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Original Research

Prediction of Prognosis Acute Pancreatitis with Inflammatory Markers and Patient Characteristics Compared to the Scoring System: Real-Life Data

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Abstract

Objectives: Acute pancreatitis (AP) is an inflammatory disease with a high morbidity and mortality rate. It is one of the most common causes of hospitalization among gastrointestinal system diseases. Inflammatory and other factors that predict the severity of AP are very important for patient management. This study will analyze the factors associated with the severity of AP.

Methods: The sample consisted of 514 patients. Demographic characteristics, comorbid diseases, causes of AP, body mass index (BMI), tobacco use, blood at admission, amylase, lipase, leukocyte, neutrophil, lymphocyte, C-reactive protein (CRP), mean platelet volume, red cell distribution width, albumin, calcium, and CRP values at 48th h were recorded. The bedside index of severity in AP (BISAP), Ranson score, neutrophil-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) values was calculated and recorded. The relationship between these parameters and the severity of AP was analyzed according to the Atlanta classification.

Results: Participants had a mean age of 55±17.8 years. More than half the participants were women (n=272, 52.9%). Biliary causes were the most common etiological causes (n=299, 58.2%). Most participants had mild pancreatitis (n=416, 80.9%). The severity of AP was associated with tobacco use, high BMI, thrombocytosis, high NLR, high PLR, high 48th h CRP, hypoalbuminemia, hypocalcemia, aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT ratio), and high Ranson and BISAP scores.

Conclusion: Biochemical markers that give rapid results in the early period can provide information about the severity of AP. We may develop new scores by combining these parameters.

Keywords: Acute pancreatitis, de ritis ratio, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognostic markers

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Acute pancreatitis (AP) is an inflammatory disease of the pancreas with multifactorial pathogenesis that causes systemic and peripancreatic tissue inflammation. Enzyme activation plays a central role in local pancreatic injury.[1] AP mostly follows a mild course, resulting in rapid clinical improvement with fluid resuscitation and the symptomatic treatment of pain and nausea. Population-based studies have shown the proportion of severe pancreatitis between 8% and 20%.[2] Despite treatment, AP can lead to complications, morbidity, and mortality. Predicting the prognosis related to disease severity in the earliest period is important in terms of providing intensive care support and other specific treatments for the patient.

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Researchers have developed scoring systems, such as Ranson score,[3] Assessment of Acute Physiology and Chronic Health (APACHE-2),[4] and Bedside Index for Severity in AP (BISAP).[5] However, the Atlanta classification revised in 2012 is the most common classification system used to assess he severity of AP.[6] Researchers also focus on the relationship between new markers of inflammation (hemogram and biochemical tests, neutrophil/lymphocyte ratio [NLR], and platelet/lymphocyte ratio [PLR]) and severity of pancreatitis.[7-9] Obesity and tobacco use are associated with the severity of AP.[10,11] The most common causes of AP are gallstones, alcohol use, and idiopathic factors. However, its causes vary from region to region.[12] Identifying etiologic causes by geography and determining practical prognostic markers can be invaluable in patient management. This study will look into the associated with the severity of AP (according to the Atlanta classification) and demographic characteristics, etiological causes, tobacco use, body mass index (BMI), leukocytes, NLR, PLR, mean platelet volume (MPV), red cell distribution width (RDW), albumin, calcium values, BISAP, and Ranson scores. Another objective of this study is to determine, in which scores or parameters are most effective in predicting the severity of AP.

Methods

Seven hundred and ninety-six AP patients were admitted to the Health Sciences University Umraniye Training and Research Hospital Gastroenterology Clinic between January 01, 2015, and January 01, 2020. The sample consisted of 514 patients. Figure 1 shows the inclusion criteria. A patient was diagnosed with AP if he/she had two of the three parameters: 1 – amylase or lipase values more than 3 times the upper limit of normal, 2 – typical abdominal pain, and 3 – typical radiological findings (According to Atlanta criteria).[6] Demographic characteristics, comorbid diseases, causes of AP, BMI, tobacco use, blood at admission, amylase, lipase, leukocyte, neutrophil, lymphocyte, hemoglobin, platelet, C-reactive protein (CRP), MPV, RDW, albumin, calcium, AST, ALT, and CRP values at 48th h were recorded. Ranson score, BISAP score, Atlanta score, AST/ALT ratio, and NLR and PLR values were calculated and recorded. In addition, the parameters evaluated in Ranson score, BISAP score, and Atlanta score are shown in Tables 1 and 2.[3,5,6]

