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Original Article

The dynamics of the lipopolysaccharide-binding protein (LBP) level in assessing the risk of adverse outcomes in operated colorectal cancer patients

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ABSTRACT

Background: The main aim of this study is to analyze changes in the lipopolysaccharide-binding protein (LBP) level in blood serum over time and assess it as a potential risk factor for the development of SIRS, infectious and inflammatory complications, organ dysfunction and mortality in patients operated on colorectal cancer (CRC).

Methods: 90 CRC patients were divided into 2 groups: Group 1—50 patients operated on for CRC without acute bowel obstruction (ABO); Group 2—40 patients operated on for CRC with ABO. To determine LBP by ELISA method venous blood was taken 1 h before surgery and 72 h after it (3rd day).

Results: LBP level on the 3rd day after surgery was lower in CRC patients with SIRS, postoperative complications, organ dysfunction and in dead patients. With an LBP value on the 3rd day after surgery being at ≤821.95 ng/mL, the risk of SIRS occurrence is 3.5 times higher, that of the postoperative complications is 5.2 times higher and death is 12.9 times higher than with its higher level (OR 3.5, CI 1.46—8.4; OR 5.2, CI 1.80—15.12; OR 12.9, CI 1.54—108.21, respectively). If the LBP value on the 3rd day after surgery is ≤ 700.15 ng/mL, the risk of organ dysfunctions is 13.5 times higher than with its higher level (OR 13.5, CI 3.536—51.54).

Conclusions: This study demonstrated that in the patients with CRC, the LBP can be used as a predictive criterion for the development of SIRS, postoperative infectious and inflammatory complications, organ dysfunction, and mortality.

1. Introduction

Colorectal cancer (CRC) ranks third in prevalence among all diagnosed malignant tumors.[1,2] The most common complication in CRC is acute bowel obstruction (ABO), which accounts for approximately 80%—85% of emergency surgical visits for this pathology.[3–5] According to various sources, postoperative mortality in ABO ranges from 5% to 32% and complications occurs in 23% of cases.[4,6,7] In ABO caused by CRC, sepsis occurs from 1.7% to 10.5%.[8–11] One of the main components in the development of sepsis in ABO is bacterial translocation,[12,13] a reliable marker of which is currently considered a lipopolysaccharide-binding protein (LBP).

LBP is an acute phase protein produced by hepatocytes in response to bacteria and their pathogen-associated molecular patterns (Pathogen-Associated Molecular Patterns, PAMPs),[14] thereby contributing to an inflammatory response cascade with the release of various cytokines (TNF-α, IL- 1, IL-6 and IL-12). In case of ABO of any genesis, microcirculation is disturbed, further ischemia and hypoxia of the intestinal wall with alternating reperfusion leads to damage to the intestinal mucosa and increases its permeability, which, in its turn, enhances bacterial translocation and activates systemic inflammatory response syndrome (SIRS) with potential subsequent development of infectious and

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inflammatory complications as well as multiple organ dysfunction and sepsis.[15] Since bacteria and their endotoxins trigger an increased production of LBP, it can be a reliable biomarker of endotoxemia associated with impaired intestinal barrier function and BT.[16,17] A number of studies have shown that LBP is a reliable biomarker of microbial translocation and the development of infectious complications and sepsis.[18–20]

The main aim of this study is to analyze changes in the LBP level in blood serum over time and assess it as a potential risk factor for the development of SIRS, infectious and inflammatory complications, organ dysfunction and mortality in operated CRC patients.

2. Material and methods

2.1. Study design

The study was conducted on the basis of four hospitals in Karaganda city, Kazakhstan. For the period 2020–2021, 90 operated CRC patients admitted to these hospitals were examined (prospective study). The inclusion criteria were as follows: patients undergoing planned surgery for a colorectal cancer, patients with malignant ABO caused by CRC over 18 years of age. The exclusion criteria were as follows: age under 18, pregnant women, patients with paralytic ABO, patients with HIV infection, liver cirrhosis, and patients with any infectious process due to another pathology.

All patients were divided into 2 groups:

- Group 1–50 patients operated on for CRC without ABO (planned surgery);
- Group 2–40 patients operated on for CRC with ABO (malignant ABO) caused by CRC.

