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NEUTROPHIL-TO-LYMPHOCYTE RATIO AS AN INFECTIOUS COMPLICATIONS BIOMARKER IN COLORECTAL SURGERY (own data, systematic review and metaanalysis)

Yuri A.Shelygin, Marina A.Sukhina, Elnur N.Nabiev, Alexey A.Ponomarenko, Marat A.Nagudov, Alexey I.Moskalev, Oleg I.Sushkov, Sergey I.Achkasov

Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya str., 2, Moscow, 123423, Russia)

BACKGROUND: biological markers of inflammation belong to the main tool for predicting the risk of infectious complications at the preclinical stage. One of such biomarkers is the neutrophil-to-lymphocyte ratio (NLR), but an insufficient number of studies does not allow us to estimate its value as a predictor of infectious complications in colorectal surgery.

AIM: to determine the predictive value of NLR as a predictor of infectious complications after colorectal surgery.

PATIENTS AND METHODS: from January 2018 to December 2019 192 patients after colorectal surgery were included in the study. The rate of infectious complications, NLR levels differences in patients with and without infectious complications were determined, the area under the curve (AUC), sensitivity, specificity, negative and positive prognostic value of NLR on the 3rd (POD) and the 6th (POD) postoperative days were assessed. A literature search and meta-analysis of the data in accordance with the preferred reporting items for systematic reviews and meta-analyses checklist (PRISMA) were conducted. The information was taken from the Medline electronic database and the E-library, scientific electronic library, among the English and Russian literature without publication date restrictions by the keywords: "neutrophil/lymphocyteratio", "neutrophil-to-lymphocyte ratio", "neutrophil lymphocyte ratio", "neutrophil ratio", "lymphocyte ratio", "colorectal", "colon", "rectum". The systematic review included all the studies related to assessing the prognostic value of NLR as a predictor of infectious complications in colorectal surgery.

RESULTS: infectious complications were detected in 29 (15.1%) of 192 patients. On the 3rd and the 6th POD, the patients with infectious complications had higher median NLR values than the patients without complications (p=0.0017 for the 3rd POD; p=0.018 for the 6th POD). On the 3rd POD, the area under the curve at the NLR cut-off point 5.13 was 0.644, sensitivity – 69.7%, specificity – 60.7% (p=0.019). On the 6th POD, similar indicators at an NLR cut-off point of 3.94 were 0.75, 75.9% and 70.6%, respectively (p<0,001). Four studies, which included 1,152 observations, were added in the meta-analysis. On the 3th POD, the summarized AUC was 0.671, sensitivity – 86.3%, specificity – 60.3% (p=0.014). The risk of infection with a biomarker above the threshold increased by more than 10 times (OR=10.2; 95% CI: 1.4-72). On the 4th POD, the above indicators were 0.711, 75.4%, 87.5%, respectively (p=0.002). Odds ratio was 51 (95% CI: 20-128).

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

[Key words: colorectal surgery, postoperative infectious complications, surgical site infection, inflammation biomarker, neutrophil-to-lymphocyte ratio]

CONFLICTS OF INTERESTS: The authors declare no conflicts of interest.

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Address for correspondence: Nabiev E.N., Ryzhikh National Medical Research Center of Coloproctology, Salyama Adilya str., 2, Moscow, 123423, Russia; e-mail: elnur.n@hotmail.com

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INTRODUCTION

Postoperative infectious morbidity (hereinafter referred to as infectious complications) is a crucial problem in colorectal surgery [1]. Their incidence can reach 20% [2], and in 3% of cases they can cause a mortality [3]. In patients operated on for colorectal cancer, the anastomotic leakage, as one of the manifestations of an infectious complication, can lead to the local disease recurrence [4] and negatively affects the overall and disease-free survival [3,5]. It is worth noting that the development of an infectious complication increases the cost and duration of treatment [6,7]. Early detection and timely active treatment approaches can reduce

the consequences of infectious complications [8]. The use of inflammation biomarkers is one of the routine tools for monitoring the postoperative period. Surgical procedures are closely associated with the development of a systemic inflammatory response, characterized by metabolic and immunological changes [9]. During this period there is an increase in circulating levels of neutrophils and reduction of lymphocytes, leading to immunosuppression, as one of the key aspects of the development of infectious complications [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 with a high risk of infectious complications. Most studies in colorectal surgery on this biomarker are devoted to estimate the role of NLR as a predictor of malignant neoplasms recurrence [11,12] and a marker of overall and disease-free survival in patients suffering from colorectal cancer [13,14]. There are a number of studies that characterize NLR as a marker of all postoperative complications in colorectal surgery, but their small number does not allow us to fully assess its clinical significance [15,16]. To answer this question, we conducted a prospective observational study to assess the predictive value of NLR as a biomarker of infectious complications in colorectal surgery. Given the lack of a systematic review of the literature and meta-analysis of data on the above problem, we searched for all available similar studies, after which we did a cumulative meta-analysis of the literature and our own data.

