Procalcitonin and BISAP score versus C-reactive protein and APACHE II score in early assessment of severity and outcome of acute pancreatitis

Prokalcitonin i BISAP skor naspram C-reaktivnog proteina i APACHE II skora u ranoj proceni težine i ishoda akutnog pankreatitisa

Mihailo Bezmarević*, Zoran Kostić*[†], Miodrag Jovanović*, Saša Micković*,
Darko Mirković*[†], Ivan Soldatović[‡], Bratislav Trifunović*[†], Janko Pejović[†§],
Svetlana Vujanić[§]

*Clinic for Abdominal and Endocrine Surgery, [§]Department of Medical Biochemistry,
Military Medical Academy, Belgrade, Serbia; [†]University of Defence, Faculty of
Medicine of the Military Medical Academy, Belgrade, Serbia, [‡]Institute of Statistics and
Informatics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Abstract

Background/Aim. Early assessment of severity and continuous monitoring of patients are the key factors for adequate treatment of acute pancreatitis (AP). The aim of this study was to determine the value of procalcitonin (PCT) and Bedside Index for Severity in Acute Pancreatitis (BISAP) scoring system as prognostic markers in early stages of AP with comparison to other established indicators such as C-reactive protein (CRP) and Acute Physiology and Chronic Health Evaluation (APACHE) II score. **Methods.** This prospective study included 51 patients (29 with severe AP). In the first 24 h of admission in all patients the APACHE II score and BISAP score, CRP and PCT serum concentrations were determined. The values of PCT serum concentrations and BISAP score were compared with values of CRP serum concentrations and APACHE II score, in relation to the severity and outcome of the disease. **Results.** Values of PCT, CRP, BISAP score and APACHE II score, measured at 24 h of admission, were significantly elevated in patients with severe form of the disease. In predicting severity of AP at 24 h of admission, sensitivity and specificity of the BISAP score were 74% and 59%, respectively, APACHE II score 89% and 69%, respectively, CRP 75% and 86%, respectively, and PCT 86% and 63%, respectively. It was found that PCT is highly significant predictor of the disease outcome ($p < 0,001$). **Conclusion.** In early assessment of AP severity, PCT has better predictive value than CRP, and similar to the APACHE II score. APACHE II score is a stronger predictor of the disease severity than BISAP score. PCT is a good predictor of AP outcome.

Key words:
pancreatitis, acute necrotizing; severity of illness index; prognosis; apache; treatment outcome.

Apstrakt

Uvod/Cilj. Rana procena težine i kontinuirano praćenje bolesnika sa akutnim pankreatitisom (AP) osnovni su preduslovi za adekvatno lečenje. Cilj rada bio je da se odredi značaj prokalcitonina (PCT) i *Bedside Index for Severity in Acute Pancreatitis* (BISAP) skoring sistema kao prognostičkih parametara u ranoj fazi AP u poređenju sa ostalim poznatim indikatorima kao što su C-reaktivni protein (CRP) i *Acute Physiology and Chronic Health Evaluation* (APACHE II) *score*. **Metode.** Ova prospektivna studija obuhvatila je 51 bolesnika (29 sa teškim oblikom AP). U prva 24 sata od prijema kod svih bolesnika određen je APACHE II skor, BISAP skor, i koncentracije CRP i PCT u serumu. Vrednosti koncentracija PCT u serumu i vrednosti BISAP skora upoređivane su sa vrednostima koncentracija CRP u serumu i APACHE II skora, u odnosu na težinu i ishod bolesti. **Rezultati.** Vrednosti PCT, CRP, BISAP i APACHE II skora, merene u prva 24 sata od prijema u bolnicu, bile su statistički značajno povišene kod bolesnika sa teškim oblikom bolesti. U proceni težine AP u prva 24 sata od prijema, utvrđene su vrednosti senzitivnosti i specifičnosti za BISAP skor (74%; 59%), APACHE II skor (89%; 69%), CRP (75%; 86%) i PCT (86%; 63%). Nađeno je da je PCT visokoznačajan prediktor ishoda bolesti ($p < 0,001$) **Zaključak.** U ranoj proceni težine AP, PCT je bolji indikator od CRP i sličan je APACHE II skoru. APACHE II skor je jači prediktor težine bolesti od BISAP skora. PCT je dobar prediktor ishoda AP.

