C-REACTIVE PROTEIN AND PROCALCITONIN AS INDEPENDENT PROGNOSTIC MARKERS IN ACUTE PANCREATITIS

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Abstract: *Severe acute pancreatitis (SAP) is one of the main causes of intra-abdominal hypertension of retroperitoneal origin, which can lead to multiple system organ failure (MSOF). Mortality rate of SAP remains high between 15% and 30%, and is the result of pancreatic necrosis infection and MSOF. Circulatory level of C-reactive protein (CRP) is an independent predictor of the evolution of acute pancreatitis. Measurement of serum CRP is the best test available to identify pancreatic necrosis. There is no correlation between serum levels of CRP and the presence of infected pancreatic necrosis. Procalcitonin is a precursor of calcitonin, which was shown to be a marker for severe bacterial and fungal infections. Materials and methods: The study included 48 patients hospitalized in the Clinical County Emergency Hospital of Sibiu, between October 2011 and January 2013, diagnosed with acute pancreatitis. Evolution of values of procalcitonin (PCT) and C-reactive protein (CRP) was analysed, as markers of prognosis in acute pancreatitis. Results: 48 hours after admission, for a cut-off value of 150 mg/L, CRP had a sensitivity (Se) of 76% and a specificity (Sp) of 88%, positive predictive value (PPV) of 81%, negative predictive value (NPV) of 86% and an accuracy of 84% for predicting the severe development of acute pancreatitis [AUC: 0.844 (95% CI: 0.732 to 0.956), p <0.001]. The maximum values of PCT had a biphasic trend with a slight increase of the maximum values on the 2nd day of hospitalization in most patients and later, 10 days after admission, in patients with septic complications. Conclusions: CRP values after 48 hours could be correlated with traditional prognostic scores (APACHE II and Ranson). PCT maximum values were associated with severe inflammation, bacterial translocation, septic complications and mortality rate in AP.*

INTRODUCTION

Severe acute pancreatitis (SAP) is one of the main causes of intra-abdominal hypertension of retroperitoneal origin, which can lead to multiple system organ failure (MSOF). Mortality rate of SAP remains high (15% and 30%) and is the result of pancreatic necrosis infection and MSOF.(1,2,3,4) Several biochemical markers, medical imaging procedures and multiple clinical and biochemical scores were used to assess the severity of acute pancreatitis and its prognosis.

C-reactive protein is a non-specific inflammatory mediator produced in hepatocytes. Production and secretion is stimulated by interleukins 1 and 6. C-reactive protein (CRP) is considered to be a useful indicator for assessing severity but only 48 hours after disease onset. Maximum concentrations in blood occur within 72 hours of the onset of pancreatitis. Circulatory level of CRP is an independent predictor of the evolution of acute pancreatitis. CRP has been imposed in recent years as a marker of the severity of acute pancreatitis due to the easy access of dosing in the current practice. Measurement of serum CRP is the best test available to identify pancreatic necrosis. CRP values of more than 120 mg/L are associated with necrosis. There is no correlation between serum levels of CRP and the presence of infected necrosis.(1,4)

Procalcitonin (PCT) is a marker for severe bacterial and fungal infections.(4) Procalcitonin is a marker of identifying sepsis and also, an important marker for identifying severe forms of acute pancreatitis.(5)

Procalcitonin values between 2 and 10 ng/ml signify the presence of sepsis with high risk of progression to severe sepsis. Procalcitonin values above 10 ng/ml signify the presence of severe sepsis or septic shock.(6) In acute pancreatitis, it allows the detection of severe forms and the differentiation between sterile and infected necrosis.(7)

PURPOSE

The aim of this prospective study is to compare serum levels of C-reactive protein (CRP) and procalcitonin (PCT) with traditional multiple variables scoring systems (APACHE II and Ranson) and to establish a correlation between these markers in the evolution of severe acute pancreatitis. The study was divided into two parts:

1. Establishing the prognostic value of CRP 48 hours after admission in patients with acute pancreatitis and comparing their values.
2. Comparing the maximum values of PCT in patients with acute pancreatitis

MATERIALS AND METHODS

The study was approved by the Ethics Committee of the Clinical County Emergency Hospital of Sibiu.