AIM

To assess the prognostic value of NLR as a predictor of infectious complications after colorectal surgery.

PATIENTS AND METHODS

The study included all the patients who required surgery for colorectal cancer or underwent reversal of Hartmann's procedure in the absence of persistent foci of infection, complicated forms of inflammatory bowel diseases, autoimmune diseases, leukopenia or leukocytosis (white blood cell levels below $4x10^9$/l and above $10x10^9$/l). The study was approved by the ethics committee of the A.N.Ryzhikh National Medical Research Center of Coloproctology. In the period from January 2018 to December 2019, the study included 192 patients. In 148 (77.0%) bowel resection was performed for colorectal cancer, and 44 (23.0%) patients underwent reversal of Hartmann's procedure

Table 1. *Characteristics of patients and surgery types*

Indicator	Result
Gender, n (%)	
Males	90(46.9%)
Females	102(53.1%)
Age, years (Me, quartiles)	62 (53;75)
Body mass index, kg/m^2 (Me, quartiles)	27,7 (24.6;31.2)
Grade of anesthetic risk, n (%)	
I	85(44.3%)
II	51(26.6%)
III	46(23.9%)
IV	10(5.2%)
Surgery type, n (%)	
Right hemicolectomy	20(10.4%)
Left hemicolectomy	16(8.3%)
Sigmoid resection	27(14.1%)
Anterior resection of the rectum	26(13.6%)
Low anterior resection of the rectum	44(22.9%)
Interspincteric resection of the rectum	12(6.2%)
Abdomino-perineal excision of the rectum	3(1.6%)
Reversal of Hartmann's procedure	44(22.9%)
Operation time, minutes (Me, quartiles)	200 (160;240)
Surgical approach, n (%)	
Open	108(56.3%)
Laparoscopic	84(43.7%)
Intraoperative bloodloss, ml (Me, quartiles)	60 (40;105)
Postoperative stay (days)(Me, quartiles)	8 (7;11)

(Table 1). The median age of the patients was 62 (53;75) years. There were no statistically significant differences in the gender distribution. Most patients had grade I anesthetic risk, and the average body mass index corresponded to normal values (Table1). There were also no significant differences in the type of surgical access (Table 1).

Neutrophils and lymphocytes in venous blood were counted on the first, third, and sixth postoperative days (POD) using the CELL-DYN Ruby device (Abbott, USA).

The neutrophil-lymphocyte ratio was calculated by dividing the absolute number of neutrophils by the absolute number oflymphocytes in the venous blood.

$$NLR = \frac{Absolute\ number\ of\ neutrophils}{Absolute\ number\ of\ lymphocytes}$$

Monitoring of infectious complications in the patients was carried out throughout the inpatient and outpatient stages of treatment until the 30th postoperative day. Surgical site infections (SSI) were registered according to the criteria of the US Center for disease control and prevention. Postoperative distant infection was diagnosed basing on the laboratory and instrumental tests [17].

The literature search and meta-analysis were done basing on the requirements of PRISMA [18] in the Medline electronic database among the English-language literature sources and the Russian-language publications in the scientific electroniclibrary E-library without restrictions on the publication date (search end on 04.06.2020) by the keywords: "neutrophil/lymphocyte ratio", "neutrophil-to-lymphocyte ratio", "neutrophil lymphocyte ratio", "neutrophil ratio", "lymphocyte ratio", "colorectal", "colon", "rectum", "neutrophil-lymphocyte ratio", "neutrophil-lymphocyte index". The systematic review includes all the studies that assess the prognostic value of NLR as a predictor of infectious complications in colorectal surgery.

Using the PubMed search system in the Medline database, the search system of E-library (http://www.elibrary.ru/) for queries containing the above keywords, 463 publications were found. During the screening, 87 papers that correspond to the study topic were selected. Then the literature reviews were excluded as follows: 7 reviews, 71 articles on the NLR assessment as a predictor of overall and disease-free survival and 6 articles on the NLR as a biomarker of all postoperative morbidity without division into infectious and non-infectious complications.

Based on the results of the systematic review of the literature, 3 studies that assess NLR as a predictor of infectious complications were selected. In addition, our own data (192 patients) were also included. The results of treatment of 1,152 patients were subjected to the meta-analysis (Fig.1) [19-21].

Statistical Processing of Results

The patients' data was entered in an Excel spreadsheet. The statistical processing and graphical presentation of the material were performed using SPSS Statictics 22.0, MedCalc version 19, Review Manager 5.4, and the RStudio electronic environment for Windows. The comparisons of the average values were made using an unpaired t-test with the Student's correction for small samples. The Mann-Whitney test was used for nonparametric distribution in the aggregate. Determination of the cut-off points of NLR values on the 3d and the 6th postoperative days as a predictor of infectious complications was performed using ROC-analysis (Receiver Operating Characteristic).

