https://doi.org/10.33878/2073-7556-2026-25-1-92-100

New approaches to prediction of colonic anastomotic leakage

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ABSTRACT *AIM: to assess the prognostic significance of markers of oxidative stress, collagen degradation and intra-abdominal hypertension in the development of colorectal anastomotic leakage.*

PATIENTS AND METHODS: retrospective case-control study was conducted including 65 patients after colorectal resection: the study group (n = 43) comprised patients who developed anastomotic leakage, and the comparison group (n = 22) included patients with an uneventful postoperative course. The groups were comparable in terms of age, sex, operative time and intraoperative blood loss (p > 0.05). On postoperative days 2–3, serum levels of malondialdehyde (MDA), free hydroxyproline, conjugated dienes, ascorbic acid, lactate and serotonin, as well as intra-abdominal pressure (IAP), were measured.

RESULTS: Patients with CAL had significantly higher median levels of MDA (4,4 [3,9–4,7] vs 3,1 [2,4–3,6] nmol/mL; p < 0.001), free hydroxyproline (18,0 [15,7–19,6] vs 12,7 [11,1–14,8] μmol/L; p < 0.001) and IAP (16,1 [14,2–17,9] vs 10.5 [8,8–15,1] mmHg; p < 0.001) on postoperative days 2–3 as compared with controls. ROC analysis showed good discriminative ability of free hydroxyproline for CAL: AUC 0.83 (95% confidence interval (CI) 0.72–0.93; p < 0.001); at a cut-off ≥ 15 μmol/L, sensitivity was 79.1% (95% CI 63.9–89.9), specificity 77.3% (95% CI 54.6–92.2), positive predictive value (PPV) 87.2% (95% CI 72.6–95.7) and negative predictive value (NPV) 65.4% (95% CI 44.3–82.8). IAP ≥ 15 mmHg yielded an AUC of 0.78 (95% CI 0.65–0.90; p < 0.001), sensitivity 69.8% and specificity 72.7%; MDA ≥ 4.0 nmol/mL — AUC 0.80 (95% CI 0.68–0.91; p < 0.001), sensitivity 74.4% and specificity 77.3%. In multivariable logistic regression, free hydroxyproline (odds ratio (OR) 1.35; 95% CI 1.08–1.69; p = 0.009), IAP (OR 1.35; 95% CI 1.10–1.65; p = 0.004) and MDA (OR 2.86; 95% CI 1.25–6.56; p = 0.013) were identified as independent predictors of CAL. The combined three-marker model showed high prognostic accuracy: AUC 0.93 (95% CI 0.84–0.98; p < 0.001); p (Hosmer-Lemeshow test) = 0.34; Nagelkerke R^2 = 0.65.

CONCLUSION: comprehensive assessment of collagenolysis markers and intra-abdominal hypertension in the early postoperative period allows highly accurate prediction of the risk of anastomotic leakage.

KEYWORDS: *colonic anastomosis suture failure, prognosis, oxidative stress, oxyproline, intra-abdominal pressure*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

FOR CITATION: Ruziboyzoda K.R., Gulov M.K., Gulov A.A., Nurzoda Z.M., Ali-Zade S.G. New approaches to prediction of colonic anastomotic leakage. *Koloproktologia.* 2026;25(1):92–100. (in Russ.). https://doi.org/10.33878/2073-7556-2026-25-1-92-100

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Received — 26.11.2025 *Revised — 18.12.2025* *Accepted for publication — 17.02.2026*

INTRODUCTION

Despite the improvement of surgical techniques, the colorectal anastomotic leakage remains one of the most pressing problems in abdominal surgery. The incidence of this complication varies from 3% to 15%, and with low colorectal anastomoses it can reach 20% or more [1,2]. CAL (or colorectal anastomotic leakage — CAL) is associated with high mortality (up to 16–22%), the need for repeated surgeries and the formation of a permanent stoma, which significantly reduces the quality of life of patients [3].

