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GENERAL

THE IMPORTANCE OF USING INFLAMMATORY BIOMARKERS AND SCORING SYSTEMS IN THE EARLY ASSESSMENT OF THE SEVERITY AND OUTCOME OF ACUTE PANCREATITIS TREATMENT

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Abstract: Acute pancreatitis (AP) is an inflammatory disease of the pancreas that causes local damage and systemic inflammatory response. Some of the numerical scoring systems used in the intensive care unit for the assessment of critically ill patients such as APACHE II and MEWS score could be used for AP, besides the scoring systems specific to AP (Ranson score, Pancreas score, BISAP). Therefore, the aim of this study was to examine the significance of inflammatory biomarkers and scoring systems in the evaluation of the severity of AP and outcomes. The study was conducted as a cohort prospective study, examining patients with AP, of both sexes. Laboratory analyses, as well as the scoring systems: Ranson, Pancreas score, Bedside Index of Severity in Acute Pancreatitis (BISAP), and Acute Physiology and Chronic Health Evaluation II (APACHE II) were collected on day zero and 48h after admission. The study included 50 patients of whom 8 died. The most reliable score for predicting AP severity was APACHE II0 and 48AUROC (0.753; 0.768) in relation to the inflammatory biomarkers. For initial prediction of the treatment outcome, APACHE II0, BISAP0, and CRP0 AUROC (0.813; 0.807; 0.753) had the highest discrimination rates and after 48h, APACHE II48, Ranson48, BISAP48, and Pancreas48 AUROC (0.917; 0.856; 0.789; 0.729). There was a statistically significant correlation between CRP0 and $BISAP_0$ ($p = 0.006$) and between PCT and all day-zero scores. All tested screening systems showed reliability in predicting AP severity and treatment outcomes. The best predictive power was demonstrated by the APACHE II score.

Keywords: acute pancreatitis, procalcitonin, numerically scoring systems, APACHE II.

Acute pancreatitis (AP) is an inflammatory disease of the pancreas that causes local damage, systemic inflammatory response, and organ insufficiency (1). The most common causes of AP are gallstones (30-45%) alcoholism (30-35%) and other causes such as drugs, infectious agents, hypercalcemia, hyperparathyroidism, hypertriglyceridemia, and benign or malignant tumors (2, 3). The diagnosis of AP is established if at least two of the following three requirements have been met:

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abdominal pain, a three-fold increase of the pancreatic amylase and/or lipase values with respect to the upper reference limit, and a positive finding on the contrast-enhanced computed tomography (CT) or, magnetic resonance (MR) or transabdominal ultrasonography (US) (4, 5). Upon the diagnosis establishment, it is very important to assess the severity of the disease and the treatment outcome. According to the Atlanta classification from 2012, there are three grades of this disease: mild, moderate, and severe AP (6).

Predicting the evolution and severity of AP

Laboratory analyses, imaging diagnostics, and clinical scoring systems can be used in predicting the severity and outcome of the disease. Numerous laboratory tests such as serum amylase and lipase, C-reactive protein (CRP), procalcitonin (PCT) values, etc. may be helpful in predicting the evolution of AP (7). The abdominal CT and MR are effective in evaluating AP, in the period from 48 to 72 h from the onset of the disease (8).

The most commonly used scoring systems in predicting the evolution and severity of AP are the Ranson score, Pancreas score, BISAP (Bedside Index of Severity in Acute Pancreatitis) score, CTSI (Computed Tomography Severity Index), although with some disadvantages such as that some require up to 48 h before they can be applied properly (4, 9). On the other hand, APACHE II (Acute Physiology and Chronic Health Evaluation) scoring system can also be used for the determination of the severity and evolution of AP, even though it is used in the intensive care units (ICU) for assessment of critically ill patients, not specific for AP (4, 9).

Since AP can be presented in a severe form, requiring treatment in the ICU, the objective of this research was to investigate the impact of values of inflammatory biomarkers, CRP and PCT, and the multifactorial scoring systems on the assessment of the severity and treatment outcome in patients with AP.

MATERIALS AND METHODS

The research was conducted as a cohort, a one-year prospective study from January 2019 to December 2019 at the Clinical Hospital Center "Bezanijska Kosa" in Belgrade, Serbia. The study included all patients of both genders admitted to the hospital, older than 18 years of age with a diagnosis of AP. The diagnosis of AP was established based on the presence of two of the following three features: abdominal pain, serum amylase, and / or lipase ≥ 3 times the upper limit of normal and a positive finding on the CT.

