Research Article

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Early Predictors of Severe Acute Pancreatitis

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BACKGROUND One of the main pathogenetic aspects of the severe course of acute pancreatitis (AP) is endothelial dysfunction. Under normal physiological conditions, the endothelium has both anticoagulant and procoagulant properties. However, with the development of AP, endothelial dysfunction often begins as a diffuse activation of coagulation, which further potentiates the progression of the systemic inflammatory response syndrome (SIRS) and thereby complicates the course of AP.

MATERIAL AND METHODS The present retrospective-prospective study included 78 patients; men — 52 (66.7%), women — 26 (33.3%) with severe AP. The mean age was 51.8±14.2 years. The patients were divided into two groups: the 1st group (n=39), based on a retrospective analysis of the data, included patients in whom the following hemostasis parameters were assessed: activated partial thromboplastin time, international normalized ratio, prothrombin. The second group (n=39) included patients in whom, in addition to the above, the following indicators were evaluated: fibrinogen, D-dimer, antithrombin III, protein C.

CONCLUSION In the course of this study, it was found that routine methods for assessing the parameters of the hemostasis system, including the determination of only activated partial thromboplastin time, international normalized ratio, prothrombin, are uninformative and do not reflect the severity of the disease. A comprehensive comprehensive study of the coagulation system already in the early stages of the disease indicates an existing tendency to a severe course, which allows anticoagulant therapy to be immediately begun, thereby reducing the number of infectious complications, cases of multiple organ failure, and reducing mortality.

Key words: acute pancreatitis, hemostasis, systemic inflammatory response syndrome, endothelial dysfunction, low molecular weight heparin preparations
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AP - acute pancreatitis
APACHE II - Assessment of Acute Physiological Disorders and Chronic Condition II Disorders
APTT - activated partial thromboplastin time
AT III - antithrombin III
D-dimer - thrombus formation marker
ICU - intensive care unit
IFS - intestinal failure syndrome
INR - international normalized ratio
FG - fibrinogen
LMWH - low molecular weight heparin
MARSHALL - Modified Organ Dysfunction Scoring System
MOF - multiple organ failure
PT - prothrombin
SAP - severe acute pancreatitis
SOFA - Organ Dysfunction Assessment Scale

INTRODUCTION

"Acute pancreatitis (AP) is initially an aseptic inflammation of the demarcation type, which is based on necrosis of the acinar cells of the pancreas, and enzymatic aggression, followed by expanding necrosis and dystrophy of the gland, in which it is possible to damage the surrounding tissues and distant organs, as well as systems and accession secondary purulent infection" [RSS, 2022].

Currently, AP is one of the most common causes of hospitalization among all diseases of the gastrointestinal tract. According to *T.N. Baron,* the incidence rate of AP in the world is 13–45 observations per 100,000 adults [1, 2]. In Russia, the incidence varies from 27 to 50 cases per 100,000 adults annually [3], while the incidence rate in the United States is 50–80 cases per 100,000 adults per year [4, 5].

One of the main pathogenetic aspects of the severe course of AP is endothelial dysfunction. Under normal physiological conditions, the endothelium has both anticoagulant and procoagulant properties [6–10]. However, with the development of AP, endothelial dysfunction often begins as a diffuse activation of coagulation, which further potentiates the progression of the systemic inflammatory response syndrome (SIRS) and, thereby, complicates the course of AP.

Today, there is a large amount of evidence indicating a cross-relationship between the inflammatory response and coagulation, as a result of which inflammation induces the activation of the hemostasis system, and the latter, in turn, affects the production of pro-inflammatory cytokines [11, 12]. The complex relationship between inflammation and coagulation may have important implications for the pathogenesis of microvascular failure and subsequent multiple organ failure (MOF) resulting from severe infection and the associated systemic inflammatory response syndrome (SIRS). One of the manifestations of SSVR is damage to the vascular endothelium, whose cells synthesize a large number of biologically active substances that play an important role in many processes in normal and pathological conditions (hemodynamics, hemostasis, immune responses, regeneration, etc.) [13, 14].

There is a relationship between the mechanisms of inflammation, coagulation and endothelial cell dysfunction with pathophysiological reactions that contribute to the generalization of the infectious process, which leads to a severe complication of AP, organ dysfunction. In a study conducted in 2016 by G.R. Samigulina et al. noted an increase in the activity of D-dimer and fibrinogen in the group of deceased patients with acute destructive pancreatitis. Blood sampling was carried out in two stages: the first was carried out on the 1^{st}-3^{rd} day from the onset of the disease, the second stage was performed on the 4^{th}-7^{th} day. However, no statistically significant differences were found with the survivor group. Thrombotic complications were treated with sodium heparin [15].

