

## **A STUDY MANAGEMENT OF ACUTE PANCREATITIS; ROLE OF RECENT CRITERIA IN PROGNOSIS AND MANAGEMENT OF ACUTE PANCREATITIS**

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### **Abstract**

**Aim :** To compare APACHE-II scoring, C-Reactive Protein (CRP), Interleukin-6 (IL-6) estimation and Contrast Enhanced Computed Tomography in assessing the severity of acute pancreatitis and prognosis of the condition.

. To determine the role of these investigations and the most accurate investigation for the detection of severity of acute pancreatitis and prognosis at 72 hours.

**Method:** The present study was conducted at the Department of General Surgery, V.S. General Hospital, Ahmedabad. The Study population consisted of first 50 cases of acute pancreatitis fulfilling the inclusion criteria. It was a prospective study.

#### **Results:**

Apache II scoring done at admission predicted severe pancreatitis in 8 cases out of 10 cases which turned out to be severe on Atlanta classification. So, there was 2 false negative cases in severe group. Apache II score at admission predicted 38 patients as mild pancreatitis thus giving false positive result in 2 cases. Pearson Chi-square test of significance was applied for the analysis of the data. This clinical scoring done at admission had a sensitivity of 80%, specificity of 95%, positive predictive value of 80%, negative predictive value of 95% and accuracy of 92%.

Serum CRP level of the patients at admission predicted 7 as severe pancreatitis out of 10 actual cases of severe pancreatitis thus giving false negative result in 3 cases. This biochemical assay labeled 26 cases as mild at admission thus giving false positive rate in 14 cases. Statistical analysis of the data yielded a p value of 0.07 (Pearson Chi-square test) indicating that the data was statistically insignificant. Estimation of serum CRP level at admission had sensitivity of 70%, specificity of 65%, PPV of 33.33%, NPV of 89.65% and accuracy of 66%.

Serum IL-6 level of the patients at admission predicted 8 as severe pancreatitis out of 10 actual cases of severe pancreatic thus giving false negative result in 2 cases. This biochemical assay labeled 36 cases as mild at admission thus giving false positive rate in 4 cases. Estimation of serum IL-6 level at admission had sensitivity of 80%, specificity of 90%, PPV of 66.67%, NPV of 94.74% and accuracy of 88%.

#### **Conclusion:**

. Evaluation of the different prognostic indications for the detection of severity at admission showed that Apache II score as well as serum IL-6 were the best indicators of severity. However, due to the complex nature of the calculation, the Apache II score might prove to be cumbersome. Whereas serum IL-6 being costly and not being easily available in the setup is its main drawback.

Serum CRP estimation at the time of admission was not accurate to determine prognosis and severity of AP as raised CRP level are dependent of hepatic synthesis secondary to circulating cytokines (IL- 6) which usually takes 2-3 days after the onset of disease.

- . Evaluation of the above score again at 72 hours, along with the CTSI score produced an equivocal result. However, when CTSI was compared with Apache II score, IL-6 and CRP for the best possible indicator for detection of severity at 72 hours, CTSI emerged as a favourable prognostic indicator owing to the relative ease of calculation
- . **Key words:** APACHE-II scoring, C-Reactive Protein (CRP), Interleukin-6 (IL-6) estimation, Contrast Enhanced Computed Tomography, assessing the severity of acute pancreatitis.

### **INTRODUCTION:**

Acute pancreatitis (AP) is a common disease of varying etiology with an overall mortality of 5 to 10%. Most cases (80-90%) are mild and self-limited with a good outcome. The remaining 10 to 20% of patients with severe disease characteristically have pancreatic necrosis or distant organ failure and one can anticipate the need for intensive care and possible operative intervention if required, with a mortality rate of up to 40%. According to the Atlanta Classification, acute pancreatitis can be classified as mild or severe depending on the development of organ failure and/or local complications.<sup>1</sup> The severe form of acute pancreatitis is characterized by the presence of one or more of the following criteria:

- . Ranson score equal to or greater than 3.
- . An APACHE II score equal to or greater than 8.
- . Failure of one or more systems, such as shock, respiratory insufficiency, renal failure, gastrointestinal bleeding, severe thrombocytopenia and hypokalemia.

