Can inflammatory markers such as lymphocyte to C-reactive protein ratio and hemoglobin, albumin, lymphocyte, and platelet score predict complications after loop ileostomy closure?

Lenfosit/C-reaktif protein oranı ve hemoglobin, albümin, lenfosit ve trombosit skoru gibi enflamatuar belirteçler loop ileostomi kapatılması sonrası komplikasyonları öngörebilir mi?

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Abstract

Aim: This study aims to investigate whether inflammatory biochemical markers such as hemoglobin, albumin, lymphocyte, platelet scores (HALP), and lymphocyte-C-reactive protein ratio (LCR) can predict complications after ileostomy closure.

Methods: Eighty-five patients who underwent loop ileostomy closure were included in this retrospective study. Alongside the patient's demographic data, surgical data, histopathology results, and biochemistry data were recorded. Complications that occurred within the first 30 days after surgery were evaluated using the Clavien-Dindo classification. Inflammation markers such as HALP and LCR were obtained using biochemical parameters.

Results: The rate of mild complications (Clavien-Dindo I and II) was 27%, while the rate of severe complications (Clavien-Dindo III and IV) was 12.94%. A statistically significant correlation was found between the development of early complications and levels of albumin, lymphocyte, neutrophil, and C-reactive protein (CRP) ($p<0.05$). Patients who developed complications had lower mean serum albumin levels and higher mean neutrophil and CRP values. There was a strong correlation between HALP score and LCR and complications in patients ($p<0.05$).

Conclusion: It was concluded that HALP and LCR measured preoperatively could be important predictors of early complications after loop ileostomy closure.

Keywords: Biochemical markers; inflammation; loop ileostomy; postoperative complications

Öz

Amaç: Bu çalışmanın amacı hemoglobin, albümin, lenfosit ve trombosit skorları (HALP) ve lenfosit-C-reaktif protein oranı (LCR) gibi inflamatuar biyokimyasal belirteçlerin ileostomi kapatılması sonrası komplikasyonları öngörüp öngöremediğini araştırmaktır.

Yöntemler: Bu retrospektif çalışmaya loop ileostomi kapatılan seksen beş hasta dahil edildi. Hastaların demografik verilerinin yanı sıra ameliyat verileri, histopatoloji sonuçları ve biyokimya verileri veritabanına kaydedildi. Ameliyattan sonraki ilk 30 gün içinde ortaya çıkan komplikasyonlar Clavien-Dindo sınıflandırması kullanılarak değerlendirildi. HALP ve LCR gibi inflamasyon belirteçleri biyokimyasal parametreler kullanılarak elde edildi.

Bulgular: Hafif komplikasyonların (Clavien-Dindo I ve II) oranı %27 iken, ciddi komplikasyonların (Clavien-Dindo III ve IV) oranı %12.94 idi. Erken komplikasyon gelişimi ile albümin, lenfosit, nötrofil ve C-reaktif protein (CRP) düzeyleri arasında istatistiksel olarak anlamlı bir korelasyon bulundu ($p<0.05$). Komplikasyon gelişen hastaların ortalama serum albümin düzeyleri daha düşük, ortalama nötrofil ve CRP değerleri ise daha yüksekti. HALP skoru ve LCR ile hastalardaki komplikasyonlar arasında güçlü bir korelasyon vardı ($p<0.05$).

Sonuç: Ameliyat öncesi ölçülen HALP ve LCR'nin loop ileostomi kapatılması sonrası erken komplikasyonların önemli belirleyicileri olabileceği sonucuna varıldı.

Anahtar Sözcükler: Ameliyat sonrası komplikasyonlar; biyokimyasal belirteçler; inflamasyon, loop ileostomi

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INTRODUCTION

Anastomotic leak is a serious complication that can occur after anterior resection of the rectum. To minimize the harmful effects of anastomotic leakage, a diverting ileostomy is often performed (1). However, it is important to note that ileostomy is not a procedure without any risks, as closure has been associated with morbidity and mortality in 0.5-4% of cases (2-4). When closing a loop ileostomy, can be done using linear staples or sutures. There have been no significant differences reported in terms of morbidity between these two techniques (5-7). Some common complications that can arise after ileostomy closure include small bowel obstruction, surgical site infection, abdominal septic complications, and enterocutaneous fistula (7).

