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# Predictive value of pre-operative blood markers in patients undergoing open and laparoscopic curative resection for colorectal cancer

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## ABSTRACT

**Introduction:** Individual risk prediction tools for post-operative morbidity assessments are increasingly becoming prominent. Blood markers obtained from peripheral blood are an essential part of the systemic inflammatory response and are good indicators of complications. The study aimed to cross-compare the ratio-based pre-operative laboratory parameters to predict post-operative complications (POCs) in patients with curative surgery for colorectal cancer.

**Materials and Methods:** This retrospective cohort and single-center study evaluated the data of 323 colorectal cancer patients who underwent curative surgery between January 2007 and November 2019 in a tertiary hospital in Istanbul, Turkey. A receiver operating characteristic (ROC) curve was generated to evaluate the ability of laboratory values to predict clinically relevant POCs. The area under the curve was computed to compare the predictive power of the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and CRP-albumin ratio (CAR). Then, the cutoff points were selected as the stratifying values for all four indexes.

**Results:** Complications developed in 109 (33.7%) of the patients postoperatively. Patients with POC had higher Charlson comorbidity index (CCI) scores and higher intra-operative bleeding. Length of hospital stay was also increased in the POC group. ROC curve analysis revealed that NLR was significantly effective in predicting POC, while LMR, PLR, and CAR were ineffective. According to multivariate analysis, CCI score ≥3, higher IOP-Bleeding, length of stay, and NLR ≥3.00 were independent risk factors influencing the POC.

**Conclusion:** Pre-operative NLR was predictive for POI. LMR, PLR, and CAR did not have any prediction for POC. In addition, CCI score, IOP-Bleeding, length of post-operative stay, and pre-operative NLR≥ 3.00 were found to be independent risk factors that influence the occurrence of POC.

**Keywords:** Colorectal cancer, CRP-albumin ratio, Lymphocyte-monocyte ratio, Neutrophil-lymphocyte ratio, Platelet-lymphocyte ratio

## Introduction

Post-operative complications (POCs) occur in up to one-third of patients undergoing colorectal procedures.[1] This condition is associated with decreased long-term survival, prolonged hospital stay, and delayed adjuvant chemotherapy.[2] Early diagnosis and treatment of POCs are important for improved clinical outcomes.[3] Accordingly, easily accessible, inexpensive, more sensitive, and spe-

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cific laboratory parameters are needed to predict the risk of complications in patients undergoing cancer surgery.

Systemic inflammation has been implicated in cancer development and progression. Several lines of evidence suggest that inflammation status correlates with clinical outcome, and the previous studies have mainly focused on prognosis.[4] Inflammation-based laboratory parameters, such as the C-reactive protein, platelet, monocyte, and neutrophil-to-lymphocyte ratio (NLR), are useful for predicting the prognosis of patients with CRC and various other types of cancer.[5-7]

This study aimed to examine whether a set of pre-operative rate-based inflammatory biomarkers predicts the risk of POCs. If so, these parameters could help identify patients at increased risk for complication, thereby optimizing the patients' conditions and procedures.

## Materials and Methods

### Patients

The study involved a total of 323 patients who underwent curative surgery for colorectal cancer between January 1, 2007, and November 30, 2019, in the Gastroenterological Surgery Department of Kosuyolu High Specialty Training and Research Hospital was retrospectively reviewed. The inclusion criteria were patients with histologically proven colorectal cancer and underwent an elective surgical procedure for curative purposes. Exclusion criteria were as follows: Patients who received chemotherapy in the past 4 weeks, emergency surgery or palliative resection, laparoscopic surgery, and hematologic disorders with no accessible records were excluded from the study. All patients received prophylactic intravenous antibiotics 1st generation cephalosporin or ciprofloxacin (in case of allergy) before skin incision repeated every 4 h. Antibiotics were administered only during surgery, and it was not continued postoperatively.