The best sensitivity and specificity values were determined based on the Euden index. To assess the predictive value of NLR relative to the threshold level, sensitivity, specificity, positive and negative predictive significance were calculated. The results were considered statistically significant at $p < 0.05$.

RESULTS

Our Own Study

Infectious complications were detected in 29 (15.1%) of 192 patients included in the study protocol (Table2). Almost half of the cases (44.9%; 13/29) in the structure of complications were organ-space SSI, most of which was represented by the anastomotic leakage (92.3%; 12/13). Two (6.9%) of 29 patients were diagnosed with a combined infection in the form of a combination of

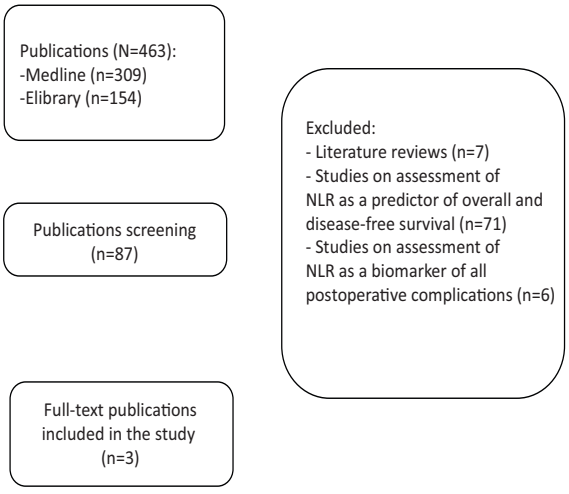


Figure 1. *Literature search diagram*

Table 2. *Types of infectious complications*

Complication type	n (%)
Organ-space SSI	13(44.9%)
Superficial SSI	9(31%)
Postoperative distant infection	5(17.2%)
Combined infectious complication	2(6.9%)
Total	29(100%)

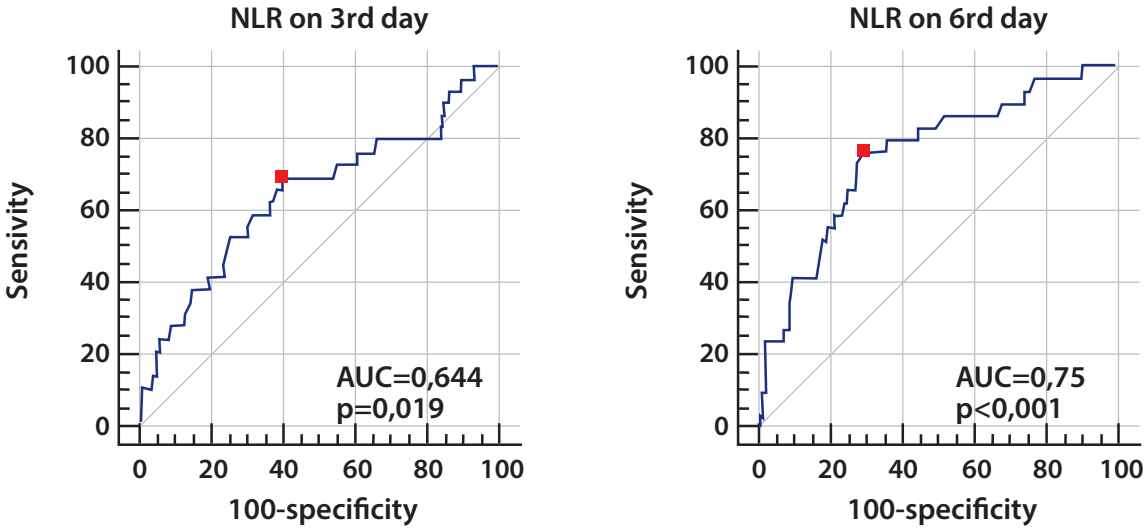


Figure 2. *ROC curve for the NLR as a predictor of infectious complications on the 3d POD and on the 6th POD*

superficial SSI and postoperative distant infection. The mean infectious complications was 7 (4;8) days after surgery.

When comparing the median levels of NLR in patients with and without infectious complications, a significant increase in the level of the biomarker was obtained for the 3d (p=0.013) and the 6th (p<0.001) POD. On the 3d POD, the median value of NLR in patients with infectious complications was 7(4.20;9.44), and on the 6th POD– 5 (4;6.7). For the patients without infectious complications, the biomarker median was 4.8 (3.37;6.95) for the 3d POD and 2.95 (2.28;4.25) for the 6th POD.