The degree of the systemic inflammatory response measured before surgery is associated with survival in cancer patients. Low levels of albumin and lymphocytes, as well as high levels of CRP, leukocytes, neutrophils, and platelets, are indicators of systemic inflammatory response (8). Various prognostic factors based on inflammation can be revealed by combinations of these parameters. Biochemical markers of the inflammatory response can be used to determine the prognosis of many malignant diseases (9). These biochemical markers have also been utilized in autoimmune, inflammatory, and infectious diseases where the severity of inflammation is crucial (10). Hemoglobin, albumin, leukocyte, and platelet values have demonstrated associations with prognosis in oncological patients in numerous settings (11-13).

The objective of this study is to investigate whether certain biochemical markers, such as hemoglobin, albumin, lymphocyte, and platelet scores (HALP), as well as the lymphocyte-C-reactive protein ratio (LCR), can predict complications after ileostomy closure.

MATERIAL AND METHODS

The study included sequential patients who underwent loop ileostomy closure a Tokat University Medical Faculty Hospital between 2013 and 2021. The patients' data was retrieved from the hospital's electronic database and analyzed retrospectively. Ethics committee approval was obtained from Tokat Gaziosmanpaşa University Clinical Research Ethics Committee for the study (date: 14.01.2021, decision no: 2021/01). Loop ileostomy closures were performed in the General Surgery clinic by experienced faculty members or under their supervision.

The study included adult patients (over 18 years of age) who underwent ileostomy closure. Loop ileostomies were performed for various reasons, including benign and malignant causes, in emergency or elective colorectal surgery settings.

The study excluded patients under 18 years of age, those with terminal or double barrel ileostomy, patients with systemic autoimmune disease and/or regular use of immunosuppressive drugs, and those with missing data.

Before the operation, all concomitant diseases (including diabetes mellitus and arterial hypertension) in the patients were stable. The blood pressure and fasting blood glucose values of the patients were within normal limits in the preoperative and early postoperative periods.

Prior to ileostomy closure, the integrity of colorectal anastomoses performed at the index operation was checked with colonoscopy and/or computed tomography with oral and intravenous contrast. 1 gram of cefazolin, as a prophylactic antibiotic, was administered before surgery. The operations were performed under general anesthesia with different incisions (peristomal, peristomal+laparoscopic, or median incisions) using either a linear stapler or sutures (with 3/0 PDS or 3/0 vicryl Lambert sutures). Some patients required resection of the loop ileostomy, while in others, anastomosis could be performed without resection. In all peristomal incisions, the skin was closed as a purse-string. Complications that developed within the first 30 days after surgery were evaluated according to the Clavien-Dindo classification. Complications such as anastomotic leakage, intra-abdominal collection, and ileus were defined based on clinical (abdominal distention, pain, nausea, vomiting, inability to pass gas and stool) and radiological (standing direct abdominal X-ray, ultrasonography, computed tomography) findings. The follow-up was conducted through the scheduled outpatient department of surgery weekly after discharge until the complete healing of the ileostomy wound. Patients who did not come to the hospital were assessed

Table 1. Demographic data of the patients in the study

Clinical characteristics			
	Mean±SD	**Min-Max**	
Age (year)	62,07±9,82	34-82	
BMI (kg/cm^2)	25,88±4,21	17,70-40,20	
Operative time (minutes)	58.66±15.38	35-150	
Mean time between the index surgery and ileostomy closure surgery (day)	102.47±108.24	8-567	
Length of hospital stay	5.59±2.85	2-19	
		n	**%**
Gender	Female	28	32,94
	Male	57	67,06
ASA	1	1	1,18
	2	32	36,47
	3	52	61,18
	4	1	1,18
Smoking	Yes	16	18,82
	No	69	81,18
Comorbid diseases	DM+HT	32	37,65
	Cardio-vascular system (CAD and AF)	8	9,41
	Previous cerebrovascular disease	2	2,35
	Respiratory system (COPD, Asthma)	10	11,76
	Chronic kidney disease	2	2,35
	No comorbidity	31	36,47
Diagnosis			
Rectal Cancer		75	88,23
Rectal Tumor (benign)		4	4,71
FAP		3	3,53
Descending colon injury		1	1,18
Iatrogenic colon perforation		1	1,18
Ulcerative Colitis		1	1,18
Index surgery			
LAR+conservative ileostomy		79	92,94
Total proctocolectomy+ileoanal anastomosis+protective ileostomy		4	4,71
Sigmoid colon repair + protective ileostomy		2	2,35
Incision	Peristomal	82	96.47
	Median	1	1.18
	Peristomal+ laparoscopic	2	2.35
Elective/emergency			
Elective		82	96,47
Emergency		3	3,53
First pathology			
Malignant		78	91,76
Benign		7	8,23
Initial pathology results			
Adenocarcinoma		78	91,76
Ulcerative colitis		1	1,18
Adenomatous polyp		4	4,71
Stab wound		1	1,18
Sigmoid colon perforation		1	1,18
Adjuvant CT	Received	35	41.18
	Did not received	50	58.8

nCT/CRT	Received	60	70.59
	Did not received	25	29.4
Stoma closure			
Resection+hand anastomosis		58	68,24
Hand anastomosis		17	20,00
Resection + anastomosis with linear stapler		7	8,24
Linear stapler anastomosis		3	3,53

