Original Article
Cent Asian J Med Sci. 2021 June;7(2):110-116. https://doi.org/10.24079/CAJMS.2021.06.005

Central Asian Journal of Medical Sciences
CAJMS

New Paradigm for Determining Necrosis, Stage and Prognosis of Severe Acute Necrotizing Pancreatitis

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Submitted: December 7, 2020
Revised: December 14, 2020
Accepted: December 4, 2021

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Objective: To determine the clinical features and diagnostic parameters of acute alcohol-induced pancreatic necrosis to develop a new system to assess the severity of acute pancreatitis, diagnose necrotic inflammation, and understand prognosis. **Methods:** We performed a retrospective chart review of patients admitted to the General Surgery Department and Gastroenterology Department of The Third Central Hospital, and The First Central Hospital in Ulaanbaatar from November 1, 2008, to January 1, 2020, admitted with acute pancreatitis, gathering clinical data using a structured form. From these data, we developed a new scoring system. **Results:** The median age of patients with acute necrotic pancreatitis was 43 (range 25-71) years, with the majority (87.4%) ages 26 to 60. Of the 31 deaths reported in the study, 24 (77.4%) were hospitalized more than 72 hours after the onset of the disease. Using the new evaluation system, 12 out of 122 patients were classified as class A (score 0-3), 69 (56.5%) were class B (score 4-6), and 41 (33.6%) of the patients were class C (score ≥7) points. **Conclusion:** The evaluation system we developed aids with early diagnosis, progression and prognosis of severe forms of acute pancreatitis. It is easy to score, and it is possible to score using information available in Mongolia's secondary and tertiary hospitals.

Keywords: Pancreatitis, Necrotize, Alcohol, Acute Necrotizing, Parenchymal Edema

Introduction

Pancreatitis is a pathological condition where the pancreas becomes inflamed, and its cells are damaged. There are two types of pancreatitis, acute and chronic. Globally, acute pancreatitis (AP) incidence is increasing year by year, but its complications and mortality are not decreasing. It has been suggested that about 40% of the AP is caused by excessive alcohol consumption, while another 40% is due to gallstones. The severity of AP ranges from mild to severe and life-threatening. Usually, mild AP has a low mortality rate (less than 1%), whereas the mortality rate of severe AP can be up to 30%. The prospective cohort study of Pang et al. showed that weekly drinkers and heavy drinking episodes were associated with a 50% excess risk of acute pancreatitis than with non-drinkers. Further, individuals with diabetes had a 34% higher risk of acute pancreatitis [1]. Razvodovsky et al. also reported the highest age-standardized sex-specific male and female pancreatitis mortality caused by

alcohol was 63.1% and 26.8%, respectively [2-5]. According to World Health Organization (WHO) statistics, almost one in five Mongolian men binge-drink weekly, and this high consumption has become the primary cause of acute pancreatitis. Domestic reports reveal that the mortality rate of AP due to the excess use of alcohol is 15.3% in Mongolia [6].

Mortality due to acute pancreatitis is caused by complications arising from several pathological conditions, including pancreatic necrosis, intoxication, hemorrhage and multiple organ failure [6, 7]. Pancreatic necrosis is complex and especially challenging, occurring in 40% to 70% of patients. Necrotizing pancreatitis (NP) can be divided into 2 phases. In the early phase, an inflammatory response syndrome occurs, caused by pro-inflammatory cytokines. The second phase is dominated by sepsis-related complications such as pulmonary, renal and cardiovascular failure arising from the infection of the necrotic pancreas. The diagnosis of acute necrotizing pancreatitis, the optimal choice of treatment tactics at different stages of the peritoneal inflammatory process, early detection of the type and location of necrotic inflammation, detection of infectious evidence of necrosis, objective assessment of the nature of the injury, as well as the severity of the patient (intoxication syndrome) are essential factors to identify the course of the disease and have prognostic significance [8-10].

There are several classification systems for the severity of acute pancreatitis internationally, including the Ranson, APACHE, and Balthazar classifications. The Ranson criteria include 11 parameters that are evaluated at admission and at 48 hours of hospitalization. It is based on age and lab results. The APACHE II scoring system is widely used, but it contains many variables, including age, medical history, Glasgow coma score, vital signs and lab values. Acute pancreatitis can also be evaluated by the Balthazar score that is based solely on computed tomography. Although the assessments mentioned above scales are widely used nowadays in clinical research, no gold-standard criteria exist. There is no systematic assessment system for differentiating acute necrotic pancreatitis usable throughout our country. Because there are not enough sufficiently trained personnel and imaging equipment, especially in rural hospitals of Mongolia, we developed a new classification system adapted to our situation.

