

## Original Research Article

# C-reactive protein levels in acute pancreatitis and its clinical significance

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### ABSTRACT

**Background:** Acute pancreatitis is one of the most common problems faced by surgeon in their practice. Alcohol being one of the most important etiology in country like India. The most common line of management has always been conservative until and unless surgery is indicated for its complications. Till date amylase and lipase have been used as diagnostic tool for it however certain prognostic tools like CRP are still under evaluation. Thus we have made an attempt to evaluate its significance as a prognostic tool in this study.

**Methods:** A hospital based observational comparative prospective study was done with 100 patients to measure C-reactive protein (CRP) levels in patients of acute pancreatitis and evaluate if CRP levels predict the severity of pancreatitis.

**Results:** The mean serum CRP level of patients with Ranson's score <3 was significantly higher as compared to mean serum CRP level of patients with Ranson's score  $\geq 3$  ( $10.54 \pm 5.00$  mg/l vs  $7.29 \pm 3.94$  mg/l). There was significant association of serum CRP and Ranson's score of patients.

**Conclusions:** The rapid response of CRP to changes in the intensity of the inflammatory stimulus suggests that it might be valuable in the assessment and monitoring of acute pancreatitis. It was observed in our study that measurement of CRP level is a simple method to assess the severity of disease.

**Keywords:** C-reactive protein, Acute pancreatitis, Ranson's score

### INTRODUCTION

In India acute pancreatitis, has been a major cause of morbidity and mortality and elsewhere. With an increasing incidence in alcoholism and biliary diseases, the major etiological factors, the incidence of acute pancreatitis is expected to increase.<sup>1</sup>

Acute pancreatitis is known to man from pre-Christ periods as the death of Alexander the Great (356-323 BC) at the age of 33 years is ascribed due to acute necrotising pancreatitis secondary to his chronic alcoholism. Wirsung

in the 17<sup>th</sup> century and Halsted in early 19th century made extensive studies on the organ and this disease condition.

Early descriptions of pancreatitis were based on the biliary etiology classically described by Opie in his paper in 1900 where in he proposed the Common channel theory.<sup>1</sup>

In 1925 Moynihan made the classical statement- "Acute pancreatitis is the most terrible of all calamities that occur in relation with abdominal viscera. The suddenness of onset, the illimitable agony which accompanies it and the

mortality attendant upon it renders it the most formidable of all catastrophes".<sup>2</sup>

Ranson in 1974, was the first to introduce a scoring system for risk stratification of patients with acute pancreatitis and to assess the mortality and morbidity for each particular patient.<sup>3</sup>

Early surgery was the rule in acute pancreatitis till 1970s. Trapnell after extensive studies published paper in 1967 describing early surgery to be positively harmful and should be avoided.<sup>3</sup> This was later on confirmed by Ranson.<sup>4</sup>

Most of the initial studies on acute pancreatitis were based on biliary etiology. But later on alcoholism was found to be a significant etiological agent especially in males. Geographical variations are noted in the etiological factors described with most of the recent European studies show biliary etiology to be predominant compared to the Asian studies show alcohol as the more significant etiological factor.

Serological evaluation of lipase and amylase has become the gold standard for diagnosing acute pancreatitis. Even though many extensive and complicated scoring systems have come, Ranson's scoring system is still the easiest and is most commonly followed.

Conservative management has become the gold standard in managing acute pancreatitis. Surgery has a minimal role in acute disease and only in cases of biliary pancreatitis, infected pancreatic necrosis and abscess formation. Overall mortality has reduced since the institution of early diagnostic techniques and effective conservative management.

This condition is well known for its recurrence and development of a large number of abdominal complications like ascites, pseudocyst, necrosis, abscess, venous thrombosis and aneurysms, and intestinal complications, which may require surgery.

One of the major causes of acute pain in the abdomen is acute pancreatitis. The variation has been noted in its clinical presentation. No complications were seen in most of the patients recovered from it. However; in some patients the complications like pancreatic ascites and necrosis have been noted, which are severe in nature; and high mortality and morbidity is noted in these patients.

