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Medicine

ICU MORTALITITY IN SEVERE ACUTE PANCREATITIS- SINGLE CENTRE EXPERIENCE

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ABSTRACT:
SEVERE ACUTE PANCREATITIS (SAP) IS A SERIOUS HEALTH PROBLEM GIVEN ITS HIGH COSTS AND INCREASED MORTALITY. OVER TIME, MULTIPLE CLINICAL FACTORS, BIOLOGICAL CONSTANTS, PROGNOSIS SCORES HAVE BEEN VALIDATED TO ESTABLISH THE PROGNOSIS IN ACUTE PANCREATITIS (AP). WE CONDUCTED A RETROSPECTIVE COHORT STUDY OF PATIENTS WITH SEVERE ACUTE PANCREATITIS ADMITTED TO THE INTENSIVE CARE UNIT (ICU) OF THE BUCHAREST UNIVERSITY EMERGENCY HOSPITAL DURING 2016-2021. WE ANALYZED ORGAN FAILURES AND MORTALITY IN ORDER TO IDENTIFY PROGNOSTIC FACTORS FOR SEVERTY. 86 PACIENTS WERE INCLUDED.THE OVERALL MORTALITY WAS 52.3% AND SERUM UREA AND CREATININE VALUES AT 48 HOURS AFTER ADMISSION WERE THE BEST LABORATORY PREDICTORS FOR MORTALITY..

KEY WORDS: SAP, ORGAN FAILURES, MORTALITY, MORTALITY PREDICTORS

INTRODUCTION

AP is a disease with potential for unfavorable evolution and in its severe forms is encumbered by increased morbidity and mortality. Globally, the incidence of AP is

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increasing in recent years in North America and Europe as a 2019 meta-analysis shows[7]. It is one of the top three causes of admission to the gastroenterology departments and the fifth leading cause of nononcologic death in the US[8]. Considering all the above, in order to decrease mortality and morbidity and to lower costs by optimizing resources it is extremely important for patient management to early identify the prognostic factors for severe forms of AP. The main objective of this study is to identify the prognostic factors associated with increased mortality. The secondary objectives are represented by the identification of prognostic factors for organ failures in patients with SAP admitted to ICU.

MATERIALS AND METHODS

We conducted a retrospective cohort study of the patients with SAP admitted to the ICU in Bucharest University Emergency Hospital between January 1, 2016 and December 31, 2021 after getting the agreement of the Ethics Commission of the Bucharest University Emergency Hospital. All patients included in the study met revised Atlanta criteria for SAP[9].The organ failures were assessed with the Marshall Score[10]. Patients who had organ failure and died within 48 hours after admission, were considered to have persistent organ failure. The exclusion criteria were age under 18 years, patients who were discharged upon request and patients with mild or moderately forms of AP admitted to the ICU. The data collection was done using the electronic registers and the patients' obsevation charts.

The following variables were recorded: age, sex, etiology, body mass index, comorbididities, chronic medication, leukocytes, neutrophils lymphocytes ratio (NLR), platelets lymphocyte ratio (PLR), hemoglobin and erythrocyte indices, hematocrit, platelets count and platelet indices, sodium (Na), amylase, lipase, alanin aminotransferase (ALT), aspartat aminotransferase (AST), international normalized ratio (INR), activated partial tromboplastin time (APTT), triglycerides and cholesterol, calcium (Ca), total and direct bilirubin (BT, BD) at admission, urea and creatinine at admission and at 48 hours after admission, BISAP score, Ranson score, organ failures, surgical procedures, death, days in ICU, days of hospitalisation.

Data processing was done using Microsoft Office 2019 Excel version 2202 and IBM Statistical Package for the Social Sciences (SPSS) version 28.0.1.1. Descriptive statistics were used for clinical, laboratory and demographic data of the patients. For numerical variables the means, standard deviation, minimum and maximum values are presented. Qualitative variables are presented as numbers and percentages. Analysis of variance (ANOVA) was used for assessing differences between numerical variables in various subgroups. Chi-square tests were used for comparing proportions defined by combinations of qualitative variables, tabulated in 2x2 and 2xn tables.

