INDICATORS OF ORGAN DEFICIENCY DEVELOPMENT IN ACUTE PANCREATITIS

Abstract. Today, acute pancreatitis remains one of the three leading reasons for hospitalization of patients in emergency departments. Despite the fact that the material and technical base of medical institutions is improving every year, it is not always possible to timely and adequately assess the severity of the condition of patients with acute pancreatitis. Underestimation of the severity of the condition can end up sadly for the patient, therefore, patients with severe acute pancreatitis should be identified in the early stages of the disease. To predict the severe course of acute pancreatitis in the early stages of the disease, it is necessary to take into account such risk factors as age, concomitant diseases, body mass index, as well as clinical and laboratory markers of severity: hematocrit, neutrophil-lymphocyte coefficient, distribution of erythrocytes by volume, glucose, urea and data from integral scales. Markers such as respiratory failure and oliguria diagnosed upon admission, as well as the level of lactate dehydrogenase, bicarbonates and acid-base balance of the blood, can also be considered prognostically significant markers of severe course. Early identification of patients with an increased risk of complications and their timely adequate therapy can improve treatment outcomes and reduce mortality rates.

Keywords: severe acute pancreatitis, risk factors, severity markers, prognosis.
Acute pancreatitis is a disease based on aseptic inflammation of the pancreas and surrounding tissues, caused by the processes of tissue autolysis under the influence of lipolytic and activated proteolytic enzymes. In studies conducted under the auspices of the WHO, there has been a constant increase in the annual incidence of acute pancreatitis, which ranges from 13 to 45 cases per 100,000 population [1-3], and in 2015 alone, the total number of deaths from acute pancreatitis amounted to 104 thousand people [4]. Most patients with acute pancreatitis are mild and require no treatment other than parenteral intravenous fluids, pain relief, and supportive care. Severe acute pancreatitis develops in about 15-20% of patients with acute pancreatitis [5-7]. According to the literature, the overall mortality rate in acute pancreatitis ranges from 3 to 5-6% [8-10], and in the severe form of the disease 20%-30% [6,11], even in specialized clinics around the world, mortality rates are not lower than 15% [12,13].

Modern ideas about the causes of the development of acute pancreatitis, including its necrotic forms, are based on facts indicating the polyetiological nature of this disease. According to the data available to date, there are about 140 different factors that cause acute pancreatitis. Most often - these are diseases of the biliary system and alcohol abuse, the priority of which varies depending on the continent, country, region and population. For example, in Greece there is a clear predominance of gallstone disease on alcohol (71.4% versus 6.0%), while in Finland the opposite situation is observed (6.3% versus 79.3%) [2]. Cases of acute pancreatitis caused by these reasons account for 70-80%, other factors account for 10-15% of the disease, and in 10-15% of cases the disease is idiopathic, that is, it is not always possible to identify the cause of acute pancreatitis. As mentioned above, calculous cholecystitis and alcohol abuse are the main risk factors for the development of acute pancreatitis, but according to recent studies, in people with asymptomatic gallbladder stones for 20-30 years, the risk of developing biliary pancreatitis did not exceed 2%, and the risk of alcoholic pancreatitis in avid alcoholics also does not exceed 2-3%. In connection with these data, a group of scientists headed by Paul Georg Lankisch (Germany) suggested that other factors, possibly genetic, should play an important role in the development of acute
pancreatitis [3,13]. Currently, studies are being conducted on the role of genes as the causes of predisposing the development of acute pancreatitis.

Despite new diagnostic methods, as well as growing knowledge about the etiopathogenesis of acute pancreatitis, it is not always possible to assess the severity of the patient’s condition in a timely and adequate manner. Underestimation of the severity of the condition can end up sadly for the patient, therefore, patients with severe acute pancreatitis should be identified in the early stages of the disease. Timely detection of a mild form of the disease is also necessary to prevent the useless waste of resources of a medical institution and health care in general. Timely, adequate treatment can improve treatment outcomes and reduce mortality rates in severe acute pancreatitis. To achieve these goals, early identification of patients with a high risk of complications, their timely diagnosis and prognosis is necessary [11, 14, 15].

According to the Atlanta 2012 classification, there are mild, moderate and severe acute pancreatitis. The initial assessment of the severity of acute pancreatitis is the cornerstone in determining the further tactics of patient management. In recent years, integral scales for scoring the parameters of the physiological state of patients have been used to assess the severity of acute pancreatitis. The most widespread are: Ranson (1974), Glasgow-Imrie (1984), APACHE II (1984), SAPS (1985), MODS (1995), SOFA (1996) and BISAP (2009) [16]. The existing «traditional» scales for determining the severity of acute pancreatitis, although they are valuable diagnostic criteria at the hospital stage, do not fully meet the requirements of practical medicine [17, 18]. For example, the Ranson, APACHE II, SAPS scales require the determination of complex indicators and parameters that go beyond the capabilities of admission departments of hospitals [17,19]. The APACHE II scale can be used to assess the severity of the patient’s clinical condition, but this scale is not specific for acute pancreatitis. The advantages of this assessment are that it is a widely tested method and can be used at any time, but it has drawbacks, that is, the parameters are «cumbersome» and not all are usually collected.