Surgical complications were defined in accordance with the Clavien-Dindo classification.[8] POC data were carried out by our surgeons from the day of surgery until hospital discharge. Post-discharge follow-up included emergency department, outpatient clinic, or readmissions to our surgery department. The patients were duly divided into groups: POC presence and POC absence. The date for the past follow-up visit of patients was taken as December 31, 2019.

The Clinical Research Ethics Committee approved the study of our institution (Ethical Committee No: 2019.7150-266).

### Data

Patients' demographic and clinicopathological data were recorded. Pre-operative variables were age, gender, Body Mass Index (BMI) and Charlson Comorbidity Index (CCI) score, localization, neoadjuvant therapy, BMI, and the ratios calculated from the blood sample. Pre-operative measurements of total blood counts were performed within the past 3 days before surgery. The NLR was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes in the venous blood. Similarly, the lymphocyte-monocyte ratio (LMR); dividing the absolute number of lymphocytes by the absolute number of monocytes, the platelet-lymphocyte ratio (PLR); dividing the absolute number of platelet by the absolute number of lymphocytes, and CRP-albumin ratio (CAR); CRP-value by albumin level.

Intra-operative and post-operative variables were intra-operative bleeding, operation time, pT stage, nodal metastasis, pM stage, laparoscopy, and length of hospital stay (LOS).

### Statistical Analysis

The software IBM® SPSS® (Statistical Package for the Social Sciences) version 23 (IBM Corp. Armonk, NY, USA) was used for statistical analysis. Qualitative data were presented as frequency and percentage. The distribution of numerical data was performed using the Kolmogorov–Smirnov test with the non-normal distribution results. These distributions were reported as median (Interquartile Range) and the Mann–Whitney U test was used to compare groups. Pearson's Chi-square test was used for the analysis of qualitative variables, and $p<0.05$ was considered significant. The reliability of NLR, LMR, PLR, and CAR calculated with pre-operative data in predicting POC was examined with Receiver Operating Characteristic (ROC) curves. The best POC prediction ability of ratios with cutoff values was determined by ROC. In the Chi-square test, the significant variables affecting POC with the only elevated ratio (NLR ≥3.00) were evaluated by multivariate logistic regression analysis, and independent risk factors were determined.

## Results

Patients' pre-operative, intra-operative, and post-operative data are presented in Table 1. POCs developed in 109 (33.7%) of the patients.

**Table 1. Patient's demographic. clinical. and histopathological characteristics**

| Variables | Postoperative Complication | | | | p |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | n (214) | 66.3% | n (109) | 33.7% | |
| Preoperative | | | | | |
| Age. years. median (IQR) | 63 (52-70) | | 63 (55-72) | | 0.248 |
| Gender | | | | | |
| Male | 122 | 57.0% | 68 | 62.4% | 0.789 |
| Female | 92 | 43.0% | 41 | 37.6% | |
| Body Mass Index (kg/m$^2$). median (IQR) | 27.5 (24.5-30.9) | | 27.3 (24.6-30.8) | | 0.997 |
| Charlson Comorbidity score | | | | | |
| 0-2 | 102 | 47.7% | 36 | 33.0% | 0.012 |
| ≥ 3 | 112 | 52.3% | 73 | 67.0% | |
| Localisation | | | | | |
| Colon | 142 | 66.4% | 71 | 65.1% | 0.976 |
| Rectum | 72 | 33.6% | 38 | 34.9% | |
| Neoadjuvant | | | | | |
| No | 171 | 79.9% | 82 | 75.2% | 0.497 |
| Yes | 43 | 20.1% | 27 | 24.8% | |
| Neutrophil-lymphocyte ratio. median (IQR) | 2.93 (2.08-4.10) | | 3.24 (2.09-4.40) | | 0.371 |
| Lymphocyte-monocyte ratio. median (IQR) | 3.05 (2.00-4.24) | | 2.67 (2.00-4.00) | | 0.597 |
| Platelet-lymphocyte ratio. median (IQR) | 160.87 (123.64-253.85) | | 197.14 (127.83-269.41) | | 0.149 |
| CRP-Albumin ratio. median (IQR) | 1.29 (0.82-4.00) | | 1.56 (0.85-2.98) | | 0.741 |
| Intraoperative/postoperative | | | | | |
| IOP-Bleeding (mL). median (IQR) | 80 (40-150) | | 140 /70-200) | | <0.001 |
| Operation time (min.). median (IQR) | 220 (170-260) | | 230 (170-260) | | 0.568 |
| pT stage | | | | | |
| pT1-pT2 | 49 | 22.9% | 15 | 13.8% | 0.905 |
| pT3-pT4 | 165 | 77.1% | 94 | 86.2% | |
| Nodal metastasis. | | | | | |
| No | 132 | 61.7% | 48 | 44.0% | 0.440 |
| Yes | 82 | 38.3% | 61 | 56.0% | |
| pM stage | | | | | |
| No | 187 | 87.4% | 91 | 83.5% | 0.195 |
| Yes | 27 | 12.6% | 18 | 16.5% | |
| Laparoscopic | | | | | |
| No | 166 | 77.6% | 87 | 79.8% | 0.643 |
| Yes | 48 | 22.4% | 22 | 20.2% | |
| Length of postoperative stay. median (IQR) | 8 (7-12) | | 11 (8-16) | | <0.001 |