In most patients, the condition is mild and resolves spontaneously, but some patients present with a florid and rapidly deteriorating inflammatory process associated with prolonged hospitalization, significant morbidity and mortality ranging between 30% and 50%. The pathogenic mechanism causes the auto-digestion of pancreas and an intense inflammatory response mediated by the immune system, which is done via the zymogens activation synthesized by pancreas. The inflammatory reaction may

be restricted to the pancreas or may progress to a systemic inflammatory response syndrome (SIRS).

The immune response does not depend on the instigating factor but is responsible for most of the subsequent damage. A detailed understanding of the pathogenic mechanisms is essential to facilitate early and effective intervention in severe pancreatitis which has high morbidity and mortality. However, means of identifying which particular case will develop a severe variety of acute pancreatitis have been lacking. Various clinical, biochemical and imaging criteria have been proposed as predictors of severity of acute pancreatitis.

The role of diagnostic markers (pancreatic enzymes such as amylase and lipase) as prognostic indicators has been a failure. Other biochemical markers like C-reactive protein (CRP), pro-calcitonin and the like are under evaluation as prognostic indicators. CRP estimation is cheap and easily available. In this study an attempt has been made to see if a single and early estimation of CRP levels is an effective predictor of morbidity and mortality in acute pancreatitis.

Hence the present study was done at our tertiary care centre to assess the role of CRP levels in acute pancreatitis and its prognostic significance.

## **METHODS**

### ***Study design***

Observational study-prospective study design.

### ***Source of data***

Patients presenting with acute pancreatitis of to OPD or to the department of Surgery of Bharati Hospital, Pune from august 2017 to august 2018.

### ***Sample size***

A total of 100 patients.

### ***Inclusion criteria***

Patients aged between 18-65 years were presented with acute pancreatitis characterized by elevated serum amylase, serum lipase and urinary amylase.

### ***Exclusion criteria***

- Chronic pancreatitis.
- Age <18 years and >65 years.

### ***Protocol of the procedure***

- Inclusion and exclusion criteria will be applied to patients presenting with acute pancreatitis to the department of Surgery-Bharati Hospital, Pune only.

- Patients will be educated about the study and only those patients consenting to participate in the study will be included. Written informed consent as given in appendix 1 will be taken from every participant included in the study.
- Database collection will include documentation of medical history, age, sex, prehospital interval, vital signs, abdominal signs, alcohol intake and duration, drug history. Blood will be drawn routinely on arrival of the patient to the Department of Surgery for whole blood cell count with differential count, platelet count, serum amylase and lipase.
- CRP level determination will be performed on the same serum sample drawn for other biochemical tests. The drawn blood will be put in different vacutainers and labelled accordingly for the different tests. If there is not enough serum for performing CRP level determination then that sample will be discarded and a fresh sample will be drawn.
- The serum sample for estimation of CRP levels will be stored at  $-70^{\circ}\text{C}$  immediately after centrifugation. The sample will be processed only after all collected samples are completed.

Patients presenting included in the study will have to undergo total and differential leukocyte counts, serum amylase, serum lipase, urinary amylase and CRP level estimation. For this patients included in the study will be informed regarding their inclusion and a written informed consent will be taken for all the patients included in the study. The institutional ethical committee approval was sought for the present study.

#### Statistical analysis

Quantitative data is presented with the help of mean and standard deviation. Comparison among the study groups is done with the help of unpaired t-test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table.

Association among the study groups is assessed with the help of Fisher test, student 't' test and Chi-square test. P value less than 0.05 is taken as significant.

## RESULTS

A hospital based observational prospective study was done with 100 patients to measure CRP levels in patients of acute pancreatitis and evaluate if CRP levels predict the severity of pancreatitis. The following observations were noted.

Majority of the patients (32%) were in the age group of 31-40 years followed by 27% patients in the age group of 21-30 years, 16% patients in the age group of 51-60 years, 14% patients in the age group of 41-50 years, 7% patients in the age group of 61-65 years and 4% patients in the age group of 18-20 years. The mean age of the patients was  $38.33 \pm 12.92$  years (Table 1).

There were 63% male patients while female patients constituted 37% of the study group (Table 2).