FAP: Familial adenomatous polyposis coli, LAR: Low anterior resection, CAD: Coronary artery disease, AF: Atrial fibrillation, COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, DM: Diabetes Mellitus, HT: Hypertension, ASA: American Society of Anaesthesiologists physical status classification, nCT/CRT: Neoadjuvant chemotherapy/chemoradiotherapy, SD: Standard deviation, Max: Maximum, Min: Minimum, n: Number, %: Percentage

through a phone call.

The variables considered in the study were demographic, clinical, and biochemical. They included age, gender, BMI (body mass index), ASA score, comorbidities, smoking, use of chemotherapy agents, time between the first operation and ileostomy closure surgery (days), operation time (minutes), postoperative hospital stay (days), incision type (peristomal, median), postoperative complications, leukocyte, lymphocyte, neutrophil, and platelet counts; hemoglobin, albumin, CRP levels. Laboratory blood values used in the study were measured at an average of 14.86±11.45 days before ileostomy closure surgery.

Inflammation markers such as HALP and LCR were obtained using biochemical parameters. HALP score calculation: Hemoglobin (g/dL) x Albumin (g/dL) x Lymphocyte (count/µl) / Platelet (count/µl).

LCR calculation: Lymphocyte (count/µl) / CRP (mg/L).

Statistical Analysis

In the analysis of the data collected in the study, Statistical Package for the Social Sciences software for Windows, version 24.0 (SPSS Inc., Chicago, IL, USA) was used. Optimal cut-off values of HALP and LCR scores were calculated using X-tile software version 3.6.1 (Yale University, NEW Haven CT, USA). In the study, descriptive statistics regarding the distribution of responses to independent variables were presented as numbers and percentages for categorical variables, and mean, standard deviation, and median for numerical variables. The compatibility of continuous variables with the assumption of normal distribution was evaluated with the Kolmogorov-Smirnow test. Survival was analyzed by the Kaplan-Meier method, with differences analyzed by log-rank test. While the distribution relationship between categorical variables was examined with the Chi-Square test, the Paired Sample T Test and Independent T-test were used to compare numerical data. One way Anova or Kruskal-Wallis Method was used to compare multiple groups. In addition, ROC Analysis was applied to determine the cut-off point for numerical variables. In multivariate analysis, independent predictors were examined to predict outcomes in early and late complications using logistic regression analysis. The results were evaluated at the 95% confidence interval, with $p<0.05$ as significant.

RESULTS

The mean age of the patients, of whom 57 (67.06%) were male, was 62.07±9.82 (min.34- max.82) years. The most common comorbidities were DM and HT in 32 (37.65%). The mean follow-up period was 40.99±24.17 (min.1,7-max.95) months. (Table 1).

Abscess drainage and debridement were the most common (7.06%) patients who underwent reoperation. Surgical site infection was observed in 9 (10,59%) patients as the reason for readmission, and some patients had more than one reason for hospitalization (Table 2).

The most common early complications were surgical site infection in 21 (24.70%) patients and ileus in 15 (17.64%) patients. Some patients had multiple early complications.

67.64% of complications were mild complications (Clavien-Dindo I and II). Nine patients (10.59%) who were mortal died in the late postoperative period (5.2 months at the earliest after ileostomy closure surgery) (Table 3). There was no mortality associated with ileostomy closure surgery.

Table 2. Data on the reoperation status of the patients and the reasons for readmission to the hospital

Features	n	%
Reoperation		
Yes	9	10,59
No	76	89,41
Reoperation types		
Abscess drainage, debridement	6	7,06
Bridectomy	1	1,18
Opening a double-barrel ileostomy	1	1,18
Percutaneous abscess drainage	1	1,18
No	76	89,41
Hospitalization within 30 days		
Yes	14	16,47
No	71	83,53
Reason for readmission		
No	71	83,53
Acute coronary syndrome	1	1,18
Intra-abdominal abscess/ hematoma	2	2,35
Brid ileus	3	3,53
Surgical site infection	9	10,59
Rectal bleeding	1	1,18
Lower extremity DVT	1	1,18

