EXPERIMENTAL ONCOLOGY

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LABORATORY PREDICTORS FOR DIAGNOSING COLORECTAL ANASTOMOTIC LEAKAGE

Background. An important concern in oncological coloproctology is colorectal anastomotic leakage (AL), which occurs in 3.5%–21% of patients. Predicting the occurrence of failure based on the results of laboratory markers can be decisive for the treatment of this complication. **Aim**. To improve the early diagnosis of AL by establishing combinations and threshold values of laboratory markers — predictors of the inflammatory process. **Materials and Method**s. The prospective study, conducted from 2020 to 2023, included 213 rectal cancer patients who underwent low anterior resection after neoadjuvant chemoradiotherapy. The inflammatory biomarkers were assessed before surgery and on the 3rd, 5th, and 7th days of the postoperative period. **Results**. AL diagnosed in 25 (11.74%) patients by the grade of severity was as follows: A (radiological) in 7 (3.29%) patients; B (clinical) — 4 (1.88%); C (clinically expressed, peritonitis) — 11 (5.16%), and P (late) — 3 (1.41%) patients. The changes in the laboratory indicators of the inflammatory response such as C-reactive protein (CRP), procalcitonin (PCT), the counts of neutrophils (NEU), lymphocytes (LYM), platelets (PLT), and neutrophil/lymphocyte ratio (NLR) were significant only in B or C AL grades. Among them, only three indicators were identified as significant for predicting AL when assessed 24 h before the onset of this complication, namely LYM (threshold value ≤ $0.97 \times 10^3/mm^3$, sensitivity 66.7% and specificity 81.3%, $p < 0.001$); PLT (threshold value > > 257 $10^3/mm^3$, sensitivity 58.6%, and specificity 86.7%, $p < 0.001$); and NLR (threshold value > 4.42, sensitivity 58.1%, and specificity 86.7%, $p < 0.001$). The three-factor model based on these selected indicators was set up, and the prognosis index (Prog) was proposed with the decision threshold $Prog_{crit} = 2.23$. The sensitivity of the model was 80% (95% CI 51.9%—95.7%), and the specificity — 74.2% (67.6%—80.2%). **Conclusion**. Based on the routine laboratory predictors used in the complex diagnosis of AL, B or C AL grades may be predicted allowing for the timely effective early diagnosis, medication, and surgical intervention..

Keywords: rectal cancer, anastomotic leakage, diagnosis of failure, biomarkers of inflammation, predictors of failure.

An important concern in oncological coloproctology is an anastomotic leakage (AL), which occurs in 3.5%—21% of patients undergoing surgery for rectal cancer, despite advances in patient management, the introduction of the latest surgical technologies, and preventive methods [1—3]. AL leads to repeated surgery due to the development of peritonitis and sepsis with a high postoperative mortality rate and subsequently with a high risk of recurrence, worse overall survival, low quality of life ofpatients as well as additional costs for the healthcare system [4—9].

Clinically, AL is characterized by the severity grade according to the classification of the Interna-

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tional Study Group of Rectal Cancer [10], namely: A — radiologically detected leakage without clinical and laboratory symptoms that does not require additional treatment; B — AL with clinical symptoms and laboratory changes that requires active medical treatment (antibiotic therapy, detoxification therapy), surgical manipulations without relaparotomy; C — clinically expressed (peritonitis, sepsis) AL requiring repeated surgery. In this study, the presented classification was supplemented by another group of AL, which is diagnosed and marked P — late AL detected during the second to third month after surgery, without clinical symptoms, as a finding of the endoscopist during a planned examination before closing the diverting colostomy (DS).

The prediction of the occurrence of AL based on the laboratory tests, the effective early diagnosis with timely administration of medication, and surgical correction are decisive in reducing postoperative mortality.

The present study is focused on the inflammation biomarkers C-reactive protein (CRP) and procalcitonin (PCT) as well as the counts of cells involved in the inflammatory process, such as neutrophils (NEU), lymphocytes (LYM), and neutrophil/lymphocyte ratio (NLR), which have confirmed their importance in diagnosing postoperative complications including AL [11—16]. Currently, the data on the role of routine laboratory parameters in predicting the occurrence of AL in the formation of low colorectal anastomosis in patients with rectal cancer after neoadjuvant chemoradiotherapy (CRT) are insufficient, which requires further research. The aim of the study was to improve the early diagnosis of AL by establishing combinations and threshold values of laboratory markers — predictors of the inflammatory process.

