CORRELATION BETWEEN INTRA-ABDOMINAL PRESSURE AND C- REACTIVE PROTEIN IN ACUTE PANCREATITIS

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Abstract: This study aimed at establishing the predictive value of the markers CRP and IAP within 48 hours from admission in patients with acute pancreatitis and to compare their predictive value. In our study, we used CRP values at 48 hours after admission, as a predictive marker for the evolution to SAP and we compared them with IAP at 48 hours and with Ranson and APACHE II scores also calculated at 48 hours. We used ROC curves for representation and comparison of APACHE II score, Ranson score, CRP and IAP at 48 hours after admission and for determining their value as predictors of progression to severe acute pancreatitis.

INTRODUCTION

Severe acute pancreatitis is one of the main causes of intra-abdominal pressure (IAP), which can lead to multiple organic dysfunctions.(1,2) Intra-abdominal hypertension (IAH) is defined as the sustained or repeated elevation of intra-abdominal pressure (IAP) over 12 mmHg (3), whereas the abdominal compartment syndrome (ACS) is the combination between IAP >20mmHg and the onset of organ dysfunction.

The mechanisms of IAH in acute pancreatitis (AP) include the elevation of capillary permeability, hypoalbuminemia, third space losses with retroperitoneal and visceral edema.(1)

The decrease of the blood flow to the mesenteric artery, following the increase of IAH leads to the alteration of the integrity of the intestinal barrier with ischemia, reperfusion, bacterial translocation and the infection of pancreatic and peripancreatic necrosis.(2)

According to some studies, patients with IAP < 12 mmHg tend to develop a mild form of pancreatitis, whereas patients with IAP ≥ 12mm Hg develop severe acute pancreatitis (SAP).(1-8) Hidalgo Rosas et al. describe in their study the evolution of severe forms of pancreatitis in patients with IAH ≥ 14 mmHg.(2) Evidence of the significant organic dysfunction were highlighted even at IAP values of 10 mmHg.(9)

The IAP increase after the onset of AP is increasingly researched. In patients suffering from AP, the IAP increase is associated with the early development of organ failure, increase in mortality and number of admission days to the ICU. The early detection of the IAH increase is of major importance in the management of AP and it can lower the morbidity and the mortality associated with the disease.(5)

More and more biochemical markers and multiple clinical, biochemical and radiological scores have been used in order to assess the severity of acute pancreatitis and its prognosis (APACHE, Ranson, C reactive protein etc.). Research is focusing on finding a single marker which can be quickly measured, in a repeated, cost-effective manner and which can avoid causing discomfort to the patient.

The circulatory level of C reactive protein (CRP) is a prognostic factor independent of AP which has become essential during the last years due to the dosing accessibility in current practice.(3) The measurement of the serum level of CRP is the best test available in order to identify pancreatic necrosis. The drawback of this prognostic test is its relevance only after 48 hours from the onset of the disease. The maximum blood concentration is established at 72 hours from the onset of pancreatitis. The CRP values higher than 120 mg/L are associated with necrosis. There is no correlation between the serum level of CRP and the presence of infected necrosis.(10)

PURPOSE

The aim of this prospective study is to compare the CRP serum levels with IAP and to establish the existence of a correlation between these markers in the SAP. The serum values of CRP and the IAP values were compared to the traditional scoring systems (APACHE II and Ranson).

The study aimed at establishing the prognostic value of CRP, IAP after 48 hours from admission of AP patients and comparing their values.

MATERIALS AND METHODS

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

From January 2011 to April 2014, a group of 48 patients admitted to the Intensive Care Unit and in the Surgical Departments of the County Clinical Emergency Hospital Sibiu, being diagnosed with acute pancreatitis, were included in this prospective, observational study. The AP diagnosis was established on admission based on clinical, laboratory data - the three times elevation of serum amylases and radiological findings. The clinical outcome of these patients has been prospectively followed until discharge or death.

Grading the different types of pancreatitis according to the severity index was performed by observing the Atlanta criteria. The laboratory and clinical data have been prospectively recorded, 48 hours for APACHE score and 48 hours for Ranson score.

The Apache II score (Acute Physiology and Chronic Health Evaluation II) is easier to apply. It is based on multiple clinical and laboratory criteria, it can be figured online and it correlates well with mortality in acute pancreatitis.

