FORECASTING AND DIAGNOSTIC APPROACHES

ПРОГНОЗИРОВАНИЕ И ДИАГНОСТИЧЕСКИЕ ПОДХОДЫ

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I-FABP and LBP as predictive markers for outcomes in surgical patients with multiple organ dysfunction: a prospective observational cohort study

Ye.M. Turgunov[1], A.V. Ogizbayeva[1,*], S.G. Assamidanova[1], O.V. Avdiyenko[1], D.N. Matyushko[1], A.K. Izdenov[2], D.K. Kaliyeva[1], K.T. Shakeyev[1]

[1] *Karaganda Medical University, Karaganda, Kazakhstan*
[2] *Ministry of Healthcare of the Republic of Kazakhstan, Astana Kazakhstan*

Abstract

INTRODUCTION: Multiple organ dysfunction syndrome (MODS) is the most common cause of death in surgical intensive care units. Today intestinal disorders have been highlighted as a driver in the development of MODS. **OBJECTIVE:** The aim of this study was to evaluate potential biomarkers of bacterial translocation (lipopolysaccharide-binding protein, LBP) and intestinal wall damage (intestinal fatty acid-binding protein, I-FABP) in surgical patients with MODS. **MATERIALS AND METHODS:** This study involved 165 surgical patients divided into two groups: 118 patients with MODS (main group) and 47 patients without MODS (control group). To identify biomarkers, blood was collected from the control group on the day of admission. In the MODS patients, blood was taken on the first day of MODS, and again on Days 3 and 7 of its development. The markers were determined using the ELISA method. **RESULTS**: In the control group, the levels of LBP and I-FABP were lower ($p < 0.05$). In the main group, the mortality rate was 31.4 % ($n = 37$). The deceased patients had higher I-FABP levels on the first day ($p = 0.035$), but LBP levels on Day 7 were conversely lower than in the surviving patients ($p = 0.016$). The threshold values of markers at which the risk of lethal outcome in surgical patients with MODS can potentially increase were calculated using ROC analysis: for LBP on the 7th day, at ≤ 2727.55 ng/mL; and for I-FABP on the 1st day, at > 120.7 pg/mL. **CONCLUSIONS**: In surgical patients with MODS, increased I-FABP and de-creased LBP may indicate intestinal wall damage and increased bacterial translocation,

I-FABP и LBP как маркеры прогнозирования исходов у хирургических пациентов с мультиорганной дисфункцией: проспективное наблюдательное когортное исследование

Е.М. Тургунов[1], А.В. Огизбаева[1,*], С.Г. Асамиданова[1], О.В. Авдиенко[1], Д.Н. Матюшко[1], А.К. Изденов[2], Д.К. Калиева[1], К.Т. Шакеев[1]

[1] *НАО «Карагандинский медицинский университет», Караганда, Казахстан*
[2] *Министерство здравоохранения Республики Казахстан, Астана, Казахстан*

Реферат

АКТУАЛЬНОСТЬ: Синдром мультиорганной дисфункции (multiple organ dysfunction syndrome — MODS) является наиболее частой причиной смерти в отделениях интенсивной терапии хирургического профиля. На сегодня предполагается, что нарушения со стороны желудочно-кишечного тракта играют важную роль в развитии MODS. **ЦЕЛИ ИССЛЕДОВАНИЯ:** Оценка потенциальных биомаркера бактериальной транслокации (липополисахарид-связывающий белок, lipopolysaccharide-binding protein [LBP]) и биомаркера повреждения кишечной стенки (кишечный белок, связывающий жирные кислоты, intestinal fatty acid-binding protein [I-FABP]) у хирургических пациентов с синдромом мультиорганной дисфункции (MODS). **МАТЕРИАЛЫ И МЕТОДЫ:** В данном исследовании приняли участие 165 пациентов хирургического профиля, разделенных на две группы: 118 пациентов с MODS (основная группа) и 47 пациентов без MODS (контрольная группа). Для выявления биомаркеров забор крови проводился у контрольной группы в день поступления, а у пациентов с MODS — в первый день диагностирования MODS, и затем на 3-й и 7-й дни его развития. Маркеры определяли методом иммуноферментного анализа (ИФА). **РЕЗУЛЬТАТЫ:** В контрольной группе уровни LBP и I-FABP были значимо ниже ($p < 0{,}05$). В основной группе летальность составила 31,4 % ($n = 37$). Умершие пациенты имели более высокие уровни I-FABP в первый день ($p = 0{,}035$), но уровни LBP на 7-й день были, наоборот, ниже, чем у выживших пациентов ($p = 0{,}016$). Пороговые which may exacerbate the course of MODS. These potential markers can be used to identify MODS patients at higher risk of adverse outcomes.

значения маркеров, при которых риск летального исхода у хирургических пациентов с MODS потенциально может увеличиться, были рассчитаны с помощью ROC-анализа: для LBP на 7-й день — ≤ 2727,55 нг/мл и для I-FABP на 1-й день — > 120,7 пг/мл. **ВЫВОДЫ:** У хирургических пациентов с MODS повышенный I-FABP и сниженный LBP могут указывать на повреждение стенки кишечника и повышенную бактериальную транслокацию, что может усугубить течение MODS. Исследуемые потенциальные маркеры могут быть использованы для выявления пациентов с MODS с более высоким риском неблагоприятных исходов.

