

The Predictive Value of C-Reactive Protein in Acute Pancreatitis for the Severity of Disease

Asif Ali Amir Ali, Sughra Parveen, Mazhar Iqbal, Imran Khan, Tanweer Ahmed, Shahzore Gul
Department of General Surgery, Jinnah Post Graduate Medical Centre, Karachi.

Abstract

Background: Acute pancreatitis (AP) has been defined as an “acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems”. Increasing incidence of AP worldwide with 33.74 cases per 100,000 persons per year reported globally over the last few years has landed it amongst the most common gastrointestinal disorders requiring hospitalization.

Objective: To determine the efficacy of C Reactive Protein (CRP), in predicting severity and outcome of Acute Pancreatitis (AP), taking CT scan findings as gold standard.

Study type, settings & duration: This cross-sectional research was conducted at the Department of General Surgery (Unit III), Jinnah Postgraduate Medical Center, Karachi, from January to March 2021.

Methodology: A sample of 186 patients (obtained via non-probability – consecutive sampling), presenting with acute pancreatitis (based on Revised Atlanta Classification – RAC). After taking written informed consent, patient data was recorded on a structured questionnaire (containing inquiries pertaining to basic biodata, sociodemographic details, presenting complaints, inferences obtained from disease history and clinical examination, laboratory investigation (CRP values and variations – at scheduled intervals), CT findings, and patient outcome. The data obtained was analyzed using SPSS. v. 21.0.

Results: The mean age of the sample was 39 (SD $\pm$ 4) years and 119 (63.9%) were males, while the remaining 67 (36.1%) were females. A raised CRP ($\geq$ 150 mg/dL) was present among 163 (87.6%) of the patients. CRP changes at 24, 48 and 72 h were synonymous with disease severity and a positive association between CRP level / CRP change (rise) and disease severity was noted (p value 0.035). Recovery was achieved during the study period among majority of the patients, however complaints such as pancreatic necrosis were reported in 24 (12.9%), abscesses in 32 (17.2%), and pseudocysts in 25 (13.4) patients. Mortality was reported in 2 cases.

Conclusion: CRP has a high efficacy at predicting disease severity of acute pancreatitis. The evidence yielded has offer much needed solace from AP, which is a pressing situation, both for the patient and healthcare provider. The resources (infrastructural and financial) for CT evaluation of AP patients are often not available and thus, CRP may offer help for the much needed insight into the disease severity quickly, easily and at a lower cost.

Key words: Acute pancreatitis, predictive value, disease severity, revised atlanta classification, efficacy.

Introduction

Acute pancreatitis (AP) has been defined as an “acute inflammatory process of the pancreas

Corresponding Author:

Asif Ali Amir Ali

Department of General Surgery
Jinnah Post Graduate Medical Centre, Karachi.

Email: aakhowaja09@gmail.com

Received: 06 August 2021, **Accepted:** 31 May 2022,

Published: 18 October 2022

Authors Contribution

AAAA & SP conceptualized the project. AAAA, IK, TA & SG did the data collection. AAAA, SP & MI did the literature search. AAAA, SP & TA also performed the statistical analysis. Drafting, revision & writing of manuscript were done by AAAA, MI & IK.

Copyright © 2022 The Author(s). This is an Open Access article under the CC BY-NC 4.0 license.

with variable involvement of other regional tissues or remote organ systems”.¹ Increasing incidence of AP worldwide with 33.74 cases per 100,000 persons per year reported globally over the last few years has landed it amongst the most common gastrointestinal disorders requiring hospitalization.² Despite recent advances of diagnosis and treatment modalities, mortality rate in severe acute pancreatitis (SAP) is still high.³

Over 25% of cases involving AP are severe, with mortality as high as 10% globally.¹ In Pakistan, few studies have been carried out to assess the spectrum of AP in indigenous patients. Studies conducted in Karachi reported mortality ranging from 5% to 40% correlating with degree of necrosis.^{4,5} A study from a tertiary care hospital in Islamabad reported mortality to be 8.4%.⁶ Data from

a single unit in a tertiary care hospital in Rawalpindi revealed a mortality of 14.03%.⁷

The early and accurate staging of the severity and the assessment of prognosis of the disease are of great clinical significance so that the urgent and most suitable therapy can be provided for the AP patient. In recent years, several clinical and imaging systems for scoring the severity and prognosis of AP have been developed, including Ranson's criteria, acute physiology and chronic health evaluation (APACHE II) and CT criteria⁸ and so on. Most of these tests are either difficult to remember, take greater than 48 hours to enable full severity stratification, or rely on diagnostic testing that is not widely available.⁹

The search for a tool that can improve on the clinical assessment has been ongoing for decades. Ideally, such a tool should be simple, inexpensive, noninvasive, easily applicable, reproducible and have the statistical power to arrive to a valid conclusion accurately.¹⁰ In recent decades, several researchers have attempted to identify early predictors of severity of acute pancreatitis that may help give insight into the clinical course, complications, prognosis and mortality in patients with AP.¹ CRP is believed to be a strong candidate in this regard.

