Persistent Systemic Inflammatory Response Syndrome predicts the need for tertiary care in Acute Pancreatitis

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Abstract

Introduction: **Patients with Acute Pancreatitis (AP) presenting with Systemic Inflammatory Response syndrome (SIRS) are more likely to have severe acute pancreatitis and are at increased risk of complications. Additionally, persistence of SIRS at 48 hrs after admission is associated with persistent organ failure and a worse outcome. We investigated the usefulness of SIRS as a criterion for referring patients to a tertiary pancreatic care centre.**

Material and Methods: **Retrospective analyses of patients admitted with AP over a one year period. Patients were classified into 2 severity groups – 1) Mild AP, 2) Moderate and Severe AP (MASP) as per the Revised Atlanta Classification. SIRS was determined at presentation and following 48 hours of best medical management. Outcomes were compared between patients who had no SIRS at presentation, transient SIRS(SIRS≤48hrs) and persistent SIRS(>48hrs).**

Results: **134 patients were included in the study. SIRS at presentation had a sensitivity of 88%(95% CI 75-96) and a specificity of 66%(95% CI 55-75) in predicting MASP. However, persistent SIRS and recovery from SIRS within 48hrs were poor predictors of MASP. Only 23/43 (53.5%) patients with MASP had persistent SIRS. Interestingly, MASP patients with persistant SIRS had a significant higher risk of complications, readmission, intervention, culture positivity and hospital stay as compared to those with transient SIRS.**

Conclusion: **Persistent SIRS could be used to identify patients with MASP requiring tertiary care. This could be used as an effective tool by community hospitals with limited facilities. Further, prospective studies are required to validate our findings.** (Acta gastroenterol. belg., **2017**, 80, **377-380**).

Key words : Pancreatitis, SIRS, and referral.

Introduction

Systemic Inflammatory Response Syndrome (SIRS) is commonly seen in patients presenting with Acute Pancreatitis (AP) (1). This is a result of widespread acinar cell injury. Additionally, the attending hypovolemia associated with AP leads to gut ischemia, bacterial translocation and endotoxemia perpetuating the existent SIRS (2). SIRS at admission was found to have a sensitivity of 80.6 % and a specificity of 65.9 % for prediction of Severe Acute Pancreatitis (SAP) (3). Additionally, the persistence of SIRS despite 48 hours of intense medical management is associated with increased morbidity and mortality (4,1). Despite these findings SIRS is not being routinely used as a clinical severity indicator in AP. We assessed the effect of transient or persistent SIRS on in-hospital course and prognosis.

Material and Methods

Patients

Demographic, clinical, laboratory, radiological and outcome data for all patients with AP admitted to the Departments of Gastroenterology and Hepatobiliary Surgery between August 2013 and July 2014 was retrospectively analyzed. Exclusion criteria included patients below the age of 18yrs and above 75yrs, those with chronic pancreatitis or recurrent acute pancreatitis, incomplete data, those refusing best medical care and other hospital transfers. The diagnosis of AP was made based on any two of the three criteria: i) Upper abdominal pain +/- vomiting +/- radiation to back ii) Serum amylase > 300U/mL or Serum Lipase > 180U/mL iii) CT or US evidence of Acute pancreatitis. SIRS was defined as the presence of two or more of these criteria : 1) Temperature >38°C (100.4°F) or <36°C (96.8°F) ; 2) Heart Rate >90 ; 3) Respiratory Rate >20 or $PaCO_2$<32mmHg ; 4) White Blood Cell (WBC) Count >12,000 or <4,000 or >10% bands. The modified Marshall scoring system was used to define Organ failure (5). The Revised Atlanta Classification was used to validate the population sample (6). Presence of SIRS was determined at admission and at 48 hours, following standard medical management. Patients were classified into three groups – Absence of SIRS, Transient SIRS (SIRS reversed within 48 hours of therapy) and, persistent SIRS (SIRS beyond 48 hours). The severity of AP was expressed as a binomial variable based on the Revised Atlanta Classification – 1. Mild Pancreatitis 2. Moderate, Moderately severe and Severe Pancreatitis (MASP). – This included patients with moderate, moderately severe and severe pancreatitis. Organ failure as a complication was not included during analysis of data for validation using the Modified Atlanta

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Table1.— **Baseline characteristics of Study Population**

Criterion	n=134	
Age	42.50±15.10	
Female:Male	33/101	
Aetiology	Alcohol	66(49%)
	Biliary	47(35%)
	Others	21(16%)
Comorbidity	DM	36/134 (27%)
	IHD	8/134 (6%)
	Hypertension	31/134 (25%)
	Br. Asthma	1/134 (0.75%)
Symptoms	Pain	134 (100%)
	Fever	20 (15%)
	Jaundice	10 (7.5%)
	Vomiting	90 (67%)
Duration of Inhospital stay	6(IQR5,2-31)	
Previous hospital stay	2(IQR1,1-7)	
Duration of Pain	3(IQR6, 1-60)	
Duration of Vomiting	1(IQR3, 1-20)	
Complications	41 (31%)	
Culture +ve	22 (16.5%)	
Readmission	33 (25%)	
WCC	13312±4781(4700-33800)	
Creatinine	1.1±1.2(0.3-10)	
BUN	16.8±14.2(3.2-97.66)	
S. Amylase	889±1027(64-6645)	
S. Lipase	1648±2005(33-11050)	

Classification, but was included during analyses for the SIRS Classification. Culture positivity was defined as demonstrable significant microflora cultured from any body fluid during the course of admission requiring antibiotic / antifungal therapy. The aim of the study was to test the ability of SIRS to predict MASP.