The following parameters were collected: age, gender, comorbidities, and etiology of AP. The vital parameters such as arterial blood pressure, heart rate, respiratory rate, body temperature, hemoglobin oxygen saturation, level of consciousness, laboratory analyses including hematology tests, biochemical analyses – blood glucose, urea, creatinine, bilirubin – total and direct, aminotransferases, amylase, lipase, lactate dehydrogenase, total proteins, albumins, sodium, potassium, calcium, CRP, PCT, arterial blood gas analyses were collected at two time points, on admission (day zero) and 48 h after admission. The biomarkers of CRP 0 and 48 and PCT 0 and 48 were collected and the following numerical scoring systems were calculated: Ranson score on admission and 48h after admission, APACHE II on admission and 48h after admission, Pancreas score on admission and 48 h after admission and BISAP score on admission and 48h after admission. According to the 2012 Atlantic classification, patients were classified according to the severity of the disease in the group with mild, moderate, or severe AP. Finally, the final outcome was assessed (6).

The research was conducted with the approval of the Ethics Committee and management of the Clinical Hospital Center "Bezanijska Kosa" which is responsible for educational, scientific, and research activities. Informed consent was obtained from all patients before the study enrollment.

Statistical analysis

All statistical analyses were carried out using the Social Science Program (version 22, SPSS Inc., Chicago, IL, USA). The categorical variables were expressed as absolute numbers and proportions and compared using either the chi-squared test or Fisher's exact test. Receiver-operating characteristic (ROC) curves and area under the curve (AUC) with 95% confidence intervals for severe acute pancreatitis and mortality were calculated for Ranson, Pancreas score, APACHE II, BISAP, CRP, and PCT on admission and after 48 h. Sensitivity and specificity were calculated for the individual scoring systems and inflammatory biomarkers, and the optimal cut-off values were selected. Correlations between each pair of scoring systems and between each scoring system and inflammatory biomarkers were assessed using Spearman's correlation analysis. P-values less than 0.05 were considered statistically significant.

Table 1. Demographic and clinical characteristics of patients with respect to the final outcome.

		Total	Survivors	Non-survivors	p-value
Total number n (%)		50 (100.0)	42 (84%)	8 (16%)	
Gender	Male, n (%)	26 (52.0)	22 (52.4)	4 (50.0)	p = 0.902
	Female, n (%)	24 (48.0)	20 (47.6)	4 (50.0)	
Age groups	36-45, n (%)	6 (12.0)	6 (14.3)	0 (0)	p = 0.454
	46-55, n (%)	7 (14.0)	5 (11.9)	2 (25.0)	
	56-65, n (%)	8 (16.0)	8 (19.0)	0 (0)	
	66-75, n (%)	21 (42.0)	17 (40.5)	4 (50.0)	
	Over 76, n (%)	8 (16.0)	6 (14.3)	2 (25.0)	
Etiology	Gallstones	30 (60.0)	26 (61.9)	4 (50.0)	p = 0.591
	Hyperlipidemia	8 (16.0)	6 (14.3)	2 (25.0)	
	Alcoholism	4 (8.0)	4 (9.5)	0 (0)	
	Idiopathic	8 (16.0)	6 (14.3)	2 (25.0)	
Form of acute pancreatitis	Mild, n (%)	20 (40.0)	18 (42.9)	2 (25.0)	p = 0.001*
	Moderate, n (%)	20 (40.0)	19 (45.2)	1 (12.5)	
	Severe, n (%)	10 (20.0)	5 (11.9)	5 (62.5)	

Statistical test used: χ^2 test; *Statistical significant if $p < 0.05$

RESULTS

The study included 50 patients of whom 8 (16%) did not survive. The frequency of the subjects' gender structure, etiology, frequency of patients who underwent surgery, and frequency of necrosis did not show a statistically significant difference with respect to survival. The demographic characteristics, etiology, and class of AP are shown in Table 1. Patients with the death outcome are statistically significantly more frequent in severe forms of pancreatitis ($\chi^2 = 10.752$, $p = 0.001$).