KEYWORDS: multiple organ dysfunction, bacterial translocation, intestinal barrier function, fatty acid-binding proteins, lipopolysaccharide-binding protein

КЛЮЧЕВЫЕ СЛОВА: мультиорганная дисфункция, бактериальная транслокация, барьерная функция кишечника, белки, связывающие жирные кислоты, липополисахарид-связывающий белок

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* *For correspondence:* Alina V. Ogizbayeva — PhD, Associate Professor of the Department of Emergency Medical Care, Anesthesiology and Resuscitation, Department of Emergency Medical Care, Anesthesiology and Resuscitation, Karaganda Medical University, Karaganda, Kazakhstan; e-mail: eleusizova.a@kgmu.kz

* *Для корреспонденции:* Алина Виталиевна Огизбаева — доктор философии (PhD), ассоциированный профессор кафедры скорой медицинской помощи, анестезиологии и реаниматологии, кафедра скорой медицинской помощи, анестезиологии и реаниматологии, НАО «Карагандинский медицинский университет», Караганда, Казахстан; e-mail: eleusizova.a@kgmu.kz

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Introduction

Multiple organ dysfunction syndrome (MODS) is the most common cause of death in surgical intensive care units (50–80 % of all deaths) [1]. For more than 30 years, intestinal disorders have been highlighted as a driver in the development of MODS [2, 3]. In intensive care unit (ICU) patients in severe/critical conditions, due to microcirculatory disorders, intestinal epithelial cell apoptosis is increased and intercellular tight junctions are disrupted, thereby increasing the permeability of the intestinal wall. As a consequence, bacteria/their toxic mediators (danger-associated molecular patterns — DAMPS) from the intestine move through the mesenteric lymphatic vessels into the systemic bloodstream (bacterial translocation), where they cause distant damage (the so-called intestinal lymphatic theory). In this case, the main target organs for translocation are the lungs, kidneys, spleen, and liver [4]. DAMPS are recognized by cells of innate immunity (macrophages, dendritic cells), as well as fibroblasts and epithelial cells, activating systemic inflammatory response syndrome (SIRS) with subsequent multiple organ dysfunction, which in turn aggravates further damage to the intestinal barrier [1, 5, 6]. Several studies have shown that surgical patients with postoperative MODS and sepsis have an increased intestinal permeability and bacterial translocation, as well as an autopsy-proven higher number of intestinal epithelial cells with apoptosis [1–3].

Therefore, assuming that surgical patients with MODS have significant changes in biomarkers of intestinal wall damage and bacterial translocation, the aim of this study was to evaluate these biomarkers in MODS patients. I-FABP (intestinal fatty acid-binding protein) was selected as a potential marker of intestinal wall damage. I-FABP plays a role in intracellular fatty acid transport, is usually present in the cytoplasm of enterocytes, and its detection in plasma indicates enterocyte membrane disruption [7]. A number of studies have proposed it as a reliable marker of intestinal barrier disruption [8].

LBP (LPS-binding protein, lipopolysaccharide-binding protein) was selected as a potential marker of bacterial translocation. LBP is a serum protein, which is involved in the identification, binding, and transport of lipopolysaccharide (LPS)/endotoxins, which is part of the bacterial cell wall. LBP is usually elevated in the systemic bloodstream under conditions of increased intestinal permeability and bacterial translocation [9]. Several studies have shown that LBP is a reliable biomarker for the development of infectious complications and sepsis [10].

Materials and methods

Study design

This prospective observational cohort study was conducted from July 2023 to August 2024 at the facilities of four hospitals in the city of Karaganda. It involved 165 surgical patients divided into two groups: Group 1 — 118 patients with MODS (main group); group 2 — 47 patients without MODS (control group). The main group was subsequently divided into two subgroups: Non-Survivors and Survivors.

Inclusion criteria: for the main group - surgical patients with signs of MODS; for the control group - patients with identical surgical pathologies without MODS.

Exclusion criteria: patients less than 18 years of age, pregnant women, patients with HIV infection. Patient may be excluded from the study if this is: the volunteer's decision to stop participating in the study; patient's decision to not follow prescribed medical instructions or safety protocols in hospital; identification of exclusion criteria during the study.

Before blood sampling, all patients and/or their relatives (legal representatives) were explained the objectives of the study; after agreeing to participate in the study, they and/or their relatives (legal representatives) signed an informed consent. All patients underwent clinical, instrumental and laboratory research methods in accordance with the clinical protocols for the management of hospitalized patients of the Ministry of Health of the Republic of Kazakhstan.

