NCJSC KMU 7-2-03/1

NON-COMMERCIAL JOINT-STOCK COMPANY
"Karaganda Medical University"

ABSTRACT

of the dissertation submitted for the degree of Doctor of Philosophy (PhD)

Biomarkers of Intestinal Barrier Damage in Predicting the Course of Multiple Organ Dysfunction

8D10100 – Medicine

Scientific Supervisors
Doctor of Medical Sciences,
Professor E.M. Turgunov
PhD A.V. Ogizbayeva

Foreign Scientific Supervisor
Doctor of Medical Sciences,
Professor A. Zlotnik
(Israel)

Karaganda, 2025 год

Relevance of the Study

Multiple Organ Dysfunction (MOD) is a complex pathological condition characterized by the simultaneous impairment of two or more organ systems, triggered by an unstable immune response or other generalized inflammatory diseases. This significantly worsens disease prognosis and increases the risk of mortality [1]. According to the definition by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM), Multiple Organ Dysfunction Syndrome (MODS) is a clinical condition in which the dysfunction of multiple organs makes it impossible to maintain homeostasis without external intervention [2]. This definition was formulated to account for the varying degrees of organ dysfunction, which can differ from case to case, and to reflect their pathogenetic link to the progressive development and emergence of a complex of clinical signs that constitute this syndrome.

The epidemiology of severe sepsis, which is the main cause of MOD development, varies significantly across countries. The incidence ranges from 13 to 300 cases per 100,000 people per year depending on the region for severe sepsis, and is 11 per 100,000 for septic shock. The mortality rate may reach up to 50% for severe sepsis and up to 80% for septic shock [3]. In Europe, the annual incidence of severe sepsis ranges from 66 to 114 cases per 100,000 people. In the United States, in 2005, the prevalence of severe sepsis among children was 0.89 per 1,000 individuals, with the highest incidence recorded among newborns—9.7 per 1,000 [4]. Multiple organ dysfunction is observed in up to 40% of adult patients admitted to intensive care units and up to 56% of pediatric patients [3; 5]. Mortality among such patients can reach up to 50% in both children and adults. MOD is one of the leading causes of death in intensive care units worldwide, with an annual mortality rate of 51% [6]. The fatal prognosis of MOD patients varies from 44% to 76% globally, depending on a number of factors [7]. When 2 to 4 organs are affected, the mortality rate ranges from 10% to 40%; when 5 organs are involved, it rises to 50%; and if 7 organs are affected, the mortality rate reaches 100% [8]. According to its mechanism of origin, multiple organ dysfunction (MOD) is classified into two types: primary and secondary.

Primary MOD occurs as a result of direct injury to an organ, and the cause of the damage is usually easily identifiable.

Secondary MOD develops as a consequence of the systemic inflammatory response syndrome (SIRS). In this case, the innate immune system responds inappropriately to inflammation, disrupting the balance between pro-inflammatory and anti-inflammatory responses [2,9]. MOD primarily arises from dysregulated and disproportionate activation of neutrophils and macrophages [10]. These cells enter a self-sustaining cycle that leads to uncontrolled damage to the vascular endothelium and other organs responsible for tissue perfusion [11]. Following the hyperactivation of neutrophils and macrophages, changes develop at the level of microcirculation, mitochondria, endothelium, epithelium, coagulation system, and neuroendocrine regulation. These processes are likely associated with molecular, cellular, and mediator-level dysfunctions [12]. At present, bacterial translocation of intestinal microbiota is considered a key mechanism in the amplification of the systemic inflammatory response leading to multiple organ dysfunction (MOD) [13].

Bacterial translocation refers to the penetration of intestinal bacteria through the intestinal mucosal barrier into normally sterile internal organs and tissues [14]. Under conditions of intermittent hypoxia, intestinal wall tissue respiration becomes insufficient, leading to excessive formation of reactive oxygen species (ROS) and products of lipid peroxidation. These processes damage the intestinal wall structure at the molecular level, resulting in bacterial translocation.

