ORIGINAL RESEARCH

Predictors, severity and associate factors of acute pancreatitis: A tertiary hospital's experience

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Abstract

Aim: Acute pancreatitis is a common disorder that occurs following an acute response to a pancreatic injury. The aim of this study was to assess predictors of severity and associated factors, as well as the association of different classification systems of severity among patients with acute pancreatitis (AP).

Methods: A retrospective case series study was conducted in Albania including 150 patients with AP between March 2021 and March 2022. Variables such as baseline characteristics, laboratory findings, and calculated scores of known severity classifications were analyzed. Patients were graded as having mild, moderate, or severe acute pancreatitis based on the Revision of the Atlanta Classification (RAC). Ordinal logistic regression was used to model the relationship between the ordinal variable (RAC categories) and the explanatory variables mentioned above.

Results: Women with AP had a higher average age than men with AP (62.5 vs. 57.5 years old, respectively, $p<0.05$). Additionally, the alcoholic etiology in males prevailed in 100% of cases, while the biliary etiology was more common in females (64.2% compared to 35.8% in males, $p<0.001$). Ordinal logistic regression showed that a one unit increase in the CT Severity Index (CTSI) and Bedside Index for Severity in Acute Pancreatitis resulted in a 0.968 and 0.430 times increase, respectively, in the ordered log-odds of being in a higher RAC classification category. The presence of Systemic Inflammatory Response Syndrome (SIRS) (vs. non-present) resulted in a 2.98 higher ordered logit. Conversely, a one unit increase in saturation level decreased the ordered log-odds by approximately 0.4 times.

Conclusion: The severity of acute pancreatitis is a medical event that requires accurate prediction, for which many classification systems have been compiled, with the RAC being the most recent consensus. CTSI, the presence of SIRS, and saturation levels are significantly associated with RAC, without excluding the discussion on the predictive value of laboratory findings, such as glycemia, azotemia, and creatinine.

Keywords: acute pancreatitis, etiology, predictors, severity.

Introduction

Acute pancreatitis is a common disorder that occurs following an acute response to a pancreatic injury [1]. Despite the controversial pathogenic theories investigated over the years, in most cases of acute pancreatitis, obstruction of the ducts by migrating gallstones and alcohol abuse are identified as major causes [2]. Other known causes of acute pancreatitis include infectious causes (viral, bacterial, parasitic), congenital pancreatic divisum, intraduct papillary mucinous tumor, endoscopic retrograde cholangiopancreatography, hypercalcemia and other combined or idiopathic causes [2, 3]. In the meantime, there are assumptions about a causal relationship between COVID-19 and acute pancreatitis, but the cause has yet to be proven, whether it is COVID-19 or idiopathic disease [4]. The activation of trypsinogen to trypsin, the formation of reactive oxygen species (ROS), and the release of proinflammatory cytokines are key factors that contribute to pancreatic inflammation [2]. Among the three diagnostic elements of this disease, are the typical clinical symptoms, increased laboratory values of pancreatic enzymes, and imagery (useful for differential diagnostics, but not always required) [5]. However, recent studies have suggested the use of point-of-care ultrasound (POCUS) as a reliable and cost-effective tool for the diagnosis and monitoring of acute pancreatitis [6]. The follow-up of this disease is important in terms of prognosis and severity. The diagnosis of acute presentation might be simple, but the main challenge is strictly forecasting the progression of the disease and its outcome [7]. Multiple AP severity classifications have placed clinicians and researchers in positions and having consistently evolved to better characterize clinical scores and other diagnostic elements, gave rise to two valid classifications, such as the Revision of the Atlanta Classification (RAC) and Determinant Based Classification [8]. According to RAC, the severity of AP of is classified as mild, moderately severe, and severe acute pancreatitis [9]. As mentioned above, there are several multi-factorial rating systems such as Ranson, the Bedside Index for Severity in Acute Pancreatitis (BISAP), the Acute Physiology and Chronic Health Evaluation (APACHE II) and modified CT Severity Index (CTSI), which

