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STUDY ON PROGNOSTIC FACTORS IN SEVERE ACUTE PANCREATITIS

PHD THESIS ABSTRACT

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LIST OF ABBREVIATIONS AND SYMBOLS

ALT	Alanine-aminotransferase
AP	Acute pancreatitis
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate-aminotransferase
AUC	Area under curve
AUROC	Area under the ROC curve
BISAP	Bedside Index of Severity in Acute Pancreatitis
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CARS	Compensatory Anti-inflammatory Response Syndrome
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CRP	C - reactive Protein
CT	Computer Tomography
CVD	Cerebrovascular Disease
DM	Diabetes Mellitus
HI	Hypoxia Index
HTA	Arterial Hypertension
IHD	Ischemic Heart Disease
MAP	Mean Arterial Pressure
MPV	Mean Platelet Volume
MR	Magnetic Resonance
NLR	Neutrophils/Lymphocytes Ratio
NPV	Negative Predictive Value
PaO2	Partial O2 Pressure
PCT	Platelet Count Test
PDW	Platelet Distribution Width
PLR	Platelets/ Lymphocytes Ratio
PPV	Positive Predictive Value

ROC	Receiver Operating Characteristic
SAP	Severe Acute Pancreatitis
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
US	Ultrasound

INTRODUCTION

Acute pancreatitis (AP) is an important public health problem, and in its severe forms it is accompanied by high morbidity and mortality, being a great resource consumer. It ranks in the first three causes of admission in the gastroenterology departments and represents the fifth cause of non-oncological death in the United States [1]. For this reason, the rapid identification of the prognostic factors of severe acute pancreatitis (SAP) makes it possible for its early and aggressive treatment with decreased morbidity, mortality and, implicitly, low costs.

SAP prognostic factors were a constant concern of specialists in the field, given the very large differences of mortality between different AP forms. In this regard, multiple prognostic scores were developed for AP starting with John H Ranson in 1974 [2], followed by a team from Glasgow Royal Infirmary led by Clement W W Imrie who released the Glasgow Criteria [3], Simplified Acute Physiology Score developed by Le Gall and the collaborators in 1983 and subsequently amended in 1993 [4], Bedside Index of Severity in Acute Pancreatitis released in 2008 by Wu et al. [5]. In 1985, Emil Jacques Balthazar creates the score on computer tomography criteria that bears his name [6], improved five years later with the addition of pancreatic necrosis enlargement by dynamic computer tomography examinations called CT Severity Index [7].

There was a constant concern for finding some clinical and paraclinical features indicating the reserved prognostic and the necessary of Intensive Care admission of patients with AP. In 1987, Pauli Pulakkainen et al. showed the value of the reactive protein in determining the severity of this pathology [8].

In the present work, in the general part, I propose a brief review of the definitions and classifications of AP and SAP, of the epidemiology, physiopathology, clinical, biological, imaging and treatment factors of SAP.

PERSONAL CONTRIBUTIONS

1. Working hypothesis and general objectives

This paper aims at carrying out the SAP profile in Romania today, more precisely in the Intensive Care Unit of the University Emergency Hospital of Bucharest, and identifying demographic, clinical, paraclinical and treatment factors that influence the SAP prognosis in this population.

The working hypothesis is represented by the fact that certain demographic, clinical, paraclinical and treatment factors are associated with the unfavorable prognosis in patients with SAP.

Objectives:

1. Performance of demographic, clinical, paraclinical, complications, treatment, prognosis scores for patients with severe acute pancreatitis..

2. Identification of demographic, clinical, paraclinical, therapeutic and complications associated with the unfavorable prognosis having as an end-point the mortality of patients with SAP.

3. Determining the accuracy of death prediction of variables associated with the unfavorable prognosis and of BISAP, Ranson, SOFA, APACHE II severity scores.

2. Material and method

In order to attain the exposed objectives, we carried out a retrospective, observational study, in which we included patients with SAP admitted in the Intensive Care Unit of the University Emergency Hospital Bucharest between January 2016-December 2021. This study received the approval of the Ethics Commission of the University Emergency Hospital Bucharest.

The criteria for study inclusion were represented by:

- patients with SAP diagnosis according to the modified Atlanta Classification [9];
- patients admitted to the Intensive Care Unit of the University Emergency Hospital Bucharest between January 2016-December 2021;
- age over 18 years-old.

The objectification of organ failure was done using the modified Marshall score [10], the presence of 2 score or higher, indicating the presence of organ failure, its persistence over 48 hours being considered persistent organic failure. Patients who had organ failure and died within the first 24 hours after admission were considered patients who had persistent organic failure.

The exclusion criteria were represented by:

- patients with mild or moderate AP forms;
- patients discharged or transferred on request.

In this study, there were included 86 patients out of the 111 examined, 25 being excluded. The registered data were taken from the patient electronic records and the clinical observation sheets.