Therefore, the study's objective is to propose and demonstrate a new scoring system based on the clinical features and readily available diagnostic parameters for acute alcohol-induced pancreatic necrosis to develop diagnostic and treatment algorithms and aid with prognosis.

Materials and Methods

Subjects

Our study was carried out using retrospective targeted sampling. From November 1, 2008, to January 1, 2020, 122 patients who were hospitalized with alcohol-induced AP were selected, and archival documents or medical records were reviewed. The research materials were the archival documents of the deceased patients admitted to the General Surgery Department and Gastroenterology Department of Third Central Hospital, and The First Central Hospital in Ulaanbaatar, Mongolia, from November 1, 2008, to January 1, 2020, with a diagnosis of alcohol-induced AP.

We retrospectively collected data from the medical history using a 90-question form developed in the first quarter of 2018 by our research team. The form gathered parameters of interest in a structured format, based on international and Mongolian guidelines and recommendations for the diagnosis and treatment of AP.

In our study, CT scans for acute pancreatitis were classified according to Balthazar score, and most cases of pancreatic necrosis and purulent necrosis were Balthazar B, C, and D grades.

The necrosis score of Balthazar based on the percentage of necrosis on CT scan is: below 30% necrosis - 2 points, 30 to 50% necrosis -4 points, over 50% necrosis - 6 points. Laboratory tests included in the assessment system for pancreatic necrosis and severity were examined to determine which of them was the most important in assessing the course and prognosis of the disease. Biopsy reports were reviewed to determine if pancreatic necrosis and inflammation were present in patients who underwent surgery.

Exclusion criteria

Patients who presented with unconsciousness, concomitant multiple organ disease or chronic multiple organ failure, cancer, acute non-alcoholic pancreatitis, chronic organ system disease with increased levels of C-reactive protein, and systemic inflammatory response syndrome caused by infectious diseases were excluded.

New classification system of acute pancreatitis severity

The scoring criteria for our new classification system are found below (Table 1). Each of the 12 items in the scoring system is given a value of 1 point for an affirmative answer. The total score is the sum of the number of questions answered affirmatively:

Table 1. New classification system of acute pancreatitis severity.

No	Parameters at admission	No	Yes
1	Leukocyte > 16 x 10^9 L	0	1
2	Abdomen pain, swelling, distension	0	1
3	Serum LDH > 450 U/L	0	1
4	Serum amylase > 1000 U/L	0	1
5	Blood glucose > 200 mg/dL	0	1
6	Systemic Inflammatory Response Syndrome	0	1
	Parameters at 48 h of hospitalization		
7	Serum Ca < 8 mg/dL	0	1
8	Serum UN > 5 mg/dL	0	1
9	C reactive protein > 120 mg/L	0	1
10	Procalcitonin > 0.8 ng/L	0	1
11	Serum lipase > 200 U/L	0	1
12	Balthazar index C, D, E	0	1
Total possible		**12 points**	

Next, we stratified the patients into one of three categories based on their total score:

Class A - Those with mild acute pancreatitis, acute pancreatic inflammation (0 - 3 points)

Class B - Those with moderate acute pancreatitis, acute necrotizing pancreatitis (4 - 6 points)

Class C - Those with severe acute pancreatitis, acute necrotizing pancreatitis (>7 points)

Statistical analysis

Descriptive statistics, including frequency, percentages, mean, standard deviation (SD), median and range, were calculated to evaluate demographic and clinical characteristics. For continuous variables, ANOVA tests with Tukey's multi-comparison test were used. For categorical variables, Chi-square and Fisher's exact tests were carried out to determine statistically significant differences. For hypothesis testing, the critical p-value was set at 0.05. The statistical analysis was performed using Stata MP version 16.0.

Ethical statement

The study was approved by the Ethical Review Sub-Committee of Ach Medical School on May 15, 2020 (№2020/5/15). In the study, the medical histories of patients admitted to the hospital with AP diagnosis were obtained from the archives of The First Central Hospital and The Third State Central Hospital. The patient's name was encrypted, no personal identifying information was used, and confidentiality was maintained.

Results

The median age of the patients with ANP was 43 years with a minimum of 25 and a maximum of 71 years of age. Of the 31 deaths reported in the study, 24 (77.4%) were hospitalized more than 72 hours after the onset of the disease (Table 2).

According to the new evaluation system, class A (mild) included patients with up to 30% of necrosis, class B (moderate) included 30-50% of necrosis and class C (severe) included patients who had over 50% necrosis, based on the CT scan. As shown in Table 3, 12 out of 122 patients were classified as class A or 0 - 3 points, 69 (56.5%) patients were class B or 4 - 6, and 41 (33.6%) patients were class C or ≥ 6 points. Of the total cases, 90.1% were rated as a severe form of ANP and pancreatic necrosis by the classification system we developed.

