

# Neutrophil to lymphocyte ratio in predicting postoperative complications and prognosis in patients with colorectal cancer

## Authors' Contribution:

A – Study Design  
B – Data Collection  
C – Statistical Analysis  
D – Data Interpretation  
E – Manuscript Preparation  
F – Literature Search  
G – Funds Collection

Julia Fuss<sup>1ABE</sup>, Anna Voloboyeva<sup>2BC</sup>, Viktor Polovjy<sup>3CD</sup>, Roksolana Yaremkevych<sup>4BD</sup>

<sup>1</sup>Department of Surgery, Hospital in Pustomy, Lviv, Ukraine

<sup>2</sup>Department of Anaesthesiology and Intensive Care, Communal Municipal Clinical Hospital, Lviv, Ukraine

<sup>3</sup>Department of Surgery, Bukovinian State Medical University, Chernovtsy, Ukraine

<sup>4</sup>Department of Surgery and Transplantology Faculty of Postgraduate Education, Lviv State Medical University, Ukraine

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## ABSTRACT:

**Introduction:** Biological markers of inflammation are among the main tools for predicting the risk of developing postoperative infectious complications at the preclinical stage. One of these biomarkers is the neutrophil-lymphocyte ratio (NLR), but the insufficient number of studies does not allow judging its value as a marker of infectious complications in colorectal surgery.

**Aim:** Aim of the study to determine the predictive value of the neutrophil-leukocyte ratio as a predictor of infectious complications after colon surgery.

**Methods:** From September 2018 to December 2021, 234 patients were enrolled in the study after colon surgery. The frequency of infectious complications, the differences in the levels of NLR in patients with and without infectious complications were determined.

**Results:** One hundred and thirty-seven patients met the criteria of NLR-low, and 97 patients were categorized as NLR-high. The NLR status was significantly correlated with T-stage, perineural invasion, and increased likelihood of complications. Univariate analysis indicated that both low albumin and meeting the criteria for the NLR-high group correlated with an increased occurrence of complications. Multivariate analysis identified NLR-high and low albumin levels as independent predictors for complications.

**Conclusion:** The neutrophil-lymphocyte ratio is a reliable predictor in predicting the risk of developing infectious complications in colorectal surgery. In addition, low values of this biomarker are a significant criterion for a safe discharge of patients from hospital. The prevalence and availability of this test makes it easily reproducible in clinical practice.

## KEYWORDS:

colorectal cancer, complications, neutrophil-lymphocyte ratio, treatment

## ABBREVIATIONS

**CBC** – complete blood count

**CRC** – Colorectal cancer

**LN** – lymph node

**LVI** – lymphovascular invasion

**N stage** – metastasis

**NLR** – neutrophil-lymphocyte ratio

**PNI** – perineural invasion

**POS** – postoperative stay

**ROC** – Receiver Operating Characteristic

**T stage** – tumor invasion

## INTRODUCTION

Colorectal cancer (CRC), despite the introduction of screening programs and equipping clinics with modern diagnostic equipment, retains a leading position in the structure of cancer morbidity and mortality throughout the world. According to the American Association of Oncologists for 2019, in the United States in the structure of the incidence of colorectal cancer it takes the fourth place, and in the structure of mortality – the second place [1]. A similar situation, according to the European Society of Medical Oncology, is observed in most European countries [2]. However, in

the United States and Europe, there was a trend towards a gradual decrease in morbidity and mortality in the period 1980–2015 [1–3], in contrast to the situation in Ukraine. According to the Association of Oncologists of Ukraine, the increase in the incidence of malignant neoplasms of the colon over the period 2008–2018 among men was up to 19.2%, among women – up to 11.8% [4]. In 2018, malignant neoplasms of the colon in the structure of morbidity of both sexes occupy the fourth place (7.8%), in the structure of mortality – the third place (8.3%). The average age of patients with newly diagnosed colorectal cancer in men is 68–70 years, and in women – 70–72 years. There are gender differences in the structure of colon cancer mortality: in women, CRC as the cause of death takes the second place and takes the leading positions in the age group of 60–69 years, in men it takes the fourth place in the age group of 70 years and older [4]. In 35% of cases, patients seek medical help at stages III–IV of the disease [4, 5] and, as a result of late diagnosis, are hospitalized in general surgical hospitals for complications of colorectal cancer. Complicated forms of cancer prevail in elderly and senile patients and range from 45.5 to 85.2% [5]. Complications of colorectal cancer include perifocal pyoinflammatory processes, tumor invasion into adjacent organs and tissues, acute intestinal obstruction, bleeding, tumor perforation, and their combinations. A significant proportion of patients with complicated CRC in old age are characterized by a blurred clinical picture and the absence of pathognomonic symptoms, which significantly complicates the diagnosis at the pre- and hospital stages,

Tab. I. Characteristics of patients and surgery types.