The main diagnostic methods for MOD include:

1. SOFA score (Sequential Organ Failure Assessment) – based on the assessment of six organ systems: respiratory, cardiovascular, hepatic, renal, neurological, and coagulation systems [15,16];
2. mNUTRIC score (modified Nutrition Risk in the Critically Ill) – evaluates the risk of malnutrition in critically ill patients [6,17];
3. APACHE II score (Acute Physiology and Chronic Health Evaluation II) – designed to assess the severity of a patient's condition and predict the outcome. It includes 12 physiological parameters such as temperature, blood pressure, oxygen level, and the presence of chronic diseases [18,19];

Detection of bacterial translocation – the process by which bacteria from the intestine enter the bloodstream and other organs, potentially contributing to the development of MOD [20]. Various biomarkers are used to detect bacterial translocation:

1. I-FABP (Intestinal Fatty Acid Binding Protein) – a protein that indicates damage to the intestinal epithelium and increased permeability. Several studies have shown that elevated I-FABP levels in blood serum or urine are associated with impaired intestinal barrier function and may serve as an early diagnostic marker for inflammatory bowel diseases [21,22];
2. CD14 – a receptor that “recognizes” the presence of infectious bacteria, activates the innate immune system, and initiates the associated inflammatory response [23]
3. Zonulin – a protein that regulates intestinal wall permeability. High levels of zonulin may indicate damage to the intestinal barrier, which is one of the mechanisms of bacterial translocation [24];
4. LBP (Lipopolysaccharide Binding Protein) – a protein that binds to lipopolysaccharides, components of bacterial cell walls. Elevated levels of LBP may reflect a systemic response to bacterial infection and translocation [25,26];
5. Reg (Regenerating gene protein) – a protein actively involved in the repair of intestinal epithelial cells after injury [19].

Based on the analysis of articles and reviews in publication databases such as PubMed, Scopus, and Web of Science, it can be stated that the prognostic value of intestinal barrier damage biomarkers (I-FABP, Zonulin, LBP, CD14, Reg) in predicting mortality in patients with MOD has not been previously investigated.

Scientific Hypotheses

Hypothesis 1:

During the progression of multiple organ dysfunction syndrome (MODS), the levels of intestinal barrier damage biomarkers increase, indicating gastrointestinal dysfunction.

Hypothesis 2:

Critical levels of intestinal barrier damage biomarkers serve as prognostic factors for the course of MODS and can be integrated into modified SOFA and APACHE scales to improve the accuracy of predicting MOD severity and patient outcomes in intensive care units.

Research Aim

To investigate the significance of intestinal barrier damage biomarkers in assessing the risk of mortality in patients with multiple organ dysfunction syndrome.

Research Objectives

1. To assess the dynamics of intestinal barrier damage biomarker levels in patients with multiple organ dysfunction syndrome of various origins.
2. To study the correlation between the levels of different intestinal barrier damage biomarkers and the severity of MODS of various etiologies.
3. To determine, using ROC analysis, the critical threshold values of intestinal barrier damage biomarkers in patients with MODS of different origins.
4. To evaluate the prognostic significance of the studied biomarkers in determining the risk of adverse outcomes in patients with MODS based on odds ratio (OR) analysis of critical biomarker levels.
5. To develop a mathematical model and algorithm for predicting the risk of mortality in patients with MODS.
6. To modify the APACHE II scoring system by incorporating the most significant intestinal barrier damage biomarkers, and to develop a web-based calculator for estimating the risk of mortality in patients with MODS.

Scientific Novelty

1. For the first time, the relationship between intestinal barrier dysfunction biomarkers and the severity of multiple organ dysfunction syndrome (MODS) has been investigated.
2. It has been demonstrated for the first time that the combination of I-FABP levels with the APACHE II score enhances the prognostic accuracy in assessing the risk of mortality in patients with MODS.
3. A new mathematical model has been developed, which determines the risk of mortality in MODS patients with an accuracy of 84.3%.

Practical Significance of the Results

The developed prognostic model, based on the combination of I-FABP levels and the APACHE II score, has been implemented in the clinical practice of four hospitals in the city of Karaganda (Appendix A). The use of this model significantly improved the accuracy of early identification of patients at high risk of mortality due to MODS (overall classification accuracy – 84.3%; 90.8% for survivors and 71.3% for non-survivors). It also accelerated clinical decision-making through the introduction of the LOP-MODS online calculator.

The model has proven effective in intensive care settings by providing a personalized approach to assessing the severity of MODS in patients. Based on this model, an online LOP-MODS calculator was developed and is accessible via QR code, allowing rapid calculation of mortality risk in MODS patients while eliminating subjective calculation errors.