DVT: Deep vein thrombosis, n: Number, %: Percentage

Table 3. Data on early complications observed in patients

Features	n	%
Early complication		
Yes	34	40,00
No	51	60,00
Type of early complication		
No	51	60,00
Cardio-vascular system AF, tachycardia, ACS	3	3,53
Intra-abdominal abscess/ hematoma	2	2,35
Anastomotic leak	1	1,18
İleus	15	17,64
Surgical site infection	21	24,70
Gastrointestinal bleeding	1	1,18
Urinary tract infection	2	2,35
Treatment of early complications		
No	51	60,00
Medical treatment	12	14,11
Surgical abscess drainage	5	5,88
Drainage and debridement (AF, tachycardia, ACS)	14	16,47
Erythrocyte suspension replacement	1	1,18
Nasogastric tube insertion	8	9,41
Percutaneous abscess drainage	1	1,18
Reoperation+resection+double barrel ileostomy opening	1	1,18
Clavien-Dindo		
I	7	8,24
II	16	18,82
III	10	11,76
IV	1	1,18
Survival		
Live	76	89,41
Ex	9	10,59
Exitus reason		
Distant metastasis	7	77,77
Multiple organ failure	2	22,22

AF: Atrial fibrillation, ACS: Acute coronary syndrome, n: Number, %: Percentage

Table 4. The relationship between HALP, LCR scores, and biochemistry data of early complications in the patients in the study

		Early complications	
		Mean ±SD	**p value**
HALP	Yes	28,61±28,45	<0,001**
	No	29,40±22,51	
	Total	29,09±24,89	
LCR	Yes	0,25±0,26	0,019**
	No	0,42±0,37	
	Total	0,35±0,34	
Hemoglobin	Yes	12,17±2,04	0,861
	No	12,09±2,02	
	Total	12,12±2,01	
Albumin	Yes	3,63±0,63	0,029**
	No	3,92±0,54	
	Total	3,80±0,590	
Lymphocyte	Yes	1,45±0,92	0,582
	No	1,36±0,69	
	Total	1,40±0,79	
Platelet	Yes	320,89±165,08	0,106
	No	268,33±130,24	
	Total	289,36±146,54	
Neutrophil	Yes	5,52±3,67	0,041**
	No	4,31±1,65	
	Total	4,79±2,70	
CRP	Yes	24,22±41,40	0,003**
	No	6,08±5,34	
	Total	13,34±27,75	

HALP: Hemoglobin, albumin, lymphocyte, and platelet score, LCR: Lympocyte-C-reactive protein ratio, CRP: C-reactive protein, SD: Standard deviation

It was determined that Capecitabine and Folfox were the most commonly used KT agents in both groups.

We observed that the longer the interval between index surgery and loop ileostomy closure surgery, the higher the rate of postoperative complications. The longer the duration of ileostomy closure surgery, the higher the rate of postoperative complications. Similarly, the longer the hospitalization period, the more frequent the postoperative complications ($p<0.05$).

A significant difference was found between the development of early complications and HALP (P: 0.001) and LCR (p: 0.019) scores. It was concluded that these scores were significant predictors of the development of early complications ($p<0.05$). The cut-off values were measured as 25.12 for HALP and 0.45 for LCR.

A significant difference was found between the development of early complications and the biochemistry data of albumin ($p = 0.029$), neutrophil ($p = 0.041$), and CRP ($p = 0.003$). Patients with early complications had a lower mean albumin value. Additionally, it was observed that the mean values of neutrophil and CRP were higher in patients with complications (Table 4).

There was no statistically significant difference between early complications and the first operation, pathology results, and stoma closure method. Similarly, there was no significant difference between the neoadjuvant and adjuvant chemotherapy given to the patients and the development of early complications ($p > 0.05$). However, the type of incision applied ($p = 0.039$) was found to be an effective variable in the development of early complications. Complications were

observed in all ileostomies closed with a median incision or laparoscopically.

The development of early complications in the patients included in the study was evaluated using ROC analysis, and curves were created to assess the rates and influencing factors of early complication development.

Factors associated with the development of early complications were compared using Multiple Logistic Regression. Upon examination of the results, HALP ($p = 0.014$) and LCR ($p = 0.007$) were identified as significant variables (Figure 1).

The relationship between early complication development and biochemistry values was also assessed using Multiple Logistic Regression. The results showed that Albumin ($p = 0.035$), lymphocyte ($p = 0.013$), neutrophil ($p = 0.009$), and CRP ($p = 0.005$) were significant variables (Figure 2).

According to the results of the Pearson correlation analysis, an inverse significant difference was found between the development of early complications and the HALP variable. Higher HALP values were associated with a lower risk of developing early complications.