Ključne reči:
pankreatitis, akutni, nekrotizujući; bolest, indeks težine; prognoza; apache; lečenje, ishod.

Correspondence to: Mihailo Bezmarević, Military Medical Academy, Clinic for General Surgery, Crnotravska 12, 11 000 Belgrade, Serbia. Phone: + 381 11 360 8550, Mob: +381 64 199 4288. E-mail: bezmarevicm@gmail.com; mihailo@t-com.me

Introduction

"Acute pancreatitis is the most terrible of all the calamities that occur in connection to the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it, render it the most formidable of catastrophes." (Moynihan, 1925) [1]

This quotation still remains true because AP is unpredictable disease, while severity and outcome is difficult to predict with relatively few effective therapeutic options. The mortality rate of severe AP (SAP) is about 25%–50%, mainly due to multiple organ failure (MOF) and infection of the necrosis [2, 3]. Early identification of patients with SAP and their continuous monitoring are essential for adequate and timely treatment in order to prevent possible complications.

Several biochemical markers [4, 5], radiological imaging procedures [6–8], and multiple clinical and biochemical scores [9–12] have been used to assess severity and outcome of AP. An ideal prognostic method should be simple, inexpensive, routinely available and highly accurate. Such a method is not available yet.

Procalcitonin (PCT) is a 116-amino acids propeptide of calcitonin who has no known hormonal activity, and can be detected in high concentrations in serum during severe bacterial or fungal but not viral infections [13–15]. It is synthesized and secreted by the inflammatory and hepatic cells in response to proinflammatory mediators. PCT was introduced as an early marker of the systemic inflammatory response, sepsis, and MOF. Further, increased serum concentration levels of PCT have been suggested to be a reliable early predictor of a severe outcome and infected pancreatic necrosis [15–18].

In a recent multicentric cohort study a new prognostic scoring system, so-called Bedside Index for Severity in Acute Pancreatitis (BISAP), for prediction of mortality of AP was proposed [19]. Using blood urea nitrogen (BUN) level > 25 mg/dL, impaired mental status, systemic inflamatory response syndrome (SIRS), age > 60 years and pleural effusion in patients with AP, investigators were able to stratify patients within the first 24 hours of hospitalisation into distinct risk groups for in hospital mortality. These authors [19] presented BISAP score as an accurate scoring system in prediction of the outcome of AP, such as Acute Physiology and Chronic Health Evaluation (APACHE) II score.

The aim of this study was to assess the value of serum PCT concentrations and value of BISAP score as prognostic markers of severity of AP in early stages of AP in comparison with CRP and APACHE II score, as well as to estimate the value of PCT and BISAP score as predictors of AP outcome.