Importance of the numerical scoring systems for predicting the severity of AP

The day-zero scores indicate a lower degree of discrimination between patients with severe AP and patients with mild or moderate AP. The most reliable scoring predictor for severe AP was APACHE II_0 AUROC (0.753). The discrimination

Table 2. Area under curve (AUROC) for predicting AP severity on day zero and 48 hours after admission.

	AUROC	95%CI	Cut-off	Sensitivity (%)	Specificity (%)
$Ranson_0$	0.600	0.452-0.736	> 1.0	90.0	32.5
APACHE II_0	0.753	0.610-0.864	> 17.0	60.0	80.0
$Pankreas_0$	0.639	0.491-0.770	> 3.0	60.0	70.0
$BISAP_0$	0.555	0.408-0.696	> 3.0	40.0	85.0
CRP_0	0.564	0.416-0.703	> 173.7	30.0	90.0
PCT_0	0.636	0.488-0.768	> 0.3	70.0	67.5
$Ranson_{48}$	0.589	0.441-0.726	> 5.0	40.0	85.0
APACHE II_{48}	0.767	0.627-0.875	> 12.0	100.0	47.5
$Pankreas_{48}$	0.575	0.427-0.714	> 4.0	30.0	92.5
$BISAP_{48}$	0.670	0.523-0.796	> 2.0	70.0	67.5
CRP_{48}	0.551	0.404-0.692	> 31.3	100.0	20.0
PCT_{48}	0.635	0.487-0.767	> 0.35	80.0	50.0

$_0$ - day zero measurement; $_{48}$-measurement 48 hours after admission; APACHE II score (Acute Physiology and Chronic Health Evaluation); BISAP score (Bedside Index of Severity in Acute Pancreatitis) score.

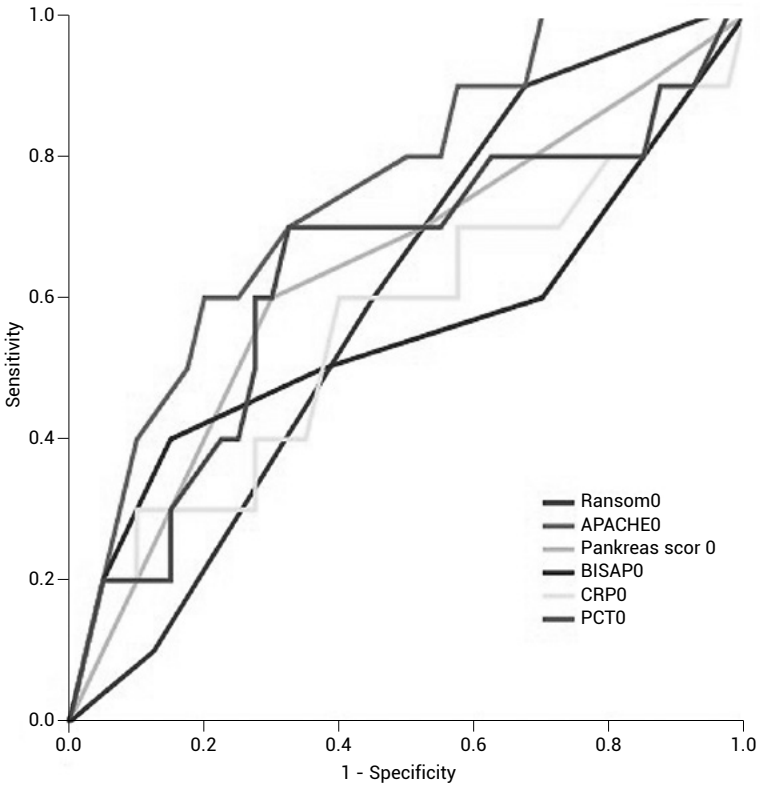

Figure 1. Area under curve (AUROC) for predicting severe AP day-zero.

