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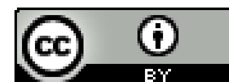

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DETERMINATION OF PREDICTORS OF COLORECTAL CANCER RECURRENCE IN RADICALLY OPERATED PATIENTS

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ABSTRACT

Introduction. The high risk of recurrence of colorectal cancer (CRC) in radically operated patients has become the reason for discussions about the issue of intensification of the observation period and the search for reliable predictors of the course of the disease. Inflammatory markers (IM) have shown promise in this aspect. The main goal of this study was to evaluate IM as predictors of CRC recurrence in radically operated patients. Of secondary importance was to determine which of the patient's and tumor's basic characteristics influence the recurrence-free survival (RFS) and overall survival (OS) in the same cohort of patients.

Materials and Methods. The data of 138 patients from the Municipal Non-Profit Enterprise of Sumy Regional Council "Sumy Regional Clinical Oncology Center" was used for the research. Patients with CRC who underwent radical surgery for stage I–III colon or rectal tumors between December 2019 and December 2020 were included. Gender, age, body mass index (BMI), tumor location, stage, T, N, neoadjuvant and adjuvant therapy, degree of tumor differentiation, and IM were evaluated as potential predictors of disease recurrence. IM were calculated based on data from clinical and biochemical blood tests performed no more than a week before the surgery. The studied IM were: neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), prognostic nutritional index (PNI), advanced lung cancer inflammation index (ALI) and level of lymphocytes x albumin (LA). ROC analysis (AUC≥0.7), Kaplan-Meier method, Log-rank test ($p < 0.05$) and multivariate Cox regression analysis with the Breslow method (confidence interval (CI) – 95%, $p < 0.05$) were used for the statistical data processing.

Results. According to the results of the ROC analysis, LA was the only statistically significant IM (AUC=0.7592). LA demonstrated a

significant effect on RFS (Log-rank p=0.0000) and OS (Log-rank p=0.0023). Patients with LA<37.5 had a higher risk of relapse and death. According to the result of the multivariate Cox regression analysis with the Breslow method, age (p=0.032), BMI (p=0.048) and LA (p=0.031) were independent factors influencing the RFS and LA (p=0.008) was the only factor influencing the OS.

Conclusions. According to the results of this study, LA was determined as an independent predictor of the course of CRC after radical surgery. Patients with a low LA level had worse RFS and OS. In addition, age and BMI have been identified as basic characteristics of the patient that reliably influence RFS. Patients older than 65 years and overweight patients had a higher risk of disease recurrence.

Keywords: colorectal cancer, inflammatory markers, recurrence, radical surgery.

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РЕЗЮМЕ

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ВИЗНАЧЕННЯ ПРЕДИКТОРІВ РЕЦИДИВУ КОЛОРЕКТАЛЬНОГО РАКУ У РАДИКАЛЬНО ПРООПЕРОВАНИХ ПАЦІЄНТІВ

Вступ. Високий ризик рецидиву колоректального раку (КРР) у радикально прооперованих пацієнтів став причиною дискусій навколо питання інтенсифікації періоду спостереження та пошуку достовірних предикторів перебігу захворювання. Маркери запалення (МЗ) виявилися перспективними в цьому аспекті. Основною метою даного дослідження було оцінити МЗ в якості предикторів рецидиву КРР у радикально прооперованих пацієнтів. Другорядною – визначити, які з базових характеристик пацієнта та пухлини впливають на безрецидивну виживаність (БРВ) та загальну виживаність (ЗВ) у цієї ж когорти пацієнтів.

Матеріали і методи. Для дослідження використано дані 138 пацієнтів КНП СОР Сумського обласного клінічного онкологічного центру. Включено хворих на КРР, яким було проведено радикальне хірургічне втручання з приводу пухлини товстої чи прямої кишки I–III стадії в період з грудня 2019 року по грудень 2020 року. Як потенційні предиктори рецидиву захворювання оцінювали стать, вік, індекс маси тіла (ІМТ), локалізацію пухлини, стадію, T, N, неоад’юванту та ад’ювантну терапію, ступінь диференціації пухлини та МЗ. Останні розраховані на основі даних клінічного та біохімічного аналізів крові, виконаних не більш як за тиждень до операції. Досліджуваними МЗ були: нейтрофільно-лімфоцитарне співвідношення (NLR), лімфоцитарно-моноцитарне співвідношення (LMR), прогностичний нутритивний індекс (PNI), прогресивний індекс запалення раку легень (ALI) та рівень лімфоцитів х альбумін (LA). Для статистичного аналізу даних використали: ROC аналіз (AUC $\geq$ 0,7), метод Каплана-Майєра, Log-rank тест ($p < 0,05$) та багатофакторний регресійний аналіз Кокса з методом Breslow (довірчий інтервал (ДІ) – 95%, $p < 0,05$).