The mean age of male patients was comparable to the mean age of female patients ( $37.92 \pm 13.16$  vs.  $39.03 \pm 12.66$  years). The difference was statistically not significant as per Student t-test ( $p > 0.05$ ) (Table 3).

**Table 1: Distribution of patients according to age.**

Age (in years)	N	%
18-20	4	4
21-30	27	27
31-40	32	32
41-50	14	14
51-60	16	16
61-65	7	7
<b>Total</b>	100	100
<b>Mean<math>\pm</math>SD</b>	$38.33 \pm 12.92$	

**Table 2: Distribution of patients according to gender.**

Gender	N	%
Male	63	63
Female	37	37
<b>Total</b>	100	100

**Table 3: Age and gender distribution of patients.**

Age (in years)	Male		Female		Total		P value
	N	%	N	%	N	%	
18-20	3	3	1	1	4	4	>0.05
21-30	17	17	10	10	27	27	
31-40	20	20	12	12	32	32	
41-50	9	9	5	5	14	14	
51-60	9	9	7	7	16	16	
61-65	5	5	2	2	7	7	
<b>Total</b>	63	63	37	37	100	100	
<b>Mean<math>\pm</math>SD</b>	$37.92 \pm 13.16$		$39.03 \pm 12.66$		$38.33 \pm 12.92$		

The most common etiology was gallstones (87%) followed by alcohol (6%), choledochal cyst (4%) and viral infection (3%) (Table 4). 88 (88%) patients had Ranson's score of <3 while 12 (12%) patients had Ranson's score of  $\geq 3$  (severe acute pancreatitis) (Table 5).

The most common complications was fluid collection [acute peri-pancreatic fluid collection (APFC) or acute necrotic collection (ANC)] (12%) followed by ascites (7%), pancreatic pseudocyst (3%) and pancreatic necrosis (1%) (Table 6).

The mean WBC and blood glucose of patients were  $13559.00 \pm 5617.79$  cells/mm<sup>3</sup> and  $134.86 \pm 52.78$  mg/dl respectively while the serum AST and serum LDH values of patient were  $59.71 \pm 53.31$  IU/l and  $284.54 \pm 366.02$  IU/l respectively. The mean amylase and lipase values of patients were  $747.58 \pm 805.44$  U/l and  $2417.20 \pm 2457.63$  U/l respectively (Table 7).

**Table 4: Distribution of patients according to etiology.**

Etiology	N	%
Gall stones	87	87
Alcohol induced	6	6
Choledochal cyst	4	4
Viral infection	3	3
Total	100	100

**Table 5: Distribution of patients according to Ranson's score.**

Ranson's score	N	%
<3	88	88
$\geq 3$	12	12
Total	100	100

**Table 9: Association of serum CRP and sex of patients.**

Serum CRP	Sex				Total		P value
	Male		Female				
	N	%	N	%	N	%	
<6 mg/l	15	15	9	9	24	24	>0.05
6-150 mg/l	48	48	28	28	76	76	
Total	63	63	37	37	100	100	
Mean $\pm$ SD	10.25 $\pm$ 4.95		9.97 $\pm$ 5.09		10.15 $\pm$ 4.98		

The mean serum CRP level of patients with Ranson's score <3 was significantly higher as compared to mean serum CRP level of patients with Ranson's score  $\geq 3$  ( $10.54 \pm 5.00$  mg/l vs.  $7.29 \pm 3.94$  mg/l). There was significant association of serum CRP and Ranson's score of patients as per Student t-test ( $p < 0.05$ ).

## DISCUSSION

A hospital based observational prospective study was done with 100 patients to measure CRP levels in patients

24 (24%) patients had normal CRP level (<6 mg/l) while 76 (76%) patients had elevated CRP levels (6-150 mg/l). The mean CRP level of patients was  $10.15 \pm 4.98$  mg/l (Table 8).

The mean serum CRP level of male and female patients was comparable ( $10.25 \pm 4.95$  vs.  $9.97 \pm 5.09$  mg/l) and statistically not significant as per Student t-test ( $p > 0.05$ ) (Table 9).

