PRESEPSIN AS THE EARLY MARKER OF PURULENT SEPTIC COMPLICATIONS IN PATIENTS WITH SEVERE ACUTE PANCREATITIS

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ABSTRACT Sepsis is the leading cause of mortality in patients with severe acute pancreatitis (SAP). High mortality rate in patients with SAP is mainly associated with purulent and inflammatory process in parapancreatic fat. Early laboratory diagnosis of infection is vitally important for timely indications for surgery and successful therapy.

AIM OF STUDY The comparison of prognostic and diagnostic values of presepsin and acute phase proteins (CRP, PCT) in the development of septic complications in patients with SAP at the early stage.

MATERIAL AND METHODS We examined 37 patients with SAP. Depending on the course and outcome of the disease, patients were divided into two groups: Group 1 (n=10) — deceased patients, Group 2 (n=27) — patients with a favorable outcome. Each of these groups was divided into two subgroups: 1A (n=8) — patients who died of sepsis, 1B (n=2) — patients who died of other causes, 2A (n=7) — patients with a favorable outcome of sepsis and 2B (n=20) — patients without septic complications.

The PSEP level was measured with PATHFAST enzyme immunoassay analyzer (LSI Medience Corporation, Japan). Descriptive statistics of quantitative characteristics were represented by medians and quartiles (Me (LQ; UQ)), values of area under the ROC curve (AUC) and 95% confidence interval. To compare the groups, the Mann–Whitney U test was used.

RESULTS The concentration of PSEP 785 pg/ml and higher on day 2–5 from the onset of the disease indicated a significant risk of purulent complications in intensive care patients with a sensitivity of 91.2% (95% CI, 77.93–97.89) and a specificity of 77.3% (95% CI, 51.59–97.91). The area under the curve for PSEP was 0.859 (AUC). PCT — 0.804 (AUC), sensitivity — 85%, specificity — 57%. CRP — 0.718 (AUC), sensitivity — 75% and specificity — 50%.

CONCLUSION Based on the data obtained, it can be concluded that PSEP has the most informative value and diagnostic sensitivity compared to other markers of inflammation for an early diagnosis of sepsis in patients with SAP.

Keywords: acute pancreatitis, presepsin, procalcitonin, pancreatic necrosis

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AUC — area under ROC-curve
CRP — C-reactive protein
IL — interleukin
LPS — lipopolysaccharide
LPSBP — lipopolysaccharide-binding peptide
MOF — multiple organ failure
PCT — procalcitonin
PSEP — presepsin
SAP — severe acute pancreatitis
SSIR — syndrome of systemic inflammatory reaction
TNF — tumor necrosis factor

Sepsis is the leading cause of death in patients with severe acute pancreatitis (SAP) [1]. In a quarter of patients, the development of pancreatitis is destructive [2]. Mortality in destructive forms of pancreatitis reaches 33-75% and is caused, mainly, by purulent-inflammatory processes in parapancreatic tissue, as well as sepsis and multiple organ failure (MOF) [3]. Such a significant mortality in destructive forms of pancreatitis is associated with untimely diagnosis and late onset of pathogenetic treatment. A characteristic feature of the SAP is the high incidence of infection of the destruction zones with pancreatonecrosis (40-70%) [4]. However, for the first week of the disease, infection is detected only in 24% of patients and in 36% on week 2. In later terms, on week 3, infectious complications are already detected in 71% of patients. At the same time, every hour of delay in the use of effective antibiotic therapy during the first 6 hours reduces the survival rate by 7.6% [5].

From the first hours after the onset of SAP, the syndrome of the systemic inflammatory reaction (SSIR) develops, which progression is associated with a risk of purulent-septic complications [6, 7]. Therefore, the diagnosis and monitoring of SSIR in the early period of acute pancreatitis is an urgent task. Common clinical criteria used for this purpose (body temperature, heart rate and respiration rate, leukocyte level) are not specific for the infection. At the same time, the use of fine needle aspiration biopsy as a method of detecting infection of pancreatogenic destruction areas has certain drawbacks due to the invasiveness of the procedure, as well as the duration of the traditional microbiological studies.