Surgical patients were diagnosed with complications of peptic ulcer disease (bleeding, perforation), severe acute or necrotizing pancreatitis, acute cholecystitis, acute appendicitis, intra-abdominal infection (abscesses, peritonitis), strangulated and incarcerate hernias, acute intestinal obstruction, wound infection (abscesses, phlegmon, gangrene), and urinary tract infection (due to ureteral obstruction by a stone). In the main group, 83.1 % of patients ($n = 98$) were operated on according to the underlying pathology, 16.9 % of patients ($n = 20$) were not operated on and received conservative therapy. In the control group, 87.2 % of patients ($n = 41$) were operated on and 12.8 % ($n = 6$) were not (table 1). Non-operated patients who received conservative therapy included patients with endoscopic therapy of ulcer bleeding, acute pancreatitis, incarcerate hernia and urinary tract infections.

MODS was scored using the SOFA (Sequential Organ Failure Assessment) scale [11, 12]. The patient was diagnosed with MODS when the SOFA scale revealed dysfunction of 2 or more organs not involved in the process that led to hospitalization in the intensive care unit. Mortality rate was also assessed using the APACHE II (Acute Physiology and Chronic Health Evaluation II) scale [12, 13].

To identify biomarkers in blood, venous blood was drawn in the control group on the day of hospital admission, and in the MODS patients on the first day of MODS staging, and again on Days 3 and 7 of its development. The LBP and I-FABP in the blood serum were determined with the method of enzyme-linked immunosorbent assay (ELISA) on the EVOLIS robotic ELISA system, using commercial kits for each of the markers studied according to the manufacturer's instructions (Cloud-Clone Corp., USA) [14].

This study is registered on ClinicalTrials.gov. Clinical trial number: NCT06221293 from April 19, 2024.

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Statistical methods

The sample calculation was done in the program Epi Info using the "StatCalc" module for cohort studies with the following parameters:

- Two-sided confidence level of 95 % and Power (80 %);
- Proportion of unexposed vs. exposed of 0.6 (according to the results of the previous studies, in average about 62 % of ICU patients have multiple organ dysfunction);
- Percentage outcome in the unexposed group 20 % in case of death from other diseases or injuries during the study;
- Percentage outcome in the exposed group 50 %.

Table 1. Surgical pathologies with which patients were hospitalized

Таблица 1. Хирургические патологии, с которыми госпитализировали пациентов

Diagnosis/Group	Patients with MODS			Patients without MODS			*p*-level
	Total	Operated on	Non-operated	Total	Operated on	Non-operated	
Complications of peptic ulcer disease (bleeding, perforation)	20	15	5	10	7	3	0.548
Severe acute or necrotizing pancreatitis	20	14	6	2	1	1	0.519
Acute cholecystitis, acute appendicitis, intra-abdominal infection (abscesses, peritonitis)	19	19	0	11	11	0	—
Strangulated and incarcerate hernias	20	18	2	4	2	2	0.115
Wound infection (abscesses, phlegmon, gangrene)	20	20	0	10	10	0	—
Urinary tract infection (due to ureteral obstruction by a stone	19	12	7	10	10	0	0.032
Total number	118	98	20	47	41	6	0.221
p-level*	0.162						
Note: * — significance of differences in diseases between study groups k = 5.							

The output table shows three different estimates of sample size needed. The most conservative Fleiss method with continuum correction (Fleiss w/CC) with the largest number of subjects in the sample was selected. The sample size is increased by 20 % in case of patient excluded from the study.

For statistical processing, STATISTICA 8.0 (StatSoft) was used. Median (Me), lower, and upper quartiles (Q1–Q3), mean (M), standard deviation (SD), 95% confidence interval (95% CI) were calculated for each quantitative indicator. The proportion and frequency of occurrence were calculated for the qualitative indicators. The non-parametric Mann–Whitney criteria, the Chi-square (χ^2) criterion, with Yates correction for $n < 10$ and Fisher's exact criterion for $n < 5$, were used. Patients for whom information on any of the predictors was missing were excluded from the data set (complete-case analysis). The threshold values of biomarkers' levels for predicting mortality were calculated using receiver operating characteristics (ROC) and the Youden J-index in the MedCalc program (MedCalc Software Ltd). The significance of the results was considered at $p < 0.05$.

Results

Patients' baseline characteristics

The control and main groups were identical in terms of age, sex, major, and concomitant pathology ($p = 0.108$, $p = 0.826$, $p = 0.162$, and $p = 0.318$, respectively; table 2 and 3). In the group of surgical patients with MODS, the mortality rate was 31.4 % ($n = 37$), of which 37.8 % ($n = 14$) died within the first two days of ICU admission.

LBP and I-FABP levels in the studied groups of surgical patients

In the control group, the LBP and I-FABP values were significantly lower than in the group of patients with MODS (table 4). In the main group, no change in the dynamics was found when comparing markers on Days 1, 3, and 7 ($p = 0.063$ for LBP, $p = 0.863$ for I-FABP; table 5).

LBP and I-FABP levels in surgical patients with MODS in terms of mortality

The deceased patients had significantly higher I-FABP scores on the first day ($p = 0.035$); conversely, LBP levels on the seventh day were lower ($p = 0.016$; table 6, fig. 1). The SOFA and APACHE II scores were significantly higher in all the deceased patients ($p < 0.001$).

The LBP level was correlated as follows:

- On Day 1 with the APACHE II scores on Day 1 ($r = -0.287$, $p < 0.05$);
- On Day 3 with the APACHE II scores on Day 1 ($r = -0.310$, $p < 0.05$) and SOFA scores on Days 1 and 3 ($r = -0.314$ and $r = 0.266$, respectively, $p < 0.05$);
- On Day 7 with mortality ($r = -0.262$, $p < 0.05$).