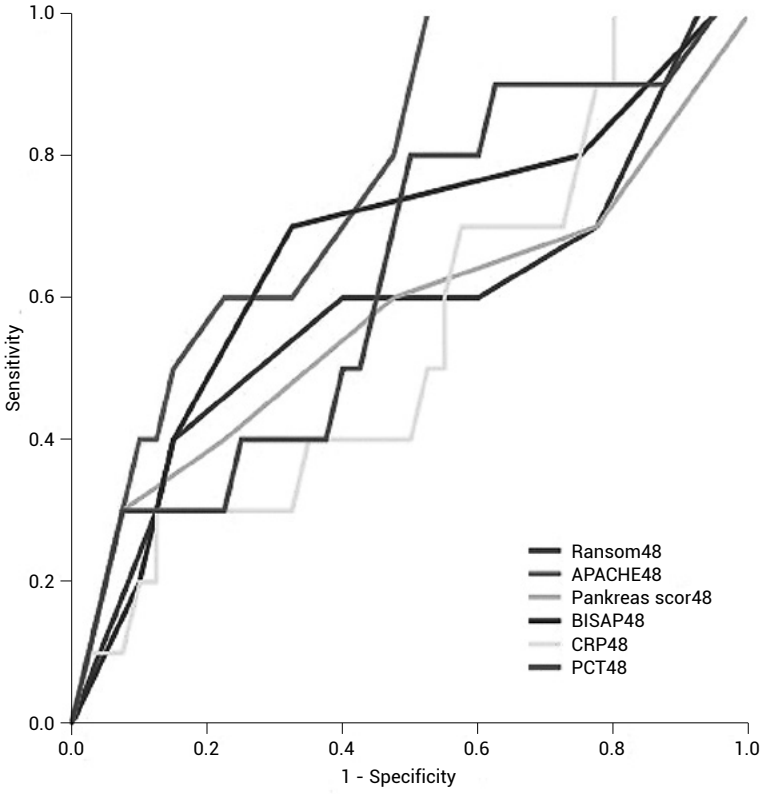

Figure 2. Area under curve (AUROC) for predicting severity of AP after 48 h.

rate was slightly lower with CRP_0 AUROC (0.564) and a slightly higher discrimination rate was obtained with PCT_0 AUROC (0.636) (Table 2, Figure 1).

The values of all scores after 48h slightly changed compared to the day-zero. The highest level of discrimination was also found with the APACHE II_{48} score AUROC (0.768) (Table 2, Figure 2). The discrimination rate was lower for CRP_{48} AUROC (0.551) and slightly better for PCT_{48} AUROC (0.635).

Importance of the numerical scoring systems for predicting mortality

The significance of the different numerical scoring systems that have calculated day zero for predicting the fatal outcome in patients with AP is shown in Table 3, Figure 3.

For the day-zero scores, a high degree of discrimination between patients with the fatal outcome and survivors was $BISAP_0$ score AUROC (0.807). The level of discrimination in other scores was lower. CRP_0 also exhibited a high degree of discrimination against AUROC (0.753) especially compared to PCT_0 AUROC (0.580). The significance of the different numerical scoring systems calculated after 48 h for predicting the fatal outcome in patients with AP is shown in Table 3, Figure 4.

For the score values after 48 h, a high degree of discrimination between the fatal outcome and survivors was found in all scores, but the most reliable scores for predicting the fatal outcome were APACHE II_{48} AUROC (0.917) and $Ranson_{48}$ score AUROC (0.856). The level of

Table 3. Area under curve (AUROC) predicting mortality in patients with AP day-zero and 48 h after admission.

	AUROC	95%CI	Cut-off	Sensitivity (%)	Specificity (%)
$Ranson_0$	0.693	0.547-0.816	≤ 2.0	59.5	87.5
$APACHE\ II_0$	0.813	0.677-0.909	≤ 15.0	69.0	87.5
$Pancreas_0$	0.695	0.549-0.817	≤ 2.0	50.0	87.5
$BISAP_0$	0.807	0.670-0.905	≤ 2.0	69.0	87.5
CRP_0	0.753	0.611-0.864	≤ 46.3	64.3	87.5
PCT_0	0.580	0.432-0.718	≤ 0.3	66.7	75.0
$Ranson_{48}$	0.856	0.727-0.939	≤ 5.0	92.9	87.5
$APACHE\ II_{48}$	0.917	0.803-0.976	≤ 17.0	90.5	87.5
$Pankreas_{48}$	0.729	0.585-0.845	≤ 2.0	57.1	87.5
$BISAP_{48}$	0.789	0.650-0.891	≤ 2.0	69.0	87.5
CRP_{48}	0.667	0.519-0.794	≤ 183.2	90.5	50.0
PCT_{48}	0.545	0.398-0.686	≤ 2.1	97.6	37.5

$_0$- day zero measurement; $_{48}$-measurement 48 hours after admission; APACHE II score (Acute Physiology and Chronic Health Evaluation); BISAP score (Bedside Index of Severity in Acute Pancreatitis) score.

discrimination in other scores was lower and somewhat less reliable for predicting fatalities. The discrimination rates of CRP_{48} (AUROC 0.664) and PCT_{48} (AUROC 0.545) were low.

