

Role of Serum Interleukin-6 and C-reactive Protein in Early Prediction of Severe Acute Pancreatitis

Abstract

Background: Early prediction of severity is an important goal in acute pancreatitis (AP), to identify 20% of patients who are likely to have a severe course. Such patients have an expected mortality of 15–20% and may benefit from early admission to high dependency or intensive care units, with parenteral or nasojejunal feeding and prophylactic antibiotics. In severe AP (SAP), multiorgan dysfunction accounts for most of early deaths. **Aims:** The aim of this article is to assess the role of serum interleukin (IL)-6 and serum C-reactive protein (CRP) in early prediction of severity of AP. **Materials and Methods:** This observational analytical study was conducted in the Department of General Surgery and Department of Biochemistry in our hospital in 62 patients as per inclusion and exclusion criteria. **Results:** IL-6 on day 1 and day 2 as well as CRP on day 2 was 100% sensitive but IL-6 on day 1 and day 2 had a maximum specificity of 88.37% among them when compared with a specificity of 81.4% of CRP on day 2. Though CRP on day 1 also had a specificity of 88.37%, its sensitivity was 89.47%. **Conclusion:** IL-6 and CRP together appear to be a promising marker for assessing the severity of AP within 48 h. We recommend to do IL-6 and CRP in patients with AP, which can help in predicting severity of the disease in patients.

Keywords: Acute pancreatitis, C-reactive protein, early prediction, interleukin-6, severity score

Introduction

Acute pancreatitis (AP) is an inflammatory disease of pancreas of highly variable severity, ranging from mild cases with low mortality to severe cases with high mortality. Initial clinical assessment alone identifies fewer than half the patients with severe AP (SAP).^[1,2] The annual incidence of AP ranges from 5 to 30 per 100,000 population.^[3,4] Gallstones and alcohol are the two main causes of AP. Approximately 50–70% of AP cases are caused by gallstones.^[3,4] Increasing age, male gender, and lower socio-economic class are associated with a higher incidence of AP.^[3]

Scoring systems incorporating clinical, biochemical, or radiological criteria for severity assessment have been in use for more than a decade. These include the criteria described by Ranson (11 criteria) in the 1970s, the Glasgow score (8 criteria),^[5,6] and the Acute Physiology and Chronic Health Evaluation (APACHE II) score (14 criteria).^[7] The sensitivity and specificity of these scoring systems for predicting SAP range between 55%

and 90%, depending on the cutoff number and the timing of scoring.^[8] The predictive value of these scoring systems is improved by the addition of information provided by abdominal computed tomography (CT). Balthazar^[9] developed a CT severity index (CTSI), with an index of ≥ 7 having a 92% positive predictive value for a severe course of AP. If done on day 4 following symptom onset, the sensitivity for detecting pancreatic necrosis was 100%.

Severity of the disease is classified as mild, moderate, and severe by the absence or presence of organ failure and local or systemic complications as described in the Modified Atlanta classification. Moderately SAP has transient organ failure of < 2 days or 48 h, whereas SAP is defined by the presence of persistent organ failure for ≥ 2 days or 48 h. Although the revised Atlanta classification of AP is simple and will help the clinician to predict the outcomes of patients with AP, it is unable to differentiate between moderately SAP and SAP before 48–72 h after onset. Due to this shortfall among these scoring systems, a less complex method is required to predict severity and outcome of AP earlier,

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which clinicians can use bedside. Serum amylase and lipase, the standard tests for AP diagnosis, are poor predictors of severity. Markers for the early prediction of AP severity include the pancreatic pro-enzyme trypsinogen-2 and its subunit trypsinogen activation peptide, as well as early inflammatory response markers such as serum interleukin (IL)-6, procalcitonin, polymorphonuclear elastase, and serum amyloid A. The more established marker C-reactive protein (CRP) has been shown to be a severity predictor at 48 h post-symptom onset if a cutoff level of 150 mg/dL is being used. Single laboratory markers for predicting the severity of AP have been investigated, but promising initial results have not always been confirmed in later studies. This study was done to assess the role of serum IL-6 and serum CRP in early prediction of severity of AP.

Aim and objectives

Role of serum IL-6 and CRP in early prediction of SAP is by: (a) correlating the serum levels of IL-6 and CRP on days 1 and 2 in cases of AP with revised Atlanta classification and (b) correlating the levels of IL-6 and CRP with modified CTSI.

