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Research Article

Biomarkers of Bacterial Translocation and Intestinal Wall Damage in Patients With Multiple Organ Dysfunction Syndrome

Yermek Turgunov[1], **Alina Ogizbayeva**[2], **Sofiko Asamidanova**[1], **Olga Avdiyenko**[3], **Dana Amanova**[1], **Nurlan Aukenov**[4] and **Miras Mugazov**[2]

[1]*Department of Surgical Diseases, NJSC Karaganda Medical University, Karaganda 100000, Kazakhstan*
[2]*Department of Emergency Medical Care, Anaesthesiology and Resuscitation, NJSC Karaganda Medical University, Karaganda 100000, Kazakhstan*
[3]*Research Laboratory of the Institute of Life Sciences, NJSC Karaganda Medical University, Karaganda 100000, Kazakhstan*
[4]*Department of Medical Science and Innovative Technologies, Department of Science and Human Resources, Ministry of Health of the Republic of Kazakhstan, Astana 010000, Kazakhstan*

Correspondence should be addressed to Alina Ogizbayeva; eleusizova.a@kgmu.kz

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Introduction: The aim of this study was to evaluate the potential biomarkers of bacterial translocation: lipopolysaccharide-binding protein (LBP) and soluble CD14 subtype (sCD14-ST), and intestinal wall damage: intestinal fatty acid binding protein (I-FABP), zonulin, and regenerating islet-derived protein-3α (REG3α), in the patients with multiple organ dysfunction syndrome (MODS).
Methods: The study involved 78 patients over the age of 18 with MODS set according to the Sequential Organ Failure Assessment (SOFA) scale. Venous blood was sampled during diagnostics of MODS, on the 3rd and on the 7th day of its development. The sCD14-ST, LBP, I-FABP, REG3α, and zonulin in blood serum were determined by enzyme-linked immunosorbent assay (ELISA).
Results: Out of 78 patients with MODS, 43 patients survived (55.1%) and 35 patients died (44.9%). Levels of sCD14-ST on Day 1, I-FABP on Day 3, and REG3α on Days 3 and 7 and SOFA scores on Days 1, 3, and 7, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores on Days 1, 3, and 7, and Modified Nutrition Risk in Critically Ill (mNUTRIC) scores on Days 1, 3, and 7 were statistically significantly higher in deceased patients ($p < 0.05$).
Conclusion: In patients with MODS, an increase in sCD14-ST, I-FABP, and REG3α in blood serum can indicate the violation of intestinal barrier function and increased bacterial translocation, which ultimately may aggravate the severity of MODS and increase the risk of death. It is required to further study the factors leading to intestinal wall permeability disorders in order to screen for timely intensive care measures that can help reduce the stay of patients in the intensive care unit (ICU) as well as mortality.

Trial Registration: ClinicalTrials.gov identifier: NCT06221293

1. Introduction

Multiple organ dysfunction syndrome (MODS) is a disorder of two or more organs/organ systems, which are not involved in the pathological process that resulted in hospitalization into the intensive care unit (ICU) [1]. The development of MODS can result in a longer stay of patients in the ICU and has a high mortality rate in critical situations (up to 100%) [2].

The factors initiating the cascade of events leading to MODS are a matter of debate. However, it has been suggested that gastrointestinal disorders may play a central role. In the ICU patients, the disorders of the gastrointestinal tract can be the result of many factors: systemic proinflammatory

reaction, increased circulating inflammatory mediators, impaired regulation of visceral blood flow and hypoperfusion of the intestinal mucosa, intestinal peristalsis disorders, insufficient enteral nutrition in the prevention of mucosal atrophy, and proliferation of pathogenic nosocomial bacteria [3, 4]. Due to microcirculation disorders, ischemia, and hypoxia of the intestinal wall, the permeability of the intestinal wall increases with its barrier function disrupted as a result of which bacteria and/or their endotoxins penetrate through damaged intestinal mucosal barrier (bacterial translocation) and further enhance the immune response, which becomes systemic and ultimately results in multiple organ dysfunction [5, 6].

Based on these changes in body systems of ICU patients, the phenomenon of bacterial translocation of intestinal microflora is currently considered to be the key mechanism of an enhanced systemic inflammatory reaction leading to MODS [5]. To date, it is vital to determine not only the translocation of the intestinal microflora itself but also to assess changes in the permeability of the intestinal wall since it is precisely the permeability that leads to the increased translocation.

The sCD14-ST (soluble CD14 subtype, presepsin) and LBP (lipopolysaccharide-binding protein) are currently being investigated as potential biomarkers of bacterial translocation.

The interaction of the membrane protein of the CD14 macrophages with peptidoglycans of Gram-positive and lipopolysaccharides of Gram-negative bacterial walls leads to the production of sCD14-ST (presepsin), which is considered a biomarker of the early phase of sepsis and a prognostic outcome factor in septic patients [7].

LBP increases the sensitivity of immune system cell receptors: macrophages, monocytes, and neutrophils to bacterial lipopolysaccharide, which leads to activation of the immune response by releasing proinflammatory mediators. LBP appears to be an effective biomarker of bacterial translocation and the development of septic complications [8].

The following markers such as: I-FABP (intestinal fatty acid binding protein), REG3α (regenerating islet-derived protein-3α), and zonulin, have been proposed as potential biomarkers of intestinal wall damage.

I-FABP is a protein located on the villi of mature enterocytes. An increase in the level of I-FABP in blood serum is correlated with the violation of the permeability of the intestinal wall, which has been proven in a number of studies [9].

The Paneth cells secrete the antimicrobial REG3α protein into the intestine, and in case of damage to the intestinal wall, the REG3α protein moves into the bloodstream. This protein is a reliable biomarker of intestinal wall damage and bacterial translocation [10].

Zonulin is a protein, which opens intracellular tight junctions between the cells of the duodenum and small intestine, which leads to an increase in the permeability of the intestinal wall. Serum zonulin is a biomarker of dysfunction and increased permeability of the intestinal barrier [11].

We assume that an increase in the studied biomarkers indicates damage to the intestinal wall and increased bacterial translocation, which can lead to the development of a systemic inflammatory response and sepsis and can affect the outcome of the disease. Therefore, the aim of this pilot study was to evaluate the biomarkers of bacterial translocation (LBP and sCD14-ST) and intestinal wall damage (I-FABP, zonulin, and REG3α) in the patients with MODS.

2. Materials and Methods

2.1. Study Design. The study was conducted at the medical premises of four hospitals in the city of Karaganda, Kazakhstan, from July to November 2023. It involved 78 patients over 18 years of age with MODS diagnosed according to the SOFA scale [12]. Mortality prediction scores APACHE II [13] and mNUTRIC scale as a nutritional screening tool were also assessed [14].

Informed consent was obtained from all hospitalized patients. Each patient was informed that if MODS developed, blood would be taken for this study. Screening was performed by physicians from the surgery, internal medicine, and intensive care departments. Patients who could not give informed consent due to the severity of their condition were excluded ($n = 23$). In the presence of relatives accompanying a patient in severe/critical condition, informed consent was obtained from them.

The patients were both surgical (after surgical interventions) and medical (without surgical interventions, with cardiovascular and pulmonary pathology). The exclusion criteria included the patients of under the age of 18, pregnant women, and those with HIV infection. The patients were later divided into groups with and without lethal outcome, depending on the outcome.