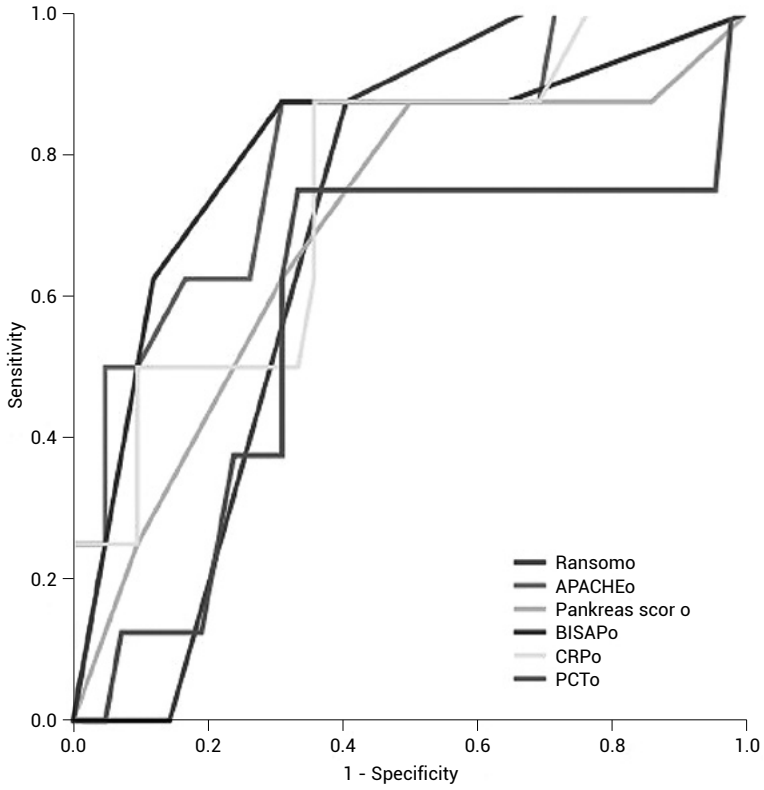

Figure 3. Area under curve (AUROC) for predicting mortality in patients with AP day-zero.

Correlation between the scores values calculated on day zero

The correlation between the score values calculated on day zero is shown in Table 4. There was a significant positive correlation between all day-zero scores. The strongest correlation existed between APACHE II 0 and Pancreas 0 score ($r = 0.859$, $p < 0.001$). The strength of connectivity was median between the following scores: Ranson 0 and BISAP 0 ($r = 0.491$, $p < 0.001$), Ranson 0 and APACHE II 0 score ($r = 0.496$, $p < 0.001$), Ranson 0 and Pancreas 0 score ($r = 0.500$, $p < 0.001$), BISAP 0 and Pancreas 0 score ($r = 0.410$, $p = 0.003$) and the smallest correlation but statistically significant, existed between BISAP 0 and APACHE II 0 ($r = 0.319$, $p = 0.024$). The correlation between the scoring values calculated after 48 h is shown in Table 4. There was a statistically significant positive correlation between all scores calculated after 48 h. The intensity of connection is stronger in most correlations than on day zero. A strong positive correlation exists between $Ranson_{48}$ and $BISAP_{48}$ values (0.701, $p < 0.001$) and $Ranson_{48}$ and $Pankreas_{48}$ scores (0.705, $p < 0.001$).