Materials and Methods

This observational analytical study was conducted in the Department of General Surgery and Department of Biochemistry, ESI-PGIMS and Model Hospital, New Delhi, India, after obtaining permission from the Institutional Ethical Committee for a period of 2 years.

Sample size

Using the formula for observational study

$$N = \frac{Z_{\alpha}^2 pq}{d^2},$$

where Z is the ordinate of standard normal distribution at $\alpha\%$ level of significance, and p is the observed sensitivity.

$$q = 1 - p,$$

d is the margin of error.

Assuming $(p)=80\%$ as the sensitivity from previous studies with 10% margin of error, the minimum required sample size at 5% level of significance is 62 patients.

Inclusion criteria

- Age group >18 and <70 years (both male and female)
- All patients attended emergency/OPD with diagnosis or diagnosed as case of AP.
- Patients willing to participate in the study.

Exclusion criteria

- Patients with chronic liver disease
- History of liver abscess <3 months

- Recurrent AP <3 months
- Chronic pancreatitis (\pm calcific)
- Severe cardiac disease
- Pregnancy

Along with all routine examination and investigations, tests that were specific to this study were done as follows:

- Serum CRP on days 1 and 2;
- Serum IL-6 on days 1 and 2;
- Contrast-enhanced computed tomography abdomen had been done on day 5 in all the patients and at the end of 4th week in unresolved cases only.

These patients were diagnosed based on clinical features and serum amylase and lipase levels. In patients with confirmed diagnosis of AP, assessment of severity of AP was done as per the revised Atlanta Classification and modified CTSI.

Observations and Results

Age

The mean age of the patients in the study was 39.21 ± 12.43 years. Most of the patients, i.e., 29.03%, were in the age group 31–40 years, whereas 24.19% of the patients were in the age group 41–50 years and 19.35% of the patients were in the age group 21–30 years, with few patients less than 20 years (5) and >50 years (12).

Gender

In this study, 45.16% (28) were females and 54.84% (34) were males.

Aetiology

Gall stone was the cause in majority [42 (67.74%)] of the patients, followed by alcohol in 11 (17.74%) and idiopathic dilated cardiomyopathy in 9 (14.52%) patients.

Severity of pancreatitis

According to the revised Atlanta classification, majority (64.52%) of the patients were categorized as mild AP and 35.48% of the patients were categorized as SAP.

According to the modified CTSI, majority (53.23%) of the patients were categorized as moderate AP followed by 30.65% of the patients as SAP and 16.13% of patients as mild AP. Mean value of the modified CTSI of study subjects was 5.13 ± 2.53 [Table 1].

Complication/sequela/mortality

In this study, complications were seen in 38.71% (24) patients. Pleural effusion was found in 18 (29.03%) patients followed by necrosis in 14 (22.58%) patients. However, seven (11.29%) patients had ascites, and very few, i.e., four patients had multi-organ dysfunction syndrome (MODS) and pseudocyst was found in only three patients. In this study, 4 out of 62 patients died due to MODS.

IL-6 and CRP

The mean value of CRP on day 1 was 8.27 ± 5.88 mg/dL which was significantly decreased to 6.35 ± 4.91 mg/dL on day 2. A significant decrease was seen in the values of IL-6 from day 1 (271.87 ± 675.94 pg/mL) to day 2 (102.13 ± 111.36 pg/mL) [Table 2].

Significant association exists between IL-6 levels and CRP levels on day 1 and day 2 with severity according to the revised Atlanta classification. IL-6 levels and CRP levels on day 1 and day 2 were significantly higher in patients categorized as SAP by the revised Atlanta classification when compared with patients categorized as mild AP. IL-6 levels on day 1 and day 2 were 74 ± 40.4 and 41.35 ± 27.94 pg/mL in patients with SAP when compared with CRP being 631.62 ± 105.45 and 212.63 ± 121.43 pg/mL on day 1 and day 2, respectively. CRP levels on day 1 and day 2 were 4.88 ± 2.9 and 3.51 ± 2.47 mg/dL, respectively, in patients with SAP when compared with patients with mild AP having CRP levels to be 14.44 ± 4.82 and 11.52 ± 3.88 mg/dL on day 1 and day 2, respectively, by the revised Atlanta classification [Table 3 and Figure 1].