After evaluating the subjects by the evaluation system and comparing them with the biopsy, we confirmed that the patients belonging to categories B and C of the evaluation system had pancreatic necrosis and inflammation.

When we assessed the prognosis with the new assessment system, we found that 100 percent of patients in category A survived, 89.8 percent of patients in category B survived, and 41.5 percent in category C survived, while 58.5 percent died. The correlation between the score and the survival was $r = -0.509$ ($p < 0.001$). In other words, the higher the score of the evaluation system, the lower the survival rate.

In Table 4, the serum laboratory parameters of the patients are shown. Statistical analysis revealed that leukocyte and neutrophil counts were significantly lower in Class A. The mean calcium for Class C patients was also significantly lower at the admission (1.78 ± 0.11 mmol/L) compared with mild pancreatitis patients. On the other hand, AST was significantly higher in Class C or severe grade patients (95.1 ± 89.8 U/L) compared to that in Class A and B (61.0 ± 89.4 and 63.4 ± 59.5 U/L, respectively). Further, serum lipase in Class A patients was significantly lower after 72 hours of admission (97.4 ± 62.9 U/L), while the same parameter was barely decreased in Class C patients (234.5 ± 106.8 U/L).

Table 2. Characteristics of patients using new acute necrotizing pancreatitis scoring system.

Variables	Acute Necrotizing Pancreatitis Classification				
	Class A (n=12)	Class B (n=69)	Class C (n=41)	Total (n=122)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	49.17 ± 12.4	42.66 ± 10.1	47.36 ± 10.4	44.9 ± 10.7	0.489
	N (%)	N (%)	N (%)	N (%)	
Gender					
Male	9 (75.0)	58 (84.1)	34 (82.9)	101 (83.8)	*0.744
Female	3 (25.0)	11 (15.9)	7 (17.1)	21 (17.2)	
Alcohol consumption (hours)					
≤48	10 (83.3)	60 (88.2)	14 (34.1)	84 (69.4)	*0.000
>48	2 (16.7)	8 (11.8)	27 (65.9)	37 (30.6)	
Hospital stay (days)					
≤14	5 (41.7)	8 (11.6)	17 (41.5)	30 (24.6)	0.004
>14	7 (59.4)	61 (57.2)	24 (58.5)	92 (75.4)	
Hospitalization Cost (TG)					
≤500,000	11 (91.7)	21 (30.4)	13 (31.7)	45 (36.9)	*0.002
>500,000	1 (8.3)	48 (69.5)	28 (68.2)	78 (63.1)	

*Fisher's exact test

Table 3. Clinical characteristics of patients using new acute necrotizing pancreatitis scoring system.

Variables	Acute Necrotizing Pancreatitis				
	Class (n=12)	Class B (n=69)	Class C (n=41)	Total (n=122)	*p-value
	N (%)	N (%)	N (%)	N (%)	
Balthazar grade					
Normal pancreas A	1 (8.3)	6 (8.7)	-	7 (5.7)	0.031
Enlarged pancreas B	11 (91.7)	63 (91.3)	41 (100)	115(94.3)	
Treatment type					
Medical	10 (83.3)	16 (23.2)	1 (2.4)	27 (22.1)	0.001
Surgery	2 (16.7)	53 (76.8)	40 (97.5)	95 (77.8)	
Chronic disease					
Yes	4 (33.3)	22 (31.9)	29 (70.7)	55 (45.1)	0.000
No	8 (66.7)	47 (68.1)	12 (29.3)	67 (54.9)	
Time of onset of pain					
≤24	6 (46.5)	22 (31.8)	3 (7.3)	31 (25.5)	0.002
>24	7 (53.8)	47 (68.2)	38 (92.7)	91 (74.5)	
Outcome					
Deceased	-	7 (10.1)	24 (58.5)	31 (25.4)	0.000
Survived	12 (100)	62 (89.9)	17 (41.5)	91 (74.6)	

*Fisher's exact test

Table 4. Serum laboratory parameters of patients using new acute necrotizing pancreatitis scoring system.