A group of scientists led by V.K. Singh in 2009 developed a clinical system for assessing the severity of acute pancreatitis - BISAP (Bedside Index of Severity in
Acute Pancreatitis - an indicator of the bedside index of severity of acute pancreatitis. The analysis revealed the five most informative variables for determining the severity of acute pancreatitis and predicting in-hospital mortality:

1) blood urea levels above 25 mmol / l;
2) impaired consciousness;
3) the presence of SIRS (SSVR);
4) age over 60;
5) the presence of effusion in the pleural cavity. If one of the listed criteria is met, one point is assigned.

A score of 2 is a statistically significant cut-off value for the diagnosis of severe acute pancreatitis, organ failure, and high mortality rates. All indicators were assessed on the first day of the patient’s stay in the hospital. Mortality ranged from 20% or more in the group with the highest risk and less than 1% in the group with the lowest [20]. Recent scientific studies have shown that using the BISAP scale, it becomes possible to identify a group of patients with an increased risk already in the first day of a patient’s stay in the hospital, even before the onset of complications [17,21,22]. And in a study conducted by Japanese scientists led by T. Ueda, it was shown that SPS (Simple Prognostic Score) is as accurate as standard integral scales. This scale uses only three factors: blood urea concentration > 8.9 mmol / L, blood lactate dehydrogenase activity > 900 U / L, and the presence of pancreatic necrosis on CT [23]. Proposed in 2011 by V. Oskarsson et al. HAPS scale (Harmless Acute Pancreatitis Score), which also uses only three factors: symptoms of peritoneal irritation, blood creatinine < 2 mg / dL (176 μmol / L), hematocrit < 43 for men and < 39 for women. This scale allows to identify the majority of patients who will never develop destructive pancreatitis or organ failure and to identify mild cases of acute pancreatitis within 30 minutes from the moment the patient is hospitalized, even by non-specialists. According to the study, the specificity of the scale for predicting mild acute pancreatitis - HAPS was 96.3%, with a corresponding positive predictive value of 98.7% [24]. Patients with mild acute pancreatitis, according to the HAPS scale and without the presence of other risk factors, do not require hospitalization and can receive treatment on an outpatient basis [24]. Complex combinations of prognostic scales are
more accurate, but extremely laborious and have very limited application in clinical practice.

Severe acute pancreatitis is characterized by the presence of local and / or systemic complications. All complications can be conditionally divided into «early» and «late». Early complications: multiple organ failure syndrome, respiratory failure, arterial hypoxemia, respiratory distress syndrome, cardiovascular failure, shock, oliguria, anuria, disseminated intravascular coagulopathy, hyperglycemia, diabetic ketoacidosis and coma, hypocalcemia. Late complications: local and retroperitoneal infections, infected pancreatic necrosis and pancreatic abscess, sepsis, pseudocyst, pancreatic encephalopathy, splenic vein thrombosis, pseudoaneurysms of the abdominal cavity. According to the Atlanta-2012 classification, exacerbation of pre-existing concomitant diseases, such as coronary heart disease (CHD), chronic lung disease, etc., developed against the background of acute pancreatitis, is also defined as a systemic complication.

After analyzing the literature data, many risk factors were identified that, under certain conditions, can lead to the development of complications in patients with acute pancreatitis. Below are the most important prognostically important risk factors for complications of acute pancreatitis. To predict the development of complications and severe course of the disease, the risk factors were divided into 3 groups: general risk factors, physiological and biochemical parameters of the organism.

According to most authors, a large amount of visceral fat in relation to skeletal muscle, in other words, obesity is considered an independent risk factor for the development of local and systemic complications in patients with acute pancreatitis [2,25,26]. Age is considered to be the next significant common risk factor, namely, patients aged 55 years and older are at an increased risk of complications [2].

Among the physiological parameters, the most important is considered to be the presence of the SIRS-systemic inflammatory response syndrome and if symptoms of SIRS are detected (hyperthermia more than 38 °C or hypothermia less than 36 °C, heart rate more than 90 beats per minute, respiratory rate more than 20 per minute, leukocytosis more than 12x10^9 / l or leukopenia less than 4x10^9 / l. SIRS - diagnosed in the presence of 2 or more of the indicated signs), this means
that the patient is at risk of developing complications. Thus, according to R. Mofidi, mortality in the group of patients with SIRS was 25.4%, and in patients with transient SIRS - 8% and 0.7% without SIRS [27].