Materials and Methods

The prospective study conducted from 2020 to 2023 included 213 rectal cancer patients who underwent low anterior resection after neoadjuvant CRT. Inclusion criteria: age 18 years and older; morphologically confirmed adenocarcinoma of various differentiation grades; according to MRI, localization of the tumor within ≤ 100 mm from the anorectal angle; stages II—III of the disease (T3-4N0M0, TanyN1-2M0); completed course of neoadjuvant CRT (44—55 Gy + 2 cycles of capecitabine or 5-Fu infusion); after the completion of CRT, a low anterior rectal resection was performed within 7 to 10 weeks. Exclusion criteria: performed operations without anastomosis formation; postoperative complications that are not related to anastomotic failure. Patients' characteristics are presented in Table 1.

The study of the inflammatory biomarkers was performed before surgery and on the 3rd, 5th, and 7th days of the postoperative period, and in patients with high indicators monitoring of blood biomarkers was continued. The counts of white blood cells (WBC), neutrophils (NEU), lymphocytes (LYM), and platelets (PLT) were measured on a hematology analyzer Pentra ES 60 "ABX Diagnostics" (France) and automatic HORIBA ABX SAS (France). The level of CRP was determined by the immunoenzyme method using the iChroma CRP test system (Boditech Med Ink, Korea) with a working range of 2.5—300 mg/L; the level of PCT — with iChroma PCT Plus test system (Boditech Med Ink, Korea) with a range of 0.1—100 ng/mL. To assess the diagnostic value of AL, threshold levels were set for CRP > 50.0 mg/L and PCT > 0.5 ng/mL.

Table 1. **Clinical and pathological characteristics of the patients with OSCC (n = 40)**

Parameter	Patients with formed low colorectal anastomosis (n = 213)
Gender, n (%):	
female	105 (49.29)
male	108 (50.71)
Mean age ± σ, years	66.9 ± 8.6
Median body mass index (min—max), kg/m^2	27.05 (24.3—29.4)
pTNM stage, n (%):	
II (pT3–4N0M0)	155 (72.77)
III (pT2–4N1–2M0)	58 (27.23)
Tumor differentiation grade, n (%):	
G1, G2	185 (86.85)
G3 + mucosal adenocarcinoma	28 (13.15)
The level of the formed anastomosis to the dentate line (mm), n (%):	
< 60	167 (78.4)
≥ 60	46 (21.6)