**Table 6: Distribution of patients according to complications.**

Complications	N	%
Fluid collection	12	12
Ascites	7	7
Pancreatic pseudocyst	3	3
Pancreatic necrosis	1	1

**Table 7: Baseline parameters of patients.**

Parameters	Mean	SD
WBC (cells/mm <sup>3</sup> )	13559.00	5617.79
Blood glucose (mg/dl)	134.86	52.78
Serum AST (IU/l)	59.71	53.31
Serum LDH (IU/l)	284.54	366.02
Amylase (U/l)	747.58	805.44
Lipase (U/l)	2417.20	2457.63

**Table 8: Serum CRP levels of patients.**

Serum CRP (mg/L)	N	%
<6 mg/l	24	24
6-150 mg/l	76	76
Total	100	100
Mean $\pm$ SD	10.15 $\pm$ 4.98	

of acute pancreatitis and evaluate if CRP levels predict the severity of pancreatitis.

Acute pancreatitis is an acute inflammation of the pancreas presenting clinically with acute abdomen.<sup>5</sup> The severe form of the disease associated with macroscopic hemorrhage and fat necrosis in and around the pancreas. It is important to identify those patients with acute pancreatitis who have an increased risk of mortality.

An important point with CRP is that although it is one of the earliest acute-phase reactants that increase in level, CRP level higher than 170 mg/dl at 48 hours has been reported to be more valuable for predicting severe acute pancreatitis and pancreatic necrosis than CRP level measurements at any time before 48 hours.<sup>6</sup> Further, the importance of CRP lies in its value for predicting the healing of acute pancreatic inflammation as follow-up CRP levels will correctly reveal which patients will develop complications or which will heal uneventfully.<sup>7</sup> Combining serum CRP level measurements taken at 48 hours later will improve the Ranson scoring system for having a higher accuracy for the differentiation of the mild and severe forms of AP.

Del et al suggested that the early diagnosis is mandatory for successful treatment and in acute pancreatitis most widely used scoring systems are often cumbersome and difficult to use in clinical practice because of their multifactorial nature.<sup>7</sup> So the number of uni-factorial prognostic indices has been employed in routine hospital practice in which CRP is the one of estimation. CRP and S-phospholipase A2 determinations are valuable in the early assessment of the severity of acute pancreatitis, but the CRP assay is much easier to include in hospital routine.

In the present study, majority of the patients (32%) were in the age group of 31-40 years followed by 27% patients in the age group of 21-30 years, 16% patients in the age group of 51-60 years, 14% patients in the age group of 41-50 years, 7% patients in the age group of 61-65 years and 4% patients in the age group of 18-20 years. The mean age of the patients was 38.33±12.92 years.

There were 63% male patients while female patients constituted 37% of the study group. The mean age of male patients was comparable to the mean age of female patients (37.92±13.16 vs. 39.03±12.66 years). The difference was statistically not significant as per Student t-test (p>0.05). This is similar to the studies of Parmar et al, Kaplan et al and Trivikraman et al.<sup>8-10</sup>

Parmar et al hospital based study evaluating the C-reactive protein in acute pancreatitis by semi quantitative method and its correlation with prognosis found majority of cases (54%) were seen in 21-40 years of age group followed by 24% patients were seen in more than 55 years of age group and overall male to female ratio was 1.77: 1. Common age group for female was 40-60 years. It was common in females between 50-60 years.<sup>8</sup>

Kaplan et al study investigating the prognostic importance of platelet-lymphocyte ratio (PLR) and neutro-phil-lymphocyte ratio (NLR) combination for patients diagnosed with acute pancreatitis and its relationship with mortality found out of 142 patients 84 were female (59.2%) and 58 male (40.8%).<sup>9</sup> The mean age of the patients was 61.6±17.4 years.

Trivikraman et al cross-sectional study found out of 100, 86 were males and 14 were females. Majority of the patients were in the age group of 30-40 years (29%).<sup>10</sup>

The most common etiology in our study was gallstones (87%) followed by alcohol (6%), choledochal cyst (4%) and viral infection (3%). This is comparable to the studies of Parmar et al, Kaplan et al Trivikraman et al and Vijayakumar.<sup>8-11</sup>

Parmar et al hospital based study evaluating the C-reactive protein in acute pancreatitis by semi quantitative method and its correlation with prognosis reported cholelithiasis was common in female age >40 years.<sup>8</sup> In male it was common between 20-40 years because of alcohol consumption.