To detect potential biomarkers in serum, venous blood was sampled three times: when detecting signs of MODS, on the 3rd and on the 7th day of its development. The sCD14-ST, LBP, I-FABP, REG3α, and zonulin in blood serum were determined by the method of 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).

This pilot study was to determine the possibility of using these potential biomarkers as predictors of the lethal outcome in patients with MODS. The results obtained will be used in a larger sample of patients in future studies.

2.2. Ethical Considerations. All procedures performed in the study were conducted in accordance with the guidelines outlined in the Helsinki Declaration and its amendments. This study was approved by the Local Commission on Bioethics (Protocol No. 2 with the assigned No. 12). Informed consent was obtained from all participants (or patient representatives) included in the study.

2.3. Statistical Methods. The sample size was calculated in the program EpiInfo. The obtained results were processed by statistical methods using the STATISTICA 8.0 program

(StatSoft) with the calculation of the median (Me), lower and upper quartiles (Q1–Q3) for each indicator, and the proportion and frequency of occurrence of qualitative signs. The nonparametric Mann–Whitney criteria for quantitative variables and the χ^2-square criterion as well as the exact Fisher's criterion for qualitative variables were used. The Spearman's correlation coefficient was used to identify the relationships, and the quantitative equivalent of the closeness of the connection of the studied markers with the outcomes of the development of multiple organ dysfunction was determined by calculating the odds ratio (OR). The threshold values of biomarker levels for predicting a fatal outcome were calculated using a ROC analysis. At the same time, the significance of the results was considered at $p < 0.05$.

3. Results

3.1. The Studied Patients' Profiles. Out of 78 patients with MODS, 43 patients survived (55.1%) and 35 patients died (44.9%), of which 21 patients died in the first two days (60% of the total mortality). The median age in the group of the deceased patients was 68.0 years old (61.0–76.0), which was statistically significantly higher than in the group of the survived, which accounted for 60.0 years old (49.0–71.0) ($p = 0.031$, Table 1).

In the group of deceased patients, the SOFA, APACHE II, and mNUTRIC scores were statistically significantly higher, both at the diagnosis of MODS, and on the 3rd and 7th days after its development ($p = 0.00004 - p = 0.001$).

All medical patients received enteral nutrition from the 2nd day of hospitalization. Surgical patients, depending on the surgical intervention performed, received enteral nutrition on average on the 3rd–5th day after surgery.

3.2. Markers of Bacterial Translocation in MODS. No statistically significant differences in bacterial translocation biomarkers were detected over time (on Days 3 and 7). Despite the fact that the LBP level on Day 1 was higher in the deceased patients, its level decreased in dynamics. Meanwhile the LBP level tended to increase in the survivors by Day 7, even though there was no difference in the LBP levels on Day 1, Day 3, and Day 7 after MODS in terms of the lethal outcome ($p = 0.3823$, $p = 0.396$, $p = 0.337$, respectively).

As for the sCD14-ST level, it was higher on Day 1 after diagnosing MODS in the group of the deceased patients ($p = 0.007$) (Table 2 and Figure 1).

The level of sCD14-ST on Day 1 correlated with the levels of I-FABP on Day 1 ($r = 0.837$), the levels of zonulin on Day 3 ($r = 0.640$), SOFA scores on Day 1 ($r = 0.663$), and APACHE II scores on Day 1 ($r = 0.604$) (Figure 2).

3.3. Markers of Intestinal Wall Damage in MODS. No statistically significant differences in intestinal wall damage biomarkers were detected over time (on Days 3 and 7). As can be seen from Figure 2, scores on SOFA, APACHE II, and mNUTRIC scales correlated with mortality ($p < 0.05$).

In deceased patients, the I-FABP level on Day 3 was statistically significantly higher than in survived patients ($p = 0.0299$) (Table 3 and Figure 3). Furthermore, the level of I-FABP on Day 1 positively correlated with the level of sCD14-ST on Day 1 ($r = 0.84$), the level of zonulin on Day 1 and Day 3 ($r = 0.65$ and $r = 0.66$, respectively), SOFA scores on Day 1 ($r = 0.81$), and APACHE II scores on Day 1 ($r = 0.78$) (Figure 2). There were also higher I-FABP levels in patients with higher scores on the SOFA, APACHE II, and mNUTRIC scales (Tables 4, 5, and 6).

There was no difference in the level of zonulin in the blood serum on the 1st, 3rd, and 7th days of MODS in terms of the lethal outcome ($p = 0.155$, $p = 0.139$, $p = 0.069$, respectively). However, there was a positive correlation of zonulin on Day 1 with the level of I-FABP on Day 1 ($r = 0.65$), the SOFA scores on Day 1 and Day 3 ($r = 0.68$ and $r = 0.63$), fatal outcome ($r = 0.92$), APACHE II scores on Day 1 ($r = 0.72$), and mNUTRIC scores on Day 3 ($r = 0.70$) (Figure 2). There were also higher zonulin levels in patients with higher scores on the SOFA, APACHE II, and mNUTRIC scales (Tables 4, 5, and 6).

In deceased patients, REG3α levels on Days 3 and 7 were statistically significantly higher than in survived patients ($p = 0.022$ and $p = 0.011$, respectively) (Table 3 and Figure 4). Furthermore, the level of REG3α on Day 3 correlated with the SOFA scores on Day 3 and Day 7 ($r = 0.67$ and $r = 0.62$, respectively), with a fatal outcome ($r = 0.63$) (Figure 2). The REG3α levels were higher in patients with higher scores on the mNUTRIC scale (Table 6).

In addition, there were higher sCD14-ST levels on Day 1 in patients with higher scores on the APACHE II and SOFA scales (Tables 4 and 5). In patients with higher scores on the mNUTRIC scale, there were higher levels of LBP on Day 1 and sCD14-ST on Days 1 and 3 (Table 6).

3.4. ROC Analysis. The analysis results of the ROC curve of the sCD14-ST level on Day 1, I-FABP on Day 3, REG3α on Day 3, the SOFA scores on Days 1 and 3, APACHE II scores on Day 1, and mNUTRIC scores on Day 3 after diagnosing MODS for predicting a fatal outcome are shown in Table 7 and Figure 5.

After diagnosing MODS, the risk of death is

- 8.1 times higher with the sCD14-ST value on Day 1 more than 168.0123 ng/mL (OR 8.1, CI 2.6–25.3).
- 11.8 times higher with the I-FABP value on Day 3 more than 133 pg/mL (OR 11.8, CI 2.9–48.6).
- 13 times higher with the REG3α value on Day 3 more than 16.69 ng/mL (OR 13, CI 1.6–108.9).
- 8.3 times higher with the SOFA scores on Day 1 more than 5 (OR 8.3, CI 2.9–22.9).
- 19.25 times higher with SOFA scores on Day 3 more than 6 (OR 19.25, CI 4.4–84.5).
- 17.6 times higher with the APACHE II scores on Day 1 more than 15 (OR 17.6, CI 4.76–65.05).
- 22.0 times higher with mNUTRIC scores on Day 3 more than 4 (OR 22.0, CI 4.74–102.15).

Table 1: The studied patients' profiles.