4 Development of local complications such as necrotizing pancreatitis, abscess formation, or pancreatic pseudocyst.<sup>2</sup>

The severe form of the disease, defined in this way, is present in up to 25% of cases.

Severe acute pancreatitis has two clinical phases. The first phase is characterized by SIRS which lasts for the first ten days. The second phase starts at the end of the second week and is characterized by infectious complications. The first four days are crucial to the evolution of acute pancreatitis, during which 15-25% of patients develop the severe form of the disease. Early aggressive & intensive treatment in the first phase can improve the survival if one can predict the severity at an early stage.

The stratification of injury severity is essential, in order to manage these patients in an intensive care unit with early and aggressive treatment and in order to improve outcome because of its potential for catastrophic deterioration.

Both anatomic and physiologic criteria are used to stage the severity of acute pancreatitis.<sup>2,3,4</sup> The most common anatomic method of staging is based on contrast-enhanced computed tomography imaging. Balthazar and Ranson developed a grading system for severity based on CT findings. This computed tomography severity index (CTSI) is derived by assessing the degree of pancreatic and peripancreatic inflammation, fluid collection and parenchymal necrosis.<sup>5,6</sup>

Balthazar and Ranson<sup>6</sup> have shown that contrast-enhanced computed tomography assessment correlated with the clinical course of the disease and with the prediction of mortality. They found a 3% mortality rate in patients with a CTSI score greater than 3 whereas patients with a CTSI score greater than 7 had a mortality rate of 17%. Similarly, the higher CTSI scores in severe pancreatitis cases with local and/or systemic complications have predicted the complicated course of the disease when compared with the CTSI score of the mild group.

Several scoring systems to assess the severity of pancreatitis have been developed. Ranson established 11 objective factors in order to identify severity in patients with acute pancreatitis. Since 69% of these cases were related to alcohol, Ranson revised the criteria for patients with biliary pancreatitis. Imrie modified Ranson's prognostic scoring system and reduced the factors to nine. Buter et al. modified the Imrie criteria by deleting age factor. Blarney et al also modified the Imrie criteria by including the age factor and deleting transaminase. The acute physiology and chronic health evaluation II system of disease severity assessment was developed by Knaus et al.<sup>2</sup> The severity scoring system of the acute physiology and chronic health evaluation (APACHE II) was applied by Larvin and McMahon in the setting of acute pancreatitis and it was demonstrated that those with scores higher than 7 were likely to have severe disease.<sup>7</sup> The APACHE II system is complex and has a low accuracy rate in identifying local complications.

The acute phase reactant C-reactive protein (CRP) is the best established and most available predictor of inflammation.<sup>8,9</sup> Serum CRP is an acute phase reactant, which is elevated in various inflammatory conditions, and serves as a non-specific inflammation marker. It is easy and economical to measure the serum CRP level. CRP is a proven predictor of severity for acute pancreatitis when serum level over 120 mg/L is measured within 48 hours after the onset of symptoms. IL-6 is the principal cytokine mediator of synthesis of acute phase proteins like CRP and fibrinogen. Levels of >400 pg/ml is indicative of inflammation.<sup>10</sup>

The purpose of present study is to assess the predictive value of the various methods for assessing the severity of pancreatitis and to make an attempt to find out the method which can predict the severity at an early stage and help guide the further management and reduce morbidity and mortality related to it.

## METHODOLOGY:

The present study was conducted at the Department of General Surgery, V.S. General Hospital, Ahmedabad. The Study population consisted of first 50 cases of acute pancreatitis fulfilling the inclusion criteria. It was a prospective study.

### **Inclusion Criteria:**

All patients with diagnosis of acute pancreatitis above 18 years of age were included in the study if they did not fall in the exclusion criteria.

### **Exclusion Criteria:**

Patients with previous history of attacks of acute pancreatitis, patients with traumatic pancreatitis and those with immunosuppression were excluded from the study.

### **Methodology:**

All patients presenting to the hospital, from August 2014 to May 2016, with diagnosis of acute pancreatitis not falling in the exclusion criteria were evaluated and followed up for 6 months. Diagnosis of acute pancreatitis was based on typical clinical history of severe acute onset upper abdominal pain radiating to back, persisting for more than 24 hours and associated with raised serum amylase and/or serum lipase more than 3 times to the upper limit of normal.