The need for early detection of the infectious process and dynamic control of treatment stimulates the search for new laboratory markers of SSIR, express methods of microbiological studies of infectious complications and sepsis that allow to quickly identify the infectious process, assess the severity of the patient's condition and predict the development of sepsis. In this regard, early diagnosis of the formation of purulent-septic complications and sepsis in patients with SAP is an urgent task.

At present, various biomarkers are used to diagnose systemic inflammatory reaction and sepsis, including interleukins (IL-1β, IL-2 and its soluble receptor (IL-2R), IL-6, IL-10), tumor necrosis factor (TNF), lipopolysaccharide binding peptide (LPSBP), and a number of others. The most common markers are C-reactive protein (CRP) and procalcitonin (PCT).

C-reactive protein (CRP) belongs to the group of proteins of the acute phase of inflammation and is synthesized primarily in hepatocytes. Synthesis of CRP is initiated by antigens, immune complexes, infectious agents and particles of necrotic tissue. The concentration of CRP increases in the first 4-6 hours from the onset of the pathological process. Most often, this marker is used to diagnose acute inflammatory conditions and necrotic processes, as well as to evaluate the effectiveness of therapeutic measures [8-10]. At the same time, an increase in the level of CRP in a number of cases may be assocoated with non-specific causes, which reduces its diagnostic significance and does not allow it to be used to confirm the infectious etiology of inflammation [11].

Procalcitonin (PCT) is a glycoprotein that is a precursor of calcitonin. Normally, PCT is synthesized by C-cells of the pancreas. In the inflammatory process caused by bacterial and fungal infections, the level of PCT increases with stimulation with endotoxins or proinflammatory cytokines (IL-1β, IL-6, TNF) for 6-12 hours. In septicemia, the PCT level exceeds 2 ng/ml [10, 11]. In case of generalized bacterial, parasitic or fungal infection with systemic manifestations, the PCT concentration increases rapidly and significantly [12]. High values of PCT are precursors of the development of sepsis and/or multi-organ failure (MOF) [8, 11, 13]. PCT has high specificity, but its values may increase in the absence of infection in the first 3 days after trauma, with extensive damage to organs and tissues, toxic damage to the liver, and in patients after organ transplantation with immunosuppression [8, 14]. This "non-infectious" increase reduces its diagnostic potential.

In recent years, publications have appeared on the high diagnostic and prognostic significance of presepsin (PSEP), a protein formed by macrophages in the process of phagocytosis of infectious agents [15-24].

In the literature analyzed by us, the informative value of PSEP as an early marker of septic complications in patients with SAP is not covered. The purpose of this study is to compare the prognostic and diagnostic significance of PSEP and acute phase proteins (CRP, PCT) for the formation of purulent-septic complications in patients with SAP at an early stage.

MATERIAL AND METHODS

The study included 37 patients with SAP who were on treatment at the N.V. Sklifosovsky Institute in the period from October 2015 to June 2016. Patients with a diagnosis of SAP depending on the course and outcome of the disease were divided into two groups: the 1st group (n=10) included deceased patients, the 2nd group (n=27) consisted of patients with a favorable outcome (Table 1). Each of these groups was divided into two subgroups: 1A group (n=8) included deceased patients diagnosed with "sepsis", 1B group (n=2) consisted of patients who died from other causes. The 2A group (n=7) included patients with sepsis, which ended in a favorable outcome, and the group 2B (n=20) incleded patients whose effective treatment was not accompanied by septic complications.