IAP was measured every 24 hours and the 48 hour

score was measured in order to assess and relate it to the accepted prognosis factors: CRP, APACHE II and Ranson scores. IAP was measured by using the technique described by Kron. et al.(11) In order to determine IAP we used a catheter set up into the urinary bladder, connected to a pressure transducer. We instilled 50 ml saline into the urinary bladder and the pubic symphysis was considered to be level 0.

Serum levels of CRP were measured using the CRP quantitative Vario method on admission and after 48 hours from the time of admission. In our study, we used the values of APACHE II, Ranson score, CRP measured 48 hours after admission.

The statistical analysis was performed using the SPSS program (Statistical Package for the Social Sciences) version 15.0, Chicago. The patients were divided into two groups: those with mild acute pancreatitis (MAP) and those with severe acute pancreatitis (SAP) based on the Atlanta classification criteria.

The variables were described in absolute numbers and percentages. The statistical interpretation was made using *t* student test, Mann - Whitney U test and Chi square test. The results of the statistical tests were presented, where applicable, with a confidence interval of 95%. A $p < 0.05$ value was considered statistically significant. The predictive scores, of specificity, sensibility, accuracy or prognosis were established by using the analysis curve of receiver operating characteristics (ROC).

RESULTS

A total number of 48 patients (28 males and 20 females) diagnosed with acute pancreatitis were included in our study, between the age range of 21-69 years old. The demographic, clinical, biochemical and paraclinical variables were described in table no. 1.

Table no. 1. The demographic, clinical and paraclinical variables of the studied group

The demographic, clinical and paraclinical, laboratory variables	
Age	69 (21)
Gender	28 males / 20 females
Etiology:	
• Biliary	31 (66%)
• Alcoholic	14 (30%)
• Dyslipidemia	2 (4%)
APACHE II at the time of admission (mean value)	12
APACHE II after 48 hours (mean value)	11.25
Ranson score at admission (mean value)	2.6
Ranson score after 48 hours (mean value)	4
C reactive protein (mg/dL) at admission	20 (150)
C reactive protein after 48 hours	120 (250)
The duration of hospitalization (no. days)	12 (97)
Deaths (%)	7 (15%)

The group of 48 patients, aged between 21-69 years ols, the mean age of the group was 45 years (21-69 years).

Out of the total of 48 cases, 23 (47.91%) of patients had mild forms of pancreatitis and 25 (52.08%) cases were diagnosed with severe acute pancreatitis.

Table no. 2. Complications of the 48 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
The failure of one organ	9 (39.1%)	1 (4%)	10 (20.8%)	0.22
Multiple organ and system 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, ASP - acute severe pancreatitis; The P value was calculated using Chi square test.

Patients with SAP were diagnosed with at least one organ failure during the time of admission (table no. 2). All patients with SAP had local pancreatic complications. The mortality rate was 15% and it was recorded in the SAP group (table no. 2). 11 out 25 (44%) patients with SAP had one organ failure at the time of admission. 24 (96%) patients with SAP developed MSOF during the development of the disease. The organ failure present in patients with MAP was transitory. All patients who had one organ failure during hospitalization survived.

Measuring the serum levels of CRP is the best test available in order to identify pancreatic necrosis. CRP values higher than 120 mh/L are associated with necrosis.(10) Wilson et al. have suggested that if the peak of the CRP concentration is higher than 210 mg/L during the days 2-4, or higher than 120 mg/L at the end of the first week, this simple factor can be as predictive as the multifactor scoring systems.(10)

The serum levels of CRP were measured at the time of admission and at 48 hours from admission. The mean values of CRP were calculated for each group (patients with MAP or patients with SAP) and compared. The difference between the two groups had a statistical significance ($p < 0.05$) (table no. 3).

Table no. 3. The comparison of the mean values of CRP in the two groups

Number of days from admission	Mean CRP values mg/dl		95% CI	P Value
	SAP	MAP		
1	148.6	24,5	21.3-202.6	0.018
2	224.7	108.3	87.4-280.8	0.001

The P value was calculated using Chi square test.

In our study we used the CRP values after 48 hours from admission, as a prediction marker in the evolution towards acute severe pancreatitis and we compared them with IAP at 48 hours and with the Ranson and APACHE II scores after 48 hours.