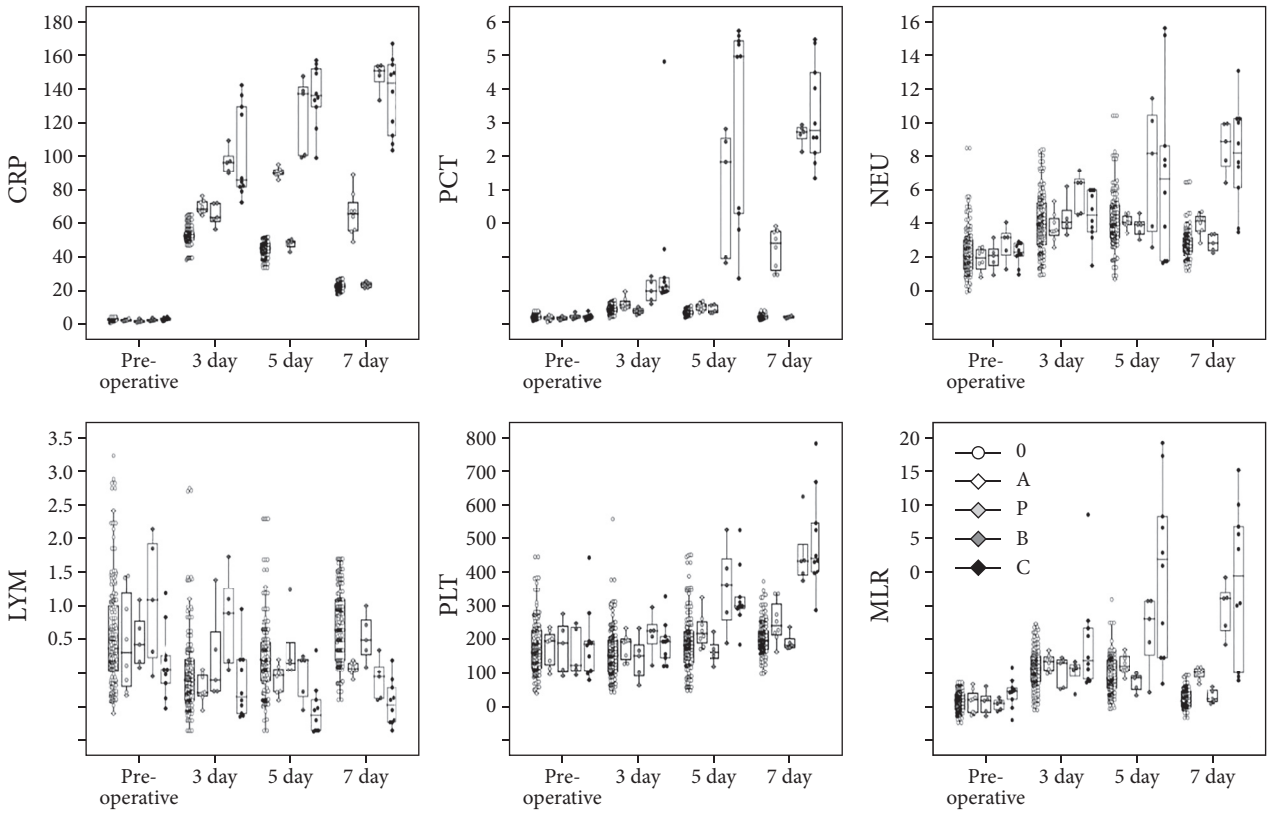

Fig. 1. Indicators of inflammatory markers in patients with rectal cancer who underwent low anterior rectal resection: 0 — patients without AL; A — patients in whom AL was diagnosed radiologically; P — diagnosed late, outpatients; B — patients with clinical symptoms and need for active medical treatment; C — the clinic is expressed with the need for repeated surgery

The research data were entered into the Excel spreadsheet. Statistical analysis was performed using Statistical software EZR v. 1.54 (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) [17]. The quantitative results were described using mean ± standard deviation (for the normal distribution) or median value and interquartile range (for the non-normal distribution). Student's test (in the case of the normal distribution) or the Mann — Whitney test (in the case of the non-normal distribution) were used for comparison. The chi-square test and Fisher's exact test were used to compare the distribution of qualitative variables. The method of building logistic regression models was used to predict the risk of early failure. The risks of progression are presented as odds ratio (OR) with corresponding 95% confidence intervals (CI). ROC curves were constructed for indicators showing good agreement (AUC > 0.7) with mention of the Youden index (maximization of sensitivity + specificity). The selection of indicators by the method of stepwise inclusion/exclusion of factor characteristics was provided. The factors that reached $p < 0.05$ were considered statistically significant.

The clinical study was approved by the Ethics Committee of the National University of Health Care of Ukraine (Protocol No. 14 dated 07.12.2020).

Results

During the postoperative period following the formation of low colorectal anastomosis in 213 patients, complications occurred in 25 (11.74%) individuals, with AL being diagnosed. The severity grades of AL were as follows: A (radiological) in 7 (3.29%) patients; B (clinical) — 4 (1.88%); C (clinically expressed, peritonitis) — 11 (5.16%), and P (late) — 3 (1.41%) patients.

The failure was diagnosed based on the clinical, X-ray, sonographic, and laboratory studies on days 3—7 of the postoperative period, except for one case of diagnosis of rectovaginal fistula on day 10.

The laboratory indicators of the inflammatory response obtained, as presented in Fig. 1 and Tab-

le 2, showed a statistically significant difference only in cases of AL severity grades B or C in comparison to patients who did not develop AL.

The median indicators of the above data were determined and used in the process of diagnosing AL and had a diagnostic value (Table 2).

The presented results testify to their possible importance in the diagnosis of AL, namely B and C severity, which requires urgent decision-making regarding medical treatment or the performance of repeated surgical intervention.

According to the aim of the study, the concern of identifying the diagnostically significant predictors 24 h before the onset of AL was considered. According to the one-factor model of logistic regression, the laboratory indicators that could be used to predict the occurrence of AL 24 h before its onset were determined.

The method of logistic regression models was used, and grade B or C failure was detected in 15 patients (case, Y = 1), 198 patients (not case, Y = 0). The study included indicators 24 h before the occurrence of B or C failure and those in which no failure was detected on the 7th day of the postoperative period. Table 3 shows the results of univariate analysis.