ROC-analysis of the level of changes in NLR on the 3d POD showed the area under the curve (AUC) equal to 0.64, which corresponds to a satisfactory data analysis model (Fig.2). In accordance with the constructed ROC curve, the cut-off point for NLR was equal to 5.13. On the 3d day after the surgery the sensitivity of NLR at the level of 5.13 was 69% (95% CI:49.2-84.7%), specificity - 60.7% (95% CI:52.8 – 68.3%), negative prognostic significance-91.7% (95% CI:86.3 – 95%), and positive prognostic significance - 23.8% (95% CI:18.6 – 29.9%). According to the data obtained, the value of NLRon the 3d POD less than 5.13 may indicate an extremely low risk of PIC - 8.3%, while if the value of NLR is more than 5.13, the risk of developing the latter is 69% (p=0.019).

On the 6th postoperative day AUC was 0.75, which proves the good quality of the data analysis model (Fig.2). The NLR sensitivity on the 6th POD at the cut-off level of biomarker – 3.94 was 75.9% (95% CI: 44.4 – 97.5%), the specificity of 70.6% (95% CI:84.5 – 98.2%), the negative predictive value was 94.3% (95% CI: 89.5 – 96.9%) and the positive predictive value - 31.4% (95% CI: 25.1-38.6%).

According to the results, on the 6th POD, the value of NLR less than 3.94 indicates a high probability of absence of infectious complications (94.3%), while at the level of NLR above 3.94, the risk of developing the latter is 75.9% (p<0.001).

Meta-analysis of Literature and Own Data

The data from the studies included in the meta-analysis is presented in table 3.

When analyzing NLR indicators as a marker of infectious

Table 3. *Characteristics of the included in the meta-analysis studies*

Authors	Year	Study type	Number of cases	Days of NLR assessment	Primary point of the study
Mik et al. (2018)	2018	Prospective observational	724	4	Organ-space SSI
Walker et al. (2018)	2018	Case-control study	136	1-5	Organ-space SSI
Shelygin et al. (2017)	2017	Prospective observational	100	3	Organ-space SSI
Shelygin et al. (2020)	2020	Prospective observational	192	3 and 6	Infectious complications

Table 3. *Characteristics of the included in the meta-analysis studies (continuation 1)*

Authors	Colon surgeries	Rectal surgeries	Others	Number of infectious complications	Infectious complications rate (%)
Mik et al. (2018)	419	305	0	33	4,6
Walker et al. (2018)	39	84	13	11	8,1
Shelygin et al. (2017)	0	100	0	20	20
Shelygin et al. (2020)	107	85	0	29	15,1

Table 3. *Characteristics of the included in the meta-analysis studies (continuation 2)*

Authors	AUC NLR 3rd day	Cut-off point NLR 3rd day	Sensitivity NLR (%) 3rd day	Specificity NLR (%) 3rd day	p, NLR 3rd day
Mik et al. (2018)	No data	НД	НД	НД	НД
Walker et al. (2018)	0,699	5,05	100	39,2	0,013
Shelygin et al. (2017)	0,65	3,7	95	83	0,26
Shelygin et al. (2020)	0,644	5,13	69	60,7	0,019

Table 3. *Characteristics of the included in the meta-analysis studies (continuation 3)*

Authors	AUC NLR 4th day	Cut-off point NLR 4th day	Sensitivity NLR (%) 4th day	Specificity NLR (%)4th day	p, NLR 4th day
Mik et al. (2018)	0,68	6,50	69	96,5	No data
Walker et al. (2018)	0,78	6,15	100	61,8	0,009
Shelygin et al. (2017)	No data	No data	No data	No data	No data
Shelygin et al. (2020)	No data	No data	No data	No data	No data