attempt to predict the severity of AP [10]. In terms of laboratory results, by aetiology, amylase and lipase pancreatic enzymes remain the diagnosis's cornerstone, although their sensitivity and specificity vary and there may be room for further lab findings that diagnose acute pancreatitis [11]. The treatment of acute pancreatitis typically involves supportive care and management of complications such as fluid and electrolyte imbalances, pancreatic necrosis, and infected pancreatic necrosis. In severe cases, surgical intervention may be required to remove necrotic tissue and prevent the development of pancreatic abscesses or systemic infection [12]. According to a systematic review that included 10 cohort studies on AP, global estimates of incidence's AP was 33·74 cases (95% CI 23·33–48·81) per 100 000 per-son-years [13]. While acute pancreatic mortality rates vary widely, in the United States the mortality rate is approximately 5% [14]. Intuitively and evidently, case fatality for patients of high severity is reported to be higher than total mortality due to AP [15]. We aim to study predictors, severity and associate factors of AP, as well as the association between different classification systems of severity among patients with AP.

Methods

A retrospective case series study was conducted during March 2021-March 2022. The sample size of this study was one hundred and fifty patients. The sampling technique included consecutive patients who presented at the University Hospital: "Mother Teresa", Tirane with suspected AP have been diagnosed and treated in Gastrohepatology Service during the period of the study. The criteria for the inclusion of participants in the study were: 1. Patients admitted in emergency or recommended by regional hospitals 2. Patients diagnosed with AP 3. Patients who have provided consent for the use of their data for the study. We obtained the data by reviewing all the medical records of the patients who met the inclusion criteria in the study. To ensure the accuracy and completeness of our data, two independent reviewers extracted the relevant information from the medical records of each patient. This methodology ensures that the study sample is representative of patients with acute pancreatitis who seek medical

care at the hospital, and that the data collected is accurate and reliable.

The information collected from the medical records was processed by statistical programs such as Microsoft-Excel and Statistical Package for Social Sciences (SPSS) version 25.0.

The statistical tests and techniques applied in the data analysis of this study are described in detail below:

At first, scores were calculated for all AP severity classification systems. The APACHE score is calculated based on the patient's physiological parameters at admission, including temperature, blood pressure, heart rate, respiratory rate, oxygenation, pH, serum potassium level, serum creatinine level, hematocrit level, and Glasgow Coma Scale (GCS) score, ranging from 0 to 71 [16]. The Ranson's criteria have been modified over time and includes the following parameters [17]:

Clinical parameters:

•Age greater than 55 years

•White blood cell count greater than 16,000/mm3

•Blood glucose greater than 200 mg/dL

•Serum LDH greater than the upper limit of normal

•AST greater than the upper limit of normal

Laboratory parameters:

•Serum calcium less than 8 mg/dL

•Hematocrit decrease of more than 10% from admission to 48 hours

•Arterial oxygen tension (PaO2) less than 60 mm Hg

•BUN increase greater than 5 mg/dL within 48 hours

•Serum albumin less than 3.2 g/dL

A score of 0-2 indicates a mild pancreatitis, whereas a score of 3 or higher indicates severe pancreatitis. While the parameters included in the BISAP score are [18]:

•Blood Urea Nitrogen (BUN) level greater than 25 mg/dL

•Impaired mental status (Glasgow Coma Scale score < 15)

•Systolic Blood Pressure (SBP) less than 90 mm Hg

•Age greater than 60 years

•Pleural effusion present on imaging

The total score ranges from 0 to 5.

The CTSI is based on two major categories of findings seen on a CT scan: pancreatic and extrapancreatic complications [19]. The pancreatic complications include gland necrosis, peri-pancreatic fluid collections, and pseudocysts. The extrapancreatic complications include peripancreatic fat necrosis, bowel wall thickening, and pleural effusion. The CTSI score ranges from 0 to 10, with higher scores indicating more severe pancreatitis.

The Atlanta 2012 revision is the most commonly used and includes three categories of acute pancreatitis [20]:

• Mild acute pancreatitis - No organ failure, and local or systemic complications are absent or transient.

• Moderate acute pancreatitis - Transient organ failure (<48 hours) or local or systemic complications without persistent organ failure.

•Severe acute pancreatitis - Persistent organ failure (>48 hours).

