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RESEARCH ARTICLE

PROGNOSTICATION OF ACUTE PANCREATITIS USING SIMPLE SIRS SCORE AND SERUM INTERLEUKIN-6 CONCENTRATION FOR EFFECTIVE INTERVENTION OF SEVERE ACUTE PANCREATITIS IN PRIMARY HEALTH CARE

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ABSTRACT

Recent diagnostic and therapeutic progress for severe acute pancreatitis (SAP) has decreased the case mortality rate. There is a therapeutic window within the first 48 h, when specific treatment may alter the outcome. An ideal scoring system and laboratory assay in the evaluation of acute pancreatitis patients should provide an early severity assessment to facilitate treatment. This should be applicable in the clinical setting, rapid, low cost, accurate and available on a 24-hour basis.

Objective: To evaluate the Systemic Inflammatory Response Syndrome (SIRS) score and Interleukin (IL)-6 for predicting severity of acute pancreatitis.

Methodology: SIRS scoring system and IL -6 levels is evaluated in 30 patients with acute pancreatitis at time of admission. These 30 patients were divided into 2 groups- mild and severe pancreatitis depending on presence of organ failure and/or local complications such as necrosis, etc. Correlation between SIRS's score and IL-6 levels and its role in predicting severity of pancreatitis was evaluated.

Results: Thirty-patients with acute pancreatitis admitted to our hospital between March 2014 to October 2015 were studied, 12 mild-group patients and 18 severe-group patients. SIRS score for severe form was > 2 while mild form had score < 2. IL-6 levels showed significant differences ($p <$ 0.005) between the severe group and the mild group on the day of admission. Even SIRS score and IL-6 levels showed significant correlation with severity of pancreatitis.

Conclusion: SIRS scoring system and IL-6 levels on the day of admission are useful for early prediction of severity of acute pancreatitis in primary health care and aides in effective management, thus reducing the morbidity and mortality of acute pancreatitis.

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INTRODUCTION

Acute pancreatitis (AP) presents with a wide paradigm of presentation ranging from mild to severe fatal cases, such as from mild abdominal pain to multi organ dysfunction syndrome. It is very necessary to classify patients with AP who are at risk for developing persistent organ failure early in the natural history of the disease. Acute pancreatitis is not a uncommon disease seen in our clinical practice of which the severity may vary from mild, oedematous to severe, necrotizing fulminant disease. A better result in severe acute pancreatitis is based on early determination of disease severity and subsequent targeted management of these high-risk patients.

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However, to classify acute pancreatitis patients as mild and severe upon presentation to emergency room based on clinical signs and symptoms are not precise. Scoring systems for acute pancreatitis patients based on clinical criteria to determine severity and prognostication are: The Ranson's prognostic criteria, Glasgow score, and the Acute Physiology and Chronic Health Evaluation-II score (APACHE-II). However Ranson`s prognostic criteria and Glasgow score`s application in clinical practice has been restricted by the time delay of at least 48 hours to judge all parameters, and by being cumbersome and time- consuming in the usage of APACHE-II, which is too late for therapeutic decision-making (Lempinen *et al*., 2005). Even though Contrast-enhanced computed tomography of abdomen is the most accurate non-invasive single investigation to determine the severity of acute pancreatitis, it cannot be advocated to all patients with acute pancreatitis due to risk of renal complications (Balthazar, 2002).