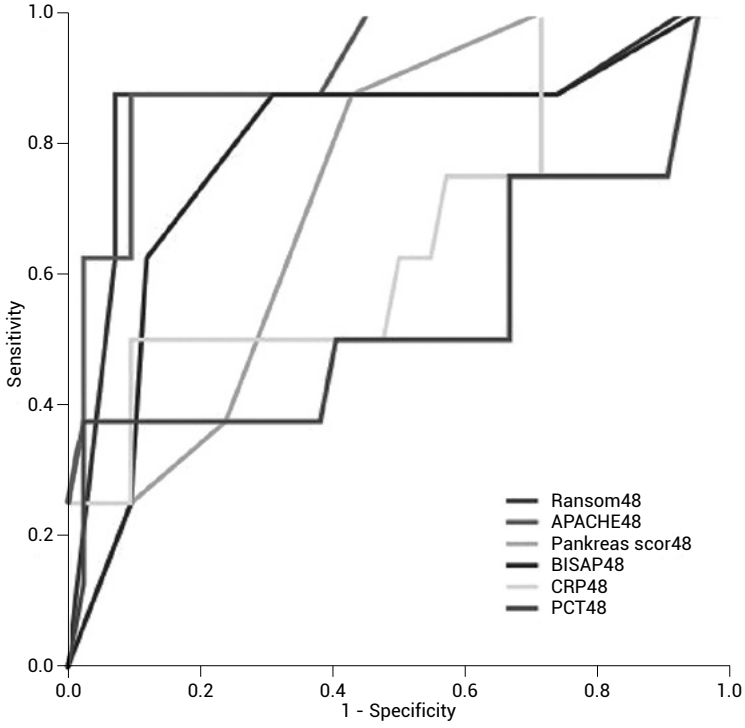

Figure 4. Area under curve (AUROC) for predicting mortality in patients with AP after 48 h.

The correlation between other scores was medium and amounts: $Ranson_{48}$ and APACHE II_{48} ($r = 0.569$, $p < 0.001$), $BISAP_{48}$ and APACHE II_{48} ($r = 0.444$, $p = 0.001$), $BISAP_{48}$ and $Pancreas_{48}$ score ($r = 0.595$, $p < 0.001$), APACHE II_{48} and $Pankreas_{48}$ score ($r = 0.458$ $p = 0.001$).

There was a statistically significant positive correlation between CRP_0 and $BISAP_0$, while the other scoring systems had no statistically significant correlation with CRP_0. There was a statistically significant positive correlation between PCT_0 and all day-zero scoring systems except the $Pancreas_0$ score. There was a statistically significant positive correlation between CRP_{48} and APACHE II_{48} and $BISAP_{48}$ scores. There was a statistically significant positive correlation between PCT_{48} and all scoring systems (Table 5).

Table 4. Correlation of scores values on day zero and 48 hours after admission.

		$Ranson_0$	$BISAP_0$	APACHE II_0	$Pankreas_0$
$Ranson_0$	r	1	0.491	0.496	0.500
	p		< 0.001*	< 0.001*	< 0.001*
$BISAP_0$	r		1	0.319	0.410
	p			0.024*	0.003*
APACHE II_0	r			1	0.859
	p				< 0.001*
$Pankreas_0$	r				1
	p				
$Ranson_{48}$	r	1	0.701	0.569	0.705
	p		< 0.001*	< 0.001*	< 0.001*
$BISAP_{48}$	r		1	0.444	0.595
	p			0.001*	< 0.001*
$APACHE_{48}$	r			1	0.458
	p				0.001*
$Pankreas_{48}$	r				1
	p				

$_0$- day zero measurement; $_{48}$- measurement 48 hours after admission; APACHE II score (Acute Physiology and Chronic Health Evaluation); BISAP score (Bedside Index of Severity in Acute Pancreatitis) score; Spearman's correlation coefficient (r) was calculated and significant relationships were marked (*).

Table 5. Correlation between CRP, PCT, and numerical scoring systems for day zero and after 48 h.

Parameter	Scoring system	Number	r	p
CRP_0	$Ranson_0$	50	0.267	0.061
	$Pankreas_0$	50	0.136	0.346
	APACHE II_0	50	0.185	0.199
	$BISAP_0$	50	0.386	0.006*
PCT_0	$Ranson_0$	50	0.295	0.038*
	$Pankreas_0$	50	0.251	0.079
	APACHE II_0	50	0.479	< 0.001*
	$BISAP_0$	50	0.537	< 0.001*
CRP_{48}	$Ranson_{48}$	50	0.162	0.260
	$Pankreas_{48}$	50	0.265	0.063
	APACHE II_{48}	50	0.406	0.003*
	$BISAP_{48}$	50	0.368	0.008*
PCT_{48}	$Ranson_{48}$	50	0.469	0.001*
	$Pankreas_{48}$	50	0.403	0.004*
	APACHE II_{48}	50	0.524	< 0.001*
	$BISAP_{48}$	50	0.682	< 0.001*

$_0$ - day zero measurement; $_{48}$ - measurement 48 hours after admission; APACHE II score (Acute Physiology and Chronic Health Evaluation); BISAP score (Bedside Index of Severity in Acute Pancreatitis) score; Spearman's correlation coefficient (r) was calculated, and significant relationships were marked (*).