All patients underwent open surgery (laparotomy). Pathohistological examination of the biopsy specimen determined the histological type of the tumor, the degree of cell differentiation as well as the degree of invasion of the intestinal wall. To assess a potential link between bacterial translocation and the prevalence of the tumor process in the intestinal wall, the latest 8th edition of the international classification of stages of malignant neoplasms TNM grouped by stages I-IV was used.[21] The SIRS signs and the degree of organ dysfunction in accordance with SOFA (Sequential Organ Failure Assessment) scale were determined.[22,23] The development of postoperative infectious and inflammatory complications in all groups was also assessed. These included suppuration of the postoperative wound, abdominal abscesses, peritonitis, anastomotic leaks and sepsis.

For enzyme immunoassay (ELISA) to determine LBP in serum venous blood was sampled 1 h before surgery and 72 h after surgery (3rd day). To detect the LBP in blood serum, a commercial ELISA Kit for Lipopolysaccharide Binding Protein (LBP, Human) was used. The LBP procedure was performed according to the manufacturer's instructions. The technique for collecting, storing blood serum and determining LBP in it is described in detail in a previous study.[24]

2.2. Ethical considerations

All procedures performed in the study was conducted in accordance with the guidelines outlined in the Helsinki Declaration and its amendments. This study was approved by the Bioethics Committee (Protocol No.6 with the assigned number No.30). Informed consent was obtained from all participants included in the study.

2.3. Statistical methods

The sample size was calculated in the program EpiInfo. The obtained results were processed by applying statistical methods, by STATISTICA v8.0 software (Stat Soft) with the calculation of the median, (Me) and the lower and upper quartiles (Q25-Q75). The statistical hypotheses for dependent groups were tested out by using the nonparametric Wilcoxon test. For independent groups, statistical hypotheses were tested for quantitative indicators using the nonparametric Mann–Whitney test and Kruskall-Wallis. For qualitative indicators, Pearson's chi-square test and Fisher's exact test were used. To determine the optimal threshold values for translocation marker, in MedCalc (MedCalc Software Ltd) ROC curves were constructed and the Youden J-index was determined. The results were considered statistically significant at $p < 0.05$.

3. Results

3.1. Comparison of patient baseline characteristics

The baseline characteristics of the patients are presented in Table 1. As it can be seen from Table 1, complication of CRC with acute bowel obstruction was more common in women ($p = 0.05$). CRC patients with ABO had a higher percentage of patients who died ($p = 0.006$).

In CRC patients with ABO, the proportion of patients with stage I was only 2.5%, and the proportion of patients with stage IV was 40% ($p = 0.003$). In patients with CRC without ABO, the most common postoperative infectious and inflammatory complication was an anastomotic leak (14% - seven cases). In CRC patients with ABO, suppuration of the wound and sepsis prevailed equally (10% - four cases each). Eight patients had a combination of several complications. Six patients developed sepsis: two in CRC patients without ABO (4%) and four in CRC patients with ABO (10%).

There was no statistical difference in tumor localization ($p = 0.24$). In both groups, tumors more affected the large intestine, mostly the sigmoid colon (36% and 42.5%, respectively). Most CRC patients with ABO underwent colostomy, which was a statistically significant difference ($p = 0.001$).

3.2. Dynamics of LBP level

Table 2 presents the statistical indicators of the LBP level before surgery and on the 3rd day after it for each study group. There were no differences in the LBP level before the surgery and on the 3rd day after it between the studied groups. However, in group with ABO there was a 3.7 times greater decrease in the level of LBP over the time compared to the CRC patients without ABO ($p = 0.002$, Table 2).

3.3. The LBP level depending on the presence/absence of SIRS, postoperative complications, organ dysfunctions and mortality

In the group with CRC without ABO in patients with organ dysfunction, the LBP level on day 3 after surgery was 27% lower than in patients without organ dysfunction ($Z = 2.44$, $p = 0.01$, Table 3).

In the group with ABO the LBP level on the 3rd day after the surgery in patients with SIRS, postoperative infectious and inflammatory complications, organ dysfunctions and mortality was significantly lower than in patients without them ($p = 0.01$, $p = 0.001$, $p = 0.007$ and $p = 0.02$, respectively) (Table 3 and Fig. 1).

Table 1
Characteristics of the patients under study.