Результати. За результатами ROC аналізу єдиним статистично значимим МЗ виявився LA (AUC=0,7592). LA продемонстрував

достовірний вплив на БРВ (Log-rank p=0,0000) та ЗВ (Log-rank p=0,0023). Вищий ризик рецидиву та смерті мали пацієнти з LA < 37,5. За результатом багатофакторного регресійного аналізу Кокса з методом Breslow незалежними факторами, що впливають на БРВ, виявилися вік (p=0,032), ІМТ (p=0,048) та LA (p=0,031), а на ЗВ тільки LA (p=0,008).

Висновки. За результатами цього дослідження LA було визначено як незалежний предиктор перебігу КРР після радикального оперативного втручання. Пацієнти з низьким рівнем LA мали гіршу БРВ та ЗВ. Разом з тим, вік та ІМТ визначено як базові характеристики, що достовірно впливають на БРВ. Пацієнти старше 65 років та пацієнти з надлишковою вагою мали вищий ризик рецидиву захворювання.

Ключові слова: колоректальний рак, маркери запалення, рецидив захворювання, радикальне оперативне втручання.

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ABBREVIATIONS

ALI – advanced lung cancer inflammation index;
AUC – area under the curves;
BMI – body mass index;
CRC – colorectal cancer;
IM – inflammatory marker;
LA – lymphocytes x albumin;
LMR – lymphocyte-monocyte ratio;
NLR – neutrophil-lymphocyte ratio;
OS – overall survival;
PNI – prognostic nutritional index;
RFS – recurrence-free survival

INTRODUCTION

For numerous types of cancer, a patient who lived 5 years after radical treatment without recurrence of the disease, customary considered by the medical community to be "free from the disease" or "cured" [1]. The 5-year survival rate of radically operated patients with colorectal cancer (CRC) varies from 92% for stage I to 53% for stage III of the disease [2]. Despite the latest approaches in diagnosis and treatment, up to 30% of stage I-III patients are at risk of disease recurrence [3].

60%-80% of all recurrences occur during the first 2 years after surgery [4]. According to statistics, these patients have worse overall survival (OS) [5]. The frequency of relapses decreases in the period from 2 to 5 years, and then reaches a plateau phase [6]. Studies show that patients who relapse after 2 years have a better prognosis [1, 4–6].

The facts described above have become the cause of discussions surrounding the issue of intensifying the observation period of radically operated patients [7, 8]. Therefore, our study is focused on the period up to 2 years after surgery.

In this study, inflammatory markers (IM) were considered as potential predictors of the course of CRC. They are a reflection of the systemic inflammatory response, which is considered an important indicator of tumor progression [9]. The ratio of the simplest indexes of clinical and biochemical blood analysis is used to calculate inflammation markers, which makes them attractive for use in clinical practice [10]. The number of publications devoted to IM, which demonstrate statistically significant results for cancer of various locations, has increased over the past few years [9, 10]. The main goal of this study was to evaluate IM as predictors of CRC recurrence in radically operated patients. Secondary importance was to determine which of the patient's and tumor's basic characteristics affect recurrence-free survival (RFS) and OS in the same cohort of patients.

MATERIALS AND METHODS

The study was conducted on the basis of data from CRC patients of the Municipal non-profit enterprise of Sumy Regional Council "Sumy Regional Clinical Oncology Center". The study included people who underwent radical surgery for a stage I-III colon or rectal tumor between December 2019 and December 2020. The pattern of patient selection is shown in Figure 1. The follow-up period for patients lasted 24 months from the date of surgery and ended for the last of them in December 2022. The time interval from the date of surgical intervention to the date of registration of disease recurrence was considered as RFS. OS was

assessed as the period from the date of surgery to the end of the 24-month follow-up period or death, whichever occurred first. The events of interest were relapse of the disease or death of the patient.