For comparisons of means that used ANOVA and proportions that used chi-square tests, p-values were calculated for the respective test values and differences were considered significant for p-values <0,05. Areas under the receiver-operating-characteristic (AUROC)

[7] J Iannuzzi, J Leung, J Quan, F Underwood, J A King, J W Windsor, G G Kaplan, A256 Global incidence of acute pancreatitis through time: A systematic review , *Journal of the Canadian Association of Gastroenterology*, Volume 2, Issue Supplement_2, March 2019, Pages 499–501

[8] Peery, A. F. *et al.* Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 143, 1179–1187 (2012)

[9] Banks, P. A. *et al.* Classification of acute pancreatitis - 2012: Revision of the Atlanta classification and definitions by international consensus. *Gut* 62, 102–111 (2013)

[10] Marshall, J. C. *et al.* Multiple Organ Dysfunction Score: A reliable descriptor of a complex clinical outcome. *Critical Care Medicine* 23, 1638–1652 (1995)

curves were calculated for the variables that were deemed to be predictors of mortality and analysis of the ROC curve was used to identify the best performing models and Kolmogorov-Smirnov statistics was used to determine the cut-off value of the selected predictors.

RESULTS

Out of the 111 patients admitted to the ICU, 86 were included in the study, 22 were excluded because they had mild and moderately severe forms of AP and 3 were discharged upon request. The summary statistics of quantitative variables recorded at the hospital admission are presented in table 1, except for for serum urea and creatinine levels that are presented at admission and at 48 hours. Also we present the days of hospitalisation.

Table 1 Summary statistics of quantitative clinical variables

	N	Minimum	Maximum	Mean	Standard deviation
Age (years)	86	27	93	57.47	16.585
L (*10³/µL)	86	1.30	30.20	14.9833	7.225
NLR	86	.40	109.50	15.0677	14.933
PLR	86	4.69	1065.00	245.4779	179.877
Hb (g/dl)	86	6.7	21.5	12.787	2.771
Ht %	86	19.60	52.30	38.4153	7.731
Plt (*10³/µL)	86	6.00	537.00	218.9010	110.837
RDW %	86	10.00	54.70	15.2958	4.871
RDW SD	80	15.1	80.0	47.838	8.143
MPV fL	85	6.60	13.60	9.3971	1.359
Ca mg/dl	86	4.40	18.00	7.4642	1.592
LDH U/L)	85	78	2291	604.71	391.598
Na (mmol/L)	86	115	149	133.91	6.840
Amylase (U/L)	86	25	9538	1115.23	1414.2
Lipase (U/L)	86	146	39955	5776.05	7616.634
Urea ad (mg/dL)	86	7.00	309.00	73.3881	66.508
Cr ad (mg/dL)	86	.50	12.70	2.1434	2.084
Urea 48 (mg/dl)	81	10.00	297.70	79.5001	59.710
Cr 48 (mg/dl)	81	.36	14.50	2.2223	1.982
Glucose (mg/dL)	86	49	1081	225.53	191.466
ALT (U/L)	86	12	960	115.49	135.004
AST (U/L)	86	15	1034	155.92	174.397
BT (mg/dL)	86	.15	37.00	3.7914	14.847
BD (mg/dL)	86	.05	16.10	1.3241	2.408
TRIG (mg/dL)	85	26	6567	415.32	915.491
Chol (mg/dL)	83	52	757	137.69	97.774
ALB (g/dL)	83	1.2	5.4	2.810	0.678
INR	86	.89	6.04	1.3853	0.661
APTT (sec)	86	19.9	81.0	30.037	8.403
Fib (mg/dL)	86	105.0	1106.0	498.850	234.045
ICU stay (days)	86	1	43	6.67	7.060
Total days	86	1	109	18.06	16.799

L-Leukocytes, NLR- neutrophils lymphocytes ratio, PLR- platelets lymphocyte ratio, Hb-Hemoglobin, Ht-Hematocrit, Plt-Platelets, RDW- Red cell distribution width, RDW SD- Red cell distribution width, MPV-Mean platelet volume, Cr-Creatinine, ad-Admission, ALT - Alanin aminotransferase , AST - Aspartat aminotransferase, BT -Total bilirubin, BD – Direct bilirubin TRIG-Triglycerides, Chol-Cholesterol, ALB-Albumin, INR- International normalized ratio, APTT- Activated partial tromboplastin time, Fib-Fibrinogen.

SAP etiology is shown in fig 1. The most frequent etiology was alcoholic, 37.2% of patients, followed by the biliary one 33.7% of patients. In 8.1% of the SAP cases the etiology

was represented by hypertriglyceridemia and in 1.2% of the cases the etiology was equaly represented by hypercalcemia, respectively AP post retrograde endoscopic cholangiopancreatography (ERCP). The etiology in 18.6% of the cases was unknown.