This prospective observational study included 48 patients admitted to the Clinical Department of Anesthesia and Intensive Care and to the Surgical Department of the Clinical County Emergency Hospital of Sibiu, diagnosed with acute pancreatitis from October 2011 to January 2013. The diagnosis of acute pancreatitis was based on clinical and laboratory criteria

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(3 times increase of serum amylase levels) and CT scan by the presence of obvious signs compatible with the diagnosis of AP. The clinical course of these patients was followed up prospectively until discharge or death.

Establishing the severity of pancreatitis was performed using the Atlanta criteria.

Pancreatic necrosis, pancreatic abscess and pancreatic pseudocyst were considered local complications. Pancreatic infection was confirmed by bacteriological examination of the fluid collected by needle aspiration or during surgery.

Laboratory and physiological data were recorded prospectively, 48 hours for APACHE II score and 48 hours for the Ranson score.

Serum C-reactive protein was measured using the CRP Vario quantitative method at admission and within 48 hours of admission.

In our study, we used the values of APACHE II and Ranson score and of CRP measured within 48 hours of admission.

Serum procalcitonin was measured by Brahms semi-quantitative method, on admission, 24 hours, 48 hours, on day 8^{th} and 10^{th} after admission and once again repeated on the 4^{th} week after admission. In our study, we used BRAHMS PCT - Q kit, an immunoassay for the semi-quantitative detection of PCT. It is a fast method with results available in 45 minutes.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 15.0, Chicago. Patients were divided into two groups: one with mild acute pancreatitis (MAP) and one with severe acute pancreatitis (SAP) based on Atlanta classification. Variables were described in absolute numbers and percentages. Statistical processing was performed with student *t* test, Mann - Whitney *U* test and Chi square test. Statistical test results were presented, where appropriate, with a confidence interval of 95%. The p value <0.05 was considered statistically significant. Scores of prediction, specificity, sensitivity, accuracy or prognosis were determined using the receiver operating characteristic curve (ROC).

RESULTS AND DISCUSSIONS

A total of 48 patients (28 men and 20 women) with acute pancreatitis were included in our study, aged between 21 and 69 years. Demographic, clinical, biochemical and laboratory variables are described in table no. 1.

Table no. 1. Demographic, clinical, biochemical and laboratory variables of the study group

Demographic, clinical, biochemical and laboratory variables	
Age (years)	69 (21)
Gender	28 men /20 women
Etiology • Gallstones • Alcohol • Dyslipidaemia	 31 (66%) 14 (30%) 2 (4%)
APACHE II score at 48 de ore (average value)	11.25
Ranson score on admission (average value) Ranson score at 48 hours (average value)	2.6 4
Length of stay (days)	12 (97)
Death (%)	7 (15%)

The 48 patients were aged between 21 and 69 years, the average age of the study group being 45 years.

Of the 48 cases, 23 (47.91%) patients had mild pancreatitis forms and 25 (52.08%) patients had severe acute pancreatitis.

Establishing the severity of pancreatitis was performed using Atlanta classification.

The increased number of patients with severe pancreatitis in the study group compared to the literature (80% MAP and 20% SAP) can be attributed to the slight increase in the number of patients with severe acute pancreatitis in recent years, taking over the patient only from surgical clinics, knowing that mild, non-biliary forms of pancreatitis are hospitalized in medical clinics, increased consumption of alcohol in our country, and probably due to the development of diagnostic procedures and the accumulation of experience regarding the diagnosis and treatment of this pathology.