The following characteristics were evaluated as predictors of the course of the disease: gender (men vs. women), age (younger than 65 vs. older than 65), body mass index (BMI) (BMI <25 vs. BMI ≥25), tumor localization (colon or rectum), stage (I vs. II-III), T (T1-2 vs. T3-4), N (N0 vs. N1-2), neoadjuvant therapy (performed or not), adjuvant therapy (performed or not), degree of tumor differentiation (G1 vs. G2-G3) and IM. BMI was calculated by formula = weight(kg) ÷ height(m)^2.

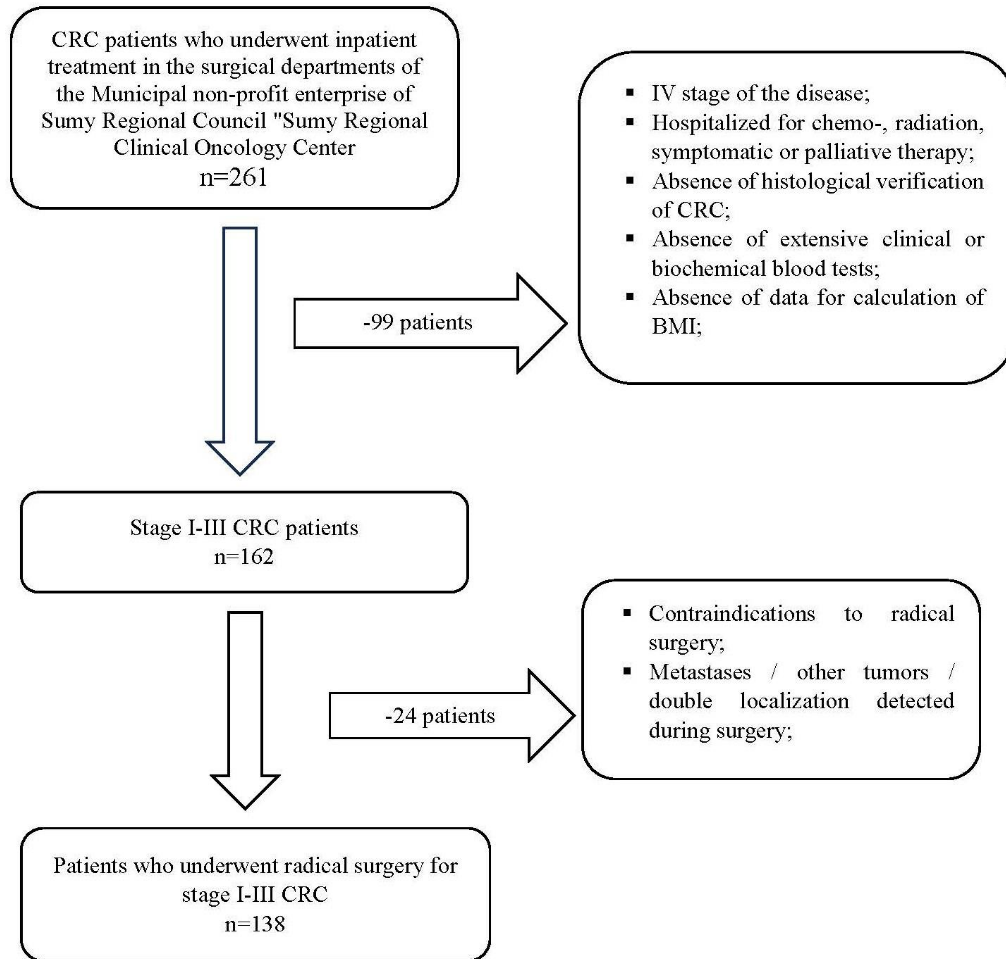

Figure 1 – Flow chart of patient cohort selection

IM were calculated based on data from clinical and biochemical blood tests performed no more than a week before surgery. Corresponding absolute numbers were calculated for results given in percentages (neutrophils, lymphocytes, monocytes). The most common IM were selected for evaluation: neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), prognostic nutritional index (PNI), advanced lung cancer inflammation index (ALI). Also, the study included the IM, which is only gaining popularity for cancer of various localizations – the level of lymphocytes x albumin (LA) [9, 11, 12]. The used formulas are shown in Table 1.