The I-FABP level was correlated as follows:

- On Day 1 with the APACHE II scores on Days 1 and 3 ($r = 0.267$ and $r = 0.273$, respectively, $p < 0.05$) and mortality ($r = 0.362$, $p < 0.05$).

Table 2. Patients' baseline characteristics

Таблица 2. Исходные характеристики пациентов

Criterion/Group		**Patients with MODS (n = 118)**		**Patients without MODS (n = 47)**		***p*-level**
		%		**%**		
Sex	Male	44.9 %		46.8 %		0.826
	Female	55.1 %		53.2 %		
Mortality	Non-Survivors	31.4 %		0 %		< 0.001
	Survivors	68.6 %		100 %		
		Me (Q1–Q3)	M±SD (95% CI)	Me (Q1–Q3)	M±SD (95% CI)	
Age		65.0 (50.0–73.0)	62.3 ± 15.8 (59.4–65.2)	61.0 (46.0–70.0)	53.8 ± 17.1 (48.8–58.8)	0.108
SOFA scores (Day 1)		4.0 (3.0–6.0)	4.6 ± 2.3 (4.2–5.0)	0.0 (0.0–0.0)	0.2 ± 0.5 (0.07–0.4)	< 0.001
APACHE II scores (Day 1)		13.0 (9.0–18.0)	13.9 ± 6.5 (12.7–15.1)	5.0 (3.0–7.0)	5.1 ± 2.9 (4.2–5.9)	< 0.001

Note: M — mean; Me — median; SD — standard deviation; Q1–Q3 — lower and upper quartiles; 95% CI — confidence interval.

Table 3. Comorbidities of the patients under study

Таблица 3. Сопутствующие заболевания у исследуемых пациентов

Comorbidities /Group	**Patients with MODS (n = 118)**	**Patients without MODS (n = 47)**	***p*-level**
Absent	31	16	0.318
Present	87	31	
cardiovascular diseases	39	16	0.591
diabetes mellitus	15	5	0.334
previous cerebrovascular accidents	3	0	0.210
chronic kidney disease	3	2	0.443
chronic cholecystitis	3	0	0.305
gastritis and peptic ulcer	6	4	0.493
chronic lung diseases (bronchial asthma, COPD)	3	0	0.305
cardiovascular diseases and diabetes mellitus	13	3	0.204
cardiovascular diseases and chronic kidney disease	2	1	0.736

Table 4. Lipopolysaccharide-binding protein (LBP) and intestinal fatty acid-binding protein (I-FABP) levels on Day 1 in both study groups

Таблица 4. Уровни липополисахарид-связывающего белка (LBP) и кишечного белка, связывающего жирные кислоты (I-FABP), на 1-й день в обеих исследуемых группах

Criterion	**Patients with MODS (n = 118)**		**Patients without MODS (n = 47)**		**Z**	***p*-level**
	Me (Q1–Q3)	**M ± SD (95% CI)**	**Me (Q1–Q3)**	**M ± SD (95% CI)**		
LBP (ng/mL)	2238.9 (1596.6–3105.5)	2601.1 ± 1420.8 (2342.1–2860.1)	716.3 (453.9–1232.9)	1112.3 ± 1309.5 (727.9–1496.8)	7.394	**< 0.001**
I-FABP (pg/mL)	97.5 (62.7–138.3)	192.5 ± 129.7 (132.4–252.6)	64.8 (27.8–138.4)	75.8 ± 54.8 (59.7–91.9)	3.145	**0.002**

Note: M — mean; Me — median; SD — standard deviation; Q1–Q3 — lower and upper quartiles; Z — Mann—Whitney criteria values; 95% CI — confidence interval.

Table 5. Lipopolysaccharide-binding protein (LBP) and intestinal fatty acid-binding protein (I-FABP) levels in patients with MODS
Таблица 5. Уровни липополисахарид-связывающего белка (LBP) и кишечного белка, связывающего жирные кислоты (I-FABP), у пациентов с мультиорганной дисфункцией (MODS)

Criterion	Me (Q1–Q3)	M ± SD (95% CI)	*p*-level
LBP on Day 1 (ng/mL)	2238.9 (1596.6–3105.5)	2601.1 ± 1420.8 (2342.1–2860.1)	0.063
LBP on Day 3 (ng/mL)	2503.9 (1600.2–3469.9)	2723.5 ± 1354.1 (2450.6–2996.4)	
LBP on Day 7 (ng/mL)	2863.9 (2055.3–4026.7)	3035.2 ± 1346.8 (2725.4–3345.1)	
I-FABP on Day 1 (pg/mL)	97.5 (62.7–138.3)	192.5 ± 129.7 (132.4–252.6)	0.863
I-FABP on Day 3 (pg/mL)	79.5 (49.4–132.5)	144.9 ± 164.3 (91.6–198.1)	
I-FABP on Day 7 (pg/mL)	81.7 (50.4–118.4)	99.4 ± 91.9 (78.2–120.6)	

Note: M — mean; Me — median; SD — standard deviation; Q1–Q3 — lower and upper quartiles; 95% CI — confidence interval.