The value of amylase in patients categorized as SAP was 913.73 ± 601.19 U/L and in mild AP it was 636.95 ± 313.3 U/L.

Though the value of amylase was higher in severe when compared with mild AP, the difference was not statistically significant. Therefore, no significant association was seen between amylase and severity, according to the revised Atlanta classification ($P > 0.05$).

Value of lipase as well as duration of hospital stay was significantly higher in patients categorized as SAP by the revised Atlanta classification when compared with patients categorized as mild AP ($P < 0.05$).

A significant association exists between IL-6 levels and CRP levels on days 1 and 2 with the modified CTSI. IL-6 and CRP levels on days 1 and 2 were significantly higher in patients categorized as SAP by the modified CTSI when compared with patients categorized as mild and moderate AP; the value of amylase and lipase was higher in SAP when compared with mild and moderate AP, and the difference was not statistically significant. No significant association was seen between amylase and lipase with severity according to the modified CTSI ($P > 0.05$).

Duration of hospital stay was significantly higher in patients categorized as SAP when compared with patients categorized as mild and moderate AP ($P < 0.05$) [Table 3 and Figure 2].

Table 1: Severity according to the revised Atlanta classification and modified CT severity index

Severity according to	Revised Atlanta Classification			Modified CTSI		
	Mild	Severe	Total	Mild	Moderate	Severe
Frequency	40	22	62	10	33	19
Percentage	64.52	35.48	100.00	16.13	53.23	30.65
				Mean \pm Std dev	5.13 \pm 2.53	
				Median (IQR)	4 (4–8)	

Table 2: Comparison of IL-6 and CRP of study subjects between day 1 and day 2

IL-6 and CRP	Mean \pm Std dev	Median (IQR)	P-value
CRP (mg/dL) day 1	8.27 ± 5.88	6.58 (3.750–12.170)	<0.0001
CRP(mg/dL) day 2	6.35 ± 4.91	4.21 (2.400–10.120)	
Interleukin-6 (pg/mL) day 1	271.87 ± 675.94	99.85 (54.700–182.400)	<0.0001
Interleukin-6 (pg/mL) day 2	102.13 ± 111.36	63.75 (28.300–127.300)	

Table 3: Association of severity according to the revised Atlanta classification with IL-6, CRP, amylase, lipase, and hospital days

Association table	Severity according to revised Atlanta classification				P-value
	Mild(n=40)		Severe (n=22)		
	Mean \pm Std dev	Median (IQR)	Mean \pm Std dev	Median (IQR)	
Interleukin-6 (pg/mL) day 1	74 ± 40.4	75.9 (47.800–98.050)	631.62 ± 1055.45	270.6 (179.600–564.300)	<0.0001
Interleukin-6 (pg/mL) day 2	41.35 ± 27.94	34.35 (18.950–54.600)	212.63 ± 121.43	159.1 (124.400–293.100)	<0.0001
CRP (mg/dL) day 1	4.88 ± 2.9	4.42 (3.305–6.235)	14.44 ± 4.82	13.78 (11.400–16.100)	<0.0001
CRP (mg/dL) day 2	3.51 ± 2.47	3.1 (1.925–4.120)	11.52 ± 3.88	10.94 (9.670–12.300)	<0.0001
Serum amylase (U/L)	636.95 ± 313.3	577 (373.500–899)	913.73 ± 601.19	646 (528–1196)	0.089
Lipase (U/L)	977.38 ± 545.79	932.5 (633.500–1187)	1605.41 ± 1474.52	1149 (928–1662)	0.026
Hospital stay (days)	7.7 ± 1.83	7 (6.500–9)	14.04 ± 2.24	13.5 (13–16)	<0.0001