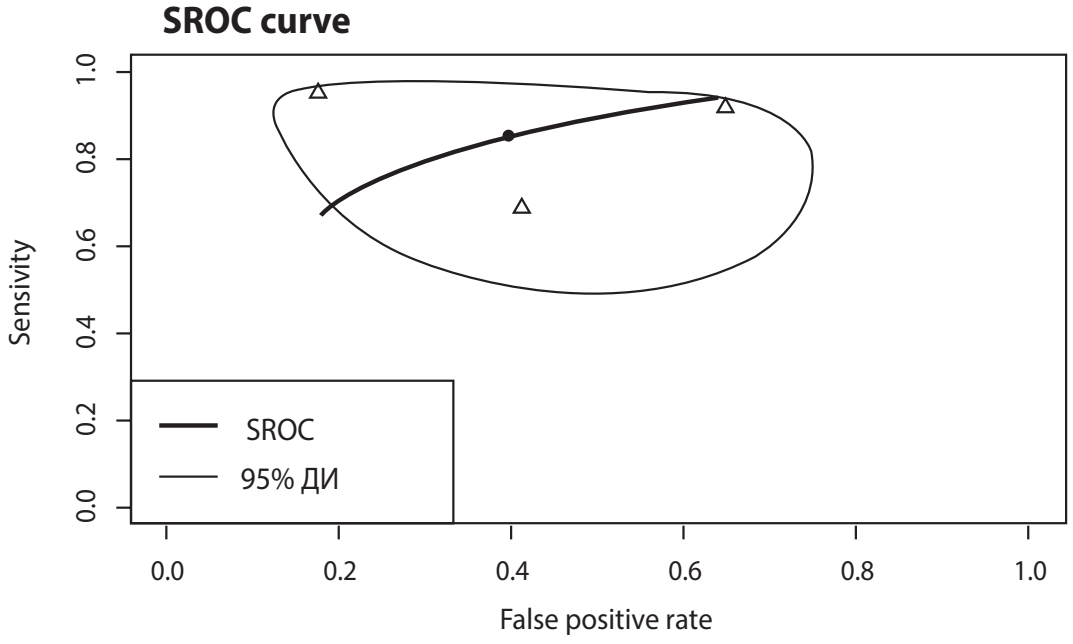
complications on the 3d day after surgery, the data on sensitivity, specificity and AUC was presented in the studies by Shelygin Yu.A. et al. (2017), Walker A. et al. (2018) and our data – in total of 428 cases. In the meta-analysis, it was found that the sensitivity of the method was 86% (95% CI: 63-95%), the specificity was 60% (95% CI:35-80%), and the combined AUC was 0.671 (p=0.014) (Fig.3). The chances of developing infectious complications when the NLR indicator is higher than the threshold value (interval 3.70-5.13) increase by more than 10 times (OR=10.2; 95% CI:1.4-72) (Fig.5).

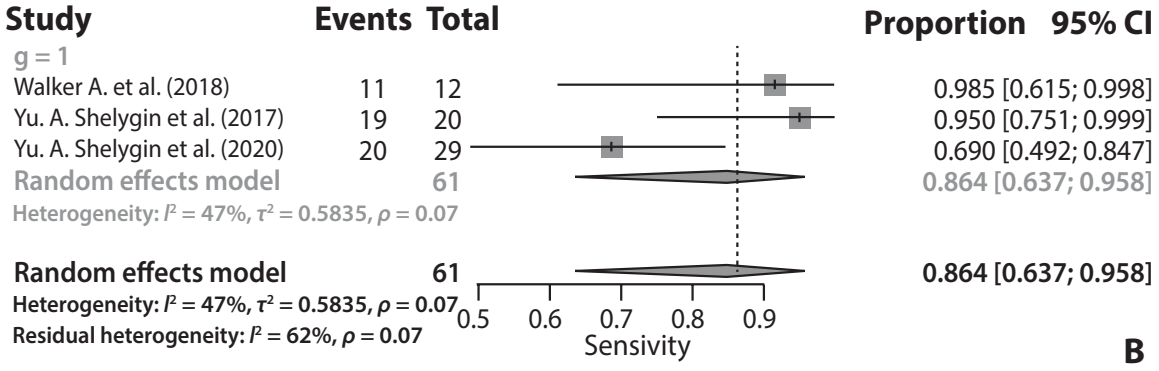
When analyzing the data corresponding to the 4th day after surgery, the data on sensitivity, specificity, and AUC was presented in 2 studies by Mik M. et al. (2018) and Walker A. et al. (2018) – in total of 860 cases.

The meta-analysis data revealed that the sensitivity of the method was 75% (95%CI: 61-85%), specificity was 87% (95%CI:50-98%), and the combined AUC was 0.71(p=0.02) (Fig.4). The chances of developing infectious complications when the NLR indicator is higher than the cut-off point (interval 6.15-6.50) increase by more than 50 times (OR=51;95% CI:20-128) (Fig.5).

DISCUSSION

Most NLR studies are aimed at assessing the correlation of the biomarker level and cancer prognosis in patients with colorectal cancer [13,14,22,23]. According to the latest meta-analysis by Li H. et al. (2019), which included 5,897 cases, a high preoperative NLR value (biomarker cut-off point - 5) has a direct correlation with the worst overall (OR=1.66; 95% CI: 1.36–2.02, p<0.001)