Statements Submitted for Defense:

1. Patients with multiple organ dysfunction syndrome (MODS) are characterized by a significant increase in the levels of biomarkers I-FABP, Zonulin, REG3α, LBP, and sCD14-ST compared to the control group, indicating a key role of intestinal permeability disruption and microbial translocation in the pathogenesis of MODS.
2. Among all studied biomarkers, the level of I-FABP demonstrated the highest prognostic significance: its median level in the MODS group was 303.10 pg/ml compared to 98.80 pg/ml in the control group ($p < 0.001$), with sensitivity of 54.9% and specificity of 64.8%. These indicators allow considering I-FABP as a reliable early marker of intestinal injury and a predictor of adverse outcomes in patients with MODS.
3. The developed mathematical model for predicting mortality, based on a combination of I-FABP and APACHE II within a single logistic regression model, provides the best prognostic accuracy (overall accuracy — 84.3%; 90.8% for survivors and 71.3% for non-survivors) and acceptable explanatory power (Nagelkerke $R^2 = 0.587$) compared to the use of APACHE II alone (overall accuracy — 81.6%; 90.82% for survivors and 64.4% for non-survivors), allowing more effective patient risk stratification.
4. The online LOP MODS calculator and mortality risk assessment algorithm, developed based on the mathematical model, are effective and convenient tools for evaluating the risk of mortality in patients with MODS.

Implementation in Practice:

The mortality prediction model for patients with multiple organ dysfunction syndrome (MODS), developed during this research and serving as the basis for the online LOP MODS calculator, has been validated and implemented in clinical practice at four multidisciplinary hospitals in the city of Karaganda.

Author's Personal Contribution to the Research:

The author personally conducted the entire complex of critical analytical work related to the completion of the dissertation research. The author independently carried out the selection and enrollment of patients, as well as the collection of venous blood samples to determine biomarkers of intestinal injury and bacterial translocation on days 1, 3, and 7 of the patient's stay in the intensive care unit.

The author completed the full cycle of statistical data processing, including distribution checks, group comparisons, ROC curve construction, logistic regression, interaction analysis, and the development of prognostic models with subsequent validation. All calculations were performed personally using the software IBM SPSS 23, Python 3, EpiInfo 7, MedCalc 20.027, STATISTICA 8.0, and Microsoft Excel 2016.

As a result of the work, in collaboration with a programmer, the author developed and registered the online LOP MODS calculator for calculating the risk of mortality based on the I-FABP + APACHE II model. This development was officially registered in the State Register of Rights to Copyrighted Works under certificate No. 56240 dated April 1, 2025.

Dissertation Defense and Presentation:

The main findings of the study were presented and discussed at the International Biomedical Forum held on April 17–18, 2025, in Karaganda, Kazakhstan; the 6th Central Asian International Scientific and Practical Conference on Medical Education held on June 2–3, 2025, also in Karaganda, Kazakhstan; the International Surgical Week (ISW) 2024 conference, which took place from August 25 to 29, 2024, in Kuala Lumpur, Malaysia; the 44th International Symposium on Intensive Care & Emergency Medicine (ISICEM 2025), held on March 18–21, 2025, in Brussels, Belgium; the Euroanaesthesia 2025 Congress, held on May 25–27, 2025, in Lisbon, Portugal; as well as at the extended meeting of the Life Sciences Institute at NAO "KMU" on June 31, 2025.

Publications:

A total of 12 scientific works have been published on the topic of the dissertation, including 1 article in a scientific journal recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the Republic of Kazakhstan; 3 publications in international scientific journals indexed in the Scopus database with a percentile above 35; 1 monograph; 5 abstracts in the proceedings of international and national conferences; and 2 certificates of registration in the State Register of Rights to Objects Protected by Copyright.

Volume and Structure of the Dissertation

The dissertation contains 114 pages of typed text and consists of an introduction, literature review, main part (materials and methods, research results), conclusion, 5 appendices, 13 tables, 39 figures, and a list of references comprising 140 sources.

This study is part of a research project funded by the Ministry of Science and Higher Education of the Republic of Kazakhstan, grant number AP19677271, titled

"Study of the Relationship between Intra-abdominal Pressure, Biomarkers of Bacterial Translocation, and Biomarkers of Intestinal Wall Damage in Multiple Organ Dysfunction Syndrome."

Study Design, Materials, and Methods

The study was conducted at four hospitals in the city of Karaganda: the Regional Clinical Hospital (KGP PHV "Oblastnaya Klinicheskaya Bolnitsa"), Multidisciplinary Hospital No. 1 (KGP PHV "Multiprofile Hospital No. 1"), Multidisciplinary Hospital No. 3 (KGP PHV "Multiprofile Hospital No. 3"), and the Clinic of the Karaganda Medical University (NAO "KMU"). From 2022 to 2023, a total of 327 patients were enrolled in the study.

The main group included 227 patients admitted to the Intensive Care Unit (ICU) with a verified diagnosis of multiple organ dysfunction syndrome (MODS) of various etiologies.

The control group consisted of 100 patients admitted to medical facilities without signs of MODS.

The main group was further divided into two subgroups depending on the disease outcome: patients with fatal outcomes and patients who survived**.** The study design was an observational prospective cohort study.