Table no. 2. Clinical characteristics of the patients with acute pancreatitis

	MAP (n = 23)	**SAP** (n = 25)	**Total**	***p* value**
Local complications	2 (8.7%)	25 (100%)	27 (56.2%)	< 0.001
SIRS	7 (30.4%)	25 (100%)	32 (66.6%)	< 0.001
Organ failure at admission	0	11 (44%)	11 (22.9%)	< 0.001
Failure of a single organ	9 (39.1%)	1 (4%)	10 (20.8%)	0.22
Multiple system organ failure	0	24 (96%)	24 (50%)	< 0.001
Pancreatic necrosis*	2 (8.7%)	25(100%)	27 (56.2%)	< 0.001
Extended pancreatic necrosis	0	8 (32%)	8 (16.6%)	0.005
Infected pancreatic necrosis	0	12 (48%)	12 (25%)	< 0.01
Sepsis	0	12 (48%)	12 (25%)	0.02
Mortality	0	7 (28%)	7 (15%)	0.01

MAP, mild acute pancreatitis; SAP, severe acute pancreatitis;
** Pancreatic necrosis 30% or less;*
P value was determined by the Chi square test.

SAP patients had at least a single organ failure during hospitalization (table no. 2). All patients with severe acute pancreatitis had local complications. The mortality rate was of 15% and was recorded in the group with SAP (table no. 2). 11 of 25 (44%) patients had single organ failure at admission. 24 (96%) patients with SAP developed MSOF during disease progression. Organ failure in patients with MAP was transient. All patients who had single organ failure during hospitalization survived.

Frequency of pancreatic necrosis, extended pancreatic necrosis and infected necrosis is shown in table no. 2. Extension of pancreatic necrosis was evidenced by CT scan.

Measurement of serum CRP is the best test available to identify pancreatic necrosis. CRP values greater than 120 mg/L are associated with necrosis. Wilson et al. have suggested that if the peak concentration of CRP is higher than 210 mg/L on days 2-4 or greater than 120 mg/L at the end of the first week, this simple factor can be as predictive as the multifactorial scoring systems.

Concentration of serum C-reactive protein was measured on admission and 48 hours after admission. Mean C-reactive protein values were determined for each group (patients with MAP and SAP patients) and were compared. The difference between the two groups reached statistical significance (p <0.05).

Table no. 3. Comparison of average CRP levels in both groups

No. of days from admission	Average CRP levels mg/L		95% CI	*p* value*
	SAP	MAP		
On admision 2	148.6 224.7	24.5 108.3	21.3-202.6 87.4-280.8	0.018 0.001

**P value was determined by the Chi square test.*

In our study, we used C-reactive protein values 48 hours after admission, as predictive marker for severe acute pancreatitis development and we compared them with the Ranson and APACHE II scores calculated at 48 hours.

The maximum measured values of PCT are shown in Table. 4 and they were compared with the occurrence of complications and mortality rate.

Of the 25 patients with SAP, 12 (48%) patients had infected pancreatic necrosis and sepsis or septic shock. Among the patients with infected pancreatic necrosis, 6 had sepsis and 6 patients had septic shock. In patients with sepsis, PCT values were in the range of 2-10 ng/ml, and in patients with septic shock, PCT values were > 10 ng/ml.

Table no. 4. Maximum PCT values for our study group

Procalcitonin	No. of patients
< 0,5 ng/ml	11 (22.91%)
0.5 - 2 ng/ml	14 (29.16%)
2 - 10 ng/ml	17 (35.41%)
>10 ng/ml	6 (12.5%)

Diagnosis of infected pancreatic necrosis was checked by CT ("gas bubble" appearance), puncture aspiration, serum levels of procalcitonin and confirmed by bacteriological cultures of samples collected by needle aspiration or intraoperatively.

Further on, the results were collated aiming at:

- evolution of CRP 48 hours after admission and correlating the measured values with traditional prognostic scores (APACHE II and Ranson);
- evolution of PCT values and the correlation between maximum PCT and disease severity.