Written informed consent was obtained from all patients for the willingness to participate in the study. The patient had the right to opt out of the study without compromising their right to get treatment.

All patients underwent the following investigations at the time of admission:

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- . Hemoglobin, Hematocrit, Total leukocyte count (TLC)
  - . Liver function tests including total serum albumin (in g/dl)
  - . Blood urea and Serum creatinine
  - . Serum Electrolytes
  - . Serum Amylase
  - . Serum Lipase
  - . Random blood sugar
  - . Serum Calcium

- . Ultrasound Abdomen to rule out any other associated pathology, gall stones, common bile duct stone & size of common bile duct. APACHE-II scoring was done at the time of admission and at 72 hours. Value of  $\geq 8$  at admission and at 72 hours was taken as indicator of severe acute pancreatitis. CRP estimation was carried at the time of admission and at 72 hours. Cut off value of  $>12\text{mg/dl}$  was taken as indicator of severe acute pancreatitis. IL-6 estimation was done at the time of admission and at 72 hours after. Severity of pancreatitis was correlated with serum levels of IL-6, with severity being stamped at  $> 400\text{ pg/ml}$  Contrast Enhanced CT abdomen was done at 72 hours. CT severity index (CTSI) was calculated by combining the scores of pancreatic inflammation and pancreatic necrosis. An index of 5 & above was taken as severe acute pancreatitis. Severity of acute pancreatitis was assessed on the basis of APACHE II scoring, CRP estimation, IL-6 estimation and Contrast Enhanced Computed Tomography findings and compared with each other to determine the prognosis and further management. All these patients were managed as per the standard guidelines for acute pancreatitis.

Assessment of severity was performed at admission and at 72 hours on the basis of Atlanta classification i.e. local complications or development of organ failure or both. Severe acute pancreatitis was defined based on systemic and local complications.

The systemic complications included in the severity were:

- Organ failure: Shock (systolic blood pressure  $<90\text{ mm Hg}$ ), Pulmonary failure ( $\text{PaO}_2 <60\text{mm Hg}$ ), Renal failure (creatinine level  $>2\text{ mg/dl}$  after rehydration) or Gastrointestinal bleeding ( $>500\text{ ml/24 hours}$ )
- Systemic fibrinolysis: Disseminated intravascular coagulation (platelets  $\square 100,000$  /cubic mm, fibrin split products  $>80\text{ } \square \square \text{g/dl}$ )
- Severe metabolic disturbance: Serum calcium level  $<7.48\text{ mg/dl}$

The local complications in the severity were:

- Pancreatic necrosis (an area of more than 3 cm diameter or involving more than 30% of pancreas in CT and contrast density increase  $< 50$  Hounsfield units in the area of necrosis after intravenous administration of contrast medium. In addition, pancreatic necrosis or peripancreatic necrosis defined at surgery characterize SAP) .
- Acute fluid collections (occur early in the course of AP, and are located in or near the pancreas, and always lack a wall of granulation or fibrous tissue)
- Abscess (a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of AP or pancreatic trauma)
- Pseudocyst (a collection of pancreatic fluid enclosed by a wall of fibrous or

granulation tissue, which arises as a consequence of AP, pancreatic trauma or chronic pancreatitis).

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### **Apache-II score**

In all the patients diagnosed with acute pancreatitis, APACHE II score was calculated as per the standard guidelines at admission and at 72 hours. A score of  $\geq 8$  at admission and at 72 hours was considered significant to predict a severe attack.

### **Estimation of CRP:**

Serum CRP was determined at admission and at 72 hours at the Dept. of Biochemistry.

Cut off level for CRP was kept at  $>12$  mg/dl

### **Estimation of IL-6**

Serum IL-6 was determined at admission and at 72 hours.

Cut off level for IL-6 was kept at  $>400$ pg/ml.

ELISA designed to measure IL-6 in cell culture supernates, serum, and plasma. It contains recombinant human IL-6 and antibodies raised against recombinant human IL-6 and has been shown to accurately quantitate the recombinant factor. This assay employs the quantitative sandwich enzyme immunoassay technique.