When referring to IAP, the cases of acute pancreatitis from the studied case-studies were divided into IAP< 12 mmHg and pancreatitis with IAP $\geq$ 12mmHg, out of which those with IAP > 20 mmHg and organ failure being included in ACS with a reserved outcome.

- 22 patients with IAP < 12 mmHg;
- 20 patients with IAH (12 mmHg $\geq$ IAH $\leq$ 20 mmHg);
- 6 patients with ACS (IAP> 20 mmHg).

Table no. 4. The IAP values in AP patients

IAP value	Severity (depending on IAP)	No. cases
IAP < 12 mmHg	AP with normal IAP	22 (45.83%)
IAP <12 m $\leq$ 20mmHg	AP with IAH	20 (41.66%)
IAP > 20 mmHg	AP with ACS	6 (12.5%)

Out of the total of 48 patients, 22 (45.83%) had mild forms of IAP, IAP < 12 mmHg, 26 (54.16%) patients had IAH (the sustained increase of IAP $\geq$ 12) out of which 6 (12.5%) patients had ACS with IAP > 20 mmHg and organ failure (table no. 4).

26 patients had IAH and ACS. In the group of patients with SAP, 22 (88%) patients had IAH with ACS. The 6 patients with ACS were in the SAP group, where they represented 24 % of cases. In the MAP group, 4 (17.39%) patients had IAH. 16

patients out of 25 (64%) with SAP had IAH after 48 hours from admission. The patients with IAH and ACS presented SIRS and MSOF frequently (table no. 2). The mortality of patients in the ACS group was 83.33% (5 patients) through MSOF and septic shock.

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The values of the prognostic markers measured at 48 hours from the point of admission were represented in table no. 5 through mean values.

Table no. 5. The values of the prognostic markers measured at 48 hours from the point of admission

	MAP	ASP	p* value
APACHE II	6.5 (5 – 14)	16 (8 – 24)	< 0,001
Ranson	2.78 (2 – 6)	5.2 (3 – 10)	0.002
CRP	108 (20 – 160)	224 (84 – 320)	< 0.001
IAP	10 (6 – 14)	16 (11 – 24)	< 0.001

MAP, Mild acute pancreatitis; ASP, acute severe pancreatitis; APACHE II, Acute Physiology And Chronic Health II; CRP, C reactive protein; IAP, intra-abdominal pressure. *The Mann - Whitney U test

In order to represent and compare the values of APACHE II, Ranson, CRP and IAP after 48 hours from the time of admission and to establish their value as prediction factors of the progression towards SAP, we used ROC curves (figures no. 1,2,3,4,5).

Figure no. 1. The ROC curve of calculated values for APACHE II after 48 hours from admission


Diagonal segments are produced by ties.
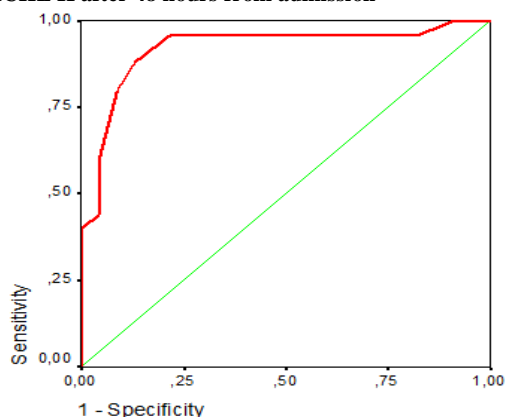
AUC (Area under the curve): 0,922.
CI 95% (Confidence Interval): 0,837 – 1.

Figure no. 2. The ROC curve of Ranson score calculated values after 48 hours

Diagonal segments are produced by ties.
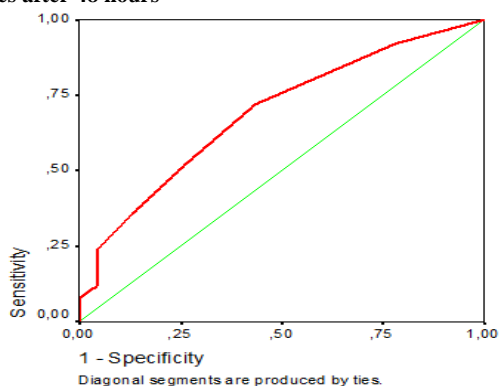
AUC (Area under the curve): 0,69.
CI 95% (Confidence Interval): 0,54 – 0,839.