Table 6. Lipopolysaccharide-binding protein (LBP) and intestinal fatty acid-binding protein (I-FABP) levels, SOFA and APACHE II scores on Day 1, Day 3, and Day 7 after diagnosing MODS in terms of mortality
Таблица 6. Уровни липополисахарид-связывающего белка (LBP) и кишечного белка, связывающего жирные кислоты (I-FABP), оценки по шкале SOFA и APACHE II на 1, 3 и 7-й день после диагностики MODS в зависимости от развития летального исхода

Criterion		Survivors (*n* = 81)		Non-Survivors (*n* = 37)		*p*-level
		Me (Q1–Q3)	M ± SD (95% CI)	Me (Q1–Q3)	M ± SD (95% CI)	
LBP (ng/mL)	Day 1	2200.1 (1450.7–3017.7)	2427.5 ± 1286.7 (2142.9–2712.0)	2387.0 (1694.1–4571.0)	2981.1 ± 1632.4 (2436.9–3525.4)	0.141
	Day 3	2544.9 (1838.8–3755.8)	2844.8 ± 1387.8 (2523.3v3166.4)	1871.4 (528.2–3267.8)	2333.2 ± 1184.3 (1821.0–2845.3)	0.114
	Day 7	3121.9 (2123.9–4069.3)	3206.5 ± 1360.2 (2861.1–3551.9)	2141.2 (1644.6–2624.5)	2218.4 ± 952.2 (1642.9–2793.9)	**0.016**
I-FABP (pg/mL)	Day 1	88.3 (57.1–135.4)	160.8 ± 182.8 (98.2–223.3)	120.9 (77.4–177.6)	261.9 ± 110.2 (125.2–398.8)	**0.035**
	Day 3	71.8 (46.7–126.6)	139.9 ± 154.4 (80.9–198.9)	101.5 (64.6–137.9)	160.7 ± 199.4 (31.2–290.1)	0.128
	Day 7	79. 8 (47.0–106.0)	90.5 ± 67.5 (73.4–107.7)	115.4 (67.7–138.3)	141.8 ± 163.3 (43.1–240.5)	0.104
SOFA scores	Day 1	3.0 (2.0–5.0)	3.9 ± 2.1 (3.5–4.4)	6.0 (4.0–8.0)	6.0 ± 2.3 (5.2v6.8)	**< 0.001**
	Day 3	3.0 (2.0–5.0)	3.4 ± 1.9 (2.9–3.8)	6.0 (4.0–8.0)	6.4 ± 2.7 (5.2–7.6)	**< 0.001**
	Day 7	1.5 (0.0–3.0)	2.0 ± 1.9 (1.5–2.5)	5.5 (3.0–10.0)	6.4 ± 3.9 (3.6–9.2)	**0.0002**
APACHE II scores	Day 1	11.0 (8.0–15.0)	12.2 ± 6.0 (10.9–13.5)	18.0 (13.0–21.0)	17.6 ± 6.2 (14.7–19.7)	**< 0.001**
	Day 3	9.0 (6.0–12.0)	9.6 ± 5.5 (8.3–10.9)	18.5 (12.0–22.5)	17.2 ± 6.0 (14.7–19.7)	**< 0.001**
	Day 7	7.0 (5.0–11.0)	8.0 ± 4.6 (6.8–9.2)	15.0 (9.0–27.0)	16.59.7 (10.1–23.2)	**0.003**

Note: M — mean; Me — median; SD — standard deviation; Q1–Q3 — lower and upper quartiles; 95% CI — confidence interval.