Table 1 – Formulas for calculating IM

IM	**Formula**
NLR	$= N \div L$
LMR	$= L \div M$
PNI	$= A + 5 \times L$
LA	$= L \times A$
ALI	$= (BMI \times (A \div 10)) \div NLR$

N – neutrophils (10^9/l); L – lymphocytes (10^9/l); M – monocytes (10^9/l); A – albumins (g/l)

Statistical analysis. Patient data were collected and organized in Excel. ROC analysis was performed to determine areas under the curves (AUC) and cut-off points for each individual IM. The cut-off point was chosen to be the value with the maximum sensitivity at a specificity higher than 50%. Further analysis of prognostic value was performed for all IM with AUC > 0.5, but only IM with AUC ≥ 0.7 was defined as statistically significant. The Kaplan-Meier method was used to visualize the survival curves of patients in groups with different levels of the studied IM. The existence of a significant difference between the groups, regarding the probability of relapse or death, was assessed using the Log-rank test ($p < 0.05$). Determination of independent predictors affecting RFS and OS was performed using multivariate Cox regression analysis with the Breslow method (confidence interval (CI) – 95%, $p < 0.05$). Stata V.18.0 software (StataCorp, Texas, USA; https://www.stata.com; 2024) was used for the final data analysis.

RESULTS

138 patients were included in the study: 74 male and 64 female. The average age was 63 years (from 34 to 83 years). The predominant localization is rectal cancer (74 patients versus 64).

During the observation period, disease progression was registered in 27 (19.6%) patients, of which 9 (33.3%) had colon cancer and 18 (66.7%) had rectal cancer. As a result of disease progression or for any other reason, 15 (10.9%) patients died, including 4 (26.7%) with colon cancer and 11 (73.3%) with rectal cancer.

According to the results of the ROC analysis, LA was the only statistically significant IM (AUC=0.7592). The other studied markers had lower AUC values: NLR (AUC = 0.6732), PNI (AUC = 0.6704), ALI (AUC = 0.6520) and LMR (AUC = 0.6172) (Figure 2). The cut-off points for NLR, LMR, PNI, LA and ALI were defined as 2.3, 4.3, 43.9, 37.5 and 31.1, respectively. The distribution of the studied group according to basic characteristics and IM is shown in Table 2.

