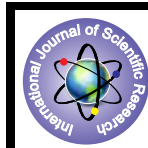


## The Evaluation of SIRS SCORE on Admission and Initial concentration of Interleukin - 6 as predictors of severe acute pancreatitis



### Medical Science

**KEYWORDS :** SIRS-Severe inflammatory response syndrome, IL-Interleukin

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### ABSTRACT

*Background: During the past 20 years many attempts have been made to create scoring systems and laboratory markers for early severity assessment of acute pancreatitis in low socioeconomic group patients, but the methods available are generally considered unsatisfactory. There seems to be therapeutic window within the first 48 h, when specific treatment alternatives may alter the patients' outcome. Good results have been obtained with early management of these patients. An ideal scoring system and laboratory assay in the evaluation of a patient with acute pancreatitis should provide an early severity assessment to facilitate the appropriate treatment modalities. Further, it should be applicable in the clinical setting, be rapid, low cost, accurate and available on a 24-hour basis. With this aim we evaluated the use SIRS score and IL-6 for predicting severity of acute pancreatitis*

*Methods: SIRS scoring system and serum concentration of IL -6 was evaluated for 30 patients with diagnosis of 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, abscess or pseudocyst. Correlation between sirs 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 December 2012 to October 2013 were studied, 12 mild-group patients and 18 severe-group patients. SIRS score for severe form was more than 2 while mild form had score < 2. Serum concentrations of IL-6 was highly significantly different ( $p < 0.005$ ) 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 pancreatitis.*

*Conclusion: The simple SIRS scoring system and serum concentration of IL-6 on the day of admission are useful for early prediction of the severity of acute pancreatitis*

### Introduction:

Acute pancreatitis (AP) is a sudden inflammation of the pancreas. AP is clinically represented with a plethora of symptoms that range from mild interstitial oedema to severe necrosis resulting in multi-organ failure (Mitchell et al 2003 Lancet). Gallstones and alcohol abuse have been cited as the leading cause of AP. Very few studies have linked social deprivation with incidences of acute pancreatitis. For instance, in a linkage study conducted by Roberts et al showed higher incidences of AP in the most socio-economic deprived group compared to the least deprived group. As AP has complex pathophysiology, one of the major challenges for clinicians is to accurately predict which patients would develop severe disease. At present there are no accepted method of practice to accurately predict the severity of the disease and the overall outcome of the disease. Various scoring systems based on clinical criteria have been used to determine severity in patients with AP such as the Ranson's prognostic criteria, Glasgow score. Their application in clinical practice is limited by the need to wait at least forty eight hours before any decision the course of treatment can be made. Another scoring system, the

Acute Physiology And Chronic Health Evaluation II (APACHE II) score is useful however it is cumbersome. Currently, contrast-enhanced computed tomography is the most accurate non-invasive method to evaluate the severity of acute pancreatitis. However, it is expensive and cannot be performed on all patients with AP due to associated risks of renal

complications. (Retalli et al 2003). Therefore, considerable interest has grown in the development of reliable biochemical

markers that reflect the severity of this would allow for better management of treatment options for patients.

Systemic Inflammatory Response Syndrome (SIRS) is the clinical manifestation of the inflammatory process mediated by cytokines that can occur after a variety of infectious and noninfectious insults.

A few studies have shown SIRS to be associated with severity of AP (Mofidi et al 2006, Singh, et al 2009). In particular, severe AP is associated with elevated serum levels of interleukin-6 (IL-6) (Pini 2012), an inflammatory cytokine released by macrophages.

Elevated levels of plasma IL-6 concentrations in patients with AP are correlated with the higher mortality rate. 6,7,10,11. Moreover, in two separate studies, IL-6 levels correlated with severity AP in patients (Heath, Pezzilli). The aim of the study was to evaluate the SIRS in assessing the severity of AP. In particular, we wanted to determine the levels of IL-6 in AP patients representing the most deprived (poor socio-economic) population.

### Methods

The demographic, clinical, laboratory and radiologic data for all patients directly admitted to our institution with a diagnosis of acute pancreatitis between December 2012-October 2013 were collected for this study. Data for all patients were prospectively collected within first 24 hours of acute pancreatitis. JSS university review board approved this study. Thirty-patients with acute pancreatitis admitted to the J.S.S Hospital, Mysore- from December 2012 to October 2013. All the patients were admitted in the Emergency unit. Diagnosis of acute pancreatitis was based

on complaints consisting of persistent upper abdominal pain. The diagnosis was confirmed by abdominal ultrasonography or abdominal computed Tomography (CT) scan examination. Patients diagnosed with AP were accessed for SIRS scoring. Blood samples were collected and assayed for IL-6 using Human IL-6 ELISA KIT (purchased?). Ranson's prognostic criteria were considered simultaneously to assess the significance of SIRS score and IL-6 levels. All patients received accepted form of medical care. Patients diagnosed as acute on 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:**

Sirs scores were given to all patients during first 24 hours of acute attack based on the criteria listed in the table. A patient was considered SIRS positive if met 2 or more of the criteria listed in the table. Serum samples were collected from the patients with fit the SIRS criteria.

