**Abstract.** Background. Acute pancreatitis is an aseptic inflammation of the pancreas with diverse complications and further development of necrosis of the gland, parapancreatic tissue and possible addition of secondary infection. A significant number of biochemical markers that can be predictors of pancreatitis complications are still being researched. However, most of them are expensive and their indicators are increased only in the first 24–48 hours after the onset of the disease, so they are not used in daily clinical routine. The purpose of this study is to evaluate the factors that indicate an elevated risk of necrosis in acute severe pancreatitis. Materials and methods. A retrospective analysis of 80 patients with acute pancreatitis was performed via creation of a multivariate logistic regression model. Results. The dependence of the risk of pancreatic necrosis on the following factor signs was found: lipase at the onset of the disease (cut-off value = 599.6 U/L, area under the receiver operating characteristic curve (AUC) = 0.72 (95% confidence interval (CI) 0.57–0.88)), severity of the disease, fibrinogen on day 3 of the disease (cut-off value = 9.7, AUC = 0.65 (95% CI 0.48–0.81)), C-reactive protein (cut-off value = 175.7 mg/L, AUC = 0.70 (95% CI 0.54–0.86)), and intra-abdominal mean capillary perfusion pressure on the first day of the disease (cut-off value ≤ 63.3 mm Hg, AUC = 0.88 (95% CI 0.77–0.99)). The autopsy results revealed the presence of necrosis and microthrombosis of the pancreas. Conclusions. Factors that may indicate an increased risk of pancreatic necrosis were high levels of lipase, fibrinogen on the third day of the disease, C-reactive protein, decreased intra-abdominal mean capillary perfusion pressure, severity of the disease, and the presence of portosplenomesentric thrombosis. Keywords: severe acute pancreatitis; pancreatic necrosis; obesity; thrombosis

**Introduction**

Acute pancreatitis (AP) is an acute aseptic inflammation of the pancreas with a demarcation character, which is based on the processes of pancreatic necrosis and enzyme autodigestion 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 a 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 in addition to autodigestion of pancreatic parenchyma by pancreatic enzymes, ischemia, occuring as a result of pancreatic edema and leading to the development of acute necrotizing pancreatitis, plays an important role [3]. In addition, there are microcirculatory disorders of the pancreas and extrapancreatic organs. Clinical studies revealed that fibrinogen degradation products (FDPs) in blood plasma are significantly higher in patients with acute pancreatitis compared to healthy individuals, and higher levels of FDPs are associated with disease severity [4]. Also, early complications of acute severe pancreatitis associated with blood supply disorders include portosplenomesentric venous thrombosis, which, according to the literature review, occurs in approximately 17.86 % of patients [5]. The given data suggest the need to prescribe anticoagulant and antithrombotic therapy in the treatment strategy for acute severe pancreatitis, as indicated in the 2019 WSES guidelines [6].

Generally, with the progress of research on coagulation mechanisms and drugs, safe and effective anticoagulants such as low-molecular-weight heparin (LMWH) were prescribed to patients with AP with satisfactory results. However, the molecular mechanism of coagulation disorders underlying...
The average severity of the disease was diagnosed in 46 (57.5 %) patients, and acute severe pancreatitis in 34 (42.5 %) patients. The Revised Atlanta Classification for Acute Pancreatitis 2012 was used to determine the severity of pancreatitis [8]. The presence of necrosis was assessed by computed tomography with intravenous contrast (CTSI Baltazar), intraoperatively and by autopsy. The clinical and morphologic classification of acute severe pancreatitis was used to evaluate intraoperative and autopsy materials [9]. Pancreatic necrosis was diagnosed in 32 (40 %) patients. Among them were 4 (5 %) patients with total transmural necrosis and 28 (35 %) with superficial subtotal and focal forms of necrosis.

Inclusion criteria: patients with moderate to severe acute pancreatitis of nutritional origin, with or without pancreatic necrosis, with no general, medical or social contraindications, patients over 18 years, 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 (pseudocysts of the pancreas, pancreatic duct dilatation and presence of concrements in the pancreatic duct), pancreatic surgery, 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 refusal of diagnosis and treatment at any stage of the study, patient death not related to the underlying disease.

Endpoints of the study:
— a logistic regression analysis to assess the factors influencing the development of pancreatic necrosis;
— study of pathomorphological changes in autopsy materials of patients with severe total transmural necrotizing pancreatitis.