Therefore, substantial interest has grown in the discovery of reliable biochemical markers that throw light on the severity of acute pancreatitis. SIRS is the clinical manifestation of the inflammatory process that can occur after a variety of infectious and noninfectious insults. SIRS has been studied in several noninfectious diseases, including trauma, cirrhosis, and subarachnoid hemorrhage. However, to date, there has been no prospective clinical study that has examined the implication of SIRS scoring in assessing severity in acute pancreatitis (Singh *et al*., 2009). An ideal laboratory biochemical marker in the evaluation of patient with acute pancreatitis should be able to provide early, accurate assessment of severity to facilitate the appropriate therapeutic strategies. Further, it should be applicable in a primary care setup satisfying features such as: be rapid, low cost, accurate and available on a 24- hour basis. Interleukin-6 biochemical marker, which is synthesised in response to tissue injury by macrophages and is a important link responsible for the synthesis of the acute-phase proteins. Studies have shown that plasma IL-6 concentrations within 24 hours of admission correlate with mortality rate (Leser *et al*., 1991; Viedma *et al*., 1992; Beaux *et al*., 1996; Heath *et al*., 1993). IL-6 distinguished between severe and mild pancreatitis with a sensitivity of 100% and a specificity of 71% in the study by Heath and co-workers and 86% and 100% in the one published by Pezzilli and co-workers (Pezzilli *et al*., 1995; Pezzilli *et al*., 1999). In the diagnosis and prognosis of severe acute pancreatitis simultaneous measurements of IL-6 and lipase play a surprising role of being more accurate. However, the kinetics of IL-6 which peaks early at Day-1 cannot be compared with the Ranson and APACHE II scores which are established at Day-2 (Heath *et al*., 1993; Bertsch, 1998; Ikeo *et al*., 1998). Thus, more research is necessary to accept IL-6 as a new useful marker for acute pancreatitis.

The primary objective of this study is to examine the use of simple SIRS scoring system in grading severity of acute pancreatitis and also evaluate the use of IL-6, a new severity marker for acute pancreatitis in their ability to hint between mild and severe disease and their clinical utility in effective management.

MATERIALS AND METHODS

All patients, clinically and radiologically diagnosed cases of pancreatitis admitted to our institution from March 2014-October 2015 were included in this study. Data for all patients were prospectively collected within first 24 hours of attack of acute pancreatitis. Thirty-patients with acute pancreatitis admitted to our institution from March 2014 to October 2015 were included for the study. It was ethically cleared from Institutional Human Ethics Committee. Inform consent was taken from all the patients were included in the study. All the patients were admitted via Emergency unit. Confirmation of acute pancreatitis was based on the chief complaints of typically persistent upper visceral pain for a few hours before consulting our emergency unit associated with 3 times normal increase of serum amylase levels and lipase levels. The diagnosis was confirmed by imaging either by abdominal ultrasound or Contrast enhanced Computed Tomography (CECT) scan examination. Patients diagnosed as acute pancreatitis were evaluated using SIRS scoring and blood samples were collected for assessing IL-6 levels using Human IL-6 (ELISA KIT). Ranson's prognostic criteria were also considered simultaneously to assess the significance of SIRS score and IL-6 levels.

All patients were treated medically according to general accepted method. Patients diagnosed as acute or chronic pancreatitis, chronic pancreatitis, patients presenting with high amylase or lipase levels in case of trauma, surgery, post endoscopic retrograde cholangio-pancreaticography, pancreatic tumors, diabetic ketoacidosis and uremia were excluded from the study.

SIRS SCORING

Systemic inflammatory response syndrome (SIRS) is defined as 2 or more SIRS criteria. SIRS scores were calculated for all patients during first 24 hours of acute attack and blood samples were collected from the subjects with SIRS positive and other criterions positive (Table-2).

SIRS is defined as the presence of 2 or more SIRS criteria

Individual SIRS criteria

Statistical analysis

Relationships between the numbers of SIRS criteria with Markers of severity were assessed using SSPS version 20 software. Consistency coefficient, product moment correlation, one way ANOVA, Independent sample t test and Chi square test.

RESULTS

A total number of 30 patients (24 male, 6 female) with a mean age of 44.0 (range 18 to 70yrs) were studied. The etiologies were alcoholic, biliary and idiopathic. These 30 patients were classified into 2 groups-mild and severe pancreatitis depending on presence of multi organ failure and/or regional complications such as pancreatic necrosis, abscess or pseudocyst of pancreas. The clinical characteristics of these patients are shown in (Table 1).