Values of prognostic markers measured 48 hours after admission are presented in Table 5 in terms of average values

Table no. 5. The average values of prognostic markers at 48 hours after admission

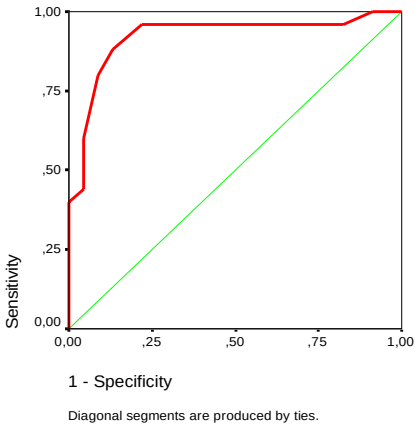
	MAP	SAP	*p** value
APACHE II score	6.5 (5 – 14)	16 (8 – 24)	< 0.001
Ranson score	2.78 (2 – 6)	5.2 (3 – 10)	0,002
CRP (mg/L)	108,3 (20 – 160)	224,7 (84 – 320)	< 0.001

MAP-Mild acute pancreatitis; SAP-severe acute pancreatitis; APACHE II-Acute Physiology and Chronic Health II; CRP-C-reactive protein
*Mann - Whitney U test

We used the ROC curve (figures no. 1,2,3) to represent and compare the values of APACHE II, Ranson scores and CPR at 48 hours after admission and to determine their value as predictors of progression towards severe acute pancreatitis.

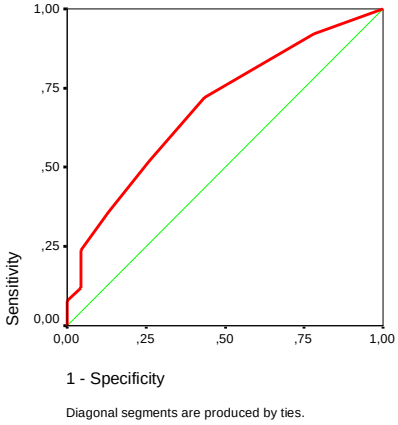
Procalcitonin values could not be represented by the ROC curve because determining its value is done by a semi-quantitative method.

Figure no. 1. The ROC curve of APACHE II score values at 48 hours from admission



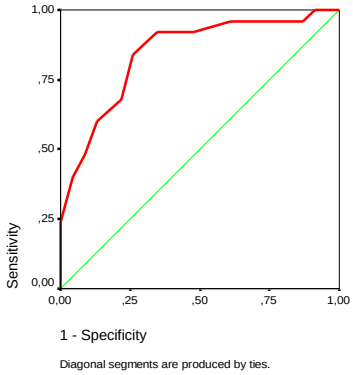
AUC (Area under the curve) is 0.922.
CI 95% (Confidence Interval): 0.837 – 1.

Figure no. 2. The ROC curve of the Ranson score at 48 hours after admission



AUC (Area under the curve) is ,69.
CI 95% (Confidence Interval): 0.54 – 0.839.

Figure no. 3. The ROC curve of CRP values at 48 hours after admission



AUC (Area under the curve) is 0.844.
CI 95% (Confidence Interval): 0.732 – 0.956

48 hours after admission, for a cut-off value of 150 mg/L, CRP had a sensitivity (Se) of 76% and a specificity (Sp) of 88%, positive predictive value (PPV) of 81%, negative

predictive value (NPV) of 86% and an accuracy of 84% for predicting the severe development of acute pancreatitis [AUC: 0.844 (95% CI: 0.732 to 0.956), p <0.001].

Sensitivity and specificity of predictive parameters in assessing the severity of AP 48 hours from admission are shown in table no. 5.

Table no. 6. The prognostic value of markers at 48 hours after admission in predicting progression towards severe acute pancreatitis

	AUC (95% CI)	*P* value	Cut - off	Sensitivity	Specificity
APACHE II score	0.922 (0.837-1)	< 0.001	8	0.91	0.84
Ranson score	0.69 (0.54-0.839)	0.002	3	0.72	0.64
CRP	0.844 (0.732-0.956)	< 0.001	150 mg/L	0.76	0.88

APACHE II-Acute Physiology and Chronic Health II; CRP-C reactive protein;

In terms of establishing a correlation between disease severity and the maximum serum procalcitonin in those 48 patients with acute pancreatitis, data are illustrated in figure no. 5 and figure no. 6.