All calculations were made using the programs MedStat, EZR (R-Statistics).

Descriptive statistics included the calculation of mean, standard deviation, median, and confidence intervals. Linear regression with coefficient of determination and area under the ROC curve (AUC) was used to determine the influence of various factors that statistically significantly affected the risk of the case with an assessment of the quality of the model. Differences were considered statistically significant at p < 0.05.

Results

A multivariate logistic regression model was built. The following factors were taken into account: age, sex, BMI, lipase, amylase, C-reactive protein, disease severity, epidural catheterization, fibrinogen, INR, prothrombin index, platelets, central venous pressure, intra-abdominal pressure, mean arterial pressure, intra-abdominal mean capillary perfusion pressure and the presence of portosplenic mesenteric thrombosis (microthrombosis and macrothrombosis). The dependence of the risk of pancreatic necrosis on the following factor signs was revealed: lipase at the onset of the disease, severity of the disease, fibrinogen on the third day of the disease, C-reactive protein and intra-abdominal mean capillary perfusion pressure on the first day of the disease (Table 2), AUC = 0.93 (95% CI 0.79—1.00), which demonstrated the relevance of the model built.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total number of patients (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50 (± 14.6)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>52 (65)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>28 (35)</td>
</tr>
<tr>
<td>BMI, kg/cm²</td>
<td>28.8 (21.2–48.4)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>31</td>
</tr>
<tr>
<td>Including diabetes mellitus</td>
<td>10</td>
</tr>
</tbody>
</table>

All patients with acute severe pancreatitis were prescribed anticoagulant therapy in a standard dosage on the second day of hospitalization.
Table 2. Risk factors for the development of necrotic complications in acute severe pancreatitis

<table>
<thead>
<tr>
<th>Factor</th>
<th>The value of the model coefficient, $b \pm m_b$</th>
<th>The level of significance of the difference between the coefficient and 0, $p$</th>
<th>The indicator of the CI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipase</td>
<td>$0.17 \pm 0.08$</td>
<td>0.032</td>
<td>1.1 (1.01–1.32)</td>
</tr>
<tr>
<td>Severity</td>
<td>$2.3 \pm 1.2$</td>
<td>0.041</td>
<td>1.09 (0.87–1.92)</td>
</tr>
<tr>
<td>Fibrinogen on day 3</td>
<td>$-8.7 \pm 4.2$</td>
<td>0.020</td>
<td>1.56 (1.07–2.28)</td>
</tr>
<tr>
<td>Intra-abdominal mean capillary perfusion pressure</td>
<td>$-15.0 \pm 6.3$</td>
<td>0.011</td>
<td>0.93 (0.88–0.98)</td>
</tr>
<tr>
<td>Presence of the portosplenic mesenteric thrombosis</td>
<td>$-0.50 \pm 0.20$</td>
<td>0.022</td>
<td>1.45 (1.05–2.0)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>$0.33 \pm 0.17$</td>
<td>0.035</td>
<td>1.37 (1.02–1.83)</td>
</tr>
</tbody>
</table>

Figure 1. ROC curve of the test for predicting the risk of necrosis depending on the level of C-reactive protein

Figure 2. ROC curve of the test for predicting the risk of necrosis depending on the level of fibrinogen
The threshold value of CRP at which the most frequent diagnosis of pancreatic necrosis was made, was determined by using ROC analysis, cut-off value ≥ 175.7 mg/L, AUC = 0.70 (95% CI 0.54–0.86) (sensitivity 78.3 % (95% CI 52.8–91.9 %), specificity 65.2 % (95% CI 46.5–85.1 %), PPV 66.7 % (95% CI 44.7–84.4 %), NPV 77.3 % (95% CI 54.6–92.2 %)) (Fig. 1).

Using ROC analysis, the threshold value of fibrinogen was determined, at which pancreatic necrosis was most often diagnosed, cut-off value ≥ 9.7, AUC = 0.65 (95% CI 0.48–0.81) (sensitivity 78.3 % (95% CI 46.5–90.3 %), specificity 56.5 % (95% CI 34.5–76.8 %), PPV 56.5 % (95% CI 34.5–76.8 %), NPV 78.3 % (95% CI 56.3–92.5 %)) (Fig. 2).