Criterion/group		Total patients ($n = 78$)	Mortality rate – ($n = 44$)	Mortality rate + ($n = 34$)	p level
Age		66.0 (54.0–73.0)	60.0 (49.0–71.0)	68.0 (61.0–76.0)	0.031
Sex	Male	51.3%	53.5%	48.6%	0.666
	Female	48.7%	46.5%	51.4%	
SOFA scale scores	Day 1	5.0 (4.0–8.0)	5.0 (3.0–5.0)	7.0 (5.0–10.0)	**0.00002**
	Day 3	5.0 (2.0–7.0)	4.0 (2.0–5.0)	7.0 (5.0–9.0)	**0.00004**
	Day 7	3.0 (1.0–4.0)	2.0 (0.0–3.0)	7.0 (4.0–9.0)	**0.0002**
APACHE II scale scores	Day 1	16.0 (12.0–22.0)	13.0 (9.5–15.5)	21.0 (18.0–24.0)	**≤ 0.001**
	Day 3	13.0 (9.0–21.0)	10.0 (7.0–16.0)	22.0 (19.0–25.0)	**≤ 0.001**
	Day 7	9.0 (6.0–15.0)	7.0 (5.0–10.0)	17.0 (15.0–22.0)	**0.001**
mNUTRIC scale scores	Day 1	4.0 (2.0–5.0)	3.0 (1.0–4.0)	5.0 (4.0–6.0)	**≤ 0.001**
	Day 3	3.0 (2.0–5.0)	2.0 (1.0–4.0)	5.0 (5.0–7.0)	**0.0001**
	Day 7	2.0 (1.0–4.0)	2.0 (1.0–3.0)	4.0 (3.0–6.0)	**0.001**
Main pathology	Medical	53.8%	44.2%	65.7%	0.058
	Surgical	46.2%	55.8%	34.3%	
Comorbidities	+	74.4%	76.7%	71.4%	0.569
	–	25.6%	23.3%	28.6%	
Mechanical ventilation	+	48.7%	6.8%	100%	**≤ 0.001**
	–	51.3%	93.2%	0%	
Vasopressors	+	53.8%	15.9%	100%	**≤ 0.001**
	–	46.2%	84.1%	0%	

Note: For the age, SOFA, APACHE II and mNUTRIC scores Me (median) and Q1–Q3 (lower and upper quartiles) are given. Significant results are marked in bold.

Table 2: The sCD14-ST and LBP levels on Day 1, Day 3, and Day 7 after diagnosing MODS depending on the lethal outcome.

Criterion	Total patients ($n = 78$)	Mortality rate – ($n = 44$)	Mortality rate + ($n = 34$)	p level
LBP level on Day 1 (ng/mL)	2655.48 (1509.70–5661.70)	2155.7 (1224.5–7270.7)	2951.1 (1804.5–5164.1)	0.382
LBP level on Day 3 (ng/mL)	2503.95 (1774.60–5206.45)	2243.1 (1669.7–5486.9)	2905.2 (2230.7–3713.5)	0.396
LBP level on Day 7 (ng/mL)	2950.43 (2094.10–4916.50)	2976.0 (2032.0–5748.4)	2677.8 (2379.8–3307.7)	0.337
sCD14-ST level on Day 1 (ng/mL)	154.74 (120.12–171.29)	146.82 (104.00–164.04)	168.68 (122.35–457.58)	**0.007**
sCD14-ST level on Day 3 (ng/mL)	153.40 (128.47–169.22)	154.93 (126.11–171.29)	151.41 (131.53–168.37)	0.961
sCD14-ST level on Day 7 (ng/mL)	128.64 (105.24–157.07)	128.81 (106.48–158.39)	125.41 (104.00–155.75)	0.779

Note: Me—median and Q1–Q3—lower and upper quartiles are given. Significant results are marked in bold.

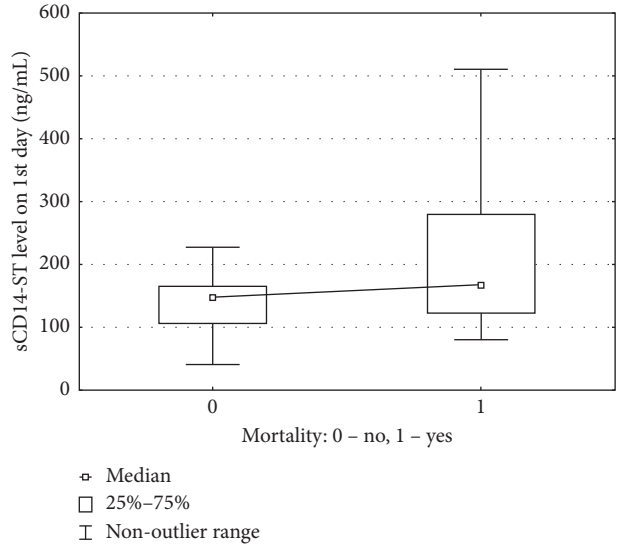

Figure 1: The sCD14-ST level on Day 1 after MODS diagnosis in deceased and survived patients.