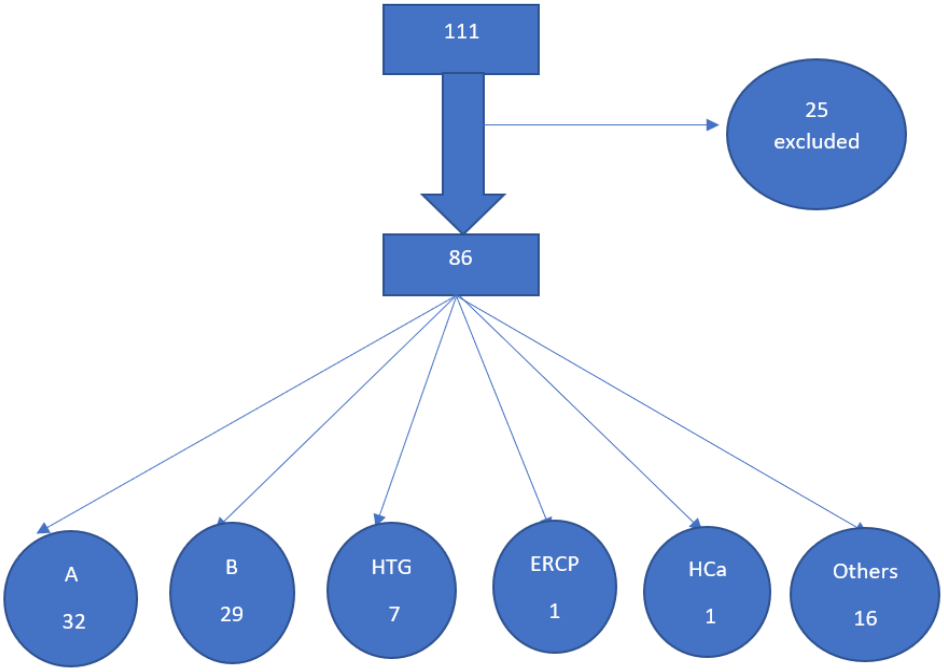

Figure 1. SAP etiology (A-alcoholic, B-biliary, HTG-Hypertriglyceridemia, HCa-hypercalcaemia)

The distribution of BISAP and Ranson scores for SAP pacients is presented in figures 2 and 3. It can be seen that the cases with highest frequencies were found for BISAP score 2 and Ranson score 5 .

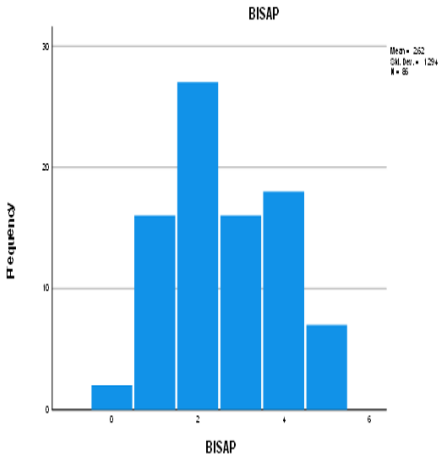

Figure 2 BISAP Score distribution

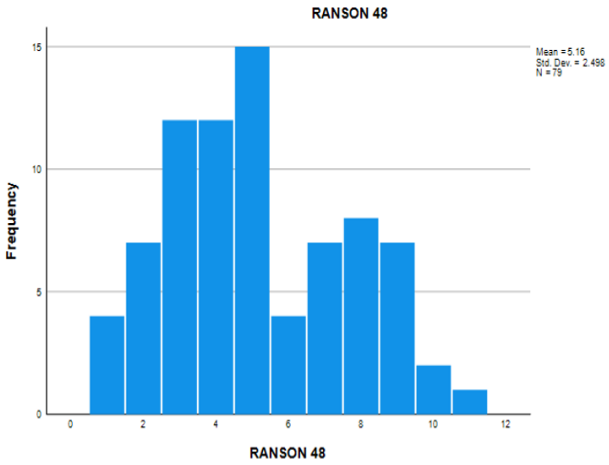

Figure 3 Ranson Score distribution

The table 2 and 3 and figures 4 and 5 represent BISAP and Ranson scores and associated mortality.