Organ failure is defined as the presence of any of the following: hypotension requiring vasopressors, acute lung injury or acute respiratory distress syndrome, renal failure requiring dialysis, or circulatory failure requiring mechanical ventilation. All these scores were treated in data analysis as numerical variables. In addition to the severity assessments, demographic data, comorbidities, clinical symptoms, laboratory results, and imaging findings were also collected and analyzed. All examinations and laboratory findings were obtained on the first day of patient admission and were also treated as numerical variables. The measurement of variables were as below: age: continuous variable measured in years, reported as mean (+ standard deviation), gender: categorical variable with two levels (male and female), reported as counts and percentages, accompanying conditions: categorical variable with three levels (non-present, another condition, 2 or more conditions), reported as counts and percentages, etiology: categorical variable with six levels (migrating gallstones, alcohol abuse, hypertriglyceridemia, idiopathic, infectious, combined), reported as counts and percentages, SIRS's presence: categorical variable with two levels (yes and no), reported as counts and percentages. Heart rate, saturation, azotemia, glucose level and creatinine were measured as numerical.

All participants in the study were informed about the purpose and objectives of the study.

Frequencies (absolute numbers) and corresponding percentages were calculated for all categorical variables. For all numerical variables, the relevant central trend and dispersion values were calculated. The Chi square test and Fisher's exact test were used to evaluate the differences between the obtained categorical variables, while the Mann Whitney U test was used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed.

Crude (unadjusted) ordinal logistic regression was used to assess the association (association) between independent variables (heart rate, saturation, glycemia, azotemia, creatinine and SIRS) and the dependent variable (RAC severity categories), and then multivariable adjusted ordinal logistic regression was applied for these variables. Multivariable adjusted ordinal logistic regression was used also to assess the association between independent variables (Ranson, BISAP, APACHE II, CTSI) and the dependent variable (RAC severity categories). Generalized Linear Model with Gamma log link was used to evaluate association of different severity' s classification categories (Ranson, BISAP, APACHE II, CTSI, RAC) with hospital stay. This model was chosen in addition of assumptions' compliance: "The dependent variable (hospital stay) always takes positive values (2-34, in our study) and its distribution was positively skewed".

In all cases, $P \leq 0.05$ values were considered statistically significant.

Results

The baseline characteristics are given in table 1. The mean age (± standard deviation) of 150 participants was 60.1±15.7. 51.3% of patients with AP were women and 48.7% were men. Women with AP have a higher average age than men with AP 62.5 vs 57.5 years old, respectively, $p<0.05$. In addition, the alcoholic etiology in males prevails in 100% of cases, while the biliary etiology is more common in females, 64.2% compared to 35.8% in males, and to a lesser extent, other etiologies, $p<0.001$. In the majority of cases (46%), the patients did not refer to having accompanying conditions, 36% of

them referred to having another condition and 18% of them referred to having at least two other conditions. 18.7% of patients were diagnosed with SIRS.

Table 1. Baseline characteristics of patients with AP

Baseline characteristics	N (%)*	Gender		P
		Males	Females	
Age	60.1 (±15.7)	57.5 (±15.2)	62.5 (±15.8)	0.035
Gender Males Females	 73 (48.7) 77 (51.3)	N/A†	N/A	N/A
Accompanying conditions Non-present Another condition 2 or more conditions	69 (46.0) 54 (36.0) 27 (18.0)	36 (52.2) 26 (48.1) 11 (40.7)	33 (47.8) 38 (51.9) 16 (59.3)	0.585
Etiology Migrating gallstones Alcohol abuse Hypertriglyceridemia Idiopathic Infectious Combined	 95 (63.3) 25 (16.7) 5 (3.3) 18 (12.0) 3 (2.0) 4 (2.7)	 34 (35.8) 25 (100.0) 2 (40.0) 8 (44.4) 1 (33.3) 3 (75.0)	 61 (64.2) 0 (0.0) 3 (60.0) 10 (55.6) 2 (66.7) 1 (25.0)	 <0.001
SIRS's presence Yes No	 28 (18.7) 122 (81.3)	 59 (48.4) 14 (50.0)	 63 (51.6) 14 (50.0)	 1.0

* Absolute numbers and their respective percentages.

† Non applied.

