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Predicting early mortality in treatment of patients with acute infectious pancreatitis using two surgical strategies

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ABSTRACT

Background: To determine the prediction of mortality and to develop a mathematical model of severe acute pancreatitis designed to predict early mortality in patients with secondary pancreatic infection. *Methods*: It study was based on data from comparing of severity scores for two surgical strategies in 103 patients who were operated with secondary pancreatic infection and the condition was assessed before surgery and after 48 hours using most significant indicators which are given nowadays the most attention worldwide. *Results:* According to the goals and objectives of the study all patients were divided into two groups: the main groups were 56 patients with secondary pancreatic infection, which used tactics of treatment step-up approach (after surgery 3 patients (5.3%) were died); the comparison groups were 47 patients with open surgical intervention (after surgery 7 patients (14.9%) were died). The main finding of this study was been that I-FABP, lactate, CRP, SBP and APP not only before surgery is superior in predicting SPI in comparison to commonly used markers such as APACHE-II, SOFA scores, and serum PCT, IL-6 in 48 hours after ones. It well-known scores have not shown the ability to predict early mortality before surgery: APACHE II scores (AUC 0.558) and SOFA (AUC 0.734). These turned out to be: APP (AUC 0.81) and I-FABP level (AUC 0.881) most suitable for building mathematical prognostic model. *Conclusions:* The assessment of effective biomarkers has made it possible to personalize surgical tactics and improve outcomes of the treatment.

Keywords: acute infectious pancreatitis, biomarkers, prediction of early mortality, mathematical model, surgical strategies, results.

1. INTRODUCTION

Acute pancreatitis (AP) is the third most common gastrointestinal disease worldwide. The epidemiological estimates presented in the study indicate that the incidence of the disease is increasing worldwide (Xiao et al., 2016). According to the WHO (2016), 33-74 cases per 100, 000 people/year in different countries of the world and 1-60 deaths per 100,000 people/year with AP were detected. The region-based analysis showed that cases of AP and mortality were significantly higher in the American region than in the regions of Europe and the Western Pacific. It accounts for greater than 300,000 emergency room visits annually in the US, which is steadily increasing, with a mean length of hospital stay of 7 days, and stationary costs exceed $ 2.5 billion. Mortality with AP ranges from 1% to 2% in general, necrosis of AP develops in 10%-20% of patients is associated with local and systemic complications and higher mortality which reaches 30% (Banks & Freeman, 2006).

Necrotizing AP which is associated with an 8 to 39% rate of death develops in approximately 20% of patients. The major cause of death, next to early organ failure, is secondary pancreatic infection (SPI) or peripancreatic necrotic tissue, leading to sepsis and multiple organ failure. SPI is a further factor that often leads to negative consequences is diagnosed in approximately 40% of patients and is associated with high mortality which exceeds 40% in the development of systemic complications (Darrivere et al., 2018). Until recently, open surgical necrosectomy was by the standard treatment of SPI. This procedure caused a severe inflammatory reaction, often resulting in prolonged multi-organ failure (MODS) and secondary local complications associated with the operation, such as bleeding and gastro-intestinal fistulas (Karakayali, 2014). The method of step-up approach in the treatment of SPI has recently been introduced which includes percutaneous drainage, endoscopic necrosectomy through the stomach or duodenum, laparoscopic necrosectomy and retroperitoneal surgical drainage (van Santvoort et al., 2010; Bakker et al., 2012).

The aim of the study was analyses a number of indicators that can be useful in determining the severity and prognosis early mortality to be able to select patients for individual surgical treatment of acute infected pancreatitis.

2. MATERIALS AND METHODS

We conducted a retro- and prospective single-centered controlled study in 103 patients with SPI who from January 2015 and to December 2020 were treated at the Kharkiv Regional Clinical Hospital, Ukraine (Table 1). The classification of the AP was used according to the recommendations of the International Consensus (2012) (Banks et al., 2013). Patients included in the study were treated in accordance with international recommendations (IAP/APA evidence-based guidelines for the management of acute pancreatitis, 2013) adapted to our local resources and procedures. In the first phase of AP all patients were treated conservatively, in the second used a differentiated surgical approach. According to the goals and objectives of the study all patients were divided into two groups: the main groups were 56 patients with SPI, which used tactics of treatment step-up approach; the comparison groups were 47 patients with open surgical intervention. The exclusion criteria were 1) the patients who were referred to the clinic from other medical institutions after primary laparotomy; 2) the patients with postoperative AP, 3) patients over 70 years old, and 4) the patients who were refusal to enroll in the study. The investigated population consists of patients with acute infected pancreatitis that were admitted and treated to a hospital. The investigated population consists of patients with acute infected pancreatitis that were admitted and treated to a hospital. The selected populations of patients were been with only necrotizing or predicted severe infected acute pancreatitis and were eligible for inclusion. In all patients were studied retrospective and prospective data of scores of severity of the condition and biomarkers for the clinical outcome as well as accuracy data (true positives, false negative, false positive, true negatives) were included for calculated. Local or systematic complications, pancreatic necrosis and organ failure were defined. Infected pancreatic necrosis was assessed by either imaging, biopsy, fine needle aspiration, perioperative assessment or autopsy. The presence of clinical and laboratory data of SPI in patients with prolonged fever (> 38.5°C for > 5 days) with elevated WBC and PCT, or the emergence of a new organ failure, or gas with CECT within pancreatic and/or peripancreatic collections, or in the presence of a combination of these factors were essential for the diagnosis.

Evaluation of important results was compared to the use of modern systems to determine the predictive criteria for early mortality: APACHE-II score, SOFA score and AGI grade (upon admission to the hospital, and 48 hours after surgery, as well as during the entire treatment period). In 103 patients with severe acute infected pancreatitis of both sexes most significant indicators were selected from the database, which are given the most attention in the world scientometric's databases: endogenous intoxication, severity of the condition, systolic blood pressure (SBP), intra-abdominal pressure (IAP), abdominal perfusion pressure (APP), Charlson Comorbidity Index (CCI), WBC count, blood hematocrit, platelets, lactate, procalcitonin (PCT), C-reactive protein (CRP), Interleukin-6, Intestinal fatty acid-binding protein (I-FABP), blood creatinine, total bilirubin levels. Assessments of the severity of damage to the digestive tract (AGI) were performed in accordance with the recommendations (2012) of the Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM) (Blaser et al., 2012). The World Society of Abdominal Compartment Syndrome (WSACS) classification was used to assess the level of intra-abdominal hypertension. Using the recommendations of the World Society of Abdominal Compartment Syndrome (2007, 2009, 2011, 2013), we developed a clinically adapted diagnosis of Abdominal Perfusion Pressure (APP) in patients with AP using the determination of abdominal perfusion pressure according to the following formula: Abdominal Perfusion Pressure = Mean Arterial Pressure - Intra-

Abdominal Pressure. Upon admission of the patients to the hospital a mathematical model investigations was developed and it was checked of the discriminant function after 48 hours after surgery in the course of complex treatment.