Table 1

Characteristics of patients with SAP

	1*A* group with sepsis (*n*=8)	1*B* group without sepsis (*n*=2)	2*A* with sepsis (*n*=7)	2*B* group without sepsis (*n*=20)
Age (years), *Me* (*LQ*; *UQ*)	46 (27; 75)	69 (61; 77)	53 (38; 76)	36 (22; 77)
Male/ female	6 / 2	0 / 2	6 /1	10 / 10
Duration of stay, *Me* (*LQ*; *UQ*)	10 (3; 60)	21 (16; 25)	10 (3; 43)	16 (4; 29)
Pancreatic necrosis				
Microfocal	1 (12.5%)	–	–	2 (10.5%)
Macrofocal	–	2 (100%)	–	3 (15.8%)
Omental bursitis	7 (87.5%)	1 (50%)	1 (12.5%)	5 (26.3%)
Subtotal/ total	4 (50%)	–	–	–

When confirming the infection of the destruction areas, patients underwent minimally invasive drainage interventions under ultrasound guidance. Traditional surgical interventions were not performed. The patients underwent a complex of laboratory tests, which included blood levels of acute phase proteins (CRP, PCT) and PSEP on day 2-5 and 12-15 from the onset of acute pancreatitis. The level of CRP was determined with the biochemical

nephelometer BN ProSpec ("Dade Behring GMBH", USA), PCT was assesssed with the immunofluorescence analyzer Vidas ("BioMérieux", France). The assessment of PSEP level in patients with SAP and healthy donors (n=51) was performed with the immunochemiluminescent PATHFAST analyzer ("LSI Medience Corporation", Japan). Statistical analysis of the obtained data was carried out with the help of GrafPad Software (Version 6, USA). The optimum cut-off value is set for each ROC curve through the Youden index. Descriptive statistics of quantitative characteristics is represented by medians and quartiles (Me (LQ; UQ)), area values under the ROC curve (AUC) and 95% confidence interval. To compare the groups, the Mann-Whitney U test was used.

POC analysis was used to assess the sensitivity, specificity, and diagnostic significance of the resulting immunological marker complex. Differences at $p < 0.05$ were assumed to be statistically significant.

RESULTS

When analyzing the results of the examination of patients with SAP, it was established that the CRP values on the 2-5th day from the onset of the disease in all groups of patients (deceased and survivors) exceeded the upper limit of the norm (Table 2). At the same time, the level of CRP (Me) in patients with established diagnosis of sepsis of 1A group exceeded the upper limit of the norm by more than 100 times, more than 60 times in patients of 1B and 2A group, and more than 46 times in 2B group (Table 2). According to the ROC analysis, the sensitivity level of CRP determination for early diagnosis of septic complications was 75%, specificity was 50% (Table 3). However, the detected changes in the level of CRP for 2-5 days were not statistically significant ($p > 0.05$) (Fig. 1). At the same time, in group 1A there was a tendency to a more significant increase in the level of CRP (Me) compared to patients of 1B, 2A group (1.7 times) and patients of group 2B (2.4 times) (Table 2). In other words, the degree of increase in the CRP depended on the severity of patients' condition.

Table 2

The biomarker values on day 2–5 from the onset of the disease in patients with sepsis and without septic complications

Parameters, reference interval	1*A* group (*n*=8) with sepsis *Me* (*LQ*; *UQ*)	1*B* group (*n*=2) without sepsis *Me* (*LQ*; *UQ*)	2*A* group (*n*=7) with sepsis *Me* (*LQ*; *UQ*)	2*B* group (*n*=20) withou sepsis *Me* (*LQ*; *UQ*)
CRP 0–3 mg/l	338,8 (203; 500)	197,0 (121.0; 244.5)	193,0 (24.3; 336)	138,5 (52.3; 277.5)
PCT <0.5 ng/ml	8,6 (4.9; 169)	0,775 (0.62; 0.93)	1,68 (0.24; 2.3)	0,28 (0.10; 0.70)
PSEP <337.0 pg/ml	976 (771; 1,011)	444,5 (104; 703)	984 (793; 1,155)	192,5 (141; 371)

Notes: CRP — C-reactive protein; PCT — procalcitonin; PSEP — presepsin

Table 3

The diagnostic value of acute-phase proteins on day 2–5 in patients with sepsis and without septic complications (ROC analysis)