Similarly, an inversely significant difference was observed between the early complication development status and the LCR variable. Higher LCR values were associated with a lower risk of developing early complications.

DISCUSSION AND CONCLUSION

The predictability of complications after loop ileostomy closure is important for both patient healthcare and the cost of treatment. The systemic inflammatory response plays a significant role in both benign and malignant diseases. In many diseases, inflammatory markers such as hemogram and albumin obtained from routine biochemical tests of patients are used. In this study, we examined whether inflammatory markers such as HALP and LCR can predict complications after loop ileostomy closure. We found that both markers are strongly associated with complications that occur after ileostomy. In other words, higher preoperative LCR and HALP scores are associated with a lower postoperative complication rate after loop ileostomy surgery.

Loop ileostomy closure can be performed with staples or by manual anastomosis. Small bowel obstruction is more common after manual anastomosis. However, there is no significant difference between these two techniques in terms of anastomotic leakage (14,15). In our study, there was no difference between manual anastomosis and stapled anastomosis in terms of complications.

The rate of complications after loop ileostomy closure ranges from 17% to 23.7%. The mortality rate has been reported to be below 1% (16,17). The most common complications are surgical site infection and intestinal obstruction. Hypoalbuminemia has been identified as an independent factor associated with complications (17). In our study, the rate of early complications was higher than what has been reported in the literature. We found that the rate of mild complications (Clavien-Dindo I and II) was 27%, and the rate of severe complications (Clavien-Dindo III and IV) was 12.94%. The most common complications in our patients were surgical site infection and ileus/intestinal obstruction.

There were no mortalities after ileostomy closure in our study. However, the complication rate of our patients was higher compared to rates reported in some articles in the literature (16,17). This difference may be attributed to our provincial healthcare organization. Since our hospital is a tertiary referral center, younger patients and uncomplicated cases are usually managed in local hospitals. On the other hand, patients with multiple comorbidities, elderly patients, and complicated cases are referred to the university hospital. This may explain the relatively higher morbidity rates observed in our study. Additionally, we found a statistically significant relationship between the development of early complications and low serum albumin levels. Patients who developed complications had lower mean serum albumin levels.

Systemic inflammation and nutritional status are factors that play a crucial role in determining treatment outcomes for many diseases. The HALP score, which is calculated using hemoglobin, albumin, lymphocyte, and platelet values, serves as an inflammatory marker that reflects both the inflammatory response and nutritional status of patients. The HALP score has been used as a marker associated with poor prog-

nosis and survival in patients with various gastrointestinal cancers, such as stomach and colon (18,19). Each component of the HALP score individually reflects the prognosis of diseases. Previous studies have shown that complications after ileostomy closure are associated with low hemoglobin levels (20). Similarly, hypoalbuminemia and malnutrition increase the risk of complications in patients undergoing ileostomy closure surgery (17). Lymphocyte counts have also been found to be associated with prognosis in patients with colorectal and gastric cancer who underwent surgery (21,22). In pediatric patients who have undergone appendectomy, low lymphocyte levels have been suggested to predict the development of intra-abdominal abscesses (23). Furthermore, platelets, which play an active role in the development of the inflammatory response, have been identified as a potential indicator of postoperative complications (24). However, the relationship between complications of ileostomy closure and the HALP score has not been investigated before. In this study, we have demonstrated a strong correlation between the HALP score and complications in our patients. We observed that the complication rate increased with decreasing HALP score.

LCR, as a marker of the inflammatory response, is confidently used to predict disease-free survival and overall survival rates in patients with colorectal cancer and gastric cancer. Low preoperative LCR values are associated with worse overall survival and disease-free survival, as well as more advanced cancer stages (25,26). LCR has also been reported as an independent factor associated with bowel ischemia in strangulated abdominal wall hernias (27). In our study, we found that LCR effectively predicted complications after loop ileostomy closure. The complication rates increased as the LCR decreased, indicating a reciprocal association.

There are some limitations to our study. Firstly, it was a retrospective, single-center study with a low number of patients, which are the three most important limitations. However, it is the first study of its kind to compare postoperative complications and inflammatory markers in patients with loop ileostomy closure. This pilot study is the first to demonstrate that LCR and HALP scores can predict complications after ileostomy closure. Low LCR and/or HALP scores measured preoperatively may indicate potential complications that could arise from loop ileostomy closure and may assist in determining the optimal timing for surgery. Prospective studies with larger patient cohorts are needed to validate and standardize the data.

In conclusion, preoperative measurement of HALP and LCR is valuable in predicting early complications after loop ileostomy closure. It may be beneficial to incorporate these inflammatory markers alongside other diagnostic tools.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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