Figure no. 5. Distribution of patients according to the day of hospitalization when they reached maximum PCT values

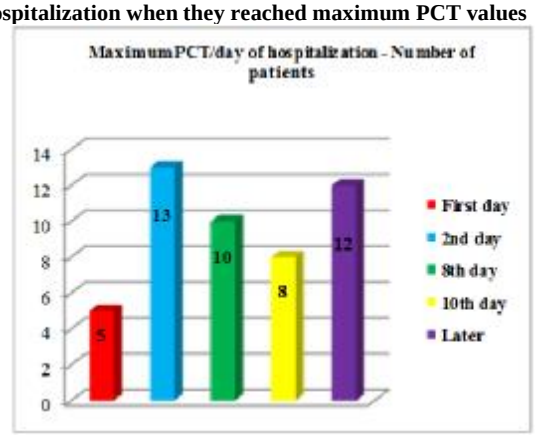
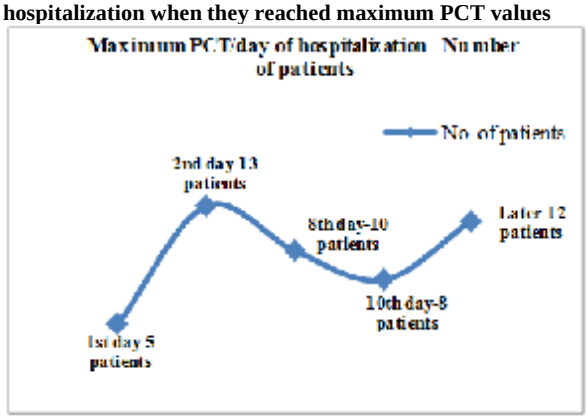


Figure no. 6. Distribution of patients according to the day of hospitalization when they reached maximum PCT values



The maximum values of PCT were recorded as follows: on the first day of hospitalization in 5 patients, on the second day in 13 patients, on the eighth day in 10 patients, on the tenth day in 8 patients and later, in 12 patients. Maximum values of PCT were significantly higher in the patients with SAP and in non-survivors.

In this study we analysed:

- Evolution of serum CRP 48 hours after admission, correlated with traditional prognostic scores (APACHE II and Ranson) within 48 hours
- Evolution of serum PCT levels in patients with acute pancreatitis and their correlation with disease severity

There are several studies that have correlated the APACHE II score at admission and within 72 hours with SAP and a high mortality rate, with values of sensitivity and specificity between 65 and 81%, respectively 77-91% (8,9,10). As in these studies, the cut-off value of the APACHE II score of 8 at 48 hours after admission, had the highest sensitivity (91%) and specificity (84%).

In clinical practice, probably the most widely used prognostic marker is the CRP, but it can be useful only 48 hours after disease onset. CRP value of 120 mg/L can detect the presence of pancreatic necrosis with an accuracy of 67-100%.(11) Some authors suggest a CRP cut-off value of 150 mg/L.(4,12,13)

In his study, Gurleyik et al., for a cut-off value of 150 mg/L, CRP had a sensitivity of 84.6% and a specificity of 73.8%, compared to our study.(13)

The values of the APACHE II score > 8 and CRP > 120 mg/L, 24 hours after admission are generally accepted as indicative of severe inflammation, as shown in several studies.(1,2,11)

In the literature, there are few studies that analyse CRP as a predictor of the severity of AP 24 hours after admission, with a cut-off value of 120 mg/L. Bezmarevic et al. analysed the predictive value of CRP 24 hours after admission with a sensitivity of 75% and a specificity of 86% for a cut-off value of CRP of 120 mg/L(2). We studied the predictive value of CRP 48 hours after admission and found a slightly higher sensitivity and specificity (Se 76%, Sp 88%) for a cut-off value of CRP of 150 mg/L. The difference might be due to the later occurrence of CRP peak value (48 hours after onset of the desease).