Methods

The study included of 51 consecutive patients with AP admitted to the Clinic for Abdominal and Endocrine Surgery, Military Medical Academy, Belgrade, Serbia, over a 14-month period (from June 2009 to September 2010). In all patients, the diagnosis of AP was established in the first three hours of admission by the presence of typical clinical symptoms for AP, serum concentrations of amylase and/or lipase above three times from the upper limit, and/or radiological evidence compatible with AP. The patients with confirmed AP were admitted to our hospital as primary or secondary referrals within 48 h after the onset of the symptoms and prospectively analyzed. The clinical course of patients was followed prospectively until discharge or death, with retrospective categorization into patients with mild AP (MAP) and severe form of the disease according to the Atlanta classification [20]. Ultrasonography was performed within 12 h of admission and contrast enhanced computed tomographic (CT) scan was performed according to the United Kingdom guidelines for the management of AP [21]. Serum CRP concentration levels were measured using a quantitatively immunoassay method (Cardio Phase, hsCRP BN2, Siemens, Germany) on admission, and 24 h and 48 h after admission. Serum levels of CRP determined at 24 h of admission with the cut-off value of 120 mg/L were accepted as an indicator for severe inflammation, as reported in previous studies [13, 22, 23]. PCT serum concentration levels were measured with a commercial quantitative assay (PCT sensitive, Kryptor, Brahms, Berlin, Germany) on admission, at 24 h and 48 h after admission, at the 8th and 10th hospital days and one more time in the 4th week of the disease. Serum concentrations of PCT measured at 24 h of admission were included in this study. In this study the value of APACHE II score calculated at 24 h of admission with the cut-off level of 8 and more was an accepted level indicator for severe inflammation, as reported in previous studies [20, 22, 24]. The BISAP score was calculated at 24 h of admission using BUN level > 25 mg/dL, impaired mental status, Systemic Inflammcetory Responsed Syndrome (SIRS), age > 60 years and pleural effusion (on chest radiography or CT) [25, 26]. Altered mental status was defined as any record of disorientation, lethargy somnolence, coma or stupor in the medical record [27]. The SIRS [28, 29] was defined by the presence of $2 \geq$ of the following criteria: pulse > 90 beats/min; respirations > 20/min or $PaCO_2$ < 32 mm Hg; body temperature > 38°C or < 36°C; white blood cells (WBC) count >12 000 or < 4000 cells/mm3 or >10% immature neutrophils (bands). Each point on the BISAP score worth 1 point [19,30], as presented in Table 1. The values of APACHE II score and BISAP score calculated at 24 h of admission were included in this study. Statistical analysis was performed using the SPSS software (Statistical package for the social sciences version 15.0, Chicago, IL, USA). The patients were divided into two groups according to severity and the outcome. Receiver operating characteristic (ROC) curves and the respective areas under the curves (AUC) were calculated. The diagnostic performances of the different parameters were further assessed by calculating sensitivity and specificity. Mann-Whitney U-test was used to test significance between the two groups. Z-test and Chi-square test were used to assess the value of the respective parameters as indicators of the disease severity and outcome. Z-test was further used to test differences between BISAP score and APACHE II score in early prediction of the AP severity. The results were expressed as median followed by the range, and mean followed by standard deviation (SD). Probability values less than 0.05 were considered as statistically significant, and probability values less than 0.001 were considered as highly statistically significant.

The Bedside Index for Severity in Acute Pancreatitis (BISAP) scoring system [19, 30]

Blood urea nitrogen >25 (mg/dL)
Impaired mental status disorientation, lethargy somnolence,
coma or stupor
SIRS (Systemic Inflammatory Response Syndrome)
Age > 60 years
Pleural effusion (on chest radiography or computed tomography)

- Each point on the BISAP score worth 1 point
Observed mortality risk with an increasing number of points: [30]
  - ▸ 0 point: mortality rate of 0.1%
  - ▸ 1 point: mortality rate of 0.4%
  - ▸ 2 points: mortality rate of 1.6%
  - ▸ 3 points: mortality rate of 3.6%
  - ▸ 4 points: mortality rate of 7.4%
  - ▸ 5 points: mortality rate of 9.5%

Results

A total of 51 patients, 34 (66.7%) males and 17 (33.3%) females, with the median age of 61 years (range 19–83) were included. Thirty-five patients (69%) were admitted within 0–12 h of symptoms onset, 5 (10%) within 12–24 h and 11 (21%) of patients within 24–48 h of symptom onset. Etiology was biliary in 28 (55%), alcoholic in 11 (21%), hyperlipidemia in 6 (12%), *post* endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in 1 (2%), pancreatic tumor in 1 (2%) and of unknown cause in 4 (8%) patients. The values of the prognostic markers at 24 h of admission are listed in Table 2.