The plotted ROC curves according to the results of the univariate analysis for indicators with good agreement (AUC > 0.7) for predicting the critical threshold of the risk of early failure with the indication of the Youden Index (maximization of sensitivity + specificity) are presented in Fig. 2. Three risk factors were identified: LYM (threshold value $\leq 0.97 \times 10^3/mm^3$, sensitivity 66.7%, and specificity 81.3%, $p < 0.001$); PLT (threshold value $> 257 \times 10^3/mm^3$, sensitivity 58.6%, and specificity

Table 2. **Laboratory indicators and AL grade (Day 7)**

Indicators	Grade of anastomotic failure				
	0	A	B	C	P
NEU ($\times 10^3$/ mm^3)	4.35 (3.28—5.47)	5.61 (4.92—5.83)	9.63** (8.37—10.62)	9.21** (7.13—10.86)	4.49 (3.98—4.73)
LYM ($\times 10^3$/ mm^3)	2.19 (1.37—2.56)	1.27 (1.21—1.32)	1.03* (0.93—1.25)	0.82** (0.71—1.08)	1.52 (1.38—1.73)
NLR (neu/lym)	2.54 (1.78—3.64)	4.35 (3.68—4.82)	9.32** (7.56—10.02)	11.08** (5.83—13.72)	2.61 (2.53—3.12)
PLT ($\times 10^3$/mm^3)	263 (224—327)	298 (277—361)	453** (446—512)	462** (448—554)	253 (247—269)
CRP (mg/L)	23.9 (17.2—28.1)	48.3 (29.7—57.2)	151.1** (143.7—155.2)	142.3** (113.4—154.2)	24.3 (21.8—25.1)
PCT (ng/mL)	0.25 (0.1—0.4)	0.46 (0.31—0.52)	3.3** (2.9—3.6)	5.3** (4.7—5.6)	0.27 (0.15—0.39)

Notes: * $p < 0.05$ and ** $p < 0.001$ as compared to the values of patients without AL.

Table 3. **One-factor logistic regression models of risk prediction 24 h before the occurrence of B or C failure**

Risk factor	Odds ratio, OR (95% CI)	The level of significance of the OR difference from 1, p	Area under the operating characteristics curve, AUC (95% CI)
NEU	1.29 (0.96—1.75)	0.090	0.58 (0.51—0.65)
LYM	0.014 (0.002—0.141)	<0.001	0.79 (0.72—0.84)
PLT	1.009 (1.003—1.015)	0.003	0.75 (0.68—0.80)
NLR	2.10 (1.41—3.13)	<0.001	0.79 (0.73—0.85)
CRP	1.21 (0.94—1.37)	0.062	0.67 (0.60—0.73)
PCT	0.92 (0.88—1.07)	0.078	0.63 (0.56—0.69)

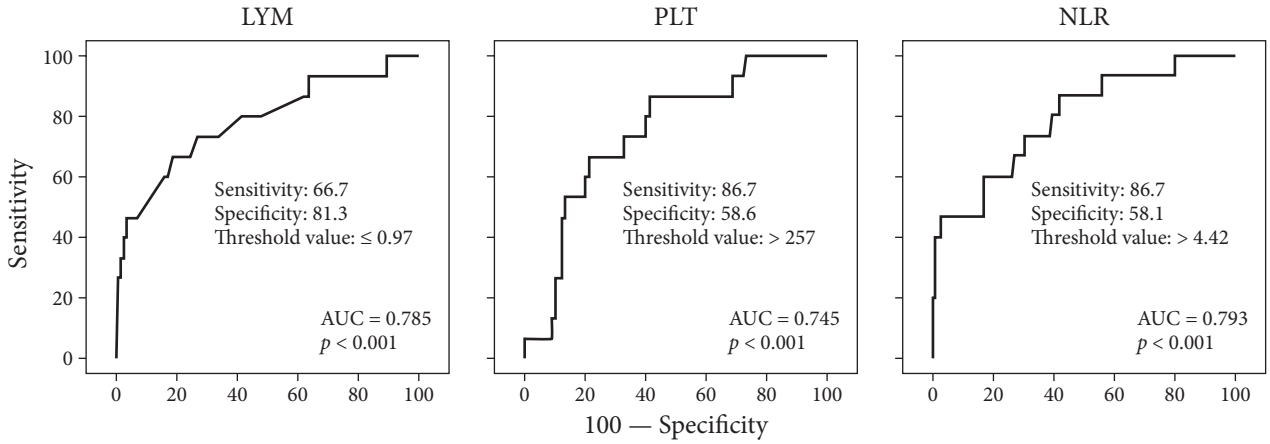

Fig. 2. ROC curves based on one-factor analysis of prediction of AL of B and C grades 24 h before the occurrence of this complication (with AUC > 0.7)