	AUC	*Cut-off*	Sensitivity, %	Specificity, %
PSEP	0.859	785 pg/ml	91	77
CRP	0.718	243 mg/ml	75	50
PCT	0.804	0.95 ng/ml	85	57

Notes: AUC — ROC curve; CRP — C-reactive protein; PCT — procalcitonin; PSEP — presepsin

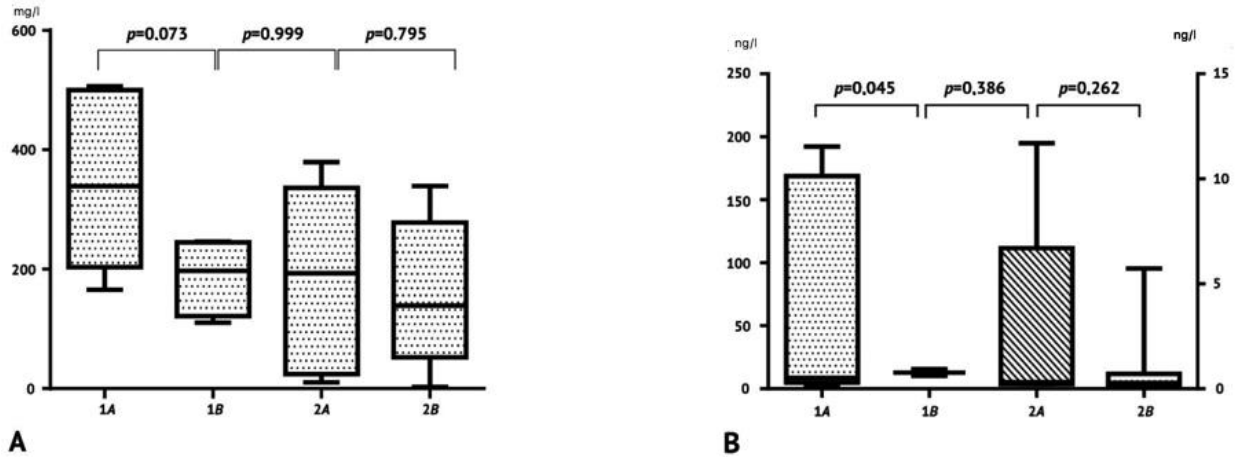

Fig. 1. CRP (A) and PCT (B) on day 2-5 from the onset of the disease in patients with sepsis and without septic complications
Notes: CRP — C-reactive protein; PCT — procalcitonin

The level of PCT (Me) on day 2-5 from the onset of the disease in patients with sepsis and adverse outcome of SAP (1A group) exceeded the upper limit of the norm by 17 times. In patients with sepsisi and favorable outcome (group 2A), the PCT value (1.68 (0.24; 2.3) ng/ml) was observed 3 times higher than the upper limit of the norm, but 5 times lower than the PCT in group 1A (Table 2). In 3 patients (42.8%) with a relatively mild course of SAP, the PCT values did not exceed the upper limit of the norm (0.2-0.3 ng/ml). In 4 patients (57.2%) with a more serious course of SAP, the PCT level ranged from 2.0 to 11.0 ng/ml. In the groups without sepsis, a slight increase in PCT level (1B and 2B) was observed - 0.775 (0.62; 0.93) ng/ml and 0.19 (0.10; 0.70) ng/ml, respectively (Table 2). In 3 patients (15%) of the 2B group, the indices (0.62-0.71 ng/ml) were higher than the reference interval. The diagnostic sensitivity of the PCT determination for predicting adverse outcomes in SAP (ROC-analysis data) on day 2-5 from the onset of the disease in our study was 85%, specificity was 57% (Fig. 3, Table 3). Statistically significant differences in assessing the level of PCT on day 2-5 from the onset of the disease were noted between groups of patients with established diagnosis of sepsis and without sepsis ($p < 0.05$), except groups 1B and 2A (Fig. 1).