Table 2 Association between BISAP score and survival

Score	Alive N (%)	Dead N (%)	TOTAL N (%)	p - value
BISAP > 2	8 (19.5%)	33 (73.3%)	41 (47.7%)	$<10^{-6}$
BISAP 0-2	33 (80.5%)	12 (26.7%)	45 (52.3%)	
TOTAL	41 (100%)	45 (100%)	86 (100%)	-

Table 3 Association between RANSON 48 score and survival

Score	Alive N (%)	Dead N (%)	TOTAL N (%)	p - value
RANSON 48 >4	9 (22.5%)	35 (89.7%)	44 (55.7%)	$<10^{-8}$
RANSON 48 0-4	31 (77.5%)	4 (10.3%)	35 (44.3%)	
TOTAL	40 (100%)	39 (100%)	79 (100%)	-

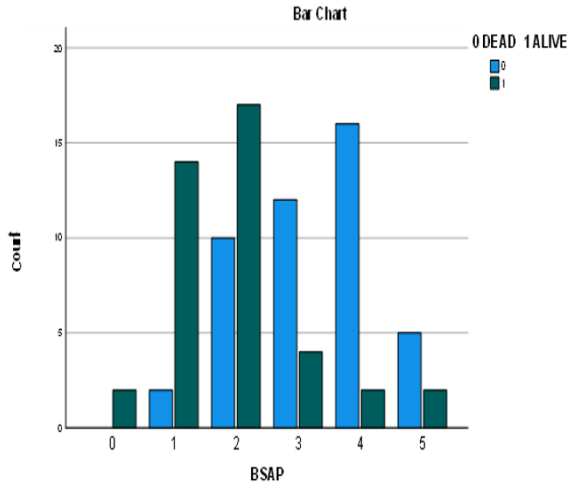

Figure 4 BISAP Score and mortality

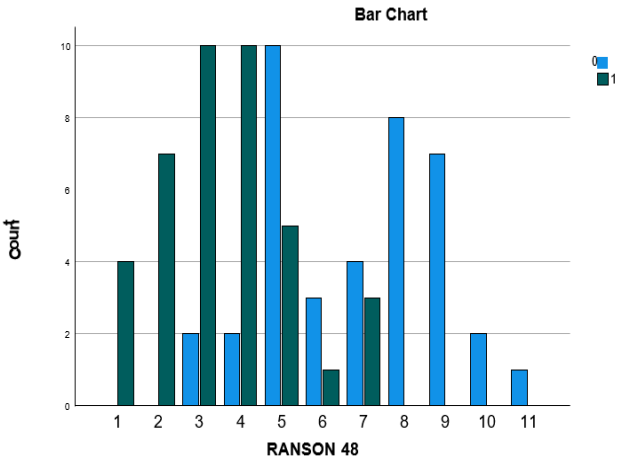

Figure 5 Ranson Score and mortality

For surviving patients the most frequent BISAP score was 2 while for dead patients most frequent BISAP score was 4. Out of 41 live patients only 8 (19.5%) had BISAP>2, whereas for 45 dead patients 33 of them (73.3%) had BISAP score >2, p for chi-square test comparing the percentages was highly significant, $p<10^{-6}$, Sb=73%, Sp=80%.

For surviving patients the most frequent RANSON 48 score was 3 or 4 while for dead patients the most frequent RANSON 48 score was 5. Out of 40 live patients with available RANSON 48 score only 9 (22.5%) had RANSON 48 >4, whereas for 39 dead patients with available RANSON 48 score 35 of them (89.7%) had with available RANSON 48 score score >4, p for chi-square test comparing the percentages was highly significant, $p<10^{-8}$, Sb=89.7%, Sp=77.5%.

The most common organ failure was the respiratory one, in 84.9% of the cases, followed by renal failure, in 70.9% of the cases. The need for continous renal replacement therapy was found at 36% of patients with SAP.

Cardiocirculatory failure was present in 62.8% of patients.

Overall mortality was 52.3%. In the table below we present comparatively a series of quantitative parameters for survivors and deceased.

