ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 07 | July - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

INTERLEUKIN-6 AND CRP AS EARLY PREDICTIVE MARKERS FOR SEVERE ACUTE PANCREATITIS

Clinical Research

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ABSTRACT

Introduction: Acute pancreatitis is a serious condition with unpredictable outcomes. Scoring systems and biochemical markers such as IL-6 and CRP can aid in predicting the severity and clinical outcomes of pancreatitis. **Objective:** This study aims to assess the accuracy of early measurement of inflammatory markers like IL-6 and CRP, in predicting severity in patients with suspected acute pancreatitis and correlate the severity with clinical outcomes. **Method:** The study is a hospital-based observational study collecting data on IL6 and CRP from patients diagnosed with acute pancreatitis based on the Atlanta guidelines. **Results:** The study included 48 patients and found that IL6 and CRP levels increased in proportion to the severity of AP, and had a strong correlation with severity calculated according to Revised Atlanta guidelines and modified CT severity index, with p-values <0.05. IL6 had a higher sensitivity of 95.45% vs 68.18 % in CRP, which suggests that both markers may be useful in predicting the severity of AP in its early stages. **Conclusion:** IL-6 and CRP can accurately predict the course of acute pancreatitis and aid in the early recognition of severe cases, enabling timely intervention

KEYWORDS

Acute pancreatitis, Interleukin 6 (IL6), C-reactive protein (CRP)

INTRODUCTION

Acute pancreatitis (AP) is a major debilitating disease of the gastrointestinal tract, having high morbidity and mortality, thus creating a huge physical, financial, and emotional stress to the affected individual [1,2].

None of the other acute abdominal differentials have an outcome that is so unpredictable at presentation as compared to that of acute pancreatitis. Two-thirds of patients would improve with supportive therapy, while the other third develops serious local and systemic complications due to an intense inflammatory response, which may progress to multiorgan failure and/or pancreatic necrosis with a 20% to 30% risk of mortality [3,4].

According to the Atlanta guidelines, a case of severe acute pancreatitis (SAP) is defined with features of acute pancreatitis with persistent organ failure lasting beyond 48 h [5]. This essentially makes the diagnosis of SAP a retrospective one, by which time a critical window for early intervention may be lost. To enable the early prediction of clinical outcomes of pancreatitis, multiple scoring systems such as Ranson [6], Glasgow [7], and APACHE II [8], in addition to novel biochemical markers such as Interleukin (IL)-6 and C-reactive protein (CRP) have been described.

Interleukin-6 is the principal cytokine mediator of the synthesis of acute-phase proteins such as fibrinogen, and CRP that can be measured in serum and urine with a commercially available RIA. Interleukins are known to degrade very rapidly in the circulation. Interleukin-6 levels in serum are reported to discriminate severe from mild cases on day 1st from the onset of the disease, and maximal levels are seen on day 1st or 2nd. Most patients with mild disease have undetectable serum levels of interleukin-6 and thus serum levels have been shown to reflect the severity of an attack of acute pancreatitis [9].

A widely accepted marker for the severity of acute pancreatitis is a CRP level of >150 mg/L. C-reactive protein (CRP) is an acute phase reactant that is synthesized by the hepatocytes. This synthesis is induced by the release of interleukin 1 and 6. Thus the CRP peak in serum is usually not maximal until about day three after the onset of pain and is always later than the peak of these interleukins. CRP is the most popular single test severity marker used today. The problem is that CRP is a rather late severity marker (days 2-4) as compared to the other markers in this overview [10].

MATERIALS AND METHODS

- The patients were selected from hospitals in Udaipur affiliated with RNTMC.
- Patients with acute pancreatitis presenting in the 2021–2022 time frame will be selected.

Study Design: It was a hospital-based cohort epidemiological study.

Study Duration: The study was planned for 18 months from June 2021 to November 2022 till the sample size is achieved and further data coding and analysis is done.

Study Subjects: All patients presenting with newly diagnosed acute pancreatitis, according to the Atlanta guidelines.

Any two of the three following criteria to be fulfilled:

I. Clinical features suggestive of acute pancreatitis
II. Serum amylase and lipase levels elevated to more than three times the upper limit of normal.
III. USG or CT showing features of acute pancreatitis.