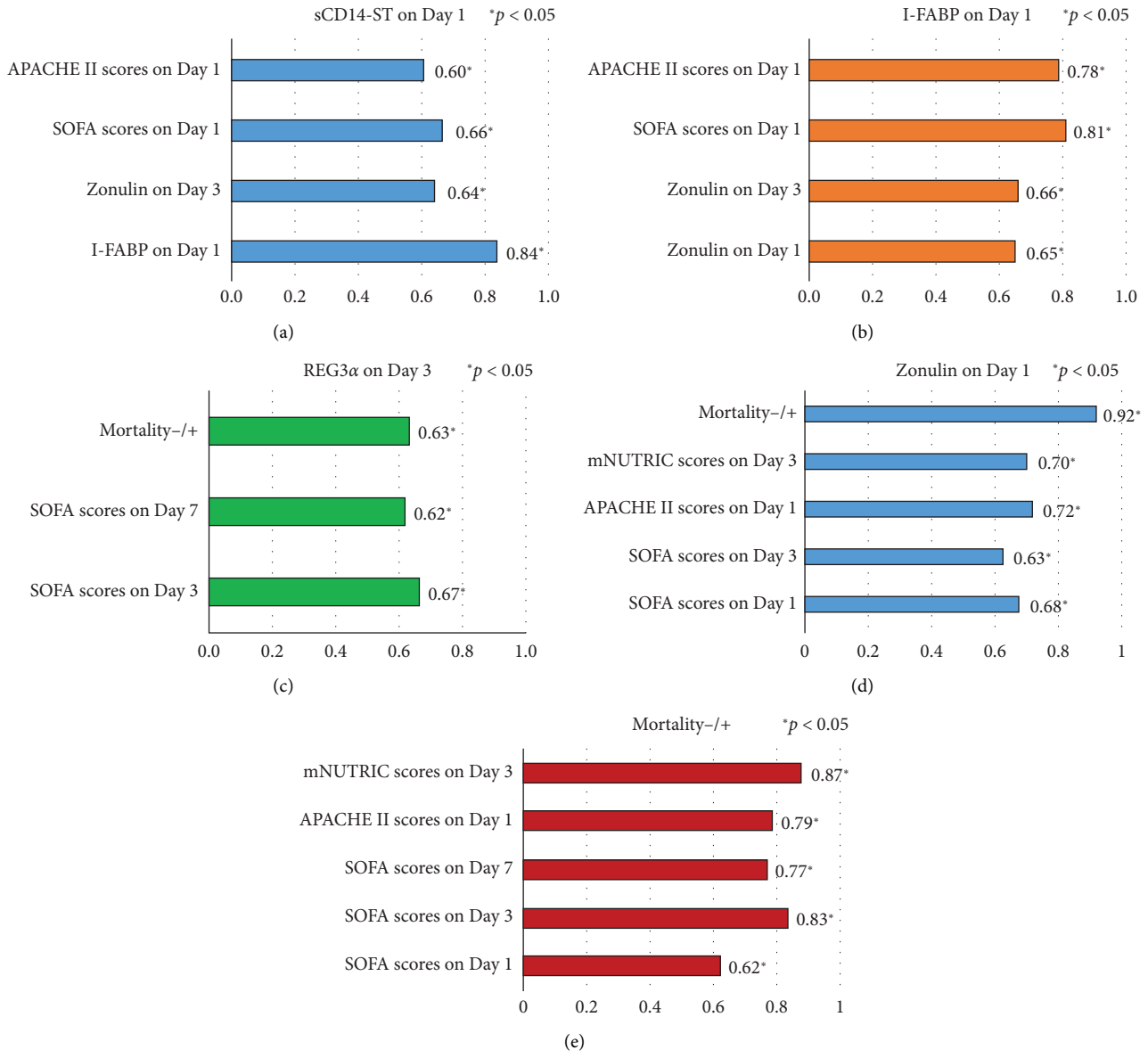

Figure 2: Statistically significant correlations between the studied indicators: (a) for sCD14-ST, (b) for I-FABP, (c) for REG3α, (d) for zonulin, and (e) for mortality.

Table 3: The I-FABP, REG3α, and zonulin levels on Day 1, Day 3, and Day 7 after diagnosing MODS in terms of the lethal outcome.

Criterion	Total patients ($n = 78$)	Mortality rate – ($n = 44$)	Mortality rate + ($n = 34$)	p level
I-FABP level on Day 1 (pg/mL)	115.10 (89.20–138.70)	105.50 (87.00–133.90)	122.50 (91.50–141.70)	0.185
I-FABP level on Day 3 (pg/mL)	108.60 (79.00–138.00)	104.35 (77.60–119.85)	137.95 (118.40–162.40)	**0.0299**
I-FABP level on Day 7 (pg/mL)	92.15 (82.85–119.95)	91.20 (81.70–121.50)	115.40 (84.30–118.40)	0.617
REG3α level on Day 1 (ng/mL)	18.14 (13.82–21.34)	16.69 (10.70–19.87)	19.27 (15.48–21.95)	0.051
REG33α level on Day 3 (ng/mL)	19.97 (12.78–29.11)	17.66 (11.46–24.70)	22.98 (20.00–36.88)	**0.022**
REG3α level on Day 7 (ng/mL)	19.87 (13.04–33.26)	18.33 (10.69–29.38)	35.89 (21.80–52.22)	**0.011**
Zonulin level on Day 1 (pg/mL)	986.40 (555.96–1541.67)	781.59 (465.20–1498.30)	1243.33 (587.10–1553.30)	0.155
Zonulin level on Day 3 (pg/mL)	810.40 (476.80–1418.33)	769.18 (444.00–1150.80)	1315.83 (545.40–1553.33)	0.139
Zonulin level on Day 7 (pg/mL)	953.07 (479.45–1553.34)	662.45 (428.40–1453.30)	1431.67 (1198.33–1590.00)	0.069

Note: Me—median and Q1–Q3—lower and upper quartiles are given. Significant results are marked in bold.

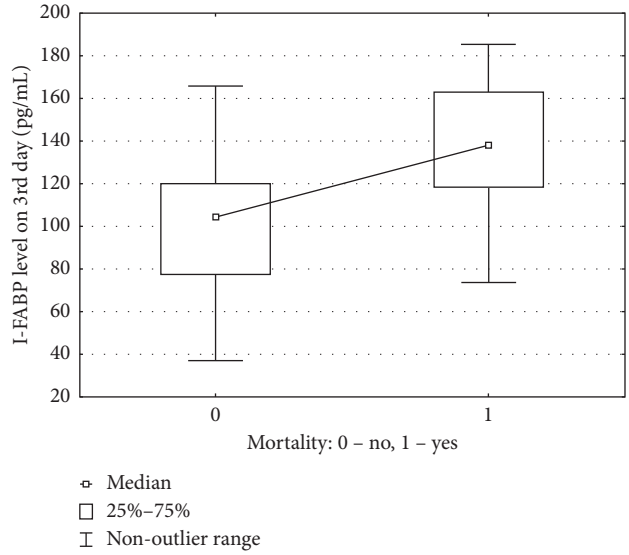

Figure 3: The I-FABP level on Day 3 after MODS diagnosis in deceased and survived patients.

Table 4: The levels of studied biomarkers in terms of APACHE II scale.

Criterion	APACHE II (scores 0–19)	APACHE II (scores 20–29)	APACHE II (scores 30 and more)	*p* level
LBP level on Day 1 (ng/mL)	2613.93 (1274.85–5710.00)	2889.00 (2069.25–5700.25)	1480.95 (956.13–1905.83)	0.086
LBP level on Day 3 (ng/mL)	2379.75 (1729.65–5767.45)	2681.65 (1952.55–3548.28)	2503.95 (2503.95–2503.95)	0.995
LBP level on Day 7 (ng/mL)	2975.95 (1981.63–5809.75)	2677.85 (2379.75–3267.05)	3429.40 (3429.40–3429.40)	0.652
sCD14-ST level on Day 1 (pg/mL)	147.28 (120.12–164.04)	165.84 (117.66–512.60)	238.59 (185.71–367.97)	**0.0154**
sCD14-ST level on Day 3 (pg/mL)	150.28 (128.47–164.10)	170.25 (154.48–195.19)	125.41 (125.41–125.41)	0.059
sCD14-ST level on Day 7 (pg/mL)	128.64 (104.00–150.95)	168.24 (107.06–226.35)	125.41 (125.41–125.41)	0.367
I-FABP level on Day 1 (pg/mL)	108.60 (89.10–138.70)	115.85 (89.15–135.15)	256.53 (135.40–376.18)	**0.0465**
I-FABP level on Day 3 (pg/mL)	107.30 (82.50–137.40)	113.15 (71.65–138.95)	138.00 (138.00–138.00)	0.683
I-FABP level on Day 7 (pg/mL)	90.15 (70.10–111.95)	115.40 (84.30–134.80)	116.90 (116.90–116.90)	0.320
REG3α level on Day 1 (ng/mL)	17.41 (13.82–20.11)	19.28 (13.82–29.95)	17.21 (11.27–52.94)	0.500
REG3α level on Day 3 (ng/mL)	18.62 (12.64–24.50)	26.65 (19.96–36.92)	21.45 (21.45–21.45)	0.174
REG3α level on Day 7 (ng/mL)	18.10 (10.32–29.51)	42.41 (19.28–52.22)	21.80 (21.80–21.80)	0.051
Zonulin level on Day 1 (ng/mL)	774.30 (453.30–1421.67)	1382.49 (661.78–1619.99)	1563.34 (1359.17–2055.99)	**0.0218**
Zonulin level on Day 3 (ng/mL)	628.16 (415.40–1131.60)	1194.50 (812.70–1558.32)	1418.33 (1418.33–1418.33)	**0.0331**
Zonulin level on Day 7 (ng/mL)	670.58 (433.55–1483.34)	1453.30 (504.50–1590.00)	1238.33 (1238.33–1238.33)	0.589

Note: Me—median and Q1–Q3—lower and upper quartiles are given. Significant results are marked in bold.