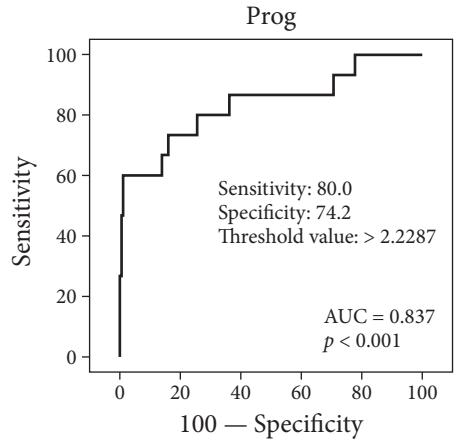

Fig. 3. ROC curve for the three-factor index for predicting failure of B and C 24 h before the occurrence

86.7%, $p < 0.001$); and NLR (threshold value > 4.42, sensitivity 58.1%, and specificity 86.7%, $p < 0.001$).

To identify the weight of these features associated with predicting the occurrence of AL of grade B or C, indicators were selected by the method of stepwise inclusion/exclusion of factor characteristics. The three-factor model built on the selected features proved as adequate (chi-square = 39.2 with 3 degrees of freedom, $p < 0.001$). Table 4 shows the results of the multivariate analysis.

Based on the identified dependences, a prognosis index (Prog) is proposed for predicting the risk of failure B or C 24 h before diagnosis:

$$Prog = -3.32 \times X1 + 0.011 \times X2 + 0.57 \times X3$$

where X1 is the LYM level, X2 is the PLT level, and X3 is the NLR level.

The area under the operating characteristics curve AUC = 0.84 (95% CI 0.78—0.88), which indicates a good consistency of the model. Having chosen the decision threshold $Prog_{crit} = 2.23$, the sensitivity of the model is 80% (95% CI 51.9%—95.7%) and the specificity is 74.2% (67.6%—80.2%).

Discussion

During the study, the laboratory parameters of serum markers of the acute phase of the inflammatory response, routinely performed in surgical inpatient units, were systematized to be used as putative predictive markers for assessing the risk of the colorectal AL in rectal cancer patients who underwent low anterior resection. Basing on the literature data, we focused on the analysis of the general clinical markers such as WBC, NEU, LYM, and PLT

Table 4. **Three-factor logistic regression model for predicting 24 h risk of B or C failure**

Risk factor	Coefficient of the model, b ± m	Level of significance of OR difference from 1, *p*	Model odds ratio, OR (95% CI)
LYM	–3.32 ± 1.45	**0.022**	0.04 (0.002—0.62)
PLT	0.011 ± 0.004	**0.007**	**1.01 (1.003—1.019)**
NLR	0.57 ± 0.25	**0.021**	**1.77 (1.09—2.88)**

[18—22] and immunoenzymatic markers such as CRP and PCT [23—27].

According to the results of our research, CRP, PCT, NEU, LYM, PLT, and NLR showed a statistically significant difference in the cases of AL severity grades B or C compared to patients who did not develop AL while they were not informative in AL severity grades A and P.

Diagnosis of AL requires the use of a complex approach involving clinical, radiological, sonographic, endoscopic, and laboratory markers of the inflammatory process. The applied diagnostic methods should be routine, the results should be obtained quickly and have diagnostic value. den Dulk et al. [28] presented the data from five Dutch centers (modified DULK score) based on the patient's clinical condition, the presence of non-wound abdominal pain, CRP levels, and respiratory rate and concluded that the diagnosis of AL remains a challenging issue requiring comprehensive study. Paliogiannis et al. [21] evaluated a 4-day series of indicators of an inflammatory process in the diagnosis of AL. The average values of the IQR NEU, LYM, and NLR indices were close to ours, except for the PLT, which was reported as 240 (182—306), whereas in our study it was 453 (446—512) for B grade AL and 462 (448—554) for C grade AL. The importance of the studied biomarkers was confirmed by Nora et al. [19], who believe that the NLR, PLT, and LYM are significant predictors not only of complications but also of generalization of malignant neoplasms of the gastrointestinal tract and may be a key for monitoring patients who have undergone surgical treatment.