Inclusion Criteria:

I. Age group: 18-65 years
II. Patients diagnosed with acute pancreatitis based on Atlanta classification.

Exclusion Criteria:

I. Patients admitted with acute pancreatitis who are associated with chronic organ failure ex. CKD, CLD, etc. at the time of admission.
II. Patients with chronic pancreatitis.
III. Age group < 18 years and > 65 years.
IV. Pregnant women

Study Procedure:

Venous blood samples were collected within 24 h of admission from all patients for estimation of serum levels of IL-6, CRP, and other routine laboratory parameters. Estimation of levels of cytokines was done in a laboratory with established internal controls. IL-6 and CRP levels were measured using an enzyme-linked immunosorbent assay at the MDRU of RNTMC Udaipur.

METHODS

socio-demographic, clinical, and laboratory data were elicited from these patients and recorded in a proforma. (Annexure).

I. Socio-demographic data - Age & Sex.
II. Clinical data - Clinical history was elicited in detail with special emphasis on abdominal pain, abdominal distention, decreased urine output, vomiting, blood vomitus, blackish stool, breathlessness, chest discomfort, swelling of legs, fever, yellowish discoloration of eyes or urine and substance abuse (alcohol and smoking). Blood pressure, Pulse rate, Temperature, Respiratory rate, and Oxygen saturation in peripheral blood (SpO2) were measured using standard procedures.
III. Clinical examination was done with special attention to

abdominal guarding, rebound tenderness, impaired mental status, and respiratory system for breath sounds.

IV. Laboratory data – IL6, CRP, amylase, lipase, and other laboratory parameters were measured.

V. Imaging – ultrasound and CT scan were done.

Data Analysis

Statistical analysis of the data obtained was done using the student's unpaired 't-test and chi-square test. A statistical package SPSS version 17.0 was used to do the analysis. A 'p-value of <0.05 was taken as significant.

RESULTS

In our study of 48 patients, 33 of them were male contributing 68.75% of the study population. The mean age of the presentation was 47.14 years. Abdominal pain (100%) and vomiting (58.3%) were the predominant symptoms seen in our study population. A symptom association of extrapancreatic features to the development of severe AP was done, which suggested that the presence of extrapancreatic features in AP had a high association with the severity of AP. Gallstone was the predominant cause of AP seen in 47.91% of patients while the alcoholic cause of AP was seen in 31.25% of the study population. According to the 2012 Atlanta classification criteria, there were 8 (16.6%) patients with SAP, 14 (29.1%) patients with MSAP, and 26 (54.1%) patients with mild AP. The mortality in our study was 6 (12.5%) patients.

Serum IL6 and CRP levels in patients with different severities of acute pancreatitis:

Within 48 hours of onset, the levels of IL6 in patients with acute pancreatitis (AP) were significantly increased. Among the AP patients, those with severe acute pancreatitis (SAP) exhibited the highest levels of IL6 (605±320.6), which were significantly higher than the levels observed in patients with mild AP (53.6±95.8) and moderately severe AP (277.1±249.5), with a p-value less than 0.001. Additionally, SAP patients had the highest levels of CRP (390.6±188.3), in comparison to moderately severe AP (186.8±129.8), and mild AP patients (109.7±76.2), with a p-value less than 0.001 [Table 1]. Furthermore, a correlation analysis was performed to assess the relationship between IL6 and CRP with the modified CT severity index, which revealed that both IL6 and CRP are effective predictive markers of SAP (p-value less than 0.05). However, IL6 showed a stronger correlation with disease severity compared to CRP (p-value 0.006 versus 0.012) [Table 2].

Table 1. Correlation of CRP and IL6 with the severity of AP

Markers	Mild		Moderate		Severe		P Value
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	
CRP	109.7	76.2	186.3	129.8	390.6	188.3	<0.001
IL6	53.6	95.8	277.1	249.5	605.0	320.6	<0.001

Both CRP and IL6 are very significantly associated with the severity of AP. It suggested early measurement of CRP and IL6 within 24 hours of the onset of the disease significantly predicts the severity of AP.

Table 2. Correlation of CRP and IL6 with modified CT Severity Index

Markers	mCTSI						P Value
	0-2		4-6		8-10		
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	
CRP	118.2	76.0	165.6	119.2	309.4	183.8	0.012
IL6	95.3	160.7	162.2	242.3	485.2	310.1	0.006

In this study, both CRP and IL6 are significantly associated with the modified CT severity index. Thus, it suggested that the severity calculated by the modified CT severity index is significantly similar to the severity calculated by both inflammatory markers.

