ORIGINAL ARTICLE

CONTENTS

Markers for predicting the severity of acute pancreatitis

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ABSTRACT

Aim: To identify markers for predicting the severity of acute pancreatitis and the possible development of pancreatic necrosis.

Materials and Methods: Prospective analysis of 81 patients with moderate and severe acute pancreatitis while performing correlation analysis, building a logistic regression model.

Results: A direct correlation of medium strength between sFGL2 and the following parameters was found D-dimer (R=0.47 (p<0.001)), C-reactive protein (R=0.3 (p=0.03)), intra-abdominal pressure (R=0.54 (p<0.0001)). It was discovered that such indicators as: BISAP score (OR=1.62 95%CI 0.99-2.66) p=0.05, sFGL2 (OR=1.01 95%CI 1.0-1.05) p=0.007, CRP (OR=1.01 95%CI 1.0-1.01) p=0.02, D-dimer (OR=2.59 95%CI 1.57-4.26) p=0.0002, intra-abdominal pressure (OR=195 95%CI 1, 39-2.72) p=0.0001 allow to predict the progression of necrotic changes in the pancreatic tissue and retroperitoneal space. And such indicators as: BISAP scale (OR=2.19 95%CI 1.33-3.59) p=0.002, sFGL2 (OR=1.01 95%CI 1.0-1.1) p=0.0002, CRP (OR=1.02 95%CI 1.01-1.02) p<0.0001, D-dimer (OR=1.99 95%CI 1.4-2.83) p=0.0001, intra-abdominal pressure (OR=2.36 95%CI 1.59-3.5) p<0.0001) may play a role in predicting worsening of acute pancreatitis.

Conclusions: It has been revealed that elevated levels of sFGL2, D-dimer and intra-abdominal pressure can predict the progression of necrotic changes in the pancreatic tissue and retroperitoneal space. And such indicators as the BISAP score, sFGL2, CRP, D-dimer and intra-abdominal pressure may play a role in predicting the deterioration of acute pancreatitis.

KEY WORDS: severe acute pancreatitis, soluble fibrinogen-like protein 2, D-dimer, intra-abdominal pressure, C-reactive protein

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INTRODUCTION

Acute pancreatitis is an acute aseptic inflammation of the pancreas of a demarcation nature, which is based on the processes of pancreatic necrosis and fermental autoaggression with further development of necrosis of the gland and parapancreatic tissue, degeneration of the gland and parapancreatic space and possible addition of secondary infection.

According to the review of global epidemiology, the cumulative incidence of acute pancreatitis is 34 cases per 100,000 people in the general population per year with 1.16 deaths [1]. Mortality among patients with persistent organ failure and pancreatic necrosis can reach 30-40% [2].

Studies have shown that apart from the autodigestion of pancreatic parenchyma by pancreatic enzymes, ischemia, occurring because of pancreatic edema and leading to the development of acute necrotizing pancreatitis, also plays an important role [3]. Moreover, microcirculatory disorders are present in the pancreas and extrapancreatic organs. Clinical studies have revealed that fibrinogen degradation products (FDP) in blood plasma are significantly higher in patients with acute pancreatitis compared to healthy individuals, and higher levels of FDP are associated with disease severity [4]. Furthermore, early complications of severe acute pancreatitis associated with blood supply disorders include portosplenomesentric venous thrombosis, which, according to the literature, occurs in approximately 17.86% of patients [5]. These data suggest the need for prescribing anticoagulant and antithrombotic therapy in the treatment strategy for severe acute pancreatitis, in accordance with the 2019 WSES treatment protocols [6].

A substantial number of biochemical markers that can be predictors of complications of acute severe necrotising pancreatitis are still being studied. More specifically, they are IL-6, IL-8, polymorphonuclear elastase, TNF-alpha, trypsin-alpha-1 protease complex, hepsidin, copeptin, ISAM-1, resistin, presipsin, and others. However, most of them are expensive and their indicators are elevated only in the first 24-48 hours after the onset of the disease, so they are not used in daily clinical practice.

One of the most promising biochemical markers is fibrinogen-like protein 2 (FGL2), which can break

Table 1. Patients characteristics

Characteristic	Total number of patients (n=81)
Age, years	49 (39-68)
Men, n (%)	45 (55,5%)
Women, n (%)	36 (44,5%)
BMI, kg/m2	28,34 (±4,256)
Comorbitities, n (%)	31

down prothrombin to thrombin and results in fibrin deposition. FGL2 leads to histopathological lesions and ischemic damage through 'immune coagulation', fibrin deposition and microthrombosis. Microvascular disorders are caused by microthrombi that are activated and formed by the action of FGL2. FGL2 can be used as a disease biomarker and therapeutic target [7].

AIM

To determine the markers for predicting the severity of acute pancreatitis and possible development of subsequent pancreatic necrosis.

MATERIALS AND METHODS

The study design was a prospective analysis of 81 patients with acute pancreatitis, who underwent enzyme-linked immunosorbent assay of serum for determining FGL2, held at the clinical base of the Department of General Surgery No. 1 of the Bogomolets National Medical University in the period from 2022 to 2024.

The given study was conducted within the framework of the research work "Development and improvement of diagnostic methods, prognosis and surgical treatment of complications of hepatopancreatoduodenal region diseases", 2023-2025 (state registration number 0123U100953). Permission to conduct the study was approved by the expert decision of the Bioethical Commission dated 20.06.2022, protocol № 159. All study procedures were carried out in line with the current legislation of Ukraine on ethics, the principles of Good Clinical Practice (ICH 6CP), and the recommendations of the Helsinki Declaration of 2013.

The sample included 81 patients, with 45 (55.5%) men and 36 (44.5%) women respectfully. The average age of the patients was 49 (39-68 Q1-Q3) years. The average body mass index (BMI) was 28.34 (±4,256) (Table 1).