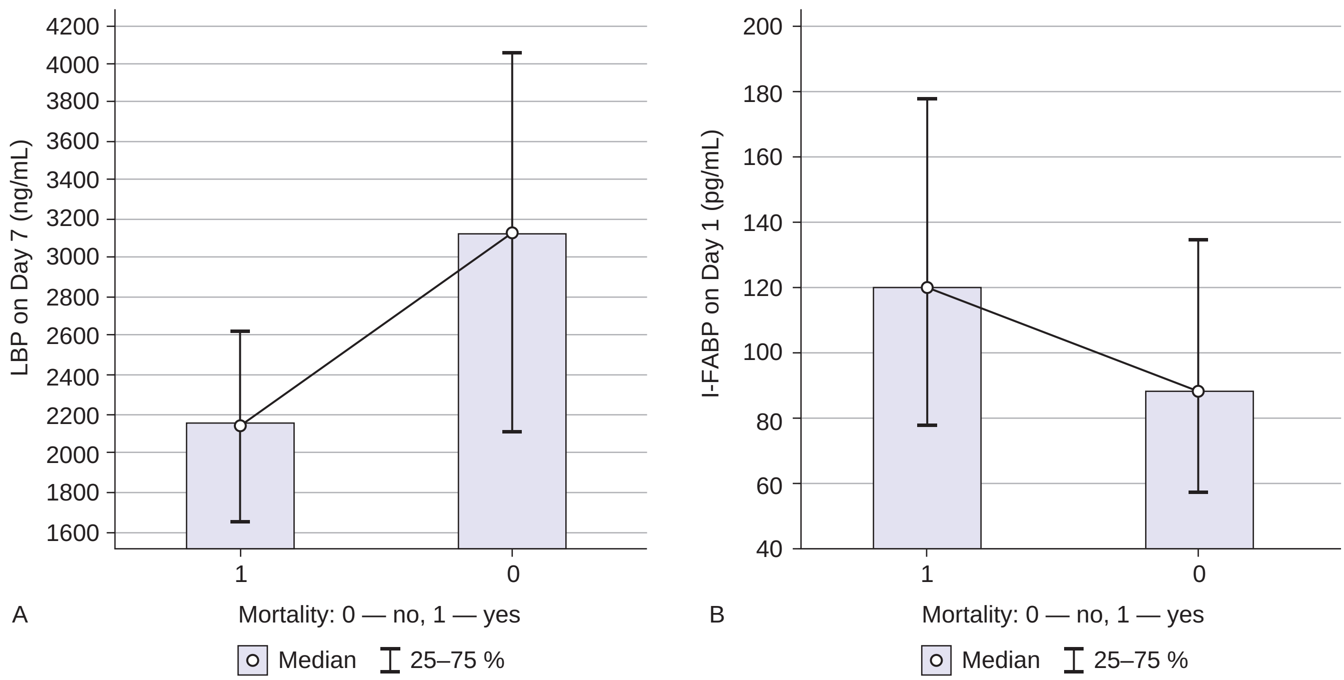

Fig. 1. Lipopolysaccharide-binding protein (LBP, A) and intestinal fatty acid-binding protein (I-FABP, B) levels in deceased and surviving surgical patients with MODS

Рис. 1. Уровни липополисахарид-связывающего белка (LBP, A) и кишечного белка, связывающего жирные кислоты (I-FABP, B), у умерших и выживших хирургических пациентов с мультиорганной дисфункцией (MODS)

- On Day 7 with the SOFA scores on Day 7 (r = 0.524, p < 0.05) and the APACHE II scores on Days 1, 3 and 7 (r = 0.356, r = 0.276, and r = 0.294, respectively, p < 0.05).

ROC analysis of studied markers in surgical patients with MODS to predict mortality

ROC analysis was used to determine the threshold values of markers, which may increase the risk of lethal outcome in surgical patients with MODS: for LBP on the 7th day of MODS development, ≤ 2727.55 ng/mL; for I-FABP on the 1st day of MODS development, >120.7 pg/mL (table 7, fig. 2). Although statistically significant differences between the deceased and surviving surgical patients with MODS were obtained for these markers, the sensitivity/specificity results were low for some markers.

Discussion

As mentioned earlier, surgical ICU patients tend to experience the phenomena of microcirculatory disturbances, ischemia, and hypoxia of the intestinal wall alternating with reperfusion, which lead to oxidative stress with subsequent damage to the integrity of the intestinal mucosa and increased permeability of the intestinal wall. As a result, bacteria/endotoxins from the intestine enter the systemic bloodstream, and being recognized by the immune system, activate systemic inflammatory response

Table 7. ROC analysis of the studied markers in surgical patients with MODS to predict mortality

Таблица 7. ROC-анализ изучаемых маркеров у хирургических больных с мультиорганной дисфункцией (MODS) для прогнозирования летального исхода

ROC analysis results	AUC (95% CI)	*p*-level	Youden's index	Optimal threshold value	Sensitivity	Specificity
LBP on Day 7 (ng/mL)	0.713 (0.597–0.811)	**0.004**	0.427	≤ 2727.55	84.62	58.06
I-FABP on Day 1 (pg/mL)	0.621 (0.528–0.709)	**0.028**	0.242	> 120.7	51.35	72.84

Note: AUC (95% CI) — the area under the ROC curve (95% CI is the confidence interval); *p*-level — the significance level.