Inclusion criteria: Patients over 18 years old with signs of MODS against the background of acute surgical or therapeutic pathology. For the control group, patients with identical pathologies but without MODS were selected.

Exclusion criteria: Patients under 18 years old, pregnant women, and patients with HIV infection.

Withdrawal criteria: A subject may be withdrawn at the investigator's discretion if continuation of the study is deemed harmful to the volunteer's health; the volunteer's decision to discontinue participation; non-compliance with medical and protective regimes; or appearance of exclusion criteria during the study.

Before sample collection, all patients were informed about the aims of the study and signed an informed consent form.

All patients underwent clinical, instrumental, and laboratory examinations according to the clinical protocols for hospitalized patients established by the Ministry of Health of the Republic of Kazakhstan (MoH RK). Diagnostic investigations were conducted within the limits appropriate for surgical, gynecological, urological, therapeutic, and other pathologies according to MON RK protocols. To assess organ function in MODS, the SOFA and APACHE II scoring systems were used.

To study the concentrations of LBP, sCD14-ST, I-FABP, Zonulin, and REG3α in blood serum by enzyme-linked immunosorbent assay (ELISA), venous blood samples were collected by the hospital nursing staff on the 1st day of MOD diagnosis, as well as on the 3rd and 7th days of its progression. In the control group, blood samples were taken on the first day of hospital admission. The laboratory analyses were performed at the Research Laboratory of the Life Sciences Institute (RLI) of NAO "Karaganda Medical University" (KMU).

Statistical processing of the results was performed using STATISTICA v8.0 (StatSoft). For each quantitative variable, median (Me), and interquartile range (Q1–

Q3) were calculated; for qualitative variables, proportions and frequencies were assessed. Differences in biomarker levels over time were analyzed using the Wilcoxon signed-rank test. The Mann–Whitney U test was used to compare quantitative data between groups, while Pearson's chi-square test and Fisher's exact test were used for qualitative variables. Spearman's correlation coefficient was calculated to assess correlation between variables.

To determine optimal cutoff values of translocation markers, ROC (receiver operating characteristic) curves were constructed, and Youden's J-index was calculated using MedCalc software (MedCalc Software Ltd). For developing the mathematical model to predict mortality, a binary logistic regression equation was calculated in SPSS with validation. Decision trees and heat maps were generated using Python. A significance level of $\alpha = 0.05$ and power of $1-\beta = 80\%$ were used. Results with a p-value < 0.05 were considered statistically significant.

Results

Based on the detection of biomarkers of bacterial translocation and intestinal barrier disruption in patients from the main and control groups, the following was found: The mean presepsin level on the day of admission in the main group was 192, which is 78.1% higher than the presepsin level in the control group ($p < 0.001$, $r = 0.912$). The level of I-FABP in the main group was 38.9% higher ($p = 0.000003$), Reg3α was 36.8% higher ($p = 0.00001$), and Zonulin was 62.2% higher ($p = 0.00001$), confirming a significant difference between the groups. In patients diagnosed with MOD, the average LBP level on the first day was 2232 ng/ml, which increased by 28.41% over time ($p = 0.081$).

Over time (comparison of biomarkers on days 1, 3, and 7), no significant changes were found in any of the biomarkers in the main group ($p = 0.081$ for LBP, $p = 0.525$ for sCD14-ST, $p = 0.862$ for I-FABP, $p = 0.538$ for Reg3α, $p = 0.111$ for Zonulin). Additionally, SOFA scores were significantly higher in deceased patients by 75% on days 1 and 3 (7.0 vs. 4.0 points, $p = 0.00001$) and by 133% on day 7 (7.0 vs. 3.0 points, $p = 0.00001$).

SOFA scores were significantly higher in deceased patients by 75% on days 1 and 3 (7.0 vs. 4.0 points, $p = 0.00001$) and by 133% on day 7 (7.0 vs. 3.0 points, $p = 0.00001$). According to the APACHE II scale, the difference was 66.7% on day 1 (20.0 vs. 12.0, $p = 0.00001$), 110.5% on day 3 (20.0 vs. 9.5, $p = 0.00001$), and 106.3% on day 7 (16.5 vs. 8.0, $p = 0.00002$), confirming a more severe condition and poorer prognosis in this group of patients. A paired comparison of each biomarker with the severity of the patients' condition, based on the SOFA and APACHE II scales, was conducted. Analysis of biomarker levels depending on the severity assessed by the APACHE II scale revealed statistically significant differences for all studied indicators (Kruskal–Wallis, $p < 0.005$).