The presence of respiratory failure in a patient, as well as a low pO2 level on admission, increases the likelihood of complications and mortality [14,28].

In connection with repeated vomiting and the passage of intravascular fluid into the intercellular space, hypovolemia develops, which in turn reduces glomerular filtration and ultimately can lead to the development of oliguria and anuria. Identification of such clinical symptoms in a patient as oliguria (decreased glomerular filtration rate of less than 90 ml / min per 1.73 m2 of body surface) and anuria upon admission increases the risk of developing pancreatic necrosis and the risk of mortality in patients with acute pancreatitis [29].

As mentioned above, as a result of increased vascular permeability, fluid exudates from the vascular bed into the tissues and serous cavities, which leads to hemoconcentration and is clinically expressed in the exicosis syndrome. That is, the higher the hematocrit, the more pronounced hypovolemia. This indicator also makes it possible to assess the degree of microcirculation disturbance, therefore, hematocrit ≥ 44% upon admission or maintaining indicators close to this within the first 24 hours after hospitalization is considered an independent risk factor for the development of pancreatic necrosis and organ failure [11,30-32]. According to Veit Phillip et al. in patients with hematocrit values below 44%, organ failure and pancreatic necrosis were observed only in 7% of patients with acute pancreatitis [2].

Hyperglycemia is also considered a risk factor for the development of complications and poor outcomes of the disease [28,33,34]. According to data reported by Paul Georg Lankisch et al. patients with a blood glucose concentration of more than 11.1 mmol / L on admission should be classified as a high-risk group, and patients with a blood glucose concentration of less than 6.9 mmol / L should be classified as a low-risk group for complications. The indicator is less than 6.9 mmol / l, also has a high negative predictive value - 92%, for predicting the development of pancreatic necrosis [35]. The presence of diabetes mellitus in
patients on admission increases the risk of complications, but at the same time does not increase the risk of hospital mortality, some studies (Hsiu-Nien Shen et al.) Even show that mortality is lower in the group of patients in whom diabetes mellitus was diagnosed earlier [36].

In surgical practice, an increased level of leukocytes is usually used as a marker of inflammation, however, according to the literature: leukocytosis, and even better, the neutrophil-lymphocyte ratio (Neutrophil-Lymphocyte Ratio (NLR) - calculated by dividing the total number of neutrophils by the number of lymphocytes), in the first days disease correlates with the development of severe acute pancreatitis and increased mortality [28,37-41]. Recent studies by M. Kaplan et al. showed that the use of the neutrophil-lymphocyte ratio in combination with the platelet-lymphocyte ratio (Platelet-Lymphocyte Ratio-PLR) is a more effective marker for determining the risk of complications and mortality in acute pancreatitis [42].

The distribution of erythrocytes by volume (RDW - Red cell Distribution Width) is a calculated indicator of the variability of erythrocytes by volume, which characterizes the degree of anisocytosis. An increase in RDW suggests the presence of a mixed population of cells (normocytes and microcytes or macrocytes and normocytes - the norm is 11-15%). To date, many scientific studies have evaluated RDW as a predictive marker for determining the risk of developing severe acute pancreatitis at the time of admission to the hospital. According to different studies, patients with RDW ≥ 13.55-16.45% had higher rates of complications with a sensitivity of 54.5-86.7% and a specificity of 73.6-77.1%, respectively [43]. The available data confirm that RDW is a useful indicator for predicting the development of complications and mortality in patients with acute pancreatitis, in connection with which RDW can also be considered an important prognostic parameter [38,44-47], although the mechanisms underlying the relationship between, RDW and disease severity are not yet fully understood.

Patients with severe acute pancreatitis on days 1-3 of the disease were observed: thrombocytopenia and inhibition of blood coagulation capacity, [48] as well as a low mean platelet volume (MPV) [49], but with the further course of the
disease, a gradual increase was observed, platelet count.

The most studied indicator for predicting severe course and mortality in acute pancreatitis is urea. In the United States and some other countries, blood urea concentration is expressed as the amount of urea nitrogen. This test is called blood urea nitrogen (BUN) and the unit is milligram per deciliter (mg/dl). This indicator was described as a significant marker for predicting the outcome of acute pancreatitis back in 1974 in the integral scale proposed by John Ranson. By assessing this indicator, one can not only judge renal function, but also the volume of intravascular fluid, because during hypovolemia, glomerular filtration processes are disrupted. Therefore, studying the change in this indicator in dynamics, we can judge the adequacy of the infusion therapy. Therefore, blood urea is also an important prognostic marker for determining the severity and predicting mortality of patients. Blood urea levels of 6.1 mmol/L and higher on admission and 8.3 mmol/L 24 hours after hospitalization are considered to be prognostic values for the development of complications of acute pancreatitis. According to the data of studies carried out with blood urea levels of 13.3 mmol/L and higher after 24 hours of hospitalization, it has a high accuracy for predicting a severe course of the disease [28, 50, 51].