Early prediction of hemostasis system disorders, performed within the first day from the onset of pain syndrome, is an integral part in improving the quality of treatment of patients with this nosology. A number of clinical trials have been conducted that have proven the effectiveness of anticoagulant therapy using low molecular weight heparin preparations (LMWH, molecular weight 3500-4300 daltons). At the same time, a positive result consisted not only in the normalization of hemostasis parameters, but also in a decrease in the severity of SIRS [8, 11, 12, 14].

So, in 2019 *M. Tozlu et al*. conducted a randomized controlled open study on the effect of LMWH on the prevention of the development of pancreatic necrosis in patients with moderate and severe pancreatitis. According to the data obtained, pancreatic necrosis was registered in 6.1% of the group where LMWH was used, while in the group where anticoagulant therapy was performed using sodium heparin, pancreatic necrosis developed in 22.9% of cases [11].

As a result of *Q. Qiu et al.* meta-analysis, which included 16 randomized controlled trials involving 1625 patients with AP, in the group where LMWH was used, a lower level of leukocytes and C-reactive protein was observed, and, accordingly, a lower score was given *on* the *SOFA* and *Balthazar scales* [16].

Aim of study: to optimize the results of AP treatment by identifying early predictors of a severe course of the disease.

MATERIAL AND METHODS

The present retrospective-prospective study included 78 patients: 52 men (66.7%) and 26 women (33.3%) with severe acute pancreatitis (SAP), who were treated at N.V. Sklifosovsky Research Institute for Emergency Medicine from 2020 to 2022. The mean age of the patients was 51.8±14.2 years.

Inclusion Criteria:

1. The presence of a diagnosis of SAP.
2. Age 18–70 years.
3. *APACHE* II more than 10.
4. *SOFA* over 2 points.
5. Intestinal failure syndrome (IFS) from 2-th degree and above.
6. Availability of informed consent of the patient.

Exclusion Criteria:

1. An agonal state.
2. Unstable hemodynamics (increasing dosages of vasopressor and inotropic support).
3. Edematous form of AP.
4. Age over 71 years.
5. The presence of chronic hematological diseases.
6. Long-term use of anticoagulants in history.
7. Thrombocytopenia.
8. The presence of cancer.
9. The presence of autoimmune diseases.
10. Active bleeding and bleeding disorders.
11. Severe liver dysfunction.
12. Injuries or surgical interventions in the central nervous system, organs of vision and hearing.
13. Syndrome of disseminated intravascular coagulation within the framework of heparin-induced thrombocytopenia.
14. Acute bacterial endocarditis and protracted endocarditis.
15. Organic disorders with an increased risk of bleeding (active peptic ulcer, hemorrhagic stroke, cerebral aneurysm or cerebral neoplasia).
16. Refusing treatment.

The patients were divided into two groups: the 1st group (n = 39), based on a retrospective analysis of the data, included patients with SAP, in whom the following hemostasis parameters were assessed: activated partial thromboplastin time (APTT), international normalized ratio (INR), prothrombin (PT). The severity of the condition upon admission was assessed according to the scales: *APACHE* II, *SOFA, MARSHALL* and amounted to 16.0±4.2, 4.5±0.9, 5.3±1.0 points, respectively (Table 1). The 2nd group (n = 39) included patients with SAP, in which, in addition to the above, the following indicators were evaluated: fibrinogen (FG), D-dimer, antithrombin III (ATIII), protein C. The severity of the condition was assessed on the scales: *APACHE* II, *SOFA, MARSHALL* and amounted to 16.2±3.4, 4.4±1.04, 5.5±0.72 points, respectively (Table 1). Patients in both groups were standardized for age, gender, and comorbidities.

Table 1

The severity of the condition of patients with severe acute pancreatitis upon admission

Scale	Comparison	Study
APACHE II	16.0±4.2	16.2±3.4
SOFA	4.5±0.9	4.4±1.04
MARSHALL	5.3±1.0	5.5±0.72

Notes: APACHE II —Acute Physiological Disorders and Chronic Disorders Assessment Scale II; MARSHALL — modified organ dysfunction score; SOFA — Organ Dysfunction Assessment Scale

Blood samples were assessed upon admission of patients to the intensive care unit (ICU).