LBP1 levels showed a significant increase with the progression of MODS severity ($p = 0.000$): median values consistently rose, reaching a maximum in the group with severe multiple organ failure. These findings confirm the importance of LBP on day 1 as an indicator of the intensity of systemic inflammatory response and microbial translocation.

A similar trend was demonstrated by the marker sCD14-ST on day 1, whose median levels increased in parallel with rising APACHE II scores ($p = 0.000$). The lowest values were observed in patients with mild organ dysfunction, whereas the highest concentrations occurred in the severe group, reflecting immune system activation in response to circulating bacterial components.

I-FABP levels on day 1, reflecting enterocyte damage, also significantly increased depending on the severity of the condition ($p = 0.003$). In the severe group, median values exceeded those in the mild group by 2–3 times, indicating progressive disruption of intestinal epithelial integrity and supporting the role of I-FABP as a potential early prognostic marker of intestinal dysfunction.

Similarly, REG3α showed a significant increase with increasing MODS severity ($p = 0.001$): median values in patients with severe multiple organ failure were more than 2.5 times higher than in the mild group, which may reflect compensatory activation of regeneration and intestinal barrier restoration mechanisms.

Particular attention should be paid to the dynamics of zonulin levels: a trend was noted with concentrations increasing from mild to moderate MODS severity, peaking in the moderate dysfunction group, followed by a decrease in the severe group ($p = 0.005$). This nonlinear pattern may indicate a phased epithelial response to injury: an initial hypersecretion of zonulin is followed by depletion amid destructive processes during severe damage.

An assessment of biomarkers of bacterial translocation and intestinal barrier integrity was conducted within the main group, comparing patients with fatal outcomes (n=102) and those who survived (n=125). In deceased patients with MODS, the level of sCD14-ST on day 1 was 23.05% higher ($p = 0.043$), I-FABP level was 40.13% higher on day 1 ($p = 0.004$) and 47.79% higher on day 3 ($p = 0.018$) compared to survivors. The level of Reg3α was 40.15% higher on day 1 ($p = 0.010$) and 51.24% higher on day 3 ($p = 0.049$) in deceased patients compared to survivors. Conversely, LBP levels in patients with fatal outcomes were 23.7% lower than those in the survivor group ($p = 0.006$). No statistically significant differences were found in zonulin levels.

The most statistically significant differences were observed in the SOFA and APACHE II scores. Patients with fatal outcomes had APACHE II scores twice as high as those without fatal outcomes, and SOFA scores in survivors were on average 4 points lower than in deceased patients ($p = 0.000002$ and $p = 0.00001$, respectively).

ROC analysis was performed to identify the most sensitive biomarkers for prognostic evaluation of fatal outcomes, and statistically significant cutoff values were determined for each biomarker. The ROC analysis showed significance only for three biomarkers — I-FABP (sensitivity 54.9%, specificity 64.8%), sCD14-ST (sensitivity 37.2%, specificity 72.9%), and Reg3α (sensitivity 60.8%, specificity 58.4%). Further prognosis of fatal outcome development in the main MODS group was conducted based on critical threshold values of these three biomarkers.

Due to the lack of a strong correlation between the three aforementioned biomarkers, the calculation of the odds ratio for the risk of fatal outcome in patients with MODS was performed separately for each biomarker, as well as in combinations of biomarkers and in combination with the SOFA and APACHE II scores. It was found that the combined elevation of I-FABP > 120.7 pg/ml, Reg3α > 20.4 ng/ml, sCD14-ST > 378 pg/ml, along with an APACHE II score > 15 on day 1 of MODS development, increased the risk of fatal outcome by 24.8 times compared to lower biomarker levels and APACHE II scores. When the elevation of all three biomarkers above critical thresholds was combined with a SOFA score > 5, the risk of fatal outcome increased by 16.53 times.

To select the most accurate risk model for fatal outcome development in patients with multiple organ dysfunction, using the SOFA and APACHE II scores and intestinal injury biomarkers, binary logistic regression was applied. The most effective predictive model was found to be APACHE II combined with I-FABP (with 75.8% of cases correctly classified, AUC = 0.81, $p < 0.0001$).

For assessing the prognostic value of the intestinal permeability marker I-FABP and the APACHE II score, a logistic regression model was created based on data from 327 patients. The probability of fatal outcome (p) was calculated using the classical logistic regression equation:

p=1/(1+e-z)

where e is the base of natural logarithms (2.71);

z = b1 • X1 + b2 • X2 + a,

Here, XXX represents the predictor values (in this case, the APACHE II score and serum I-FABP concentration), b are the regression coefficients, and a is the intercept calculated during analysis.