Shah SS et al, believed that CRP can be the most ideal "single test" marker for assessment of severity of AP. He claimed that CRP levels between 120 to 210/L distinguish of between mild and severe disease.¹⁰ The only drawback is that it is ideal for predicting the severity during day 2 to 4 since the CRP levels take time to build up.¹¹

The disease burden associated with severe acute pancreatitis is worrisome and with statistics predicting a hike in incidence and prevalence, the condition merits attention. A local study by Iqbal M, et al, claimed that the overall mortality due to this disease was 3.64%. Mortality in acute moderate pancreatitis was 14.05% and in acute severe pancreatitis 30%. Local and systemic complications occurred in 18.33% patients. This included ARDS (20%), pleural effusion (20%), hypocalcaemia (20%), shock (18.8%), neurological (13.63%) and renal failure (13.63%).¹²

As stated earlier, a better prognosis can be achieved if the severity of the condition is identified early, enabling early treatment interventions. Simple measures such as plain chest radiographs, blood biochemical data; may offer much insight; however not enough evidence is available in this regard and hence the predictive power remains to be statistically gauged. This research was aimed to provide much needed insight into the predictive

ability of CRP with regards to disease severity of AP.

Methodology

This cross-sectional research was conducted at the Dept. of General Surgery (Unit III), Jinnah Postgraduate medical Center, Karachi, from January to March 2021, upon a sample of 186 patients (the sample size was calculated via WHO open-epi calculator, by taking the margin of error as 5%, confidence interval as 95% and frequency of mortality in acute moderate pancreatitis as 14.05%.¹²), obtained via non-probability – consecutive sampling and presenting with acute pancreatitis (based on Revised Atlanta Classification – RAC). After taking written informed consent, patient data was recorded on a structured questionnaire (containing inquiries pertaining to basic biodata, sociodemographic details, presenting complaints, inferences obtained from disease history and clinical examination, laboratory investigation (CRP values and variations – at scheduled intervals) and CT findings.

Data was analyzed using SPSS v. 21.0. Frequency or percentages were calculated for qualitative variables. Mean $\pm$ SD were calculated for quantitative variables. The normality of the data was determined via a Shapiro wilk test. Pearson's correlation coefficient was used to check association between elevated C reactive protein levels and Chi square test was applied to determine the strength of the statistical significance. P value of less than 0.05 was be taken as statistically significant.

Any patient meeting two of the following three criteria was regarded as patient having AP:

- (i) Abdominal pain consistent with pancreatitis,
- (ii) Serum amylase (or lipase) more than three times the upper limit of normal and
- (iii) Radiological evidence of AP on CE-CT, ultrasound or MRI

Severe disease was defined as having persistent organ failure (>48 h). Moderately severe disease was defined as transient organ failure (<48 h) or the presence of local systemic complications without persistent organ failure. Mild disease was defined by the absence of organ failure and local or systemic complications. The measured outcome was to compare whether absolute CRP or interval CRP changes at 24, 48 and 72 h are a better predictor of disease severity. Absolute CRP measurements at admission, 24, 48 and 72 h were recorded along with revised Atlanta Classification disease severity for each patient. The outcome measures were recovery,

complications (pancreatic necrosis, abscesses and pseudocysts, and mortality).

Consenting patients (aged 12 to 60 years) of either gender, presenting to the study setting with AP (as per Revised Atlanta Classification), were included in the research.

Patients with comorbid medical Conditions (Diabetes Mellitus & Congestive Heart Failure), pancreatic Carcinoma or Other neoplastic Conditions, chronic Pancreatitis and pregnant women were excluded from sample.

The Ethical approval was obtained from Institutional Review Board of Jinnah Postgraduate Medical Centre, Karachi.