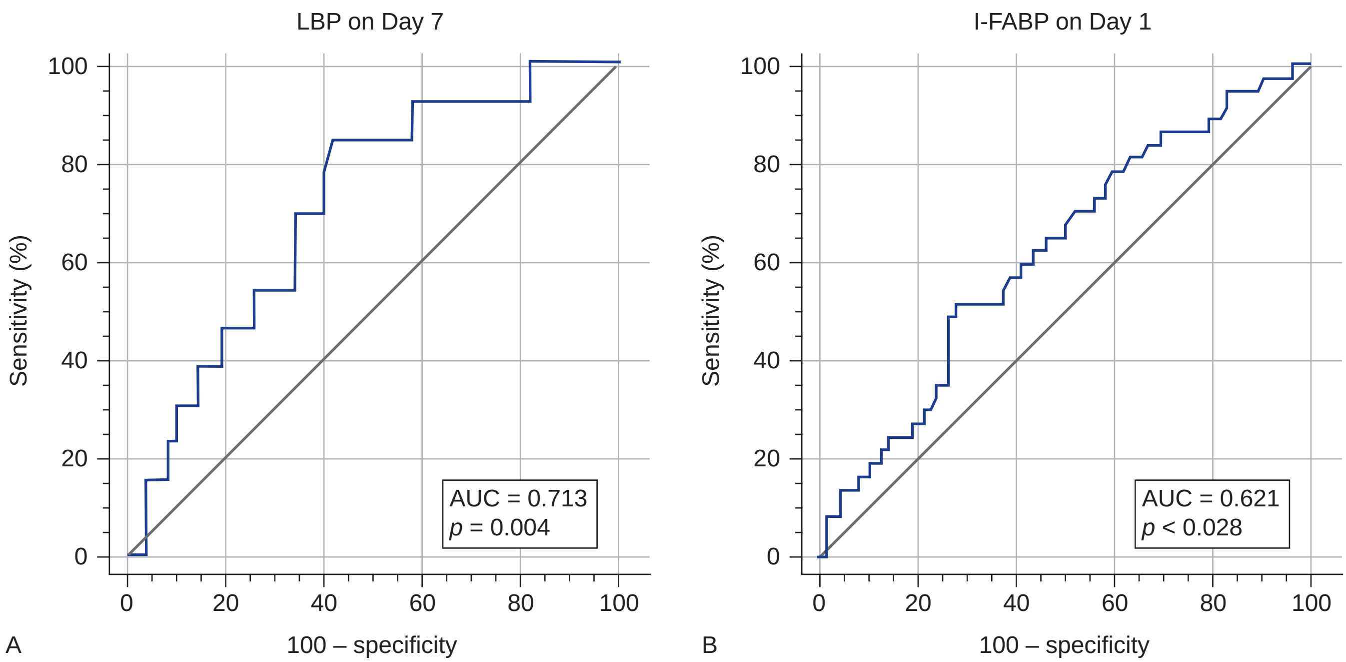

Fig. 2. ROC analysis of lipopolysaccharide-binding protein (LBP, A) and intestinal fatty acid-binding protein (I-FABP, B) to predict mortality in surgical patients with MODS

Рис. 2. ROC-анализ липополисахарид-связывающего белка (LBP, A) и кишечного белка, связывающего жирные кислоты (I-FABP, B), для прогнозирования летального исхода у хирургических пациентов с мультиорганной дисфункцией (MODS)

syndrome with subsequent development of multiple organ dysfunction, which further exacerbates abnormalities in the intestinal mucosa, forming a vicious cycle. Ultimately, the intestine becomes the major pro-inflammatory organ driving the systemic inflammatory response [5]. The development of MODS leads to longer stay time in ICUs and also increases the risk of mortality (up to 50–80 %) [1]. This study involved 165 surgical patients divided into two groups: patients with MODS and without MODS (control group with identical surgical pathology, p = 0.162). The control and main groups were identical in terms of age, sex, comorbidities (p > 0.05). In the control group all patients survived, and in group of surgical patients with MODS, the mortality rate was 31.4 % (n = 37), of which 14 patients died in the first two days of ICU admission, which is a rather high mortality rate.

Due to its long half-life, LBP levels are detected in serum after bacteremia for a long time, and it is therefore a relatively reliable marker to identify bacterial translocation [15]. According to previous studies, high serum LBP levels were observed in patients with SIRS, sepsis, and septic shock compared to a group of healthy patients [15], and in non-survivors compared to survivors. High serum LBP levels were present at admission and gradually decreased on the following days [10]. LBP has also been found to be elevated in patients after laparoscopic surgery because persistently elevated abdominal pressure during surgery leads to impaired intestinal barrier function and subsequent bacterial translocation [10]. This study also confirms that higher levels of LBP are observed in surgical patients with MODS than in the patients without this complication.

Despite this, worse outcomes were observed in the patients with lower LBP levels at follow-up: the deceased MODS patients had significantly lower LBP levels on Day 7 (2141.15 ng/mL) than the surviving patients (3121.93 ng/mL). Weak inverse correlation was found between LBP with mortality, APACHE II and SOFA scores. The threshold value of LBP on Day 7 at which the risk of mortality can potentially increase was determined to be ≤ 2727.55 ng/mL, but the specificity of this result was only 58.06 %. Also, in study of 327 ICU patients deceased patients with MODS had a significantly lower LBP level on Day 7 (2379.75 ng/mL) than did surviving patients (3118.85 ng/mL) [16]. However, the results obtained can also be explained with the data of earlier studies: a decrease in LBP levels over time was observed in 71.3 % of survivors and 38.5 % of non-surviving patients, with significantly worse outcome results in the patients with lower LBP levels. It is assumed that high levels of LBP contribute to the body's defense against bacteria/endotoxins [10]; in the acute phase of inflammation, higher LBP levels can inhibit the binding of lipopolysaccharide to monocytes in blood, thereby reducing the production of cytokines. The ICU patients in critical condition cannot synthesize it in a sufficient amount to adequately respond to the systemic microbial infection [10]. The obtained results may support the hypothesis that in surgical patients with MODS with a more unfavorable course and a high risk of lethal outcome, the LBP level decreases in dynamics, which provides insight into the increased bacterial translocation in this category of patients, which aggravates the course of multiple organ dysfunction.