Statistical analyses

Statistical data processing was performed using the trial version of STATISTICA 13.3 EN. Initially, statistical analysis was performed using descriptive statistics. Using the Tukey test, the presence of emissions was checked and the normality of the distributions (Shapiro-Wilkie test) of the selected indicators was assessed. Continuous data was presented as Me (Q1; Q3), where Me is the median, Q1 and Q3 is the interquartile range (IQR). The Spearman correlation coefficient and criterion $\chi 2$ were used for all patients; the nonparametric Mann-Whitney test was used for pairwise comparisons of means in independent groups, and the Wilcoxon test was used for dependent samples. Zero hypotheses (H0) in statistical tests were rejected at a significance level of $p > 0.05$. When predicting the outcome of treatment, the greatest accuracy and adequacy in terms of a posteriori classification was obtained by discriminant analysis. Prediction of treatment was carried out not only with the use of multidimensional statistical methods, but also with the help of various scores of the severity of the condition or disorders of the physiological condition of the patient in AP: APACHE II score and SOFA score in the dynamics of treatment. To assess the diagnostic significance of the studied scales and biomarkers, an ROC analysis was performed: the sensitivity, specificity, and area under the ROC curve were determined for each score and each biomarker and the significance of the differences between them were assessed and taking into account its 95% confidence interval. The prognostic efficacy of the models was assessed by discrimination based on the AUC index. The efficacy of the model was considered limited at AUC ≥ 0.70; good - at AUC ≥ 0.80; excellent - at AUC ≥ 0.90.

3. RESULTS

In connection with the fact that when deciding on the choice of treatment program the presence of complications AP plays a fundamental role and their timely diagnosis is extremely important, the search was most sought for the confirmation of significant clinical signs. As the main symptoms of SPI the most commonly observed were pain, weakness, nausea and vomiting, body weight loss, infiltration in the abdominal cavity, fever (above 38°C), leukocytosis (above $12x10^9/l$), jaundice; high concentration of PCT serum.

Until recently (in comparison group), as the standard surgical treatment of suspected or confirmed SPI we used open method of execution laparotomy (upper-middle or subcostal transverse) necrosectomy, drainage (47 patients, 100%) and including programmed re-laparotomy (8 patients, 17.0%). SPI was confirmed in all patients who were analyzed. Postoperative complications occurred in 26 (55.3%): erosive bleeding (4), fistulas stomach and colon (2), MODS (20). After surgery 7 patients (14.9%) were died: 2 patients who were operated up to 2 weeks, 3 patients who were operated up to 4 weeks, and 2 patients who were operated in 4 weeks after onset of AP. In generally, in 39 (83%) patients of this group used necrosectomy and drainage ("closed" technique) and in 8 (17%) we used "open" treatment methods, including in 6 of them using VAC-therapy.

The strategy of treating patients with suspects confirmed SPI was significantly different in the main group. In this group, 41(73.2%) patients were treated by percutaneous controlled ultrasound and laparoscopic, 11 (19.6%) by VARDs and drainage, 5 (8.9%) through the wall of the stomach or duodenum with purulent fluid collections and pseudocysts. In 8 (14.3%) open operations were performed (local lumbotomy, upper medial, left or right-winged local laparotomy with pancreatic necrosectomy and dranages) including 5 patients using decompressive VAC-laparostomy. Postoperative complications arose in 11 (19.6%) patients: erosive bleeding (3), fistula of the large intestine (1), progressive MODS (7). After surgery 3 patients (5.3%) were died: 2 of them had a 30-day mortality (operated up to 4 weeks from the onset of AP) and 1 patient had 90-day mortality (Figure 1).

Table 1 Demographic, clinical and laboratory characteristics of patients with AP

Indicators	1st group (n=56)	2nd group (n=47)	1st group (n=56)	2nd group (n=47)	Survivor (n=93)	Non-survivor (n=10)
	Before surgery		After 48 hours		Before surgery	
Ages, Me [IQR]	52 [18-70]	51 [23-69]	–	–	–	–
	P=0.133					
Sex: - male - female	89 (47.8%) 97 (52.2%)	21 (46.7%) 24(53.3%)				
	NA		NA		NA	
CCI	1.5	1.5				

(points), Me [IQR]	[1-6]	[1-6]				
	P=0.16					
WBC count (×10⁹ /L), Me [IQR]	13.7 [12.6-17.3]	17.8 [12.8-22.2]	14.5 [13.9-23.2]	16.2 [14.8-26.4]	15.6 [12.6-24.1]	24.3 [16.4-28.6]
	P=0.000		P=0.000		P=0.000	
PLT (×10³/L), Me [IQR]	274.5 [212.8-322.6]	271.9 [236.5-309.7]	269.5 [138.9-336.4]	268.9 [198.9-273.2]	265.5 [198.9-336.4]	174.6 [138.9-254.1]
	P=0.056		P=0.078		P=0.001	
Hematocrit(%), Me [IQR]	38.7 [35.8-42.1]	39.2 [36.4-43.8]	39.2 [32.4-49.6]	38.7 [35.6-46.8]	33.6 [32.4-39.5]	44.8[38.4-49.6]
	P=0.251		P=0.068		P=0.000	
Creatinine (mg/dl), Me [IQR]	0.98 [0.86-0.102]	0.99 [0.102-2.21]	0.86 [0.84-0.96]	1.17 [0.93-2.11]	0.93 [0.86-0.101]	1.82 [1.46-2.21]
	P=0.234		P=0.000		P=0.000	
Total bilirubin (μmol/L), Me [IQR]	20.5 [12.8-70.4]	20.4 [15.2-54.6]	18.9 [14.1-101.8]	19.1 [14.3-66.8]	16.5 [12.8-43.7]	47.5 [28.6-101.8]
	P=0.124		P=0.271		P=0.000	
Lactate (mmol/L), Me [IQR]	2.1 [1.9-3.2]	1.9 [1.8-2.2]	2.2 [1.9-2.9]	2.4 [1.8-6.2]	2.0 [1.8-3.7]	4.3 [2.9-6.2]
	P=0.000		P=0.000		P=0.000	
PCT (pg/mL), Me [IQR]	14.474 [2.341-42.328]	13.892 [2.462-35.544]	18.262 [2.711-43.021]	17.511 [6.457-24.873]	17.784 [2.341-43.021]	33.245 [14.456-42.328]
	P=0.358		P=0.177		P=0.000	
IL-6 (pg/ml), Me [IQR]	37.6 [13.3-56.4]	38.3 [15.2-61.1]	45.9 [14.6-68.7]	66.6 [13.3-86.5]	34.7 [13.3–42.3]	67.2 [35.8–86.5)
	P=0.074		P=0.127		P=0.000	
CRP (mg/L), Me [IQR]	143 [121-166]	175 [130-201]	164 [138-173]	190 [150-233]	153 [121-177]	251 [180-233]
	P=0.000		P=0.000		P=0.000	
I-FABP (pg/ml), Me [IQR]	645.6 [445.6-1023.3]	897.4 [512.4-2349.7	567.8 [476.4-1023.6]	892.3 [578.7-1221.2]	698.2 [445.6-1023.6]	1092.3 [892.4-3009.2]
	P=0.000		P=0.000P=0.000			
APP (mm Hg), Me [IQR]	72.2 [66.5-78.1]	66.4 [60.1-72.3]	76.2 [68.4-78.5]	68.5 [58.4-72.5]	75.4 [60.1-78.3]	59.2 [56.3-64.7]
	P=0.000		P=0.000		P=0.000	
SBP (mmHg), Me [IQR]	115.5 [90-130]	125.5 [70-130]	123 [90-150]	120 [100-140]	130 [90-150]	85 [70-110]
	P=0.000	P=0.000	P=0.000		P=0.000	
APACHE II score (points), Me [IQR]	24 [11-31]	12 [6-17]	22 [10-32]	14 [8-21]	11 [4-21]	24 [15-32]
	P=0.000		P=0.000		P=0.000	
SOFA score (points), Me [IQR]	9 [7-11]	12 [8-14]	10 [6-14]	14 [10-16]	8 [6-11]	14 [9-16]
	P=0.000		P=0.000		P=0.000	
AGI grade (points), Me [IQR]	2 [1-4]	2 [1-4]	2 [1-3]	3 [1-4]	2 [1-4]	3 [2-4]
	P=0.443		P=0.000		P=0.000	