All patients with severe acute pancreatitis of nutritional etiology received anticoagulant therapy in a standard dosage from the second day of hospitalisation. Patients, requiring endoscopic papillosphincterotomy, had anticoagulant therapy started 12 hours after the intervention

The moderate severity of the disease was determined in 41 (50.6%) patients, while severe acute pancreatitis was specified in 40 (49.3%) patients. Patient characteristics are presented in Table 2. The Revised Atlanta Classification for Acute Pancreatitis 2012 was used to determine the severity of pancreatitis [8]. The presence of pancreatic tissue necrosis was assessed based on computed tomography with intravenous contrast (CTSI Baltazar), intraoperatively and by autopsy. The clinical and morphological classification of acute severe pancreatitis was used to evaluate intraoperative and autopsy materials [9]. Pancreatic necrosis was diagnosed in 32 (39.5%) patients. Among them, there were 4 (4.9%) patients with total transmural necrosis and 28 (34.5%) with superficial subtotal and focal forms of necrosis.

The groups differed statistically significantly in the levels of the following indicators: D-dimer, C-reactive protein, bilirubin, gamma-glutamine transpeptidase, alkaline phosphatase, creatinine, urea, fibrinogen, and intra-abdominal pressure.

Blood samples were taken 15-24 hours after hospitalisation. The obtained serum was evaluated for the presence of lipemia. Repeated sampling was performed 48 hours after hospitalisation.

According to the instructions provided, after serum collection, the latter was stored at -20°C prior to the analysis.

Serum was analysed using an enzyme-linked immunosorbent assay Human FGL-2 ELISA Kit, code EH3064.

Inclusion criteria: patients with moderate to severe acute pancreatitis, with or without pancreatic necrosis, without any medical or social contraindications, patients over 18 years of age, patient consent to participate in the study and subsequent outpatient monitoring.

Non-inclusion criteria: patients with COVID-19 (severe course), chronic fibrotic degenerative pancreatitis in the acute stage (presence of pseudocysts, virsungoectasia and virsungolithiasis), pancreatic surgery; presence of oncological pathology; long-term use of high doses of anticoagulants and antiplatelet agents before the onset of the disease.

Exclusion criteria: patients with mild acute pancreatitis, patient's refusal of diagnosis and treatment at any stage of the study, patient's death not related to the underlying disease, as well as patients with hypertriglyceridemic acute pancreatitis.

Endpoints of the study:

- To identify factors that predict the deterioration of acute pancreatitis and development of pancreatic necrosis.

Table 2. General characteristics of patients with acute pancreatitis in the study groups

Indicator	Group of patients with moderate acute pancreatitis (MAP) (n=41)	Group of patients with severe acute pancreatitis (SAP) (n=40)	P-value
Age	44,5 (38-58)*	53 (43-72)	0,156
Sex (men/women)	16/15	19/11	
BMI (kg/м2)	27,83 (±4,752)	28,83 (±3,708)	0,335
Intraabdominal pressure (mm Hg)	5,3(4,6-6,1)	10,75 (8,8-11,8)	<0,001
Amylase (U/l)	1449,5 (728-2137)	1676,5 (940-2503)	0,405
Lipase (U/l)	1502 (±979,8)	1753 (±1040)	0,36
Bilirubin (μmol/l)	20,1 (15,1-28,7)	26,65 (15-52,8)	0,041
Alanine aminotransferase (U/l)	84,35 (34,9-263,9)	105,3 (73,9-327)	0,349
Aspartate aminotransferase (U/l)	134,5 (53,2-324,8)	180,35 (67-348,2)	0,658
C-reactive protein (mg/l)	105 (37,78-150)	250 (205-303,33)	<0,001
Gamma-glutamine transpeptidase (U/l)	65,5 (30-110)	182 (120-494)	0,018
Alkaline phosphatase (U/l)	88,5 (57-100)	133 (106-180)	0,018
Glucose (mmol/l)	6,97 (6,41-7,7)	6,62 (5,86-9,72)	0,371
Creatinin (μmol/l)	84 (75-95)	101 (92-131)	0,006
Blood urea nitrogen (mmol/l)	5,9 (4,5-7,9)	7,45 (6,3-10,5)	0,022
Prothrombin index (%)	96,4 (90-109,2)	92,2 (85,6-101,9)	0,393
Fibrinogen (g\l)	5,63 (4,5-7)	7,14 (6-12)	0,015
International normalized ratio	1,016 (±0,136)	1,05 (±0,1659)	0,36
D-dimer (pg/ml)	0,5 (0,4-1)	4 (2,88-5)	<0,001
Hemoglobin (g/l)	148,4 (±16,06)	157,9 (±21,27)	0,084
White blood cells (109/l)	11,95 (10,2-14,4)	13,5 (9,4-16,8)	0,109
Platelets (109/l)	189 (141-237)	167,5 (138-212)	0,334

Note:* - median (Q1-Q3)

- To conduct a correlation analysis between the level of sFGL2 and other biochemical parameters.

Statistical software used in this study included MedStat, EZR (R-STATISTICS). The Shapiro-Wilk test was used to assess the normality of continuous variables. Categorical data were presented as numbers (percentages). All continuous variables were presented as median (interquartile range [Q1-Q3]) and standard deviation. The Mann-Whitney U test was performed to compare continuous variables in the two given groups. Bivariate correlation was analysed using the Spearman correlation test. A logistic regression model was performed to determine the effect of sFGL2 and other biochemical parameters (C-reactive protein, D-dimer, lipase, fibrinogen) and BISAP on the severity of acute pancreatitis. The independent association was determined by the odds ratio (OR) and 95% confidence interval (CI). A ROC curve was constructed and the optimal cut-off values for serum levels of sFGL 2 were selected, while the corresponding sensitivity and specificity values were obtained. The p-value < 0.05 was considered statistically significant.

RESULTS

The Spearman's rank correlation method revealed the presence of a correlation of average strength R=0.47 (p<0.001) between sFGL2 and D-dimer, whereas an increase in D-dimer was accompanied by an average increase in sFGL2 (Fig 1).

A direct correlation of average strength R=0.3 (p=0.03) was found while analysing the relationship between CRP and sFGL2. On average, an increase in sFGL2 is accompanied by an increase in CRP (Fig. 2).

A direct correlation of average strength R=0.54 (p<0.0001) was found while analysing the relationship between intra-abdominal pressure and sFGL2. On average, an increase in intra-abdominal pressure was accompanied by an increase in sFGL2 (Fig. 3).

