M, Ito S, Tajika M, Yatabe Y, Yasui H, Muro K. Establishment and validation of prognostic nomograms in first-line metastatic gastric cancer patients. J Gastrointest Oncol 2018; 9: 52-63.

21) Wang S, Liu J, Wang S, Zhao H, Ge S, Wang W. Adverse effects of anastomotic leakage on local recurrence and survival after curative anterior resection for rectal cancer: A systematic review and meta-analysis. World J Surg 2017; 41: 277-284.

22) Tan WS, Tang CL, Shi L, Eu KW. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 2009; 96: 462-472.

23) Yu CY, Qin TT, Dong YY, Shen XN. Risk factors for prolongation of ileostomy closure operation. Eur Rev Med Pharmacol Sci 2022; 26: 8684-8692.

24) Zhou L, Qin Z, Wang L. Risk factors and incidence of non-closure stoma in patients with anterior resection of rectal cancer with temporary stoma: A systematic review and meta-analysis. Eur J Surg Oncol 2023; 49: 107120.

25) Portale G, Cavallin F, Cipollari C, Spolverato Y, Di Miceli D, Zuin M, Mazzeo A, Morabito A, Sava T, Fiscon V. Preoperative prognostic nutritional ındex was not predictive of short-term complications after laparoscopic resection for rectal cancer. Langenbecks Arch Surg 2023; 408: 263.

26) Yu L, Wu W, Xia S, Li Y, Xu Z. Visceral obesity and anastomotic leakage rates in colorectal cancer: a systematic review and meta-analysis. Front Oncol 2023; 13: 1224196.

27) McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg 2015; 102: 462-479.

28) Parthasarathy M, Greensmith M, Bowers D, Groot-Wassink T. Risk factors for anastomotic leakage after colorectal resection: a retrospective analysis of 17 518 patients. Colorectal Dis 2017; 19: 288-298.

29) Shimura T, Toiyama Y, Hiro J, Imaoka H, Fujikawa H, Kobayashi M, Ohi M, Inoue Y, Mohri Y, Kusunoki M. Monitoring perioperative serum albumin can identify anastomotic leakage in colorectal cancer patients with curative intent. Asian J Surg 2018; 4: 30-38.

30) Warschkow R, Beutner U, Steffen T, Müller SA, Schmied BM, Güller U, Tarantino I. Safe and early discharge after colorectal surgery due to C-reactive protein: a diagnostic meta-analysis of 1832 patients. Ann Surg 2012; 256: 245-250.

31) Ge X, Cao Y, Wang H, Ding C, Tian H, Zhang X, Gong J, Zhu W, Li N. Diagnostic accuracy of the postoperative ratio of C-reactive protein to albumin for complications after colorectal surgery. World J Surg Oncol 2017; 15: 15.

32) Radulescu D, Baleanu VD, Padureanu V, Radulescu PM, Bordu S, Patrascu S, Socea B, Bacalbasa N, Surlin MV, Georgescu I, Georgescu EF. Neutrophil/Lymphocyte ratio as predictor of anastomotic leak after gastric cancer surgery. Diagnostics (Basel) 2020; 10: 799.

33) Schwartz M, Moalem G. Beneficial immune activity after CNS injury: prospects for vaccination. J Neuroimmunol 2001; 113: 185-192.

34) Vidal AC, Howard LE, de Hoedt A, Cooperberg MR, Kane CJ, Aronson WJ, Terris MK, Amling CL, Taioli E, Fowke JH, Freedland SJ. Neutrophil, lymphocyte and platelet counts, and risk of prostate cancer outcomes in white and black men: results from the SEARCH database. Cancer Causes Control 2018; 29: 581-588.

35) Kumarasamy C, Sabarimurugan S, Madurantakam RM, Lakhotiya K, Samiappan S, Baxi S, Nachimuthu R, Gothandam KM, Jayaraj R. Prognostic significance of blood inflammatory biomarkers NLR, PLR, and LMR in cancer-A protocol for systematic review and meta-analysis. Medicine (Baltimore) 2019; 98: e14834.

36) Pantoja Pachajoa DA, Gielis M, Palacios Huatuco RM, Benitez MN, Avila MN, Doniquian AM, Alvarez FA, Parodi M. Neutrophil-to-lymphocyte ratio vs C-reactive protein as early predictors of anastomotic leakage after colorectal surgery: A retrospective cohort study. Ann Med Surg (Lond) 2021; 64: 102201.

37) Morimoto M, Taniguchi K, Yamamoto O, Naka T, Sugitani A, Fujiwara Y. Preoperative white blood cell count predicts anastomotic leakage in patients with left-sided colorectal cancer. PLoS One 2021; 16: e0258713.

38) Reudink M, Huisman DE, van Rooijen SJ, Lieverse AG, Kroon HM, Roumen RMH, Daams F, Slooter GD; LekCheck study group. Association between intraoperative blood glucose and anastomotic leakage in colorectal surgery. J Gastrointest Surg 2021; 25: 2619-2627.

39) Su'a BU, Mikaere HL, Rahiri JL, Bissett IB, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. Br J Surg 2017; 104: 503-512.