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Original Research Article

To Determine the Prognostic Value of C - Reactive Protein (CRP) and Tumor Necrosis Factor (TNF)-α as Predictors of Systemic Complications in Acute Pancreatitis

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ABSTRACT

Background: Early assessment of severity in acute pancreatitis (AP) is a key measure to provide rational and effective management.
Aim: of this study is to determine the prognostic value of C - reactive protein (CRP) and Tumor Necrosis Factor (TNF)-α as predictors of systemic complications in AP.
Materials and Methods: total 210 patients with confirmed AP were enrolled in the study. The severity of AP was defined according to Atlanta criteria. Measurements of CRP and TNF-α were performed on the 1st day and on 3rd day of admission.
Results: on day 1st & day 3rd serum levels of CRP found highly significantly different ($p < 0.000$) between the severe group and the mild group and TNF-α was found higher ($p < 0.05$) in the severe group than in mild cases on day 1st only. On day 1and day 3, CRP had a higher sensitivity (83.3%, 78.6%) and accuracy (80%, 75.8%) compared with TNF-α showed low level of sensitivity and diagnostic accuracy on both the days.
Conclusion: our study confirmed that by determining the serum concentration of CRP on the 3rd day of admission represents a valuable diagnostic tool in the assessment of severity and course of disease in patients with acute pancreatitis.
Keywords: acute pancreatitis; CRP; systemic complications; TNF-α

INTRODUCTION

Acute pancreatitis is a disorder primarily of the exocrine pancreas that involves varying degrees of acute inflammation associated with parenchymal injury of the gland. [1] According to National Health Service (NHS), UK, less than 1 in every 100,000 people develops acute pancreatitis each year. It is slightly more common in men than in women. Nearly 60%–80% of all cases of AP in developed countries are attributable to either gallstone disease or alcohol abuse. [2,3]

The revised Atlanta classification system has classified AP into mild, moderate and severe. [4,5] More than 80% of acute pancreatitic attacks are mild and self-limiting and resolve without serious complications. In 20% of cases, however, it can be severe and complicated by major morbidity or mortality. [2,6,7] Moderate acute pancreatitis is characterized by the presence of transient organ failure or local/systemic complications. [9] Persistent organ failure is the feature of severe acute pancreatitis which is associated with a high rate of mortality.

Despite intense research over centuries, the exact pathogenesis of AP remains elusive. Although many theories

have been proposed, none of them appear to be complete. Some of the propositions include abnormal biliopancreatic duct common pathway theory, pancreatic auto digestion theory, gallstone migration theory, enzyme activation theory, kinin and complement activation theory, microcirculation disturbance theory, and pancreatic acinar cell apoptosis and necrosis theory, all of which are still controversial. [2]

Recent studies have suggested that the serum levels of interleukins and TNF-α may be used to identify patients who are prone to develop local or systemic complications and were compared with CRP which has been employed in the prediction of severity of acute pancreatitis and early identification of such patients could lead to a more intensive management that would result to a decreased morbidity and mortality of that potentially fatal disease. [8-10] In the view of above literature the present study was conceived with the aim to correlate the levels of Tumor Necrosis factor- alpha (TNF alpha) and C-Reactive Protein (CRP) in determining the severity and complications of acute pancreatitis

MATERIALS AND METHODS

Study Subjects

The present clinico-observational study was carried in 210 patients of acute pancreatitis with mild and severe form as diagnosed by clinicians of S.M.S. Medical College and Hospital, Jaipur (Rajasthan).

Ethical approval and Informed consent

The study protocol was reviewed by the Ethical Committee of SMS Medical College and Hospital and was granted ethical clearance. After explaining the purpose and details of the study, a written informed consent was obtained from the participants. It was emphasized that strict confidentiality would be maintained at all times and that the participants or guardians could withdraw at any time without being penalized. After informed consent, patients were interviewed using a structural questionnaire to ascertain demographic and medical history and undergo a physical examination including name, age, sex, height, weight, BMI, pulse, BP, respiratory rate, past history, personal history, family history, drug history and occupation history. After completing the history and physical examination patients were underwent blood investigations.

Inclusion Criteria

1. An 18-60 year old patients of either sex, diagnosed with acute pancreatitis. The diagnosis of acute pancreatitis was established by the criteria set by the Atlanta guidelines, [11] namely, any two of the following three criteria to be fulfilled:
   a. Clinical features suggestive of acute pancreatitis.
   b. Serum amylase or lipase levels elevated to more than three times the upper limit of normal.
   c. Ultrasonography (USG) or computed tomography showing features of acute pancreatitis.
2. Onset of pain to be within 24 h before admission to the hospital.
3. Patients predicted to develop SAP by the following criteria on admission: Patients fulfilling the diagnostic criteria for a systemic inflammatory response syndrome (SIRS), defined by the presence of two or more of the following:
   i. Rectal temperature >38°C (100.4F) or <36°C (96.8F).
   ii. Heart rate >90 beats/min.
   iii. Respiratory rate >20/min or PaCO2 <32 mmHg.
   iv. White blood cell count>12,000/mm3, <4000/mm3 or >10% bands.