There was no correlation revealed between sFGL2 and such indicators as lipase (R=0.07, p=0.62), fibrinogen (R=0.2, p=0.15), BISAP (R=0.2, p=0.15).

The method of building logistic regression models on the total cohort of patients was used in order to analyse the development of pancreatic necrosis and the severity of acute pancreatitis. The univariate model was built

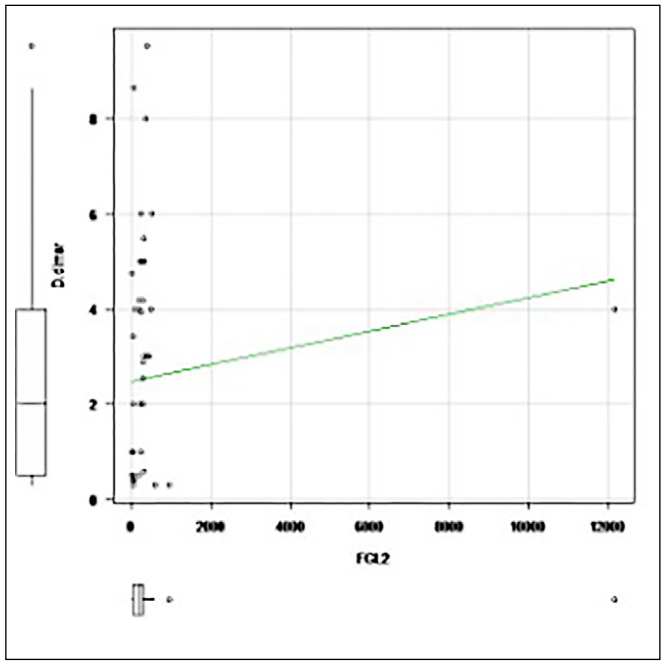

Fig. 1. Correlation analysis of the relationship between sFGL2 and D-dimer in patients with acute pancreatitis.

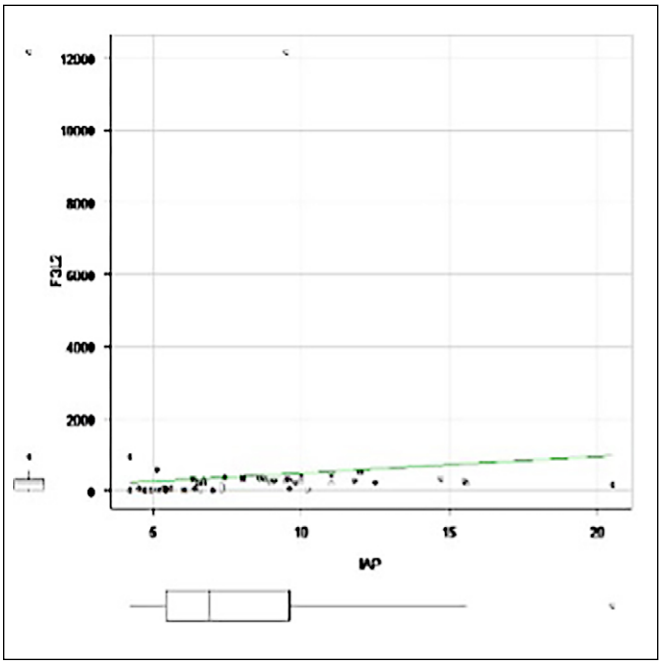

Fig. 3. Correlation analysis of the relationship between sFGL2 and intra-abdominal pressure in patients with acute pancreatitis.

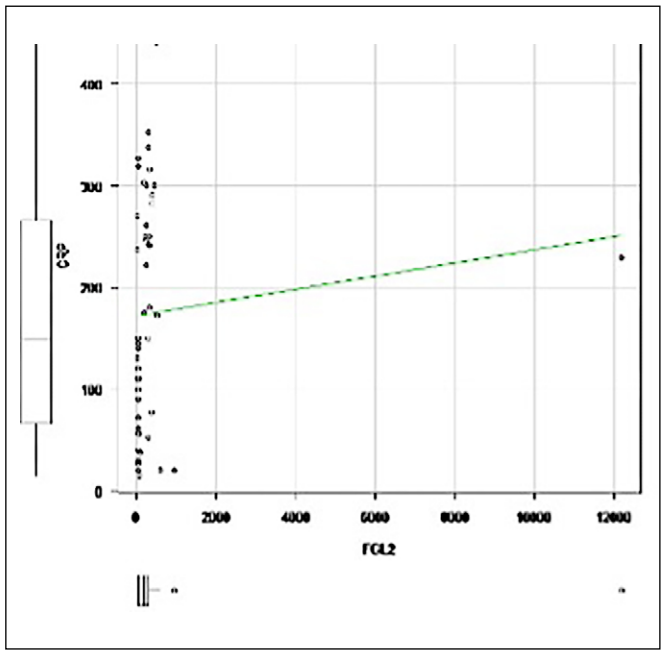

Fig. 2. Correlation analysis of the relationship between sFGL2 and C-reactive protein in patients with acute pancreatitis.

considering the following factors: body mass index, BISAP, intra-abdominal pressure, lipase, C-reactive protein, fibrinogen, soluble fibrinogen-like protein 2, international normalisation ratio, prothrombin index, D-dimer, platelets, leukocytes. The risk of pancreatic necrosis was found to be associated with: BISAP score (OR=1.62 95%CI 0.99-2.66) p=0.05, sFGL2 (OR=1.01 95%CI 1.0-1.05) p=0.007, CRP (OR=1.01 95%CI 1.0-1.01) p=0, 02, D-dimer (OR=2.59 95%CI 1.57-4.26) p=0.0002, intra-abdominal pressure (OR=195 95%CI 1.39-2.72) p=0.0001.

A logistic model for predicting the risk of pancreatic necrosis was built based on the selected factor features (AUC=0.93 95%CI 0.87-1.0) p<0.05, which is evidence of the adequacy and very good quality of the model.

It was found that the risk of pancreatic necrosis increases with increased levels of sFGL2 (OR=1.96 95%CI 1.27-3.03) p=0.002, D-dimer (OR=2.57 95%CI 1.45-4.56) p=0.01 and intra-abdominal pressure (OR=172 95%CI 1.2-2.46) p=0.003.