The results of crude (unadjusted) ordinal logistic regression are given in Table 2. A one unit increase in heart rate, azotemia, glycemia, creatinine would result in a 0.043, 0.020 and 0.05, 1.18 times increase in the ordered log-odds of being in a higher RAC classification category. Also the ordered logit for the presence of Systemic inflammatory response syndrome (SIRS) (vs. non present) was 3.32 higher. Conversely, one unit increase in saturation level, decrease the ordered log-odds by 0.486 times.

Table 2. Association between RAC classification categories and clinical examinations and laboratory findings; results from unadjusted ordinal logistic regression models

Parameter	Estimate	Std. Error	Wald	df	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Heart rate	.043	.012	13.711	1	.000	.020	.066
Saturation	-.486	.113	18.465	1	.000	-.708	-.264
Azotemia	.020	.008	6.960	1	.008	.005	.035
Glycemia	.005	.002	6.800	1	.009	.001	.009
Creatinine	1.184	.396	8.955	1	.003	.409	1.960
[SIRS=yes]	3.220	.594	29.362	1	.000	2.1	4.4
[reference]	0[a]	.	.	0	.	.	.

The results of multivariate adjusted ordinal logistic regression are given in Table 3. A one unit increase in saturation level would result in 3.96 times decrease in the ordered log-odds of being in a higher RAC classification category. The ordered logit for the presence of Systemic inflammatory response syndrome (SIRS) (vs. non present) was 2.98 higher.

Table 3. Association between RAC classification categories and clinical examinations and laboratory findings; results from multivariable-adjusted ordinal logistic regression

		Estimate	Std. Error	Wald	df	P	95% CI	
							Lower	Upper
Threshold	[Atlanta classification = 1]	-37.702	11.312	11.108	1	.001	-59.873	-15.531
	[Atlanta classification = 2]	-33.626	11.177	9.051	1	.003	-55.532	-11.719
Location	Heart rate	.002	.015	.012	1	.914	-.027	.030
	Saturation	-.396	.113	12.270	1	.000*	-.618	-.175
	Azotemia	-.013	.013	.989	1	.320	-.039	.013
	Glycemia	.000	.002	.008	1	.930	-.004	.005
	Creatinine	.524	.489	1.151	1	.283	-.434	1.482
	[SIRS=yes]	2.983	.697	18.343	1	.000*	1.618	4.348
	[reference]	0[a]	.	.	0	.	.	.

*Significance at $p<0.05$.

The results of ordinal logistic regression are given in Table 4. A one unit increase in CTSI and BISAP would result in 0.968 and 0.430 times increase in the ordered log-odds of being in a higher RAC classification category.

Table 4. Ordinal logistic regression, with the dependent variable (RAC classification categories) and independent variable (other severity classification categories of AP)

		Estimate	Std. Error	Wald	df	P	95% CI	
							Lower	Upper
Threshold	[Atlanta classification = 1]	3.729	.547	46.555	1	.000	2.658	4.801
	[Atlanta classification = 2]	8.784	1.203	53.335	1	.000	6.426	11.141
Location	APACHEII	.081	.059	1.885	1	.170	-.035	.197
	Ranson	.213	.162	1.719	1	.190	-.105	.530
	BISAP	.430	.237	3.288	1	.070	-.035	.894
	CTSI	.968	.184	27.533	1	.000	.606	1.329
*Significance at p≤0.05								

The results of Generalized Linear Model with Gamma log link are given in Table 5. A one unit increase in Ranson and Atlanta would result in 0.069 and 0.227 unit increase in hospital stay.

Table 5. Generalized Linear Model with Gamma log link, with the dependent variable (hospital stay) and independent variable (severity classification categories of AP)

Parameter	B	Std. Error	95% Wald CI		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	P
(Intercept)	1.836	.0853	1.669	2.003	463.308	1	.000
APACHEII	-.015	.0097	-.034	.004	2.411	1	.120
Ranson	.069	.0280	.014	.124	6.039	1	.014*
BISAP	.003	.0387	-.073	.078	.004	1	.947
Atlanta classification	.227	.0717	.087	.368	10.070	1	.002*
CTSI	.023	.0264	-.029	.074	.732	1	.392
(Scale)	.150[a]	.0169	.121	.187			
Dependent Variable: Hospital stay Model: (Intercept), APACHEII, Ranson, BISAP, Atlanta classification, CTSI							
a. Maximum likelihood estimate.							