Note: P - Mann-Whitney test; NA - not applicable.

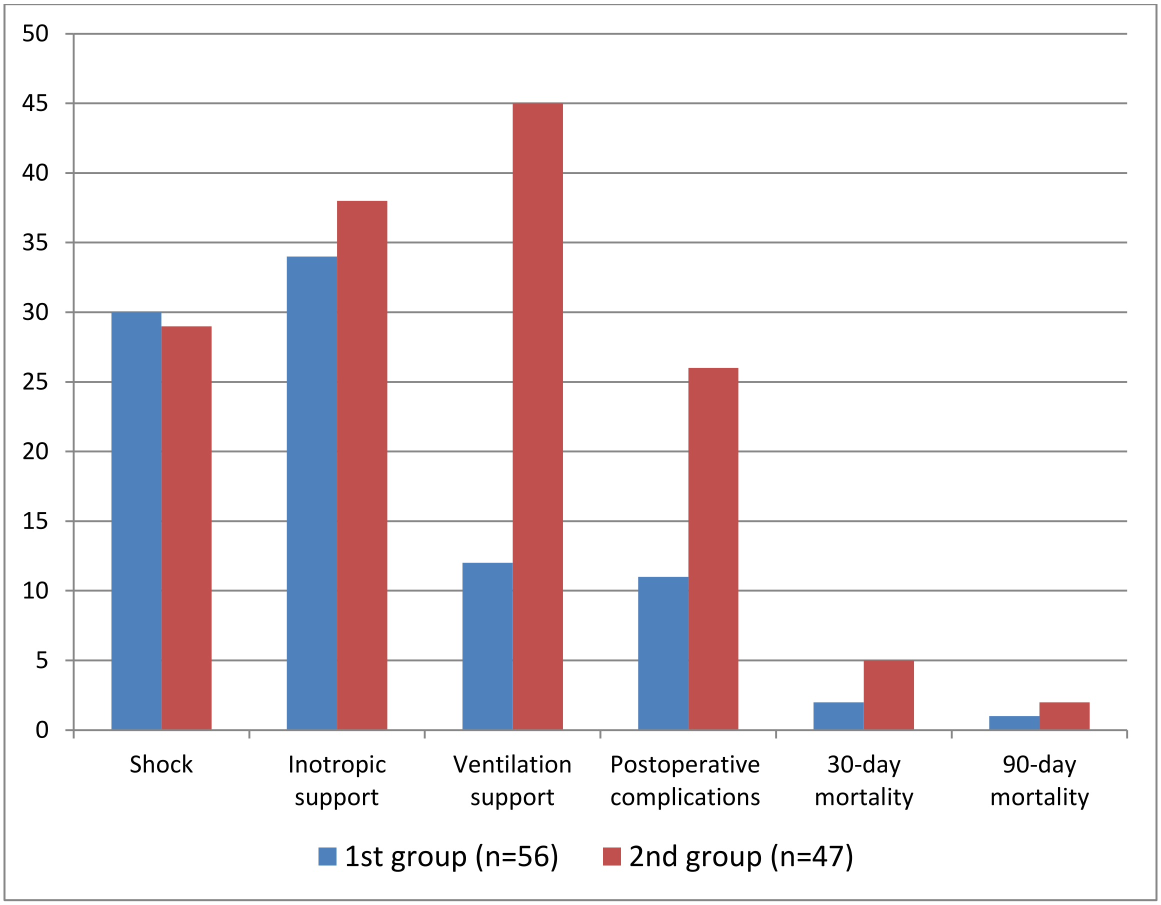

Figure 1 The severity of the disease, types of organ support and the results of patient's treatment.

At the first stage of the study, we selected the AUC indicators of which were ≥0.8 before the operation. These turned out to be: SBP(optimal cut-off value of 115.0 mm Hg, AUC 0.806, 95% CI 0.689-0.875); APP (optimal cut-off value of 71.45 mm Hg, AUC 0.81, 95% CI 0.667-0.881); Lactate (optimal cut-off value of 2.15 mmol/L, AUC 0.802, 95% CI 0.708-0.864); CRP (optimal cut-off value of 152 mg/L, AUC 0.839, 95% CI 0.722-0.912); I-FABP (optimal cut-off value of 668.95 pg/ml, AUC 0.881, 95% CI 0.767-0.982) (Table 2). Wherein, the ability of selected SOFA and APACHE II scores to predict early mortality in patients upon operations with SPI according to ROC curve analysis testified that these two severity scores have been with certain limitations in predicting early mortality during this study period. It should be noted that the APACHE II score had an optimal cut-off value of 11.5 points (AUC 0.558, 95% CI 0.409-0.545) before surgery with a sensitivity of 80% and low specificity, which was 42.1%, and after surgery: cut-off value was 13.0 points (AUC 0.878, 95% CI 0.693-0.911), sensitivity 81% and specificity 87.5%. The SOFA score had an optimal cut-off of 9.5 points (AUC 0.734, 95% CI 0.628-0.781) before surgery at a sensitivity of 66.7% and specificity of 77.8%, and in 48 hours after surgery 9.5 points (AUC 0.771, 95% CI 0.675-0.846) at sensitivity of 48.1% and specificity of 100% (Table 2). The mean level of systolic blood pressure (AUC 0.806) and perfusion pressure of the abdominal cavity (AUC 0.81) turned out to be the most acceptable for using the prognosis before surgery (Table 2; Figures 2 and 3). After that we intended to perform analysis for studies of biomarkers, but as it turned out, only a few biomarkers have had a good predictive value before surgery. The method of logistic regression and ROC analysis were showed that only blood lactate (AUC 0.802) with a sensitivity of 55.6% and a specificity of 93.3%, CRP level (AUC 0.839) with a sensitivity of 77.8% and a specificity of 81.3%, and I-FABP level (AUC 0.881) with a sensitivity of 89.5% and a specificity of 78.9% had a predictive value out of 10 studied biomarkers (Table 2, Figures 4-6).