Data registration was done using Microsoft Office 2019 Excel version 2202.

The following variables were recorded:

- Age at the time of hospital admission
- Sex
- Alcohol consumption
- The environment origin (urban or rural)
- BMI
- Ethanol, biliary, hypertriglyceridemia, hypercalcemia, post ERCP etiology, and where it was not identified the etiology was categorized as unknown
- Comorbidities: DM, HTA, ischemic heart disease (IHD), chronic renal disease (CKD), neoplastic disease, liver cirrhosis
- Variables within the first 24 hours after admission:

  - number of leukocytes, NLR, PLR, hemoglobin, hematocrit, number of platelets, PDW, RDW-SD, MPV, PCT, amylase, lipase, total calcium, LDH, sodemia, ALT, AST, BT, BD, urea, creatinine, glycemia, ketone bodies in the urine; it should be mentioned that the values of urea and creatinine were also recorded after 48 hours;

  - BISAP score;

  - the amount of fluids administered within the first 24 hours:<2500 ml, 2500-4000 ml, >4000 ml

  - pleural effusion.
- Ranson score at 48 hours
- Variables at admission in the Intensive Care Unit: pH, lactate, APACHE II and SOFA scores
- Necrosis
- Compartment syndrome
- Abscesses
- Clostridium Difficile Infection
- Organ failure (lung, heart, kidney)
- Other complications: colon necrosis, gastric necrosis, haemorrhage
- Antibiotic prophylaxis

- Type of nutrition used in Intensive Care Unit (enteral, parenteral, mixed)
- Surgeries
- Kidney replacement therapy
- Total number of hospitalization days
- Total number of ICU days
- Survival or deceased status during hospitalization

The statistical analysis was carried out using IBM SPSS Statistics Programs Version 28.0.1.1 and Microsoft Excel 2019 version 2202 on the data collected from 86 patients.

There were calculated the descriptive statistical indicators for clinical, laboratory and demographic data. For the numerical variables there are presented the means, the standard, median, minimum and maximum deviation. Qualitative variables are presented in the form of numbers and percentages.

There were analyzed the associations between the studied primary result (death) and the different qualitative or quantitative variables that could be predictors for death. The Chi-square test was used to compare the proportions defined by the associations of the variable resulting with the qualitative variables, analyzed in the 2x2 and 2xn contingency tables and for which the mortality was calculated in each subgroup as a proportion of the dead in the total observations of the respective subgroup. The variation analysis (ANOVA) was used to evaluate the differences between the quantitative variables in the subgroups of deceased and survivors by comparing the means registered by the respectable variables in each subgroup, with the verification of compliance with the conditions for applying this analysis by comparing variants in subgroups with the Levene test. For variables that did not meet these conditions there was used the Mann-Whitney U test. For proportion comparisons (which used chi- square tests) and mean (which used ANOVA), the P values were calculated for the values of the respective tests and the differences were considered statistically significant for the P value <0.05.

Areas Under the Receiver-Operating-Characteristic-(AUROC) and trusted intervals for these areas were calculated for the numerical variables that were considered to be potential predictors of death, selected on the statistically significant association with the resulting variable (death).

It is considered that a variable is a predictor of death if AUROC differs significantly from the random model for which the area is 0.5 (death). Depending on the AUROC value, the accuracy of prediction is great (0.9-1), moderate (0.7-0.9) and weak (0.5-0.7).[11]

There was identified of the selected predictors (who had AUROC> 0.7) and there were calculated the sensitivity and specificity for the respective threshold value of the studied variable.

3. Results and discussion

0bjective 1 - Performance of demographic, clinical, paraclinical profile of patients with severe acute pancreatitis

In this study, I conducted a profile of patients with demographic, biological, local and systemic complications, therapeutic measures and prognostic scores on a small group of patients, 86, the small number of patients not being unusual for this pathology in the specialized literature.[12–14]

In the group of 86 patients included in the study, the mean age was 57.47 years-old and the population studied was mainly represented by males (61.6%).

The most common etiology was the ethanol one(37.2%), followed by the biliary one (33.7). In a review of the AP incidence and etiology performed by Roberts et al. in 2017 the countries of Southern Europe had biliary etiology/ethanolic etiology ratios ranging from 5/1 to 10/1, while in the Eastern Europe countries ethanol etiology was dominant and in Western and Northern Europe the proportions are similar. [15] Part of the patients included in the study had the etiology that we considered as unknown (18.6%), since it was not identified during the hospitalization period. I think that sustained efforts must be made in order to identify the AP etiology, given that this guides us into the correct and complete therapeutic management of patients with SAP.

Regarding the sex and etiology distribution, ethanolic etiology was predominantly represented by men, 90.6%, explained by more frequent ethanol consumption among men, and the biliary one in women, 58.6%, this data being consistent with the specialized literature.[16] For the unknown etiology, the number of men was equal to that of women. Overall, the majority population was male (61.6%).