Table 1. Clinical characteristics of patients

Demographic data	Mild pancreatitis	Severe pancreatitis
Male:Female	11:1	15:3
Age(mean)yrs	43	48
Etiology		
Alcoholic	9	10
Biliary	2	5
Idiopathic	1	3

DISCUSSION

Acute pancreatitis is a frequently encountered disease, wherein in majority of patients it is self-limiting with an uneventful recovery and a mortality of less than 2 % (Beger *et al*., 2001). Progression to severe acute pancreatitis is seen in about 20 % of the attacks. Inspite of significant improvements in the treatment, the mortality remains between 15 and 25 % (Beger, 1999; Tsiotos *et al*., 1998). The knowledge on pathophysiology of acute pancreatitis is limited. The etiology of acute pancreatitis is usually very variable, but irrespective of the etiological factor, premature intra-acinar activation of trypsinogen to trypsin within the pancreas is presumed to play a vital role as an early precipitating event in acinar cell injury (Steer, 1998; Hietaranta, 2001). Henceforth, it has become increasingly evident that severe acute pancreatitis progresses in two phases. In the first phase, extensive inflammation and necrosis of pancreas which is followed by a systemic

Table 2. Evaluation of SIRS scoring on admission patients

SIRS scores	Number	MEAN±SD	95% confidence interval for mean		Minimum	Maximum
			Lower bound	Upper bound		
2	12	25.49±20.33	12.57	38.40	02.10	58.47
3	17	94.22±47.08	70.00	118.43	26.46	190.81
4	1	108.18±00.00	.	.	108.19	108.19
Total	30		48.20	86.18	02.10	190.81

Table 3. Relation between SIRS score and care in the hospital

SIRS score	Emergency ward		ICU		Total	
	Number	Percentage (%)	Number	Percentage (%)	Number	Percentage (%)
2	12	60.00	0	00.00	12	38.70
3	7	35.00	10	90.00	17	54.84
4	1	05.00	1	10.00	2	06.46
Total	20	100.00	11	100.00	31	100.00

Table 4. Relation between SIRS score and complications

SIRS score	Total	ARDS		MODS		Pseudocyst	
		Number	Percentage (%)	Number	Percentage (%)	Number	Percentage (%)
2.00	12	0	0	0	0	1	8.3
3.00	17	12	70.6	07	41.1	09	52.9
4.00	1	1	100	1	100	1	100
Total	30	13	43.3	08	26.6	11	36.6
P		<0.0001		0.001		0.001	

Table 5. Relation between Interleukin 6 levels and Admission place in the hospital

Group statistics					
IL-6(pg/ml)	Admission place	Number	Mean	Std. Deviation	Std. Error mean
	Emergency ward	19	34.35	23.116	5.30
	ICU	11	123.98	30.790	9.28

(Chi-square test, p<0.000)

Table 6. Relation between Interleukin- 6 score and complications

	Interleukin-6 (pg/ml)						p
	Yes			No			
	N	Mean	SD	N	Mean	SD	
ARDS	13	102.75	48.95	17	40.00	32.80	<0.001
MODS	8	115.19	53.18	22	49.74	37.83	0.001
Pseudo cyst	11	93.26	54.08	19	52.10	43.42	0.03

(Chi-square test, p=0.001)

Table 7. Depicts the correlation between Interleukin-6, Lipase, Amylase

Correlations				
		Lipase	Interleukin	Amylase
Lipase	Pearson correlation	1	0.597(**)	0.746(**)
	Significance(2-tailed)	.	0.000	0.000
	N	30	30	30
IL-6	Pearson correlation	0.597 (**)	1	0.480(**)
	Significance(2-tailed)	0.000	.	0.007
	N	30	30	30
Amylase	Pearson correlation	.746(**)	0.480(**)	1
	Significance(2-tailed)	0.000	0.007	.
	N	30	30	30
** correlation at 0.01(2-tailed)				

inflammatory response syndrome that may lead to multiple organ dysfunction syndromes within the first week, without any apparent bacterial infection (McKay *et al*., 1999). If this process is not curbed and reversed by innate defences or therapeutic interventions, the second phase ensues usually after the second week of onset, and is related to the occurrence of infected pancreatic necrosis or fluid collections with eventual progression to overt sepsis, multiple organ dysfunction syndrome and death.