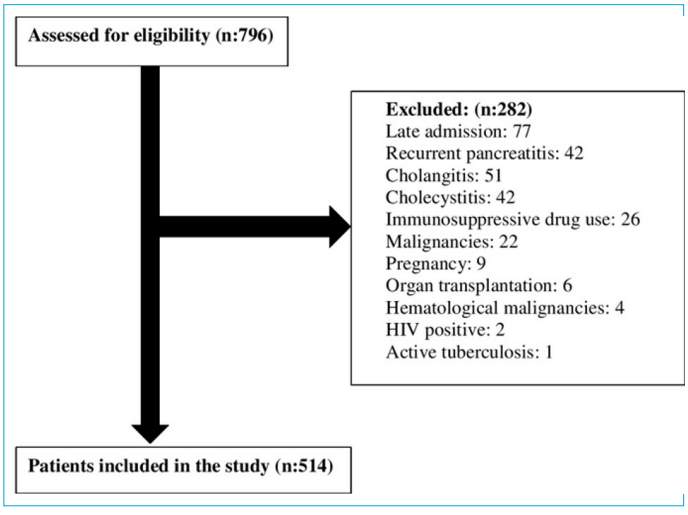

Figure 1. Inclusion and Exclusion Criteria.

Late admission: The patient's admission to the hospital one day after the onset of pain, or referral from another centre; Recurrent pancreatitis: Repeated hospitalizations due to acute pancreatitis.

Table 1. Ranson's criteria and BISAP score

Ranson's criteria (1 point each)	BISAP score (1 point each)
On admission	BUN >25
WBC >16.000/µL	Impaired mental status
Age >55 years	SIRS
Glucose >200 mg/dL	Age >60 years
AST >250 IU/L	Pleural effusions
LDH >350 IU/L	
Within 48 h of admission	
HCT decrease >10%	
BUN increase >5	
Serum calcium <8 mg/dL	
Arterial pO_2 <60 mmHg	
Base deficit >4 mEq/L	
Fluid needs >6 L	

WBC: White blood cells; AST: Aspart aminotransferase; LDH: Lactate dehydrogenase; HCT: Hematocrit; BUN: Blood urea nitrogen; SIRS: Systemic inflammatory response syndrome.

Table 2. Revised atlanta classification

A. Mild acute pancreatitis
   I. No organ failure
   II. No local or systemic complications
B. Moderately severe acute pancreatitis
   I. Organ failure that resolves within 48 h (transient organ failure and/or
   II. Local or systemic complications without persistent organ failure
C. Severe acute pancreatitis: Persistent organ failure (>48 h)
   I. Single organ failure
   II. Multiple organ failure

Local complication: acute fluid collections; pancreatic necrosis; aacute pseudocyst; and pancreatic abscess.

Organ failure and systemic complications: shock: SBP <90 mmHg; pulmonary insufficiency: PaO_2 ≤60 mmHg; penal failure: creatinine ≥170 µmol/L (≥2 mg/dL) after rehydration; gastrointestinal bleeding: 500 mL in 24 h; disseminated intravascular coagulation: platelets ≤100, 000/mm^3, fibrinogen <1.0 g/L and fibrin-split products >80 µg/L; and severe metabolic disturbances: calcium ≤1.87 mmol/L or ≤7.5 mg/dL.

All patients were hospitalized and followed up. All patients, except those with hypercalcemia etiology, were administered (IV) 5–10 mL/kg/h ringer lactate solution. Patients hospitalized for hypercalcemia were administered (IV) 5–10 mL/kg/h isotonic sodium chloride. Vital signs were monitored. Daily laboratory analysis was performed. Cross-sectional imaging was performed to detect local complications in patients whose abdominal pain did not regress and/or serum amylase lipase values did not regress 3 times below the reference limit at the 72nd h of treatment. Participants were classified as mild pancreatitis (MSAP), moderate pancreatitis (MAP), and SAP according to the 2012 revision of the Atlanta classification.[6] The general characteristics, inflammatory and laboratory indicators, and prognostic scores of the patients were compared according to the severity of AP.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Umraniye Training and ResearchHospital (Date: March 18, 2020 and No: B.10.1.TKH.4.34.H.GP.0.01/70).