**Table 2. Individual SIRS criteria :**

Temperature - >38°c or <36°c Respiratory rate -> 20 breaths/minute or Paco2 >32 mm hg Pulse -> 90 beats/minute WBC - <4000 cells/mm3 or >12,000 cells/mm3 or >10% immature Bands note.

**Statistical analysis**

Relationships between the numbers of SIRS criteria with Markers of severity were assessed using SSPS version 20 software:

1. Consistency coefficient:
2. Product moment correlation
3. One way anova
4. Independent sample t test
5. Chi square test
6. I am not sure how to modify this one.

**Results:**

A total number of 30 patients, 24 males, and six females whose ages ranged from 18- 70 years(mean age= 44). were studied. The etiologies were alcoholic, biliary and idiopathic. 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, abscess or pseudocyst. The clinical characteristics of these patients are shown in Table 1

**Table 1: Clinical characteristics of patients**

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

Sirs scores	N	Mean	Std. Deviation	Std. Error	95% confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
2.00	12	25.4915	20.33058	5.86893	12.5741	38.4089	2.10	58.47

3.00	17	94.2214	47.08998	11.42100	70.0099	118.4328	26.46	190.81
4.00	1	108.1860	.	.	.	.	108.19	108.19
<b>Total</b>	<b>30</b>	<b>67.1949</b>	<b>50.85265</b>	<b>9.28438</b>	<b>48.2062</b>	<b>86.1836</b>	<b>2.10</b>	<b>190.81</b>

In table 1, the number 9 is given for alcoholic. Please specify what this means. It would be beneficial if we got raw data of the patients.

**Table 2: Evaluation of SIRS scoring on admission patients**  
Based on the clinical characteristics of the patients, we did

**Table:2 Showing relation between SIRS score and care in the hospital**

SIRS score	Emergency ward(%)	ICU(%)	Total
2	12(100)	0	12
3	7(41.2)	10	17
4	1(100)	1	1
<b>Total</b>	<b>19</b>	<b>11</b>	<b>30</b>

What is ARDs, MODS?

**Table 4: Showing relation between Sirs score and complications**

S i r s score	Total	ARDS		MODS		Pseudocyst	
		No	%	No	%	No	%
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
<b>Total</b>	<b>30</b>	<b>13</b>	<b>43.3</b>	<b>08</b>	<b>26.6</b>	<b>11</b>	<b>36.6</b>
<b>p</b>		<b>&lt;0.0001</b>		<b>0.001</b>		<b>0.001</b>	

Shown in table 5, IL-6 levels were measured from serum samples taken from patients admitted either to the ER or the ICU. The mean IL-6 levels of patients within the ER was 34±23.11 and the ICU were 123±30.7 pg/ml (? Please ask). These results clearly demonstrate a correlation between higher IL-6 levels in the serum of patients admitted to the ICU compared to patients in the ER.

We next wanted to determine if there is correlation between the levels of IL-6 and the complications associated with it. Overall, patients with higher IL-6 levels were associated with ARDS and MODS whilst lower IL-6 levels were associated with pseudocyst. Moreover, patients with higher IL-6 levels also received a higher SIRS score. These results indicate that there is a strong correlation between higher IL- 6 levels and a high SIRS score. Together these, highlight the severity of AP within these patients.

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

	Group statistics				
	Admission place	N	Mean	Std. Deviation	Std. Error mean
Interleukin-6(pg/ml)	Emergency ward	19	34.3518	23.11625	5.30323
	ICU	11	123.9238	30.79082	9.28378

Chi-square test, p<0.000

**Table :6 Relation between Interleukin- 6 levels and complications**

	Interleukin-6 (pg/ml)						p
	Yes			No			
	N	Mean	SD	N	Mean	SD	
ARDS	13	102.7561	48.95706	17	40.0011	32.80711	<0.001
MODS	8	115.1940	53.18928	22	49.7407	37.83201	0.001
Pseudo cyst	11	93.2639	54.08587	19	52.1023	43.42138	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	.597(**)	.746(**)
	Significance(2-tailed)	.	.000	.000
	N	30	30	30
Interleukin 6	Pearson correlation	.597(**)	1	.480(**)
	Significance(2-tailed)	.000	.	.007
	N	30	30	30
Amylase	Pearson correlation	.746(**)	.480(**)	1
	Significance(2-tailed)	.000	.007	.
	N	30	30	30

\*\* correlation at 0.01(2-tailed)...