Criteria/Group		CRC without ABO	CRC with ABO	p-value
Age		66.5 (54.0–73.0)	67.5 (58.5–78)	0.34
Sex	Male	56%	35%	**0.05**
	Female	**44%**	**65%**	
SIRS	–	62%	47.5%	0.17
	+	38%	52.5%	
Complications	–	78%	72.5%	0.55
	+	22%	27.5%	
Organ dysfunctions	–	90%	80%	0.15
	+	10%	20%	
Mortality rate	–	98%	80%	**0.006**
	+	**2%**	**20%**	
Tumor stages	I	16%	**2.5%**	**0.003**
	II	44%	35%	
	III	28%	22.5%	
	IV	12%	**40%**	
Tumor invasion of intestinal wall	T1	–	–	0.31
	T2	12%	–	
	T3	18%	35%	
	T4	70%	65%	
Tumor localization	Rectum	20%	12.5%	0.24
	Rectosigmoid junction	12%	10%	
	Large intestine:	68%	77.5%	
	Cecum	10%	7.5%	
	Ascending colon	12%	7.5%	
	Hepatic flexure	4%	5%	
	Transverse colon	0%	10%	
	Splenic flexure	2%	5%	
	Descending colon	4%	0%	
	Sigmoid colon	36%	42.5%	
Type of surgery	Open surgery with anastomotic technique	62%	25%	**0.001**
	Open surgery with colostomy	38%	75%	

For criteria "Age" Me – median and Q25-Q75– lower and upper quartiles are given. p-value – significance level, SIRS - systemic inflammatory response syndrome.

Table 2
Statistical indicators of the LBP level (ng/mL) in the studied groups.

Group/Indicators	Me	Q25-Q75	Z	p-value
Colorectal cancer without acute bowel obstruction				
LBP before the surgery, ng/mL	971.4	816.9–1277.5	1.15	0.25
LBP on the 3rd day after the surgery, ng/mL	897.9	712.5–1220.9		
Colorectal cancer with acute bowel obstruction				
LBP before the surgery, ng/mL	1164.4	826.4–1509.7	**3.13**	**0.002**
LBP on the 3rd day after the surgery, ng/mL	890.9	703.2–1213.7		

Me – median, p-value – significance level, Q25-Q75– lower and upper quartiles, Z – the Wilcoxon test value.

Table 3
The LBP levels on the 3rd day after surgery in studied groups.

Indicators		Me	Q25-Q75	Z	p-value
Colorectal cancer without acute bowel obstruction					
SIRS	–	945.9	712.5–1543.1	−1.39	0.17
	+	786.2	700.2–1034.4		
Complications	–	898.7	712.5–1407.4	−1.14	0.26
	+	773.9	700.2–1034.4		
Organ dysfunctions	–	927.4	767.7–1271.8	**2.44**	**0.02**
	+	675.6	552.8–700.2		
Mortality rate	–	898.7	743.2–1220.9	–	–
	+	700.2 (1 patient)	–		
Colorectal cancer with acute bowel obstruction					
SIRS	–	1074.8	847.6–1308.4	**−2.55**	**0.01**
	+	792.3	536.8–1062.5		
Complications	–	1074.8	838.7–1295.9	**3.33**	**0.001**
	+	566.5	528.2–812.0		
Organ dysfunctions	–	1019.1	795.4–1266.3	**2.69**	**0.007**
	+	551.6	532.5–807.1		
Mortality rate	–	1019.1	789.2–1266.3	**2.37**	**0.02**
	+	679.4	532.5–817.0		

Me – median, p-value – significance level, Q25-Q75– lower and upper quartiles, SIRS - systemic inflammatory response syndrome, Z – the Wilcoxon test value.