SIRS is the clinical manifestation of the inflammatory process that can occur after a variety of infectious and noninfectious insults. SIRS has been studied in several non-infectious diseases, including trauma, cirrhosis, and subarachnoid haemorrhage. However, to date, there has been no prospective clinical study that has examined the utility of SIRS in evaluating severity in acute pancreatitis. The clinically-based data of prognostic criteria of Ranson's and Glasgow require a 2-day delay after the onset of the disease and are so

cumbersome to memorize, and even more cumbersome is the APACHE II scoring system. Based on SIRS scoring applied in the study we found that the number of patients having SIRS score 2:12 patients, whereas SIRS score 3:17 patients, SIRS score 4:1 patient (Table-2). Most of the patients who require hospitalization with acute pancreatitis have SIRS on day-1. Study done on utility of sirs scoring in predicting acute pancreatitis showed that the severity of acute pancreatitis is greater among patients with SIRS on day-1 and, moreover among those with 3 or 4 SIRS criteria, compared with those without SIRS on day-1. Our study using SIRS scoring for grading pancreatitis showed that patients with SIRS score 2 required non ICU care and self limiting with uneventful recovery with conservative management, while patients with SIRS score 3 and 4 required ICU care with or without ventilator support and prolonged hospitalisation as depicted in (Table-3). Meanwhile our study confirms with simultaneous increase in SIRS score, patients developed complications like Acute Respiratory Distress Syndrome (ARDS), Multi Organ Dysfunction Syndrome (MODS), Pseudo cyst, etc as shown in (Table-4). Henceforth evaluation SIRS score predicted severe disease with high sensitivity (85%–100%) if present on day-1. On the contrary the absence of SIRS on day-1 was associated with a high negative predictive value (98%–100%). Patients with a higher number of systemic inflammatory response (SIR) criteria on day-1 and persistent SIRS had a multiplied risk for severe disease ($p<0.01$)

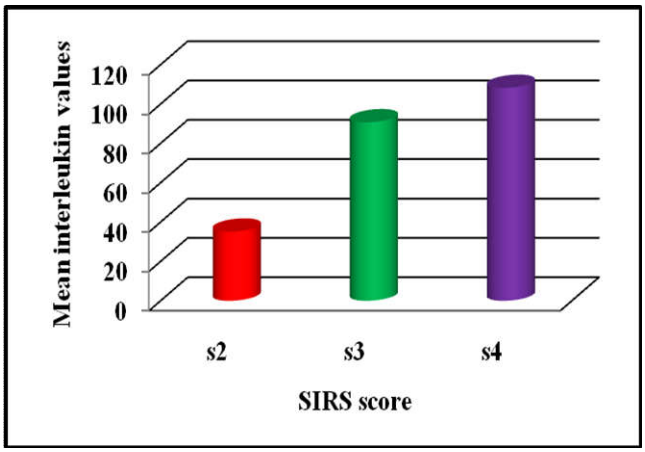

Fig. 1. Relation between the SIRS score and interleukin 6 (n=total no of patients)

The keystone in diagnosis of acute pancreatitis is clinical assessment, amylase and lipase measurements, supported by imaging methods. However, the serum levels of amylase and lipase do not correlate with the severity of the acute pancreatitis and its nonspecific. The diagnosis of acute pancreatitis is not always straightforward, as shown by the many cases diagnosed only at autopsy (Lankisch *et al*., 1991; Appelros, 1999). The limited clinical assessment to differentiate acute pancreatitis as severe and mild has led to potentially worse outcomes in majority of acute pancreatitis patients. The role of pro-inflammatory cytokines is considered to be crucial in the pathogenesis of severe acute pancreatitis. It has been reported that many single markers are applicable to assess the severity of acute pancreatitis. The mediators of acute phase protein response-cytokines were considered as earlier predictors. However, there is no single method is ideal in assessing the severity of the disease. Individual preference and available institutional facilities influence the method chosen for prognostic assessment of acute pancreatitis.