Statistical Analysis

All statistical procedures were performed using SPSS software (version 25.0, SPSS Inc., Chicago, IL, institutionally registered software). The distribution of the data was found to be normal with the Kolmogorov–Smirnov test. While evaluating the study data, the descriptive statistical methods mean, sstandard deviation, frequency, and percentage were used. One-way ANOVA test was used to compare more than two groups for parametric data. Chi-square test was used when investigating the difference between groups for categorical data. Significance was evaluated at $p<0.05$ for all values.

Table 3. General characteristics and etiological causes

Parameters	n STD (%)
Age (years)	55±17.80
Gender	
Female	272 (52.9)
Male	242 (47.1)
Comorbidities	
Hypertension	141 (27.4)
Diabetes	68 (13.2)
Coronary artery disease	40 (7.8)
Congestive heart failure	17 (3.3)
Chronic renal failure	9 (1.8)
Chronic obstructive pulmonary disease	12 (2.3)
Asthma	19 (3.7)
Cerebrovascular diseases	9 (1.8)
Other diseases	84 (16.3)
Pancreatitis etiology	
Biliary	299 (58.2)
Alcohol	44 (8.6)
Idiopathic	98 (19.1)
Drug	29 (5.6)
Post-ERCP	20 (3.9)
Hypertriglyceridemia	19 (3.7)
Hypercalcemia	2 (0.4)
Autoimmune	2 (0.4)
Trauma	1 (0.2)
BMI	24.1±3.1
Hospitalization (day)	5.56±4.52

ERCP: Endoscopic retrograde cholangiopancreatography; BMI: Body mass index; Other diseases: Rheumatoid arthritis, Alzheimer, Dyslipidemia, Ankylosing spondylitis, Parkinson, Hypothyroidism, Dementia, Benign prostatic hyperplasia.

Results

The sample consisted of 514 patients. Participants had a mean age of 55±17.8 years. More than half the participants were women (52.9%). Our results showed that the three most common etiologic causes of AP were biliary in 299 (58.2%) patients, idiopathic in 98 (19.1%) patients, and alcohol-related causes in 44 (8.6%) patients. After these three etiological causes, drug use in 29 (5.6%) patients, post-ERCP in 20 (3.9%) patients, hypertriglyceridemia in 19 (3.7%) patients, hypercalcemia in 2 (0.4%) patients, autoimmune pancreatitis in 2 (0.4%) patients, and 1 (0.4%) patient had trauma-related AP. Table 3 shows the participants' general characteristics. Participants had MSAP (80.9%; n=416), MAP (14.8%; n=76), or SAP (4.3%; n=22). Three participants (0.6%) died due to AP. BMI elevation and smoking were found to be statistically significantly different between MAP, MSAP, and SAP patient groups ($p=0.000$). There was no statistical difference between the patient groups in serum amylase and lipase levels at admission to the hospital ($p=0.657$, $p=0.524$). Platelet count was statistically significantly different between NLR and PLR, MAP, MSAP, and SAP patient groups ($p=0.000$). There was no statistical difference between the CRP values of the patient groups at the time of admission to the hospital, but a statistically significant difference was found between the CRP values at the 48th h ($p=0.000$). Albumin and calcium levels were statistically significantly different in MAP, MSAP, and SAP patient groups ($p=0.000$). In addition, AST/ALT ratio, Ranson score, and BISAP score were statistically significantly different in MAP, MSAP, and SAP patient groups ($p=0.000$). Table 4 shows the risk factors related with MSAP and SAP.