Using ROC-analysis, the cut-off value of D-dimer, at which pancreatic necrosis was most often diagnosed, was determined with cut-off value = 2.54 μg/ml AUC = 0.90 (95% CI 0.83-0.98) (sensitivity 80.6% (95% CI 64.2%-94.2%), specificity 91.7% (95% CI 62.5%-92.5%), PPV 80% (95% CI 61.4-92.3%) NPV 83.3% (95% CI 65.3%-94.4%)) (Fig. 4).

Using ROC-analysis, the cut-off value of sFGL2, at which pancreatic necrosis was most often diagnosed, was determined with the cut-off value = 80pg/ml AUC = 0.85 (95% CI 0.75-0.95) (sensitivity 69.4% (95% CI 44.9%-70.9%), specificity 100% (95% CI 80.4%-100%), PPV 91.7% (95% CI 81.6-97.2%) NPV 83.3% (95% CI 65.3%-94.4%)) (Fig. 5).

Using ROC-analysis, the threshold value of intra-abdominal pressure at which pancreatic necrosis was most often diagnosed was determined, cut-off value = 8.5 mmHg. AUC = 0.9 (95% CI 0.82-0.98) (sensitivity 83.3% (95% CI 73.4%-92.9%), specificity 87.5% (95% CI 70.8%-97.6%), PPV 80% (95% CI 61.4-92.3%) NPV 90% (95% CI 73.5%-97.9%)) (Fig. 6).

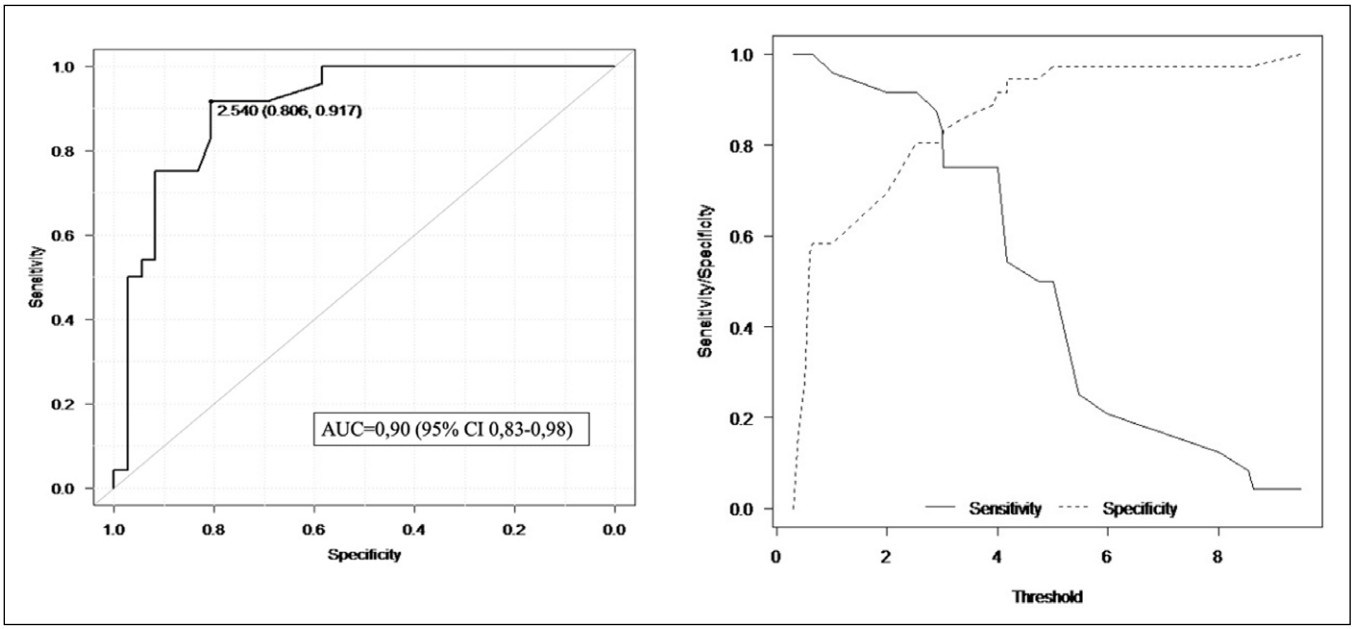

Fig. 4. ROC curve of the test for predicting the risk of necrosis depending on the level of D-dimer.