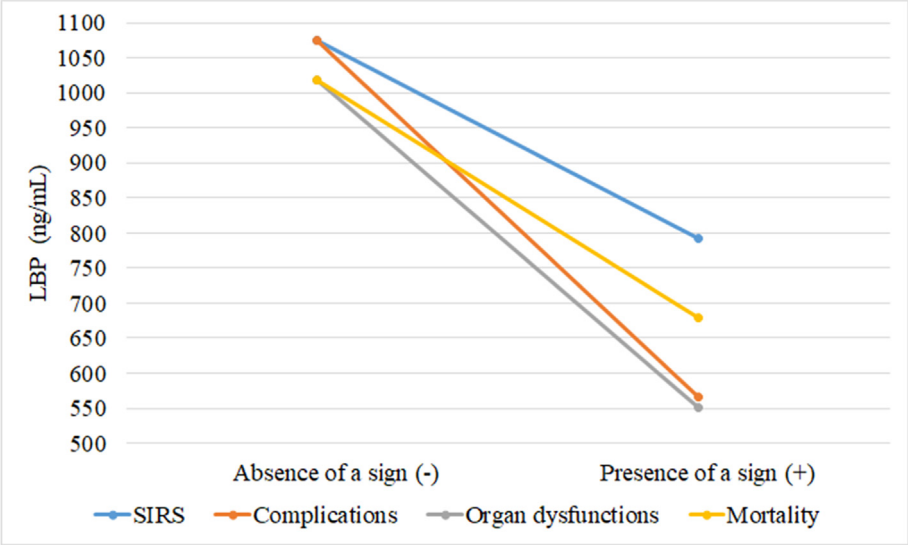

Fig. 1. The lipopolysaccharide-binding protein (LBP) level on the 3rd day after surgery in CRC patients with ABO and with or without such indicators as: systemic inflammatory response syndrome (SIRS), postoperative infectious and inflammatory complications, organ dysfunctions and mortality.

3.4. ROC analysis

Based on the data obtained the total cohort of patients with CRC (with and without ABO) was analyzed to determine the prognostic significance of LBP. In the CRC patients with SIRS, postoperative complications, organ dysfunctions and mortality, the LBP level on the 3rd day after surgery was significantly lower ($p = 0.003$, $p = 0.001$, $p = 0.001$ and $p = 0.01$, respectively, Table 4).

The results of the LBP level ROC-curve analysis on the 3rd day after surgery to predict SIRS, postoperative infectious and inflammatory complications, organ dysfunctions and mortality are shown in Table 5 and in Figs. 2 and 3. With an LBP level on the 3rd day after surgery being at ≤821.95 ng/mL, the risk of SIRS occurrence is 3.5 times higher, the risk of postoperative complications is 5.2 times higher and the risk of death is 12.9 times higher than with its higher level (OR 3.5, CI 1.46–8.4; OR 5.2, CI 1.80–15.12; OR 12.9, CI 1.54–108.21, respectively). If the LBP value on the 3rd day after surgery is ≤ 700.15 ng/mL, the risk of organ dysfunctions is 13.5 times higher than with its higher level (OR 13.5, CI 3.536–51.54).

4. Discussion

According to the literature review, the LBP level due to its long half-life (2–3 days) is detected in the serum after bacteremia for a long time, and therefore it is a relatively reliable marker for the diagnosis of BT.[25] In the study with the patients undergoing laparoscopic or open resection of the esophagus, the patients after laparoscopic surgery had significantly higher plasma levels of LBP, thus, the researchers concluded that increased intra-abdominal pressure led to impaired intestinal barrier function and subsequent bacterial translocation.[26] Previously, in patients with CRC and malignant ABO, the LBP in blood serum as well as the occurrence of SIRS and infectious and inflammatory complications have not been studied in detail and in dynamics.

Our previous pilot study with the patients operated on for CRC ($n = 36$) showed that the level of LBP on the 3rd day after surgery tended to decrease. The decrease in LBP on the 3rd day after surgery more than 280 ng/mL increased the risk of SIRS by 6.6 times (OR 6.6, 95% CI: 1.1–40.9) and postoperative infectious complications by 12 times (OR 12.0, 95% CI: 1.8–80.4).[24,27]

In the present study, in the CRC patients with ABO, the proportion of patients with stage I was only 2.5%, and the proportion of patients with stage IV was 40% ($p = 0.003$). This fact may indicate that patients with stage I colon tumors develop ABO less frequently than with further progression and spread of the tumor process. A 3.7 times greater decrease in the LBP level was observed over time in CRC patients with ABO ($p = 0.002$). Similarly, in this group of the patients with SIRS, postoperative infectious and inflammatory complications, organ dysfunctions and mortality, the level of LBP on the 3rd day was lower than in the patients without them ($p = 0.01$, $p = 0.001$, $p = 0.007$ and $p = 0.02$, respectively). In patients with malignant ABO, in addition to the changes in the intestinal wall due to the presence of a tumor and bowel obstruction, there is an increase in intra-abdominal pressure, which enhances BT. It can be

Table 4
Statistical indicators of the LBP level on the 3rd day after surgery in patients with colorectal cancer, depending on the development of SIRS, postoperative complications, organ dysfunctions and mortality.