Table 4. Factors associated with acute pancreatitis severity

Parameters	MAP n=416 (80.9%) (Mean±SD)	MSAP n=76 (14. 8) (Mean±SD)	SAP n=22 (4.3) (Mean±SD)	p*
Gender				
Female	222 (53.4)	41 (53.9)	9 (40.9)	0.512†
Male	194 (46.6)	35 (46.1)	13 (59.1)	
Age	54.85±17.63	54.08±19.80	55.73±14.29	0.941†
BMI	23.9±2.5	27.5±3.8	28.5±2.8	0.000*
Tobacco use	35 (8.4)	21 (27.6)	8 (36.4)	0.000†
Hospitalization (day)	4.00±1.01	10.12±3.31	19.36±10.78	0.000†
Etiology				
Biliary	255 (61.3)	34 (44.7)	10 (45.5)	0.000†
Alcohol	22 (5.3)	18 (23.7)	4 (18.2)	0.002†
Idiopathic	77 (18.5)	17 (22.4)	4 (18.2)	0.000†
Amylase U/L	1433.11±962.7	1372.45±808.88	1578.91±933.76	0.657*
Lipase U/L	1686.17±1632.76	1743.92±1233.37	2084.32±2437.09	0.524*
Leukocyte u/L	9.69±3.6	10.26±4.01	11.35±3.55	0.069*
Hemoglobin g/dL	12.68±1.73	12.55±2.07	13.01±1.26	0.563*
Platelet u/L	218.30±69.44	304.84±97.53	332.31±115.70	0.000*
NLR	3.87±2.02	7.37±2.99	10.18±3.37	0.000*
PLR	130.19±74.30	287.39±140.25	360.97±157.58	0.000*
MPV fL	8.59±1.63	8.3±1.29	8.19±1.2	0.195*
RDW fL	13.53±1.22	13.67±1.16	13.75±1.59	0.491*
CRP mg/L	1.82±1.87	1.79±1.82	2.58±2.81	0.188*
48th h CRP mg/L	7.26±3.23	14.77±6.26	18.96±5.9	0.000*
Albumin g/dL	3.71±0.41	3.3±0.37	3.08±0.44	0.000*
Calcium mg/dL	8.73±0.56	8.47±0.44	8.29±0.41	0.000*
AST IU/L	131.63±159.78	172.61±261.32	174.23±190.56	0.123*
ALT IU/L	158.42±183.45	119.55±170.45	119.09±146.93	0.158*
AST/ALT	1.02±0.62	1.48±0.58	1.64±0.73	0.000*
Ranson Score	1.08±1.09	1.67±1.06	2.91±1.19	0.000*
BISAP Score	0.86±0.80	1.74±0.87	3.77±0.75	0.000*

Data are shown as median (interquartile range) or n (%). BMI: body mass index; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; MPV: mean platelet volume; RDW: red cell distribution width; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase. *One-way ANOVA† Chi-square.

Discussion

Eight in ten AP patients present with a mild edematous form and are discharged after a couple of days. However, two in ten AP patients develop a severe or complicated course of pancreatitis characterized by early or delayed systemic and local complications. Our results showed that eight in ten participants had MSAP (80.9%), which is consistent with the literature.[13]

Although there are various scoring systems (Ranson score, Balthazar score, SOFA score, APACHE II score, and Marshall score) to assess pancreatitis severity early (<24 h), they are not used very commonly in clinical practice.[13,14] It is more practical to use the BISAP score to diagnose SAP.[15] In addition, some clinical and laboratory parameters can provide information about the prognosis of pancreatitis at the time of admission.[16] This study analyzed the relationship between clinical and laboratory parameters at admission and BISAP and Ranson scores and AP severity

Our results showed that the three most common etiologic causes of AP were biliary in 299 (58.2%) patients, idiopathic in 98 (19.1%) patients, and alcohol-related causes in 44 (8.6%) patients. Biliary causes were higher, while alcohol-related causes were lower than those reported by earlier studies.[17,18] This is probably because alcohol consumption is low in Turkey. A similar result was found in a study conducted in our country.[19] In their meta-analysis, Roberts et al. (2017) [20] have reported that the biliary/alcohol ratio is higher in Southern European countries (including Turkey) than in Northern European countries.

Obesity is an independent risk factor for SAP.[21] We found that SAP (28.5±2.8) and MSAP (27.5±3.8) participants had a higher mean BMI than MAP participants (23.9±2.5). In their meta-analysis, Cruz-Monserrate, Conwell, and Krishna (2016) have also found that a BMI >25 increases the risk for SAP.[22] There is a positive correlation between tobacco use and AP.[23-25] In this study, we found that tobacco use was statistically higher in MSAP and SAP than in MAP. Epigenetic changes or environmental stimuli combined with smoking can further advance pancreatic damage.[26]

CRP is one of the most important biomarkers related to the severity of AP. It is widely used despite the delayed increase peaking 72 h after the onset of symptoms.[27] We could not detect any difference in CRP levels between patient groups at admission. However, the SAP, MSAP, and MAP groups had a 48th-h CRP level of 18.96±5.9 mg/L, 14.77±6.26 mg/L, and 7.26±3.23 mg/L, respectively. CRP levels above 15 mg/L 48 h after admission help differentiate MSAP from SAP.[27]

NLR attracts the attention of many researchers because it has such advantages as rapid detection, high sensitivity, low cost, and non-invasiveness.[28] Furthermore, like increased NLR, PLR has been associated with inflammatory states and poor outcomes in SAP are explained by uncontrolled SIRS and its progression to multi-organ dysfunction syndrome.[29] We detected a positive association with NLR and PLR to AP severity, which is consistent with the literature.[30-32]