Discussion

The total incidence of acute pancreatitis has increased by 3.07% per year, constituting an important issue for the health care system [21]. Comparing the overall mortality rate of acute pancreatitis (4-5%) with the mortality rate of severity acute pancreatitis (16%), the evidence shows that the timely prediction of severity with all the necessary diagnostic tools can significantly reduce the attributable risk of this pathology [14, 15]. Consistent to the literature, our study shows a mortality rate of 4.7% for AP, but with a high mortality rate of 63.6% for the high risk severity category. In this framework, in accordance with the purpose of our study, we researched the associated predictive factors of severity, believing that the calculation of the values of diagnostic indicators can prevent high severity cases and thus reduce the mortality rate.

The baseline characteristics of the individuals in the study showed that women with AP have a higher average age than men with AP. These differences can be explained in terms of etiological justification, since it is known that cholelithiasis has been determined as the main cause of AP among the older patients, with a higher frequency in women [22]. In the same vein, alcoholic etiology is most common in middle-aged males [23]. The results of our study showed that, the alcoholic etiology in males prevails in 100% of cases, while the biliary etiology is more common in females, 64.2% compared to 35.8%, $p<0.001$. There were no significant differences regarding the presence of concomitant diseases or SIRS, between men and women with AP. The severity of acute pancreatitis is already known to be higher in patients with SIRS than in patients without SIRS [24]. Our analysis of the data showed that the presence of SIRS increases the likelihood of the patient falling into the most severe severity categories by about three times. The role of SIRS in predicting the severity of AP has also been evaluated using scoring systems, such as the BISAP and the Systemic Inflammatory Response Syndrome Criteria (SIRS-C). A study by Wu et al. (2019) found that the SIRS-C score had a higher accuracy in predicting the severity of AP compared to the BISAP score [25]. Acute pancreatitis may cause chemical changes that affect pulmonary function, causing the oxygen level in your blood to drop to dangerously low levels [26]. After applying

the multivariate adjusted ordinal logistic regression model, high levels of oxygen (saturation) were associated with a lower coefficient (-.486) of moving to the most severe severity categories. Hypoxemia has been shown to be associated with increased severity of AP, as measured by APACHE II score and the Revised Atlanta Classification (RAC) criteria [27]. Regarding other indicators and laboratory findings such as heat rate, azotemia, creatinine serume levels and glycemia, though they were not significant after the adjusted multivariable model, their crude (unadjusted) value's increase was associated with a higher likelihood of the patient exceeding the more serious severity categories. In fact, elevated serum creatinin (on or 48 hours after admission) is a known unfavorable prognostic parameter in acute pancreatitis [28]. Even glycemia, azotemia and heart rate can be used as indicators for evaluating the severity of AP [29-31]. Our results showed that a unit increase in the levels of glucose and nitrogen in serum, as well as heart rate, would result in 0.05, 0.20 and 0.43 times increase in the ordered log-odds of being in a higher RAC classification category. In fact, several studies have shown that patients with hyperglycemia on admission had a higher risk of developing systemic complications, including acute respiratory distress syndrome, renal failure, and sepsis and had a higher incidence of pancreatic necrosis, infected pancreatic necrosis, and multi-organ failure [32]. Azotemia, defined as an elevation in serum creatinine and blood urea nitrogen (BUN) levels, is a common complication of acute pancreatitis and it has been shown to be associated with worse outcomes, correlated with the severity of acute pancreatitis, as determined by (APACHE II) score, including higher mortality rates and longer hospital stays [33].

The Atlanta classification remains the most widely used severity classification system. However, it has several limitations, including the inability to accurately predict disease severity at admission and the inability to identify patients who are at risk of developing complications. To overcome these limitations, several other classification systems have been proposed [20]. Ranson's criteria, which were introduced in 1974, have been used to predict AP severity, although they have several limitations, including poor sensitivity and specificity,

the BISAP score, which includes five easily obtainable variables, has been found to be useful in predicting AP severity and The APACHE-II score, which is a more comprehensive scoring system, has been found to be useful in predicting AP severity and mortality [34].