In their study, Simona Bota et al. found a sensitivity of 77.2% and a specificity of 89.9% for CRP cut-off value of 120 mg/L, compared to our study.(14)

We chose to analyse the predictive value of CRP 48 after admission since it is known that serum CRP levels increase 48 hours after disease onset.

Procalcitonin is used in clinical practice for the diagnosis of SAP and for monitoring disease prognosis.(1,2,4,5,7) Pancreatic infection and sepsis are major complications in SAP, with significant impact on disease management and prognosis. Several studies, including that of Bettina M. Rau et al. showed that, in patients with SAP who developed infected pancreatic necrosis and MODS, or in those who died, significantly higher concentrations of maximum PCT levels were found during disease progression, compared to those in whom these complications were missing.(15) In contrast, no differences were observed for CRP, which is a marker of sterile pancreatic necrosis, not infected. Serum procalcitonin values greater than 3.8 ng/ml are predictive of organ dysfunction occurrence.(4) A recent study on the role of procalcitonin in identifying patients with severe acute pancreatitis and poor outcome assigns a sensitivity of 72% and a specificity of 86% for this test..(4)

The maximum values of PCT have a biphasic trend with an increase of the maximum values on the 2nd day of hospitalization in most patients and later and after the 10th day in a large number of patients. In the early stages of AP, PCT

growth can be caused due to inflammation.(2,16,17,18) Later elevation of PCT can be caused by infection of pancreatic necrosis, abscess and/or sepsis.(19,20,21)

Pancreatic necrosis infection is the most important risk factor for mortality due to AP and, typically occurs during the second or third week of disease in 40-70% of patients with necrotizing pancreatitis. Prevention, early diagnosis and optimal treatment of infection in SAP are crucial for the evolution of this disease.(4)

Early detection of bacterial translocation in intestines and identifying the factors that determine the translocation can reduce local and systemic complications in acute pancreatitis.(22,23,24) In this regard, antibiotic prophylaxis and abdominal decompression may reduce mortality in patients with AP.

We decided to use the maximum values of PCT for the following reasons. First, the maximum values of PCT are associated with severe inflammation, with bacterial translocation, which are influencing the mortality rate in AP. PCT high values were recorded in those with septic complications and in non-survivors.

CONCLUSIONS

CRP values 48 hours after admission could be correlated with traditional prognostic scores (APACHE II and Ranson). In our study, we found a CRP cut-off value of 150 mg/L at 48 hours after admission to have the same predictive value as the traditional scores.

PCT maximum values are associated with severe inflammation, bacterial translocation, also influencing the mortality rate in AP. PCT high values were recorded in those with septic complications, high number of hospitalization days and in non-survivors. PCT maximum values had a biphasic trend with a maximum level on the 2nd day of admission in the majority of patients and later after the 10th day in a large number of patients. In the early stages of AP, PCT growth is caused by inflammation. Later growth of PCT is due to pancreatic necrosis infection, abscess and/or sepsis.