DISCUSSION

In this study, we tried to examine the significance of APACHE II, BISAP, Ranson, and Pancreas scores for predicting AP severity and treatment outcomes. APACHE II is the most commonly used scoring system to assess AP severity and predict the treatment outcomes, although not specific to AP patients, it requires monitoring of 35 different parameters. It has been used since 1985 and many clinical practice guides still recommend the application of this score today, since it is the best score in discriminating patients with mild and moderately severe AP versus severe AP (4). It is also advised that it should be calculated on admission to the hospital and repeated within the first three days of hospitalization. In our AP severity prediction study, the most reliable was the APACHE II score, both at the day-zero and the 48-hour count. Similar results were obtained from a study that showed that APACHE II was a more reliable scoring system for predicting severe AP compared to 3 other systems: Ranson, BISAP, and CTSI (10). A study from 2018 concluded that APACHE II is a useful prognostic system for predicting AP severity and may be crucial for identifying patients who require tertiary care and who need urgent resuscitation, especially in less developed countries (4). For predicting severe AP, APACHE II was less precise than the CTSI score but more precise than BISAP and Ranson (4). Another study that compared several scoring systems for predicting severe AP, also showed that APACHE II has greater accuracy compared to Ranson and BISAP (11).

It has also been proved that scoring such as BISAP, Ranson, CTSI and APACHE II can predict the severity, local complications, and mortality in patients with hyperlipidemic AP while APACHE II showed the best value for predicting the severity and treatment outcomes, but could not anticipate the local complications, while CTSI was much more accurate (12).

BISAP was introduced as a simple and accurate scoring for assessment of the risk of mortality in patients with early-stage AP with only 5 variables, which gives it an advantage over the APACHE II score (12). BISAP had similar results as Ranson, APACHE II, and MTCSI scores for predicting AP severity and treatment outcomes (12). In our study, APACHE II and BISAP were the most reliable day-zero predictors of death, while APACHE II and Ranson were most accurate after 48 h.

Ranson's score calculates values for 5 parameters at hospital admission and 6 parameters after 48 h so it needs time for calculation (12). Studies have shown that it cannot predict severe forms of AP but is effective in predicting mortality (12). It also

has a poor prognostic value and it was better than APACHE II only for predicting the local complications, while Ranson showed better results for predicting pancreatic necrosis compared to APACHE II but this difference was not significant (4).

The pancreas score monitors 8 variables in the first 48 h after hospital admission. However, the disadvantage of Pancreas and Ranson scores is that they usually take up to 48 h before they can be applied properly. In our study, the Pancreas score was less reliable for mortality prediction than the APACHE II score after 48 h.

In addition to the scoring systems, PCT monitoring enables early and reliable identification of patients at risk of developing severe forms of AP with pancreatic necrosis, as well as predicting the treatment outcomes (13). One study found that plasma PCT values correlate with the need for antibiotics and can predict severe AP and organ failure (14). In our study, the day-zero PCT values positively correlated with all scores except the Pancreas score, and after 48 h, there was a statistically significant positive correlation with all scores.

On the other hand, when it comes to predicting the severity of AP, the day-zero CRP values were not significant, which is also consistent with the literature data (15). However, when it comes to predicting mortality, initially measured CRP values have good prognostic values (16). However, it has also been proved that in order to predict the progression of AP, the initial PCT values were less accurate than Ranson and BISAP scores, which showed a significantly better correlation (17). In our research, after 48 h, both inflammatory biomarkers had a lower prognostic value for the treatment outcome compared to the scoring systems.

The main limitation of this study is that it included a low number of patients however, despite that fact, the correlation between the prognostic effect of inflammatory biomarkers and the multifactorial scoring systems such as Ranson, APACHE II, BISAP, and Pancreas score was more than evident.

CONCLUSIONS

All of the tested scoring systems measured at admission to the hospital and after 48 h are in a positive correlation. APACHE II score, especially the one calculated 48 h after admission, proved to be most effective in predicting the treatment outcomes for patients with AP. PCT was slightly more effective in predicting the disease severity, while CRP was slightly more effective in predicting the treatment outcome.

Conflicts of interest

The authors declare no conflict of interest.

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