When analyzing the results of determining the value of PSEP in patients with sepsis of two groups (1A and 2A), it was found that the level of PSEP (Me) exceeded the value of the reference interval of the donor group (111.0 (66.3-195.9) pg/ml) 9 times , and the upper limit of the norm (manufacturer data in the description of reagent sets) is 3 times (Table 2). The general tendency of PSEP index growth in groups of patients with sepsis (1A - 976 pg/ml and 2A - 984 pg/ml, respectively) was noted in comparison with groups of patients without septic complications (1B and 2B) more than 2 and 5 times, respectively ($p < 0.05$, which is statistically significant) (Fig. 2). According to the ROC analysis, PSEP had the greatest diagnostic significance for early detection of septic complications on day 2-5 from the onset of the disease (threshold value of 785.0 pg/ml, sensitivity 91%, specificity 77%) (Table 3). There were statistically insignificant differences in the values of PSEP in severe septic patients 1A and 2A groups ($p=0.612$) (Table 2). At the same time, when comparing the groups of patients with the established diagnosis of sepsis and without sepsis on day 2-5 according to PSEP level, the differences were statistically significant ($p<0.05$) (Fig. 2).

Fig. 2. PSEP on day 2-5 from the onset of the disease in patients with sepsis and without septic complications
Notes: PSEP — presepsin

When assessing PSEP as a prognostic indicator of purulent-septic complications of SAP, it was shown that in patients it is advisable to measure the concentration of PSEP on day 1-3 from the onset of the disease. The concentration of PSEP in the blood plasma more than 785.0 pg/ml was an unfavorable prognostic sign (the area under the curve during the ROC analysis on the graph was 0.859, the sensitivity was 91%, the specificity was 77%) (Fig. 3, Table 3). Therefore, in the early stages of systemic infection developmnt, PSEP is a sensitive and specific marker of sepsis.

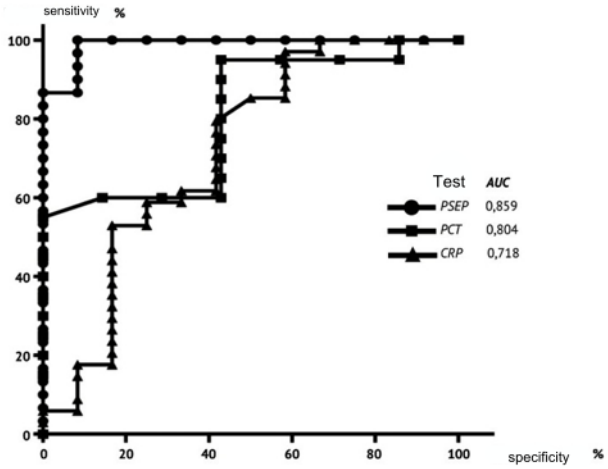

Fig. 3. ROC curves for PSEP, PCT, CRP on day 2-5 in patients with sepsis and without septic complications
Notes: CRP — C-reactive protein; PCT — procalcitonin; PSEP — presepsin

The results of examination of patients with SAP on days 12-15 from the onset of the disease showed that the blood level of CRP (Me) exceeded the upper value of the norm in groups of patients with the established diagnosis of sepsis by 47 times in 1A, by more than 30 times in 2A, by 19 times in 1B and by 17 times in 2B (Table 4). The value of CRP in septic patients with an adverse outcome of the 1A group was 1.4 times higher than that of patients in group 2A (p=0.1905). However, there was a general trend towards a decrease in CRP values in all patients (deceased and survivors), regardless of the differences in the groups (Table 4). At the same time, in the groups of severe septic patients 1A and patients without sepsis 1B with an unfavorable outcome, with subsequent development of sepsis and MOF, a statistically insignificant decrease in the level of CRP was revealed in comparison with the initial result (2-5 days) by 2.4 and 3.5 times, respectively. When assessing the level of CRP using ROC analysis, the area under the curve was 0.67, which makes it possible to consider the diagnostic significance of this indicator to be low (Fig. 4). To predict secondary infection in patients with SAP with the help of CRP, the level of 194 mg/l was sensitive by 71%, but had a low specificity of 52%. In the groups of patients without sepsis (1B and 2B), statistically insignificant differences were observed (p=0.2644) (Table 4).