Inflammation reduces red blood cell (RBC) half-life, affects iron metabolism and erythropoiesis, and increases hemolysis, resulting in increased RBC size and heterogeneity. Therefore, RDW can be used as a non-specific inflammatory indicator.[33] There is a correlation between RDW and AP severity.[32] AP may increase platelet consumption due to pancreatitis region and distant organ inflammation and cause a decrease in MPV value.[34] We found that the SAP and MSAP groups had lower MPV but higher RDW than the MAP group. However, the difference was statistically insignificant. We excluded patients who were admitted to the clinic late. MPV and RDW may not change significantly early in the inflammatory process and may not be an early indicator of the severity of AP.

We detected that hypocalcemia and hypoalbuminemia were associated with the severity of AP, which is consistent with the literature.[35-37] Albumin maintains osmotic pressure, binds endogenous/exogenous substances with high vascular permeability, prevents coagulation, buffers acid-base status, and has antioxidant, anti-inflammatory, and anti-apoptosis effects.[38,39] Therefore, hypoalbuminemia may predict persistent organ failure and severe inflammation rather than being a marker of AP severity. We think that AP causes hypoalbuminemia and that the higher the hypoalbuminemia, the more complicated the AP. The causes of early-phase hypocalcemia in AP are the self-digestion of mesenteric fat by pancreatic enzymes, the release of free fatty acids that form calcium salts, transient hypoparathyroidism, and hypomagnesemia.[40-42] Therefore, calcium levels may decrease with an increase in the severity of inflammation and may predict the severity of AP.

In our study, no correlation was found between AST and ALT levels and the severity of the disease, but it was found that the AST/ALT ratio related the severity of the disease. Fernando De Ritis (1957) was the first to define the ratio of serum activities of AST and ALT.[43] This ratio, also known as the De Ritis ratio, is used as a marker in the prognosis of many diseases.[44] A high De Ritis ratio in AP may be an early marker of severe inflammation and cell destruction resulting from organ failure. To the best of our knowledge, this is the first study to show associated with the severity of AP and De Ritis ratio. However, the low number of patients in the SAP group and the higher incidence of biliary etiology in the MAP group may have affected this result.

We detected a positive correlation between Ranson and BISAP scores and the severity of AP, which is consistent with the literature.[32] The main limitation of the Ranson criteria is that evaluation cannot be completed until 48 h after admission, which may miss an early therapeutic window and increase mortality. Both BISAP and Ranson scoring systems accurately predict the severity of AP, but the former is more effective because it is easier to use than the latter.

The mortality rate was 0.6% in this study. Research shows that the AP-related mortality rate ranges from 2.5% to 12.5%.[13,15,27,31] The low mortality rate in this study may be because we administered (IV) 5–10 mL/kg/h (aggressively) hydration on the 1st day and the breadth of patients' exclusion criteria from the study. We observed that the higher the AP severity, the longer the hospitalization. Determining the parameters of the severity of AP is effective in predicting morbidity and mortality rates and increased workload and costs. AP is one of the most common causes of hospitalization due to the gastrointestinal tract. Therefore, health-care professionals involved in patient management should carefully evaluate the parameters related to the severity of AP. In this study, it was determined that BISAP and Ranson scores were associated with the severity of AP. In addition, in this study, it was determined that laboratory parameters (platelet, NLR, PLR, albumin, calcium, 48th h CRP value, and AST/ALT ratio) that gave results in a short time were associated with the severity of AP. Predicting the severity of AP early may be effective in reducing morbidity and mortality with closer follow-up of the patient and more

aggressive treatment. Perhaps, with future studies, these laboratory parameters can be used in the development of new scoring systems that predict the severity of AP.

This study was conducted in one of the centers evaluating the highest number of AP patients in Turkey. The strengths of the study are the inclusion criteria, sample size, and the broad spectrum of parameters. The limitation of the study is that it was retrospective.

Conclusion

High BMI, tobacco use, high NLR, high PLR, thrombocytosis, and high CRP (48th h) levels were found to be associated with the severity of AP. MPV and RDW may not predict the severity of AP in the early admission. Hypoalbuminemia, hypocalcemia, Ranson, and BİSAP scores were found to be associated with the severity of AP.

Disclosures

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Umraniye Training and Research Hospital (Date: 18/03/2020 & No: B.10.1.TKH.4.34.H.GP.0.01/70).

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