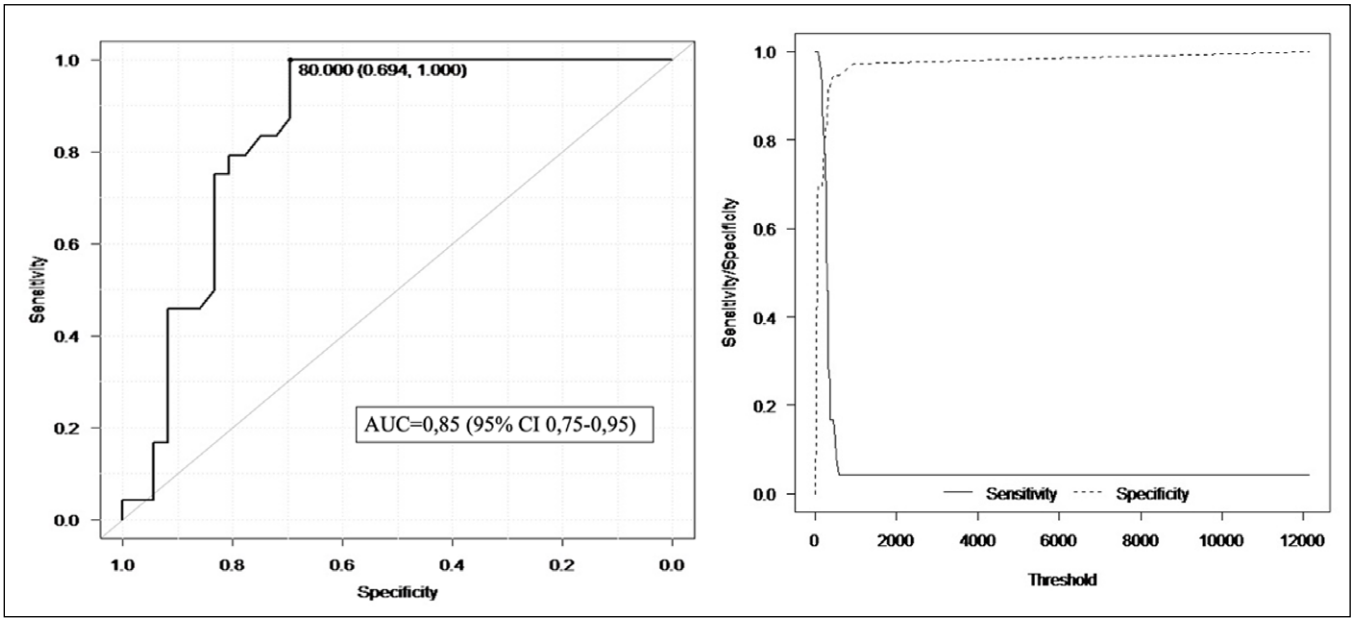

Fig. 5. ROC curve of the test for predicting the risk of necrosis depending on the level of sFGL2.

When building a univariate model, the following factors were considered: body mass index, BISAP, intra-abdominal pressure, lipase, C-reactive protein, fibrinogen, soluble fibrinogen-like protein 2, international normalisation ratio, prothrombin index, D-dimer, platelets, leukocytes. It has been found that the severity of acute pancreatitis is associated with: BISAP scale (OR=2.19 95%CI 1.33-3.59) p=0.002, sFGL2 (OR=1.01 95%CI 1.0-1.1) p=0.0002, CRP (OR=1.02 95%CI 1.01-1.02) p<0, 0001, D-dimer (OR=1.99 95%CI 1.4-2.83) p=0.0001, intra-abdominal pressure (OR=2.36 95%CI 1.59-3.5) p<0.0001.

In multivariate analysis with the evaluation of statistically significant factors, risk factors for severe acute pancreatitis were identified (AUC=0.97 95%CI 0.94-1.0) p<0.05.

It was revealed that the risk of severe acute pancreatitis increases with the elevation of sFGL2 (OR=1.01 95%CI 1, 0-1.01) p=0.006, CRP (OR=1.02 95%CI 1.0-1.03) p=0.005, D-dimer (OR=1.86 95%CI 1.11-3.1) p=0.02, intra-abdominal pressure (OR=1.88 95%CI 1.16-3.05) p=0.01.

Using ROC analysis, we determined the threshold value of D-dimer, at which the risk of severe acute pancreatitis increases. The Cut-off value = 0.65 μg/ml AUC = 0.88 (95% CI 0.79-0.97) (sensitivity 66.7% (95% CI 51.6%-76.9%), specificity 96.7% (95% CI 76.2%-99%),

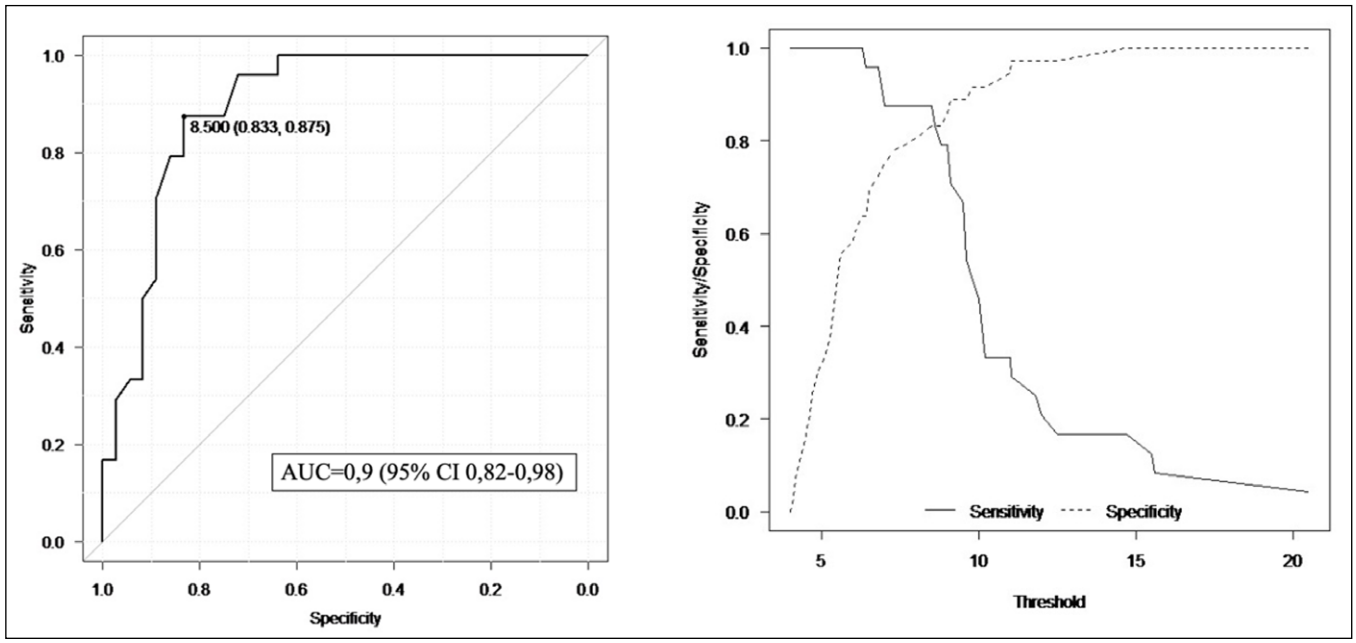

Fig. 6. ROC curve of the test for predicting the risk of necrosis depending on the level of intra-abdominal pressure.