The obtained data were processed statistically. For each variational series, the mean value (*M*), standard deviation (σ) were calculated for the values of the parametric distribution, the median (*Me*), minimum (*Min*) and maximum (*Max*) — for the values of the non-parametric distribution. Correlation was evaluated with the calculation of the Pearson correlation coefficient. When assessing the statistical significance of differences and changes, $p < 0.05$ was taken as the threshold value.

RESULTS

In patients of the 1st group, on the 1st day, no statistically significant differences (from normal values) were found in the studied parameters (Table 2). Patients underwent anticoagulant therapy using sodium heparin. The number of infectious complications in this group was 33.3%, cases of MOF — 46%, deaths — 30.7%.

Table 2

Hemostasis parameters of patients in the comparison group (Me (Min–Max))

Index	Reference values	Patient Values
APTT, s	25.0–31.3	31.7 (22.4–67.2)
INR	0.8–1.2	1.2 (1.0–1.9)
PT, %	70–130	95.7 (61.8–138.4)

Notes: APTT — activated partial thromboplastin time; INR — international normalized ratio; PT — prothrombin

In patients of the 2nd group, already on the 1st day in the ICU, there was a statistically significant increase in the levels of FG 5.6 (3.8; 5.9) g/l, D-dimer 7.6 (5.2; 15.2) ng/ml, decrease in the level of ATIII 71.5 (42.3; 100.2)%; other parameters did not go beyond the reference values (Table 3).

Table 3

Parameters of hemostasis in patients of the main group (Me (Min–Max))

Index	Reference values	Patient Values
APTT, s	25.0–31.3	32.6 (23.8–65.0)
INR	0.8–1.2	1.2 (0.8–2.6)
PT, %	70–130	78.0 (58–103.1)
FG, g/l	1.8–3.5	5.6 (3.8–5.9)*
D-dimer, mg/ml	0.17–0.23	7.6 (5.2–15.2)*
ATIII, %	98.1–107.7	71.5 (42.3–100.2)*

Notes: * — p <0.05, compared with normal values; AT III — antithrombin III; APTT — activated partial thromboplastin time; D-dimer — a marker of thrombus formation; INR — international normalized ratio; PT — prothrombin; FG — fibrinogen

In order to assess the correlation, the Pearson index was used. Thus, the correlation between APTT, INR and PT in both groups and the severity on the *SOFA* and *MARSHALL scales* was not revealed, while between the level of FG and the severity assessment on the *MARSHALL scale* was 0.8 and 0,5 on the *SOFA scale*; the correlation between the level of D-dimer and the severity assessment on the *MARSHAL* and *SOFA scales* was equally equal to 0.5; the correlation between ATIII and the severity assessment on the *MARSHAL scale* was 0.4 and 0.3 on the *SOFA scale*. Thus, the change in the level of FG has the greatest sensitivity. Determination of this indicator in the early period of AP development has an important prognostic significance. In turn, moderate sensitivity is observed with a change in the level of ATIII, and the lowest sensitivity is observed with an increase in the level of D-dimer.

The data obtained made it possible to change the therapeutic tactics, which consisted in prescribing anticoagulant therapy using LMWH preparations (with a molecular weight of 3,500–4,300 daltons). The number of infectious complications among patients of the 2nd group was 20.5%. MOF developed in 30.7% of cases, the mortality in this group was 17.9%.

CONCLUSION

In the course of this study, it was found that standard methods for assessing the parameters of the hemostasis system, including the determination of only activated partial thromboplastin time, international normalized ratio and prothrombin, are uninformative and do not reflect the severity of the disease. An extensive comprehensive study of the coagulation system already in the early stages of the disease indicates an existing tendency to a severe course, which allows you to immediately begin anticoagulant therapy and thereby reduce the number of purulent-septic complications, cases of multiple organ failure, and reduce mortality.

1. An increase in the level of fibrinogen, D-dimer, a decrease in the level of antithrombin III are observed in patients with acute pancreatitis already in the early stages of the disease.

2. The described changes in the hemostasis system indicate the severe nature of the course of acute pancreatitis.

3. Evaluation of a detailed coagulogram upon admission of patients with acute pancreatitis to the intensive care unit makes it possible to timely start anticoagulant therapy using low molecular weight heparin.

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