In recent years, considerable attention has been paid to early laboratory predictors of CAL. The most studied are C-reactive protein (CRP) and procalcitonin (PCT), for which meta-analyses have shown diagnostic value on the 3–5 days after colorectal resections (AUC 0.80–0.84; sensitivity 70–100%, specificity 80–90% at various thresholds) [4,5]. However, these markers mainly reflect a systemic inflammatory response and do not provide information about local mechanisms such as oxidative

stress, degradation of the collagen matrix, tissue hypoxia and intra-abdominal hypertension, which play a key role in the strength of the anastomosis. A promising direction is the search for markers reflecting the pathogenetic mechanisms of insolvency: local ischemia, oxidative stress and impaired metabolism of connective tissue (collagenolysis) [6]. In addition, intra-abdominal hypertension syndrome (IAH) plays an important role, which directly impairs microcirculation in the intestinal wall [7].

Experimental studies demonstrate the key role of free radical processes and collagen matrix disorders in the healing of colorectal anastomoses: the effects of hypoxia, hyperbaric oxygenation, and antioxidant therapy (vitamin C, N-acetylcysteine, and coenzyme Q10) are accompanied by changes in levels of MDA, free oxyproline, and suture strength [8].

In this regard, it seems promising to search for complex prognostic indicators that reflect not only the inflammatory response, but also local processes in the intestinal wall — oxidative damage, collagenolysis, motor disorders and intra-abdominal hemodynamics.

AIM

To evaluate the prognostic value of biochemical markers of oxidative stress, collagen degradation, and intra-abdominal pressure in the early diagnosis of intestinal anastomosis failure.

PATIENTS AND METHODS

A retrospective case-control observational study was performed. The case histories of 65 patients who underwent planned and delayed large intestine resections with the formation of a primary anastomosis for benign diseases (dolichosigma, dolichocolon, megadolichosigma, dolichosigma with a combination of Pyre's syndrome, etc.), as well as the elimination of colorectal stomas for the period of 2021–2025, were analyzed.

Inclusion criteria:

– aged over 18;
– resection of the colon with the formation of an end-to-end or side-to-side anastomosis, or the elimination of a colostomy with the imposition of a colorectal anastomosis;
– benign nature of the disease (absence of colorectal cancer and other malignant neoplasms);
– informed consent of the patient.

Exclusion criteria:

– malignant neoplasms (to exclude paraneoplastic effects on markers);
– general peritonitis at the time of surgery;
– severe comorbidities in the decompensation stage, significantly affecting the prognosis;
– lack of key laboratory parameters.

The patients were divided into two groups. The main group consisted of 43 patients who developed CAL in the early postoperative period (up to 14 days). This diagnosis was verified clinically, radiographically (contrast output), endoscopically, or by relaparotomy.

The comparison group was formed retrospectively from patients who had undergone similar resection procedures and met the same inclusion and exclusion criteria. The selection took into account comparability by gender, age, and type of surgery (the level of anastomosis). The age difference between the patients of the two groups in most cases did not exceed 5 years; there were also no significant differences in the duration of surgery and the volume of intraoperative blood loss ($p > 0.05$).

Thus, the study included the entire available cohort of patients meeting the criteria for the specified period, without additional "cleansing" of the main group; the retrospective selection concerned only the comparison group.

On the 2–3 days of the postoperative period, the following indicators were evaluated in all patients:

- Markers of oxidative stress: malondialdehyde (MDA), diene conjugates (DC);
- Antioxidant protection: ascorbic acid;
- Marker of collagen degradation: free oxyproline;
- Plasma lactate as an indicator of tissue hypoxia;

• Intra-abdominal pressure (IAP).

The level of MDA in blood serum was determined by reaction with 2-thiobarbituric acid and optical density was recorded spectrophotometrically.

Diene conjugates were evaluated using the standard Gavrilov's method.

The concentration of ascorbic acid in the blood serum was determined by Tilemans' method.