REFERENCES

1. Lipsett PA. Acute Pancreatitis. Textbook of Critical Care. Fifth Edition, edited by Mitchell P. Fink, Edward Abraham, Jean-Louis Vincent, Patrick M. Kochanek. 2005;122:1021-32.
2. Bezmarevic M, Mirkovic D, Soldatovic I, Stamenkovic D, Mitrovic N, Perisic N, Marjanovic I, Mickovic S, Karanikolas M. Correlation between procalcitonin and intra-abdominal pressure and their role in prediction of the severity of acute pancreatitis. Pancreatology. 2012;12:337-343.
3. Hidalgo Rosas JM, Navarro Soto S, MD, Serra Araci J, Rebasa Cladera P, Hernandez Borlan R, Vazquez Sanchez A, Bory Ros F, Grande Posa L. Intra-abdominal pressure as a marker of severity in acute pancreatitis. Original Communications. J. Surg; 2007. p. 173-178.
4. Lipsett PA. Acute Pancreatitis. Textbook of Critical Care. 6th Edition, edited by Mitchell P. Fink, Edward Abraham, Jean-Louis Vincent, Patrick M. Kochanek. 2011;104:785-94.
5. Beger HG, Rau B, Mayer J, Pralle U. Natural Course of Acute Pancreatitis, World J Surg. 1997;21(2):130-135.
6. B.R.A.H.M.S – PCT – Q - Rapid diagnosis of septic infections; 2012.
7. Grigoraş I. Pancreatita acută - forma severă. Jurnalul de Chirurgie, Iaşi. 2005;1(1):9-20.
8. Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379 - 400.
9. Gravante G, Garcea G, Ong SL, Metcalfe MS, Berry DP, Lloyd DM, et al. Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. Pancreatology. 2009;9:601-14.
10. Pezzilli R, Mancini F. Assessment of severity of acute pancreatitis: a comparison between old and most recent modalities used to evaluate this perennial problem. World J Gastroenterol.1999;5(4):283 - 5.
11. Wilson C, Heads A, Shenkin A, Imrie CW. C-reactive protein, antiproteases and complement factors as objective markers of severity in acute pancreatitis. Br J Surg. 1989;76:177-181.
12. Creţu D. Contribuţii la diagnosticul şi tratamentul pancreatitei acute. Teză de doctorat. Sibiu; 2011. p. 6-51.
13. Gurleyic G, Emir S, Kilicoglu G, Arman A, Saglam. Computed tomography severity index, Apache II score, and serum CRP concentration for predicting the severity of acute pancreatitis. JOP. 2005;6(6):562-7.
14. Bota B, Sporea I, Sirli R, Popescu A, Strain M, Focsa M, Danila M, Chisevescu D. Predictive factors for severe evolution in acute pancreatitis and a new score for predicting a severe outcome. Ann Gastroenterol. 2013;26(2):156-62.
15. Rau BM, Kemppainen EA, Gumles AA, Buchler MW, Wegscheider K, Bassi C, Puolakkainen PA, Berger HG. Early Assessment of Pancreatic Infections and Overall Prognosis in Severe Acute Pancreatitis by Procalcitonin (PCT). Ann Surg. 2007;245(5): 45-754.
16. Madl C, Druml C. Systemic consequences of ileus. Best Pract Res Clin Gastroenterol. 2003;17(3):445-56.
17. Maruna P, Frasko R, Gurlich R. Plasma procalcitonin in patients with ileus. Relations to other inflammatory parameters. Physiol Res. 2008;57:48-6.
18. Grollman AI, Goodman S, Fine A. Localized paralytic ileus: an early roentgen sign in acute pancreatitis. Surg Gynecol Obstet. 1950;91(1):65-70.
19. Al-Nawas B, Krammer I, Shah PM. Procalcitonin in the diagnosis of severe infections. Eur J Med Res. 1996;1:331-3.
20. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaund J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infections. Lancet. 1993;341:515-8.
21. Kylanpaa-Back MI, Takala A, Kemppainen E, Puolakkainen P, Repo H. Procalcitonin strip test in early detection of severe pancreatitis. Br J Surg. 2001;88:222-7.
22. Luiten EJ, Hop WC, Endtz HP, Bruining HA. Prognostic importance of gram – negative intestinal colonization preceding pancreatic infection in severe acute pancreatitis: results of a controlled clinical trial of selective decontamination. Intensive Care Med. 1998;24:438-45.
23. Runkel NS, Moody FG, Smith GS, Rodriguez LF, LaRocco MT, Miller TA. The role of the gut in the development of sepsis in acute pancreatitis. J Surg Res. 1991;51:18-23.
24. Gianotti L, Munda R, Alexander JW. Pancreatitis – induced microbial translocation: a study of the mechanisms. Res Surg; 1992.