In 48 hours after surgery, the most prognostic significant were APACHE II score (AUC 0.878), SBP (AUC 0.821), APP (AUC 0.816), PTL (AUC 0.87), lactate level (AUC 0.811), IL-6 level (AUC 0.832), CRP level (AUC 0.867), and I-FABP level (AUC 0.911) (Table 3). Finally, it was shown that all indicators that were studied appropriated for analysis by the criteria survivors/non-survivors patients (Table 4).

Table 2 Area under the ROC Curves for the study of indicators in patients upon admission

Indicators	optimal cut-off	sensitivity	specificity	AUC
APACHE II score, points	11.5	0.8	0.421	0.558
SOFA score, points	9.5	0.667	0.778	0.734
SBP, mm Hg	115.0	0.821	0.731	0.806
APP, mm Hg	71.45	0.833	0.778	0.81
WBC count, ×10⁹/L	15.55	0.75	0.542	0.651
PLT, ×10³/L	255.6	0.813	0.65	0.723
Hematocrit, %	39.15	0.75	0.579	0.671
Creatinine, mg/dl	0.935	0.867	0.25	0.513
Total bilirubin, μmol/L	13.85	0.6	0.75	0.669
PCT, pg/mL	12.162	0.556	0.6	0.59
Lactate, mmol/L	2.15	0.556	0.933	0.802
IL-6, pg/ml	37.45	0.833	0.375	0.601
CRP, mg/L	152.0	0.778	0.813	0.839
I-FABP, pg/ml	668.95	0.895	0.789	0.881

Table 3 Area under the ROC Curves for the study of indicators in patients in 48 hours

Indicators	optimal cut-off	sensitivity	specificity	AUC
APACHE II score, points	13.0	0.81	0.875	0.878
SOFA score, points	9.5	0.481	1.0	0.771
SBP, mm Hg	115.0	0.833	0.654	0.821
APP, mm Hg	70.3	0.875	0.778	0.816
WBC count, ×10⁹/L	16.2	0.667	0.792	0.762
PLT, ×10³/L	247.6	0.875	0.85	0.87
Hematocrit, %	39.15	0.625	0.662	0.577
Creatinine, mg/dl	1.105	0.611	0.938	0.729
Total bilirubin, μmol/L	41.1	0.95	0.45	0.681
PCT, pg/mL	19.952	0.267	0.911	0.547
Lactate, mmol/L	2.55	0.667	0.822	0.811
IL-6, pg/ml	47.6	0.708	0.875	0.832
CRP, mg/L	161.0	0.828	0.813	0.867
I-FABP, pg/ml	864.85	0.947	0.842	0.911

Table 4 Area under the ROC Curves for the study of indicators in survivors/non-survivors patients

Indicators	optimal cut-off	sensitivity	specificity	AUC
APACHE II score, points	14.5	0.813	1.0	0.934
SOFA score, points	11.5	0.963	0.8	0.891
SBP, mm Hg	85.0	1.0	0.423	0.801
APP, mm Hg	62.5	0.958	0.9	0.979
WBC count, ×10⁹/L	17.45	0.875	0.917	0.933
PLT, ×10³/L	255.55	0.813	1.0	0.875
Hematocrit, %	41.31	0.781	0.9	0.814
Creatinine, mg/dl	1.084	0.906	1.0	0.961
Total bilirubin, μmol/L	42.0	0.750	0.850	0.886

PCT, pg/mL	21.369	0.889	0.9	0.919
Lactate, mmol/L	3.15	0.977	0.8	0.97
IL-6, pg/ml	65.25	1.0	0.778	0.824
CRP, mg/L	179.0	0.833	1.0	0.86
I-FABP, pg/ml	965.9	0.947	0.9	0.9

Evaluation of different prognosis indicators allowed to develop a mathematical model by criteria: severity and prediction of survivors / non-survivors patients. Intestinal fattyacid binding protein (I-FABP) is known to be present in small intestinal epithelial cells, and its characteristics allow its use in peripheral blood to be used as a sensitive and specific marker of enterocyte damage in AP. We proposed to assess gastrointestinal disorders in patients with AP by determining the level of I-FABP in blood plasma inorder to early assess the severity and predict the further course of the disease. Significant differences were found between APACHE II score, AGI grade, APP and I-FABP levels in plasma when Wilcoxon was tested before surgery and after 48 hours after surgery and intensive care. We strong correlations were found for these indicators using correlation Spearman's coefficient. The statistics between the studied subjects in patients with acute pancreatitis are shown in Table 5.

Table 5 Statistic data between the indicators studied in patients with acute pancreatitis

Indicators	Before surgery	In 48 hours	Wilcoxon'scriterion	Spearman'scriterion
APACHE II score, Me [IQR]	12.5 [2-21]	10.5 [3-27]	W=158.0, z=1.935, p=0.042	**r=0.825**
AGI grade, Me [IQR]	2 [1-4]	2 [1-4]	W=126.0, z=1.944, p<0.02	**r=0.674**
APP (mm Hg), Me [IQR]	68.1 [57.2-78.5]	63.8 [53.2-77.3]	W=382.0, z=4.518, p=0.000	**r=0.909**
I-FABP (pg/ml), Me [IQR]	**658.1 [448.6-1123.3]**	**994.6 [445.6-3009.2]**	**W= –308.0, z=3.763, p=0.000**	**r=0.797**

The results of the study showed that the AGI was from 1 to 4 degrees of severity, both in before surgery and after 48 hours of intensive treatment (Table 1). There were showed statistically significant differences in Wilcoxon's and Spearman's criteria for APACHE II score, AGI grade, APP and I-FABP, and correlations were established between AGI grade and the severity of patients APACHE II score and I-FABP level after 48 hours of complex treatment of AP. Serum I-FABP levels have had good prognostic value for assessing the degree of damage compared to baseline AGI grade. Intra-group correlations between indicators in patients with AP are shown in Table 6.

Table 6 Intra-group correlations between indicators in pathients with AP

Indicators	APACHE II score (48 hours)	AGI grade (48 hours)	APP (48 hours)	I-FABP (48 hours)
APACHE II score (48 hours)	1,0000	0,918	– 0,823	**0,914**
AGI grade (48 hours)	0,918	1,0000	– 0,425	**0,912**
APP ((48 hours)	– 0,823	– 0,425	1,0000	**– 0,908**
I-FABP (48 hours)	**0,914**	**0,912**	**– 0,908**	**1,0000**

Based on the analysis of the studied indicators, a method of early diagnosis of small bowel damage with the development of intestinal insufficiency in AP was developed, which included assessment of physiological and anatomical parameters of the abdominal cavity, determination of I-FABP in plasma and perfusion pressure (APP) in the abdominal cavity further calculation of the coefficient of damage to the digestive tract. We also have proposed a method for assessing the severity and choice of treatment for acute destructive pancreatitis by calculating the coefficient (k), which have included indicators of the level of intestinal fatty acid-binding protein (I-FABP), and perfusion pressure (APP) in the abdominal cavity in the dynamics of complex treatment of the patient which was determined to the formula:

$$k = \frac{APP_2^2 \times I\text{-}FABP_1 \times I\text{-}FABP_3}{APP_1 \times APP_3 \times I\text{-}FABP_2^2}$$

Note:

APP_1 - perfusion pressure in the abdominal cavity (initial data);

APP_2 - perfusion pressure in the abdominal cavity (in 24 hours after intensive treatment);

APP_3 - perfusion pressure in the abdominal cavity (in 48 hours after intensive treatment);

$I\text{-}FABP_1$ - Intestinal fatty acid-binding protein (initial data);

$I\text{-}FABP_2$ - Intestinal fatty acid-binding protein (in 24 hours after intensive treatment);

$I\text{-}FABP_3$ - Intestinal fatty acid-binding protein (in 48 hours after intensive treatment).