Twenty-two (43%) patients fully recovered and were classified into the group with MAP. Twenty-nine (57%) patients developed significant complications and were classified in the group with severe form of the disease. Seventeen of 29 patients with SAP had local complications. All patients with SAP had an organ failure of one or more organ systems during hospitalization. Overall mortality rate was 18% (9 patients), and 31% (9 patients) was in patients with SAP. Four patients died in the first week as a result of MOF, and the remaining 5 patients developed an organ failure (one or more organ systems) in addition to local complications.

The APACHE II scores calculated at 24 h of admission, and serum concentration of CRP and PCT values measured at 24 hours of admission were highly significantly higher in patients with SAP than in patients with MAD ($p < 0.001$). The BISAP scores calculated at 24 h of admission were significantly higher in the patients with SAP than those with mild attacks ($p = 0.008$, Z = -2.668). ROC curves for the observed values of BISAP and APACHE II score at 24 h of admission are shown in Figure 1, and sensitivity and specificity for the respective values are presented in Table 3.
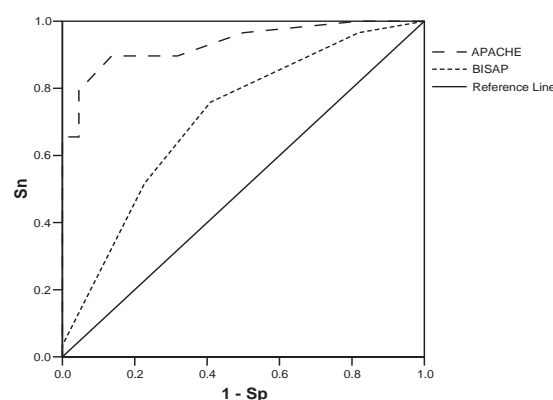

Fig. 1 – ROC curves for the BISAP and APACHE II score calculated at 24 h of admission in patients with acute pancreatitis

ROC – receiver operating characteristic, APACHE II – Acute Physiology and Chronic Health Evaluation II, Sn – Sensitivity; 1-Sp – Specificity, BISAP – Bedside Index for Severity in Acute Pancreatitis

Table 2

The values of the prognostic markers of acute pancreatitis (AP) at 24 h of admission

Parameters	AP	N	Mean	Median	Minimum	Maximum	Range	SD
APACHE II score [a]	Severe	29	15.79	16.00	7	23	16	4.701
	Mild	22	7.95	7.50	6	14	8	1.838
	Total	51	12.41	10.00	6	23	17	5.401
C-reactive protein (mg/L) [a]	Severe	29	161.45	160.00	67	332	265	63.138
	Mild	22	74.64	75.00	13	166	153	44.841
	Total	51	124.00	112.00	13	332	319	70.445
Procalcitonin (ng/mL) [a, b]	Severe	29	2.5072	0.7500	0.09	34.66	34.57	6.73732
	Mild	22	0.2600	0.2250	0.05	0.87	0.82	0.20281
	Total	51	1.5378	0.3600	0.05	34.66	34.61	5.16721
BISAP score [c]	Severe	29	3.2759	4.0000	1.00	5.00	4.00	0.95978
	Mild	22	2.4545	2.0000	1.00	4.00	3.00	1.05683
	Total	51	2.9216	3.0000	1.00	5.00	4.00	1.07412

[a] Mann-Whitney U test, $p < 0.001$; [b] Chi-square test, $p < 0.001$; [c] Z-test, $p = 0.008$.
N – number of patients, SD – standard deviation, APACHE II – Acute physiology and chronic health evaluation II
BISAP – Bedside Index for Severity in Acute Pancreatitis

Table 3

Ability of prognostic markers measured at 24 h of admission to predict acute pancreatitis (AP) severity

Test result variable(s)	AUC	SE	p value	Asymptotic 95% Confidence Interval		Cut off	Sensitivity	Specificity
				Lower Bound	Upper Bound			
APACHE II score	0.933	0.034	0.000	0.867	1.000	8	0.89	0.69
C-reactive protein	0.876	0.048	0.000	0.783	0.969	120 mg/L	0.75	0.86
Procalcitonin	0.830	0.055	0.000	0.721	0.939	0.25 ng/mL	0.86	0.63
BISAP score	0.710	0.074	0.011	0.565	0.855	3	0.74	0.59