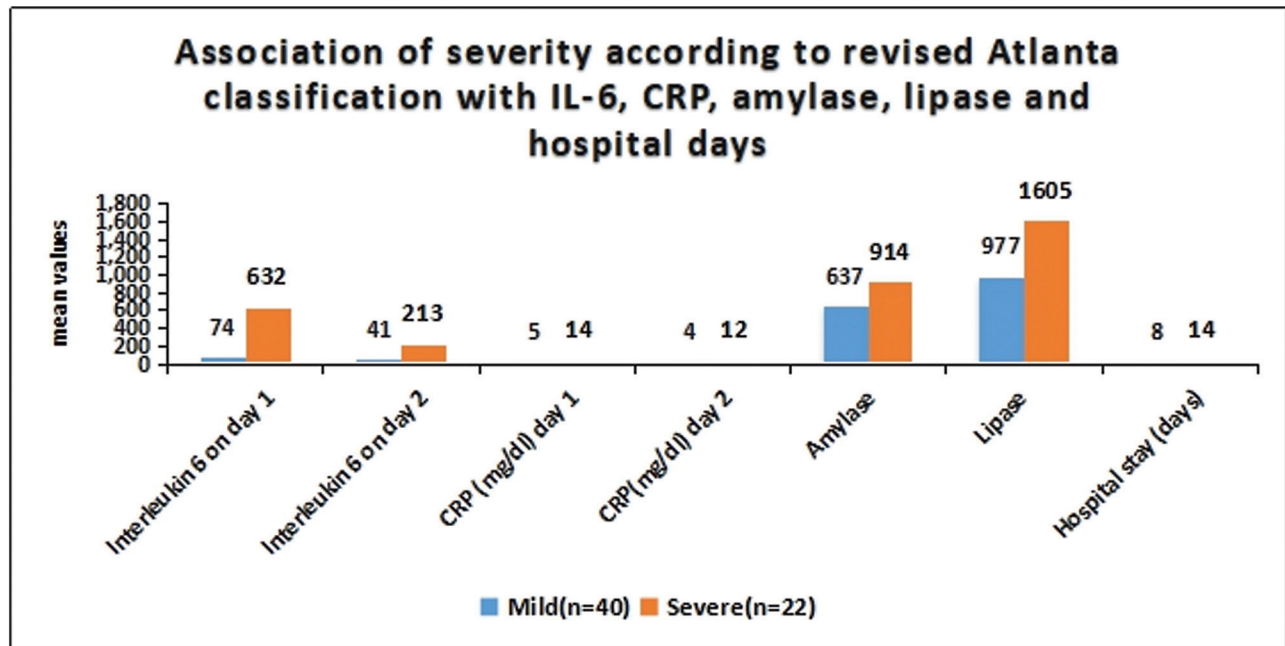


Figure 1: Association of severity according to the revised Atlanta classification with IL-6, CRP, amylase, lipase, and hospital days