Using ROC analysis, the threshold value of lipase was determined, at which the most frequent diagnosis of pancreatic necrosis was made, cut-off value ≥ 599.6 U/l, AUC = 0.72 (95% CI 0.57–0.88) (sensitivity 56.5 % (95% CI 34.5–76.8 %), specificity 91.3 % (95% CI 72–98.9 %), PPV 67.7 % (95% CI 48.6–83.3 %), NPV 86.7 % (95% CI 59.5–98.3 %)) (Fig. 3).

The threshold value of intra-abdominal mean capillary perfusion pressure, at which the most frequent diagnosis of pancreatic necrosis was made, was determined by ROC analysis, cut-off value ≤ 63.3 mm Hg, AUC = 0.88 (95% CI 0.77–0.99) (sensitivity 84 % (95% CI 66.9–98.7 %), specificity 90.5 % (95% CI 69.6–98.8 %), PPV 73.1 % (95% CI 52.2–88.4 %), NPV 70.8 % (95% CI 48.9–87.4 %)) (Fig. 4).
Necrosis and microthrombosis of the pancreatic parenchyma and adjacent connective tissue were detected according to the results of autopsy studies conducted in 4 patients with severe pancreatitis (Fig. 5–7).

**Discussion**

One of the earliest events in AP is trypsinogen activation and trypsin-mediated pancreatic cell death. The activation of inflammatory cascades, endoplasmic reticulum stress, autophagy, and mitochondrial dysfunction in acinar cells are important for the development of a deep systemic inflammatory response and the extent of pancreatic tissue damage.

Platelets play an important role among numerous components influencing changes in the coagulation system in AP and subsequent thrombotic and necrotic complications.

Platelets are cellular components of the blood coagulation system, mediating vascular permeability, leukocyte chemotaxis, and the synthesis of inflammatory factors, ultimately leading to platelet-leukocyte-endothelial interactions caused by P-selectin and neutrophil extracellular traps (NETs), which partially explain coagulopathy in patients with acute severe pancreatitis.

According to F. Acehan et al. in 2022, the following factors were identified as risk ones for the development of acute necrotizing pancreatitis: leukocytes, hematocrit, lactate dehydrogenase and C-reactive protein [10].

According to a systematic review and meta-analysis by Wang Li et al. in 2022, the risk factors for the development of infected pancreatic necrosis were identified as follows: high levels of lipase, C-reactive protein, procalcitonin, and a high APACHE II score [11].

Studies are being conducted using artificial intelligence to predict pancreatic necrosis. One of the results of the studies conducted by S. Kiss et al. in 2022 found that such factors as glucose, C-reactive protein, alkaline phosphatase, gender, and leukocyte count had the greatest impact on the development of pancreatic necrosis [12].

The results of a prospective cohort study by G. Barauskas et al. found that the level of C-reactive protein above 110 mg/L on the third day of the disease increases the risk of pancreatic necrosis [13].

The study by J. Fujiiwara et al. in 2021 (211 patients) found that the risk of developing limited necrosis in AP increases when the C-reactive protein level exceeds 185.5 mg/L [14].

According to a meta-analysis by H.M. Asim Riaz et al. in 2023, such indicators as C-reactive protein, procalcitonin, and lactate dehydrogenase played a role in predicting the occurrence of pancreatic necrosis. It was determined that the level of C-reactive protein above 200 mg/L has a high sensitivity, and the level of 140 mg/L has a high specificity [15].

A retrospective study by J. Zheng et al. in 2023 found that increased levels of fibrinogen degradation products (above 23.155) and D-dimer (above 6.475) were independent factors in the risk of splanchic vein thrombosis [16].

Fibrinogen was studied in combination with prealbumin — prealbumin/fibrinogen ratio, as a promising predictor of the severity of AP. The threshold value of the prealbumin/fibrinogen ratio was determined, at which the diagnosis of acute severe pancreatitis was most often made, using ROC analysis, cut-off value = 31.70 mg/g (sensitivity 76.5 %, specificity 94.1 %, PPV 89.6 %, NPV 85.6 %) [17].

According to the literature review and WSES 2019, the diagnostic criterion for AP is an increase in lipase levels three
times the normal level of 480 U/L [6]. However, lipase is not a specific indicator of pancreatic necrosis.

According to meta-analysis containing 19 articles with data on 9997 patients, conducted by Dalma Dobszai et al. in 2019 there was established a correlation between obesity in patients with AP and the risk of mortality. Moreover, it was found that a BMI above 25 increases the risk of severe AP, while a BMI > 30 raises the risk of mortality. A BMI < 18.5 carries an almost two times higher risk of mortality in AP [18].