The intestinal fatty acid-binding protein is localized in enterocytes and is released only after they are damaged, so an increase in this protein is a potential marker of intestinal damage. The increased I-FABP at ICU admission correlated with the elevated lactate levels and higher organ dysfunction scale score (SOFA and APACHE II), and was associated with the higher mortality within 28 days [17, 18]. I-FABP is very sensitive as it can be detected in the early stage of small intestinal ischemia, even when histologic damage is insignificant [19], and a threshold value > 100 pg/mL indicates ischemia and necrosis of the intestinal mucosa [20]. In this study, it was found that I-FABP levels were significantly higher in the surgical patients with MODS (97.50 pg/mL) than in the patients without this complication (64.76 pg/mL). The I-FABP levels were significantly higher in the deceased MODS patients (120.88 pg/mL) than in the surviving patients (88.30 pg/mL). Weak to moderate correlations were found between I-FABP with mortality, APACHE II and SOFA scores. The threshold value of I-FABP on Day 1 at which the risk of mortality can potentially increase was determined to be > 120.7 pg/mL, however, the sensitivity of this result was only 51.35 %. Obtained results does not contradict previous studies, in study of 327 ICU patients the threshold value of I-FABP was defined as > 118.2 pg/mL [16], however, there was patients with different pathology, nor only surgical, but also therapeutic patients. In the present study, we aimed to evaluate possible indicators of gastrointestinal dysfunction (namely, increased intestinal permeability leading to increased bacterial translocation) specifically in surgical patients, with the expectation that most surgical patients will have a higher risk of gastrointestinal disorders, including impaired intestinal permeability, due to surgical and endoscopic interventions.

The results of this study may support the hypothesis that surgical patients with MODS with a more unfavorable course and a high risk of mortality have higher levels of I-FABP, which indicates increased intestinal wall permeability. In turn, the impaired intestinal wall integrity leads to increased bacterial translocation, resulting in an enhanced systemic immune response, a worsened course of organ dysfunction, and an increased risk of mortality. Despite the fact that today there are scales that with a high probability determine the risk of death (in one of the studies APACHE II was having sensitivity of 89.9 % and specificity of 97.6 % (AUC = 0.983), SOFA had 90.1 % and 96.6 % (AUC = 0.986) [21], modern scales for assessing MODS do not include an assessment of gastrointestinal dysfunction, which plays an important role in the initiation and aggravation of the course of multiple organ dysfunction. Therefore, given that I-FABP is a biomarker that signals intestinal wall damage and dysfunction, its combination with the already known APACHE II and SOFA scales may allow for a more accurate prediction of mortality in patients with MODS.

A potential limitation of this study may be the heterogeneity of patients selected in terms of their underlying disease that led to the development of MODS (surgical pathologies were different in terms of localization, etiology, pathogenesis, and the course of the disease). This may have resulted in the low results for sensitivity and specificity in the ROC analysis. Also, further studies need to select a strategy for handling missing data to reduce systematic errors, and it is necessary to evaluate the combination of the markers under study with the already known MODS scales to improve their prognostic value.

Conclusion

In surgical patients with MODS, the increased I-FABP and decreased serum LBP may indicate the increased intestinal wall permeability and increased bacterial translocation, which may exacerbate the course of multiple organ dysfunction and increase the risk of mortality. The potential markers of intestinal wall damage and bacterial translocation under investigation could be used to identify MODS patients at higher risk of adverse outcomes after more studies are conducted, with the goal of reducing the ICU stay time and mortality rates.

Disclosure. The authors declare no competing interests.

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Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

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Ethics approval. This study was conducted in accordance with the Ethical Guidelines for Medical Research with Human Subjects as established by the Ministry of Health of the Republic of Kazakhstan and was conducted in accordance with the guidelines of the Helsinki Declaration and its amendments (1975, revised in 2013). This study was approved by the Local Commission on Bioethics of Karaganda Medical University (Protocol No. 2 with the assigned number No. 12. from 20.09.2022). Informed consent was obtained from all the participants (or patients' representatives).

Этическое утверждение. Данное исследование проводилось в соответствии с этическими принципами проведения медицинских исследований с участием людей, утвержденными Министерством здравоохранения Республики Казахстан и проводилось в соответствии с положениями Хельсинкской декларации и поправками к ней (1975 г., пересмотрено в 2013 г.). Исследование одобрено локальной комиссией по биоэтике НАО «Карагандинский медицинский университет», протокол № 2 с присвоенным № 12 от 20.09.2022. Информированное согласие было получено от всех участников исследования или их законных представителей.

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Data Availability Statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Декларация о наличии данных. Данные, подтверждающие выводы этого исследования, можно получить у корреспондирующего автора по обоснованному запросу.

Author's ORCID:

Turgunov Ye.M. — 0000-0002-6486-3847
Ogizbayeva A.V. — 0000-0003-1006-1870
Assamidanova S.G. — 0000-0002-9819-3079
Avdiyenko O.V. — 0000-0001-9122-1279
Matyushko D.N. — 0000-0002-7884-0507
Izdenov A.K. — 0000-0002-7162-4529
Kaliyeva D.K. — 0000-0001-9265-7103
Shakeyev K.T. — 0000-0002-7802-1464

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