Variables	Acute Necrotizing Pancreatitis				*p-value
	Class A (n=12)	Class B (n=69)	Class C (n=41)	Total (n=122)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Leukocytes at admission[a] (10^9/L)	12.12 ± 5.2	14.54 ± 3.9	18.62 ± 4.9	15.7 ± 4.9	0.000
Leukocytes at 24 hours[b]	11.34 ± 4.7	14.24 ± 4.2	15.30 ± 3.2	14.32 ± 4.1	0.005
Neutrophils at admission[c] (10^9/L)	74.9 ± 11.4	78.5 ± 18.8	84.8 ± 11.0	80.3 ± 16.2	0.021
Amylase at admission[d,e] (U/L)	937.2 ± 1183.9	1058.8 ± 1280.6	1701.5 ± 1016.7	1262.8 ± 1220.8	0.008
LDH at 48 hours[f,g,h] (U/L)	367.0 ± 135.9	509.3 ± 235.3	570 ± 98.2	515.8 ± 198.0	0.003
Blood sugar (mmol/L)	7.05 ± 3.73	7.24 ± 4.1	8.9 ± 6.19	7.8 ± 4.88	0.098
Ca at admission[i,j] (mmol/L)	2.10 ± 0.29	1.99 ± 0.23	1.78 ± 0.11	1.93 ± 0.23	0.000
Ca at 72 hours[k]	2.05 ± 0.26	1.9 ± 0.21	1.7 ± 0.15	1.87 ± 0.22	0.000
CRP[l,m] (mg/dL)	95.83 ± 45.21	170.29 ± 59.59	180.13 ± 67.01	166.27 ± 65.05	0.001
AST[n,o] (U/L)	61.0 ± 89.4	63.4 ± 59.5	95.1 ± 89.8	73.9 ± 74.9	0.041
Creatinine[p] (uM/L)	110.9 ± 38.2	73.6 ± 44.6	99.3 ± 120.0	141.5 ± 80.9	0.002
Lipase at admission[q,r] (U/L)	125.8 ± 97.1	231.7 ± 169.7	255.1 ± 130.9	228.9 ± 153.9	0.026
Lipase at 72 hours[s]	97.4 ± 62.9	192.1 ± 144.4	234.5 ± 106.8	201.7 ± 129.9	0.006

*ANOVA test; Tukey multiple post hoc comparison tests: [a]Class A vs. Class C, $p < 0.030$; [b]Class B vs. Class C, $p < 0.035$; [c]Class B vs. Class C, $p < 0.002$; [d]Class A vs. Class B, $p < 0.045$; [e]Class A vs. Class C, $p < 0.045$; [f]Class A vs. Class B, $p < 0.006$; [g]Class A vs. Class C, $p < 0.003$; ; [h]Class B vs. Class C, $p < 0.003$; [i]Class A vs. Class C, $p < 0.050$; [j]Class B vs. Class C, $p < 0.026$; [k]Class B vs. Class C, $p < 0.021$; [l]Class A vs. Class B, $p < 0.045$; [m]Class A vs. Class C, $p < 0.045$; [n]Class B vs. Class C, $p < 0.005$; [o]Class A vs. Class C, $p < 0.012$; ; [p]Class B vs. Class C, $p < 0.001$; [q]Class A vs. Class C, $p < 0.002$; [r]Class A vs. Class B, $p < 0.0134$; ; [s]Class B vs. Class C, $p < 0.045$.

Discussion

Serum pancreatic enzyme measurement is the "gold standard" for the diagnosis of AP [8]. In an episode of AP, amylase, lipase, elastase, and trypsin are released into the bloodstream simultaneously, but the clearance varies depending on the timing of blood sampling. Amylase is an enzyme secreted mainly by the pancreas and salivary glands, but also the small intestine, ovaries, adipose tissue, and skeletal muscles. There are two major isoforms of amylase: pancreatic and salivary, and its leading function is the digestion of starch, glycogen, and related poly- and oligosaccharides by hydrolysis [9]. In AP, serum amylase levels usually rise within 6 to 24 h, peak at 48 h, and decrease to normal or near-normal levels over the next 3 to 7 days [10-12]. Late hospitalization and late treatment of patients with ANP disease have been shown to affect the prognosis of the disease adversely.

Lipase is another enzyme secreted by the pancreas. AP is the main reason for an increase in lipase. Many investigators emphasize that lipase is more specific but can also be found elevated in non-pancreatic diseases such as renal disease, appendicitis, acute cholecystitis, chronic pancreatitis, bowel obstruction, etc. [10, 11]. In AP, serum lipase remains elevated for a longer period than serum amylase. It rises within 4 to 8 h, peaks at 24 h, and decreases to normal or near-normal levels over the next 8 to 14 days [13].

A Cochrane review comparing the diagnostic accuracy of different pancreatic enzymes in the diagnosis of AP showed a sensitivity and specificity of 72% and 93% for serum amylase and 79% and 89% for serum lipase, respectively [14]. Our study found an increase in lipase during ANP, which is of diagnostic value or statistically significant, especially in the diagnosis of necrotic inflammation ($p < 0.01$).