4. Discussion

As mentioned above, despite the rich range of etiological causes of severe and critical conditions in ICU patients, MODS is a common pathogenic pathway to death for most patients. Mortality in the ICU patients with MODS varies from 20% to 100% [2]. In this study, the mortality rate was 44.9%, which is a fairly high indicator. In patients with MODS, microcirculation disorders occur in various organs, including the intestine, in connection with which the permeability of the intestinal wall is disrupted and bacterial translocation increases. All these factors are able to aggravate multiple organ dysfunction, sepsis, and possible death [5, 6].

In addition, since the degree of inflammation is a determinant factor of nutritional risk, patients in ICU are at high malnutrition risk (40%–50%) [15]. The nutritional status deteriorates because of catabolic stress, systemic inflammatory response syndrome (SIRS), and MODS. All this is associated with worse clinical outcome [16]. In one systematic review, mNUTRIC was one of the best effectiveness tools of nutritional assessment of critically ill patients [17]. Therefore, we decided to evaluate the relationship between markers of intestinal damage and the nutritional status assessed by mNUTRIC in patients with MODS. Wang et al. found a suitable cutoff > 4 for the mNUTRIC score to predict the 28-day mortality (AUC = 0.763, CI 0.740–0.786) and mortality increased with increasing scores ($p \leq 0.001$) [18]. In this study, the result was similar: the risk of death was 22.0 times higher (OR 22.0, CI 4.74–102.15) with mNUTRIC scores on Day 3 after diagnosing MODS > 4 (AUC = 0.843, CI 0.718–0.927).

LBP is an acute phase protein produced by hepatocytes in response to bacteremia and pathogen-associated molecular patterns (PAMPs). It specifically interacts with lipid A of bacterial lipopolysaccharide, then binds to the CD14 receptor of myeloid cells, and promotes a cascade of

Table 5: The levels of studied biomarkers in terms of SOFA scale.

Criterion	SOFA (scores 0–5)	SOFA (scores 6–9)	SOFA (scores 10 and more)	*p* level
LBP level on Day 1 (ng/mL)	2208.80 (1274.85–4525.15)	4159.90 (1709.05–5710.00)	2655.48 (2007.15–3155.80)	0.551
LBP level on Day 3 (ng/mL)	2317.63 (1492.60–4743.48)	2503.95 (1848.25–5805.40)	2951.10 (2503.95–7716.05)	0.492
LBP level on Day 7 (ng/mL)	2975.95 (2156.20–5748.35)	2559.07 (543.25–3672.90)	3429.40 (3429.40–3429.40)	0.569
sCD14-ST level on Day 1 (pg/mL)	147.31 (107.06–165.33)	143.76 (119.09–165.52)	486.74 (172.60–521.40)	**0.001**
sCD14-ST level on Day 3 (pg/mL)	153.40 (127.37–170.25)	155.88 (128.47–168.37)	140.71 (125.41–522.80)	0.959
sCD14-ST level on Day 7 (pg/mL)	128.47 (104.00–148.20)	142.28 (106.48–168.24)	125.41 (125.41–125.41)	0.696
I-FABP level on Day 1 (pg/mL)	105.50 (76.20–135.80)	116.90 (91.20–131.30)	139.10 (113.30–267.10)	**0.0421**
I-FABP level on Day 3 (pg/mL)	104.25 (74.70–138.05)	118.40 (103.70–137.90)	138.00 (51.50–295.20)	0.585
I-FABP level on Day 7 (pg/mL)	89.10 (70.10–118.40)	102.85 (87.00–121.50)	116.90 (116.90–116.90)	0.603
REG3α level on Day 1 (ng/mL)	17.50 (13.14–20.31)	18.04 (14.56–21.95)	19.87 (15.70–21.34)	0.604
REG3α level on Day 3 (ng/mL)	19.28 (12.32–29.91)	20.11 (12.78–27.59)	21.45 (20.86–36.88)	0.550
REG3α level on Day 7 (ng/mL)	19.36 (13.93–30.63)	22.04 (12.14–42.41)	21.80 (21.80–21.80)	0.817
Zonulin level on Day 1 (ng/mL)	734.66 (441.46–1421.67)	1210.00 (698.56–1640.00)	1359.17 (990.00–1961.00)	**0.0296**
Zonulin level on Day 3 (ng/mL)	682.31 (444.00–1171.65)	886.28 (482.50–1470.00)	1563.30 (1418.33–3144.70)	0.065
Zonulin level on Day 7 (ng/mL)	974.73 (525.40–1535.00)	562.70 (194.60–1590.00)	1238.33 (1238.33–1238.33)	0.657

Note: Me—median and Q1–Q3—lower and upper quartiles are given. Significant results are marked in bold.

Table 6: The levels of studied biomarkers in terms of mNUTRIC scale.

Criterion	MNUTRIC (scores 0–4)	MNUTRIC (scores 5–9)	*p* level
LBP level on Day 1 (ng/mL)	1991.22 (1199.35–4780.05)	3799.13 (2032.00–6108.75)	**0.0485**
LBP level on Day 3 (ng/mL)	2081.65 (1375.50–4835.35)	2905.22 (2156.18–4759.43)	0.251
LBP level on Day 7 (ng/mL)	3050.48 (2156.20–5871.15)	2677.85 (2379.75–3267.05)	0.219
sCD14-ST level on Day 1 (pg/mL)	144.34 (102.47–158.10)	170.10 (143.76–510.50)	**0.0054**
sCD14-ST level on Day 3 (pg/mL)	149.88 (116.24–164.10)	168.80 (143.76–195.19)	**0.018**
sCD14-ST level on Day 7 (pg/mL)	133.23 (104.00–153.70)	125.41 (107.06–171.48)	0.406
I-FABP level on Day 1 (pg/mL)	101.00 (76.20–126.90)	123.05 (93.70–136.40)	0.093
I-FABP level on Day 3 (pg/mL)	103.50 (76.20–121.50)	131.55 (88.45–140.50)	0.161
I-FABP level on Day 7 (pg/mL)	88.05 (70.10–101.90)	116.90 (110.70–121.50)	**0.0495**
REG3α level on Day 1 (ng/mL)	16.24 (12.43–19.74)	20.30 (18.79–34.46)	**0.0229**
REG3α level on Day 3 (ng/mL)	16.69 (11.42–25.89)	22.02 (20.06–36.92)	**0.0384**
REG3α level on Day 7 (ng/mL)	17.70 (9.94–29.38)	28.13 (20.38–48.13)	**0.0174**
Zonulin level on Day 1 (ng/mL)	714.81 (447.38–1250.00)	1439.17 (818.90–1686.67)	**0.0119**
Zonulin level on Day 3 (ng/mL)	631.77 (415.40–1131.60)	1214.51 (812.70–1558.32)	**0.0088**
Zonulin level on Day 7 (ng/mL)	641.67 (401.90–1535.00)	1431.67 (1198.33–1571.67)	0.242

Note: Me—median and Q1–Q3—lower and upper quartiles are given. Significant results are marked in bold.