Regarding the results of our study of AP severity classification systems, we found the increase in the CTSI score and to a lesser extent BISAP was accompanied by an increase in the probability of moving into the highly severe category in the RAC. The results were not significant for other classification systems such as: APACHEII and Ranson. In fact, another study estimates that BISAP is the best predictor of severity (in terms of organ failure) [34]. The available evidence suggests that the CTSI is a useful tool for predicting the severity of AP and complements the RAC [35]. While the RAC is widely used and has a long history of research, the CTSI provides an objective and reproducible way to assess the severity of AP based on CT imaging findings.

All classification systems have shown in various studies a satisfactory Area Under Curve, in terms of predictive accuracy [34]. However, in addition to accuracy results, combination of different regression models can help more with updating current classification systems, even taking into account new diagnostic elements. Another study found a moderate correlation between the Ranson criteria and the APACHE II score ($r = 0.58$) in predicting mortality in patients with acute pancreatitis [36]. In general, different scoring systems may have different strengths and limitations, and their correlations may vary depending on the patient population and the specific outcomes being assessed. Therefore, it is important to use a combination of different severity scores and clinical judgment to accurately assess and manage patients with acute pancreatitis.

Most patients with AP can leave the hospital after 5-10 days (usually 1 week required to recover), however, recovery takes longer in serious cases, as complications that require extra treatment may occur [37]. In this line of thought, our study predicted that the increase in RAC and Ranson is significantly associated with hospital stay's extension. Studies show that Ranson is also comparable to the RAC in predicting mortality from AP [38].

We believe that RAC Atalanta is a good classification for the severity of AP. We also believe that computed tomography and glycemia can play an important role in predicting and classifying severity of AP. However, it is worth discussing the fact that although Ranson did not produce a significant positive association with RAC, on the contrary, it produced significant positive association with hospital stay. Based on an exclusionary logic, on predictors of severity, glucose can actually be the predictor (determinant found only in Ranson) that influences the severity of RAC and possibly hospital stay. The length of hospital stay is significantly higher in patients classified as severely acute pancreatitis, compared to patients in the category of mild and moderate acute pancreatitis likely due to increased tissue damage from inflammatory mediators [39].

In fact, another study supports the idea that serum glucose at (190 mg/dL) or higher was the single best predictor of severe pancreatitis in non-diabetic patients [40]. With regard to the pathophysiological mechanisms, the importance of acid cell death in the form of apoptosis and necrosis as a determinant of the severity of pancreatitis is underlined [41]. This can be a valid biological justification for the glucose increase, considering that the acinar-derived cells secreted insulin and it was precisely their apoptosis that affects the severity of AP [42]. The findings of this study could contribute to a better understanding of the epidemiology, pathogenesis, and management of acute pancreatitis, and guide clinicians in making more accurate and timely diagnoses and treatment decisions for patients with this condition.

Although this study provides valuable insights, there are a few limitations that should be acknowledged. One such limitation is the relatively low number of patients for some categories of variables, which may have impacted the statistical power of the analysis. Additionally, the retrospective design of the study may have introduced biases and limited the scope of the findings. Finally, the potential selection bias of the case series should also be considered when interpreting the results, as this may have affected the representativeness of the sample.

Conclusion

The severity of acute pancreatitis is a medical event that requires accurate prediction, for which numerous classification systems have been developed, with the RAC being a recent consensus. CTSI, the presence of SIRS, and saturation levels are all significantly associated with RAC, but the predictive value of laboratory findings, such as glycemia, azotemia, and creatinine, should also be considered.

Of these severity classifications, RAC and Ranson are considered the most reliable predictors of hospital stay. However, it is worth noting that the discussion surrounding the predictive value of laboratory findings, such as glycemia, should not be overlooked. By accurately predicting the severity of acute pancreatitis and length of hospital stay, clinicians can make informed decisions and provide timely interventions for their patients.

Statement of Ethics

This study was approved by the Ethics Committee of the University Hospital "Mother Theresa". Confidentiality and privacy of participation were assured. All the participants gave their consent for anonymous use of their data for research purposes. Finally, the study was conducted in accordance with the Helsinki Declaration protocol, which outlines the ethical principles for medical research involving human subjects, further ensuring the ethical integrity of the study.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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