This model showed how many times the patient's condition has changed during the corresponding treatment. Then the difference in the conditions of patients upon admission and after 48 hours can be described as follows: AGIR = (1-k) * 100%. By means of the variance analysis of the received results it is established that at coefficient $k < 1$ there was an improvement of the general condition of the patient and the patient was recommended to continue conservative treatment, when $k > 1$ its deterioration with the development of systemic disorders and it was recommended to supplement the treatment with minimally invasive interventions, depending on the type of development of local complications of the disease, wherein the spread of the initial indicators looked like as showed in Figure 7.

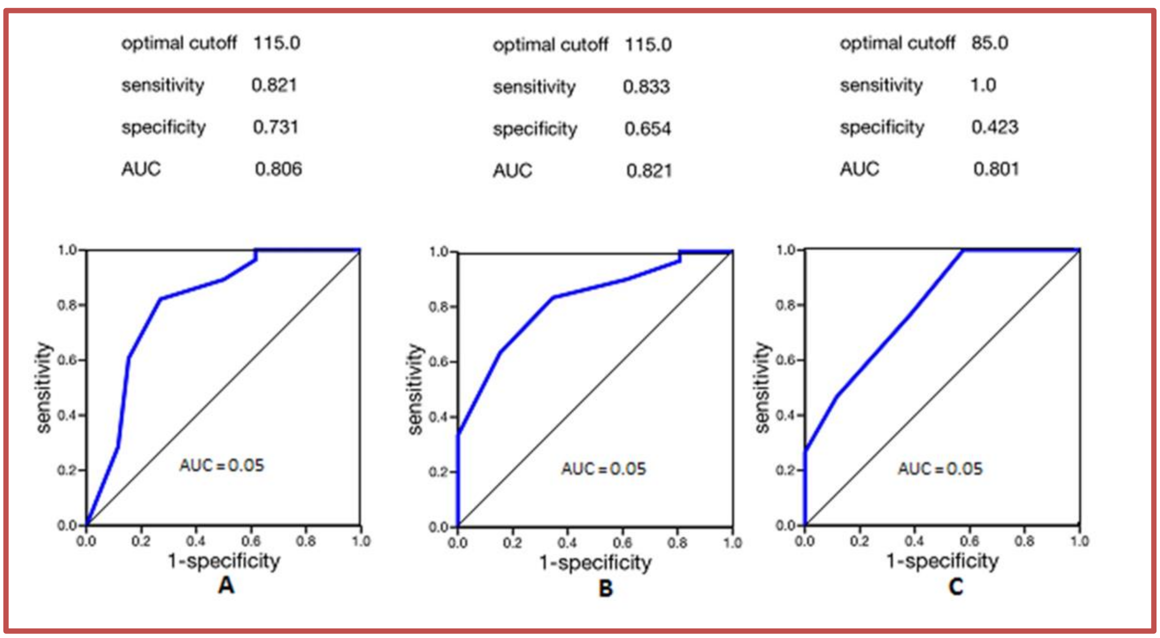

Figure 2 ROC curves of measured values systolic blood pressure in patients with AP before surgery (A), in 48 hours (B), and in survivors and in non-survivors patients with AP (C).

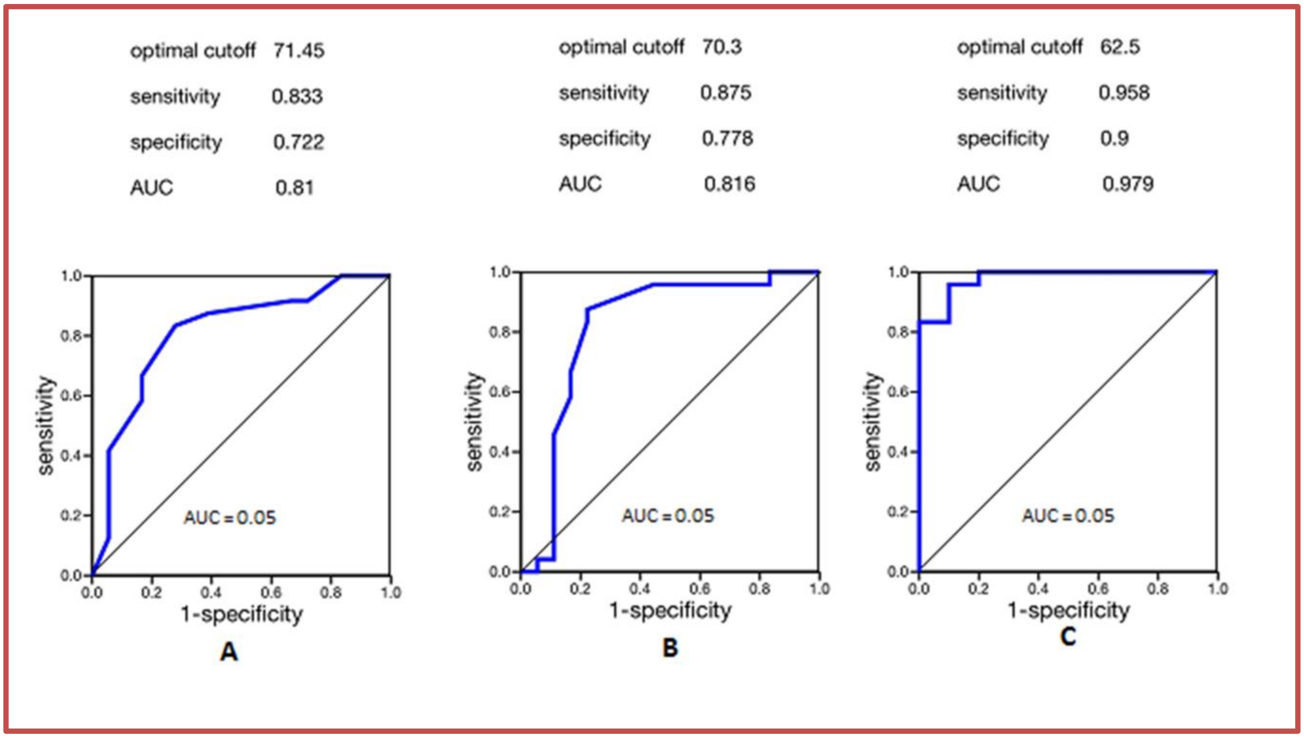

Figure 3 ROC curves of measured values abdominal perfusion pressure in patients with AP before surgery (A), in 48 hours (B), and in survivors and in non-survivors patients with AP (C).