An ideal laboratory biochemical marker in the evaluation of patient with acute pancreatitis should be able to provide early, accurate assessment of severity to facilitate the appropriate therapeutic strategies. Further, it should be applicable in a primary care setup satisfying features such as: be rapid, low cost, accurate and available on a 24- hour basis. IL-6 is the major mediator for acute phase protein synthesised in liver (20). It distinguishes between severe and mild acute pancreatitis with 86 % to 100 % sensitivity and 71 % to 100 % specificity. Peak concentrations of IL-6 are reached 24 to 48 h before those of CRP. A rapid assay for serum concentration of IL-6 is available for the routine use (Appelros, 1999; Pezzilli *et al*., 1995; Chen *et al*., 1999; Messmann *et al*., 1997). Our study confirmed severity of pancreatitis increased with raise in serum IL -6 levels measurement. Patients with high initial IL-6 levels developed more complications and needed ICU care as shown on (Table-5 and Table-6) respectively. Furthermore our statistical analysis for finding correlation of IL-6 with other routine inflammatory markers such as lipase and amylase showed significant correlation as depicted in (Table 7). SIRS which is simple scoring also correlated with serum IL-6 levels as shown in chart below. SIRS score increased simultaneously with IL-6 levels (Fig-1)

Conclusion

The events that regulate the severity of AP are usually unknown. The exact mechanisms by which diverse etiological factors induce an attack are still inconclusive, but once the disease path physiologic process is triggered, common inflammatory and repair pathways are initiated. The local inflammatory reaction at the site of injury which, if precipitated, leads to a systemic inflammatory response syndrome and it is this response that is believed to be ultimately responsible for the majority of the morbidity and mortality. Henceforth SIRS scoring which is simple, rapid, and accurate scoring can used as alternative to Multi-factorial scoring systems, as the Ranson's prognostic signs ,the Glasgow score ,and APACHE II which are evaluated only 48 hours after admission, which is too late for therapeutic decision-making.. Pro-inflammatory cytokines are considered to be important in the pathogenesis of severe acute pancreatitis. IL-6 is the key mediator for acute phase protein. It distinguishes between severe and mild acute pancreatitis with 86 % to 100 % sensitivity and 71 % to 100 % specificity. A rapid assay for serum concentration of IL-6 is available for the routine use. Even SIRS scoring and IL-6 levels correlated well with severity of pancreatitis. In conclusion, determining the serum concentration of IL-6 on the first day together with use of simple SIRS scoring at admission are helpful in earlier prediction and assessment of the severity of acute pancreatitis, its effective initial management and henceforth prevent its dreadful complications.

Summary

Acute pancreatitis is a frequently encountered disease, wherein in majority of patients it is self-limiting with an uneventful recovery and a mortality of less than 2 % (13). Progression to severe acute pancreatitis is seen in about 20 % of the attacks. Inspite of significant improvements in the treatment, the mortality remains between 15 and 25 % (14-15). An ideal scoring system and laboratory assay in the evaluation of acute pancreatitis patients should provide an early severity assessment to facilitate treatment. With this background our

study evaluated the utility of SIRS score and IL-6 in the prognostication of severe acute pancreatitis in primary health care setup. To sum up, we found that determining the serum concentration of IL-6 on the first day together with use of simple SIRS scoring at admission are helpful in earlier prediction and assessment of the severity of acute pancreatitis, its effective initial management and henceforth prevent its dreadful complications

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Ethics Committee Approval: Ethics Committee approval was received for this study from Ethical Committee of Rajarajeswari Medical College

Inform Consent: Written informed consent was obtained from the patients who participated in the study.

Conflict of Interest: No conflict of interest was declared by the authors.

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