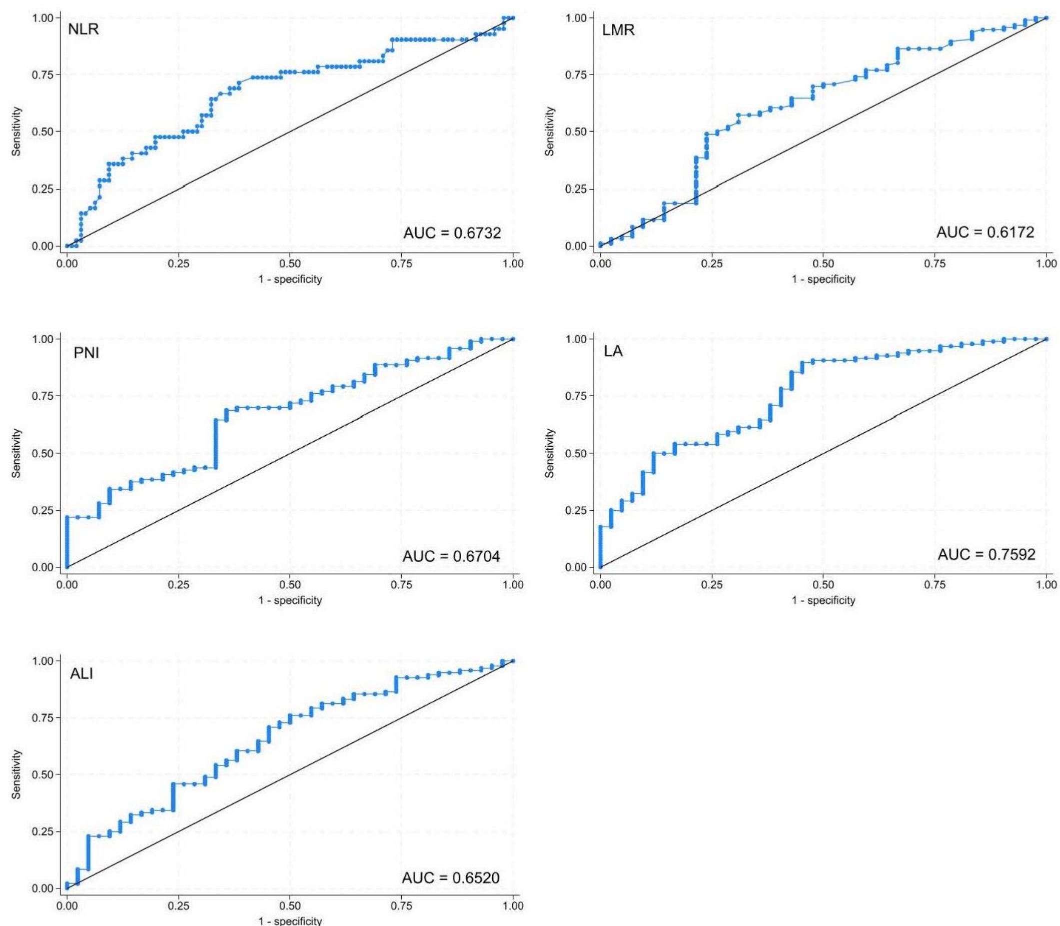

Figure 2 – Assessment of prognostic value of IM using ROC curves

Table 2 – Basic characteristics of the patient, tumor and IM

Characteristics	Allocation criterion	Total number of patients n (%) n =138
Age (years)	Average Interval <65 ≥65	63 34-83 68 (49,3) 70 (50,7)
Sex	Men Women	74 (53,6) 64 (46,4).
BMI	<25 (normal weight) ≥25 (overweight or obese)	50 (36,2) 88 (63,8)
Tumor location	Colon Rectum	64 (46,4) 74 (53,6)
Stage	I II-III	11 (8) 127 (92)
T	T1-2 T3-4	12 (8,7) 126 (91,3)
N	N0 N1-2	92 (66,7) 46 (33,3)
Degree of tumor differentiation	G1 G2-G3	82 (59,4) 56 (40,6)
Neoadjuvant therapy	Performed Not performed	58 (42) 80 (58)
Adjuvant therapy	Performed Not performed	74 (53,6) 64 (46,4)
NLR	<2,3 (low) ≥2,3 (high)	57 (41,3) 81 (58,7)
LMR	<4,3 (low) ≥4,3 (high)	53 (38,4) 85 (61,6)
PNI	<43,9 (low) ≥43,9 (high)	51 (37,0) 87 (63,0)
LA	<37,5 (low) ≥37,5 (high)	31 (22,5) 107 (77,5)
ALI	<31,1 (low) ≥31,1 (high)	49 (35,5) 89 (64,5)

The Kaplan-Meier method had limitations in this study, as the median survival time was not reached during the follow-up period. It was determined that each of the evaluated IM had a significant effect on RFS: NLR (Log-rank p=0.0186), LMR (Log-rank p=0.0033), PNI (Log-rank p=0.0165), LA (Log-rank p=0.0000), ALI (Log-rank p=0.0114). Patients with NLR ≥ 2.3, LMR < 4.3, PNI < 43.9, LA < 37.5, ALI < 31.1 had a higher risk of relapse (Figure 3).

Only LA demonstrated a significant effect on OS (Log-rank p=0.0023). Patients with LA < 37.5 had a higher risk of death (Figure 4).

Based on the results of multivariate Cox regression analysis with the Breslow method, age (p=0.032), BMI (p=0.048) and LA (p=0.031) were found to be independent factors affecting RFS (Table 3). Only LA (p=0.008) was determined as an independent predictor of OS (Table 4).

Figure 5 shows the Kaplan-Meier curves for baseline patient characteristics that showed a significant effect on RFS. Based on the obtained data, patients younger than 65 years old (Log-rank p=0.0491), as well as patients with a normal BMI (Log-rank p=0.0466) have a lower risk of the disease recurrence.

Discussion. From the 5 studied IM LA appeared to be the only statistically significant. According to the results of this study, stage I-III patients with a low LA level before radical surgery had worse RFS and OS.