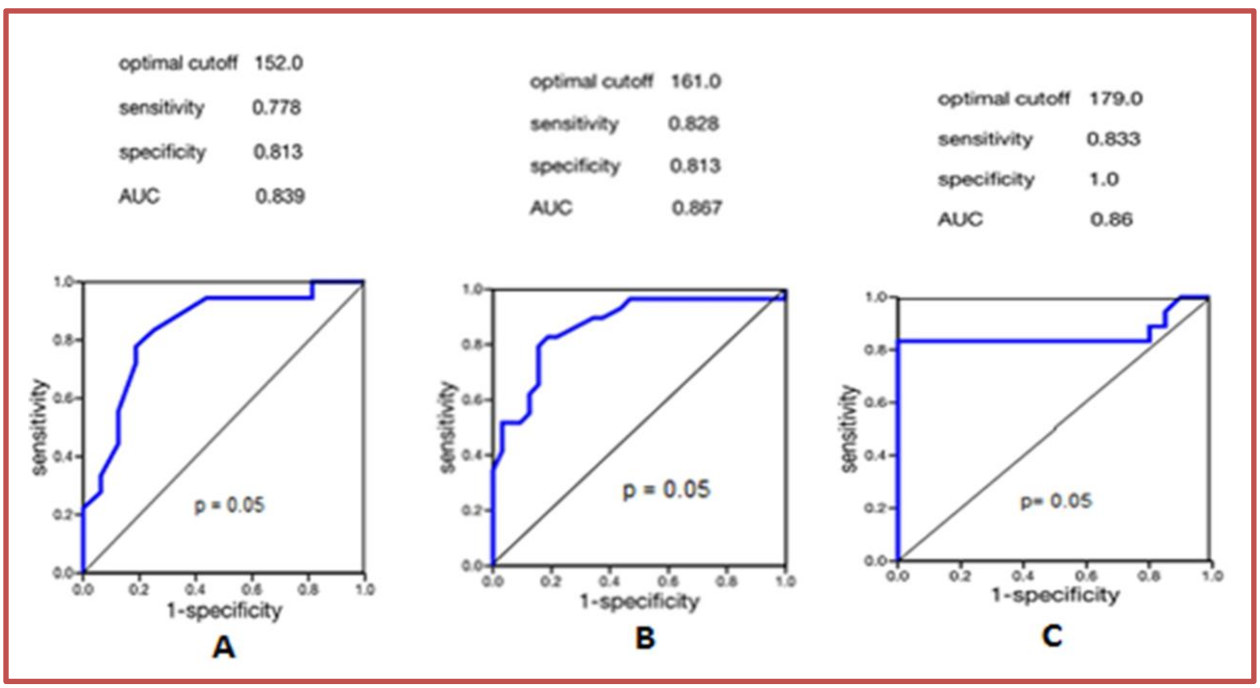

Figure 4 ROC curves of measured values C-reactive protein in patients with AP before surgery (A), in 48 hours (B), and in survivors and in non-survivors patients with AP (C).

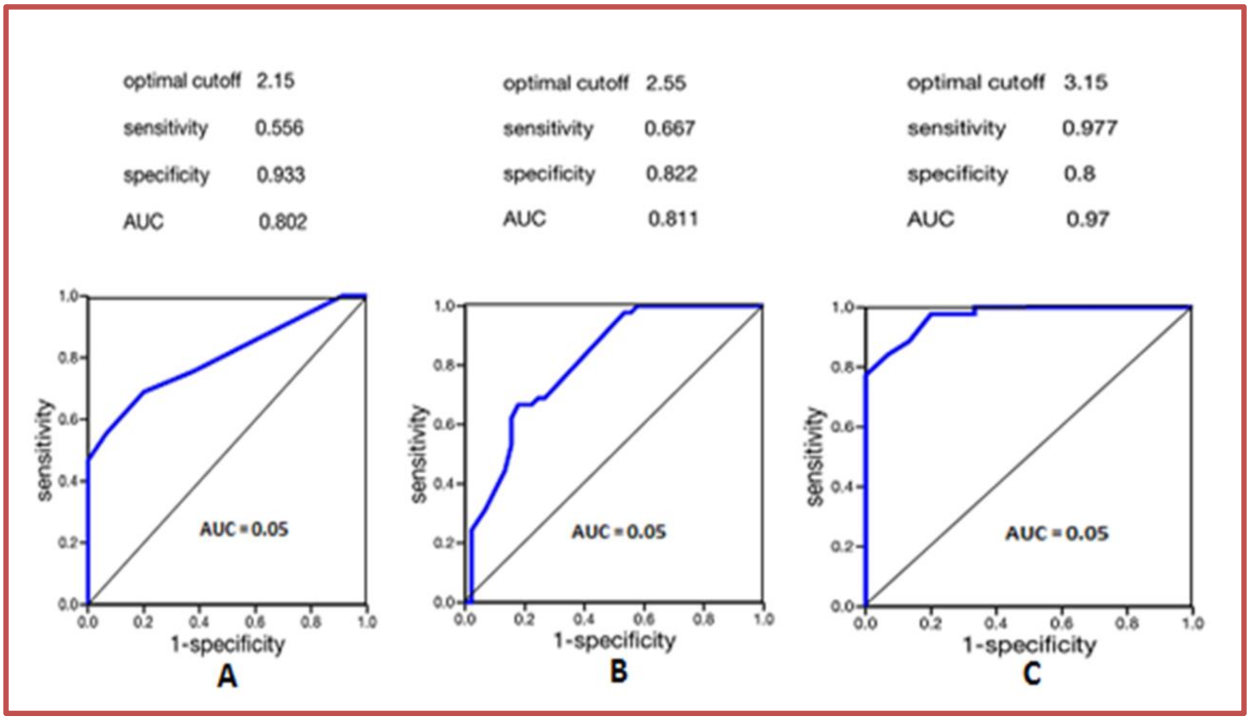

Figure 5 ROC curves of measured values Lactate in patients with AP before surgery (A), in 48 hours (B), and in survivors and in non-survivors patients with AP (C).