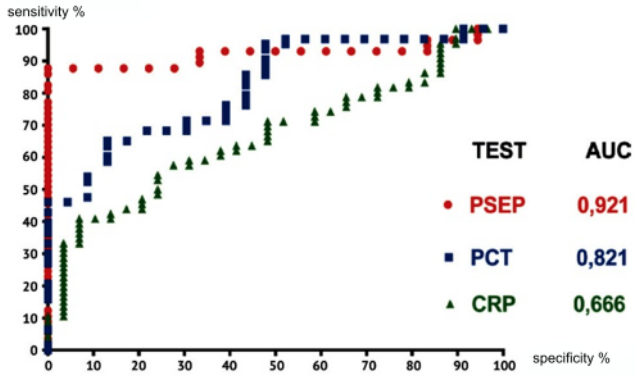

Fig. 4. ROC curves for PSEP, PCT, CRP on days 12–15 in patients with sepsis and without septic complications
Notes: CRP — C-reactive protein; PCT — procalcitonin; PSEP — presepsin

Table 4

The biomarkers values on day 12–15 from the onset of the disease in patients with sepsis and without septic complications

Parameters, reference interval	1*A* group (*n*=8) with sepsis *Me* (*LQ*; *UQ*	1*B* group (*n*=2) without sepsis *Me* (*LQ*; *UQ*	2*A* group (*n*=7) with sepsis *Me* (*LQ*; *UQ*	2*B* group (*n*=20) without sepsis *Me* (*LQ*; *UQ*
CRP 0–3 mg/l	141.0 (95.7; 177.0)	56.0 (43.0; 247.0)	98.0 (56.5; 104.5)	52.5 (24.5; 143.0)
PCT <0.5 ng/ml	7.2 (1.7; 19.7)	2.2 (1.2; 3.5)	0.14 (0.15; 0.27)	0.1 (0.04; 0.17)
PSEP <337.0 pg/ml	1,012.0 (853; 1,108.0)	546.3 (546; 547)	296.0 (281; 488)	188.5 (144; 255)

Notes: CRP — C-reactive protein; PCT — procalcitonin; PSEP — presepsin

The level of PCT in the blood of patients with the subsequent fatal outcome of the disease (1A and 1B) on day 12-15 statistically significantly exceeded the upper limit of the norm by 14 and 4 times, respectively ($p<0.05$) (Table 4). However, when analyzing the dynamics of PCT results in patients with sepsis and an unfavorable outcome (1A) on day 2-5 and 12-15 from the onset of the disease, there was a tendency to a statistically insignificant decrease in the index by 1.2 times in comparison with the initial values ($p>0.05$). At the same time, the level of PCT on day 12-15 in the groups of patients with favorable outcome (2A and 2B) decreased and did not exceed the upper norm (0.14 ng/ml and 0.1 ng/ml, respectively) (Table 4) .

The values of PSEP (Me) on day 12-15 in patients of 1A group exceeded those in patients who did not have septic complications of group 1B by 1.9 times ($p=0.1333$), and by 5.4 times in group 2B ($p=0.020$) and exceeded the value of the reference interval of the donor group by 9.1 times (Table 4). In the groups of patients with favorable outcome (2A and 2B) on day 12-15, the values of PSEP (Me) corresponded to the reference interval (296.0 and 188.5 pg/ml) (Table 4). The results show that the increase in PSEP in patients with SAP is associated with generalization of the infectious process, and a decrease occurrs due to the activity of the recovery processes.