Indicators		Me	Q25-Q75	Z	p-value
SIRS	–	991.9	792.3–1407.4	**2.92**	**0.003**
	+	792.3	611.1–1048.4		
Complications	–	950.8	778.4–1302.2	**3.21**	**0.001**
	+	770.8	552.8–927.4		
Organ dysfunctions	–	945.9	773.9–1271.8	**3.67**	**0.001**
	+	566.5	536.8–792.3		
Mortality rate	–	933.6	761.6–1236.7	**2.59**	**0.01**
	+	700.1	536.8–812.0		

Me – median, p-value – significance level, Q25-Q75– lower and upper quartiles, SIRS - systemic inflammatory response syndrome, Z – the Wilcoxon test value.

Table 5
The Results of ROC-curve analysis of the LBP level on the 3rd day after surgery in patients with colorectal cancer to predict SIRS, postoperative infectious and inflammatory complications, organ dysfunctions and mortality.

	AUC (95% CI)	Optimal threshold LBP value	Sensitivity	Specificity	Youden J-index	p-value
SIRS	0.68 (0.57–0.77)	≤821.95	60	72	0.32	**0.002**
Complications	0.73 (0.63–0.82)	≤821.95	72.73	67.65	0.40	**0.001**
Organ dysfunctions	0.82 (0.72–0.89)	≤700.15	69.23	85.71	0.55	**0.001**
Mortality rate	0.76 (0.66–0.85)	≤821.95	88.89	62.96	0.52	**0.001**

AUC (95% CI) – area under the ROC-curve (95% confidence interval), p-value – significance level, SIRS - systemic inflammatory response syndrome.

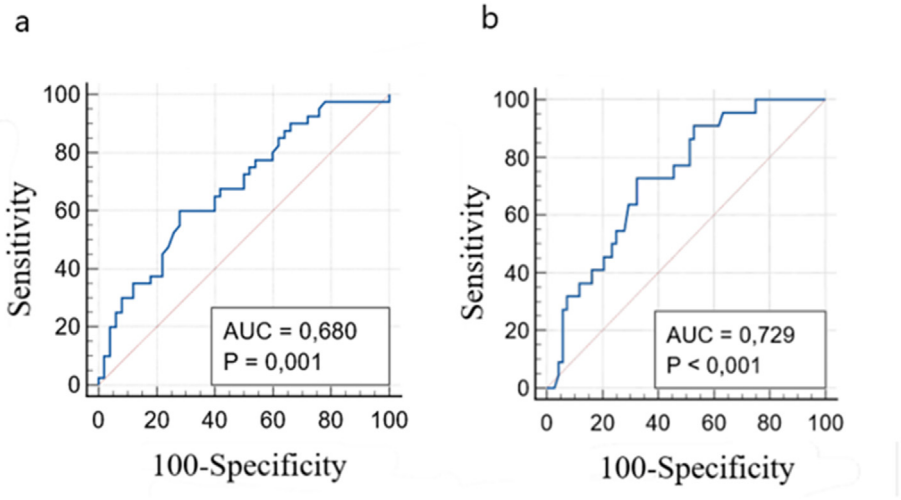

Fig. 2. ROC-curves of the lipopolysaccharide-binding protein (LBP) level on the 3rd day after surgery to predict systemic inflammatory response syndrome (SIRS) (a) and post-operative infectious and inflammatory complications (b). AUC - Area Under Curve, p – significance level.