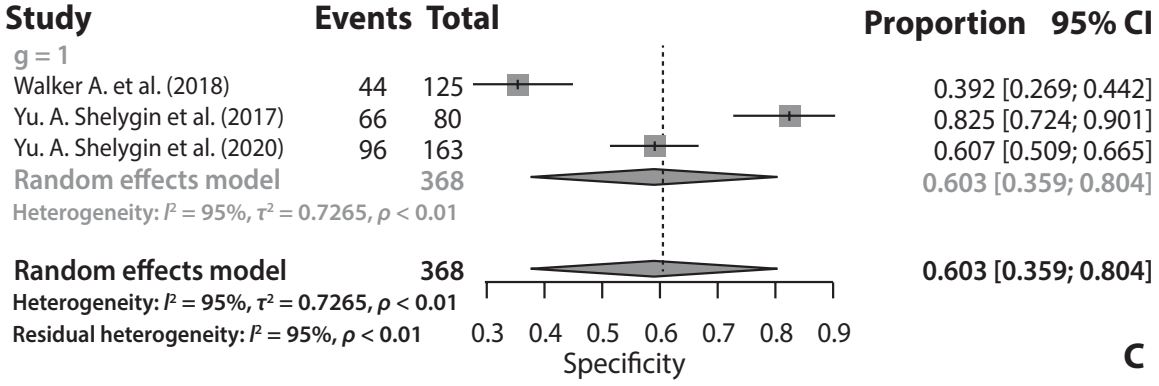
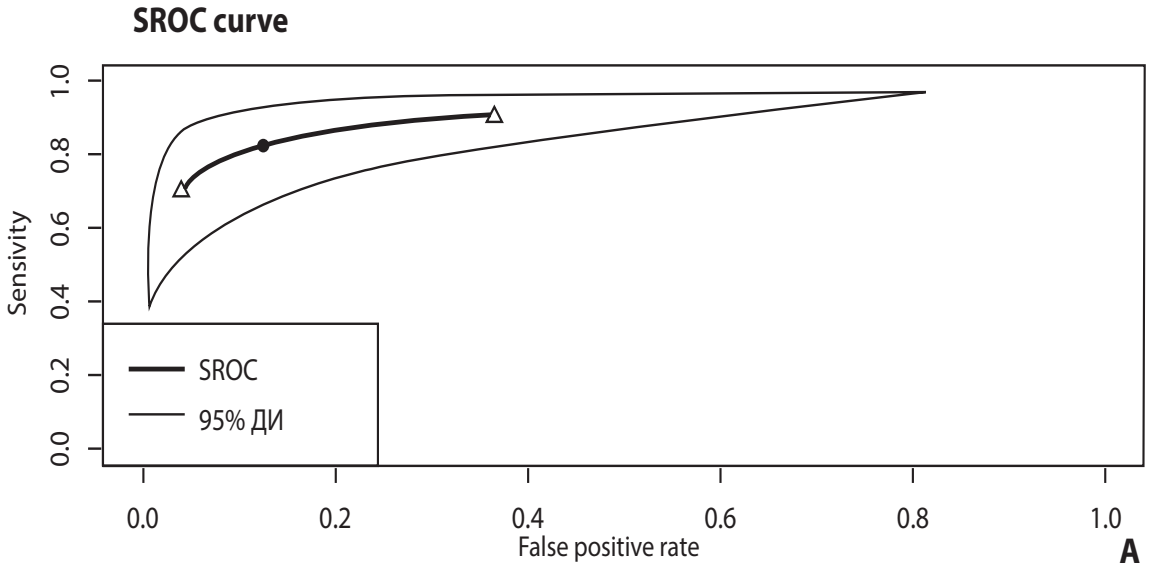
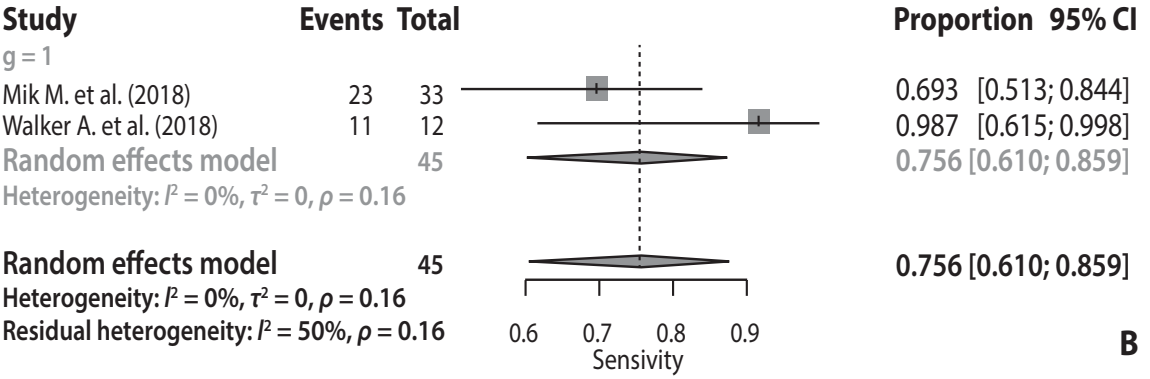