The ROC AUC values for predicting adverse outcomes in SAP were: PCT 0.821, with a sensitivity of 84%, a specificity of 57%; PSEP 0.921, with a sensitivity of 88% and a specificity of 78% (Table 5), which confirms the good diagnostic significance of these indicators. The data of Table. 5 show that PSEP has greater diagnostic sensitivity and specificity for detection of septic complications of SAP. The PCT value had high sensitivity but low specificity.

Table 5

The diagnostic value of acute-phase proteins on days 12–15 in patients with sepsis and without septic complications (ROC analysis)

Parameters, reference interval	*AUC*	*Cut-off*	Sensitivity, %	Specificity, %
CRP 0–3mg/l	0.666	194 mg/l	71	52
PCT <0.5 ng/ml	0.821	0.98 ng/ml	84	57
PSEP <337.0 pg/ml	0.921	810 pg/ml	88	78

Notes: CRP — C-reactive protein; PCT — procalcitonin; PSEP — presepsin

Simultaneous assessment of PSEP and PCT significantly increased the specificity of the data obtained.

DISCUSSION

Currently, there is a limited number of tests that allow early detection of the development of septic complications in patients with SAP to be performed. To diagnose sepsis and identify in a short time groups of high risk, it is necessary to include more specific and pathogenetically significant markers of this severe process into the screening scheme. In the presented study, the informative value of PSEP as an early marker of sepsis in patients with SAP was studied in comparison with acute phase proteins (CRP and PCT).

It was found that the elevated CRP level, measured in dynamics, was not a guaranteed indicator of secondary infection and could not be used for the prediction of sepsis and mortality, due to the lack of sensitivity and specificity of this indicator.

Measurement of PCT concentration in dynamics allowed the following conclusion to be drawn: if the septic process developed in the SSIR, the PCT increased more significantly than the level of CRP, reflecting the severity of this process to a greater extent. The highest PCT concentrations were observed in patients with septic shock and MOF. However, PCT values in patients with sepsis varied widely, which made it difficult to diagnose infectious complications in these patients properly (Tables 2, 4).

In addition, for differential diagnosis and monitoring of sepsis in patients with SAP, the dynamics of PCT and CRP have the greatest clinical significance, and not their absolute value.

It was found that in patients with septic complications of SAP, the blood level of PSEP was of high prognostic and diagnostic value. The concentration of PSEP 785 pg/ml and higher on day 2-5 from the onset of the disease indicated a significant risk of purulent complications in patients of intensive care units with a sensitivity of 91.2% (95% Cl, 77.93-97.89) and specificity of 77.3% (95% Cl, 51.59-97.91). Therefore, the PSEP test can be used as an early marker for predicting the severity of pancreatic necrosis and evaluating the effectiveness of surgical treatment.

The availability and wide adoption of the CRP test in clinical practice gives great advantages in its use. However, PCT and PSEP tests with high sensitivity and specificity for early diagnosis of sepsis in SAP allow early initiation of etiotropic therapy to be performed and shortens hospitalization time. The disadvantage of PCT and PSEP tests is the need for using special equipment and the lack of experience of their widespread use in clinical practice.

CONCLUSION

Based on the data obtained, it can be stated that PSEP has the greatest informative significance and diagnostic sensitivity in comparison with other markers of inflammation for the early diagnosis of sepsis in patients with SAP. The high concentration of PSEP in blood is a predivtor of an unfavorable outcome within 5 days from the onset of the disease.

FINDINGS

1. On day 2-5 after the onset of the disease, the most prognostically significantfor the development of indectious complications after SAP are PSEP — 0.859 (AUC), sensitivity — 91%, specificity — 77% and PCT — 0.804 (AUC), sensitivity — 85%, specificity — 57%. CRP has a smaller prognostic significance (AUC 0.718, sensitivity 75%, and specificity 50%).

2. Earle analysis of PSEP and PCT biomarkers helps identify groups of patients with high risk of purulent-septic complications and cmonitor the effectiveness of treatment of patients with severe acute pancreatitis.

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