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

Diagonal segments are produced by ties.
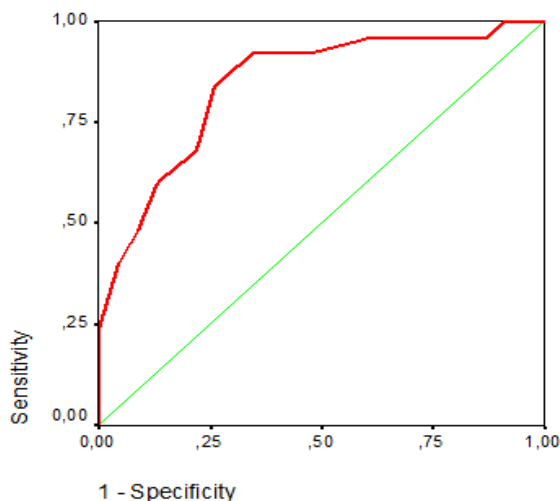
AUC (Area under the curve): 0,844.
CI 95% (Confidence Interval): 0,732 – 0,956

At 48 hours from admission, for a cut-off value of 150 mg/L, CRP has a sensitivity (Se) of 76% and a specificity (Sp) of 88%, positive predictive value (PPV) of 81%, the negative predictive value (NPV) of 86% and an accuracy of 84 % to predict the evolution of acute severe pancreatitis [AUC: 0.844 (95% CI: 0.732 – 0.956), p<0.001].

Figure no. 4. The ROC curve of the measured values of IAP after 48 hours from the point of admission

Diagonal segments are produced by ties.
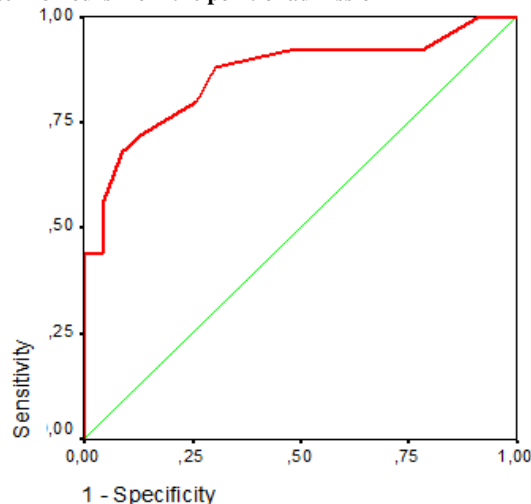
AUC (Area under the curve): 0,861.
CI 95% (Confidence Interval): 0,753 – 0,969.

At 48 hours from admission, for a cut-off value of 12 mmHg, IAP has a sensitivity (Se) of 74% and a specificity (Sp) of 80%, positive predictive value (PPV) of 73%, negative predictive value (NPV) of 76% and 75% accuracy for the prediction of acute severe pancreatitis [AUC: 0.861 (95% CI: 0,753 – 0.969), p<0.001].

Figure no. 5. The ROC curve of the measured and calculated values of APACHE II, Ranson, CRP și IAP scores at 48 hours from admission

Diagonal segments are produced by ties.
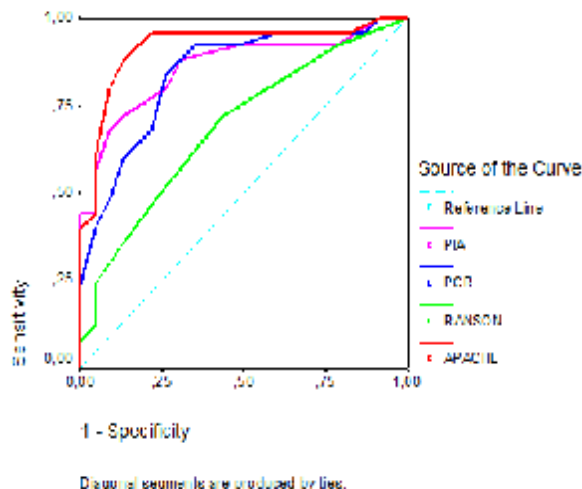
The sensitivity and specificity of predicting parameters used in the assessment of predicting parameters used in the assessment of AP severity at 48 hours from admission are presented in table no. 6.