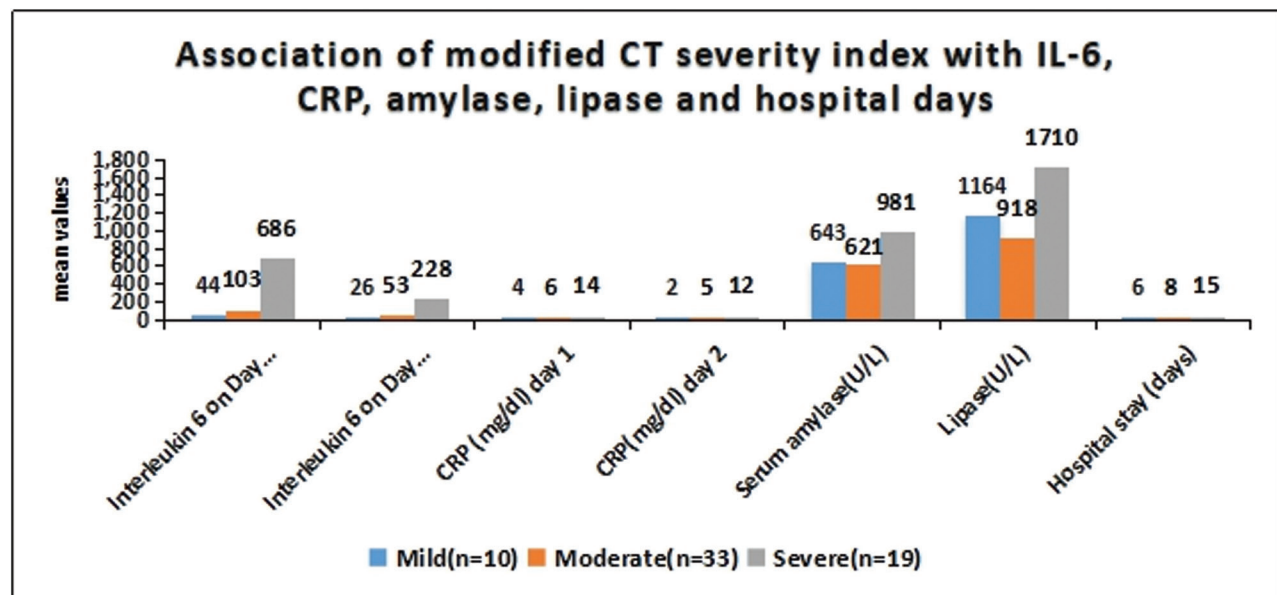


Figure 2: Association of the modified CT severity index with IL-6, CRP, amylase, lipase, and hospital days

A significant positive correlation exists between CRP levels on day 1 and day 2 and IL-6 levels on day 1 and day 2, with modified CTSI with correlation coefficients of 0.771, 0.792, 0.863, and 0.852, respectively.

A significant positive correlation exists between CRP levels on day 1 and day 2 and IL-6 levels on day 1 and day 2 with hospital days with correlation coefficient of 0.671, 0.644, 0.787, and 0.788, respectively [Table 4 and Figure 2].

Fair significant agreement exists between modified CTSI and severity according to the revised Atlanta classification with a kappa value of 0.324, as shown in Table 5 and Figure 2.

Interpretation of the area under the receiver operating characteristic (ROC) curve showed that the performance of IL-6 on day 1, IL-6 on day 2, CRP on day 1, and CRP on day 2 was excellent [area under the curve (AUC) 0.968; 95% confidence interval (CI): 0.889–0.996, AUC 0.984; 95% CI: 0.914–1.000, AUC 0.923; 95% CI: 0.826–0.975, and AUC 0.935; 95% CI: 0.842–0.982, respectively] for predicting SAP. There is always a trade-off between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity). A cutoff point at which the combination of both sensitivity and specificity gives the maximum predictive value was derived from our findings. Cutoff point of IL-6 on day 1, IL-6 on day 2, CRP on day

Table 4: Correlation of CRP and IL-6 with hospital days and modified CT severity index

Correlation table		Hospital stay (days)	Modified CT severity index
CRP (mg/dL) day 1	Correlation coefficient	0.671	0.771
	<i>P</i> -value	<0.0001	<0.0001
	<i>n</i>	62	62
CRP(mg/dL) day 2	Correlation coefficient	0.644	0.792
	<i>P</i> -value	<0.0001	<0.0001
	<i>n</i>	62	62
Interleukin-6 (pg/mL) day 1	Correlation coefficient	0.787	0.863
	<i>P</i> -value	<0.0001	<0.0001
	<i>n</i>	62	62
Interleukin-6 (pg/mL) day 2	Correlation coefficient	0.788	0.852
	<i>P</i> -value	<0.0001	<0.0001
	<i>n</i>	62	62

Table 5: Inter-rater kappa agreement of modified CT severity index and severity according to the revised Atlanta classification

Modified CT severity index	Severity according to revised Atlanta classification		Total (<i>n</i> =62)	<i>P</i> -value	Kappa
	Mild (<i>n</i> =40)	Severe (<i>n</i> =22)			
Mild	10 (16.13%)	0 (0.00%)	10 (16.13%)	<0.0001	0.324
Moderate	30 (48.39%)	3 (4.84%)	33 (53.23%)		
Severe	0 (0.00%)	19 (30.65%)	19 (30.65%)		
Total	40 (64.52%)	22 (35.48%)	62 (100.00%)		

Table 6: Receiver operating characteristic curve for predicting severe acute pancreatitis

Prediction of severe acute pancreatitis	Area under the ROC curve (AUC)	Standard error	95% Confidence interval	<i>P</i> -value	Cutoff
Interleukin-6 (pg/mL) day 1	0.968	0.0203	0.889–0.996	<0.0001	>137
Interleukin-6 (pg/mL) day 2	0.984	0.011	0.914–1.000	<0.0001	>77.3
CRP (mg/dL) day 1	0.923	0.0329	0.826–0.975	<0.0001	>9.6
CRP(mg/dL) day 2	0.935	0.0292	0.842–0.982	<0.0001	>5.6