Kaplan et al study investigating the prognostic importance of platelet-lymphocyte ratio and neutro-phil-lymphocyte ratio combination for patients diagnosed with acute pancreatitis and its relationship with mortality found most common etiology was gallstones (n:117).<sup>9</sup> Alcohol use (2.8%), hypertriglyceridemia (2.1%), hereditary reasons (8.5%), ERCP complication (1.4%) were the other causes.

Trivikraman et al cross-sectional study observed among the various etiological factors of acute pancreatitis, 65% was due to alcohol, followed by gall stones (17%) and idiopathic pancreatitis (13%).<sup>10</sup> Most common etiology among males was alcohol (65%) and most common etiology among female was gall stones (12%).

Vijayakumar study evaluating C-reactive protein as a predictor of severity of AP observed 36 patients with severe AP had alcohol-induced disease, 5 patients had a gallstone related disease, and 7 had acute pancreatitis of unknown etiology.<sup>11</sup> In the mild group, 76 patients had alcohol-induced disease, 16 patients had gallstone related pancreatitis, and 10 patients had AP of other etiologies. In the severe-disease group, 29 (61%) of 48 patients had >30% pancreatic necrosis or other local complications on contrast-enhanced CT, 26% (55%) had organ failure.

In our study, 88 (88%) patients had Ranson's score of <3 while 12 (12%) patients had Ranson's score of ≥3 (severe acute pancreatitis). This is consistent with the study of Kaplan et al.<sup>9</sup>

Kaplan et al study investigating the prognostic importance of PLR and NLR combination for patients diagnosed with acute pancreatitis and its relationship with mortality reported 60.6% had a Ranson score of 02 (n:86), 28.2% had a Ranson score of 3-4 (n:40), and 11.3% had a Ranson score of 5-6 (n:16).<sup>9</sup>

The most common complications in the present study was fluid collection by APFC or ANC (12%) followed by ascites (7%), pancreatic pseudocyst (3%) and pancreatic

necrosis (1%). This was concordant to the study of Kaplan et al.<sup>9</sup>

Kaplan et al study investigating the prognostic importance of PLR and NLR combination for patients diagnosed with acute pancreatitis and its relationship with mortality observed. In terms of pancreatitis associated complications, 4.9% of the patients had acute renal failure (ARF) (n:7), 3.5% had abscess (n:5), 2.8% had sepsis (n:4), 4.9% had pseudocyst (n:7), 1.4% had ascites (n:2), 1.4% had hematoma (n:2), 1.4% had cholangitis (n:2), and 9.2% other pancreatitis complications.<sup>9</sup>

It was observed in the present study that the mean WBC and Blood glucose of patients were  $13559.00 \pm 5617.79$  cells/mm<sup>3</sup> and  $134.86 \pm 52.78$  mg/dl respectively while the serum AST and serum LDH values of patients were  $59.71 \pm 53.31$  IU/l and  $284.54 \pm 366.02$  IU/l respectively. The mean amylase and lipase values of patients were  $747.58 \pm 805.44$  U/l and  $2417.20 \pm 2457.63$  U/l respectively.

24 (24%) patients in our study had normal CRP level (<6 mg/l) while 76 (76%) patients had elevated CRP levels (6-150 mg/l). The mean CRP level of patients was  $10.15 \pm 4.98$  mg/l. These findings were consistent with the studies of Parmar et al, Trivikraman et al and Vijayakumar.<sup>8-11</sup>

Parmar et al hospital based study evaluating the CRP in acute pancreatitis by semi quantitative method and its correlation with prognosis observed 48 (96%) patients had elevated CRP level, out of 50, 22 patients (44%) had C-reactive protein level between 6 mg/l to 150 mg/l and 26 patients (52%) had CRP level >150 mg/l, found to be significant ( $p < 0.05$ ) to predict the severity of acute pancreatitis.<sup>8</sup>

Kaplan et al study investigating the prognostic importance of PLR and NLR combination for patients diagnosed with acute pancreatitis and its relationship with mortality reported number of patients with a Ranson score of 5-6 was found to be higher in the high-risk group compared to other groups.<sup>9</sup> 40% mortality score was found in 70% of the high-risk group, 20% of the medium risk group, and 3.7% of the low-risk group.