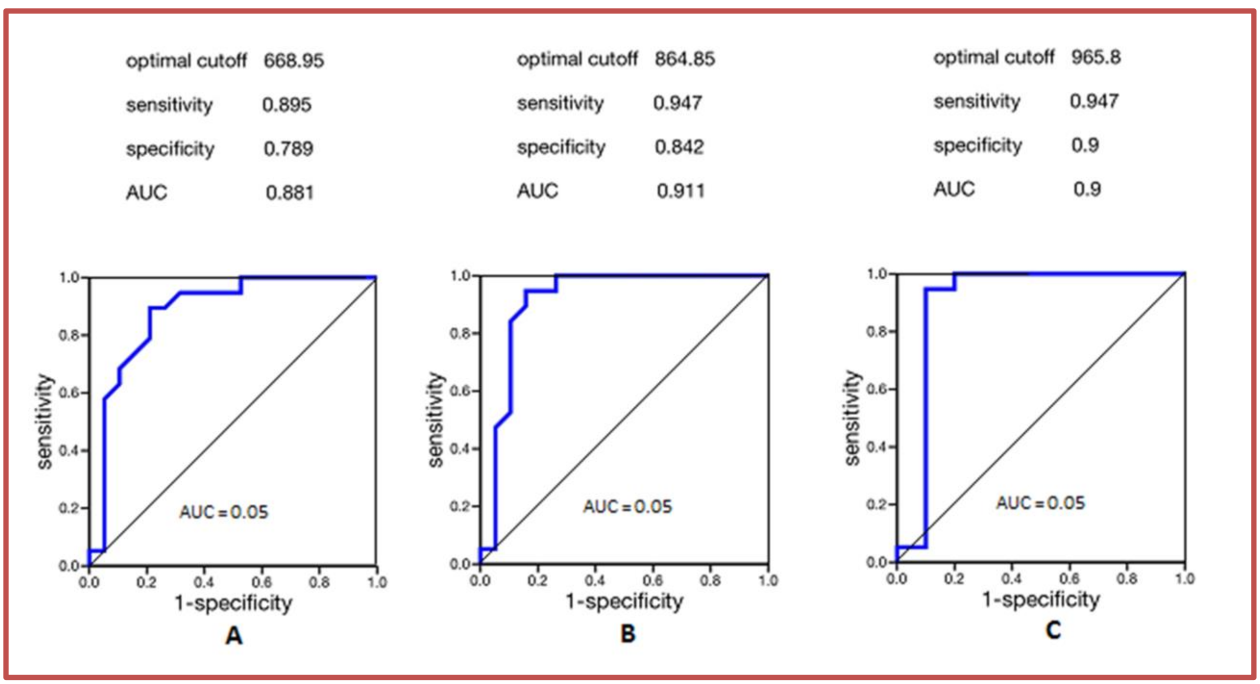

Figure 6 ROC curves of measured values I-FABP in patients with AP before surgery (A), in 48 hours (B), and in survivors and in non-survivors patients with AP (C).

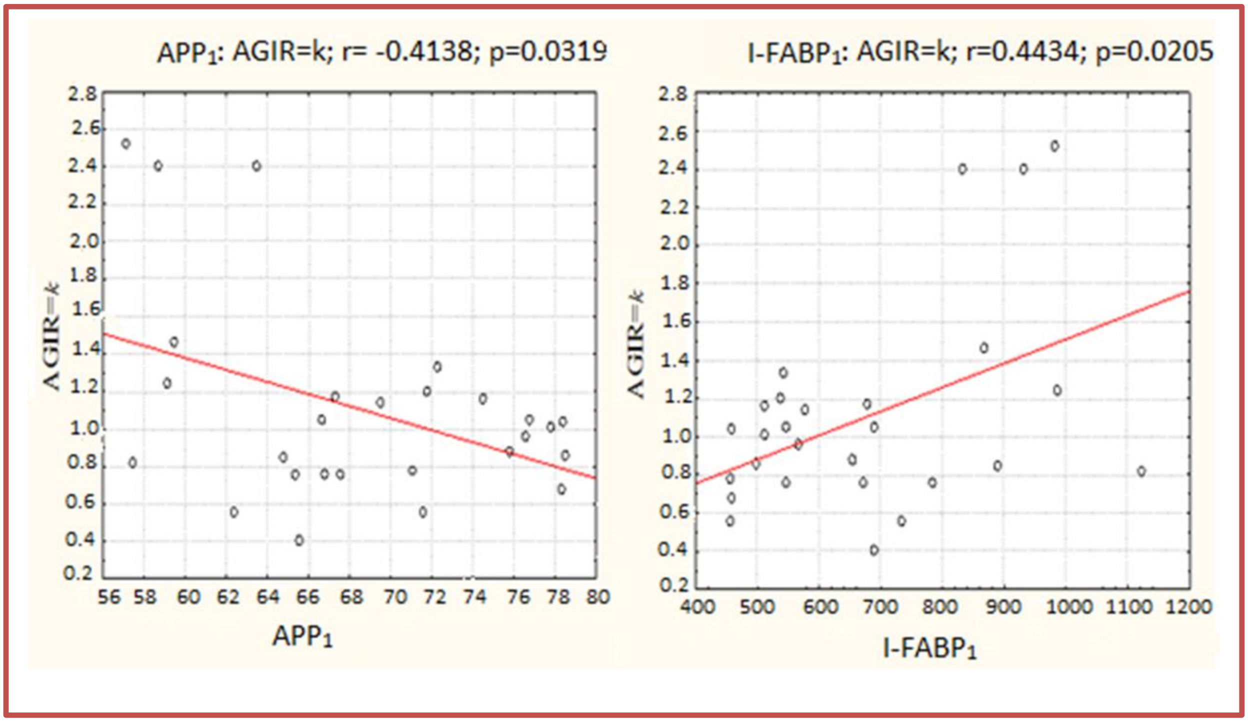

Figure 7 Graph of scattering of initial data and coefficient of severity of patients (AGIR) on levels of intestinal fatty acid-binding protein (I-FABP) and perfusion pressure (APP) in the abdominal cavity.

4. DISCUSSION

Understanding the pathophysiological essence of multiple dysfunctions of organs in AP as a result of the study showed the multifactorial nature of these critical processes that lead to damage to the cellular structures of organs and tissues. It is believed that some biomarkers, such as lactate, fatty acid binding protein (I-FABP), and others, can be used as possible markers to determine the severity of patients with severe infection, including severe acute pancreatitis, sepsis and septic shock (Kryvoruchko et al., 2019). It is known that hypoxia in critical patients enhances the production of vascular endothelial growth factor, which is a powerful activator of angiogenesis and is responsible for increasing capillary permeability and loss of capillary fluid, occurs due to the formation of factor-1α caused by hypoxia (Eltzschig & Carmeliet, 2011). In addition, hypoxia is one of the main causes of mitochondrial dysfunction in the body, when there is a decrease in the activity of mitochondrial chain enzymes, pathological activation of free radical oxidation and apoptosis, and as a consequence of reduced energy production, which is recently considered a key factor in systemic disorders (Green, 2010). Due to a significant increase in metabolism, which did not correspond to energy expenditure in terms of basic metabolism, tissue oxygen demand increases, and in the conditions of AS decreased blood circulation and arterial hypoxia is accompanied by tissue hypoxia, acidosis, increased blood lactate (Huet et al., 2011; Hunter, 2010).