In the studied group a higher percentage of the urban population was observed (58.1%).

Regarding behaviors, many of the patients, 46.55%, are represented by smokers, smoking being a risk factor for AP both in men and women [17]. 53.5% of patients were ethanol consumers.

The BMI analysis of the patients pointed out that more than half of patients (55.8%) were overweight or presented obesity of different degrees, obesity being one of the factors that aggravate the AP progression as we shown in the general part..

Comorbidity analysis revealed significant percentages of hypertensive patients (42.2%), diabetics (30.2%), or with ICD (24.4%). In conclusion, this population is one presenting risk factors for AP.

The mean number of leukocytes was above the upper normal values, the NLR mean was also above the upper normal values, indicating an increased extent of the inflammatory response in these patients. As shown in the general part, a value above 12 of NLR in patients with AP is associated with the severity of the disease.[18]

The mean values of hemoglobin and hematocrit, the number of platelets were within normal limits, as well as the RDW-SD, MPV, PCT values. The mean values of PDW, 17.73 FL were slightly increased to the upper limit and similar to the values found by Wang et al. in a study with acute pancreatitis and persistent organic dysfunction.[19]

The analysis of platelet indicators was performed for a smaller number of patients, considering that not all indicators are reported on each of the existing tests in the hospital.

The average calcium values were below the lower normal limits (7.46 ± 1.59 mg/dl), only 30.23% of patients being normocalcemic.

The mean values of the sodemia were under the lower normal values and can be explained, among others, by hyponatremia that occurs in chronic consumers of ethanol, pseudohyponatremia from pancreatitis with etiology of hypertriglyceridemia.

The mean values of the urea at hospital admission were 73.3 mg/dl and the median was 54 mg/dl , values higher than 25 mg/dl, the cut-off associated in a study with AP severity.[20]

The median creatinine at admission was 1.38 mg/dl, above the upper normal values, the increased creatinine values in the first 24 hours in patients with AP being associated with an unfavorable prognosis.

Both urea and creatinine values were higher at 48 hours than at admission, explained by suboptimal volemic repletion and increased protein catabolism.

The pH median at Intensive Care Unit admission was 7.3, but the pH value had extreme variations, from severe metabolic acidosis to metabolic alkalosis. The median lactate at ICU admission was of 2.3 mmoL/L.

Analyzing organ failure, I found that the most common was lung failure, followed by kidney failure in terms of the frequency of occurrence in the studied population, while heart

failure was on the last place. Compaňy et al., in a study on 67 patients with SAP, obtained the same results in terms of organ dysfunction distribution.[14]

Pacreatic necrosis could be objectified in 74.4 % of patients. This result is most likely due to the retrospective design of the study. Considering that, until 2017 there was no electronic images storage system in the University Emergency Hospital of Bucharest and the fact that the existing images in the computer system were not re -analyzed by a radiologist for this study, I decided not to include a radiological score in evaluating patients with SAP.

Pancreatic abscesses were highlighted in 13.9% of patients with SAP.

Complications of patients with SAP like perforations or bleeding were also counted for the purpose of creating an overall image of patients with SAP. I identified 2 patients with colonic necrosis and one with gastric necrosis, rare complications of severe acute pancreatitis, as well as a patient with splenic vein thrombosis and one with portal vein thrombosis.

Antibiotic prophylaxis was given in 60% of patients. This high percentage can be explained by the fact that all patients included in the study had a SAP diagnosis, Japanese guidelines recommending the use of antibiotic prophylaxis in patients with SAP.[21] These results correlate with the administration of antibiotic prophylaxis in high percentages in Europe and especially in Eastern Europe, as well as in Asia [22].

Most patients, 63%, received enteral nutrition and 22% of patients received mixed nutrition when enteral nutrition could not provide the energy needs. Parenteral nutrition was administered to patients who had contraindications for the administration of enteral nutrition. The very important role of enteral nutrition was highlighted in the general part, showing its benefits in the prevention of systemic and local complications. In a methanalysis made by Yao et al., enteral nutrition, compared to the parenteral one, was associated with reduced mortality and organ failure in patients with SAP [23].

The treatment of pancreatic necrosis was performed exclusively surgically under general anesthesia, the minimal-invasive techniques of approaching pancreatic necrosis not being available in this case.

Regarding the amount of fluids administered in the first 24 hours, 53% of patients received between 2500-4000 ml of fluids in the first 24 hours and 33% under 2500 ml in the first 24 hours, while the rest received over 4000 ml fluid on 24 hours.

Clostridium Difficile infection was identified in 14 patients representing 16.3% of total patients with SAP. In a single-center study conducted by Maatman et al., who analyzed a group of patients with necrotic pancreatitis between 2005-2018, there was identified a

percentage of 10% of patients with Clostridium Difficile infection who associated an increased number of hospitalization days and higher rates of readmission [24].

The mean duration of hospitalization period was 18 days with a median of 14 days and the mean stationary duration in Intensive Care Unit was 6.6 days with a 4.5 -day median. The total number of hospitalization days in Intensive Care Unit is similar to that obtained in a study on 53 patients with SAP in Romania [13].

The intra-hospital mortality of patients with SAP registered in the current hospitalization was 52.3%, higher than that reported in international studies that reaches 40% [25], but similar to that of a recent study in Romania, where the mortality was 60.4% [13].

As I showed above, the early mortality was 30.2%, reflecting the severity of the disease in patients who died in the first 7 days. These results are in accordance with those of other studies in which early mortality was increased, explained by the presence of systemic complications within SIRS [13, 14].

Some possible explanations of increased intra-hospital mortality would be late presentation to hospital, the overcrowding of the Intensive Care Unit, but also that the Emergency University Hospital is a tertiary center to which the severe cases are addressed to. Rapid identification of patients with severity criteria, immediate taking over in Intensive Care and aggressive treatment are measures that can reduce the mortality of patients with SAP.

I believe that the implementation of a system with regional centers specialized in the treatment of SAP to take over patients with AP who present at hospital with the severity criteria could be a solution to decrease mortality.

Objective 2 – Identification of demographic, clinical, paraclinical, therapeutic factors associated with an unfavorable prognosis having as an end-point the mortality of patients with SAP

The results obtained in this research are summarized in the tables below:

Table 3.1 Demographic and clinical variables in survivors and deceased

Data	Deceased N (%)	Survivors N (%)	p value
Group	45 (52.3%)	41 (47.7)	
DEMOGRAPHIC			
Sex			p=0.905
female	17 (51.5%)	16 (48.5%)	
male	28 (52.8%)	25 (47.2%)	
Age (years old)	*62.89*	*51.41*	*p<0.001*
Environment			p= 0.714

urban	27 (54%)	23 (46%)	
rural	18 (50%)	18 (50%)	
ETIOLOGY			
Biliary	15 (51.7%)	14 (48.3%)	0.937
Ethanol	15 (46.9%)	17 (53.1%)	0.436
ERCP	0	1 (100%)	-
Hypercalcemia	1 (100%)	0	-
Hypertrygliceridemia	2 (28.6%)	5 (71.4%)	0.189
Unknown	12 (75%)	4 (25%)	*0.044*
BMI			
0-underweight	3 (33.3%)	6 (66.7%)	
1-normal weight	12 (41.4%)	17 (58.6%)	
2-overweight	12 (60%)	8 (40%)	
3-Ist degree obesity	12(57.1%)	9 (42.9%)	
4-IInd degree obesity	4 (100%)	0	
5-IIIrd degree obesity	2 (66.7%)	1 (33.3%)	
SMOKING	18 (45%)	22 (55%)	0.205
ICD	15 (71.4%)	6 (28.6%)	*0.044*
HTA	21(55.3%)	17 (44.7%)	0.627
DM	14 (53.8%)	12 (46.2%)	0.853
CKD	4 (57.1%)	3 (42.9%)	0.766
CVD	5 (71.4%)	2 (28.6%)	0.291

Table 3.2 Paraclinical characteristics in survivors and deceased

PARACLINICAL CHARACTERISTICS	Deceased	Survivors	p value
Leukocyte no. (* $10^3/\mu L$)	16.12 (7.83)	13.73 (6.35)	p=0.126
NLR	15.96 (16.55)	14.07 (9.8)	p=0.848
PLR	229.18 (184.9)	263.35 (174.70)	p=0.107
Hemoglobin (g/dl)	13.15 (2.84)	12.38 (2.66)	p=0.101
Hematocrit (%)	39.77 (7.77)	36.92 (7.49)	P=0.087
Red-cell no. (*$10^3/\mu L$)	196.07 (91.70)	243.95 (124.99)	p=0.022
PDW (fL)	16.69 (3.67)	18.72 (4.47)	p=0.403
RDW-SD (fL)	48.97 (7.04)	46.45 (9.22)	p=0.170
MPV (fL)	9.57 (1.2)	9.20 (1.51)	p=0.056
PCT (%)	0.19 (0.089)	0.18 (0.093)	p=0.416
Calcemia (mg/dl)	7.19 (2.01)	7.75 (0.86)	p<0.001
LDH (U/L)	729.69 (368.46)	464.10 (372.58)	p< 0.01
Sodium (mmol/L)	134.33 (7.79)	133.44 (5.67)	p=0.307
Amylase (U/L)	1174.53 (1173.47)	1050.15 (1651.36)	p=0.343
Lipase (U/L)	7016.91 (9840.07)	4414.12 (3624.18)	p=0.559
Urea (mg/dl)			
Admission	78.91 (60.19)	67.32 (73.08)	p=0.427
At 48 h	96.15 (52.85)	63.24 (62.11)	p=0.006
Creatinine (mg/dl)			
Admission	2.23 (1.56)	2.04 (2.04)	p=0.334
At 48 h	2.64 (1.58)	1.81 (2.25)	p=0.012
Glycemia (mg/dl)	239.16 (185.44)	210.59 (199.08)	p=0.246
ALT (U/L)	137.69 (119.10)	91.12 (148.20)	p=0.055

AST (U/L)	190.98 (173.83)	117.44 (168.79)	p=0.025
BT (mg/dl)	2.95 (3.74)	1.39 (1.71)	p=0.004
BD (mg/dl)	1.83 (2.97)	0.76 (1.40)	p=0.005
INR	1.39 (0.49)	1.37 (0.81)	p=0.428
APTT (sec)	30.55 (10.33)	29.46 (5.65)	p=0.276
Fibrinogen (mg/dL)	473.18 (250.99)	527.02 (213.41)	p=0.298
pH	7.22 (0.15)	7.33 (0.11)	p<0.001
Lactate (mmol/L)	4.57 (4.09)	2.20 (1.20)	p<0.001
Ketonuria	12 (48%)	13 (52%)	p=0.607
Pleural effusion	17 (60.71%)	11 (39.29%)	p=0.279

Table 3.3 Complications in survivors and deceased

COMPLICATIONS	Deceased	Survivors	p value
Compartment syndrome	5 (100%)	0	p=0.057
Pancreatic necrosis	34 (53.1%)	30 (46.9%)	p=0.497
Pancreatic abscess	7 (58.3%)	5 (41.7%)	p=0.653
Clostridium Difficile infection	6 (42.9%)	8 (57.1%)	p=0.629
Lung failure	45 (61.6%)	28 (38.4%)	p< 0.001
Heart failure	44 (83%)	9 (17%)	p< 0.001
Kidney failure	44 (72.1%)	17 (27.9%)	p<0.001

Table 3.4 Treatment in survivors and deceased

TREATMENT	Deceased	Survivors	p value
Antibiotic prophylaxis	30 (57.7%)	22 (42.3%)	p=0.218
Enteral nutrition	35 (47.9%)	38 (52.1%)	p=0.054
Administered fluids (ml)			p=0.978
0 (<2500)	15 (53.6%)	13 (46.4%)	
1 (2500-4000)	24(52.2%)	22 (47.8%)	
2 >4000	6 (50%)	6 (50%)	
Surgeries	20 (52.6%)	18 (47.4%)	p=0.960
CRRT	27 (81.7%)	4 (18.3%)	p<0.001

Table 3.5 Prognosis scores in survivors and deceased

PROGNOSIS SCORES	Deceased	Survivors	p value
BISAP			p<0.001
≤2	5 (13.1%)	33 (86.9%)	
>2	40 (83.3 %)	8 (16.7%)	
Ranson			p<0.001
1-4	4 (11.4%)	31 (88.6%)	
>4	35 (79.5%)	9 (20.5%)	
APACHE II	25.60 (7.26)	13.56 (5.26)	p<0.001
SOFA	10.49 (3.18)	3.88 (2.15)	p<0.001

Most of the studies in the literature focus on AP progression to SAP or AP mortality. In this study, I analyzed the mortality caused by SAP with the help of clinical, paraclinical, therapeutic and prognostic scores and, thereby, the results interpretation related to the specialized literature is a difficult one. Another impedance that makes the comparison of results with the specialized literature difficult is the different composition of the groups according to the SAP etiology and the difference between the variables included in the study for death prediction.

The unknown etiology had the most unfavorable prognosis, patients with unknown etiology having a mortality of 75%, far above the mortality of the group as a whole. These results correlate with those of other studies in which the etiology classified as "others" or idiopathic had the highest mortality rates [13, 25]. Possible explanations would be the rapid death until the incomplete therapeutic etiology could be identified due to the unknown cause of acute pancreatitis. In conclusion, sustained efforts should be made to identify the AP etiology.

There were no significant differences between survivors and deceased related to sex ($p = 0.905$). This result correlates with the results of other studies in the specialized literature in which sex was not associated with the unfavorable prognosis [13, 14, 26]. In this study, the origin environment (urban, rural) was not associated with an unfavorable prognosis ($p = 0.714$). Old age was associated with the unfavorable prognosis in patients with SAP in the studied group, $p < 0.001$, this being a factor associated with mortality in other studies, as well [14, 25]. Smoking was not associated with death, the differences in mortality between smokers and non-smokers being statistically insignificant ($p=0.205$).