Trivikraman et al cross-sectional study reported CRP levels were found to be in moderate agreement with CT severity index with a sensitivity of 66.7%, specificity of 86.3%, positive predictive value of 64.3% and a negative predictive value of 87.5% and a K score of 0.524.<sup>10</sup> Trivikraman et al cross-sectional study observed on the basis of CRP levels >150, severe pancreatitis was diagnosed in 16% alcoholic pancreatitis, 9% gall stone pancreatitis and 1% each of idiopathic, malignancy and trauma induced pancreatitis.<sup>10</sup>

Vijayakumar study evaluating CRP as a predictor of severity of AP reported 22 of the mild disease had raised

CRP levels on admission and 34 at 48 hours and all 14 pts who had higher than 210 mg/dl on admission developed severe disease.<sup>11</sup>

Joshi et al observed a marked variation was seen in CRP levels of two groups of extensive pancreatic necrosis and minimal pancreatic necrosis indicating that in individual cases CRP alone is not a good indicator of necrosis.<sup>12</sup>

In the present study, the mean serum CRP level of male and female patients was comparable ( $10.25 \pm 4.95$  vs.  $9.97 \pm 5.09$  mg/l) and statistically not significant as per Student t-test ( $p > 0.05$ ). The mean serum CRP level of patients with Ranson's score <3 was significantly higher as compared to mean serum CRP level of patients with Ranson's score  $\geq 3$  ( $10.54 \pm 5.00$  mg/l vs.  $7.29 \pm 3.94$  mg/l). There was significant association of serum CRP and Ranson's score of patients as per Student t-test ( $p < 0.05$ ). Similar observations were noted in the results of Kaplan et al, Trivikraman et al, Vijayakumar, Joshi et al, Ustundag et al, Sharma et al, Gurleyik et al, Pezzilli et al.<sup>9-16</sup>

Ustundag et al study on CRP for determining the severity of AP the help of the Ranson scoring system reported out of the 4 groups patients in group 3 had the highest accuracy (92%) among those in the other groups (Group 1: 80%, Group 2: 88%, and Group 4: 76%) for making a differentiation between the mild and severe forms of AP.<sup>13</sup> The combination of a Ranson score of  $\geq 3$  with a CRP level of  $\geq 150$  mg/dl in Group 3 was understood to be more valuable and accurate than only CRP level elevation in the setting of existing acute biliary and or gall bladder inflammatory pathologies.

Sharma et al study on determining the CRP in acute pancreatitis relation to the severity of process and to the nature of the tissue reaction reported out of 20 patients of acute pancreatitis, 12 were having severe disease with CRP level between 96-192 mg/l, while in mild disease 7 patients were having severe disease with CRP level between 24-48 mg/l and only 1 patient was having normal CRP level i.e., below 6 mg/l.<sup>14</sup>

Gurleyik et al study found that Ranson score 4 or above, APACHE II score 8 or above, baseline IL-6, and C-reactive protein level 150 mg/l respectively were regarded as strong predictors of acute pancreatitis. C-reactive protein level at 24, 48, 72 hour ( $p = 0.02$ ) were significantly high. The sensitivity was 83.3% and specificity was 71% and accuracy was 73.3%.<sup>15</sup>

Pezzilli et al found that CRP greater than 100 mg/l indicate severe acute pancreatitis in 60-80% of patients.<sup>16</sup>

## CONCLUSION

Acute pancreatitis is a protean disease capable of wide clinical variation, ranging from mild discomfort to apocalyptic prostration. One of the first acute-phase

reactants rising in level in our body during every kind of inflammation and/or infection is the CRP. The rapid response of CRP to changes in the intensity of the inflammatory stimulus suggests that it might be valuable in the assessment and monitoring of acute pancreatitis. It was observed in our study that measurement of CRP level is a simple method to assess the severity of disease.

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