A prospective study of 30 patients with AP was conducted in the Department of General Surgery No. 1 of the Bogomolets National Medical University in 2017 with an aim to analyze the impact of the obesity on severity in AP. It was found that the most significant correlation was established between the visceral fat area, BMI and severity, including systemic (multiple organ failure syndrome (MOFS), systemic inflammatory response syndrome (SIRS)) and local complications (in accordance to CTSI Balthazar scale) [19].

An increase in intra-abdominal pressure slows down blood flow, which, in turn, affects thrombosis at all levels of splanchnic blood flow, due to the fact that it affects all hydrostatic and hydrodynamic processes in the abdominal cavity [7]. The calculation of intra-abdominal mean capillary perfusion pressure allows more accurate prediction and assessment of patients with acute abdominal pathology with a possibility of hypoperfusion and ischemia in the abdominal cavity [7]. Moreover, increased intra-abdominal and decreased intra-abdominal mean capillary perfusion pressure may affect the risk of early infection in acute necrotizing pancreatitis [20].

According to our study, it was determined that such factors as increased levels of lipase (cut-off value = 599.6 U/l), C-reactive protein (cut-off value = 175.7 mg/l), fibrinogen (cut-off value = 9.7), BMI (cut-off value = 29) as well as the severity of the disease, reduced intra-abdominal mean capillary perfusion pressure (cut-off value ≤ 63.3 mm Hg) and the presence of portosplenomesenteric thrombosis influenced the development of pancreatic necrosis. In contrast, other factors such as age, gender, amylase, epidural catheterization, central venous pressure, intra-abdominal pressure, and mean arterial pressure did not have a statistically significant effect on the development of pancreatic necrosis.

Conclusions

In our study factors that may indicate an increased risk of pancreatic necrosis were identified as follows: high levels of lipase, fibrinogen on the third day of the disease high levels of lipase, fibrinogen on the third day of the disease, C-reactive protein, increased BMI, decreased intra-abdominal mean capillary perfusion pressure, severity of the disease, and the presence of portosplenomesenteric thrombosis. The presence of microthrombosis and necrosis of pancreatic tissue and para-pancreatic tissue was confirmed by histological examination.

References


Фактори ризику панкреонекрозу при гостром панкреатиті у хворих на ожиріння

Резюме. Актуальність. Гострий панкреатит — асептичне запалення підшлункової залози з різноманітними ускладненнями, подальшим розвитком некрозу залози та парапанкреатичної клітковини і можливим приєднанням вторинної інфекції. Значна кількість біохімічних маркерів, які можуть бути предикторами розвитку ускладнень панкреатиту, ще досліджується. Однак більшість із них дорогі, а їхні показники підвищаються лише в перші 24–48 годин від початку захворювання. Тому їх не використовують у повсякденній клінічній практиці.

Метою цього дослідження є оцінка факторів, що вказують на підвищений ризик розвитку некрозу при гостром тяжкому панкреатиті у хворих на ожиріння.

Матеріал і методи. Ретроспективний аналіз 80 пацієнтів з гострим панкреатитом шляхом побудови багатофакторної логістичної регресійної моделі.

Результати. Встановлено залежність ризику панкреонекрозу від таких факторних ознак: ліпаза на початку захворювання (порогове значення = 599,6 Од/л, AUС = 0,72 (95% ДІ 0,57–0,88)), тяжкість захворювання, фібриноген на третю добу хвороби (порогове значення = 9,7, AUС = 0,65 (95% ДІ 0,48–0,81)), С-реактивний білок (порогове значення = 175,7 мг/л, AUС = 0,70 (95% ДІ 0,54–0,86)), внутрішньочеревний середній капілярний перфузійний тиск у першу добу захворювання (порогове значення 63,3 мм рт.ст., AUС = 0,88 (95% ДІ 0,77–0,99)). За результатами розтину виявлено наявність некрозу та мікро-тромбозу підшлункової залози.

Висновки. Факторами, які можуть вказувати на підвищений ризик розвитку панкреонекрозу, були високий рівень ліпази, фібриногену на третій день захворювання, С-реактивного білка, зниження внутрішньочеревного середнього капілярного перфузійного тиску, тяжкість захворювання та наявність портоспленомезентарного тромбозу.

Ключові слова: гострий панкреатит; панкреонекроз; ожиріння; тромбоз