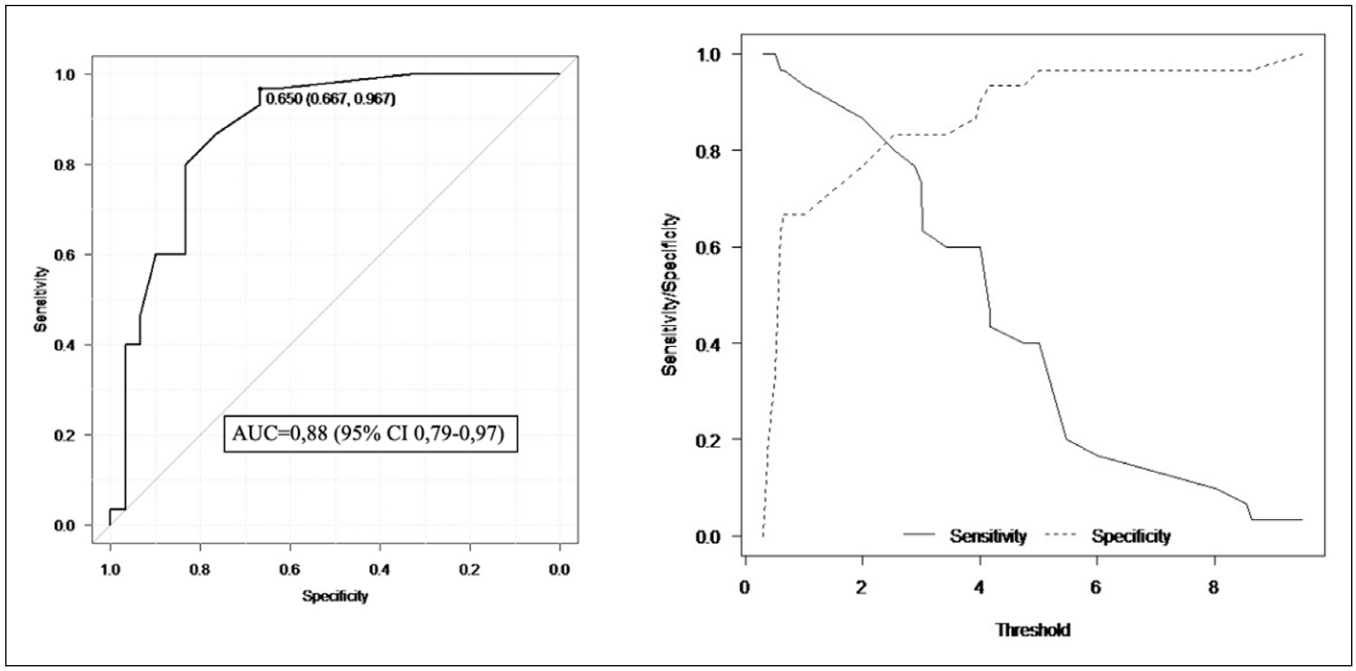

Fig. 7. ROC curve of the test for predicting the severity depending on the level of D-dimer.

PPV 96.7% (95% CI 82.8-100%) NPV 66.7% (95% CI 47.2%-82.7%)) (Fig. 7).

The threshold value of CRP, at which the risk of severe acute pancreatitis increases, was determined using ROC analysis. Cut-off value = 172 mg/l AUC = 0.86 (95% CI 0.77-0.96) (sensitivity 80% (95% CI 61.4%-92.3%), specificity 86.2% (95% CI 69.3%-96.2%), PPV 81.2% (95% CI 63.6-92.8%), NPV 85.7% (95% CI 67.3%-96%)) (Fig. 8).

The threshold value of sFGL2, at which the risk of severe acute pancreatitis increases, was determined Using ROC analysis. Cut-off value= 145 pg/ml AUC=0.91 (95% CI 0.81-1) (sensitivity 86.7% (95% CI 69.3%-96.2%), specificity 100% (95% CI 81%-100%), PPV 93.3% (95% CI 83.8-98.2%), NPV 88.2% (95% CI 72.5%-96.7%)) (Fig. 9).

ROC analysis was used to determine the threshold value of intra-abdominal pressure at which the risk of severe acute pancreatitis increases. Cut-off value = 7.2 mmHg. AUC=0.94 (95% CI 0.88-1) (sensitivity 86.7% (95% CI 69.3%-96.2%), specificity 100% (95% CI 83.3%-100%), PPV 88.2% (95% CI 72.5-96.7%), NPV 93.3% (95% CI 83.8%-98.2%)) (Fig. 10).