Studies have shown that a low level of bicarbonates in the peripheral blood has a direct correlation with a high incidence of organ failure in acute pancreatitis [52, 53]. Another study by F. Valverde-López et al. revealed that a higher level of lactates in arterial blood in acute pancreatitis is an independent risk factor for the development of a severe course of the disease [9], as well as the development of infected pancreatic necrosis. Wenqing Shu et al. believe that the lactate level ≥2.1 mmol/L at admission has a positive predictive value for predicting the development of infected pancreatic necrosis, with a sensitivity of 67.2% and a specificity of 82.0%, and negative 87% and 60%, respectively [54]. According to these data, the detection of acidosis in a patient upon admission should be considered an independent risk factor for the development of complications and, therefore, all patients with acute pancreatitis, already in the first hours after the diagnosis, need to conduct a blood test for acid-base balance and correct it when identifying deviations.
Some studies have shown that lactate dehydrogenase (LDH) is a zinc-containing intracellular enzyme that catalyzes the oxidation of lactic acid into pyruvate and is found in almost all cells of the body, in diseases accompanied by tissue damage and cell destruction, the LDH activity in the blood increases, the norm is 135 - 225 U / k) can also serve as a predictor of the development of pancreatic necrosis and multiple organ failure. According to Jing Cui et al. An LDH value of 647 U / L or more predicts the development of multiple organ failure with a sensitivity of 76.2% and a specificity of 98.8% [55].

The most well-studied parameter is C-reactive protein (CRP), which is an acute phase protein produced by hepatocytes in response to cytokines in inflammation of various etiologies. The concentration of CRP> 150 mg / L within 48 hours after the onset of the disease in clinical practice is used to predict the development of severe acute pancreatitis. According to S.M. Staubli et al. using a threshold value of 110 to 150 mg / l at the time of hospitalization, we are able to predict a severe course of the disease with a sensitivity of 38 to 61% and a specificity of 89-90%, respectively [56]. The main disadvantage of the C-reactive protein assay is that peak levels are only reached after 48-72 hours. The level of C-reactive protein ≥150 mg / l on the third day of illness in combination with other research methods can be used as a prognostic factor for the development of severe acute pancreatitis [9,56].

Procalcitonin is the most sensitive laboratory test for detecting pancreatic infection, and low serum values are strong negative predictors of infected necrosis. A procalcitonin value of 3.8 ng / ml or higher within 96 hours of symptom onset indicated pancreatic necrosis with sensitivity and specificity of 93% and 79%, respectively. Determination of the concentration of procalcitonin is a highly specific and sensitive biochemical test in the differential diagnosis of infected and sterile pancreatic necrosis [56,57].

In recent years, a fairly large number of studies have been conducted on the predictive value of blood biomarkers for predicting the course of the disease in acute pancreatitis. The most informative are considered to be the following: IL-6, IL-8, IL-10, IL-12, IL-15, IL-17, MMP-9 (Matrix metallopeptidase-9), HMGB1 (high-mobility group protein B1 or amphoterin ), Cortisol Binding Globulin (CBG), angiopoietin-2,
D-dimer, and others. Studies have shown promising predictive results, but their use in routine clinical practice is limited by the high cost and complexity of the analysis.

A number of studies have shown the advantages of early enteral nutrition, which consist in a statistically significant reduction in the risk of local and extrapancreatic infectious complications, as well as in a decrease in mortality [58-60]. Recent research in this area by A.P. Shah et al. it is recommended to start feeding after relieving pain [61], therefore, we attributed starvation of the patient after the first day from the onset of the disease to a risk factor for complications.

CONCLUSIONS

To predict the severe course of acute pancreatitis in the early stages of the disease, it is necessary to take into account host-specific factors (age, comorbidities, body mass index), clinical risk factors (biochemical and physiological parameters), and prognostic scale data. Patients over 60 years of age and / or obese have a high risk of developing severe acute pancreatitis. Respiratory failure and oliguria diagnosed on admission in the same way are considered predictors of severe disease. According to the integral scales, patients with a score of Ranson ≥ 3, APACHE-II ≥ 8 and BISAP ≥ 3 have a high risk of complications and severe acute pancreatitis.

Hematocrit, neutrophil-lymphocyte ratio (NLR), and red blood cell volume distribution (RDW) are useful and yet available indicators for predicting the development of complications in patients with acute pancreatitis. Biochemical blood parameters such as glucose, urea, creatinine, lactate dehydrogenase, bicarbonate levels and blood acid-base balance can be considered prognostically significant markers of severe acute pancreatitis, and therefore, it is necessary to consider the introduction of these tests into the diagnostic standards for acute pancreatitis.

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References:


