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UNIVERISTY OF MEDICINE AND PHARMACY

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DOCTORAL SCHOOL

MEDICINE DOMAIN

PROGNOSTIC MODELS FOR THE IMMEDIATE EVOLUTION OF PATIENTS WITH ACUTE PANCREATITIS

DOCTORAL THESIS SUMMARY

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2025

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Introduction

An emergency condition such as acute pancreatitis (AP), whose progression can be positively influenced and directed toward resolution with minimal organ damage, warrants the concerted efforts of both healthcare professionals and researchers in developing the optimal management plan. This conviction has guided my choice of research topic.

The incidence of acute pancreatitis, its associated mortality rate, and the disability resulting from this condition are increasing, representing a growing burden on society [1]. As a result, the development of prognostic scoring systems for acute pancreatitis has been an ongoing concern in the medical community since the previous century.

Research hypothesis: Certain clinical and biological parameters — including C-reactive protein (CRP), serum calcium, leukocyte count, etiology, and pain intensity measured on the Visual Analogue Scale (VAS) — may serve as prognostic factors for the severity of acute pancreatitis.

Objective: To develop a new predictive score for severe forms of acute pancreatitis tailored to local clinical practice.

I. General section

1. Acute Pancreatitis

1.1. Definition, Epidemiology, Etiology, Pathophysiology and Anatomical pathology

Acute pancreatitis (AP) is a heterogeneous condition, briefly defined as acute inflammation of the pancreas, with variable clinical evolution. Its incidence rate varies across different regions. The most common etiologies are alcohol consumption and biliary tract disease. The pathophysiological mechanisms of AP are not yet fully elucidated. Its multifactorial pathogenesis involves calcium (Ca^{2+}) overload, premature activation of trypsinogen, impaired autophagy, endoplasmic reticulum (ER) stress, and the involvement of exosomes [2]. From a histopathological perspective, AP is characterized by inflammatory and necrotic changes in the pancreatic and peripancreatic tissues.

1.5. Clinical Presentation

According to studies in the literature, pain is the primary symptom of AP at presentation, reported in approximately 95% of cases, and is associated with a number of characteristic features [3–7]. Patients typically present to the hospital within 12–24 hours from symptom onset [4]. Loss of appetite, nausea, and intractable vomiting are also frequent, occurring in 65–90% of cases [3–7]. Fever (ranging from low-grade to high-grade) is variably reported, with prevalence rates ranging from 6–7% up to 60%, depending on the study [6,7]. Muscle spasms secondary to hypocalcemia, including tetany in severe cases, have also been described. The presence of tetany is considered a negative prognostic factor and is associated with increased mortality [8].

1.6. Differential Diagnosis

The differential diagnosis of AP primarily involves distinguishing between various causes of abdominal pain, as well as other etiologies of hyperamylasemia and/or hyperlipasemia. Diagnosis is based on clinical findings and laboratory investigations [5]. Imaging studies are critical for diagnostic confirmation, particularly contrast-enhanced computed tomography (CECT). Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) offer superior visualization of the pancreatic and biliary

ducts, and are more sensitive than CT — even with contrast — in detecting choledocholithiasis [5,6].

1.8. Positive Diagnosis

According to the revised Atlanta Classification (2012), a positive diagnosis of acute pancreatitis (AP) requires the presence of at least two out of the following three criteria [9]:

a) Abdominal pain characteristic of AP (acute-onset epigastric pain that is persistent, severe, and often radiates to the back);

b) Serum lipase (or amylase) level at least three times the upper limit of normal;

c) Imaging findings consistent with AP on contrast-enhanced computed tomography (CECT), or, less frequently, on abdominal magnetic resonance imaging (MRI) or ultrasonography.

1.9. Complications, Treatment, Evolution and Prognosis in Acute Pancreatitis

Complications of AP include: abdominal compartment syndrome, metabolic acidosis, acute kidney injury, acute respiratory distress syndrome (ARDS), ascites, mesenteric ischemia, progression to chronic pancreatitis, disseminated intravascular coagulation (DIC), gastric varices, paralytic ileus, mesenteric vein thrombosis, pancreatic abscess, pseudoaneurysm of the pancreatic arteries, pancreatic necrosis, pseudocyst formation, and splenic vein thrombosis.

The management of AP focuses on early supportive care and the treatment of complications. Early management includes moderate fluid resuscitation with intravenous crystalloids, oral feeding as tolerated (on-demand feeding), and adequate analgesia. In cases of mild biliary AP, early cholecystectomy during the same hospital admission is considered the standard of care.

Approximately 20% of patients with AP develop moderate or severe forms of the disease, which are associated with local complications such as pancreatic necrosis, peripancreatic fluid collections, venous thromboses, pseudoaneurysms, and organ failure. Mortality in severe AP can reach rates as high as 40 %. Stratifying patients according to the predicted severity of disease may improve outcomes and allow for targeted interventions [10].

2. Classifications and Severity Scores in Acute Pancreatitis

2.1. Classifications for severity of acute pancreatitis

Several classifications have been developed to assess the severity of acute pancreatitis (AP), including the Marseille Classification, the Cambridge Classification, the Atlanta Classification, and the Determinant-Based Classification. The most widely used among these is the 1992 Atlanta Classification, which was developed by an international panel of experts in the field. According to this classification, the severity of AP is determined by the presence or absence of organ failure and local complications, in conjunction with a Ranson score ≥3 or an APACHE II score ≥8. Complications considered in this system include pancreatic abscess, acute pseudocyst, and pancreatic necrosis. Organ failure refers to shock, pulmonary insufficiency, renal failure, and gastrointestinal bleeding. Infected pancreatic necrosis is considered to carry a higher risk of mortality than pancreatic abscess [11,12].

2.2. Severity Scores in AP

Over the years, numerous scoring systems have been developed to evaluate the severity of AP. Some were created specifically for AP, while others were originally intended for use in other critical conditions but have been found applicable to AP. These include: Ranson Score, APACHE Score, Modified Marshall Score, SOFA Score, Quick SOFA (qSOFA), BISAP Score, Glasgow Score, POP Score, HAPS Score, SAPS Score, Balthazar Score, CT Severity Index, Japanese Severity Score, Pediatric Acute Pancreatitis Score, Japanese Pediatric Score, LOD Score, BALI Score, ASAP Score, PASS Score, Simplified Prognostic Score, PANC-3 Score, MODS Score, SPC, BOFS, SIRS Criteria, Early Warning Score (EWS).

2.2.1 Ranson Score

The Ranson score was the first prognostic scoring system developed for AP, introduced in 1974 [10,11,13]. It is used to assess severity and estimate mortality risk in acute pancreatitis. The score comprises 11 parameters, 5 of which are assessed at admission and 6 after 48 hours. The Ranson score predicts PA organ failure, necrosis, mortality and severity with area under the curve (AUC) of 0.84, 0.56, 0.80 and 0.81, respectively. [10, 11, 13, 15] Scores of <3, ≥3 and ≥6 indicate a mortality of 0–3%, 11–15 % and 40%, respectively [5, 10, 11, 16-18].

2.2.2 APACHE Score

In 1981, the Acute Physiology and Chronic Health Evaluation (APACHE) score was developed and has been revised four times to date. The most widely used version remains the second one – APACHE II. Although the APACHE score is intended to assess mortality in the intensive care unit, it has a high sensitivity for predicting complicated acute pancreatitis. It includes approximately 14 criteria such as: history of organ failure or deficiency (NYHA class IV congestive heart failure, chronic kidney disease requiring dialysis, cirrhosis), acute kidney injury, temperature, mean arterial pressure, age, respiratory rate, heart rate, leukocytes, sodium, potassium, blood pH, serum creatinine, hematocrit, Glasgow Coma Scale (GCS), blood oxygenation. Some of the variables may not be available outside the intensive care unit (ICU). In practice, to assess severity, the score includes both the patient's chronic medical status and the acute pathology. The worst outcomes in the first 24 hours are considered [11, 19-21].

2.2.7 BISAP Score

The Bedside Index for Severity in Acute Pancreatitis score (BISAP) predicts mortality risk using fewer variables, making it simpler to use and thus more appropriate for the emergency department. The data used from the first 24 hours are: urea, Glasgow Coma Score, evidence of SIRS, age, and the presence of pleural effusion. A score of zero is associated with a mortality of less than 1%, while patients with a maximum score of five have a mortality rate of 22%. The validation cohort showed similar performance for predicting mortality for the BISAP score compared to the APACHE II score, but it was not validated to predict length of hospital stay, need for intensive care measures, or indication for surgery [11, 22, 23].

II. Personal Contributions

3. Development of a Predictive Score for the Severity of Acute Pancreatitis

3.1. Introduction (Working Hypothesis and General Objectives)

The ability to predict the severity of the disease allows the identification of patients at high risk of mortality and morbidity and the early establishment of appropriate treatment and monitoring, improving the prognosis and reducing unnecessary hospitalization and, implicitly, the costs and complications secondary to prolonged hospitalization. For this reason, studying prognostic factors in AP and identifying a severity score has been and continues to be a common topic and of great interest in the specialized literature, despite the existence of prognostic scores already available.

Local studies, even small ones, continue to provide valuable insights into local protocols and procedures, which are related to factors such as geographical region, type of hospital, specific patient population that addresses the medical institution, current local practice and, last but not least, available resources. Thus, the use of an appropriate severity score allows the development of personalized local therapeutic protocols in tertiary care centers. At the same time, in a primary care center, it offers the physician the possibility of selecting patients who require referral to a specialist. An optimal severity score should have good predictive power, be able to be determined early, involve few resources, be financially advantageous and be easy to use in a given region/institution.

Working hypothesis: some clinical and biological parameters such as C-reactive protein, calcium, leukocyte count, etiology or pain level on the VAS scale are prognostic factors for the severity of AP.

3.2. Materials and Methods

This paper is a retrospective study, conducted over a 4-year period, carried out on a cohort of 172 patients who presented to the emergency room of the Bucharest University Emergency Hospital (SUUB), were diagnosed with AP and were subsequently hospitalized in the gastroenterology, internal medicine and general surgery departments [29]. The study complies with the “Ethical Principles for Medical Research on Human Subjects” of the World Medical Association Declaration of Helsinki.

The working method used was that of documentary analysis (collection and processing of data from electronic or physical medical records of patients). Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 29.0 (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY, USA: IBM Corp).

Inclusion criteria were: positive diagnosis of AP, age over 18 years (adult patients), admission from the emergency room of the Emergency University Hospital Bucharest to gastroenterology, internal medicine or surgery departments.

The diagnosis of AP was established based on the definition from the revised Atlanta Classification of 2012 [9].

The following variables were included in the study: demographic data (age, sex), the existence of comorbidities or other important antecedents, particular cases of pregnancy/confinement, smoking/non-smoking status, etiology of AP, presence of obesity, body mass index (BMI), pain assessment on the VAS scale, body temperature, blood pressure and ventricular rate on admission, laboratory tests and imaging investigations, cultures, days of hospitalization, admission ward, intensive care unit stay, data regarding multiple organ failure, treatment administered, existence of ERCP procedures or surgical interventions during admission, complications, development/resolution of the case.

The following moments in the progres of the disease were taken into account, according to which the following variables were defined, which are referred to further in the study:

- ***moment 1***: at presentation, when alanine aminotransferase (ALT1), aspartate aminotransferase (AST1), hemoglobin 1, hematocrit 1, amylase 1, lipase 1, urea 1, creatinine 1, total bilirubin (TB) 1, direct bilirubin (DB) 1, etc. were determined

- ***moment 2***: 24 hours after presentation, when ALT2, AST2, hemoglobin 2, hematocrit 2, amylase 2, lipase 2, urea 2, creatinine 2, TB2, DB2, etc. were determined.

- ***moment 3:*** 48 hours after presentation: ALT3, AST3, amylase 3, lipase 3, TB3, DB3.

To facilitate the presentation of the results, we will refer to mild and moderate forms of AP as moderate AP later in the text.

3.3. Results

3.3.1. Demographic Characteristics of Patients

Sex of the patients included in the study

Among the 172 patients included in the study, 95 (92.2%) men and 62 (89.9%) women presented moderate pancreatitis, and 8 men (7.8%) and 7 women (10.1%) had severe pancreatitis, with no statistically significant differences according to gender in terms of the distribution of patients by severity of acute pancreatitis (p=0.588). The severity of acute pancreatitis does not correlate statistically significantly with the sex of the patients included in the research (rho=0.041; p=0.591). There were no statistically significant differences in terms of the distribution of study participants according to sex and the morphological form of acute pancreatitis (p=0.333).

Age of the patients included in the study

In the study group, the distribution of patients according to age is Gaussian (p=0.847), with a mean of 56.24±16.37 years. The age of patients with moderate acute pancreatitis in the study was 55.90±16.23 years, which was not statistically significant (p=0.388) compared to that of patients with severe pancreatitis included in the study (59.73±18.01 years) [29]. The age of patients included in the study with acute pancreatitis did not differ statistically significantly depending on its morphological form (p=0.988).

3.3.2. Medical History of Study Participants

The prevalence of smoking among patients with moderate pancreatitis is 29.9%, statistically insignificant (p=0.878) compared to the prevalence of smoking among patients with severe pancreatitis (33.3%).

The weight status of patients is not statistically significant different depending on the severity of pancreatitis (p=0.916). The prevalence of obesity among patients with moderate pancreatitis is 25.5%, and among those with severe pancreatitis it is 40.0%, but without statistically significant differences (p=0.225).

The prevalence of diabetes mellitus in patients with severe pancreatitis is 46.7%, statistically significant higher (p=0.016) compared to the prevalence of diabetes in patients with moderate forms of the disease.

The prevalence of cardiovascular diseases does not differ statistically significantly depending on the severity of pancreatitis (p=0.543), nor does the prevalence of arterial hypertension present statistically significant differences (p=0.595).

The distribution of patients according to the type of etiology and severity of pancreatitis shows a higher share of single etiology among patients with moderate pancreatitis (91.7 %) compared to 66.7% among those with severe pancreatitis, while multiple etiology occurs in 8.3% of those with moderate pancreatitis and 33.3% of those with severe pancreatitis, the differences being statistically significant (p=0.002). Among patients with moderate disease, the most common etiology is biliary etiology (43.3%), followed by alcoholic etiology (36.9%), and among those with severe disease, non-alcoholic, non-biliary etiology (nonA-nonB etiology) is the most common (53.3%) [29]. The difference in the etiology of pancreatitis according to the severity of the disease is statistically significant (p=0.012) [24].

Regarding the presence of previous episodes of acute pancreatitis, this is found in 28.7% of those with moderate disease and 26.7% of those with severe disease (p=0.870).

3.3.3. Imaging Investigations

Chest X-ray

Among the 172 patients included in the study, pleural effusion or other changes were found on chest X-ray in 41.40% of those with moderate acute pancreatitis and in 73.33% of those with severe acute pancreatitis. The difference in the presence of changes visible on chest X-ray is statistically significant, with pleural effusion and other changes occurring more frequently in patients with severe acute pancreatitis compared to the moderate form of the disease (73.3% vs 41.4%; p=0.017).

Abdominal ultrasound

The prevalence of gallstones identified by ultrasound is statistically insignificant higher (p=0.610) among patients with moderate acute pancreatitis (33.12%) compared to those with the severe form (26.67%). Gallstone sizes in patients with moderate acute pancreatitis show a median value of 13 mm (9–20), statistically insignificant different (p=0.762) compared to patients with the severe form of acute pancreatitis, where the median value is 16 mm (9.5–19.5). There are no statistically significant differences regarding the size of extrahepatic bile ducts depending on the severity of the disease (p=0.915).

The difference in the presence of ultrasound visible collections is not statistically significant (p=0.113), but it is clinically relevant, with collections being detected more than

twice as frequently in patients with severe pancreatitis. The size of ultrasound visible collections in patients with moderate acute pancreatitis recorded a median value of 9 mm (4–18), not statistically significant different (p=0.253) compared to that of patients with severe acute pancreatitis, where the median value was 18 mm (11–18).

Abdominal CT

Among the 172 patients participating in the study, 104 patients (60.5%) underwent a computed tomography (CT) examination.

On abdominal computed tomography examination, visible collections were found in 53.85% of those with moderate acute pancreatitis and in 76.92% of those with severe acute pancreatitis. The statistical difference in the presence of visible collections on CT is not significant (p=0.116). However, we can emphasize the superior ability of the computed tomography to visualize the collections (56.7% of all patients investigated) compared to the ultrasound examination (12.2% of patients). The sizes of the visible collections on CT in patients with moderate pancreatitis show a median value of 18 mm (13–30), statistically significant different (p=0.003) compared to those of patients with severe acute pancreatitis, where the median value is 40 mm (28–75).

There are no statistically significant differences at the CT exam regarding the size of the extrahepatic bile ducts depending on the severity of the disease (p=0.223) either.

Among patients with moderate acute pancreatitis, 58% had a first abdominal CT scan, and among those with severe acute pancreatitis, 86.7% had an abdominal CT scan, the difference being statistically significant (p=0.030).

The percentage of patients who had a second CT scan was statistically significant (p=0.006) higher among patients with severe acute pancreatitis (33.3%) compared to those with moderate acute pancreatitis (9.6%).

Among patients who had a CT scan, there were no statistically significant differences according to the severity of the disease regarding the moment of examination in relation to the time elapsed since admission (p=0.488).

At the first CT scan, there was a statistically significant difference between patients with moderate acute pancreatitis and those with severe disease (p=0.002), this difference not being recorded in the case of the second CT scan (p=0.801). At the first CT scan, edematous

pancreatitis is found in 82.4% of patients with the moderate form and in 53.8% of those with the severe form. The necrotic form is present in 9.9% of patients with the moderate form and in 46.2% of those with the severe form.

3.3.4. Pain Evolution

The pain level on the VAS scale is statistically significant higher for patients with severe pancreatitis compared to those with moderate pancreatitis. Also, a downward trend in the pain level on the VAS scale can be observed during the evolution, both for patients with moderate pancreatitis and for those with severe pancreatitis [24].

3.3.5. Biological Parameters

Among the biological parameters studied, the following had a Gaussian distribution: hemoglobin 1, calcium 1, and hematocrit (hematocrit 1, hematocrit 2). For white blood cell count (WBC), hemoglobin 2, blood glucose, C-reactive protein (CRP), amylase (amylase 1, amylase 2, amylase 3), lipase (lipase 1, lipase 2, lipase 3), urea 1, urea 2, creatinine 1, creatinine 2, AST, ALT, total bilirubin (BT), direct bilirubin (BD), total cholesterol, and triglycerides, the distribution is not normal.

No statistically significant differences were observed based on the severity of acute pancreatitis for INR, hemoglobin, hematocrit, calcium at presentation (CA1), or total cholesterol.

WBC among patients with severe acute pancreatitis (Me = 19,080.00; 25th percentile = 10,100.00; 75th percentile = 21,800.00) is statistically significant higher ($p = 0.037$) compared to patients with moderate acute pancreatitis (Me = 12,280.00; 25th percentile = 9,350.00; 75th percentile = 15,700.00).

Glucose levels among patients with severe acute pancreatitis (Me = 209.00; 25th percentile = 143.00; 75th percentile = 336.00) are statistically significant higher ($p = 0.029$) compared to those with moderate acute pancreatitis (Me = 138.00; 25th percentile = 113.00; 75th percentile = 183.00).

C-reactive protein values in patients with severe acute pancreatitis (Me = 223.00; 25th percentile = 126.00; 75th percentile = 320.00) are statistically significant higher ($p = 0.002$) than in patients with moderate forms (Me = 85.00; 25th percentile = 33.50; 75th percentile = 171.50) [24].

Amylase values in patients with moderate acute pancreatitis show statistically significant changes across the three evaluation moments, with values decreasing significantly from moment 1 to moment 3 ($p < 0.001$). A similar trend was observed in patients with severe acute pancreatitis ($p < 0.001$).

As with amylase, lipase values also show statistically significant changes over the three evaluation moments, with measurements decreasing significantly from moment 1 to moment 3 in both moderate ($p < 0.001$) and severe acute pancreatitis patients ($p < 0.001$). Lipase 3 values among patients with severe acute pancreatitis (1377.13 ± 1366.10) are statistically significant higher ($p = 0.034$) than those among patients with moderate forms (777.72 ± 1230.17); the differences observed for lipase 1 and 2 were not statistically significant ($p = 0.706$ and $p = 0.294$, respectively).

Urea 1 levels in patients with severe acute pancreatitis (71.66 ± 69.79) are statistically significant higher ($p = 0.015$) than those in patients with moderate forms (36.85 ± 20.65). Urea 2 levels in patients with severe disease (75.07 ± 48.25) are also statistically significant higher ($p = 0.001$) compared to patients with moderate pancreatitis (37.34 ± 24.13).

Creatinine 1 values in patients with severe acute pancreatitis (2.17 ± 2.25) are statistically significant higher ($p < 0.001$) compared to those in patients with moderate disease (1.04 ± 0.46). Creatinine 2 values among patients with severe acute pancreatitis (2.26 ± 1.43) are also statistically significant higher ($p = 0.030$) than in those with moderate disease (1.05 ± 0.58).

AST values among patients with moderate acute pancreatitis show statistically significant changes between the three evaluation moments, with values decreasing significantly from the first to the third moment ($p < 0.001$). Similar patterns were observed for ALT ($p < 0.001$), total bilirubin (BT) ($p < 0.001$), and direct bilirubin (BD) ($p < 0.001$).

BD 3 values among patients with severe acute pancreatitis (1.12 ± 1.23) are statistically significant higher ($p = 0.035$) compared to BD 3 values among patients with moderate forms (0.67 ± 0.98).

The median total cholesterol level among patients with severe pancreatitis is 247.00 mg/dL (142.00–321.00), not statistically significant higher ($p = 0.081$) compared to the median total cholesterol among patients with moderate pancreatitis, which is 175.00 mg/dL (148.40–220.00).

The median triglyceride level among patients with severe pancreatitis is 289.00 mg/dL (105.00–1225.00), statistically significant higher ($p = 0.001$) than the median triglycerides among patients with moderate pancreatitis, which is 100.00 mg/dL (66.00–146.00).

3.3.6. Clinical and Evolutive Aspects

There were no statistically significant differences in the type of hospitalization (emergency or intra-/extra-hospital transfer), the type of ward (medical vs. surgical), or the number of previous episodes based on the severity of acute pancreatitis ($p = 0.660$, $p = 0.346$, and $p = 0.961$, respectively).

The distribution of hospitalization duration was not Gaussian ($p < 0.001$). The number of hospitalization days differed statistically significant depending on the severity of acute pancreatitis (Mann–Whitney test = 731.50; $p = 0.015$), being significantly higher in patients with severe acute pancreatitis compared to those with the moderate form.

At admission, Systemic Inflammatory Response Syndrome (SIRS) was identified in 29.9% of patients with the moderate form and in 80.0% of those with the severe form. Thus, the presence of SIRS was statistically significant more frequent in severe cases ($p < 0.001$).

The presence of organ failure at admission was also significantly higher in patients with severe acute pancreatitis (73.3%) compared to those with the moderate form (5,1%). Temporary organ failure (less than 48 hours) was found in 5.1% of moderate cases and 13.3% of severe cases and persistent organ failure (more than 48 hours) was present in 1.9% of patients with moderate form and in 73.3% of those with severe form. Both temporary and persistent organ failure were significantly more common in severe cases ($p < 0.001$). There were no statistically significant differences in the type of organ failure (renal, pulmonary, cardiovascular) depending on disease severity ($p = 0.240$). Multiple organ failure was not observed in any patient with moderate acute pancreatitis, but was present in 33.3% (5 patients) of those with severe disease—this difference being statistically significant ($p < 0.001$).

Intensive care unit (ICU) admission was significantly more frequent in patients with severe acute pancreatitis (66.7%) compared to those with the moderate form (1.9%) ($p < 0.001$).

Surgical complications occurred significantly less often in patients with moderate acute pancreatitis (9.6%) than in those with the severe form (26.7%) ($p = 0.043$). The most frequent surgical complications were pancreatic in nature.

Likewise, medical complications were statistically significant less frequent ($p < 0.001$) in moderate cases (28%) compared to severe cases (93.3%). The most common complications involved the digestive, cardiovascular, and neurological systems.

Diarrhea was more frequently reported in severe cases ($p = 0.001$). The incidence of Clostridium difficile infection did not differ significantly between the two groups.

Late complications occurred exclusively in patients with severe acute pancreatitis, the difference being statistically significant ($p < 0.001$). Among these patients, one developed postoperative colonization with Staphylococcus aureus and Klebsiella, while three others experienced cardiorespiratory arrest.

One patient with severe acute pancreatitis required surgical reintervention ($p < 0.001$), and another required readmission. The need for readmission was statistically insignificant lower in severe cases compared to moderate ones ($p = 0.493$).

A total of eight deaths were recorded in the study, with a significantly higher frequency in patients with severe acute pancreatitis ($p < 0.001$). There were no statistically significant differences regarding the time of death based on disease severity.

3.3.7. Pharmacological Treatment

Antibiotics were administered significantly more frequently ($p < 0.001$) to patients with severe acute pancreatitis (100%) compared to those with the moderate form (over 50%). Among patients with severe acute pancreatitis, 66.7% received Tienam. Metronidazole was used in 14.47% of patients with moderate acute pancreatitis and in 33.33% of those with the severe form, without the difference reaching statistical significance ($p = 0.058$).

Somatostatin was administered in 7.64% of moderate cases and 6.66% of severe cases, with no statistically significant difference between groups ($p = 0.891$)

In terms of fluid therapy, there were no statistically significant differences between the two forms of acute pancreatitis in the volume of fluids administered in the first 24 hours ($p = 0.926$). A total of 78.98% of patients with moderate and 80.00% of those with severe pancreatitis received at least 2000 mL of fluids during this period. The average volume of fluids administered in 24 hours was slightly higher in moderate cases (3414.65 ± 1361.64 mL) compared to severe cases (3400.00 ± 1391.29 mL), without a statistically significant difference ($p = 0.968$).

The relationship between the amount of solution and the severity of AP for each type of fluid was also studied. No statistically significant differences were recorded in the case of Ringer's solution or glucose solution. Regarding the amount of saline administered in 24 hours, there are statistically significant differences between the two forms of AP ($p<0.001$), 5.73% of those with moderate form and 40.00% of those with severe form of acute pancreatitis received 1500 ml of saline or more in 24 hours. The average amount of saline administered in the first 24 and 72 hours to patients with severe AP is statistically significant higher ($p=0.036$ for 24 hours, respectively $p=0.031$ for 72 hours) compared to that of patients with moderate AP.

3.3.8. Surgical Treatment

A history of cholecystectomy was recorded in 10.19% of patients with moderate and 16.67% of those with severe pancreatitis, with no statistically signs of peritoneal irritation were significantly more frequent in severe cases (26.7%) than in moderate ones (6.4%) ($p = 0.006$).

Surgical intervention was required in 33 patients: 7 with severe and 26 with moderate acute pancreatitis. The frequency of surgical treatment was significantly higher in the severe group (46.7%) compared to the moderate group (16.6%) ($p = 0.005$).

The time interval from hospitalization to surgery varied, but did not differ significantly according to the severity of the disease ($p = 0.275$).

The classical (open) surgery was significantly more frequent in patients with severe acute pancreatitis ($p = 0.035$). All surgeries in the severe group were performed using an open approach, while in the moderate group, both open (57.7%) and laparoscopic (42.3%) approaches were used.

Ascites was significantly more frequent in the severe group (46.7%) compared to the moderate group (3.2%) ($p < 0.001$).

In the case of patients who required surgery, statistically significant differences were recorded in terms of the appearance of the pancreas and the presence of necrosis in the peripancreatic tissues, depending on the severity of acute pancreatitis ($p<0.001$). Among those with the moderate form, 92.3% had an edematous appearance of the pancreas, and 7.7% had a necrotic appearance. All patients with severe acute pancreatitis who underwent surgery had a necrotic appearance of the pancreas. Regarding the presence of necrosis in the peripancreatic

tissues evidenced during surgery, 11.5% of patients with the moderate form and 85.7% of those with the severe form of acute pancreatitis presented necrosis of the peripancreatic tissues.

Among the patients who underwent surgery, intraoperative collections were identified in 13 of them (39.4%). The presence of collections in patients with severe disease was statistically significantly higher than in those with moderate acute pancreatitis (85.7% vs 26.9%, p=0.005).

Regarding the surgical procedures performed, statistically significantly higher percentages were recorded among patients with severe disease compared to those with moderate acute pancreatitis, in terms of the frequency of cholecystectomies (40.0% vs 16.6%, p=0.026), the need for necrosectomies (26.7% vs 0.6%, p<0.001), the need for multiple drainages (26.7% vs 1.3%, p<0.001), or cholecystostomy (6.7% vs 0%, p=0.001).

3.3.9. Prediction of Acute Pancreatitis Severity

A list of parameters was selected, based on existing data in the literature, which correlate with the severity of acute pancreatitis: sex, age, etiology of acute pancreatitis, body mass index, personal pathological history (diabetes mellitus, acute pancreatitis), biological parameters (INR, ALT, VAS, WBC, hematocrit, amylase, lipase, CA, C-reactive protein), and the amount of fluids in the first 24 hours. As presented in previous chapters, there are statistically significant differences between patients with moderate acute pancreatitis and those with severe acute pancreatitis in terms of the etiology of acute pancreatitis (p=0.012), determined by the higher frequency of nonA-nonB etiology in patients with severe acute pancreatitis (p=0.007), the presence of diabetes mellitus (significantly higher frequency in those with severe pancreatitis; p=0.016), the high level of pain on the VAS scale (p=0.003), WBC (p=0.037), and C-reactive protein (p=0.002).

The correlation between the severity of acute pancreatitis and the studied parameters was analyzed. Thus, it was found that the severity of acute pancreatitis was positively correlated with C-reactive protein (p=0.002), the presence of nonA-nonB etiology (p=0.003), VAS 0 (p=0.003), the presence of DM (p=0.016), and WBC 1 (p=0.037), and negatively with CA1 (p=0.014).

In order to study the prediction of the severity of acute pancreatitis, these parameters were analyzed using linear logistic regression. Its results showed that the severity of PA is associated with increased values of CRP, WBC1, VAS0, and decreased values of CA1. Also, the severity of PA is associated with nonA-nonB etiology and the presence of diabetes mellitus. Using multiple linear regression, the variables that are associated with the severity of acute pancreatitis were selected. The parameter that shows the strongest association with the severity of acute pancreatitis is C-reactive protein [24].

Based on the results, three models were selected: the first one includes only CRP as a predictor of the severity of acute pancreatitis, the second one excludes CRP and includes the parameters that have statistical significance (nonA-nonB etiology, VAS0, CA1, and WBC1), and the third one includes the parameters that, together with CRP, show statistical significance (nonA-nonB etiology and VAS0) [24].

Using the variables that are significantly associated with the severity of acute pancreatitis, prediction scores for the severity of acute pancreatitis can be obtained.

The regression equation for the CRP predictive model is:

CRP = 0,993 + 0,001 x CRP [24]

For a CRP threshold of 221.5 mg/L, the AUC (area under the curve) is 0.739 (95% CI: 0.619–0.859), reflecting that CRP is an acceptable predictor of AP severity.

The Acute Pancreatitis Severity Score I (PAPS I score) prediction excludes the C-reactive protein value. The regression equation for the PAPS I score is:

PAPS Score I = 1,237 + 0,144 x nonA-nonB etiology (0 – no; 1 – yes) + 0,001 x WBC1 +0,027 x VAS0 [24]

PAPS I score has a poor predictive value for the severity of acute pancreatitis (AUC=0.667; 95% CI=0.502–0.832), with the best cutoff value being 20,5.

In the case of the third model, the regression equation is::

PAPS Score II = 1,189 + 0,001 x CRP (mg/L) + 0,135 x nonA-nonB etiology (0 – no; 1 – yes) + 0,025 x VAS0 – 0,047 x CA1 [24]

The highest AUC value is for the PAPS II score (AUC=0.830; 95% CI=0.721–0.939), its value being considered very good for use in clinical practice.

The AUC value for PAPS II was 0.830 (0.721–0.939), being higher compared to that of the RANSON score, which was 0.647 (0.490–0.804), and closely followed by that of the BISAP score, which was 0.803 (0.684–0.922).

A cut-off value of CRP was set at 221.5 mg/L. We compared the three models (CRP, PAPS I score, and PAPS II score) with the BISAP score and the Ranson score.

For the studied cohort, the Ranson score demonstrated a sensitivity of 53.3%, a specificity of 68.2%, a positive predictive value (PPV) of 13.8%, and an negative predictive value (NPV) of 93.9%, recording an AUC of 0.647.

The BISAP score calculated for the evaluated AP patients had a sensitivity of 60%, a specificity of 83.4%, a PPV of 25.7%, and an NPV of 95.6% in predicting severity, with an AUC of 0.808.

Among the three models presented, PAPS II has the best performance and shows superior characteristics compared to the BISAP score and the Ranson score.

3.4. Discussions

Finding a simple solution for triaging patients with acute pancreatitis into mild, moderate, or severe forms of the disease has always been a goal for healthcare professionals, in order to provide the best care to patients and achieve the best possible outcomes. A retrospective study conducted at Changhai Hospital developed the new Chinese Simple Scoring System (CSSS). This score uses six factors: blood glucose, C-reactive protein, serum creatinine, lactate dehydrogenase, and the extent of pancreatic necrosis. The AUROC for CSSS in predicting mortality was 0.838. The score was found to be the most accurate. The accuracy was lower for APACHE II, Ranson, MCTSI, and BISAP, in that order [24, 25]. Another study from China improved a widely used score, such as Ranson, by developing the modified Ranson score. The latter had a higher accuracy than the original Ranson score in predicting severity, organ failure, and pancreatic infection or necrosis. This study, as well as others of its kind, demonstrates an ongoing research effort to improve severity scores [24, 26].

A study by Anum Arif et al. in 2019 showed sensitivity (69.2%) and specificity (77.8%) values for the BISAP score comparable to those in our study [24, 27].

There are some studies that report better specificity and sensitivity for predicting disease severity using the Ranson and BISAP scores. A study published in 2024 by Zhu J et al. shows, following a meta-analysis, a sensitivity for predicting severity of 95% for the Ranson

score and 67% for the BISAP score; a specificity of 74% for the Ranson score and 95% for the BISAP score; and an accuracy of 95% for the Ranson score and 94% for the BISAP score, respectively [24, 28].

Comparing the PAPS II score with the Ranson and BISAP scores, we highlight the following: although the NPV has comparable values for all three scores, the Ranson score has the lowest PPV, while the BISAP score and the PAPS II score have similar PPV values. The highest specificity is demonstrated by the BISAP score. However, the highest sensitivity belongs to the PAPS II score [24].

The Ranson score and the BISAP score have the best accuracy for the studied cohort..

The PAPS II score is easy to use and memorize, cost-effective, and time-efficient, even more so than the BISAP score. The PAPS II score uses 4 parameters, which are immediately available in the Emergency Department, while the BISAP score uses 8 parameters, also immediately available. The Ranson score uses 11 parameters with variable availability in the hospital setting and requires 48 hours to be determined. Thus, the PAPS II score is considered to be highly applicable in clinical practice [24].

The main limitation of this study is the relatively small sample size and the limited number of severe AP cases included. In addition, the retrospective design of the study inherently limits the control over the quality and consistency of data collection. Furthermore, the predictive score was not compared with another widely used scoring system, such as the APACHE II score. Elevated CRP levels and elevated white blood cell (WBC) counts, although significant, are not specific to AP and can occur in various clinical scenarios and settings, including infections. Moreover, elevated CRP levels may be associated with underlying liver disease, which is often found in patients with alcoholic AP [24].

3.5. Conclusions

Our study identified the following parameters as being associated with the severity of AP: non A-non B etiology, presence of diabetes mellitus, VAS pain level, WBC, and CRP. A score was developed using these parameters, intended to help identify patients at risk of developing severe AP. For these patients, a CT scan should be performed (if not already done), and admission to the intensive care unit should be organized, as patients with severe forms will require close monitoring. This score is easy to use, accessible to Emergency Departments or any other department or medical institution, and rapidly applicable. In the future, I am

interested in comparing this score with other widely used scores, such as the APACHE score. I also plan to validate this score in a large group of patients, both within the medical institution where I work and in other hospitals.

Bibliography (selective)

1. Li C, Jiang M, Pan C, Li J, Xu L. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990–2019. BMC Gastroenterology. 2021 Aug 25;21(1).

2. Zheng Z, Ding YX, Qu YX, Cao F, Li F. A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management. Annals of Translational Medicine [Internet]. 2021 Jan 1;9(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7859757/

3. Swaroop VS. Severe Acute Pancreatitis. JAMA. 2004 Jun 16;291(23):2865.

4. Johnson CD, Besselink MG, Carter R. Acute pancreatitis. BMJ [Internet]. 2014 Aug 12;349(aug12 4):g4859–9. Available from: https://www.bmj.com/bmj/section-pdf/762669?path=/bmj/349/7971/Clinical_Review.full.pdf

5. Banks PA, Freeman ML. Practice Guidelines in Acute Pancreatitis. The American Journal of Gastroenterology. 2006 Oct;101(10):2379–400.

6. Cappell MS. Acute Pancreatitis: Etiology, Clinical Presentation, Diagnosis, and Therapy. Medical Clinics of North America [Internet]. 2008 Jul;92(4):889–923. Available from: http://www.ubccriticalcaremedicine.ca/academic/jc_article/Acute%20Pancreatitis%20Review%20Cappel%20Med%20Clin%20North%20Am%202008%20(Jan-08-09).pdf

7. Thakur S, Kaur R, Bhatia L, Bansal R, Singh A, Singh J. Acute Pancreatitis: Clinical Profile of 60 Patients. Cureus. 2023 Dec 28;

8. Şehnaz Evrimler, Münteha Çakmakçı, Adnan Karaibrahimoğlu, Mustafa Kayan. The prognostic value of fat necrosis deposits on CT imaging in acute pancreatitis. TURKISH JOURNAL OF MEDICAL SCIENCES [Internet]. 2020 Dec 22 [cited 2024 Oct 15];51(2):749–56. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203172/

9. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut [Internet]. 2013;62(1):102–11. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23100216

10. Metri A, Bush N, Singh VK. Predicting the severity of acute pancreatitis: Current approaches and future directions. Surgery Open Science [Internet]. 2024 Jun 1;19:109–17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11033200/

11. Florina Cofaru, Nica S, Fierbințeanu-Braticevici C. Assessment of severity of acute pancreatitis over time. Romanian Journal of Internal Medicine. 2020 Jun 1;58(2):47–54.

12. Talukdar R. Classification Systems for the Severity of Acute Pancreatitis. Pancreapedia: The Exocrine Pancreas Knowledge Base [Internet]. 2015 Jun 4 [cited 2019 Aug 10]; Available from: https://pancreapedia.org/node/9006

13. Ong Y, Shelat VG. Ranson score to stratify severity in Acute Pancreatitis remains valid – Old is gold. Expert Review of Gastroenterology & Hepatology. 2021 May 13;15(8):865–77.

14. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. Surgery, Gynecology & Obstetrics

[Internet]. 1974 Jul 1;139(1):69–81. Available from: https://pubmed.ncbi.nlm.nih.gov/4834279/
15. Lee DW, Cho CM. Predicting Severity of Acute Pancreatitis. Medicina [Internet]. 2022 Jun 1;58(6):787. Available from: https://www.mdpi.com/1648-9144/58/6/787/htm
16. Blum T, Maisonneuve P, Lowenfels AB, Lankisch PG. Fatal Outcome in Acute Pancreatitis: Its Occurrence and Early Prediction. Pancreatology [Internet]. 2001 [cited 2022 Sep 12];1(3):237–41. Available from: https://www.karger.com/Article/Abstract/55817
17. Talamini G, Generoso Uomo, Raffaele Pezzilli, Billi P, Bassi C, Cavallini G, et al. Serum creatinine and chest radiographs in the early assessment of acute pancreatitis. The American Journal of Surgery. 1999 Jan 1;177(1):7–14.
18. Lankisch PG, Struckmann K, Assmus C, Lehnick D, Maisonneuve P, Lowenfels AB. Do we need a computed tomography examination in all patients with acute pancreatitis within 72 h after admission to hospital for the detection of pancreatic necrosis? Scandinavian journal of gastroenterology [Internet]. 2001 Apr;36(4):432–6. Available from: https://pubmed.ncbi.nlm.nih.gov/11336171/
19. Jones J, Smith H. APACHE score. Radiopaediaorg [Internet]. 2018 May 12 [cited 2019 Aug 10]; Available from: https://radiopaedia.org/articles/apache-score-2
20. KNAUS WA, ZIMMERMAN JE, WAGNER DP, DRAPER EA, LAWRENCE DE. APACHE—acute physiology and chronic health evaluation: a physiologically based classification system. Critical Care Medicine. 1981 Aug;9(8):591–7.
21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Critical Care Medicine [Internet]. 1985 Oct 1 [cited 2019 Oct 8];13(10):818–29. Available from: https://www.ncbi.nlm.nih.gov/pubmed/3928249
22. Gao W, Yang HX, Ma CE. The Value of BISAP Score for Predicting Mortality and Severity in Acute Pancreatitis: A Systematic Review and Meta-Analysis. Sastre J, editor. PLOS ONE. 2015 Jun 19;10(6):e0130412.
23. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI Scores in Predicting Organ Failure, Complications, and Mortality in Acute Pancreatitis. American Journal of Gastroenterology. 2010 Feb;105(2):435–41.
24. Liță (Cofaru) FA, Eremia IA, Nica S, Brîndușe LA, Zărnescu NO, Moldoveanu AC, et al. Predictive Value of Several Parameters for Severity of Acute Pancreatitis in a Cohort of 172 Patients. Diagnostics [Internet]. 2025 Feb 11 [cited 2025 Apr 9];15(4):435. Available from: https://www.mdpi.com/2075-4418/15/4/435
25. Wang L, Zeng YB, Chen JY, Luo Q, Wang R, Zhang R, et al. A simple new scoring system for predicting the mortality of severe acute pancreatitis. Medicine. 2020 Jun 5;99(23):e20646.
26. Luo X, Wang J, Wu Q, Peng P, Liao G, Liang C, et al. A modified Ranson score to predict disease severity, organ failure, pancreatic necrosis, and pancreatic infection in patients with acute pancreatitis. Frontiers in medicine [Internet]. 2023 Jun 2 [cited 2023 Jul 17];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10273837/

27. Arif A, Jaleel F, Rashid K. Accuracy of BISAP score in prediction of severe acute pancreatitis. Pakistan Journal of Medical Sciences. 2019 Jun 29;35(4).
28. Zhu J, Wu L, Wang Y, Fang M, Liu Q, Zhang X. Predictive value of the Ranson and BISAP scoring systems for the severity and prognosis of acute pancreatitis: A systematic review and meta-analysis. PloS One [Internet]. 2024;19(4):e0302046. Available from: https://pubmed.ncbi.nlm.nih.gov/38687745/

LIST OF SCIENTIFIC PAPERS

A. List of Scientific Papers Developed in Connection with the Doctoral Thesis:

1. **Cofaru FA**, Nica S, Fierbințeanu-Braticevici C. ***Assessment of severity of acute pancreatitis over time***. Rom J Intern Med. 2020 Jun 1;58(2):47-54. doi: 10.2478/rjim-2020-0003. PMID: 32097123. (Chapter 2, page 47-53, 59, 60)
https://sciendo.com/article/10.2478/rjim-2020-0003

2. **Liță Cofaru FA**, Eremia IA, Nica S, Brîndușe LA, Zărnescu NO, Moldoveanu AC, Goran LG, Fierbințeanu-Braticevici C. ***Predictive Value of Several Parameters for Severity of Acute Pancreatitis in a Cohort of 172 Patients***. Diagnostics (Basel). 2025 Feb 11;15(4):435. doi: 10.3390/diagnostics15040435. PMID: 40002586; PMCID: PMC11854639. (Chapter 3, page 65, 75, 78, 134-152, 157, 160, 161)
https://www.mdpi.com/2075-4418/15/4/435

B. List of Scientific Papers Published During the Doctoral Studies:

1. Goran LG, **Liţă (Cofaru) FA**, Fierbinţeanu-Braticevici C. ***Acute-on-Chronic Liver Failure: Steps Towards Consensus***. Diagnostics (Basel). 2025 Mar 17;15(6):751. doi: 10.3390/diagnostics15060751. PMID: 40150093; PMCID: PMC11941433.
https://www.mdpi.com/2075-4418/15/6/751

2. Eremia IA, Anghel CA, ***Cofaru FA***, Nica S. ***Early Presentation of Boerhaave Syndrome in the Emergency Department: A Case Report and Review of the Literature***. Diagnostics (Basel). 2024 Jul 24;14(15):1592. doi: 10.3390/diagnostics14151592. PMID: 39125468; PMCID: PMC11311301.
https://www.mdpi.com/2075-4418/14/15/1592

3. Nica S, Albu A, Nica R, Ciornei C, **Cofaru F**, Eremia I, Cimponeriu D. ***Addressability to the Emergency Department of patients with acute post-COVID 19 clinical symptoms***. Romanian Journal of Military Medicine. 2022 Feb 28; CXXV(2):275-280. doi: 10.55453/rjmm.2022.125.2.15.

http://www.revistamedicinamilitara.ro/wp-content/uploads/2022/05/Addressability-to-the-Emergency-Department-of-patients-with-acute-post-COVID-19-clinical-symptoms.pdf

4. **Cofaru F**, Nica S, Iancu A, Eremia IA. ***The safety of the savior – an important goal in 21st century Europe***. Romanian Journal of Medical Practice. 2020;15(4):382-385. doi: 10.37897/RJMP.2020.4.3.
https://rjmp.com.ro/articles/2020.4/RJMP_2020_4_Art-03.pdf

5. Eremia IA, Nica S, **Cofaru F**, Iancu A. ***Diagnosis in the Emergency Deprtment – a continuous challenge (case report)***. Romanian Journal of Medical Practice. 2020;15(3):340-343. doi: 10.37897/RJMP.2020.3.14.
https://rjmp.com.ro/articles/2020.3/RJMP_2020_3_Art-14.pdf