Table no. 6. The prognosis value of markers measured after 48 hours from the time of admission, when predicting the progression to 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	0.76	0.88
IAH	0.861 (0.753-0.969)	<0.001	12	0.74	0.80

APACHE II, Acute Physiology And Chronic Health II; CRP, C reactive protein; IAH intra-abdominal hypertension.

When referring to the prediction of severity in the first 48 hours from admission, IAP had a sensitivity and a specificity better than the Ranson score and similar to CRP. Both CRP and IAP could be correlated with APACHE II score in the prediction of severity of acute pancreatitis. IAP can be used as a predictor of AP severity.

DISCUSSIONS

In this study, we have analyzed the correlation between the serum values of CRP and IAP values after 48 hours from admission correlated with the traditional scoring systems (APACHE II and Ranson) after 48 hours.

This study evaluates the IAP role as a prognostic factor of AP severity and it correlates the IAP values and the CRP ones at 48 hours after the admission of the AP patients.

There are several studies which have correlated the APACHE II score on admission and in the first 72 hours with AP severity, with sensitivity and specificity values of 65 and 81%, 77-91% respectively.(12,13,14,15) As in these studies, the cut-off value of 8 for APACHE II score at 48 hours from the time of admission, had the highest sensitivity (91%) and specificity (84%).

In clinical practice, probably the most common prognostic marker would be CRP, but it can be useful only after 48 hours from the onset of the disease. The CRP value over 120 mg/L can detect the presence of pancreatic necrosis with an accuracy of 67-100% Some authors suggest a cut-off value of CRP of 150 mg/L.(16,17,18)

In his study, Gurleyik et al. (18), for a cut-off value of 150 mg/L, CRP had a sensitivity of 84.6% and a specificity of 73.8%, as compared to our study.

The values of APACHE II ≥ 8 and CRP ≥120 mg/L, at 24 hours from admission are generally accepted as indicators of severe inflammation, as it is shown in several studies.(1,10,15)

In other studies in this field, there are some that analyze CRP as a prediction factor for the severity of AP at 24 hours from admission, with a cut-off value of 120 mg/L. This is also the study of Bezmarevic et al. who have analyzed the predictive value of CRP at 24 hours from admission with a sensitivity of 75% and a specificity of 86% for a cut-off value of CRP of 120 mg/L.(1) We have studied the predictive value of CRP at 48 hours from admission and we have found slightly higher sensitivity and specificity (Se 76%, Sp 88%) for a CRP cut-off value of 150 mg/L. The difference may be due to the late emergence of CRP peak value (after 48 hours from the onset).

Simona Bota et al. (19) have noticed that for the CRP cut-off value of 120 mg/L, the sensitivity was 77.2% and specificity 89.9%, as compared to our study.

We have decided to analyze the CRP and IAP predictive values at 48 hours from admission because it is known that the CRP serum levels rise after 48 hours from the onset of the disease and also the predictive value for IAP is better after 48 hours from admission. Nevertheless, the measurement of IAP should be made only after the control of pain.(2)

In our study, we have observed that IAP after 48 hours from admission was significantly higher in patients who developed severe types of AP. The mortality in patients with ACS was extremely high.

IAP at 48 hours could be correlated both with CRP values and the APACHE II and Ranson at 48 hours. The cut-off value could be correlated both with CRP values and with APACHE II and Ranson after 48 hours. The IAP cut-off value after 48 hours was 12 mmHg, with a sensitivity of 75% and a specificity of 80%. In accordance with other studies, in our study the IAP after 48 hours from admission could be correlated with the CRP serum values after 48 hours, having the same predictive value. As IAP indirectly affects the degree of inflammation in AP patients, it can be a good marker for disease severity.