Statistical Analyses

Analysis was done using STATVIEW (SAS Institute Inc., Carney, NC). Descriptive statistics was used to present demographic, treatment and outcome data. Parametric data between groups was compared using the student't' test / ANOVA or the chi sq test as applicable. Non parametric data between two groups was compared using Fisher's exact test or Mann-Whitney 'U' Test as applicable. Statistical significance was defined as $p \leq 0.05$.

Results

134/209 (25% females) patients were included in the study (Fig. 1). 1 patient died during the course of admission. The predominant aetiology was alcohol followed by choledocholithiasis. The demographic, symptom and treatment variables are shown in Table 1. Based on the Modified Atlanta Classification 91 patients had mild, 37 moderate/Moderately severe and 6 severe pancreatitis. Increasing severity of AP was significantly associated with increased in-hospital stay, complications, readmission, need for ICU admission, culture positivity and the need for radiololgical/surgical intervention (Table 2).

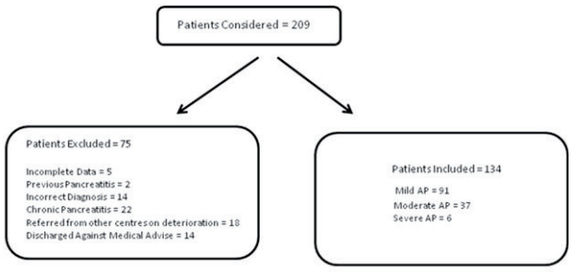

Fig. 1. — Flow Chart of patients considered and recruited into study

65/134 (48.5%) patients did not present with SIRS, or develop SIRS at 48 hours. Of the remaining, 32 (24%) recovered from SIRS at 48 hours and 37(27.5%), had persistent or new onset SIRS at 48 hours. There was a progressive significant increase in the risk of complications, readmission, need for ICU admission, culture positivity and the need for radiololgical/surgical intervention and in-hospital stay when comparing patients in the three groups (Tabel 3).

SIRS at presentation had a sensitivity of 88% (95%CI75-96) and a specificity of 66% (95%CI 55-75) in predicting MASP. However, presence of SIRS at 48 hours had a specificity of 87 % (95%CI78-93) and a sensitivity of only 58% (95%CI 42-73) in predicting

Table 2.— **Comparison of severity groups based on the Modified Atlanta Classification**

Atlanta Grade	Mild	Mod and Mod Severe	Severe	p value
n	91	37	6	
In hospital Stay	5(3,2-12)	7(5,3-31)	13(9,8-22)	<0.0001
Culture	9	10	3	0.0045
Complications (Excludes Organ Failure)	16	19	4	<0.0001
ICU stay	17	17	5	0.0082
Intervention	2	5	2	0.0074
Mortality	0	0	1	-
Readmission	18	15	0	<0.01

Table 3. — **Comparison of Severity groups based on the SIRS Classification**

SIRS Classification	SIRS-ve at presentation	Transient SIRS	Persistant SIRS	p value
n	65	32	37	
In hospital Stay	5(3.25,2-12)	5(4.75,3-14)	8(8,4-31)	<0.0001
Culture	5	6	11	0.014
Complications	9	12	20	<0.0001
ICU stay	6	11	18	<0.0001
Intervention	1	1	7	0.004
Mortality	0	0	1	-
Readmission	1	4	12	<0.0001

Table 4. — **Diagnostic accuracy of SIRS at various time points in predicting severity of AP**

SIRS as a Predictor of MASP			
	Transient SIRS	Persistant SIRS	Recovery from SIRS at 48hrs
Sensitivity	88(75-96)	58(42-73)	61(42-77)
Specificity	66(55-75)	87(78-93)	68(48-84)
PPV	55(43-67)	68(50-82)	69(49-85)
NPV	92(83-97)	82(72-89)	59(41-76)

Table 5. — **Comparison between patient groups with and without SIRS at 48 hours who were eventually categorized as MASP**

	Persistant SIRS	Transient SIRS	P value
Complications	17/23	8/20	0.03
Culture +ve	10/23	3/20	0.05
Readmission	12/23	3/20	0.02
ICU admission	12/23	7/20	0.35
Need for Intubation	5/23	1/20	0.19
Intervention	7/23	0/20	0.01
Organ Failure	11/23	6/20	0.35
Dialysis	2/23	3/20	0.35
Hospital Stay	10(IQR9.75,6-31)	6.5(IQR5,3-12)	0.001

MASP. In addition the recovery from SIRS within 48 hours of admission was again a poor predictor of MASP (Table 4).