### **Computed Tomography Severity Index**

CECT abdomen of the patients was done at 72 hours of admission, in the Dept. of Radio-Diagnosis, 64 slice Computed Tomography scanner.

Low osmolar, non-ionic, iodinated contrast was used for obtaining the contrast films. The contrast was given at a dose of 1 ml/kg body weight.

The computed tomography severity index (CTSI) is derived by assessing the degree of pancreatic and peri-pancreatic inflammation, fluid collection and parenchymal necrosis. The maximum score of CTSI is 10.

A score of  $\geq 5$  is taken as an indicator of severe acute pancreatitis.

### **RESULTS:**

The analysis of the data obtained from this study gave the following results. The tests for statistical significance were applied where appropriate. A result was considered significant when the p value was less than 0.5

### **TABLE 1. AGE DISTRIBUTION OF PATIENTS**

<b>Age interval (in years)</b>	<b>Number of Patients</b>
≤20	2
21-30	7
31-40	21
41-50	6
>50	14

The average age of the patients in this study was 42 years. The patients in the fourth decade constituted a majority of the population (42%) included in the study. A total of 4% patients were ≤20 years of age, 14% were 21 to 30 years of age, 42% were 31 to 40 years, 12% were 41 to 50 years and 28% were >50 years age group. The youngest patient in the study was 20 years old and the oldest was 65 years old.

**TABLE 2. SEX RATIO OF PATIENTS**

<b>Sex</b>	<b>Number of patients</b>
Female	15
Male	35

The study included 35 (70%) male patients and 15 (30%) female patients. The cases were recruited without any gender bias.

**TABLE 3. ETIOLOGY OF PANCREATITIS**

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<b>Etiology</b>	<b>Number of Patients</b>
Gall Stone Disease	11
Alcohol	30
Idiopathic	9

The study consisted of 11 patients of AP secondary to cholelithiasis (22%), 30 patients had alcohol (60%) as the etiology and in 9 patients a clear cause of the disease was not evident (18%).

**TABLE 4. SEVERITY OF ACUTE PANCREATITIS**

<b>Severity</b>	<b>Number of Patients</b>
Mild	40
Severe	10

The patients were classified into the mild group and the severe group as per the Atlanta Classification as described in the section of material & methods. This classification has been considered as the gold standard for this study. As per the classification, 40 (80%) patients had mild pancreatitis and 10 (20%) patients had severe pancreatitis.

**TABLE 5. CLINICAL OUTCOME**

<b>Outcome</b>	<b>Number of Patients</b>
Discharge	45
Death	5

A total of 5 (10%) deaths were recorded during the study. Out of five deaths, four were due to multiple organ failure, due to infected necrosis or pancreatic abscess & remaining one death was due to peritonitis resulting from pancreatic ascites. Rest of the patients were discharged when their clinical and biochemical parameters returned to the normal. All mortalities were recorded in the severe group as per Atlanta Classification.

**TABLE 6. COMPLICATIONS**

<b>Complications</b>	<b>Number of Patients</b>
Multiple Organ Failure	4
Necrosis	5
Infected necrosis	3
Pleural effusion	6
Pancreatic abscess	1
Pseudocyst	2
Infected pseudocyst	1
Pancreatic ascites	1

COMPARISON OF APACHE II SCORE, SERUM CRP AND IL-6 LEVELS AT ADMISSION IN DETERMINING THE SEVERITY OF ACUTE PANCREATITIS

<b>Criterion</b>	<b>Apache II Score</b>	<b>Serum CRP</b>	<b>Serum IL-6</b>
Sensitivity	80%	70%	80%
Specificity	95%	65%	90%
Positive Predictive Value	80%	33.33%	66.67%
Negative Predictive Value	95%	89.65%	94.74%

COMPARISON OF APACHE II SCORE, SERUM CRP, IL-6 LEVELS AND CTSI SCORE AT 72 HOURS IN DETERMINING THE SEVERITY OF ACUTE PANCREATITIS