Of the comorbidities studied, HTA, DM, ICD, CKD, neoplasia and cirrhosis, the only one that was associated with the death was ICD ($p = 0.044$). The presence of comorbidities is related both to the AP severity and the mortality of patients with AP in numerous studies [27, 28]. A greater mortality of overweight and obese patients was observed compared to the normal weight or obese, obesity being related to both the increase of the AP incidence and its severity.[29]

Although NLR and the number of leukocytes were more increased in deceased patients than in survivors, the differences were not statistically significant ($p = 0.424$ and 0.063, respectively). In our study, there were no significant statistical differences between survivors and deceased ($p = 0.107$) in terms of PLR either. These indicators were not statistically associated with death. NLR is associated with the unfavorable prognosis in patients with AP [18], but in this study group, which includes only SAP patients, I did not identify this

association. The results of this study are discordant in terms of NLR and PLR with those of a recent study with a smaller number of patients that did not include patients with ethanol etiology of SAP, in which they were associated with death [13].

Although hemoglobin values were higher in deceased patients than in survivors, the difference did not reach a statistical significance, ($p = 0.202$), but the increased hematocrit values were associated with death, $p = 0.044$, this variable being associated with the AP severity [30].

RDW-SD had higher values in survivors compared to the deceased, but the differences were not statistically significant, unlike the study of Zhang in 2019, which obtained statistically significant differences [31].

Although PDW values were lower for survivors, they were statistically associated with death ($p = 0.403$). There are studies in which PDW was associated with the unfavorable prognosis of AP, correlating with the onset of organ dysfunctions.[19] MPV and PCT did not correlate with death in this study, $p = 0.056$ and $p = 0.416$, respectively. The role of these hematological indicators in patients with SAP is difficult to establish because of the different compositions of patients included in SAP etiology.

There were statistically significant differences between the calcium values of survivors and the deceased ($p <0.001$), hypocalcemia being one of the components of the Ranson score that stratifies the AP severity, being associated with increasing mortality and hospitalization in critical patients [32].

LDH, another parameter of 11 in Ranson score, also had higher values in the deceased than in the survivors, $p <0.001$. In a study that included 105 patients with AP, Jing et al. identified LDH as an independent prognostic factor for persistent organ failure.[33] There were no statistically significant differences between survivors and deceased in terms of sodemia, amylase and lipase values, the latter not being included in the scores for establishing the AP severity.

We found statistically significant differences between the two groups for urea and creatinine 48 hours after hospital admission, with $P = 0.006$ and $P = 0.001$, respectively. The values of urea and creatinine at 48 hours in deceased patients were higher than in the case of survivors and higher than the values at hospital admission, correlating with death, as opposed to the values of urea and creatinine at admission, where there were not obtained any statistically significant differences between survivors and deceased. From this data, there results the importance of hydro-electrolytic and acid-basic re-balancing measures in patients with SAP patients.

We found differences between the ALT si AST values at hospital admission in patients with SAP, these being higher in survivors compared to the deceased, in AST being statistically significant, p = 0.025, and in the case of ALT the differences were at the limit of statistical significance, namely p = 0.055. Also the BT and BD values were statistically increased in the deceased patients than in survivors, p = 0.004 and 0.005, respectively. Increased values of transaminases and bilirubin correlate with the AP severity and reflect the changes in the liver infusion determined by systemic and local mediators [34].

The pH value at admission in Intensive Care was significantly smaller in survivors compared to the deceased, p <0.001, and the lactate values were significantly higher in the deceased patients than in survivors, p <0.001. The low pH and increased lactate values proved to be strong predictors for the mortality of Intensive Care patients, in a study by Schork et al [35].

The role of these parameters at Intensive Care admission in the prediction of mortality in patients with SAP remains to be established in studies with a higher number of patients.

The presence of ketonuria and pleural effusion at hospital admission were not associated with increasing mortality of patients with SAP.

The presence of lung, heart, kidney failure was associated with death, p <0.001, and the presence of pancreatic necrosis and pancreatic abscesses were not statistically associated with death, these results being similar to those of other studies. [14] As a conclusion, the mortality of patients with SAP is due especially to systemic complications and less to local complications.

The presence of Clostridium Difficile infection was not associated with death in patients with SAP in this study. The study of Maatman et al., published in 2020, showed that the presence of this infection was not associated with mortality in patients with acute necrotic pancreatitis.

Although the number of the deceased who received antibiotic prophylaxis was higher than that of survivors, the differences were not statistically significant, p = 0.218. I consider that updating national guides and increasing access to these are necessary for the judicious use of antibiotics in AP.

The percentage of the deceased was higher among those who did not receive enteral nutrition than in those who received enteral nutrition, (p = 0.054), but this result should be interpreted cautiously as patients who did not receive enteral nutrition were those whose severe state did not allow the administration of enteral nutrition. There were no statistically significant differences between the mortality of patients in terms of the quantity of fluids

administered within the first 24 hours for the established intervals (under 2500 ml, 2500-4000ml, over 4000 ml).

In this study, surgical interventions themselves did not correlate with death, a result that differs from the one obtained by Mihoc et al., where their presence was a risk factor for death. Our result must be carefully analyzed taking into consideration that, in the case of compartment syndrome, all patients underwent surgery and died in this study, with a p value close to the statistical significance ($p = 0.057$). The presence of intra abdominal hypertension occurs in the first days of AP progression and it is determined by the inflammatory process that leads to the development of pancreatic and peripancreatic edema and ascites [36], the compartment syndrome representing an early fatal complication of SAP in this study.

The use of renal replacement techniques in patients with kidney failure has strongly correlated with mortality ($p <0.001$), a result that was expected given that the presence of kidney failure was associated with mortality.

Regarding the plasma exchange technique used in patients with etiology of hypertriglyceridemia, there were no statistically significant differences between the group of survivors and the deceased. As shown in the general part, the role of these techniques in the treatment of hypertriglyceridemia is not yet well established [37, 38].

The total number of hospitalization days in the deceased was significantly lower than that of survivors, as most deaths occurred through systemic complications.

Regarding the prognostic scores of AP, the BISAP score above 2 and Ranson score above 4 were correlated with the mortality of patients with SAP ($p <0.001$).

Statistically significant differences were also between the values of APACHE II and SOFA scores at Intensive Care admission, these scores being initially developed for assessing the prognosis in heterogeneous populations of critical patients. The mean of the APACHE II score for the survivors was 13.5 and 25.6 for the deceased, $p <0.001$, while the mean of SOFA score was 3.8 for the survivors and 10.4 for the deceased of, $p <0.001$.

Objective 3 - Determining the accuracy of death prediction of variables that have been associated with the unfavorable prognosis and of the severity scores.

Of the AST values registered at hospital admission, the number of platelets, BT and BD proved to be weak predictors for the death of patients with SAP, presenting AUROC values lower than 0.7. Calcemia values and LDH at admission and urea and creatinine values at 48 hours had AUREOC between 0.7 and 0.8, being modest predictors for death in patients with SAP, as well as pH and lactate values at Intensive Care admission.

The BISAP, Ranson, APACHE II and SOFA severity scores used to assess the severity in AP proved useful for the mortality evaluation in SAP.

The BISAP and Ranson scores were good predictors for mortality in the patients with SAP included in the study, with AUROC between 0.8 and 0.9, with AUROC 0.857 BISAP and 0.899 for Ranson score. The cut-off value calculated for the BISAP score was >2 and for the Ranson score> 4, with a sensitivity of 88.9% and a specificity of 80.5% for the BISAP score and 89.7% and 77.5% for the Ranson score.

The APACHE II and SOFA scores at Intensive Care admission were excellent predictors of patients with SAP with AUROC values between 0.9-1. The cut-off value calculated for the APACHE II score was >17 with a sensitivity of 86.6% and a specificity of 80.5% and the SOFA score >8 had a sensitivity of 80% and a specificity of 97.6%.

These results must be validated by future studies as, due to the different design of literature studies, for patients with SAP they are difficult to be interpreted.

4. Conclusions and Personal Contributions

Personal contributions

I conducted a retrospective, single-centered study that aimed at analyzing the prognostic factors in SAP patients, having 3 main objectives.

Objective 1 performs a complex image of patients with SAP from the demographic, clinical, paraclinical, treatment and complications point of view on a small group, but a significant group for this pathology.

Objectives 2 and 3 of this study were intended to identify the prognostic factors for death in patients with SAP and to determine the accuracy of predicting death in some variables.

The three research objectives were attained and we, thus, conclude the following:

1. The most common etiology of patients with SAP was alcohol, 37.2%, followed at a short distance by the biliary etiology (33.7%).

2. Overall, the majority population was of males from the urban area, with the mean age of 57.47. In SAP patients with biliary etiology, the predominance of the females was observed, while in those with ethanolic etiology the predominance was of males.

3. 46.5% of patients were smokers and 53.5% were alcohol consumers, while 55.8% were overweight or obese.

4. Of comorbidities, the most common was HTA (44.2%), followed by DM, (30.2%) and ICD, (24.4%).

5. The presence of ketonuria at admission was highlighted in 29.1% of patients, while the presence of pleural effusion in 32.6% of patients, most commonly being highlighted by the left side.

6. Of the patients with SAP, 47.6% had a BISAP score higher than 2 and 51.2% had a Ranson score over 4.

7. The means of APACHE II and SOFA scores at Intensive Care admission were 19.86 and 7.34, respectively.

8. Pancreatic necrosis was highlighted in 74.4% of patients, 5.8% of them had compartment syndrome, and 13.95% had pancreatic abscesses.

9. 44.2% of patients required surgery for compartment syndrome, pancreatic necrosis excision, other complications such as gastric or colonic necrosis.

10. 16.3% of SAP patients had Clostridium Difficile infection.