The level of free oxyproline in blood serum was studied using Bergman-Loxley's method modified by Tetyaneu S.S. Plasma lactate level was determined by colorimetric method with reaction with paraoxydiphenyl. The value of intra-abdominal pressure (IAP, mmHg) was evaluated according to the standard procedure through the bladder using a graduated system, in the patient's supine position, on exhalation, 5–10 minutes after catheterization, with a volume of solution injected into the bladder of no more than 25 ml.

Statistical Analysis

Statistical data processing was performed using IBM SPSS Statistics 22.0 packages (IBM Corp., USA) and MedCalc (MedCalc Software Ltd., Ostend, Belgium).

The normality of the distribution of quantitative data was checked by Shapiro-Wilk's test.

Taking into account the relatively small sample size and the revealed deviations from the normal distribution, most quantitative features were described in the form of median and interquartile range — Me [Q1–Q3]. Nonparametric Mann-Whitney's U–test was used to compare quantitative features between two independent groups. Qualitative features were presented in the form of absolute values (n) and fractions (%); differences between groups were assessed using Pearson's χ^2-test, with expected rate < 5 in ⩾ 20% of cells using the exact Fisher's test.

A univariate binary logistic regression analysis was performed to study the risk factors of CAL. For each predictor, the odds ratio (OR) with a 95% coincidence interval (CI) using Wald's test and the p-value were calculated. The initial pool of variables for multivariate logistic regression included values that demonstrated an association with outcome in the univariate analysis ($p < 0.10$) and had pathogenetic justification (clinical and demographic characteristics, intraoperative parameters, indicators of oxidative stress, markers of collagen degradation, IAP). The multivariate model was built using the forward stepwise method of predictors. The quality of the final predictive model was assessed using Nigelkirk pseudo-R^2 test and Hosmer-Lemeshow's test. The predictive value of individual quantitative indicators and the integral model was assessed using ROC analysis with the calculation of the area under the ROC curve (AUC), 95% CI and p-values. The optimal threshold values were determined by Juden's index. For the selected thresholds, sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were calculated using 95% CI using Clopper-Pearson's test. The predictive characteristics of the integral model were evaluated by the values of the predicted probability of the CAL obtained from the multivariate logistic regression. The results were considered statistically significant at $p < 0.05$.

RESULTS

The study included 65 patients, including 37 (56.9%) men and 28 (43.1%) women. In the main group (CAL) there were 25 (58.1%) men and 18 (41.9%) women; in the control group — 12 (54.5%) and 10 (45.5%) ($p = 0.99$). The age of patients in the groups did not significantly differ: the median (Me [Q1–Q3]) was 63.0 [57.4–69.0] years in the CAL group and 61.2 [56.9–70.0] years in the group without insolvency ($p = 0.91$).

The operation time was comparable: 144.9 [132.3–155.1] min. versus 136.3 [124.8–150.2] min. ($p = 0.182$), as well as the volume of intraoperative blood loss — 280 [222.7–337.3] ml versus 260 [207.4–312.6] ml ($p = 0.360$). Thus, the groups did not differ in the main basic clinical, demographic and intraoperative characteristics (Table 1).

The MDA level in patients with CAL was 4.4 [3.9–4.7] nmol/ml, which was significantly higher than

Table 1. *Clinical and laboratory characteristics of patients with and without CAL (univariate analysis), Me [Q1–Q3]*

Indicator	CAL (*n* = 43)	Without complications (*n* = 22)	*p*-value
Gender and age features			
Age, years	63.0 [57.4–69.0]	61.2 [56.9–70.0]	0.914
Males, *n* (%)	25 (58.1)	12 (54.5)	0.797
Intraoperative values			
Operation time, min.	144.9 [132.3–155.1]	136.3 [124.8–150.2]	0.182
Bloodloss, ml	280 [222.7–337.3]	260 [207.4–312.6]	0.360
Laboratory parameters (on days 2–3)			
MDA, nmol/ml	4.4 [3.9–4.7]	3.1 [2.4–3.6]	< 0.001
Diene conjugates, mmol/ml	3.1 [2.8–3.4]	1.9 [1.7–2.1]	< 0.001
Ascorbic acid, mmol/l	52.4 [47.6–56.4]	65.1 [59.7–70.4]	< 0.001
Lactate, mmol/l	2.7 [2.3–3.1]	1.6 [1.4–1.8]	< 0.001
Free oxyproline, mmol/l	18.0 [15.7–19.6]	12.7 [11.1–14.8]	< 0.001
Serotonin, mmol/l	0.6 [0.5–0.7]	0.9 [0.8–0.9]	< 0.001
IAP, mmHg	16.1 [14.2–17.9]	10.5 [8.8–15.1]	< 0.001