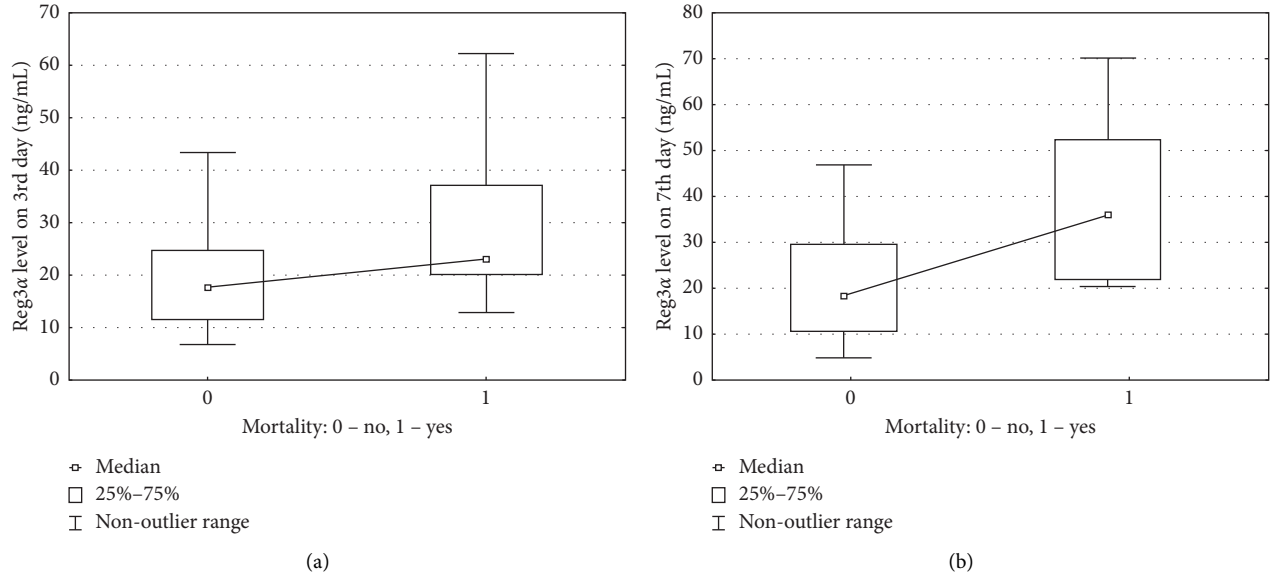

Figure 4: The REG3α levels on Day 3 (a) and Day 7 (b) after MODS diagnosis in deceased and survived patients.

Table 7: Results of ROC analysis of the studied parameters in patients with MODS to predict a fatal outcome.

ROC-analysis results	AUC (95% CI)	*p* level	Youden J-index	Optimal threshold value	Sensitivity	Specificity
sCD14-ST on Day 1	0.680 (0.564–0.781)	**0.005**	0.398	> 168.0123	51.43	88.37
I-FABP on Day 3	0.696 (0.556–0.814)	**0.041**	0.5393	> 133	71.43	82.50
REG3α on Day 3	0.707 (0.568–0.823)	**0.004**	0.4286	> 16.69	92.86	50.00
SOFA scale scores on Day 1	0.781 (0.673–0.867)	< **0.001**	0.4817	> 5	71.43	76.74
SOFA scale scores on Day 3	0.862 (0.743–0.940)	< **0.001**	0.6083	> 6	73.33	87.50
APACHE II scale scores on Day 1	0.861 (0.764–0.929)	< **0.001**	0.6618	> 15	91.18	75.00
mNUTRIC scale scores on Day 3	0.843 (0.718–0.927)	< **0.001**	0.6462	> 4	80.00	84.62

Note: AUC (95% CI) is the area under the ROC curve (95% CI is the confidence interval), and *p* level is the significance level. Significant results are marked in bold.

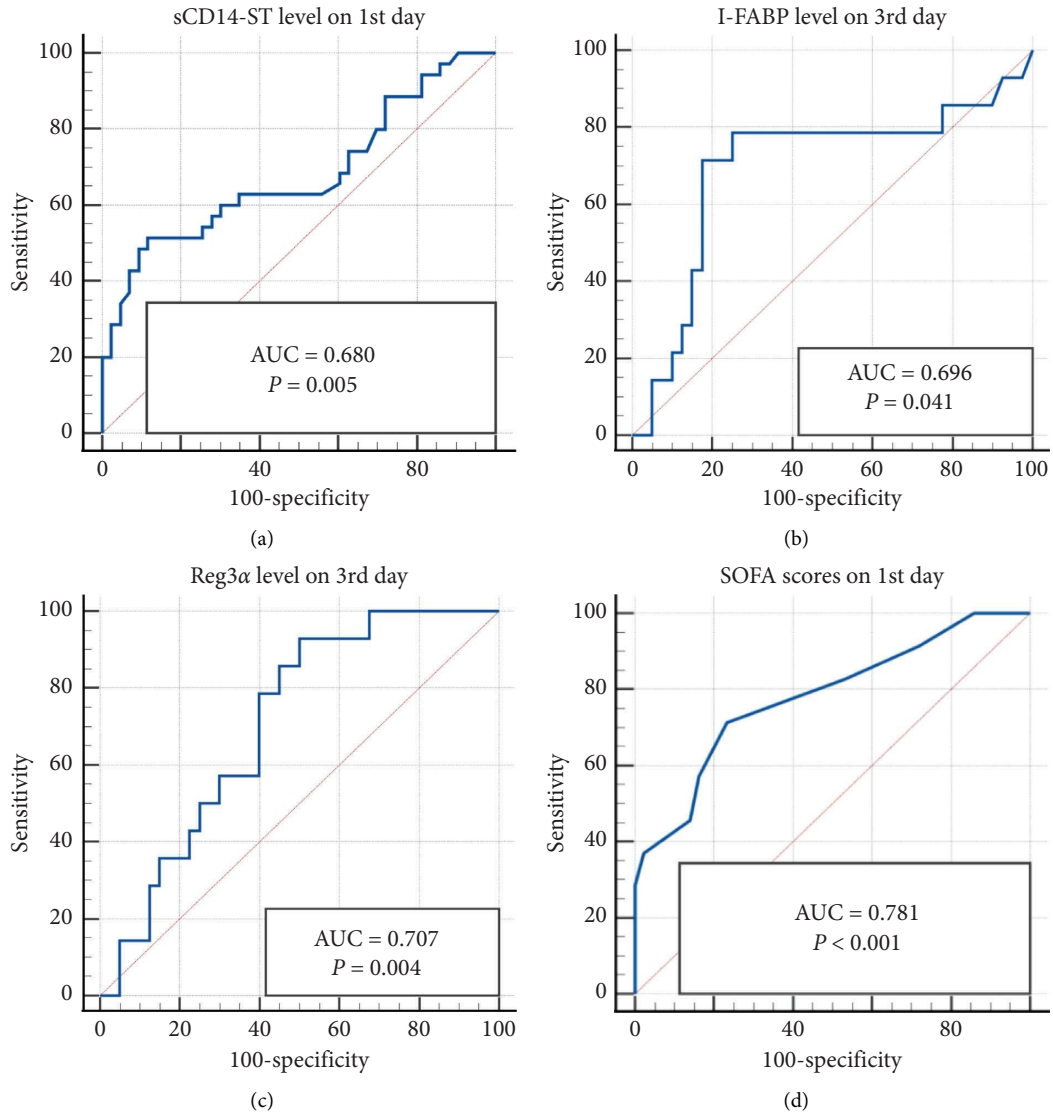

Figure 5: Continued.