The hypothesis explaining the prognostic value of LA is based on the understanding of the mechanism of interaction of lymphocytes and albumin with tumor cells [13]. Lymphocytes, in the context of antitumor protection, are responsible for two fundamental processes. The first is a cytotoxic cell-mediated immune response. Lymphocytes include a pool of T cells, natural killer cells, and B cells that directly recognize and induce the destruction of malignant cells [14]. Interesting that, under the influence of tumor cells, they are also involved in developing of the resistance against drugs [15]. The second is the production of cytokines

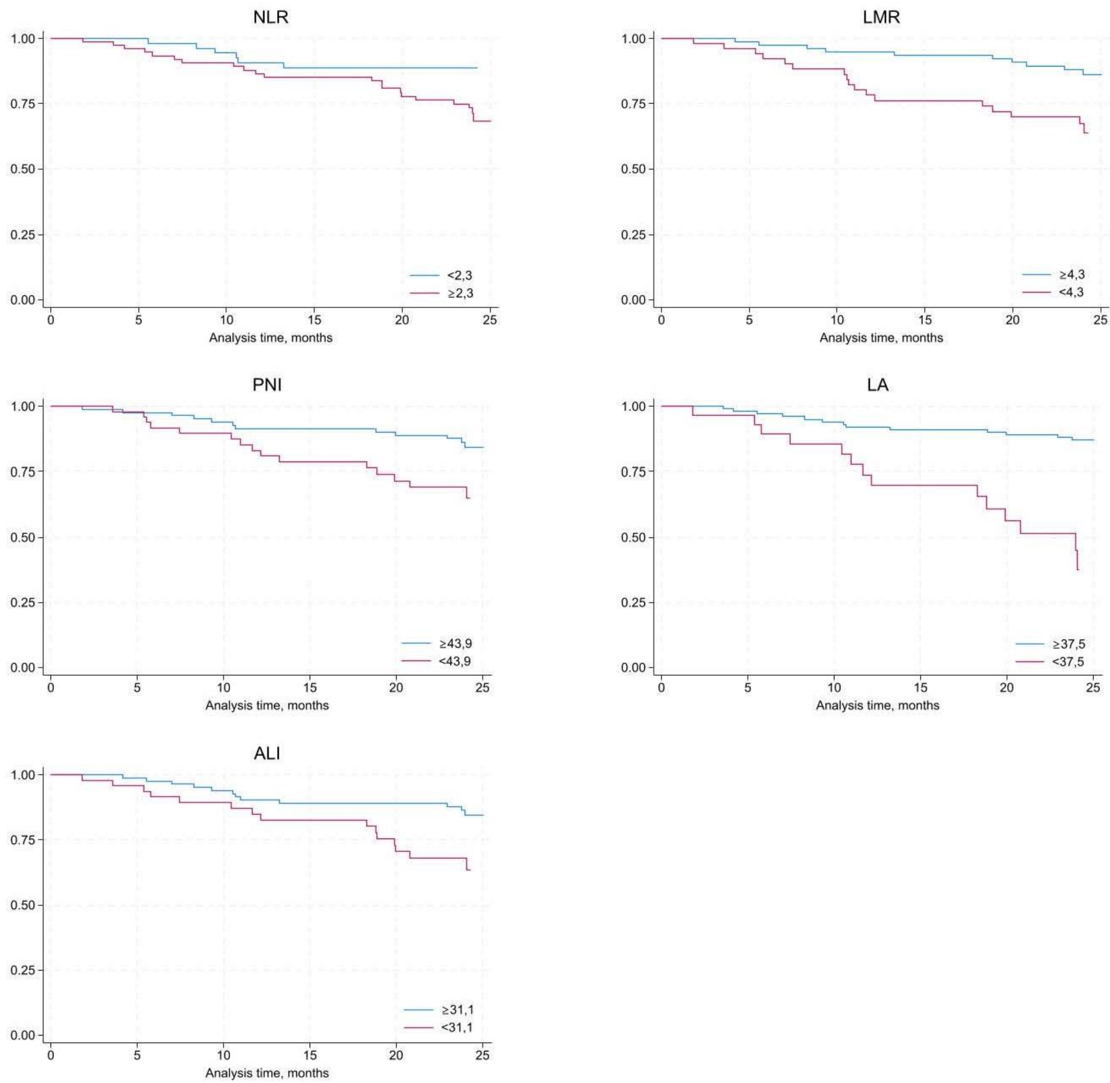

Figure 3 – RFS curves for groups evaluated by the levels of NLR, ALI, LA, LMR PNI

that inhibit the growth of tumor cells. These include, for example, interleukin-2 (IL-2) and tumor necrosis factor, which are synthesized by CD4 T-lymphocytes [16].