Out of the 43 patients who had MASP, 23 (53.5%) had SIRS at 48 hours. Within this MASP population patients with SIRS at 48 hours had a significant higher risk of complications, readmission, intervention, culture positivity and hospital stay as compared to those without SIRS at 48 hours (Table 5).

Discussion

The initial management of AP is essentially supportive with controlled fluid resuscitation, early enteral nutrition and exclusion of sepsis (7). Initial radiological investigation includes an ultrasound to rule out gall stones and a CT only in case of diagnostic dilemma. An urgent ERCP within 24 hours is only indicated for biliary pancreatitis with an obstructing calculus and cholangitis (8,9). Radiological, endoscopic or surgical intervention is usually indicated only after the 2nd or 3rd week of onset (7). Hence, most patients can be safely managed at any hospital for the first 48 hours of admission. The challenge is to identify patients who will go on to require intervention or, prolonged intensive care in a tertiary centre.

Around 20% of patients presenting with AP develop complications necessitating prolonged hospital stay, critical care, interventional and surgical expertise (7). Hence, it is imperative to identify this sub group of patients and refer them to a suitable facility. Various scoring systems used for risk stratification including the Ransons, Glasgow, BISAP, APACHE II and HAPS have been adopted with sensitivities and specificities of 70-90% (3). However, they are often constrained by their modest predictive values at best, availability of resources and, the need for observing trends (over 48 hours). The Revised Atlanta Classification emphasizes the importance of the presence and persistence of Organ failure as well as radiological criteria in determining severity. Hence, it cannot be adopted as a method to stratify risk and the need for upgrading care (5,6). Previous data has suggested that SIRS by itself could predict severe AP and persistence could predict ongoing organ failure (1,4,10). Hence, we analyzed the trends in SIRS as a criteria to predict MASP and also evaluated its usefulness as a tool to refer patients to a tertiary centre.

In accordance with previous published data, our data shows that SIRS at presentation has a sensitivity of 88%(95%CI 75-96) in predicting MASP. In contrast, persistent SIRS has a poor sensitivity but a higher specificity [87% (95%CI78-93)] in predicting MASP. Around half the patients with MASP (20/43, 47%) had recovered from SIRS within 48 hours. Hence, recovery from SIRS or, absence of SIRS could not be used as a reliable tool to exclude MASP. Interestingly however, amongst patients with MASP, those with transient SIRS recovered earlier [In-hospital stay -6.5 (IQR5,3-12) vs. 10 (IQR9.75,6-31) ; p = 0.001] and had a significantly lower complication, readmission, culture positive and radiological intervention/surgical rates as compared to those with persistent SIRS. Hence, MASP t patients with transient SIRS are less likely to require an intervention and hence, can be managed at a secondary facility.

Previous studies looking at SIRS in AP have tried to establish a relationship between SIRS and organ failure and thereby, outcome (4,10). Buter *et al.* showed that both deteriorating organ failure and persistant SIRS predicted mortality on unvariate analyses but SIRS lost its significance on multivariate analyses (10). A temporal relationship between SIRS and organ failure could not be established as some patients presented very early on with organ failure. Hence, the opportunity to prevent organ failure in such patients if at all possible was non-existent. Johnson et al. reported that persistant organ failure (>48 hours after admission) was associated with mortality and morbidity of 35% and 77%, in contrast to <1% and 29% in patients with transient organ failure (<48hrs) (4). What is not clear is how many of these patients with organ failure actually required specialist treatment. The aim of our study was to look at the ability of SIRS to predict the need for tertiary care and hence, would guide early referral. It does not seek to use SIRS as a predictor of organ failure. as often organ failure as defined in AP may not require tertiary care facilities. We have demonstrated that the presence of SIRS at 48 hours could be used as

an indication to transfer patients to a tertiary centre. Although the sensitivity of this is poor in predicting MASP, none of the patients in the MASP group in our patient population with transient SIRS required any surgical or radiological intervention.

The pathophysiological mechanisms underlying the differential behavior of patients with MASP is likely to be related to the impact of AP on the gut. It is increasingly being recognized that the 'gut' is the most important organ that contributes to perpetuating the inflammation and subsequent infection in AP (2,11). Strategies including early aggressive fluid resuscitation and early enteral nutrition enable reversal of gut hypoxia and restoration of gut mucosal integrity. It is quite possible that patients with MASP who reverse their SIRS in 48 hours manage to do so because of reversal of gut hypoxia and hence, their lower risk of infection and other complications (11).

There are several limitations to this study. The retrospective nature of the study excluded 25 patients due to inadequate data. Further, our study excluded patients who were transferred from other hospitals ; a group that accounted for an additional 4 in-hospital deaths. It is unclear as to whether these patients died because of disease severity or inadequate management from the referring hospital. However, we have demonstrated that trends in SIRS over the first 48 hours could be used to identify patients with MASP requiring tertiary care. The quality of medical care including the referral patterns vary widely between countries. Primary care hospitals can vary widely in the array of tests that are available as well as the standard of care provided. Hence, we believe that SIRS can be used universally irrespective of the available facilities. Further, prospective studies are required to validate our findings.

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