Table 7: Diagnostic test of IL-6 and CRP for predicting severe acute pancreatitis

Diagnostic test	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Interleukin-6 (pg/mL) day 1	100% (82.4–100)	88.37% (74.9–96.1)	79.2% (57.8–92.9)	100% (90.7–100)
Interleukin-6 (pg/mL) day 2	100% (82.4–100)	88.37% (74.9–96.1)	79.2% (57.8–92.9)	100% (90.7–100)
CRP (mg/dL) day 1	89.47% (66.9–98.7)	88.37% (74.9–96.1)	77.3% (54.6–92.2)	95% (83.1–99.4)
CRP (mg/dL) day 2	100% (82.4–100)	81.4% (66.6–91.6)	70.4% (49.8–86.2)	100% (90–100)

1, and CRP on day 2 for predicting SAP was 137, 77.3, 9.6, and 5.6, respectively. IL-6 on day 2 had a maximum AUC of 0.984 and so was the best predictor of SAP [Table 6].

IL-6 on day 1 and day 2 and CRP on day 2 were 100% sensitive, but IL-6 on day 1 and day 2 had a maximum specificity of 88.37% among them when compared with a specificity of 81.4% of CRP on day 2. CRP on day 1 had a specificity of 88.37% and a sensitivity of 89.47% [Table 7].

Discussion

In this study, a significant positive correlation was found between CRP levels on day 1 and day 2 and IL-6 levels on day 1 and day 2 with duration of hospital stay. Kolber *et al.*,^[10]

in their study, also found that IL-6 and CRP concentrations were positively correlated with the length of hospital stay, i.e., patients with higher CRP and IL-6 value have severe pancreatitis and require prolonged hospitalization and even ICU stay is required in most of them. High morbidity and mortality in severe AP contributed to longer hospital stay. Value of lipase and duration of hospital stay were significantly higher in patients categorized as SAP by the revised Atlanta classification when compared with patients categorized as mild AP [Table 3].

Four out of 62 (6.45%) patients died due to SAP. In this study, the major cause of death observed was MODS. Mann *et al.*^[11] and Banerjee *et al.*^[12] separately noted that in

Table 8: Association of modified CT severity index with IL-6, CRP, amylase, lipase, and hospital days

Association table		Modified CT severity index			P-value
		Mild (n=10)	Moderate (n=33)	Severe (n=19)	
Interleukin-6 (pg/mL) day 1	Mean ± Std dev	43.9 ± 42.05	102.76 ± 82.35	685.56 ± 1128.48	<0.0001
	Median (IQR)	19.55 (15.100–78.300)	88.1 (54.050–112.900)	268.1 (180.300–584.775)	
Interleukin-6 (pg/mL) day 2	Mean ± Std dev	25.78 ± 18	52.54 ± 34.54	228.42 ± 123.14	<0.0001
	Median (IQR)	17.6 (9.800–41.900)	43.6 (25.925–73.850)	174.1 (131.825–296.775)	
CRP (mg/dL) day 1	Mean ± Std dev	3.73 ± 2.53	6.15 ± 3.99	14.36 ± 5.19	<0.0001
	Median (IQR)	3.57 (2.090–4.520)	4.88 (3.458–7.600)	13.64 (11.100–16.537)	
CRP (mg/dL) day 2	Mean ± Std dev	2.26 ± 1.54	4.54 ± 3.19	11.65 ± 4.15	<0.0001
	Median (IQR)	1.72 (1.210–3.200)	3.4 (2.260–5.577)	11.1 (9.250–12.565)	
Serum amylase (U/L)	Mean ± Std dev	642.8 ± 356.64	621.33 ± 294.29	981.47 ± 620.2	0.08
	Median (IQR)	649.5 (327–960)	548 (375.750–864.500)	735 (530.500–1292.750)	
Lipase (U/L)	Mean ± Std dev	1163.6 ± 914.4	918.06 ± 340.68	1709.58 ± 1564.63	0.054
	Median (IQR)	906.5 (560–1327)	962(660.750–1130)	1162 (947.250–1753.500)	
Hospital stay (days)	Mean ± Std dev	6.4 ± 1.26	8.39 ± 1.97	14.53 ± 1.9	<0.0001
	Median (IQR)	6.5 (5–7)	8(7–9)	14 (13–16)	

AP the average mortality rate approaches 2–10%, whereas Steinberg and Tenner^[13] noted a mortality of 2–9% in their study.