## DISCUSSION:

Severe AP is associated with high mortality rate which largely affects people representing poor socio-economic background. We have demonstrated that the severity of the AP can be predicted by analysing serum IL-6 levels of these patients. In our study, a group of 30 patients were analysed representing low socio-economic background and found a correlation between higher IL-6 levels and patients given a high SIRS score. This study further provides support for the use of a relatively inexpensive, rapid and less subjective test to predict the outcome of AP and therefore has the potential to advance patient management.

AP has a complex pathophysiology that has a mortality rate ranging from 2-10%. In most cases, the disorder is mild. However, in severe cases, the mortality rate can be 20%. The aetiology of acute pancreatitis can be very variable, but regardless of the etiological factor, premature intra-acinar activation of trypsinogen to trypsin within the pancreas is thought to play a key role as an early triggering event in acinar cell injury [19,20]. Severe AP progresses in two phases. In the first phase, extensive pancreatic inflammation and necrosis are followed by a systemic inflammatory response syndrome that may lead to multiple organ dysfunction syndrome within the first week, without any apparent bacterial infection (not sure where this came from) [21 (?)]. Unless this process is arrested and reversed by natural defences or therapeutic

interventions, the second phase ensues usually after the second week of onset, and is related to the formation of infected pancreatic necrosis or fluid collections with possible progression to overt sepsis, multiple organ dysfunction syndrome and death.

SIRS is systemic inflammatory response in infectious and non-infectious insults. SIRS has been studied in several non-infectious diseases, including trauma, cirrhosis, and subarachnoid haemorrhage. Most patients with AP exhibit SIRS within the first day of hospitalization.

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 2. Meanwhile our study confirms with simultaneous increase in SIRS score, patients developed complications like ARDS, MODS, Pseudocyst, etc as shown in Table 4. Henceforth evaluation SIRS score on day 1 predicted severe disease with high sensitivity (85%–100%). 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 an increased risk for severe disease ( $P < .01$ ).

Besides clinical assessment, amylase and lipase measurements, and imaging are used in the diagnosis of AP. However, the non-specific increases of amylase and lipase are well known and neither correlates with the severity of the acute pancreatitis. The diagnosis of acute pancreatitis is not always straightforward, and in many cases diagnosed at autopsy [22,23]. The ability of the clinicians to assess the severity of AP is poor and a significant number of patients misdiagnosed as having a mild disease and are given incorrect method of care.

Pro-inflammatory cytokines are considered to be important in the pathogenesis of severe AP and many single inflammatory markers have been assessed to predict the severity of the disease. However, there is no single, standard method to assess the severity of the disease.

IL-6 is the key mediator for acute phase protein synthesis in the liver [23]. Various studies have demonstrated the levels of IL-6 is a highly sensitive method to distinguish between mild and severe AP. Moreover, the concentrations of IL-6 can be assessed at least 24 hours earlier as compared to levels of the cytokines such as C-reactive protein (CRP).

Our study confirmed severity of pancreatitis increased levels of serum IL-6. Patients with higher IL-6 levels developed more complications and needed ICU care as shown on table 5 and 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. Therefore, determining the serum concentration of IL-6 within 24 hours, and SIRS scoring, can be used to accurately predict the severity of AP in the most deprived socio-economic population. It can be used as an alternative to the routinely used scoring systems such as APACHE, Glasgow score and Ranson's prognostic signs.

## Conclusion:

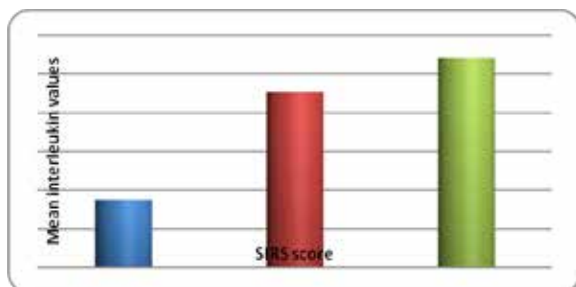
The events that regulate the severity of AP are for the most part unknown. The exact mechanisms by which diverse etiological factors induce an attack are still unclear, but once the disease process is initiated, common inflammatory and repair pathways are invoked. There is a local inflammatory reaction at the site of injury which, if marked, leads to a systemic inflammatory response syndrome, and it is this systemic 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 be used as an alternative to Multi-factorial scoring systems, as the Ranson's prognostic signs, the Glasgow score, and APACHE II which are evaluated only 48 h after admission, which is too late for therapeutic decision-making. Proinflammatory 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**

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.

**Table 8: Relation between the sirs score and interleukin 6 (n=total no of patients)**



**Depicts relation between sirs score and interleukin 6**

S2	35.11
S3	90.7
S4	108.18

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