AUC – Area under curve; SE – standard error, APACHE II – Acute Physiology and Chronic Health Evaluation II, BISAP – Bedside Index for Severity in Acute Pancreatitis

In testing differences between the BISAP score and APACHE II score (difference between AUC of respective parameters), and their strengths to predict a severe form of AP with accuracy, APACHE II score was significantly stronger predictor of disease severity than BISAP score (Table 4).

The values distribution of APACHE II score, BISAP score, CRP and PCT noted at 24 h of admission in survivors and nonsurvivos are presented in Figure 2.

Table 4

Differences in the strenghts of respective parameters to predict severe form of acute pancreatitis

Parameters	CRP	PCT	BISAP score
APACHE II score	Z = 0.969; p = 0.332	Z = 0.830; p = 0.111	Z=2.738; p = 0.006
C-reactive protein		Z = 0.630; p = 0.528	Z=1.882; p = 0.059
Procalcitonin			Z=1.302; p = 0.193

Z – Z-test, APACHE II – Acute Physiology and Chronic Health Evaluation II score;
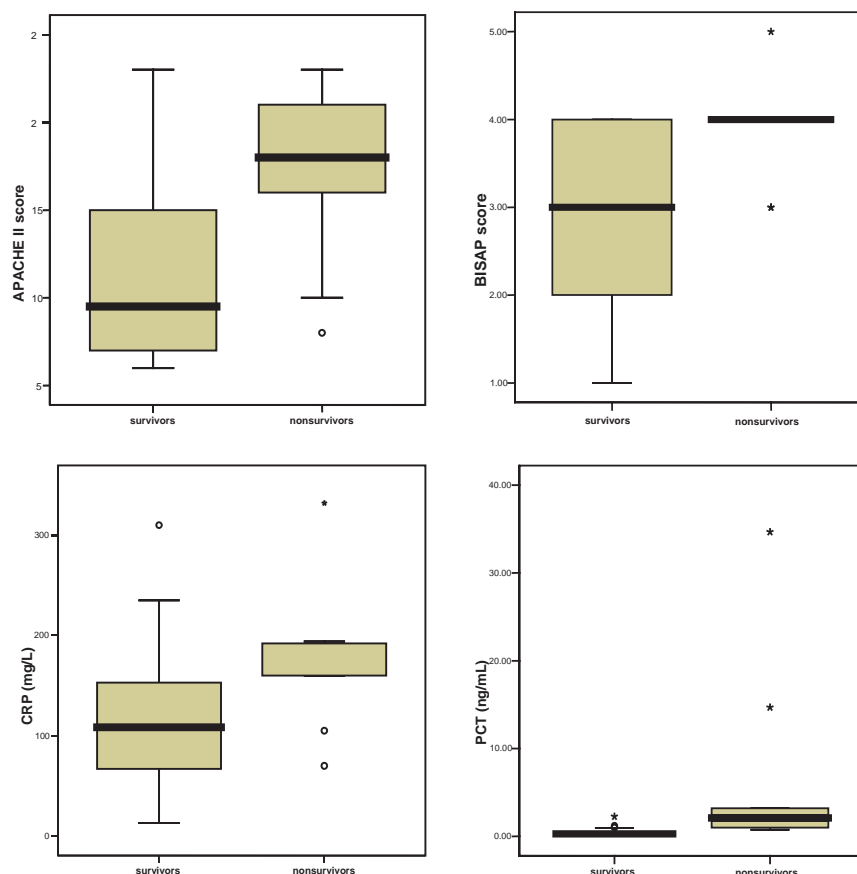BISAP – Bedside Index for Severity in Acute Pancreatitis