Figure 3. *Summarized ROC curve (SROC) (A), forest-plot of sensitivity (B) and specificity (C) for NLR as a predictor of infectious complications on the 3d POD*





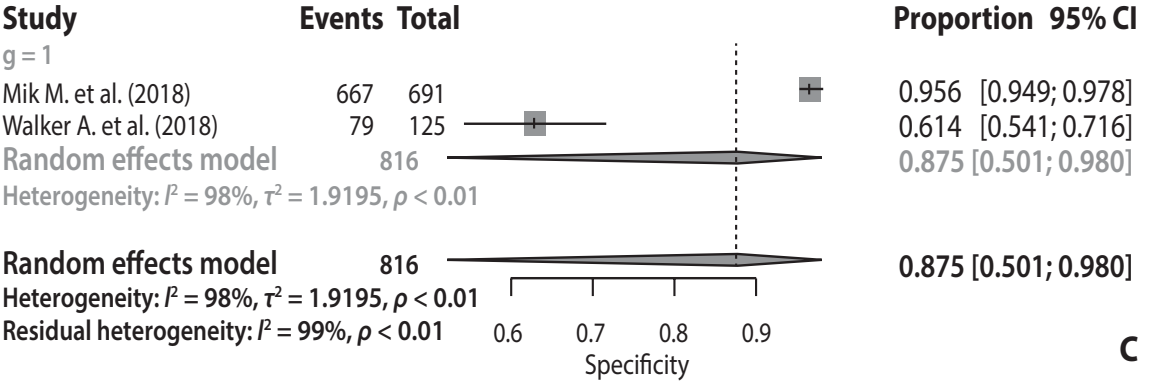


Figure 4. *Summarized ROC curve (SROC) (A), forest-plot of sensitivity (B) and specificity (C) for NLR as a predictor of infectious complications on the 4th POD*

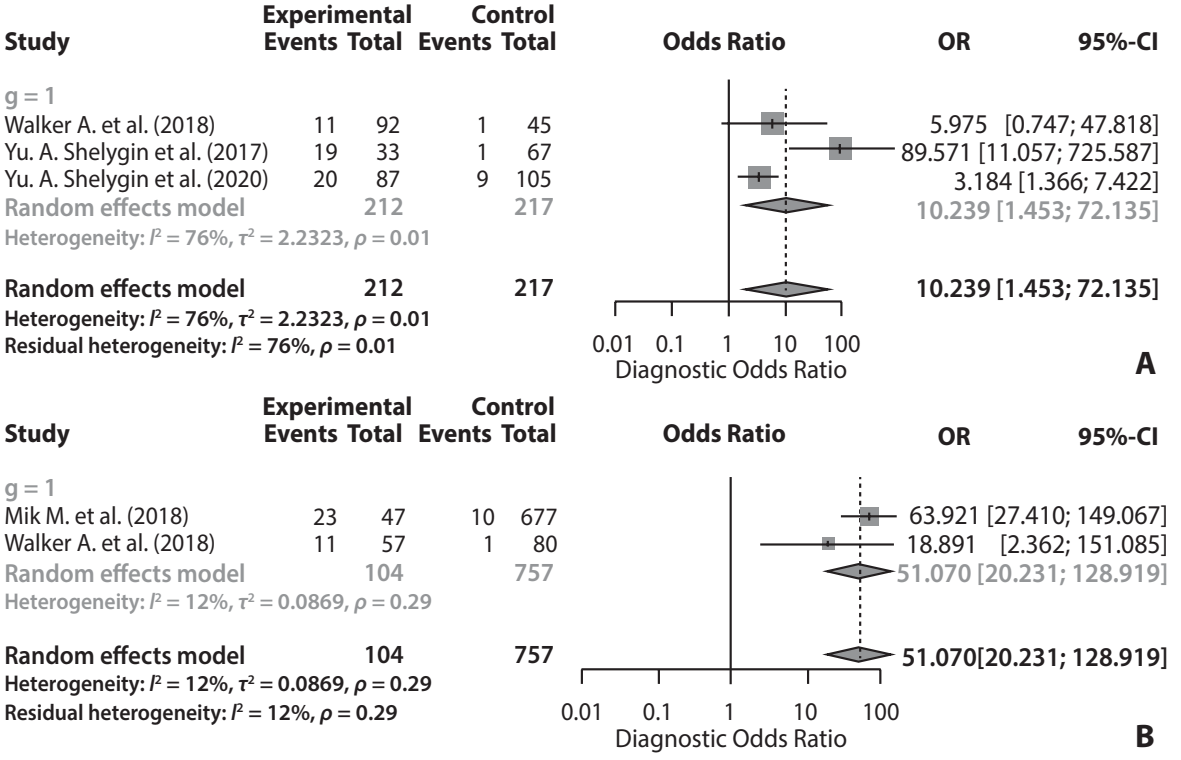


Figure 5. *Forest-plot of odds ratio after NLR risingon 3d (A) and 4th (B) POD*

and disease-free survival (OR=1.54; 95% CI: 1.18-2.02, p=0.002).