DISCUSSION

Acute pancreatitis is a disease with significant morbidity and mortality in which the progression can be altered by early intervention. Various scores and single prognostic markers have been suggested to predict the severity of pancreatitis on admission or after a couple of days, this itself suggests that none of the available markers or scores are the gold standard to predict the severity of the disease. With this prospective study in a tertiary institution, we wanted to determine whether modern imaging methods and laboratory findings, including interleukin 6 and C reactive protein, can predict the course of the disease accurately and delineate between mild and severe forms of acute pancreatitis.

Severity Markers

I. IL-6 :

In our study, we found that levels of serum IL6 increased in proportion to the severity of AP, and had a strong correlation with severity calculated according to Revised Atlanta guidelines and modified CT severity index with p-value <0.001, and 0.006 respectively. This is similar to several studies that had demonstrated an association between IL6 and severe AP and reported that IL6 is a useful marker for the prediction of the severity of acute pancreatitis in its early stages (Jiang et al[11], Stimac et al[12], Inagaki et al[13], Rao et al[14] all of them reported a p-value of <0.05).

II. CRP :

In our study, we found that levels of CRP are increased in proportion to the severity of AP, and had a strong correlation with severity calculated according to Atlanta guidelines and modified CT severity index with p-value <0.001 and 0.012 respectively. This is similar to previous studies by Wilson et al[8], Sternby et al[15], all of which reported a p-value <0.05.

III. Other markers :

In our study, we also found a significant correlation in the severity of AP with urea, creatinine, albumin, calcium, haematocrit, and haemoglobin with a p-value <0.05. All of which are single prognostic markers in predicting the severity of pancreatitis. These are similar to previous studies done by Kolber et al[16], Z Ahmed et al[17], Ćeranić et al[18], Lankisch et al[19] with a p-value <0.05.

Comparison between CRP and IL6 :

In this study, we found both IL6 and CRP had a sensitivity of 95.45% and 68.18% for predicting the severity but had low specificity of 57.69% and 80.7% respectively. It can be explained by the fact that IL6 and CRP are inflammatory markers and are raised in many diseases being nonspecific. These results are comparable to previous studies done by Heath et al[20] which showed sensitivity and specificity of IL6 are 100% and 71%, and Li et al[21] which reported the sensitivity and specificity of CRP are 76.47% and 74.19%. Pezilli et al [22] reported that CRP had a lower prognostic efficiency than IL6 (sensitivity of 100% vs 87%) similar to our study with a sensitivity of 95.45% vs 68.18%. A recent study showed that IL6 was closely related to the severity of AP, whereas CRP had low predictive accuracy for severe AP (Nieminen et al[23]). Duarte-Rojo et al[24] found that during the first 48 hours after admission, IL6 was more accurate than CRP. Our study also revealed that IL6 and CRP both have a strong correlation with severity, but IL6 has a higher predictive value than CRP.

Complications And Outcome :

A study found that IL6 is a good marker of peri pancreatic necrosis (Karpavicius et al[25]) and previously published results showed that infected pancreatic necrosis can aggravate prognosis (Kolber et al [16]). Our study also compared the predictive values of IL6 and CRP for pancreatic necrosis, other complications, and mortality. The results indicated that IL6 was more accurate than CRP for the prediction of pancreatic necrosis (raised in 90% vs 70%), other complications, and mortality. Serum IL6 and CRP levels are also significantly associated with a stay in the hospital (p-value <0.001). Serum IL6 and CRP both are good predictors of mortality (p-value <0.001), similar to the study done by Li et al [21] (p-value <0.05). IL6 is better than CRP in predicting mortality (raised in 100% vs 83.33% cases).

Drawing on the experience, a prospective study aiming to precisely assess the values of inflammatory cytokines for predicting severe AP would need to have a large sample size with frequent measurements of inflammatory markers in a short duration of 24 hours since disease onset, comparison of data with radiological imaging scoring systems.

CONCLUSION

IL6 and CRP measured within 24 -36 hours of the onset of AP, with a cut-off value of ≥28.90 pg/ml and ≥150 mg/dl respectively are significant in predicting the progression of AP from mild to severe AP, pancreatic necrosis, and mortality. IL6 is better than CRP in predicting the severity of AP, pancreatic necrosis, and mortality.

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