11. The most common organ failure was represented by lung failure, followed by kidney failure. 34.9% of patients had one organ failure and 53.5% presented three organ failures.

12. 60% of SAP patients received antibiotic prophylaxis.

13. 63% of patients received enteral nutrition, while 22% received mixed, enteral and parenteral nutrition.

14. 36% required renal replacement therapy.

15. The mean of hospitalization days in Intensive Care Unit was of 6.62 days and the mean of total hospitalization period was of 18.06 days.

16. The mortality at 7 days was 30.2% and the general mortality was 52.3%.

17. The most unfavorable prognosis was in the patients with unknown etiology, with a mortality of 75%, the unknown etiology being a risk factor for death.

18. Sex, home environment and smoking are not risk factors for death.

19. Old age and the presence of ischemic heart disease were associated with death.

20. In overweight and obese patients, mortality was higher than in normal or underweight patients.

21. The low number of platelets, low calcemic values were associated with death.

22. Increased values of LDH, AST, BT and BD at hospital admission were also associated with death.

23. We did not identify any associations between NLR, PLR, erythrocyte or platelet indices and death.

24. The association of death with increased urea and creatinine values was found 48 hours after hospital admission, as well as the high lactate values and low pH values measured at ICU admission.

25. The presence of ketoneuria and pleural effusion at the hospital intake are not risk factors for death.

26. The presence of organ, lung, kidney, heart failure represents risk factors for death.

27. The average of the Apache II and SOFA scores was significantly higher in survivors compared to the deceased with $P < 0.001$

28. Clostridium Difficile infection is not a risk factor for death.

29. The total number of hospitalization days of the deceased was significantly smaller ($p = 0.01$) than of survivors.

30. The presence of pancreatic necrosis and pancreatic abscesses did not influence survival.

31. The use of renal replacement therapy in patients with SAP is a risk factor for death.

32. The number of platelets, BT and BD are weak predictors for death.

33. Calcemia, LDH, urea at 48 hours, creatinine at 48 hours and age have moderate accuracy for death prediction in patients with SAP.

34. BISAP, Ranson, APACHE II and SOFA scores are useful tools in the prediction of mortality in patients with SAP. APACHE II and SOFA scores calculated at ICU admission had a higher prediction accuracy for death than BISAP and Ranson scores.

Conclusions

SAP is an extremely serious condition, with high mortality, which requires a multidisciplinary approach, preferably in tertiary centers, as it is a high resource consumer and a burden for health systems, the treatment of this pathology being extremely complex, as it requires supportive therapy and treatment for specific complications.

The mortality of patients with SAP is mainly related to systemic complications, their rapid identification, prompt admission to Intensive Care, monitoring and advanced support of vital functions representing key elements for SAP management.

The calculation of BIASP, Ranson, APACHE II, SOFA scores is important in order to predict death better than the studied individual variables.

The approach of this extremely complex pathology requires, besides a trained multidisciplinary team, the composition of national diagnostic and treatment guides updated periodically.

Changes in the lifestyle that includes maintaining a normal weight and a normal level of triglycerides, limiting alcohol and smoking consumption are measures to be taken to prevent and limit the severity of AP.

As a perspective, I believe that the establishment of regional centers for the treatment of SAP where trained multidisciplinary teams treat this pathology, where minimally invasive techniques of approaching pancreatic necrosis are available, represent a solution for the appropriate management of this condition.

Limitations of the study

The main limitation of this study is its retrospective nature, due to difiicult data collection and the small number of patients selected from a single center.

Another limitation of the study is that it did not include an imaging prognosis, on the one hand because of the retrospective nature of the study, considering that imaging results in an electronic format was not available for all patients, and, on the other hand, that the imaging results were not reviewed by a radiologist to calculate the prognostic imaging scores.

Research directions

Considering the increased mortality of patients with SAP, it is necessary to carry out a prospective, multi-center study for the assessment of the prognostic factors in SAP. The advantages are represented by a larger number of patients evaluated and treated according to the treatment definitions and guides used in a certain period of time, allowing a comparative study of the prognostic factors according to SAP etiology, as well.

The clinical utility of Plasma Exchange in decreased mortality and morbidity in patients with hypertriglyceridemia should also be investigated in randomized clinical trials in which this technique is compared to the conventional treatment for hypertriglyceridemia.

SAP is a complex pathology, with a reserved prognosis that has as central element the imbalance of the immune response to pancreatic injury, consequently, I believe that one of the main research directions is the development of immunomodulatory therapies and their transfer to clinical practice.

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1. **Petre R**, Băleanu V-D, Vasile D, et al. Hypertriglyceridemic pancreatitis and diabetic ketoacidosis. *Research and Science Today* 2021; 22: 125–130.
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2. **Petre R**, Vasile D, Băleanu V, et al. ICU mortalitity in severe acute pancreatitis- single centre experience. *Research and Science Today* 2022; 23: 103–111.
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