IQR: Interquartile Range. IOP: Intra Operative. CRP: C Reactive Protein.

Patients with POC had higher CCI scores (p=0.012) and higher intra-operative bleeding (<0.001). LOS was also increased in the POI group (11 days vs. 8 days p<0.001). Other variables were statistically insignificant between patients with and without POC, when the relationship between the preoperatively calculated ratios and POC was evaluated by ROC analysis (Fig. 1). Comparison of the ratios with each other revealed that only NLR was the ability to predict the POC (Table 2).

The relationship of the variables according to the cutoff values of the predictive NLR determined by the ROC is presented in Table 3. The patients were divided into two groups: The low NLR group (n=158) and the high NLR group (n=165) using the cutoff value of 3.00. Patients with high NLR had higher POC rates than the low NLR group (39.9% vs. 28.9%, respectively. P=0.038). Patients who received neoadjuvant therapy and rectum localization had higher NLR (p<0.001 vs. p=0.004, respectively).

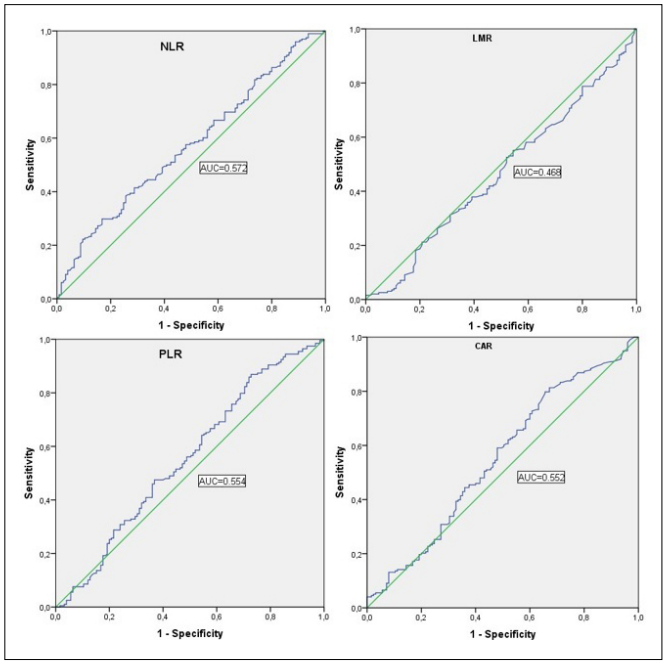


**Figure 1.** NLR, LMR, PLR, and CAR analysis with ROC curve in predicting POC.

Elevated pre-operative NLR score and variables affecting POC in Table 1 were included in multivariate analysis. Accordingly, CCI score, IOP-Bleeding, length of post-operative stay, and pre-operative NLR ≥3.00 were found to be independent risk factors that influence the occurrence of POC (Table 4).