A high preoperative value of NLR also has a direct correlation with the risk of complications after surgeries. The study by Palin R. et al. (2017) demonstrated a statistically significant correlation (p=0.031) between a high biomarker value (the cut-off point of the NLR - 5 level) and an increased risk of death within 30 days in patients operated on for colorectal cancer in an emergency [24].

A high level of NLR after surgery is also associated with an increase in the incidence of complications [15,16]. In the study by Benlice C. et al. (2019), 1,328 patients who underwent colorectal surgery were included. On the 2nd day after the surgery, NLR was 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 time of introduction of the accelerated recovery program in surgery, when treatment in the postoperative period is aimed at safely reducing the patient's stay in hospital, and the postoperative hospital stay is on average 5 days [7], there is a need for routine use of inexpensive, accessible and highly informative biomarkers for safe discharge of the patient.

NLR, having a high negative significance (91.7% on the third and 94.3% on the sixth POD), can be one of them. We made a systematic review of the literature, based on the results of which 3 studies aimed at estimation the predictive value of NLR in relation to infectious complications in colorectal surgery were found.

After combining the data from the found publications and our own study based on the results of the 3d POD of the meta-analysis at the biomarker cut-off point in the range of 3.7-5.13, the combined AUC was 0.671, sensitivity - 86.3%, specificity - 60.3% (p=0.014), and the increase in the chance of developing an infectious complication was more than 10 times (OR=10.2; 95% CI: 1.4-72).

On the 4th day after the surgery with NLR in the range of 6.15-6.50, the similar indicators were equal to 0.711, 75.4% and 87.5%, respectively (p=0.002), and the chance of developing an infectious complication with a biomarker value above the threshold increased more than 50 times (OR=51; 95% CI: 20-128). The results can

indicate that with an increase of postoperative days there is an increase in test accuracy and specificity, but its sensitivity is reduced. However, due to the small number of the works included in the meta-analysis, there is the need for continuation of a prospective study to assess postoperative NLR as a predictor of infectious complications in colorectal surgery.

The other common biomarkers in the diagnosis of infectious complications are C-reactive protein (CRP) and procalcitonin (PCT).

The meta-analysis by Cousin F. et al. (2016), which included 11 studies and 2,692 patients, assessed the predictive value of CRP and PCT as markers of organ-space SSI in colorectal surgery [25]. On the 3d POD for CRP, the combined AUC for CRP was 0.8, sensitivity 75%, specificity 72%, and for PCT 0.78, 69% and 71%, respectively. Comparing these data with the results obtained in the study, we can note a higher accuracy and specificity of the CRP and PCT test, but lower sensitivity. On the 4th POD the authors obtained similar values of the area under the curve (AUC) – 0.79 for CRP and 0.72 for PCT, an increase in the sensitivity of the test – 78% for CRP and PCT, but a decrease in specificity to 71% for CRP and 52% for PCT, which does not correlate with our results. Analyzing the AUC values, we can say that CRP and PCT have a higher predictive value than NLR as a predictor of infectious complications in colorectal surgery (on the 3d POD AUC for CRP – 0.8, for PCT– 0.72, and for NLR – 0.671, on the 4th POD - 0.79, 0.72 and 0.711, respectively). However, given the wide availability of clinical blood test and its low cost, NLR can become a new option in the structure of clinical blood test, allowing to effectively predict the risk of infectious complications in colorectal surgery.

CONCLUSION

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

THE PARTICIPATION OF THE AUTHORS:

Concept and design of the study: *Shelygin Yu.A., Achkasov S.I., Sukhina M.A.*

Collection and processing of the material: *Sukhina M.A., Nabiev E.N.*

Statistical processing: *Ponomarenko A.A., Nabiev E.N., Nagudov A.A.*

Writing of the text: *Nabiev E.N.*

Editing: *Shelygin Yu.A., Achkasov S.I., Sushkov O.I., Moskalev A.I.*

ORCID

Shelygin Yu.A. https://orcid.org/0000-0002-8480-9362

Sukhina M.A. https://orcid.org/0000-0003-4795-0751

Nabiev E.N. https://orcid.org/0000-0003-3774-8795

Ponomarenko A.A. https://orcid.org/0000-0001-7203-1859

Nagudov M.A. https://orcid.org/0000-0002-0735-2100

Sushkov O.I. https://orcid.org/0000-0001-9780-7916

Moskalev A.I. https://orcid.org/0000-0002-3248-1633

Achkasov S.I. https://orcid.org/0000-0001-9294-5447

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