A number of publications demonstrate the value of lymphocytes for predicting the course of CRC. Dou et al. [17] and Kitayama et al. [18] in their studies evaluated the relationship between the level of lymphocytes and the response to neoadjuvant chemotherapy in patients with rectal cancer. Both studies concluded that low lymphocyte counts were associated with poorer response to treatment. Noh et al. [19] conducted a similar study for patients with colon cancer after radical resection and adjuvant chemotherapy. Scientists have found that a high level of lymphocytes after chemotherapy is associated with a better RFS.

The mechanism of interaction between albumin and the tumor is multifaceted and has not yet been fully explored [20]. Babson et al. [21] were the first to try to explain it. In their research, they assumed that the tumor is a "trap" for plasma proteins and uses their catabolism products for its growth. Kratz [22, 23] in his publications supported this hypothesis and emphasized that albumin is a possible source of nutrition for tumor growth.

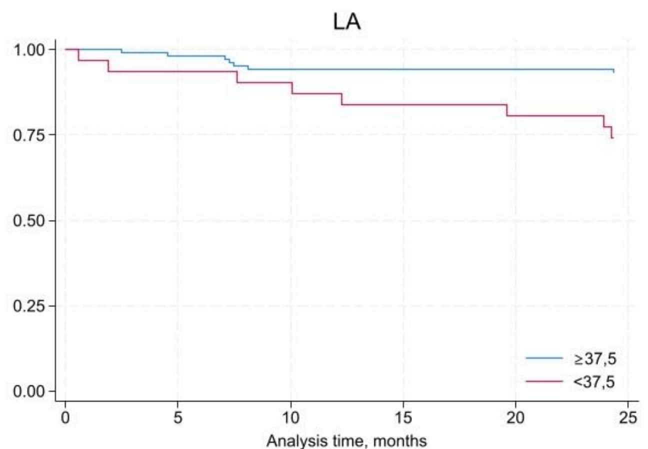

Figure 4 –OS curve for groups evaluated by the levels of LA

Table 3 – Multivariate regression analysis to determine the factors that influence the RFS

Characteristics	RFS
	Hazard Ratio (95% CI), p value
Age	2,62 (1,09 – 6,30), **0,032**
Sex	2,33 (0,91 – 5,97), 0,078
BMI	2,85 (1,01 – 8,05), **0,048**
Tumor location	0,85 (0,18 – 4,00), 0,838
Stage	16,75 (1,93 – 2,06), 0,161
T	0,86 (0,18 – 4,23), 0,854
N	1,88 (0,73 – 4,86), 0,194
Degree of tumor differentiation	1,81 (0,70 – 4,68), 0,219
Neoadjuvant therapy	3,23 (0,75 – 13,89), 0,115
Adjuvant therapy	1,48 (0,62 – 3,57), 0,379
NLR	1,15 (0,31 – 4,28), 0,832
LMR	1,36 (0,57 – 3,22), 0,487
PNI	1,54 (0,62 – 3,78), 0,350
LA	3,73 (0,70 – 4,68), **0,031**
ALI	1,32 (0,41 – 2,26), 0,644

Another theory of interaction is based on the fact that albumin is one of the so-called negative acute phase proteins. Its synthesis in the liver is inhibited in response to the increased concentration of inflammatory cytokines, including IL-6 [20]. Unlike IL-2 described above, the source of this cytokine can be tumor cells. IL-6 promotes an active inflammatory process and creates a favorable microenvironment for tumor growth [24].

Seaton [25] in his publication, among other things, demonstrated the direct antitumor effect of albumin. It is based on its antioxidant properties and participation in the process of stabilizing of the DNA replication.

Table 4 – Multivariate regression analysis to determine the factors that influence the OS

Characteristics	OS
	Hazard Ratio (95% CI), p value
Age	1,69 (0,52 – 5,49), 0,387
Sex	2,14 (0,63 – 7,28), 0,221
BMI	0,33 (0,10 – 1,16), 0,084
Tumor location	0,83 (0,12 – 5,93), 0,850
Stage	15,36 (0,78 – 301,29), 0,072
T	1,02 (0,22 – 4,73), 0,981
N	1,01 (0,30 – 3,43), 0,982
Degree of tumor differentiation	1,42 (0,42 – 4,81), 0,574
Neoadjuvant therapy	3,62 (0,47 – 28,13), 0,219
Adjuvant therapy	1,17 (0,36 – 3,83), 0,794
NLR	1,85 (0,34 – 9,99), 0,473
LMR	0,26 (0,06 – 1,02), 0,053
PNI	0,86 (0,25 – 3,01), 0,819
LA	10,82 (1,89 – 62,03), **0,008**
ALI	0,40 (0,88 – 1,78), 0,228

The prognostic value of albumin levels in patients with gastrointestinal tumors was demonstrated in a review by Gupta et al. [26]. According to the results of the search, in 26 of the 29 analyzed papers, a high level of albumin was associated with a better RFS. In addition, the issue of the relationship between hypoalbuminemia and a high level of postoperative complications and postoperative mortality in patients with CRC is widely covered in the scientific literature [27, 28].