The outcome of treating any surgical complication depends on timely diagnosis**,** den Dulk et al. [29] presented data that a two-day delay in diagnosing AL results in an increase in mortality rate from 24% to 39%. In the present study, we attempted to investigate biomarkers that predicted the risk of AL 24 h before the occurrence of such complication, especially in cases of severe grades B or C, which required timely drug therapy, surgical manipulations, or repeated surgical intervention. Our research identified that the changes in three laboratory parameters LYM, PLT, and NLR were statistically significant 24 h before the onset of AL. A three-factor model was built accounting for these selected features, which made it possible to propose a prognosis index for predicting the risk of failure grade B or C 24 h before its onset. The plotted ROC curves indicated consistency of the model, AUC = 0.84 (95% CI 0.78—0.88), enabling an early diagnosis of AL severity grades B and C facilitating prompt medication or surgical intervention.

We believe that the pursuit of the predictive markers requires comprehensive study and research; however, their values can be realized only within a complex diagnostic algorithm. The use of laboratory predictors in the complex diagnosis of AL as a routine method provides an opportunity to obtain quick results for interpretation. The sooner the suspicion of AL is identified, the more effective the early diagnosis and the more timely selection of treatment tactics contingent upon the severity of AL.

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ЛАБОРАТОРНІ ПРЕДИКТОРИ ДЛЯ ДІАГНОСТИКИ / НЕСПРОМОЖНОСТІ КОЛОРЕКТАЛЬНОГО АНАСТОМОЗУ

Стан проблеми. На сьогодні важливим питанням онкологічної колопроктології є неспроможність колоректального анастомозу (AL), яка виникає у 3,5—21% оперованих пацієнтів. Вирішальним є передбачення виникнення неспроможності на основі результатів лабораторних маркерів — предикторів. **Мета роботи**. Покращити ранню діагностику AL шляхом встановлення комбінацій та граничних значень лабораторних маркерів — предикторів запального процесу. **Матеріали та методи**. Дослідження проспективне, проводилося з 2020 по 2023 рік, охоплювало хворих на рак прямої кишки, яким виконано низьку передню резекцію після неоад'ювантної CRT. Дослідження показників біомаркерів запалення виконували до оперативного втручання та на 3-ю, 5-у та 7-у добу післяопераційного періоду. **Результати**. AL, діагностована у 25 (11,74%) пацієнтів, за ступенем важкості була наступною: A (рентгенологічна) у 7 (3,29%) пацієнтів; B (клінічна) – 4 (1,88%); C (клінічно виражена, перитоніт) – 11 (5,16%) і P (пізня) – 3 (1,41%) пацієнтів. Лабораторні показники запальної відповіді, а саме CRP, PCT, NEU, LYM, PLT, NLR, мали статистично значимі ($p < 0.001$) результати лише в діагностиці B чи C ступеня важкості AL. Виділено 3 фактори прогнозу за 24 години до виникнення AL, а саме: LYM з критерієм ≤ 0,97, чутливістю 66,7 і специфічністю 81,3, $p < 0.001$; PLT з критерієм > 257, чутливістю 58,6 і специфічністю 86,7, $p < 0.001$ та NLR з критерієм > 4,42, чутливістю 58,1 і специфічністю 86,7, $p < 0.001$. Побудована трифакторна модель на виділених ознаках адекватна хі-квадрат = 39.2 при 3-ох ступенях свободи, ($p < 0.001$). Запропоновано індекс (Prog) прогнозування, при виборі порогу прийняття рішення $Pro_{gcrit} = 2.23$ чутливість моделі становить 80% (95% CI 51.9—95.7%), специфічність – 74.2% (67.6—80.2%). **Висновки**. Використані лабораторні предиктори у комплексній діагностиці AL є рутинними, результати отримували швидко, які були статистично значимі ($p < 0.001$) у діагностиці B чи C ступеня важкості AL з вчасним проведення ефективної ранньої діагностики, призначенням медикаментозної та хірургічної корекції.

Ключові слова: рак прямої кишки, неспроможність анастомозу, діагностика неспроможності, біомаркери запалення, предиктори неспроможності.