The resulting equation for risk estimation was:

z = -5,102 + 0,002 • (level of I-FABP in blood) + 0,273 • (APACHE II score).

If the calculated probability $p < 0.5$, the risk of fatal outcome is considered low, and the patient is likely to survive; if $p \geq 0.5$, a high risk of fatal outcome is predicted.

Random stratification using a ranked variable allowed for splitting the dataset into an 80/20 ratio, resulting in 261 patients in the training subgroup and 66 in the validation subgroup. Compared to the model based solely on the APACHE II score (overall classification accuracy of 81.6%, sensitivity of 90.82% among survivors, and 64.4% among non-survivors), the combined logistic model incorporating I-FABP, trained on the primary cohort, demonstrated improved performance: overall accuracy reached 84.3%, sensitivity among survivors remained at 90.8%, while sensitivity among non-survivors increased to 71.3%. The Nagelkerke R^2 coefficient was

0.587, indicating an acceptable level of explanatory power of the model. The most significant predictor was the APACHE II score (Exp(B) = 1.314, $p < 0.001$), while I-FABP was also statistically significant, though with a less pronounced effect (Exp(B) = 1.002, $p = 0.024$).

Despite promising performance during training, the model's accuracy deteriorated upon validation: sensitivity dropped to 53.3%, precision in predicting lethal outcomes was 40%, F1-score was 0.457, and the area under the ROC curve (AUC) was 0.733, indicating moderate diagnostic accuracy. Thus, although the model remains statistically significant and shows balanced sensitivity and specificity in the training set, its generalizability in the validation cohort is limited [27].

To further explore the nature of the interaction between I-FABP and APACHE II, decision tree analysis and heatmap visualization were employed. A decision tree with a minimum node size of 20 observations identified a critically vulnerable subgroup: among patients with APACHE II scores >15 and I-FABP levels >120.7 pg/mL, the risk of fatal outcome reached 71%. The heatmap analysis, visualizing mortality risk as a function of I-FABP concentration and APACHE II score, confirmed a distinct synergistic interaction between these predictors: the highest mortality risk was observed in the zone where I-FABP exceeded 120–130 pg/mL and APACHE II scores were above 15.

This finding is supported by logistic regression results, which indicated a statistically significant interaction term ($p = 0.037$); however, its clinical relevance remained minimal (Exp(B) = 1.000). The application of visualization techniques, including decision trees and heatmaps, enabled the identification of a clinically relevant high-risk zone that was not fully captured by the logistic model alone.

Based on the logistic regression equation, an online calculator, **LOP MODS** (Lethal Outcome Prediction of Multiple Organ Dysfunction Syndrome), was developed. This calculator integrates individual I-FABP concentrations and APACHE II scores to estimate the probability of mortality. The calculator is accessible via QR code or active hyperlink from any internet-enabled device. The LOP MODS tool has already been implemented in four medical institutions in Karaganda.

Based on heatmap and decision tree analyses, a risk assessment algorithm was also created, using the established thresholds: I-FABP >120.7 pg/mL and APACHE II >15 points. Using odds ratio calculations, three patient risk groups were identified:

- **High-risk group**: APACHE II >15 + I-FABP >120.7 pg/mL and APACHE II >15 + I-FABP <120.7 pg/mL.
- **Moderate-risk group**: APACHE II <15 + I-FABP >120.7 pg/mL.
- **Low-risk group**: APACHE II <15 + I-FABP <120.7 pg/mL

Conclusions:

1. **In patients with multiple organ dysfunction syndrome (MODS), a statistically significant increase in the concentrations of biomarkers associated with intestinal barrier damage and bacterial translocation was identified.** Median I-FABP levels in the MODS group were three times higher than in the control group ($p < 0.001$); sCD14-ST, LBP, and Zonulin were elevated 1.7-fold ($p < 0.001$, $p < 0.001$, and $p = 0.011$, respectively), while REG3α levels were 2.6 times higher ($p < 0.001$). However, no significant dynamics were observed for any of the biomarkers across Days 1, 3, and 7 (p-level = 0.081 for LBP; 0.525 for sCD14-ST; 0.862 for I-FABP; 0.538 for Reg3α; and 0.111 for Zonulin).
2. **Correlation analysis across the total patient sample (including both MODS and non-MODS patients) revealed significant positive associations between biomarkers and severity scores.** The strongest correlations were observed between APACHE II and SOFA, Reg3α, sCD14-ST, and LBP (r = 0.771, 0.360, 0.474, 0.400, respectively). SOFA score also showed strong correlations with LBP, Reg3α, Zonulin, and sCD14-ST (r = 0.462, 0.345, 0.343, 0.618, respectively). Weaker correlations were found between APACHE II and Zonulin, I-FABP (r = 0.294 and 0.233), and between SOFA and I-FABP (r = 0.247). Additional weaker correlations included Zonulin with Reg3α and I-FABP (r = 0.112 and 0.144), and Reg3α with I-FABP, sCD14-ST, and LBP (r = 0.120, 0.269, 0.176).
   In the MODS subgroup alone, the strongest associations were observed between I-FABP and Zonulin (r = 0.770), sCD14-ST and SOFA (r = 0.870), and Reg3α and sCD14-ST (r = 0.570). Other correlations were weak, including inverse relationships between SOFA and Zonulin (r = -0.008), SOFA and LBP (r = -0.180), and Reg3α and LBP (r = -0.104).
3. **ROC analysis confirmed the high discriminative capacity of the studied biomarkers.** Among all biomarkers, I-FABP showed the highest area under the curve (AUC = 0.612), with sensitivity of 54.9% and specificity of 84.9% at the cutoff >120.7 pg/mL ($p = 0.003$), confirming its leading role in predicting adverse outcomes in MODS patients. Logistic regression performed on the training dataset incorporating I-FABP showed improved classification accuracy (overall — 84.3%, survivors — 90.8%, non-survivors — 71.3%) and acceptable explanatory power (Nagelkerke $R^2 = 0.587$).
4. **Odds ratio (OR) analysis demonstrated a substantial increase in the risk of fatal outcomes with rising values in the integrated risk scale (Risk4grp).** Specifically, when APACHE II exceeded 15 points and I-FABP >120.7 pg/mL, the risk of mortality increased 15.7-fold. Even when APACHE II remained ≤15 but I-FABP reached or exceeded the threshold, the risk still rose 6.6-fold ($p < 0.001$), justifying classification of this group as moderate-risk. Patients with both values below threshold were classified as low-risk for mortality.

5. **The logistic regression-based mathematical model combining I-FABP levels and APACHE II scores demonstrated superior predictive capability** (overall accuracy — 84.3%, survivors — 90.8%, non-survivors — 71.3%; Nagelkerke R^2 = 0.587) compared to the model using APACHE II alone (81.6%, 90.82%, 64.4%; respective R^2 lower).
6. **The developed LOP MODS algorithm and online calculator significantly enhance prognostic accuracy in predicting mortality risk in MODS,** achieving an overall predictive accuracy of 84.3%.

Список литературы:

1. Gourd N.M., Nikitas N. Multiple organ dysfunction syndrome // Journal of Intensive Care Medicine. – 2020. – Vol. 35, № 12. – P. 1564–1575.
2. Dmytriiev D. Multiple organ dysfunction syndrome: what do we know about pain management? A narrative review // Anaesthesia, Pain & Intensive Care. — 2019. — Т. 23, № 1. — С. 84–91.
3. Oz E., Salturk C., Karakurt Z., Yazicioglu Mocin O., Adiguzel N., Gungor G. и др. Risk factors for multiorgan failure and mortality in severe sepsis patients who need intensive care unit follow-up // Tuberk Toraks. — 2015. — Т. 63, № 3. — С. 147–157. — [PubMed].
4. Bingold T.M., Lefering R., Zacharowski K., Meybohm P., Waydhas C., Rosenberger P. и др. Individual organ failure and concomitant risk of mortality differs according to the type of admission to ICU – a retrospective study of SOFA score of 23,795 patients // PLOS ONE. — 2015. — Т. 10, № 8. — e0134329.