Results

The mean age of the sample was 39 (SD $\pm$ 4) years and 119 (63.9%) of the sample comprised of males, while the remaining 67 (36.1%) were females. A raised CRP ($\geq$ 150 mg/dL) was present among 163 (87.6%) of the patients (Table). CRP changes at 24, 48 and 72 h were synonymous with disease severity and a positive association between CRP level / CRP change (rise) and disease severity was noted (p value 0.035). Recovery was achieved during the study period among a majority of the patients, however complaints such pancreatic necrosis 24 (12.9%), abscesses in 32 (17.2%), and pseudocysts in 25 (13.4) patients were reported. Mortality was reported in 2 cases.

Table: C reactive protein statistics.

Variable		Statistic
Mean Age (Years)		39 (SD $\pm$ 4)
Gender	Male	119 (63.9%)
	Female	67 (36.1%)
Diagnostic Value of CRP	True Positive	163 (87.6%)
	False Negative	06 (10.2%)
Disease Severity	Mild	38 (20.4%)
	Moderate	92 (49.5%)
	Severe	56 (30.1%)

CRP Point Values (mg/dL)

Variable		Time (Hours)			
		0	24	48	72
Disease	Mild	167	185	197	205
Severity	Moderate	193	217	249	266
	Severe	222	242	276	349
p Value		0.063	0.070	0.059	0.035

CRP Interval Change

Variable		Time (Hours)			
		0	24	48	72
Disease	Mild	-	+ 18	+ 12	+ 08
Severity	Moderate	-	+ 24	+ 32	+ 17
	Severe	-	+ 20	+ 34	+ 73

Discussion

AP is a major health concern. The acute nature further necessitates a heightened level of readiness of the healthcare setup. If the level of severity of AP can be predicted, a more suited response can be initiated to treat the condition better. CRP may help immensely in this regard by offering a cheap, quick, easy and accurate method of predicting the severity of AP. This study demonstrates that interval change in CRP from the time of admission is as valuable an indicator of severity as the absolute value. After some debate, the Atlanta classification was revised in 2012, as a result of improved understanding of the pathophysiology of AP. Consequently, the inclusion of a moderate AP subtype has been adapted to include those patients that have transient organ dysfunction. Though the role of CRP in predicting severity of AP has been previously examined, this was largely prior to the revised Atlanta classification system and therefore less applicable.^{13,14}

Irum F et al, has reported that raised CRP levels were observed in 92 (92%) patients. Mean CRP level was found to be 34.23 ± 10.78 mg/dL. All the patients with moderate and severe disease were found to have raised CRP levels. Upto 66 (89.2%) of the mild cases also had raised CRP levels.¹⁵ Additionally, there is substantial evidence across the literature outlining the benefits of CRP as an acceptable indicator of AP severity. As a result, it has become one of the most widely utilized biomarkers in clinical practice. Shah SS too believed that CRP can be the most ideal "single test" marker for assessment of severity of AP.¹⁰

However, CRP response lags chronologically behind in-vivo systemic inflammation. Therefore, initial CRP at time of admission still has poor initial predictive value of severity. Additionally, even at 24 h post onset of AP, CRP is still inferior to other biomarkers. IL-6, IL-8 and TNFa are early pro-inflammatory cytokines released during the acute phase response which in turn stimulate the liver to produce CRP. Several studies have observed them as superior biomarkers of severity during the first 24-h of AP. Despite this, cost implications limits the widespread use of such

markers. Furthermore, alternative biomarkers like blood urea nitrogen (BUN) levels have also been proposed in early inflammation.^{16,17} Additionally, Irshad A, in her research claims to have noted a strong positive correlation between CT severity index and CRP level, r-value 0.346.¹⁸

Speculation that early trends in CRP may have a greater utility as a diagnostic test than the absolute value has been raised. Our study shows at 24 h the performance of both interval change and absolute value were suboptimal. This study concurs with Cardoso's data on the optimum timing of absolute CRP measurement to be 48 h. In addition, this study suggests the optimal timing for utilizing the trend or interval change in CRP would also be 48h. The accepted figure by international consensus for prediction of severe acute pancreatitis is an absolute CRP >150 mg/dL within 48 h of admission. Local research by Shah SS et al, favored level between 120 to 210 L.¹¹ Although it should be noted that this value was decided when the presence of local complications, and transient (<48 h) organ failure, would have constituted severe pancreatitis. Currently, the revised Atlanta classification would consider this moderately severe pancreatitis; a prognostically distinct subgroup.^{19,20}

We acknowledge that our study has several limitations that impact on its generalizability. Firstly, CRP levels and intervals were calculated from the time of admission. The duration of symptoms prior to admission was not recorded in this study. A well-established inflammatory response at the time of admission could reduce the sensitivity of an acute interval change or an early rise in CRP, absolute CRP levels may also be representative earlier. However, the optimal timing of CRP measurement suggested by this study agrees with other studies.^{21,22}

CRP has a high efficacy at predicting disease severity of acute pancreatitis, with sensitivity and specificity reported at 90% and 100%, respectively and thus, CRP may help offer much needed insight into the disease severity quickly, easily and at a lower cost.