Note: p is according to U-Mann–Whitney's test for quantitative features and Pearson's χ2-test (if necessary– exact Fisher's test) for qualitative features

in patients without CAL (3.1 [2.4–3.6] nmol/ml; $p < 0.001$). The concentration of diene conjugates (DC) was also significantly increased in the CAL group (3.1 [2.8–3.4] versus 1.9 [1.7–2.1] mmol/ml; $p < 0.001$), while the ascorbic acid level was significantly lower than 52.4 [47.6–56.4] versus 65.5 [59.7–70.4] mmol/l; $p < 0.001$).

Higher lactate content was recorded in patients with CAL (2.7 [2.3–3.1] versus 1.6 [1.4–1.8] mmol/l; $p < 0.001$) and free oxyproline (18.0 [15.7–19.6] vs. 12.7 [11.1–14.8] mmol/l; $p < 0.001$), and the concentration of serotonin, on the contrary, was reduced (0.6 [0.5–0.7] versus 0.9 [0.8–0.9] mmol/l; $p < 0.001$).

Intraabdominal pressure (IAP) in patients with CAL reached 16.1 [14.2–17.9] mmHg and significantly exceeded the corresponding indicator in patients without anastomosis leakage (10.5 [8.8–15.1]] mmHg; $p < 0.001$). There were no significant differences between the groups in terms of sex and age characteristics and intraoperative parameters.

Thus, the level of free oxyproline in the main group was significantly higher than in the comparison group (18.0 [15.7–19.6] versus 12.7 [11.1–14.8] mmol/l; $p < 0.001$), which indicates active destruction of the collagen matrix in the anastomosis zone. The values of IAP in the CAL group corresponded to grade I–II intra-abdominal hypertension, while in the control group they remained within acceptable values.

To build a multivariate logistic regression model, the initial pool of predictors included indicators that demonstrated a potential association with CAL in theunivariate analysis ($p < 0.10$) and had pathogenetic justification (clinical and demographic characteristics, intraoperative parameters, markers of oxidative stress and collagenolysis, IAP). As a result of step-by-step inclusion of predictors, three independent factors entered the final model: the level of free oxyproline, MDA and IAP on the 2–3 days after surgery.

In the final model, an increase in the concentration of free oxyproline by 1 micromol/l was associated with an increased risk of CAL (OR 1.35; 95% CI 1.08–1.69; $p = 0.009$). For IAP, every additional 1 mmHg led to an increased chance of anastomosis failure (OR 1.35; 95% CI 1.10–1.65; $p = 0.004$). An increase in the level of MDA by 1 nmol/ml was also an independent predictor of CAL (OR 2.86; 95% CI 1.25–6.56; $p = 0.013$) (Table 2).

Table 2. *Independent predictors of CAL (multivariate logistic regression analysis)*

Indicator	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Free oxyproline, mmol/l	1.50	1.22–1.85	< 0.001	1.35	1.08–1.69	0.009
IAP, mmHg	1.34	1.14–1.58	< 0.001	1.35	1.10–1.65	0.004
MDA, nmol/ml	3.06	1.61–5.79	< 0.001	2.86	1.25–6.56	0.013

Note: OR is odds ratio; 95% CI is 95% coincidence interval (Wald's method)

Table 3. *Diagnostic value of indicators and the integral model in predicting CAL (ROC analysis)*