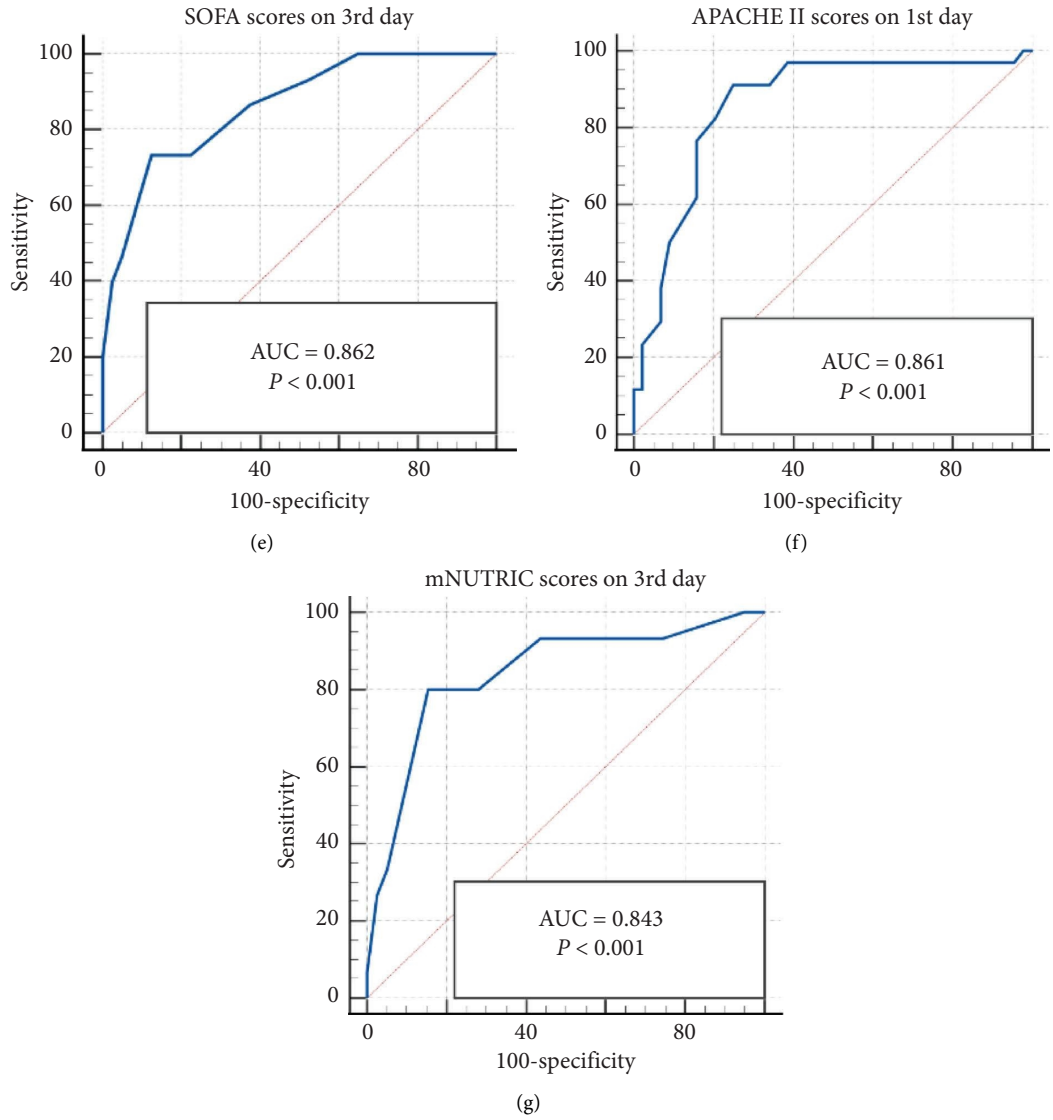

FIGURE 5: The ROC analysis of the sCD14-ST level on Day 1 (a), I-FABP on Day 3 (b), REG3α on Day 3 (c), the SOFA scores on Day 1 and Day 3 (d, e), APACHE II scores on Day 1 (f), and mNUTRIC scores on Day 3 (g) after diagnosing MODS to predict a fatal outcome.

inflammatory responses [19]. Unlike lipopolysaccharide, the LBP level in the blood serum can be determined within a few days of bacteremia, and therefore it is considered a reliable marker of bacterial translocation [20]. Compared to healthy people, patients with SIRS, sepsis, and septic shock have an increased level of LBP. However, higher levels of LBP, as an important component of antimicrobial protection, contribute to a decrease in cytokine production. In one study, significantly worse results were observed in patients with severe sepsis with less elevated LBP levels [21]. In previous study, the corresponding results were obtained in patients with colorectal cancer: patients with lower LBP levels on Day 3 after surgery and with a more pronounced decrease in LBP levels are more likely to develop SIRS, infectious and inflammatory complications, organ dysfunction, and death [22]. However, despite the fact that the LBP level on Day 1 was higher in deceased patients, its level in dynamics got decreased in deceased patients. On the contrary, its level tended to increase on Day 7 in survived patients. The LBP level did not differ in any of the studied parameters in this study. This might be due to the high mortality rate in the first two days, and therefore statistically, it was impossible to identify any differences. In addition, it should be noticed that he LBP levels were higher in patients with higher scores on the mNUTRIC scale. We did not find any literature data on the study of LBP in terms of assessment on the mNUTRIC scale. Maybe in patients admitted to the ICU with MODS high LBP level can be because of the violation of intestinal barrier function and increased bacterial translocation, and because of that these patients have high mNUTRIC score and they are in high risk of malnutrition. More large prospective studies are needed to evaluate this association.

The mCD-14 is a membrane glycoprotein that binds to the components of Gram-positive and Gram-negative bacteria through Toll-like receptors (TLRs), thereby triggering the production of various cytokines and phagocytosis

of bacterial pathogens with the formation of sCD14-ST [7]. The sCD14-ST has reliable diagnostic accuracy in sepsis, and its level in patients with sepsis was significantly higher than in patients without it [23]. It is an accurate diagnostic marker for the differential diagnosis of SIRS and sepsis as well as a predictor of outcome and risk of death [24]. In a study by Endo et al., the level of sCD14-ST also correlated with the severity of sepsis and changes in SOFA scores [25]. Levels of plasma sCD14-ST were positively correlated with APACHE II score in septic patients, and thus it was considered a valuable marker for early diagnosis of sepsis and risk stratification [26, 27]. In addition, in a study by Takahashi et al., the prognostic significance of sCD14-ST in relation to the 28-day mortality was shown [28]. This study confirmed that the level of sCD14-ST was higher on Day 1 of MODS in the group of deceased patients and in patients with higher scores on the APACHE II and mNUTRIC scales. The level of sCD14-ST on Day 1 positively correlated with SOFA scores ($r = 0.663$). It was revealed that the risk of death was 8.1 times higher (OR 8.1, CI 2.6–25.3) with the sCD14-ST value on Day 1 after diagnosing MODS > 168.0123 ng/mL. Again, we did not find any literature data on the study of sCD14-ST in terms of assessment on the mNUTRIC scale. Perhaps, in this situation, results of this study can be explained by the same reasoning that we assumed with LBP.