The diagnosis was made on the basis of consistent clinical picture combined with three fold increase in the levels of serum amylase or lipase and consistent morphological findings obtained by USG or/and CT scan within 72 hrs of admission.

Exclusion Criteria

1. Patients with known immunodeficient status.

2. Primary hypertriglyceridemia.
3. On long-term cyclooxygenase inhibitors (more than 3 months).
4. Severe cardiac disease.
5. Pre-existing hepatic disorders (total bilirubin >1.5 times the upper limit of normal).
6. Psychiatric disorders.
7. Pre-existing renal compromise (serum creatinine>2.0mg/dl).
8. Received parenteral nutrition within 2 weeks of the study. Patients with high amylase or lipase due to trauma, surgery, post ERCP, pancreatic tumor, uremia, diabetic ketoacidosis.

Patient screening and selection

At initial screening, the diagnosis of acute pancreatitis and presence of SIRS was confirmed on clinical, biochemical (serum lipase, renal function tests, liver function tests, serum electrolytes, complete hemogram, arterial blood gas analyses) and radiological investigations (USG, contrast-enhanced computed tomography abdomen). After verifying the absence of any exclusion criteria, total 210 patients were divided into 2 groups (Group A was a mild disease group and Group B was a severe disease group) according to the Atlanta criteria10 – the definition of severe acute pancreatitis is associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst.

Severe pancreatitis is further characterized by 3 or more Ranson criteria or 8 or more APACHE (Acute Physiology and Chronic Health Evaluation) points. Organ failure is defined as shock, pulmonary insufficiency, renal failure or gastrointestinal bleeding more than 500 mL/24 hours. Systemic complications, such as disseminated intravascular coagulation or severe metabolic disturbance may also be seen.

Mild acute pancreatitis is associated with minimal organ dysfunction and an uneventful recovery, and it lacks the described features of severe acute pancreatitis as well as the local complications. Patients with mild acute pancreatitis respond to appropriate fluid administration with prompt normalization of physical signs and laboratory values.

Laboratory protocol

Venous blood sample was taken from all subjects from the anti cubital vein under all aseptic precautions. Serum samples for TNF-α and CRP were collected on admission (day 1) and on the morning of day 3 after admission. All the blood serum samples were frozen immediately after collection and stored at -20 C until analysis. Serum levels of TNF-α were determined with ELISA method. The minimum detectable values of TNF-α were 5pg/mL. The CRP was determined with Latex Turbidimetry method (Turbilatex) with normal range 0~0.8 mg/dL.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA).

Descriptive statistics included computation of percentages, means and standard deviations were calculated. Analysis was performed with Mann-Whitney rank sum test. The correlations between serum markers were analyzed by Pearson and Spearman's correlation. For all tests, confidence interval and p-value were set at 95% and ≤ 0.05 respectively. Cut-off values were chosen as values that achieved the highest sensitivity and specificity as well as positive predictive value (PPV) and negative predictive values (NPVs).

RESULTS

Table 1: Portrayed demographic and clinical characteristics of the study participants as out of total 210 patients 129 (61.5%) males and 81(38.5) female with a mean age of 48.0±1.9 were studied. 151(71.9) patients were diagnosed as mild acute pancreatitis and 59 (28.1) patients were the severe cases. The aetiologies were alcoholic 100 (47.6), biliary 77 (36.6) and idiopathic 33 (15.7) respectively.

Table 2: revealed that on day 1st& day 3rd serum levels of CRP were highly significantly different ($p < 0.000$) between the severe group and the mild group. TNF-α was also higher ($p < 0.05$) in the severe group than in mild cases on day 1st only.

Table 3: revealed no significant correlation between TNF-α and CRP (p= 0.070 & 0.074).

Table 4: on day 1 and day 3, the CRP had good values in sensitivity (83.3%) and accuracy (80.0%). The TNF-α had lowest sensitivity and diagnostic accuracy on both the days.