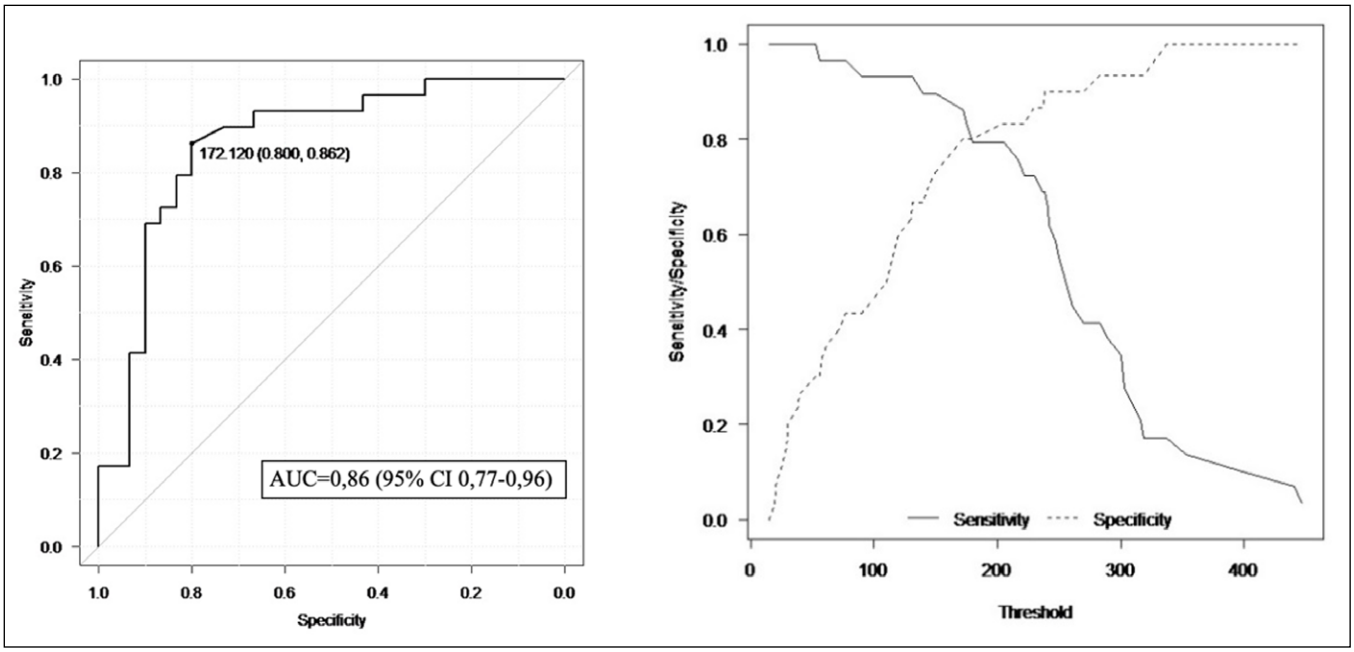

Fig. 8. ROC curve of the test for predicting the degree of severity depending on the level of C-reactive protein.

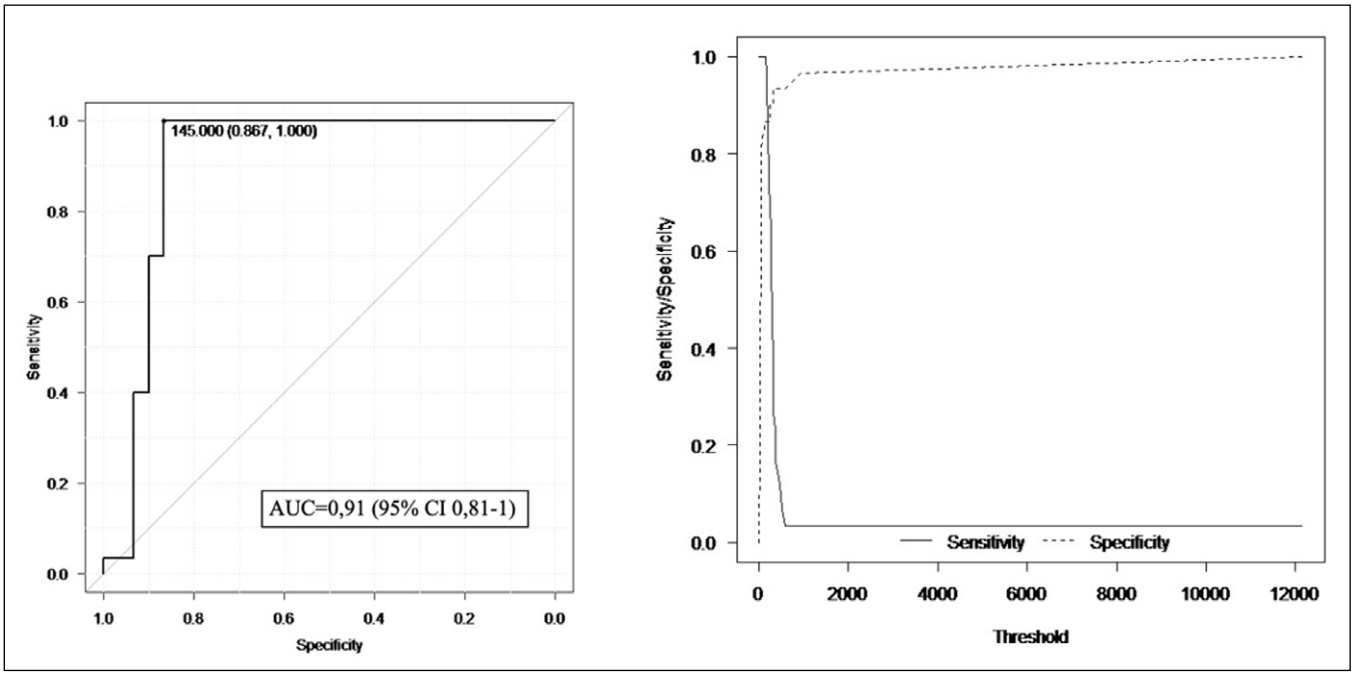

Fig. 9. ROC curve of the test for predicting the severity of the disease depending on the level of sFGL2.

DISCUSSION

Severe acute pancreatitis is a rapidly progressive disease with a high mortality rate; however, the underlying pathophysiological mechanisms have not been fully defined yet. Nowadays, the leading pathogenesis of severe acute pancreatitis is associated with microcirculatory and coagulation disorders, the development of a systemic inflammatory response syndrome and multiple organ failure. Inflammatory mediators, such as interleukin (IL)-6, IL-1β and tumour necrosis factor α (TNF-α), released during acute inflammatory reactions, are not only involved in the inflammatory process, but may also be responsible for systemic activation of haemostasis in patients with severe acute pancreatitis. It is believed that intravascular coagulation and thromboembolism play an important role in the pathogenesis of severe acute pancreatitis and are associated with its severity.

Acute inflammatory events during disease progression can lead to dysregulation of the coagulation cascade. In patients with severe acute pancreatitis,