Table 4 Quantitative clinical variables in survivors and deceased

	Mean		p value
	Alive	Dead	
Age (years)	51.41	62.96	<0.01
L (*10³/µL)	13.731	16.124	0.12
Hb (mg/dL)	12.388	13.151	0.20
Ht %	36.92	39.77	0.08
Plt *10³/µL	243.951	196.077	0.04
Uree ad (mg/dL)	73.089	78.915	0.42
Cr ad (mg/dL)	2.04	2.23	0.66
Uree 48 (mg/dL)	63.24	96.15	0.01
Cr 48 (mg/dL)	1.81	2.64	0.05
Glucose (mg/dL)	210.59	239.16	0.47
AST (U/L)	117.44	190.98	0.05
ALT (U/L)	91.12	137.69	0.11
Na (mmol/L)	133.44	134.33	0.54
BD (mg/dL)	0.76	1.83	0.039
INR	1.37	1.39	0.85
APTT (sec)	29.46	30.55	0.55
Total stay (days)	27.7	9.4	<0.01

L-Leukocytes, Hb-Hemoglobin, Ht-Hematocrit, Plt-Platelet, Cr-Creatinine, ad-Admission

The ROC analyses for serum urea and creatinine at 48 hours (Figure 6) showed a mortality cut off-value of 63 mg/dL for urea (sensibility 0.775 and specificity 0.659) and a cut off-value of 1.89 mg/dl for creatinine (sensibility 0.675 and specificity 0.707). The prediction model quality is shown in Figure 7.

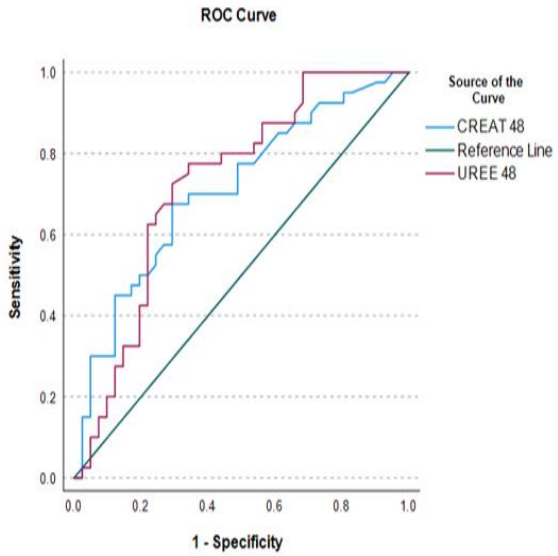

Figure 6. ROC analysis urea and creatinine

Figure 7. Model quality for urea and creatinine

We performed ROC analysis for NLR, PLR, RDW, RDW-SD , PCT, PDW, MPV none of them being a good prediction model for mortality.(Figures 8 and 9).

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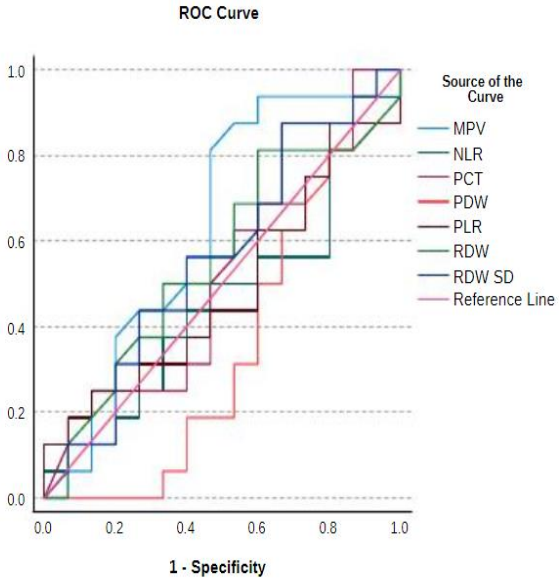

Figure 8. ROC analysis for MPV, NLR, PCT, PDW, PLR, RDW, RDW SD

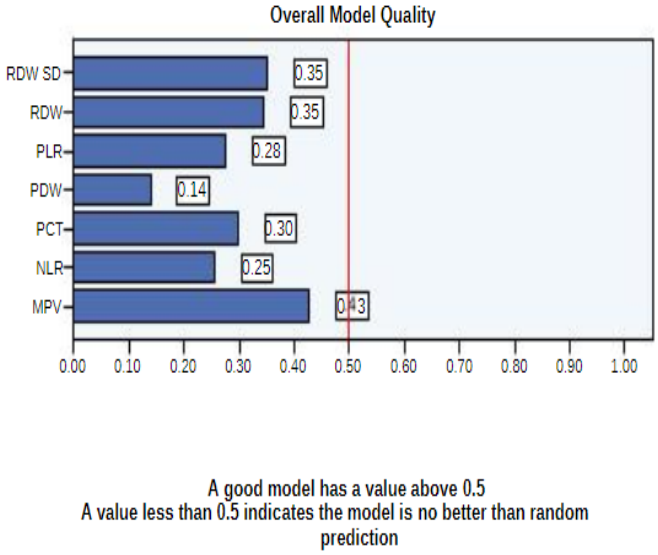

Figure 9. Prediction models for MPV, NLR, PCT, PDW, PLR, RDW,RDW SD

The presence of ischemic heart disease, systemic inflammatory response syndrome, respiratory failure, renal failure, cardiocirculatory failure, days of mechanical ventilation ($p<0.01$), ventilator associated pneumonia ($p=0.045$), the presence of abdominal compartment syndrome were correlated with mortality ($p=0.02$).