VARIABLE	N	%
Age (year)	72.8	100
Gender		
Male	125	53.4
Female	109	46.6
BMI (kg/m <sup>2</sup> )*		
Low (<25)	145	61.9
High (≥25)	89	38.1
Degree of anesthetic risk, n (%)		
I	104	44.3
II	64	27.4
III	53	22.7
IV	13	5.6
Tumor location		
Ascending & Cecum	154	65.8
Transverse	39	16.7
Descending	27	11.5
Sigmoid	10	4.3
Rectum	4	1.7
Surgery type, n (%)		
Right-sided hemicolectomy	34	14.5
Left-sided hemicolectomy	22	9.4
Sigmoid colon resection	31	13.3
Anterior rectal resection	61	26
Low anterior rectal resection	15	6.4
Abdominal anal rectal resection	4	1.7
Reconstructive surgery	67	28.7
T stage		
T1/T2	80	34.2
T3/T4	154	65.8
N stage		
No	178	76
N+	56	24
NLR†		
Low (<3)	158	67.5
High (≥3)	76	32.5
Complications		
Yes	143	61.1
No	91	38.9

and concomitant somatic pathology worsens the prognosis and treatment results. Postoperative infectious complications (herein after infectious complications) are an urgent problem of colorectal surgery [1]. Their frequency can reach 20% [2], and in 3% of observations can cause death [3]. In patients operated on for colon cancer, a leaky interintestinal anastomosis, as one of the manifestations of an infectious complication, can lead to a local recurrence of the disease [4] and negatively affect overall and relapse-free survival [3, 5]. It should be noted that the development of an infectious complication increases the cost and duration of treatment [6, 7]. Early detection and timely active treatment tactics can reduce the consequences of infectious complications [8].

The use of biomarkers of inflammation is one of the routine tools in postoperative monitoring. Surgical interventions are closely related to the development of a systemic inflammatory response of the body, characterized by metabolic and immunological changes [9]. During this period, there is an increase in the level of circulating neutrophils in the blood and a decrease in the level of lymphocytes, which leads to immunosuppression as one of the key aspects of the development of an infectious complication [10]. In this regard, the assessment of the level of neutrophil-lymphocyte ratio (NLR) can serve as a simple and effective tool for identifying patients at high risk of developing infectious complications. Most studies in colorectal surgery using this biomarker are devoted to the study of the role of NLR as a predictor of recurrence of malignant neoplasms [11, 12] and a marker of overall and disease-free survival in patients with colon cancer [13, 14]. There are a number of studies that characterize NLRs as a marker of all postoperative complications in colorectal surgery, but their small number does not allow a full assessment of its clinical significance [15, 16]. To answer this question, we conducted a study to assess the predictive value of NLR as a biomarker of infectious complications in colorectal surgery.

## AIM

To determine the predictive value of NLR as a predictor of infectious complications after colon surgery.

## METHODS

The study included all patients who required surgical treatment for colorectal cancer or underwent reconstructive colon surgery provided there were no persistent foci of infection, complicated forms of inflammatory bowel diseases, autoimmune diseases, leukopenia or leukocytosis (the level of leukocytes is lower than  $4 \times 10^9/l$  and above  $10 \times 10^9/l$ ).

In the period from September 2018 to December 2021, the study included 234 patients operated on in Regional hospital in Pustomyty, in Communal Municipal Clinical Hospital 8, in the Department of Surgery of Bukovinian State Medical University and in the Department of Surgery and Transplantology Faculty of Postgraduate Education. In 148 (63.3%) of 234 cases, colon resection was performed for colorectal cancer, and 86 (36.7%) patients underwent reconstructive surgery with the elimination of a single-barrel colostomy after Hartmann-type operations. The median age of the patients was 62 (53; 75) years. There were no statistically significant differences in gender distribution. Most of the patients had a grade I anesthetic risk, and the mean body mass index corresponded to normal values. There were also no significant differences in the type of operational access.