## Discussion

In this study, we investigated the significance of the pre-operative NLR as a marker for predicting POCs in patients with CRC who undergo potentially curative surgery. In addition, the effect of open and laparoscopic surgery on POCs was not observed in this study.

This parameter may be simple, routinely available, and clinically useful in identifying patients at high risk of developing complications.

Numerous studies show a close relationship between inflammation and cancer.[9] Past decade, the systemic inflammatory response markers were clinically useful to identify patients at high risk of tumor progression in a variety of common solid tumors such as gastrointestinal cancer. There are studies conducted with various biomarkers to identify prognosis and predict potential relapse of colorectal cancer.[10] Peripheral inflammatory markers, including different white blood cells and acute-phase proteins, have been reported to correlate with various types of malignancies.[5,11] A combined analysis of these parameters could be applied widely in the clinic to reflect the combined information of these two processes. The most repeatedly validated approach is the NLR. Other validated examples are the PLR and the LMR score. Furthermore, a similar approach, CAR, has been recently validated.[12]

High NLR values indicate high neutrophil or low lympho-

**Table 2. Assessment of the reliability of NLR, LMR, PLR, and CAR in predicting postoperative complication with ROC curves and comparison between the ratios**

| | AUC | 95% CI | Cutoff | Sensitivity% | Specificity% | Youden Index | p |
|---|---|---|---|---|---|---|---|
| NLR | 0.572 | 0.508-0.635 | 3.00 | 54.0 | 53.6 | 0.076 | 0.030 |
| LMR | 0.468 | 0.403-0.532 | 3.00 | 49.0 | 48.8 | -0.022 | 0.326 |
| PLR | 0.554 | 0.488-0.620 | 168.08 | 53.0 | 52.8 | 0.058 | 0.102 |
| CAR | 0.552 | 0.486-0.617 | 1.38 | 53.5 | 52.8 | 0.063 | 0.118 |

AUC: Area Under Curve; CI: Confidence Interval.

**Table 3. Relationship between preoperative NLR with cutoff-values and demographic and clinicopathological features**

| Variables | NLR< 3.00 (n=158) (48.9%) | | NLR≥ 3.00 (n=165) (51.1%) | | p |
|---|---|---|---|---|---|
| Preoperative | | | | | |
| Age. years. median (IQR) | 63 (53-70) | | 63 (53-73) | | 0.803 |
| Gender. n (%) | | | | | |
| Male | 106 | 58.9% | 84 | 58.7% | 0.979 |
| Female | 74 | 41.1% | 59 | 41.3% | |
| Body Mass Index (kg/m$^2$). median (IQR) | 27.7 (24.6-31.2) | | 27.3(24.2-30.7) | | 0.546 |
| Charlson Comorbidity Index | | | | | |
| 0-2 | 77 | 42.8% | 61 | 42.7% | 0.973 |
| ≥ 3 | 103 | 57.2% | 82 | 57.3% | |
| Localisation | | | | | |
| Colon | 131 | 72.8% | 82 | 57.3% | 0.004 |
| Rectum | 49 | 27.2% | 61 | 42.7% | |
| Neoadjuvant | | | | | |
| No | 154 | 85.6% | 99 | 69.2% | <0.001 |
| Yes | 26 | 14.4% | 44 | 30.8% | |
| Intraoperative/postoperative | | | | | |
| IOP-Bleeding (mL). median (IQR) | 90 (48-173) | | 100 (50-180) | | 0.350 |
| Operation time (min.). median (IQR) | 230 (178-270) | | 220 (170-250) | | 0.114 |
| pT stage | | | | | |
| pT1-pT2 | 34 | 18.9% | 30 | 21.0% | 0.640 |
| pT3-pT4 | 146 | 81.1% | 113 | 79.0% | |
| Nodal metastasis. n (%) | | | | | |
| No | 92 | 51.1% | 88 | 61.5% | 0.061 |
| Yes | 88 | 48.9% | 55 | 38.5% | |
| pM stage | | | | | |
| No | 150 | 83.3% | 128 | 89.5% | 0.111 |
| Yes | 30 | 16.7% | 15 | 10.5% | |
| Laparoscopic | | | | | |
| No | 135 | 75.0% | 118 | 82.5% | 0.103 |
| Yes | 45 | 25% | 25 | 17.5% | |
| Complication | | | | | |
| No | 128 | 71.1% | 86 | 60.1% | 0.038 |
| Yes | 52 | 28.9% | 57 | 39.9% | |
| Length of postoperative stay. median (IQR) | 8 (7-14) | | 8 (7-14) | | 0.519 |