Surgical decompression is generally accepted as a therapeutic measure of patients with SAP and ACS. Until now, the right timing for the decompression is unknown and there are no experimental data, despite the increasing mortality rate in these patients. In their study, made on the swine model, Ke L. et al show that decompression performed on SAP with IAP of 25 mmHg was associated with a significant decrease of mortality, hemodynamic improvement and of organ function, even the attenuation of histological injury and the inflammation intensity.(20)

Together with other researchers, they also conclude that decompression performed too early or too late must be avoided due to the unfavourable evolution in these cases. Early decompression may cause and enhance the release of proinflammatory cytokines which lead to secondary injury in the evolution of MSOF.(21) On the other hand, the prolonged interval between the timing of diagnosing ACS and performing the decompression, with the persistence of elevated IAP determines splanchnic ischemia, reperfusion and bacterial translocation from the gastrointestinal lumen and subsequent

pancreatic infection.(8)

Early detection and prompt treatment of IAH through decompression should be essential in the prevention of the subsequent development of organ dysfunction in AP patients.(8)

CONCLUSIONS

IAP measured after 48 hours from admission could be correlated with CRP and the APACHE II and Ranson scores after 48 hours. For a cut-off value after 48 hours of 12 mmHg, IAP had the highest sensitivity and specificity. In our study, we have found the CRP cut-off value after 48 hours from the time of admission was of 150 mmHg/L.

In the prediction of the severity of acute pancreatitis during the first 48 hours from admission, IAP had a sensitivity and a specificity higher than the Ranson score and similar specificity with APACHE II. IAP sensitivity and specificity after 48 hours from admission are similar to those of CRP after 48 hours.

IAH after 48 hours from the time of admission can be used as a predictor for AP severity.

REFERENCES

1. 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.
2. Hidalgo Rosas JM, MD, Navarro Soto S, MD, Serra Araci J, MD, Rebasa Cladera P, MD, Hernandez Borlan R, MD, Vazquez Sanchez A, MD, Bory Ros F, MD and Grande Posa L, MD. Intra-abdominal pressure as a marker of severity in acute pancreatitis. Original Communications. J Surg. 2007;173-178.
3. Papavramidis TS, Marinis AD, Pliakos I, Kesisoglou I and Papavramidou N. Abdominal compartment syndrome – Intra-abdominal hypertension: Defining, diagnosing, and managing. J Emerg Trauma Shock. 2011;279-29.
4. Kron IL, Harman PK, Nolan SP. The measurement of intraabdominal pressure as a criterion for abdominal reexploration. Ann Surg. 1984;199:28-30.
5. De Waele JJ, Haste E, Blot S, Decruyenaere J, Colardyn F. Intra-abdominal hypertension in patients with severe acute pancreatitis. Crit Care. 2005;9:452-7.
6. Pupelis G, Austrums E, Snippe K, Berzins M. Clinical significance of increased intra-abdominal pressure in severe acute pancreatitis. Acta Chir Belg. 2002;102:71-4.
7. Windsor JA. Search for prognostic markers for acute pancreatitis. Lancet. 2000;355:1924-5.
8. Hong Chen, Fei Li, Jia-Guo Jia. Abdominal compartment syndrome in patients with severe acute pancreatitis in early stage. World J Gastroenterol. 2008;14(22):3541-3548.
9. Sugrue M, Buist MD, Hourihan F, Deane S, Bauman A, Hilmann K. Prospective study of intraabdominal hypertension and renal function after laparotomy. Br J Surg. 1995;82:235-38.
10. 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.
11. Kron IL, Harman K, Nolan SP. The Measurement of Intra-abdominal Pressure as a Criterion for Abdominal Re-exploration. Ann Surg. 1984;199(1):28-30.
12. Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379 - 400.
13. 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.
14. 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.
15. 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.
16. Crețu D. Contribuții la diagnosticul și tratamentul pancreatitei acute. Teză de doctorat. Sibiu; 2011. p. 6-51.
17. 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.
18. 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.
19. Bota S, 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.
20. Ke L, Ni HB, Tong YH, Li WQ, Li N, Li JS. The importance of timing of decompression in severe acute pancreatitis combined with abdominal compartment syndrome. J Trauma Acute Care Surg. 2013;74(4):1060-6.
21. Rezende-Neto JB, Moore EE, Melo de Andrade MV, Teixeira MM, Lisboa FA, Arantes RM, de Souza DG, da Cunha-Melo JR. Systemic inflammatory response secondary to abdominal compartment syndrome: stage for multiple organ failure. J Trauma. 2002 Dec;53(6):1121-8.