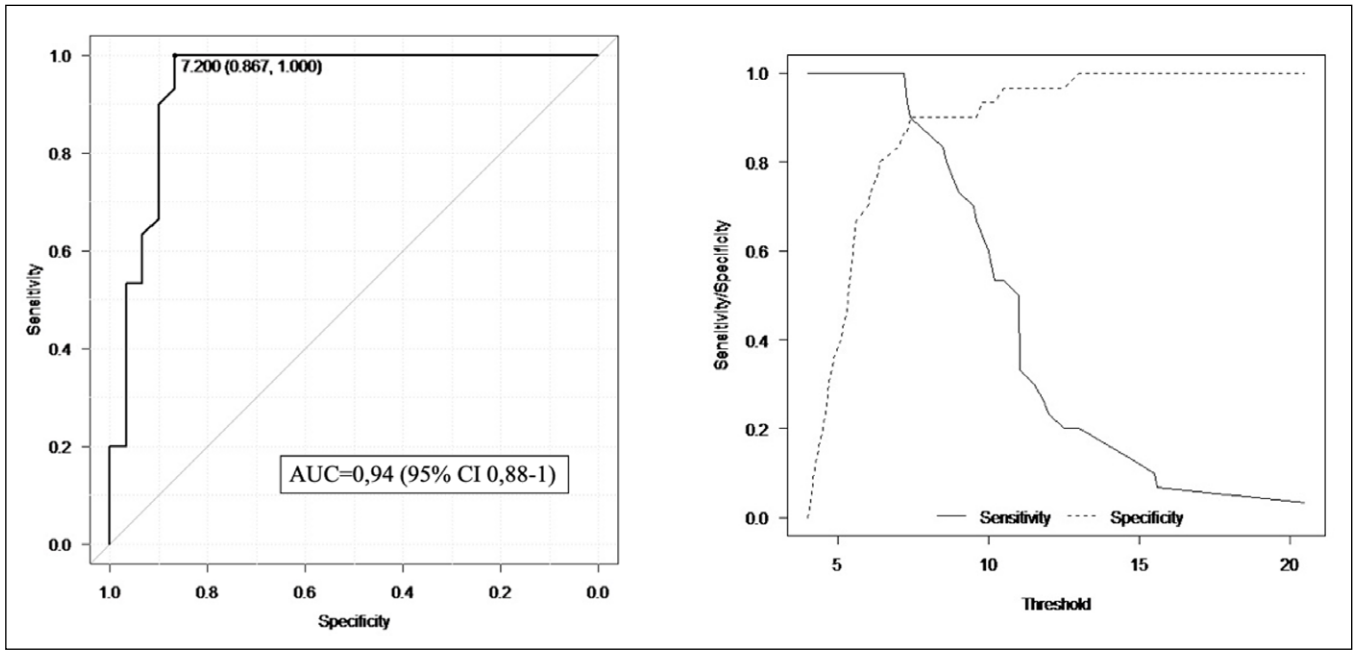

Fig. 10. ROC curve of the test for predicting the degree of severity depending on the level of intra-abdominal pressure.

thrombin and platelets are deposited not only in the local blood vessels of the pancreas, but also in the connective tissue and intercellular spaces. Studies have shown that such biochemical parameters as prothrombin time, D-dimer and coagulation time may have prognostic value, and direct anticoagulant therapy has been shown to be useful in the treatment of acute severe pancreatitis. These findings suggest that coagulation and inflammation in severe acute pancreatitis are interrelated, and thus microthrombosis plays a crucial role in the pathogenesis of the disease. Yet, the exact pathophysiological mechanism remains unknown [10].

Fibrinogen-like protein 2 (FGL2) is a multifunctional immunomodulatory protein that plays an important role in the normal physiology and pathogenesis of various diseases, including infectious, autoimmune and tumor genesis [7].

FGL2 is a new member of the fibrinogen-related protein superfamily, which includes fibrinogen, tenascin, ficolin and angiopoietin. FGL2 is a direct prothrombinase with serine protease activity. FGL2 can cleave prothrombin to thrombin in a non-canonical way, resulting in fibrin deposition. FGL2 leads to histopathological lesions and ischaemic damage through 'immune coagulation', fibrin deposition and microthrombosis. Microvascular disorders are caused by microthrombi that are activated and formed by the action of FGL2 [11].

It is believed that coagulation disorders are critical in the pathogenesis of severe acute pancreatitis. With the activation of the hemostatic system during severe acute pancreatitis, microthrombosis occurs in the microvascular bed, DIC syndrome may appear, and thrombosis of larger diameter vessels of the splanchnic basin, which was analysed in a single-centre retrospective analysis by Nawacki et al. in 2021 [12].

The given study analysed 111 patients with moderate to severe acute pancreatitis. Splanchnic vein thrombosis was detected in 30.6% of cases. Portal vein thrombosis was most common (47.1% - 16 patients)[12].

Severe complications, such as multiple organ failure syndrome, can also be associated with microcirculatory disorders, microthrombosis, endothelial damage and hypercoagulability occurring in the early phase of severe acute pancreatitis. There is indeed a link between the activation of proinflammatory cytokines and the coagulation system, but the specific pathophysiological mechanisms of this link remain unclear.

Fibrinogen-like protein 2, also known as FGL2-proteinase, has been proposed as one of the key factors, together with factor Xa, influencing microthrombosis by activating prothrombinase into thrombinase, which in turn initiates microthrombosis [13].

FGL2 exists in two structurally distinct forms: membrane-associated FFL2 (mFGL2) and soluble FGL2 (sFGL2). sFGL2 acts as a direct prothrombinase and triggers immunogenic coagulation by cleaving prothrombin in a non-classical manner [7].

In contrast, sFGL2 has an immunomodulatory effect and consequently is involved in modulating responses to tissue damage, fetal loss, malignancy, viral infection, acute allograft rejection, and autoimmune diseases[7].

In 2019, a study conducted by Wen-Bin Xu et al., aimed to investigate sFGL2 as a marker of delirium in patients with acute pancreatitis. The following study included

184 patients with acute pancreatitis. A comparison with a group of healthy patients was performed and it was determined that the elevation of sFGL2 is closely related to the severity of acute pancreatitis and has the potential to diagnose delirium after an episode of acute pancreatitis. Using statistical analysis and ROC curve construction, the threshold value of sFGL2 as a predictor of delirium in patients with acute pancreatitis was determined to be 244.6 pg/ml [14].

Our study compared patients with acute severe pancreatitis and patients with moderate acute pancreatitis to determine the possibility of using sFGL2 as a marker for the prognosis of acute pancreatitis severity and pancreatic necrosis.

CONCLUSIONS

sFGL2 can be used as a marker for assessing the severity of acute pancreatitis and predicting necrotic changes in the pancreas and surrounding tissues.

Based on the results of the study, a correlation between sFGL2 and the following parameters was found D-dimer, C-reactive protein and intra-abdominal pressure.

It was discovered that elevated levels of sFGL2, D-dimer and intra-abdominal pressure allow to predict the progression of necrotic changes in the pancreatic tissue and retroperitoneal space; and such indicators as BISAP, sFGL2, CRP, D-dimer and intra-abdominal pressure can be utilized for defining the severity of acute pancreatitis.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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