Fig. 2 – Distribution of values of APACHE II score, BISAP score, C – reactive protein, (CRP) and procalcitonin (PCT) noted at 24 h of admission in survivors and nonsurvivos
APACHE II – Acute Physiology and Chronic Health Evaluation II; BISAP – Bedside Index for Severity in Acute Pancreatitis

Between survivors and nonsurvivors there was a significant difference in APACHE II scores (Chi-square=9.222, p = 0.002; Z=-2.891, p = 0.004), BISAP scores (Z=-2.975, p = 0.003) and serum values of CRP (Chi-square=6.317, p = 0.012; Z=-2.434, p = 0.015), and a highly significant difference in serum concentrations of PCT (Chi-square=23.592, p < 0.001; Z=-4.177, p < 0.001) registered in 24 h of admission.

In serial measurements of serum concentrations of PCT it was registered that the most patients had maximal serum values of PCT noted in the first few days of hospitalization. The highest measured concentration values of PCT during hospitalization were significantly higher in nonsurvivors than survivors (Chi-square 33.157; p < 0.001).

Discussion

Early assessment of AP severity is essential for adequate and timely treatment. Moreover, it helps in reducing the mortality rate and can help in preventing numerous complications during the course of the disease. The scoring systems and biochemical markers which are being used for assessment of severity are also helpful for continuous monitoring of patients with AP. Although evaluation of AP severity demands a lot of procedures which are usually expensive, it can indirectly reduce a duration of hospital stay and improve cost benefit of the treatment. In this study, we investigated the value of PCT and BISAP score for prediction of severity and outcome in patients with AP. The predictive values were compared to the traditional biochemical marker and scoring system rutinely used in clinical practice, such as CRP and APACHE II score.

The APACHE II severity of the disease scoring system can be performed at admission and daily to help in identifying patients with SAP [22, 24, 31]. A variety of reports have correlated a higher APACHE II score at admission and during the first 72 h with a severe form of the disease and higher mortality rate. The sensitivity, specificity, as well as positive and negative predictive values ranges between 65%–81%, 77%–91%, 23%–69% and 86%–99%, respectively, have been reported [22, 32, 33]. Our results are similar to other studies. Agarwal et al. [34] reported that one of the potential weaknesses of APACHE II score is the fact that in patients older than 65 years there is a higher possibility of a false-positive score. We found that APACHE II score was highly significantly higher in patients with SAP than in patients with MAP. Also, APACHE II score in our study was significantly higher in nonsurvivors than survovors noted at 24 h of admission.

In the mid-1980s, several studies showed that the hepatic production of CRP was increased after any type of inflammation, and subsequently the protein was proposed as a prognostic factor in AP [2, 5, 7, 13]. Several investigators evaluated this marker as a predictor for severity when it was measured on admission, and in 24, 48 or 72 h after admission, and employed variable cut-off levels ranged between 110 mg/L and 150 mg/L [13]. With the CRP cut-off value of 115 mg/L measured at 24 h after admission Chen et al [35] reported the sensitivity of 44% and specificity of 96% in prediction of severity of

AP. Leser et al. [36] reported the sensitivity and specificity rate of 67% and 79% for CRP as a predictor of severity of AP measured in 24/48 h after admission with the cut-off value of 100 mg/L. Just a few reports evaluated value of CRP as a predictor of severity of AP at 24 h of admission with the cut-off value of 120 mg/L [37, 38], but without exactly noted time of onset of symptoms or noted values of sensitivity and specificity. A possible flaw of this marker is the fact that it reaches its peak only after 36–72 h after admission, and the results of this test may not be entirely reliable at admission in assessing the severity of disease [39, 40]. As compared with other studies, we found a high sensitivity, but lower specificity in our research. Such finding could be a result of later appearance of the peak values. In our study serum concentration of CRP was highly significantly higher in patients with SAP, and significantly higher in nonsurvivors than survivors, registered at 24 h of admission.