5. Arunachala S., Kumar J. mNUTRIC score in ICU mortality prediction: an emerging frontier or yet another transient trend? // Indian Journal of Critical Care Medicine. — 2024. — T. 28, № 5. — C. 422–423.
6. Arunachala S., Kumar J. mNUTRIC score in ICU mortality prediction: an emerging frontier or yet another transient trend? // Indian Journal of Critical Care Medicine. — 2024. — T. 28, № 5. — C. 422–423.
7. Zheng G., Lyu J., Huang J., Xiang D., Xie M., Zeng Q. Experimental treatments for mitochondrial dysfunction in sepsis: a narrative review // Journal of Research in Medical Sciences. — 2015. — T. 20, № 2. — C. 185–195
8. Li N., Song Z., Wang J. и др. Prognostic value of natriuretic peptides in severe trauma patients with multiple organ dysfunction syndrome // Experimental and Therapeutic Medicine. — 2015. — T. 10, № 2. — C. 792–796.
9. Page R.L., O'Bryant C.L., Cheng D., Dow T.J., Ky B., Strin C.M. и др. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association // Circulation. — 2016. — T. 134, № 6. — C. e32–e69.
10. Gharib S.A., Mar D., Bomsztyk K. и др. System-wide mapping of activated circuitry in experimental systemic inflammatory response syndrome // Shock. — 2016. — T. 45, № 2. — C. 148–156.
11. Thiessen S.E., Van den Berghe G., Vanhorebeek I. Mitochondrial and endoplasmic reticulum dysfunction and related defense mechanisms in critical illness-induced multiple organ failure // Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. — 2017. — T. 1863, № 10. — C. 2534–2545.
12. Wang Y.L., Shen H.H., Cheng P.Y. и др. 17-DMAG, an HSP90 inhibitor, ameliorates multiple organ dysfunction syndrome via induction of HSP70 in endotoxemic rats // PLoS ONE. — 2016. — T. 11, № 5. — e0155583.
13. Klingensmith N.J., Coopersmith C.M. The gut as the motor of multiple organ dysfunction in critical illness // Critical Care Clinics. — 2016. — T. 32, № 2. — C. 203–212.
14. Churpek M.M., Zadravecz F.J., Winslow C., Howell M.D., Edelson D.P. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients // American Journal of Respiratory and Critical Care Medicine. — 2015. — T. 192, № 8. — C. 958–964.
15. Moreno R., Rhodes A., Piquilloud L. и др. The Sequential Organ Failure Assessment (SOFA) Score: has the time come for an update? // Critical Care. — 2023. — T. 27, № 1. — C. 15.
16. Aperstein Y., Cohen L., Bendavid I. и др. Improved ICU mortality prediction based on SOFA scores and gastrointestinal parameters // PLoS ONE. — 2019. — T. 14, № 9. — e0222599.
17. Kaur H., Chandran V.P., Rashid M. и др. The significance of APACHE II as a predictor of mortality in paraquat poisoning: a systematic review and meta-

analysis // Journal of Forensic and Legal Medicine. — 2023. — T. 97. — C. 102548.
18. Mutchmore A., Lamontagne F., Chassé M. и др. Automated APACHE II and SOFA score calculation using real-world electronic medical record data in a single center // Journal of Clinical Monitoring and Computing. — 2023. — T. 37, № 4. — C. 1023–1033.
19. Zhang R.X., Zhang W.W., Luo Y.T., Liu G.W. An mNUTRIC-based nomogram for predicting the in-hospital death risk in patients with acute stroke // European Journal of Clinical Nutrition. — 2022. — T. 76, № 10. — C. 1464–1469.
20. Potruch A., Schwartz A., Ilan Y. The role of bacterial translocation in sepsis: a new target for therapy // Therapeutic Advances in Gastroenterology. — 2022. — T. 15. — C. 17562848221094214.
21. Doukas P., Bassett C., Krabbe H. и др. IFABP levels predict visceral malperfusion in the first hours after open thoracoabdominal aortic repair // Frontiers in Cardiovascular Medicine. — 2023. — T. 10. — C. 1200967.
22. Huang X., Zhou Y., Sun Y., Wang Q. Intestinal fatty acid binding protein: a rising therapeutic target in lipid metabolism // Progress in Lipid Research. — 2022. — T. 87. — C. 101178.
23. Ciesielska A., Ben Amor I., Kwiatkowska K. Białko CD14 jako modulator odpowiedzi zapalnej [CD14 protein as a modulator of the inflammatory response] // Postepy Biochemii. — 2024. — T. 69, № 4. — C. 274–282. — Polish.
24. Marino M., Mignozzi S., Michels K.B. и др. Serum zonulin and colorectal cancer risk // Scientific Reports. — 2024. — T. 14, № 1. — C. 28171.
25. Meng L., Song Z., Liu A. и др. Effects of lipopolysaccharide-binding protein (LBP) single nucleotide polymorphism (SNP) in infections, inflammatory diseases, metabolic disorders and cancers // Frontiers in Immunology. — 2021. — T. 12. — C. 681810.
26. Turgunov Y., Ogizbayeva A., Akhmaltdinova L. и др. Lipopolysaccharide-binding protein as a risk factor for development of infectious and inflammatory postsurgical complications in colorectal cancer patients // Contemporary Oncology (Poznan). — 2021. — T. 25, № 3. — C. 198–203.
27. Огизбаева А. В., Тургунов Е. М., Асамиданова С. Г. Биомаркеры бактериальной транслокации и повреждения кишечной стенки в прогнозировании исходов при синдроме мультиорганной дисфункции. Монография / ТОО «Типография АРКО», 2025. — 87 с.