The main finding of this study is that Intestinal fatty acid-binding protein (I-FABP), lactate, CRP, SBP and APP not only before surgery is superior in predicting SPI in comparison to commonly used markers such as APACHE-II, SOFA scores, and serum PCT, IL-6, but in 48 hours after ones. So, it was demonstrated that lactate (sensitivity 82.8%, specificity 81.3%, area under the ROC curve 0.867 before surgery) and C-reactive protein (sensitivity 74.3%, specificity 86.7% area under the ROC curve 0.85 preoperative) in assessing systolic blood pressure (sensitivity 93.8%, specificity 86.2%, area under the ROC curve 0.961 before surgery) and perfusion pressure in the abdominal cavity (sensitivity 76%, specificity 88%, area under the ROC curve 0.893 before surgery) and showed the significance of these indicators for predicting early mortality.

Many studies have confirmed that the level of IL-6 in the blood serum is an early prognostic factor for assessing the severity of the patient's condition (Krüttgen & Rose-John, 2012; Purushothaman et al., 2011). The studies have shown that increased concentration of this cytokine in the serum can be determined during various acute conditions: after major operations, severe burns, bacterial infections, donor kidney rejection, as well as severe AS. IL-6 is the main mediator of the synthesis of acute phase proteins (fibrinogen, haptoglobin and C-reactive protein), produced by mononuclear phagocytes and endothelial cells in response to stimulation of their TNFα and IL-1. However, in our study these facts were not confirmed: before surgery in patients with SPI level of IL-6 in the blood serum (AUC 0.601) had possessed a sensitivity 83.3% and a low specificity (37.5%). As well PCT is widely regarded as a highly sensitive biomarker of bacterial infection, offering general and emergency surgeons a key tool to aid in the management of surgical infections (Sartelli et al., 2021). Our data showed that PCT was not confirmed as a biomarker that can be used as a prognostic one: before surgery in patients with SPI, the PCT level in blood serum (AUC 0.59) had a sensitivity of 55.3% and a low specificity of 60.0% and after 48 hours this indicator had an AUC of 0.547 with a sensitivity of 26.7% and a specificity of 91.1%.

As is known, the intestine plays a central role in the pathogenesis of MOF in AP, when against the background of a defect of all parts of the immune system is the penetration of bacteria and their toxins through the intestinal mucosa (Vollmar et al., 1999). Hypoxia of the intestinal wall, activation of lipid peroxidation processes in the membrane structures of epitheliocytes, activation of the enzymatic system of xanthine oxidase, localized in the apex of the villi of the intestinal mucosa, as well as suppression of immune reactivity, leads to transient bacteria in the blood and lymphatic system, which then causes increased vascular spasm, and subsequently stable dilatation (Walley, 2011; Zimmerman et al., 1996). Intestinal insufficiency, indeed, becomes the "motor" of the thanatogenesis of the AP. Since there are many risk factors for mortality in AP (early MODS, the use of vasopressors, mechanical ventilation, surgical stress, the development of SPI and late MODS), in severe AP, vomiting, bloating, the development of dynamic intestinal obstruction, which becomes the "motor of MODS development" often appear both in the first and in the second period of the disease (Boyko et al., 2002). As you know, the digestive tract function is very complex; many researchers have tried to develop various assessment systems to assess its severity in the ICU.

The AGI score, proposed by the ESICM working group (Blaser et al., 2012), which includes abdominal signs and symptoms, IAP scores, and organ function, is considered an important indicator for assessing AT function in ICU patients. This classification is now classical and accepted by various medical societies. The results obtained in this study showed that the AGI index was from 1 to 4 degrees of severity at admission to the hospital, and after 48 hours of intensive treatment. At the same time, the presence of statistically significant differences according to the Wilcoxon and Spearman criteria for assessing APACHE II, the degree of AGI, APP and I-FABP at admission and after 48 hours of intensive care was revealed. Also, correlations were established between the severity index of AGI patients on the APACHE II scale and I-FABP after 48 hours of complex treatment with AP, and the level of I-FABP in blood serum had a good predictive value for assessing damage to the digestive tract. Understanding the pathophysiological basis of PT dysfunction in OP as a result of previous studies has shown that this may be the result of the action of many factors that lead to damage to enterocytes, and an objective biomarker of enterocyte damage, which is I-FABP, can be used to predict the consequences of a number of critical conditions: acute decompensated heart failure and cardiac arrest (Kitai et al., 2017), septic shock and severe acute pancreatitis (Grimaldi et al., 2013; Sekino et al., 2017).

Despite the encouraging statistical data we obtained and intragroup correlations between the studied indicators in patients with AP, the subsequent assessment of the construction of models for assessing the severity of the patient's condition, the degree of damage to the digestive tract using significant indicators and the assessment of the adequacy of comparisons and the accuracy of the quality of prognosis by analyzing the curves of operational characteristics found that the severity of patients' condition can be predicted by the level of APP before surgery, since the APACHE II and SOFA scores showed their limitations before surgery. At the same time, the level of I-FABP in the blood serum correlated well with the degree of AGI and the severity of patients, which have made it possible to create a prognostic model taking into account the preliminary determination of these parameters.

It is well known that rapid diagnosis and effective treatment of SPI are critical for this patient population and are based on 1) minimal invasiveness, timing of surgery and decision making; 2) predicting systemic disorders before and after surgery; 3) postoperative treatment. Over the past three decades, the management of these patients has undergone a change using two basic principles such as "source control" and "damage control", using a variety of sophisticated and highly accurate non-invasive imaging techniques available to the surgeon and using more effectivelly a step up approach in treatment of patients. The mortality rate of patients with SPI, which is usually associated with septic shock and MOF, is currently high. In our opinion, the use of early diagnosis, the choice of appropriate surgical methods to identify and eliminate the source of infection, and individual treatment of complications after surgery was factors that reduce patient mortality. This study showed that the prognosis of treatment of patients with AP and SPI is most suitable for assessing postoperative complications and mortality, since the proposed mathematical model allow predicting the development of complications and mortality.

5. CONCLUSION

Development of secondary pancreatic infection in patients with acute pancreatitis is a common clinical problem that is associated with longer hospital stay and may be characterized by an increased frequency of complications, including increased mortality. So far, no ideal markers have been found for these patients. Nevertheless, previous study based on evaluate different scores of severity and inflammation-related biomarkers that are most often used for prognosis in these patients according to modern literature, seems to be the closest to the aim of discovering effective markers. We share the point of view of many researchers that the use of a set of tests, rather than a single biomarker, brings us closer to the discovery of a test, or rather a set of markers, ideally suited for the early diagnosis of early mortality in both phases of acute pancreatitis. However, this claim requires further confirmation in clinical trials.

Compliance with ethical standards

The work has cleared by the Ethics Committee of Kharkiv National Medical University, Ukraine (the protocol №9, Desemder, 12, 2020).

Competing interests

The authors declare that they have no competing interests.

Informed consent process

Informed consent was obtained from all participants included in the study.

Contribution of the authors

All authors have contributed equally to this work. All authors have read and approved the final manuscript. All authors have agreed to publish this manuscript.

Kryvoruchko I.A: designed the study, analyzed, wrote the manuscript.

Sykal M.O: designed the study, collected, analyzed.

Yevtushenko O.V: analyzed and interpreted data, and drafted the manuscript.

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Data and materials availability

All data associated with this study are present in the paper.

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