The actual pathophysiologic role of PCT is still under investigation, and it was assumed that PCT might be also an acute phase protein [40]. In SIRS, regardless of the cause, the first released cytokines are tissue necrosis factor-alpha (TNF-a) and interleukin (IL)-1. Under their influence, the production of other proinflammatory cytokines such as IL-6, IL-8 and interferon gamma starts. These cytokines, especially IL-6, stimulate the release of CRP and PCT [41–43]. This is an indirect way of excretion, while the release of PCT is primarly induced *via* microbial toxins (*eg* endotoxin) [44]. Those various stimuli increase gene expression, which is responsible for secretion of PCT, and constitutive release of PCT from all parenchymal tissues and differentiated cell types throughout the body, including the liver, kidney, adiposities and muscle [45]. Serum concentrations of PCT was evaluated for its utility as predictor of severity and outcome of the AP in several studies [17, 46–51]. The predictive value of PCT in our study was comparable to the results of Kylanapa-Back et al. [17]. In the study of these investigators its sensitivity and specificity were 92% and 84%, respectively, with the cut-off value of 0.5 ng/mL. In our study these values were 86% and 63%, but with much lower cut-off value, such as 0.25 ng/mL. Pindak et al. [48] found that at 12 h after admission value of PCT was better than value of CRP in predicting the course and fatal outcome of the disease. In our study, the concentrations of PCT measured at 24 h of admission were highly significantly higher in nonsurvivors than survivors. Also, PCT levels measured at 24 h of admission were highly significantly higher in patients with SAP than in patients with MAP. While PCT was an excellent predictor of disease's course and fatal outcome, the serum levels of CRP measured at 24 h of admission were good predictor of disease's course but not so good in predicting fatal outcome in AP. Confirmation for the fact that elevated serum concentrations of PCT can be found in acute inflammation, not only in infectious conditions, is that the maximal recorded PCT values were in the first few days of hospitalization in the most of patients, when there was relatively small possibility for pancreatic infection.

The most commonly utilised prediction scoring system for clinical studies on AP is APACHE II score. For calculating

the APACHE II score it requires the collection of a large number of parameters. An optimal scoring system for predicting severity and outcome of AP should be simple, accurate and able to be calculated in the first 24 h of hospitalization. With the usage of population-based data researchers from the United States developed and presented BISAP score, as a very simple and easy to use [19]. In addition, they cited that each of the parameters in BISAP score can be easily obtained early in the course of hospital admission. In the study of these authors there was no significant difference in the predictive accuracy between the BISAP score and the APACHE II score; in subgroup analysis, the BISAP score was effective in predicting mortality rates in patients without the evidence of early organ failure, and BISAP score was able to achieve a similar level of predictive accuracy to the more complex APACHE II score, with far fewer variables. We found that the APACHE II score was a better predictor of AP severity than BISAP score with sensitivity of 89% and specificity of 69%, while the BISAP score had specifity of 74%, asnd sensitivity of 59%. Further, with much greater AUC the APACHE II score was significantly stronger predictor of the disease severity than BISAP score ($Z=2.738$; $p = 0.006$). The value of the BISAP score in early prediction of AP mortality was similar to the APACHE II score. A possible explanation of why the BISAP score had lower ability to predict SAP than APACHE II score is because our study included a smaller number of patients then the study of authors from the United States [19]. Although difficult to perform, APACHE II score is multipoint system and provides a more objective clinical picture in patients with AP. Anyway, due to simplicity and easily obtained parameters, BISAP score should gain broad acceptance in routine use not by replacing clinical assessment, but rather by complementing and objectifying it.

Conclusion

In early prediction of AP severity, PCT has a better predictive value than CRP, and similar predictive value as the APACHE II score. PCT is a better predictor of fatal outcome in AP measured at 24 h of admission than CRP, BISAP score and APACHE II score. APACHE II score is a stronger predictor of disease severity than BISAP score. In early prediction of AP outcome, BISAP score has similar value to the APACHE II score. PCT analysis is simple, routinely available and a highly accurate method in early assessment of AP severity and outcome.

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