Regarding the secondary objectives of the study, respiratory failure was more frequent in patients with biliary etiology than in those with alcoholic etiology (93.1% of the patients with biliary etiology versus 78.1% of the patients with alcoholic etiology). Respiratory failure was correlated with SIRS presence ($p<0.01$), BISAP score values ($p=0.019$) and Ranson score values ($p=0.01$), as well as with the RDW SD value ($p=0.009$) and in terms of age the p value was at the limit of statistical significance $p=0.059$.

Cardiocirculatory failure was correlated with a p value <0.05 with presence of SIRS, Ranson and BISAP score, age, LDH, AST, urea at admission and at 48 hours as well as with NLR values.

The presence of renal insufficiency was correlated with the presence of SIRS ($p=0.011$) and with the levels of urea and creatinine at admission and at 48 hours ($p<0.01$), with the Ranson and BISAP scores, age ($p=0.03$), platelets count ($p=0.039$) and RDW ($p=0.035$).

DISCUSSION

The SAP etiology in this study was predominantly alcoholic, followed by the biliary etiology, corresponding to that described in studies for Eastern Europe[11]. The third etiology was hypertriglyceridemia. The association between hypertriglyceridaemia AP, ketoacidosis

[11] J Iannuzzi, J Leung, J Quan, F Underwood, J A King, J W Windsor, G G Kaplan, A256 Global incidence of acute pancreatitis through time: A systematic review , *Journal of the Canadian Association of Gastroenterology*, Volume 2, Issue Supplement_2, March 2019, Pages 499–501; Roberts, S. E. *et al.* The incidence and aetiology of acute pancreatitis across Europe. *Pancreatology* 17, 155–165 (2017).

and hyperglycemia, a rare triad with diagnostic and therapeutic challenges was encountered in 2 cases. In 18.8% of cases the etiology it was unknown.

The general mortality rate was 52.3%, higher than reported in international studies[12] but similar to mortality reported in studies in Romania[13]. This increased mortality rate may be linked to overcrowding of intensive care units and late hospital presentation. As seen in table 2, the average days of hospitalization in the deceased is statistically significant lower ($p<0.01$) than in survivors, which may indicate that the former have severe forms at the hospital admission[14].

AP etiology of the patients included in the study did not have statistically significant correlations with mortality. Of the laboratory parameters, the values of urea and creatinine at 48 hours were best correlated with mortality (ROC analysis showing the cut-off values), these results are similar to those found in international studies[15].

Platelets number and AST value parameters included in different prognostic scores (Ranson Score, SOFA Score)[16] were correlated with mortality in ICU pacients with SAP.

The presence of comorbidities is closely related to the unfavorable prognosis in AP[17] also having a major impact on costs[18]. Of all comorbidities we have studied (ischemic heart disease, obesity, diabetes mellitus, cerebrovascular disease, hypertension, dyslipidemia, neoplasia), ischemic heart disease was the only one that was correlated with mortality ($p=0.04$).

ROC analysis of NLR, PLR and various erythrocyte and platelets indices, did not show significant correlations with mortality, the results reported in the literature being conflictual, subsequent studies being necessary to establish their role in SAP mortality prediction[19].

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SIRS is the key element in AP pathophysiology, but also is common in other diseases that require intensive care admision. The SIRS score, initially elaborated in order to define sepsis and septic shock[20], was correlated in our study with the presence of organ failures, as well as with the mortality ($p < 0.01$). The SIRS Score is one of the determinants of BISAP score, elaborated and validated for mortality in AP on a large number of patients[21]. Both Ranson and BISAP scores in our study were correlated with the mortality and with the presence of organ failures.

CONCLUSION

Age, SIRS, Ranson and BISAP scores are useful tools for prediction of the mortality and the organ failures. Urea and serum creatine at 48 hours were found to be the the best laboratory markers for mortality in SAP patients.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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All authors had the same contribution.

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