Table 1: Demographic and clinical characteristics of the study participants

	MILD (n = 151)	SEVERE (n = 59)	Total (n = 210)
Male:Female	78:49	51:32	129:81
Age (yr.)	46.9±1.2	49.5±2.3	48.0±1.9
Etiology			
Alcoholic	81 (62.7)	19 (23.4)	100 (47.6)
Biliary	28 (21.7)	49 (60.5)	77 (36.6)
Idiopathic	20 (15.6)	13 (16.1)	33 (15.7)

Table2: Mean serum concentration level of biomarkers at day1 & day3

VARIABLES		Day 1 Mean ± SD	Day 3 Mean ± SD
TNF-α	Mild	1.5 ± 0.7	1.3 ± 0.6
	Severe	5.3± 1.9	4.1± 2.5
	p-value	0.042*	0.07
CRP	Mild	5.7 ± 2.7	6.2 ± 2.3
	Severe	14.6 ± 2.9	24.5 ± 2.1
	p-value	0.021*	0.013*

Test applied: Mann-Whitney rank sum test. ** indicate highly significant ($p < 0.000$),
* indicate significant($p < 0.05$)

Table 3: Correlation between serum TNF- α and CRP on days 1 and 3

Variables	Day 1	Day 3
TNF-α /CRP	0.462	0.331
	(p = 0.07)	(p = 0.074)

TNF-α = tumor necrosis factor- α; CRP = C-reactive protein.

Table 4: Sensitivity, specificity and accuracy of the 2 biomarkers in predicting severity of acute pancreatitis

	Day 1	Day 3
Sensitivity (%)		
TNF-α	57.1	50.0
CRP	83.3	78.6
Specificity (%)		
TNF-α	79.5	68.9
CRP	73.7	77.7
Accuracy (%)		
TNF-α	75.8	63.3
CRP	80.0	75.8

Cutoff values: TNF-α = 2 pg/mL; CRP = 18 mg/dL.

DISCUSSION

The need for an early risk recognition and determination of best possible treatment modalities led to a series of investigations trying to establish an objective, rational and clinically manageable severity assessment tool in patients with AP. The initial acinar cell damage in the early stage of acute pancreatitis of any aetiology is caused by a hyper secretion of pancreatic proteolytic enzymes. As a result there is an overproduction of inflammatory mediators and free oxygen radicals. Tissue macrophages are the main source of pro-inflammatory and anti-inflammatory cytokines that attract neutrophils and more macrophages and induce the production of proteases, elastases and phospholipases. These enzymes as well as free oxygen radicals cause tissue damage mainly vascular endothelial necrosis which leads to circulatory stasis. The increase of pro-inflammatory and decrease of anti-inflammatory cytokines are crucial factors in the progression of inflammation of severe acute pancreatitis.

Already from the decade of 1980s staging of the severity of acute pancreatitis using serum criteria was employed. [12] Many clinical trials have employed the use of either cytokines or serum amyloid A and pro-calcitonin (PCT) as prognosticators of the severity of acute pancreatitis. [13,14] Many authors suggest that PCT may accurately predict infected pancreatic necrosis. Other studies over the last few years have suggested that the serum levels of interleukins and TNF-*α* may be used to identify patients who are prone to develop local or systemic complications and were compared with CRP which has been employed in the prediction of severity of acute pancreatitis. Early identification of such patients could lead to a more intensive management that would result to a decreased morbidity and mortality of that potentially fatal disease. [8]

The serum TNF- α levels measured in the present investigation were surprisingly low and showed that it had

significant difference between severe and mild groups on the first day. In predicting the severity of acute pancreatitis, TNF-α was not as good as CRP in the early stage (days 1 and 3) of the acute pancreatitis. Banks *et al.* [15] reported that TNF- α was higher in the severe pancreatitis group but not significantly different from the mild disease group. Exley *et al.* [16] showed the association between TNF-*α* and biliary pancreatitis was stronger. In our series, gallstone pancreatitis was 36.6% of the total study population. The present results suggest that early TNF-α measurement is of limited clinical value in the prediction of a severe or complicated disease course in acute pancreatitis.

Our data showed that CRP had a relatively higher sensitivity and diagnostic accuracy on day 3. Serum CRP concentration is perhaps the best available single marker of the severity of acute pancreatitis. Recent investigations have demonstrated that when determined soon after admission, it accurately predicts complications in 50-80 percent. [17,18] Similarly in the present study, the accuracy of CRP in predicting complicated pancreatitis was between 74 and 78 per cent, depending on the cut-off level chosen. Some of the inaccuracy may be explained by the 24-48 h delay in serum CRP reaching peak levels in severe acute pancreatitis.

CONCLUSION

Our study confirmed that by determining the serum concentration of CRP on the 3rd day of admission represent a valuable diagnostic tool in the assessment of severity and course of disease in patients with acute pancreatitis. Routine use of pro-inflammatory cytokines as predicting factors of severity of acute pancreatitis is still not feasible in most hospitals due to high costs and inaccessibility of analytic methods. Therefore, development of new and more accessible laboratory equipment, as well as methods of analysis could help the clinicians in the early recognition of development of systemic complications and improve the management of severe acute pancreatitis.

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