We examined clinical variables including age, sex, obesity rate, length of hospital stay, complications, and tumor site. Pathologic variables assessed included tumor invasion (T stage), lymph node (LN) metastasis (N stage), lymphovascular invasion (LVI), and perineural invasion (PNI). Tumor location was classified into five zones: ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. NLR values and blood test results were obtained from a peripheral blood smear performed within one month prior

**Tab. II.** Comparison of demographic characteristics and laboratory findings with stage I-II and stage III-IV tumors.

VARIABLES	TOTAL (N = 198)	STAGES T1/T2 (N = 80)	STAGES T3/T4 (N = 154)	P-VALUE
	Mean ± SD	Mean ± SD	Mean ± SD	
Platelet, K/mL	341.30 ± 125.84	338.82 ± 126.38	334.41 ± 124.54	0.754
Neutrophil, K/mL	7.41 ± 3.87	6.84 ± 4.1	8.45 ± 4.21	0.015
Lymphocyte, K/ml	1.87 ± 0.735	1.81 ± 0.698	1.65 ± 0.698	0.038
NLR	5.64 ± 5.45	4.62 ± 4.79	6.51 ± 5.61	0.041
PLR	241.02 ± 135.41	220.42 ± 131.28	249.25 ± 139.45	0.089

to surgery. Postoperative complications were grouped by Clavien-Dindo classification and those meeting the criteria for a score of grade III or higher were categorized as a major complication. The length of postoperative stay (POS) was calculated as the number of days from surgery to discharge from hospital.

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. NLR values less than or equal to three were classified as low, where levels greater than 3 were defined as high. Complete blood count analyses were performed using the Sysmex XN-2000 and XN-3000 analyzers (CELL-DYN Ruby [Abbott; CIAA]). Of all 107 patients, no deaths occurred during the postoperative stay.

Patient data were entered into an Excel spreadsheet. Statistical processing and graphic presentation of the material were performed using SPSS Statistics 22.0, MedCalc version 19, Review Manager 5.4 and RStudio for Windows. Mean comparisons were made using an unpaired t-test with Student's correction for small samples. The Mann-Whitney test was used with a nonparametric population distribution. The cutoff points for NLR values on postoperative days 3 and 6 as a predictor of infectious complications were determined using the Receiver Operating Characteristic (ROC) analysis. The values of the best sensitivity and specificity were determined based on the Youden index. To assess the predictive value of NLR relative to the threshold level, the sensitivity, specificity, positive and negative predictive values were calculated. The results were considered statistically significant at  $p < 0.05$ .

## RESULTS

Of all 234 patients, 125 were male and 109 were female. The mean age was 72.8 years (69.6 for males and 75.2 for females). Tumor type was defined as colon cancer in 137 patients and rectal cancer in the remaining 97 patients. The location of colon cancer was the ascending colon and cecum in 77 cases, the transverse colon in 39, and the descending and sigmoid colon in 41. Laparoscopic procedures were performed in a total of 88 cases and converted to laparotomy in eleven. Subjects were divided into two groups by T stage, either T1/T2 or T3/T4. The majority of patients (154, 65.8%) were stage T3/4 (Tab. I).

Tab. II. presents the data of laboratory analyzes of patients with different stages of the disease.

Infectious complications were detected in 59 (25.2%) of 234 patients included in the study protocol. Almost half of the observations (44.9%;) in the structure of complications were organospatial SSI, most of which was represented by the failure of the interintestinal

**Tab. III.** Types of infectious complications.

COMPLICATION TYPE	N (%)
Organo-spatial SSI	25 (42.4%)
Surface SSI	17 (28.8%)
Postoperative distant operation	11 (18.6%)
Combined infectious complications	6 (10.2%)
Total	59 (100%)

**Tab. IV.** Relationship of NLR\* with various clinicopathologic parameters.

VARIABLE	NLR < 3	NLR ≥ 3	P-VALUE
Gender			0.396
Male	89 (71.2%)	36 (28.8%)	
Female	62 (56.9%)	47 (43.1%)	
Location			0.245
Colon	140 (60.9%)	90 (39.1%)	
Rectum	3 (75%)	1 (25%)	
T stage			0.013
T1/T2	54 (67.5%)	26 (32.5%)	
T3/T4	87 (56.5%)	67 (43.5%)	
N stage			0.456
NO	114 (64.1%)	64 (35.9%)	
N+	41 (73.2%)	15 (26.8%)	
Complication			0.04
Yes	74 (51.7%)	69 (48.3%)	
No	32 (35.2%)	59 (64.8%)	

anastomosis (92.3%;). Two (6.9%) of 59 patients had a combined infection in the form of a combination of superficial SSI and postoperative distant infection. The median time of development of infectious complications was 7 (4; 8) days after surgery.