In this study, majority (53.23%) of the patients were categorized as moderate AP followed by 30.65% as SAP and 16.13% as mild AP according to the modified CTSI, whereas according to the revised Atlanta classification, majority (64.52%) of the patients were categorized as mild AP and 35.48% were categorized as SAP. A fair significant correlation was noted between the modified CTSI and severity according to the revised Atlanta classification with a kappa value of 0.324 [Table 5].

In the present study, IL-6 levels were found to be significantly higher on day 1 and day 2 in AP [Table 8]. The levels of IL-6 were found to be significantly higher in severe AP cases when compared with mild/moderate AP cases [Table 8]. The levels of IL-6 decreased significantly on day 2 of AP and the decrease was found to be significant. In the present study, a cutoff value of IL-6 >137 pg/mL on day 1 and a cutoff value of >77.3 pg/mL on day 2 showed a sensitivity and specificity of 100% and 88.4%, respectively. However, in a study by Rao and Kunte, IL-6 >28.90 pg/mL had a sensitivity and specificity of 62.86% and 80%, respectively.^[14] In another study by Sathyanarayan *et al.*,^[15] it was found that the level of IL-6 was significantly higher in patients who develop organ failure compared with those who did not show a sensitivity and specificity of 81.8% and 77.7%, respectively.^[15]

In the present study, CRP levels on day 1 and day 2 were significantly higher in AP [Table 8]. The levels of CRP were found to be significantly higher in SAP when compared with mild/moderate AP cases [Table 8]. In the present study, the cutoff value of CRP >9.6 mg/dL on day 1 showed a sensitivity and a specificity of 89.4% and 88.37%, respectively, and the cut-off value of CRP >5.6 mg/dL on day 2 showed a sensitivity and specificity of 100% and

81.4%, respectively. However in the study by Gurda-Duda *et al.*,^[16] the sensitivity and specificity of serum CRP at admission in detecting the severity of AP were found to be 63.6% and 65.5%, respectively.

A significant positive correlation was found between IL-6 and CRP levels on day 1 and day 2, with correlation coefficients of 0.734 and 0.712, respectively, in our study. Similar results were found in the study of Goral and Berekatoglu Mete.^[17] In response to tissue injury, IL-6 is produced promptly but transiently and it contributes to host defense through stimulation of acute phase response, immune responses, and hematopoiesis. After synthesis at the local level, IL-6 moves to liver through blood stream where it induces acute phase protein such as CRP and serum amyloid A.^[18]

A significant association was seen between IL-6 levels and CRP levels on day 1 and day 2 with severity, according to the revised Atlanta classification and modified CTSI. A similar positive association of IL-6 and CRP with Atlanta classification was observed by Rao and Kunte.^[14] However, Agarwal *et al.*^[19] found that no correlation exists between IL-6 level and CTSI. Interpretation of the area under the ROC curve showed that the performance of IL-6 on day 1, IL-6 on day 2, CRP on day 1, and CRP on day 2 was excellent for predicting SAP. IL-6 on day 2 had a maximum AUC of 0.984 and so was the best predictor of SAP.

Overall, serum IL-6 and CRP were more sensitive and specific in determining severity of AP.

Conclusion

IL-6 on day 1 and day 2 and CRP on day 2 were 100% sensitive, but IL-6 on day 1 and day 2 had a maximum specificity of 88.37% among them, when compared with a specificity of 81.4% of CRP on day 2. Though CRP on day 1 had a specificity of 88.37%, its sensitivity was 89.47%.

The ROC curve showed that the performance of IL-6 on day 1, IL-6 on day 2, CRP on day 1, and CRP on day 2 was excellent for predicting SAP. IL-6 on day 2 had a maximum AUC of 0.984 and so was the best early predictor of SAP.

IL-6 and CRP together appear to be promising markers for assessing the severity of AP within 48 h. We recommend doing IL-6 and CRP in cases of pancreatitis which can help in predicting the severity of the disease in patients and hence timely intensive management can be done.

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Conflicts of interest

There are no conflicts of interest.

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