LA has only recently come into the focus of scientific attention. Yamamoto et al. [29] were the first to describe LA as a new prognostic marker for patients with stage II/III rectal cancer after radical surgery. In their study, based on data from 448 patients, they assessed the significance of 11 different IM. Among them, only LA demonstrated a reliable effect on RFS and OS. Patients with low levels of this IM had a higher risk of relapse and death. Later, Rencuzogullari et al. [30] came to the same conclusion.

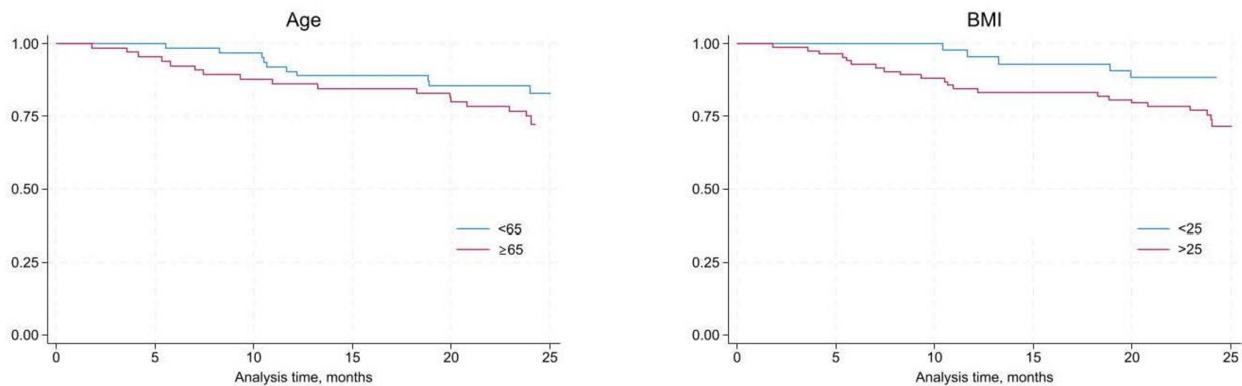

Figure 5 – RFS curves for groups assessed by age and BMI

In this study, age and BMI were identified as basic characteristics that reliably affect RFS. Patients older than 65 years and overweight patients had a higher risk of disease recurrence.

Age is often evaluated as a predictor of the course of CRC, but there is no consensus among scientists regarding the cut-off point for this indicator. Zafar et al. [31] in their study, after analyzing data from 8,249 patients, identified age over 60 as one of the independent predictors of CRC relapse. Qaderi et al. [3] after processing data from 5,412 patients determined that patients aged 65 to 74 years have the highest risk of relapse. A Mima et al. [32] determined that patients with worse RFS and OS are those older than 75. At the same time, there are publications in which no relationship between age and the probability of recurrence of CRC was established [33, 34].

In contrast to age, the impact of BMI has been reliably proven. Doleman et al. [35] conducted a meta-analysis of the results of 18 studies and found that overweight patients have a higher risk of recurrence and mortality from CRC. And Chiu et al. [36] reached the same conclusion after analyzing data from 41,015 CRC patients.

The obtained results may be useful for improving the existing clinical recommendations for the monitoring of radically operated CRC patients by identifying groups of high-risk of disease recurrence. The limitations of this study were the relatively small number of patients and the short follow-up period.

CONCLUSIONS

According to the results of this study, LA was determined as an independent predictor of the course of CRC after radical surgery. Patients with a low LA level had worse RFS and OS. In addition, age and BMI have been identified as basic characteristics of the patient that reliably influence RFS. Patients older than 65 years and overweight patients had a higher risk of disease recurrence.

AUTHOR CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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None.

CONFLICT OF INTEREST

The author declared no potential conflicts of interest to the research, authorship, and/or publication of this article.

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