Indicator	Free oxyproline, mmol/l	IAP, mmHg	MDA, nmol/ml
Threshold values	⩾ 15 mmol/l	⩾ 15 mmHg.	⩾ 4.0 nmol/ml
AUC (95% CI)	0.83 (0.72–0.93)	0.78 (0.65–0.90)	0.80 (0.68–0.91)
Sensitivity, %	79.1	69.8	74.4
Specificity, %	77.3	72.7	77.3
PPV, %	87.2	83.3	86.5
NPV, %	65.4	55.2	60.7
Accuracy, %	78.5	70.8	75.4

Note: Threshold values are selected based on Juden's index. AUC is the area under the ROC curve, PPV is a positive predictive value; NPV is a negative predictive value. 95% CI for sensitivity, specificity, PPV, NPV, and accuracy were calculated using Clopper-Pearson's method.

The inclusion of age, gender, operation time, blood loss, and other clinical and demographic parameters in the model did not significantly improve the quality of the model and was not accompanied by a significant contribution to the risk of CAL ($p > 0.05$ for the corresponding coefficients), so these variables were excluded at the stages of step selection.

The quality of the final model was satisfactory: AUC 0.93 (95% CI 0.84–0.98; $p < 0.001$); Nigelkirk's

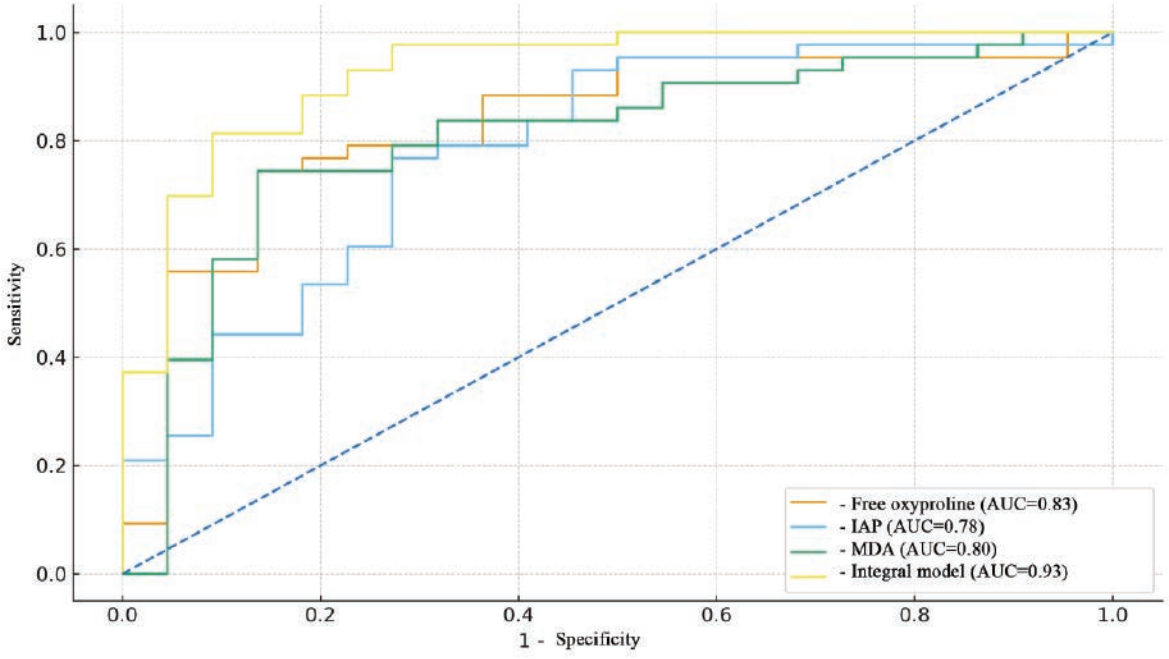

Figure 1. *ROC curves for free hydroxyproline, intra-abdominal pressure, malondialdehyde, and the integrated model in predicting colonic anastomotic leakage. Free hydroxyproline: AUC 0.83; intra-abdominal pressure: AUC 0.78; malondialdehyde: AUC 0.80; integrated model: AUC 0.93*

pseudo-R2 0.65; Hosmer-Lemeshow's test $\chi^2 = 9.0$; $p = 0.34$, indicating a good agreement between the observed and predicted probabilities.