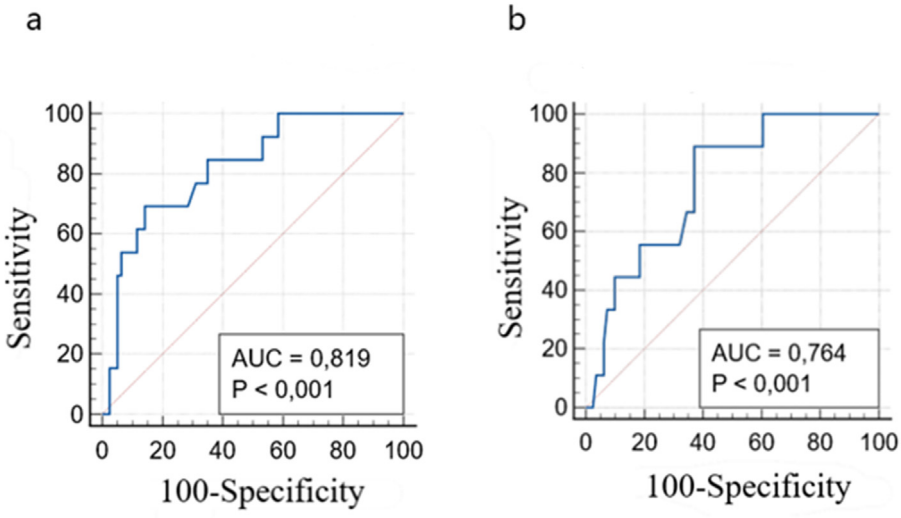

Fig. 3. ROC-curves of the lipopolysaccharide-binding protein (LBP) level on the 3rd day after surgery to predict organ dysfunctions (a) and mortality (b). AUC - Area Under Curve, p – significance level.

assumed that the dynamic decrease in the level of LBP could be associated with the normalization of intra-abdominal pressure, elimination of obstruction, and removal of the tumor itself, which together increased the BT.

In a number of studies, the level of LBP in the blood serum was significantly higher in patients with SIRS, sepsis and septic shock compared with a group of healthy people.[18,19,28–31] Despite the results of previous studies, significantly worse outcomes in the present study were observed in the patients with lower LBP levels on the 3rd day and a more significant decrease over time. In the total cohort of patients with CRC (with and without ABO) with SIRS, postoperative complications, organ dysfunctions and mortality, the LBP level on the 3rd day after surgery was significantly lower ($p = 0.003$, $p = 0.001$, $p = 0.001$ and $p = 0.01$, respectively). It was found that with the LBP value on the 3rd day after surgery at ≤ 821.95 ng/mL, the risk of SIRS occurrence is 3.5 times higher, the

risk of postoperative complications is 5.2 times higher and the risk of mortality rate is 12.9 times higher than with its higher level (OR 3.5, CI 1.46–8.4; OR 5.2, CI 1.80–15.12; OR 12.9, CI 1.54–108.21, respectively). In case the LBP level on the 3rd day after surgery is $\leq$ 700.15 ng/mL, the risk of organ dysfunctions is 13.5 times higher than with its higher level (OR 13.5, CI 3.536–51.54).

It is worth noting that several studies, which included the patients with sepsis and septic shock have shown that LBP is an important part of the antimicrobial defense system and its higher concentrations in the acute phase of inflammation can inhibit the binding of lipopolysaccharide (LPS) to monocytes in blood plasma, thereby reducing the production of cytokines.[29,32] In the experimental study in mice, intraperitoneal administration of LBP inhibited LPS-mediated cytokine release and prevented hepatic failure, resulting in a significant reduction in mortality in those with bacteremia.[33] The authors concluded that the LBP-deficient mice are significantly more susceptible to intraperitoneal Salmonella infection, and that high concentrations of LBP have a protective effect against LPS and bacterial infection and may represent a physiological defense mechanism against infection. It should also be noted that in the study of Opal S.M., the septic patients with less elevated LBP had significantly worse outcomes. The authors suggested that the patients with rapidly progressive sepsis could not adequately synthesize LBP, thereby failing to adequately respond to any systemic microbial infection.[28] In the operated patients with CRC, a decrease in the LBP level is possible due to immunodeficiency and inability to develop an adequate immune response to infectious stimuli, which can lead to infectious and inflammatory complications, organ dysfunctions, sepsis, and even death.

5. Conclusion

The present study demonstrated that in operated colorectal cancer patients, the LBP level in the blood serum can be used as a predictive criterion for the development of adverse outcomes: SIRS, postoperative infectious and inflammatory complications, organ dysfunction, and mortality. Significantly, worse results and prognosis were observed in those patients with a lower level of LBP on the 3rd day after surgery and a more significant decrease in its dynamics.

Declaration of competing interest

The Authors declares that there is no conflict of interest.

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The data availability statement

The data generated in this study are available upon request from the corresponding author.

Ethical considerations

All procedures performed in the study was conducted in accordance with the guidelines outlined in the Helsinki Declaration and its amendments. This study was approved by the Bioethics Committee of the NJSC “Karaganda Medical University” (Protocol No.6 with the assigned number No.30). Informed consent was obtained from all participants included in the study.

Registration of research studies

This study is registered on ClinicalTrials.gov - ID: NCT05229822 (not randomized clinical trial, studied patients were not randomized into groups because this was deemed irrelevant to this study). URL: https://clinicaltrials.gov/ct2/show/NCT05229822?term=NCT05229822&draw=2&rank=1.

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