**Table 4. Multivariate Logistic Regression Analysis for elevated preoperative NLR Score**

| | POC | |
|---|---|---|
| **Variables** | **OR (95% CI)** | **p** |
| CCI score ≥3 | 1.576 (0.950-2.613) | 0.048 |
| IOP-Bleeding | 1.077 (0.1001-1.005) | <0.001 |
| Length of postoperative stay | 1.058 (1.023-1.095) | 0.001 |
| NLR ≥ 3.00 | 1.675 (1.027-2.730) | 0.039 |

OR: Odds Ratio. CCI: Charlson Comorbidity Index. IOP: Intraoperative. POC: Postoperative Complication.

cyte counts. Both components are markers of systemic inflammatory response and lead to a reduced immune response with a predisposition to bacterial infections.[13] The complication relationship with NLR has been examined in various articles. Cook et al.[14] reported that post-operative NLR predicts complications following colorectal surgery. In the study of Vulliamy et al.,[15] a correlation was found between post-operative NLR values and complications in esophageal cancer. Mohri et al.[16] emphasized that NLR independently predicted the POCs after gastrectomy. Similarly, in our study, there was a significant relationship between pre-operative NLR and POC (p=0.039).

According to Kawada et al.[17] reported that intra-operative bleeding of 100 ml or more was associated with anastomotic leakage. Similarly, in our study, it was observed that bleeding of 100 ml or more was associated with POCs.

The previous studies have shown that open surgery, increased comorbidity, long operation time, and POCs are involved in a prolonged LOS.[18] In our study, CCI was associated with POCs reflecting high comorbidity, while surgery time and surgical procedures (open/laparoscopy) did not reflect POCs. However, those with POCs had a significantly prolonged LOS.

There are some limitations associated with this study. First, we evaluated a relatively small number of patients, and the study design was retrospective. Second, we did not examine the patients' underlying diseases affecting the serum level, such as liver cirrhosis and chronic renal failure. Third, the optimum cutoff value for the pre-operative ratio is unknown, although we set it in this study using the ROC analysis.

## Conclusion

Our study demonstrated that the NLR is closely associated with POC in patients who underwent curative surgery for colorectal cancer. NLR is easily obtained from the widely available findings of routine blood tests and may thus be useful in the clinical setting.

### Disclosures

**Ethichs Committee Approval:** The Clinical Research Ethics Committee approved the study of our institution (Ethical Committee No: 2019.7150-266).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – A.S.S., S.G., O.U., M.D.; Design – A.S.S., S.G., O.U., İ.E.S.; Supervision – A.S.S., S.G., B.Ş., E.P.; Materials – A.S.S., O.U., B.Ş., İ.E.S.; Data collection and/or processing – A.S.S., B.Ş., İ.E.S., E.P.; Analysis and/ or interpretation – A.S.S., S.G., E.P., M.D.; Literature search – A.S.S., O.U., İ.E.S., B.Ş.; Writing – A.S.S., S.G., E.P., M.D.; Critical review – A.S.S., O.U., B.Ş., İ.E.S.

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