To assess the prognostic significance of individual markers, a *ROC* analysis was performed.

In the *ROC* analysis, the level of free oxyproline on the 2nd-3rd days after the surgery demonstrated a good discriminating ability against CAL: AUC 0.83 (95% CI 0.72–0.93; $p < 0.001$). The optimal threshold value of > 15.0 mmol/l provided sensitivity of 79.1% and specificity of 77.3%, positive prognostic value (PPV) of 87.2% and negative prognostic value (NPV) of 65.4%, overall accuracy of 78.5% (Table 3).

The diagnostic effectiveness of free oxyproline, IAP and MDA in predicting CAL is shown in Table 3 and Figure 1. Free oxyproline demonstrated a good discriminating ability: AUC 0.83 (95% CI 0.72–0.93; $p < 0.001$). The threshold value of ⩾ 15 mmol/l provided sensitivity of 79.1% and specificity of 77.3%, with PPV of 87.2% and NPV of 65.4%. For IAP, the threshold value of ⩾ 15 mmHg was characterized by an AUC of 0.78 (95% CI 0.65–0.90; $p < 0.001$), sensitivity of 69.8%, and specificity of 72.7%. For MDA with the threshold value of ⩾ 4.0 nmol/ml, the AUC was 0.80 (95% CI 0.68–0.91; $p < 0.001$), sensitivity — 74.4%, specificity — 77.3%.

The integral model, including free oxyproline, IAP and MDA, demonstrated the highest prognostic accuracy: AUC 0.93 (95% CI 0.84–0.98; $p < 0.001$), surpassing each of the individual markers in the area under the *ROC* curve (Fig. 1).

Thus, the indicators reflecting the intensity of collagenolysis (free oxyproline), the severity of intra-abdominal hypertension (IAP) and the level of lipid peroxidation (MDA) have high prognostic significance in relation to the risk of CAL and can be used for early differentiation of patients according to the degree of risk.

DISCUSSION

The data obtained confirm the multivariate nature of anastomosis failure, as indicated by modern reviews [9].

A number of metaanalyses and systematic reviews have shown that the dynamics of CRP and PCT in the first 3–5 days after colorectal resections provides an AUC of the order of 0.80–0.90, allowing us to reliably exclude CAL (CAL) at low values and timely suspect a complication with their increase [10]. However, these markers primarily reflect systemic inflammation, while local processes in the anastomosis area (oxidative stress, collagen degradation, and microcirculation disorders) remain less studied. Unlike the widely used inflammatory markers (CRP), the indicators we studied reflect specific pathophysiological links.

A special feature of the presented work is the emphasis on indicators reflecting the structural and functional state of the connective tissue and the collagen framework of the intestinal wall. An increase in the level of free oxyproline in patients with CAL indicates the activation of collagenolysis and increased breakdown of mature collagen in the anastomosis zone. Classical studies of extracellular matrix changes during colorectal surgery have shown that an imbalance between collagen synthesis and degradation is associated with an increased risk of CAL [11]. Newer data confirm the role of MMP-9 and other matrix remodeling enzymes as markers of an unfavorable course after colorectal resections [12].

In our example, it was free oxyproline that turned out to be one of the most significant independent predictors of CAL: OR 1.32 for every 1 mmol/l and AUC 0.84 with a sensitivity of 80% and a specificity of 78% at a threshold > 15 mmol/L. These indicators are comparable to the AUC range described for "classical" biomarkers (CRP, PCT) and confirm that markers of collagen degradation can potentially occupy an important place in early prediction algorithms.