Many textbooks consider the C-reactive protein (CRP) as the gold standard for disease severity assessment [15]. Using a cutoff value from 110 to 150 mg/l, the sensitivity and specificity ranged from 38 to 61%, and 89 to 90%, respectively, at the time of hospital admission [15]. The major drawback of C-reactive

protein is that peak levels are reached only after 48 to 72 h.

In our study, C-reactive protein was one of the most important tests for severe disease and necrosis in the ANP. Some studies have shown that procalcitonin is important in determining the severity of acute pancreatitis and in predicting the risk of infecting pancreatitis [16]. Procalcitonin is indicated in patients with confirmed pancreatic necrosis to predict necrotic infection. [16-19]. A procalcitonin value of 3.8 ng/ml or higher within 96 h after onset of symptoms indicated pancreatic necrosis with a sensitivity and specificity of 93% and 79% [16, 17].

In our study, an increase in procalcitonin levels was statistically significant ($p < 0.01$) in determining the severity and severity of the disease. Studies by Staubli et al. [12] and Yang [18] have shown that pancreatic necrosis is 93% and 79% sensitive and specific if procalcitonin levels are 3.8 ng / mL or higher within 96 hours of the onset of symptoms [13, 17]. Studies by Valverde-Lopez F [17] have shown that a drop in blood calcium levels (1.8 mmol / l) occurs during ACS, which is often seen as a symptom of ASA necrosis [19].

It was possible that the serum calcium level was reduced ($p < 0.01$) in the necrotic form of ANP compared with normal tissue. Therefore, blood calcium levels are considered one of the most important tests for patients with ANP in our study. The positive predictive value for the Ranson score ranges from 28.6 to 49% (sensitivity 75–87%, specificity 68–77.5%), for the Glasgow score from 59 to 66% (sensitivity 61–71%, specificity 88–89%), for the APACHE II score, 55.6% after 48 h (sensitivity 83.3%, specificity 91%), and for the APACHE-O score 54–80% (sensitivity 69–74%, specificity 86–90%). All these scores can only be assessed after 48 h and thus do not enable risk stratification on admission. Despite their weaknesses, these scores are still useful to prove or exclude severe disease [20].

One study of 161 patients evaluated using the parameters for early predictability most widely used in AP. The authors determined the significant cutoff values for prediction of severe AP were Ranson ≥3, BISAP ≥2, APACHE-II ≥8, CTSI ≥3, and CRP at 24 h ≥21 mg/dl (>210 mg/l). They concluded that different scoring systems showed similar predictive accuracy for the severity of AP, but APACHE-II demonstrated the highest accuracy for predicting severe acute pancreatitis [21-24].

Using our new scoring system, 69 of 122 (56.5%) patients were category B (score > 3) and 41 (33.6%) patients in category C (score > 7). By our new system, 90.1% of all cases were in severe acute necrotizing pancreatitis. Of the patients classified A category by our new scoring system, 100% survived, and 89.8% of patients in class B survived, while less than half (41.5%) of the patients classified in category C survived. The correlation between our new scoring system and the patient's survival was evaluated using the correlation analysis and was significant ($p < 0.001$).

Our scoring system is equally effective compared to others. But it is easier to use in the hospitals of developing countries because it uses only a few highly sensitive indicators. We note that our study has limitations, namely, small sample size and limited follow-up. The sampling was conducted mainly in Third and The First Central Hospitals located in Ulaanbaatar. Thus, the future direction of this study includes the application of the scoring system to other hospitals, especially in central hospitals of 21 aimags as well as district hospitals in Ulaanbaatar.

Conclusions

In Mongolia, relatively young men suffer from alcohol-induced pancreatitis. Factors contributing to necrosis in acute pancreatitis include alcohol abuse, prolonged alcohol use, delayed hospitalization, and delayed treatment. In our study, clinical signs and laboratory findings effectively distinguish severe forms of acute pancreatitis, early diagnosis, assessment of prognosis, and development of surgical treatments. Clinical signs include abdominal pain, bloating, and abdominal muscle stiffness. Laboratory tests include an increase in white blood cells, neutrophils, serum LDH, serum lipase, C-reactive protein and a decrease in hematocrit, serum calcium. The new evaluation system that we have developed for early diagnosis, progression and prognosis of severe forms of acute pancreatitis is easy to evaluate. The criteria used in the evaluation system are available in the secondary and tertiary hospitals of our country.

Conflict of Interest

The authors state no conflict of interest.

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