<b>Criterion</b>	<b>Apache II Score</b>	<b>Serum CRP</b>	<b>Serum IL-6</b>
Sensitivity	80%	80%	80%
Specificity	100%	85%	95%
Positive Predictive Value	100%	57.14%	80%
Negative Predictive Value	95.24%	94.44%	95%

**DISCUSSION:**

Acute pancreatitis is a common ailment encountered by the surgeons, in any part of the world, and forms a good proportion of emergency admissions in emergency unit. It is of utmost importance to make an early diagnosis and assess the severity of acute pancreatitis in the beginning, to identify those patients with severe or necrotizing disease who will benefit from an early intensive care therapy. Additionally, in view of new therapeutical concepts(e.g. antibiotic therapy in severe forms) and for the evaluation of new drugs, patients should be staged into mild and

severe disease as early as possible. In most cases, it is difficult to assess the severity clinically on hospital admission. This study was conducted to compare between Apache II scoring, serum CRP, serum IL-6 levels and Contrast Enhanced Computed Tomography findings in assessing the severity of acute pancreatitis and to guide prognosis and management. This study was also aimed at identifying the investigation best suited for detection of severity of the condition at 72 hours.

Majority of patients in our study were in the age group of 31-40 years (42%) followed closely by patients over the age of 50 years (28%). The age range was 20-65 years. The average age of the patients in our study was 42 years.

In our study, males outnumbered females and the male to female ratio was 2.3:1.

AP among males is the fact that alcoholism forms the major cause of pancreatitis. Alcohol induced pancreatitis is more often seen in males. In our study, also cases related to alcoholism were males. Female patients were significantly affected with Gall stone disease as compared to male patients

The commonest etiological factor in our study was alcoholism i.e. alcohol (60%) followed by gallstones (22%). 9 patients were idiopathic (18%) in nature. In a study by W Uhl et al. the incidence of biliary tract pathology was in the range of 36-38%. Marshall J B, in a study found that biliary pathology and alcohol account for 60- 80 % cases of AP. Steinberg et al. mentioned that biliary disease is the most common cause of AP in the United States, Asia and most of Western Europe.

10 patients (20%) in our study developed severe pancreatitis according to Atlanta classification. The remaining 40 patients (80%) had mild pancreatitis. Similar results were seen in other studies. Marko Lempinen et al. noted development of severe pancreatitis in 28% of their cases. Winslet et al. recorded severe pancreatitis in 27% of admitted patients.

Out of the 50 patients in the study, there was mortality in 5 patients (10%) and all of them belonged to severe group according to the Atlanta classification. The cause of death was multiple organ failure secondary to sepsis due to infected necrosis or pancreatic abscess in 4 cases and one death due to peritonitis due to pancreatic ascites. The multiple organ failure encountered was respiratory failure. Steinberg noted a mortality of 2-9% in his study. Mannel al, Banerjee et al, and Grönroos et al. separately noted that in acute pancreatitis the average mortality rate approaches 2-10%. The probable reason for the increased mortality rate in our study may be due to the fact that the sample size in the severe group was small.

The various complications noted in our patients belonging to the severe group (n=10) in order of frequency were necrosis (5/10), pleural effusion (6/10), multiple organ failure (4/10), infected necrosis (3/10), pancreatic abscess (1/10), pseudocyst (2/10), pancreatic ascites (1/10). The mild group also showed <30% necrosis in 2 patients (2/20) and one patient of the two presented later during follow-up with infected pseudocyst. Beger et al. noted the incidence of complications in the natural history of pancreatitis as being pancreaticoedema in 71%, sterile necrosis in 14%, infected necrosis in 6%, pancreatic abscess in 3% and pseudocysts in 6 % cases. Viedma et al, Lankisch et al, and Toh et al. noted that respiratory failure was the most common type of organ failure in AP.

## **CONCLUSION:**

In conclusion, we would like to state that, Apache II score or serum IL-6 can be used as a prognostic indicator of severity of AP at admission, based on which a proper triage and further management can be initiated for the correction of systemic complications. Once the condition of the patient stabilizes and 72 hours have elapsed, a CECT abdomen scan of the patient is to be done for the proper staging of the patient based on local complications and for guiding the management of the same.

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