Zonulin plays a significant role in the permeability of the intestinal wall. To start "breaking down" the dense compounds, it is assumed that zonulin activates the epidermal growth factor receptor (EGFR) via proteinase-activated receptor 2 (PAR2). The activation of these two receptors reduces transepithelial electrical resistance, which leads to an increase in intestinal permeability [29]. Therefore, serum zonulin is considered to be a biomarker for the stability of tight contacts and the integrity of the paracellular barrier [30]. Serum zonulin was significantly elevated in patients with bacteremic sepsis, regardless of the genesis of sepsis: abdominal and nonabdominal. The authors also showed that zonulin levels differed significantly between survivors and nonsurvivors and correlated with APACHE II and qSOFA scores and serum endotoxin concentrations. It is also seen that zonulin plays a prognostic role in relation to the 28-day mortality. The threshold value of zonulin in blood serum for predicting mortality as demonstrated in the ROC analysis was higher than 1.5 ng/mL [11]. It is also worth noting that in the study by Donmez-Altuntas et al., zonulin levels were high in trauma patients and again positively correlated with APACHE II and daily SOFA scores [31]. Results from the other study provided evidence that higher zonulin levels are associated with a progressively higher mNUTRIC score in ICU patients [32]. In this study, a positive correlation of zonulin with sCD14-ST levels, I-FABP levels, SOFA, APACHE II, and mNUTRIC scale scores and death was revealed. There were also higher zonulin levels in patients with higher scores on the SOFA, APACHE II, and mNUTRIC scales. These results may suggest that an increase in zonulin levels in the blood indicates impaired permeability of the intestinal wall. As a result of this, bacterial translocation increases (increased sCD14-ST), organ dysfunction worsens, and the risk of death increases.

I-FABP is a cytosolic protein specific to mature enterocytes of the small intestine [33]. Low levels of I-FABP can be detected in the blood due to the constant release of mature enterocytes from the villi as part of normal intestinal homeostasis, whereas with damage to enterocytes, destruction of their membrane, the I-FABP levels in the blood are significantly increased [30, 34]. High plasma levels of I-FABP were associated with significantly higher mortality in the group of COVID-19 patients with sepsis [35]. It has also been shown that serum I-FABP levels correlate with general severity indicators such as APACHE II and SOFA [31, 36]. An increase in I-FABP in plasma of more than 100 pg/mL indicates acute mesenteric ischemia and necrosis of enterocytes with sensitivity of 79.0% and specificity of 91.3% [37]. There is evidence that I-FABP is very sensitive as it can be detected at an early stage of small intestine ischemia, even when histological damage is insignificant [35]. This study confirms the previous ones: in deceased patients, the level of I-FABP on Day 3 was statistically significantly higher than in survived patients, and the level of I-FABP positively correlated with the level of sCD14-ST, zonulin, SOFA, and APACHE II scores. Higher I-FABP levels were in patients with higher scores on the SOFA, APACHE II, and mNUTRIC scales. It was revealed that the risk of death is 11.8 times higher with the value of I-FABP on Day 3 after diagnosing of MODS > 133 pg/mL than at its lower level (OR 11.8, CI 2.9–48.6). Results from the study provided evidence that I-FABP levels in the blood indicate impaired permeability of the intestinal wall, which can lead to increased bacterial translocation and development of multiple organ dysfunction.

REG3α is an antimicrobial C-type lectin peptide produced and secreted by the Paneth cells in the intestinal lumen, which helps to contain bacterial infection by binding to peptidoglycans in the cell wall of some bacteria and has the ability to destroy some Gram-positive bacteria [38]. REG3α also helps to maintain the integrity of the intestinal barrier by reducing oxidative stress and inflammatory reactions in intestinal epithelial cells, thereby reducing their apoptosis [39, 40]. When the integrity of the intestinal epithelial barrier is violated, REG3α penetrates through the epithelium, moves into its own plate of the mucous membrane, and subsequently enters the systemic circulation [10]. Since the increased intestinal damage allows microbial products to enter the bloodstream, it also contributes to systemic inflammation and immune activation; therefore, researchers found that serum REG3α levels correlated with levels of lipopolysaccharide, IL-6, and IL-8 [29]. In addition, REG3α demonstrated a moderate correlation with bacterial translocation markers (sCD14 and LBP) [41]. In this study, REG3α levels in deceased patients on Days 3 and 7 were statistically significantly higher than in survived patients, and REG3α levels positively correlated with SOFA scores and mortality. Higher REG3α levels were in patients with higher scores on the mNUTRIC scale. It was revealed that the risk of death was 13 times higher (OR 13, CI 1.6–108.9) with the REG3α value on Day 3 after diagnosing MODS > 16.69 ng/mL. These results may indicate that in violation of the permeability of the intestinal wall, the level of REG3α in

the blood serum increases, as a result of which bacterial translocation increases, organ dysfunction worsens, and the risk of death increases.

We did not find any literature data on the study of I-FABP and REG3α in terms of assessment on the mNUTRIC scale. We can assume that the results obtained are identical to the results with zonulin. The gut is considered to play an important role in pathophysiologic processes of critical illness [32]. As of today, an important cause of the development and severity of MODS is the violation of the intestinal barrier followed by increased translocation of intestinal microflora into the systemic bloodstream, which is ultimately able to aggravate organ dysfunction and the development of fatal outcomes.

These potential biomarkers of intestinal wall damage and bacterial translocation in combination with mNUTRIC, SOFA, APACHE II scores to make a decision to start early administration of nutrition support and adequate treatment to prevent the intestinal barrier damage, bacterial translocation, SIRS, and MODS as well as improving the survival rate.

The potential limitations of this study may be the small number of patients studied as well as the heterogeneity of sampling for the underlying disease that led to the development of MODS. Despite the various limitations of the study, these potential biomarkers are interesting candidates for identifying patients with a high risk of death, which can help to screen individual patients for timely, rapid, and possibly aggressive intensive care measures to reduce the stay of patients in the ICU and lower mortality rates. Since this study was a pilot one, it is planned to conduct a study with a larger number of patients, divided into subgroups with homogeneous diseases (surgical and medical), as well as with the presence of a control group in accordance with the selected pathologies that led to the development of MODS.

5. Conclusions

In patients with MODS, an increase in sCD14-ST, I-FABP, and REG3α in blood serum can indicate the violation of intestinal barrier function and increased bacterial translocation, which ultimately may aggravate the severity of multiple organ dysfunction and increase the risk of death. It is required to further study the factors leading to gastrointestinal disorders and intestinal wall permeability in order to screen for timely intensive care measures to reduce the stay of patients in the ICU and lower mortality rate.

Data Availability Statement

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

Disclosure

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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