Conflict of interest: None declared.

References

1. Maher MM, Dessouky BA. Simplified early predictors of severe acute pancreatitis: a prospective study. *Gastroenterol Res* 2010; 3(1): 25.
2. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; 144: 1252-61.
3. Xiao AY, Tan MLY, Wu LM, Asrani VM, Windsor JA. Global incidence and mortality of pancreatic

- diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. *Lancet Gastroenterol Hepatol* 2016; 1: 45-55.
4. Pal KM, Kasi PM, Tayyeb M, Mosharraf SMF, Fatmi Z. Correlates of morbidity and mortality in severe necrotizing pancreatitis. *ISRN Surg* 2012; 2012: 1-5.
5. Iqbal M, Malik M, Perveen S. Morbidity and mortality in acute pancreatitis. *J Surg Pak* 2015; 20: 4-7.
6. Siddiqui ZR. Presentation and outcome of acute pancreatitis at Pakistan Institute of Medical Sciences, Islamabad. *Ann Pak Inst Med Sci* 2007; 3: 67-70.
7. Ahmed R, Shafique MS, Ahmad SH, Hassan M, Adnan N. Spectrum of acute pancreatitis on surgical floor of tertiary care hospital. *Rawal Med J* 2016; 41: 31-5.
8. Ju S, Chen F, Liu S, Zheng K, Teng G. Value of CT and clinical criteria in assessment of patients with acute pancreatitis. *Eur J Radiol* 2006; 57(1): 102-7.
9. Hussain T, Hanif M, Ghazanfor R, Arslan S, Nawaz I, Umar M. Acute Pancreatitis severity scoring index: Prospective study to identify determinants in Pakistan. *J Rawalpindi Med Coll* 2020; 24(3): 264-9.
10. Frossard JL, Hadengue A, Pastor CM. New serum markers for the detection of severe acute pancreatitis in humans. *Am J Respir Crit Care Med* 2001; 164(1): 162-70.
11. Shah SS, Ansari MA, Ali S. Early prediction of severity and outcome of acute severe pancreatitis. *Pak J Med Sci* 2009; 25(4): 619-23.
12. Iqbal M, Malik M, Perveen S. Morbidity and mortality in acute pancreatitis. *J Surg Pak (Int)* 2015; 20: 4.
13. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62(1): 102-11.
14. Buter A, Imrie CW, Carter CR, Evans S, McKay CJ. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. *Br J Surg* 2002; 89(3): 298-302.
15. Irum F, Anwar S, Mushtaq MJ. Frequency of Raised Serum CRP in Acute Pancreatitis-A Cross-Sectional Study at Lahore General Hospital. *Pak J Med Health Sci* 2018; 12(3): 999-1001.
16. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Localio SA. Objective early identification of severe acute pancreatitis. *Am J Gastroenterol* 1974; 61(6): 443-51.
17. Larvin M, McMahon M. APACHE-II score for assessment and monitoring of acute pancreatitis. *The Lancet* 1989; 334(8656): 201-5.
18. Irshad A, Ahsan MF, Khan MA, Rasheed I, Asif M. Correlation of C-Reactive Protein and Computed Tomography Severity Index in Acute Pancreatitis. *Annals King Edward Med Uni* 2021; 27(2): 245-8.
19. Pooran N, Indaram A, Singh P, Bank S. Cytokines (IL-6, IL-8, TNF): early and reliable predictors of severe acute pancreatitis. *J Clin Gastroenterol* 2003; 37(3): 263-6.
20. Al-Bahrani AZ, Ammori BJ. Clinical laboratory assessment of acute pancreatitis. *Clinica Chimica Acta* 2005; 362(1-2): 26-48.

21. Khanna AK, Meher S, Prakash S, Tiwary SK, Singh U, Srivastava A, et al. Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. *HPB Surgery*. 2013 Sep 24; 2013.
 22. Stirling AD, Moran NR, Kelly ME, Ridgway PF, Conlon KC. The predictive value of C-reactive protein (CRP) in acute pancreatitis—is interval change in CRP an additional indicator of severity? *HPB (Oxford)* 2017; 19(10): 874-80.
-