Intraabdominal hypertension is an equally significant component of the pathogenesis of CAL. An increase in IAP leads to a decrease in splanchnic perfusion, deterioration of microcirculation in the intestinal wall, an increase in intraluminal pressure and mechanical stress on the suture line. Although there are few special studies devoted

to IAP as a quantitative predictor of CAL, data on intra-abdominal hypertension in abdominal surgery generally demonstrate its clear association with postoperative organ dysfunction and complications. In this model, the IAP is ⩾ 15 mmHg on the 2nd-3rd days after surgery, there was an AUC of 0.78, a sensitivity of 74% and a specificity of 72%, and the logistic coefficient (OR 1.20 per each 1 mmHg) indicates a pronounced dose-dependent nature of the risk.

The integral model, including free oxyproline, IAP, and MDA, showed an AUC of 0.90, which is comparable to the best combined scales proposed for CRP, PCT, and clinical assessment systems (for example, Dutch leakage score, etc.) [10].

From a practical point of view, the data obtained form the concept of early risk stratification. Patients who already have free oxyproline > 15 mmol/L, IAP ⩾ 15 mmHg and MDA > 4 nmol/ml detected on the 2–3 days after surgery can be classified as high-risk patients with CALand considered in relation to: enhanced monitoring, stricter control of IAP, correction of oxidative stress and a lower threshold for performing diagnostic relaparotomy or anastomosis revision.

Obviously, the proposed model requires validation on independent samples and comparison with existing algorithms based on CRP, PCT and clinical and radiological criteria. However, the comparability of our conditional AUC and OR with the data of modern studies on CAL biomarkers indicates that the inclusion of indicators of oxidative stress, collagenolysis and IAP in multivariate scales has real prospects [13].

CAL remains one of the most serious complications of resection and reconstructive operations on the large intestine; its development is due to a combination of microcirculation disorders, oxidative stress, degradation of the collagen matrix and intra-abdominal hypertension.

Thus, in patients with CAL, as early as 2–3 days after surgery, are shown pronounced changes in the pro- and antioxidant balance (increased MDA and diene conjugates, decreased ascorbic acid), tissue hypoxia (increased lactate), increased collagenolysis (increased free oxyproline), decreased serotonin concentration, and a significant increase in IAP compared to patients with a favorable course of the postoperative period.

The combined prognostic model, including free oxyproline, IAP, and MDA, has a high diagnostic value (AUC = 0.90) with a sensitivity of about 85% and a specificity of about 80% and is comparable in accuracy to the best published algorithms based on CRP, procalcitonin, and clinical scales.

For the final assessment of the clinical significance of the proposed prognostic indicators, prospective studies involving large independent cohorts of patients and direct comparison with existing biomarker and clinical radiological models are needed.

LIMITATIONS OF THE STUDY

The present study was performed in a retrospective case–control design with comparable group of patients without CAL. This approach makes it possible to better control the effect of basic confounders, but limits the generalizability of the obtained prognostic model for the entire population of patients who underwent colorectal resection. An additional limitation is the relatively small sample size and the lack of external (inter-center) validation of the model. Prospective studies on independent cohort samples are needed to definitively confirm the results obtained.

CONCLUSION

Determination of the level of free oxyproline, MDA, and IAP in the early postoperative period can serve as the basis for personalized management tactics for patients at high risk of CAL, including enhanced monitoring, aggressive control of intraabdominal pressure, correction of oxidative stress, and timely diagnostic or therapeutic relaparotomy.

In the multivariate model, independent predictors of the failure of colonic anastomosis sutures

were the level of free oxyproline, the value of IAP, and the concentration of MDA on the 2–3 days after surgery. Each of these indicators demonstrated moderate to good discriminating ability, and their combination provided higher prediction accuracy compared with the use of individual markers. The final assessment of the clinical significance of the proposed prognostic indicators requires prospective validation on larger independent patient samples and direct comparison with existing biomarker and clinical radiological models.

AUTHOR CONTRIBUTIONS

Study conception and design: *Kahramon R. Ruziboyzoda, Mahmadshoh K. Gulov, Afzalsho A. Gulov, Sukhrob G. Ali-Zade*

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