Correlation between NLR and clinic-pathological variables (Tab. III.). A total of 158 patients met the criteria for the NLR-low group with the remaining 76 who met the criteria for the NLR high group. T stage, perineural invasion, and occurrence of complications were identified as factors correlated with NLR value. NLR levels were significantly elevated in cases that were categorized as T3/4 ( $P = 0.013$ ), which comprised 65.8% of all patients, while 34.2% of patients met the criteria for stage T1/2.

Of patients with complications, 25.6% were categorized as NLR high and 4.4% were designated as NLR low. There were no significant correlations between NLR and any other factors (Tab. IV.).

Univariate analysis found that the occurrence of complications was significantly associated with the clinicopathological variables of NLR. The univariate analysis revealed that complications occurred in 18 of 76 patients in the NLR-high group, and 9 of 158 in the NLR-low group, which was statistically significant ( $P = 0.04$ ).

A multivariate analysis examining the relationship between complications and clinicopathological variables showed that a high NLR in a group of patients was a predictor of complications ( $P = 0.016$ , odds ratio 9.827).

## DISCUSSION

Most NLR are aimed at evaluating studies of the correlation between the level of biomarkers and oncological prognosis of diseases in patients with colorectal cancer [13, 14]. According to the latest meta-analysis by Li H. et al. (2019), which included 5897 cases, a high preoperative NLR value (cutoff point of the biomarker level – 5) has a direct correlation with the worst overall (RR = 1.66; 95% CI: 1.36–2.02,  $P < 0.001$ ) and disease-free survival (RR = 1.54; 95% CI: 1.18–2.02,  $P = 0.002$ ).

The high preoperative value of NLR also has a direct correlation with the risk of complications after surgical treatment.

Palin R. et al. (2017) in their study demonstrated a statistically significant relationship ( $P = 0.031$ ) between a high biomarker value (cutoff point of the NLR level – 5) and an increased risk of death within 30 days in patients undergoing emergency surgery for colorectal cancer [17].

A high level of NLR after surgery is also associated with an increased incidence of complications [15, 16]. A study by Benlice C. et al. (2019) included 1328 patients undergoing colon surgery. On the 2nd day after surgery, NLR turned out to be a significant predictor of all complications without differentiation into infectious and non-infectious with a biomarker level greater than or equal to 9.2 (OR = 1.43; 95% CI: 1.03–1.98;  $P = 0.02$ ) [16].

In the era of the introduction of the program of accelerated recovery in surgery, when treatment in the postoperative period is aimed at

safely reducing the patient's stay in the hospital, and the postoperative bed-day is, on average, 5 days [7], there is a need for routine use of inexpensive, affordable and highly informative biomarkers of safe patient discharge from hospital. One of them, having a high negative significance (91.7% – on the third and 94.3% – on the sixth POD), can be an NLR.

Since the purpose of this study was to predict the development of short-term complications in the early postoperative period, we used a cutoff value that included extended periods. Rather than cutoff values calculated from a complicated statistical process, the most commonly used cutoff value of  $NLR \geq 3$  was applied to determine its association with various clinical variables [16, 18].

The current study is limited by the retrospective nature of the analysis, and the lack of exclusion of patients with asymptomatic inflammatory conditions, drug history or family history. The current study was also limited by a relatively small sample size. Furthermore, the dynamic changes that occur using complete blood count (CBC) could have influenced the accuracy of test results due to differing periods of blood sample collection. Thus, it should be taken into consideration that blood sample collection was carried out within one month prior to surgery, and the results may vary due to differences in the timing of collection [19, 20]. Although this study used a cutoff value of 3, additional studies are warranted to determine which NLR cutoff value is most appropriate. Therefore, more prospective studies with a larger sample size in the future are crucial to elucidate the prognostic value of NLR in predicting postoperative complications of patients with CRC [21, 22].

## CONCLUSION

The neutrophil-lymphocyte ratio is a reliable predictor in predicting the risk of developing infectious complications in colorectal surgery. The high predictive value of CRP and PCT, as well as high availability and low cost of performing a clinical blood test, make NLR a more promising test in clinical practice. In addition, low values of this biomarker are an important criterion for the early safe discharge of patients from hospital.

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Corresponding author: Julia Fuss MD; Department of Surgery, Hospital in Pustomyty, Lviv; Gorbaczewskogo street 4, 36, Lviv 79041, Ukraine; Phone: +38 067 989 19 35; E-mail: [juliafuss78@gmail.com](mailto:juliafuss78@gmail.com)

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