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ORIGINAL ARTICLE

C-Reactive Protein as a Prognostic Indicator: Navigating the Challenge of Predicting Severity and Mortality in Acute Pancreatitis

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ABSTRACT

Objective: The main goal was to evaluate the effectiveness of C-reactive protein (CRP) in assessing acute pancreatitis severity 48 hours after onset by contrasting its results with CT scans.

Methodology: This cross-sectional study, which lasted six months from May to December 2019 at the Department of General Surgery, Pakistan Institute of Medical Sciences, comprised 150 suspected cases. CT scans and serum samples were taken 48 hours after the onset of symptoms. A postgraduate trainee created reports using a standard proforma to record CT scan results and CRP levels.

Results: The average age of the patients was 45.03±10.86 years, with severe acute pancreatitis confirmed in 28.7% of cases by CT scans. CRP demonstrated notable diagnostic values: sensitivity 81.4%, specificity 92.52%, PPV 81.4%, NPV 92.52%, and an overall accuracy of 89.33%.

Conclusion: CRP, a product of interleukin-1 and interleukin-6 responses by the liver, emerges as a valuable and cost-effective biomarker. Its consistent elevation in correlation with pancreatitis severity, especially within the critical 48-hour window, suggests its potential as a reliable predictor. This study underscores CRP's diagnostic utility and accessibility, emphasizing its role in assessing acute pancreatitis severity.

Key Words: C-reactive protein, CT scan, Acute pancreatitis

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [2,4]Critical analysis and manuscript review; [5,6]Data analysis; Manuscript editing

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Introduction

Acute pancreatitis, the most common pancreatic disease in both children and adults, is characterized by a rapidly progressing inflammation of the pancreas that is reversible but continues to cause inflammation to the organ.[1]

In the US, there are 40 cases of acute pancreatitis for every 100,000 adults annually. This is an increasing incidence. In 2009, the most common gastrointestinal diagnosis for hospitalization in the US was acute pancreatitis.[2]

Nonetheless, a portion of patients experience severe illness regardless of the severity of the initial injury. It has a high mortality rate of up to 45% and morbidity. In addition to trauma, viral infections, and systemic diseases, cholelithiasis and alcohol consumption account for 50% of adult cases of acute pancreatitis.[3] In developed nations, alcohol consumption accounts for 80% of pancreatitis cases, while in developing nations, malnutrition accounts for 83% of cases.[4]

Patients who have acute pancreatitis typically die between 10% and 15% of the time. More often than not, patients with biliary pancreatitis die from the condition, but over the past 20 years, supportive care has improved, resulting in a decline in mortality.[5]Sepsis affects 22.8% of all deaths, followed by cardiovascular failure (21.1%), respiratory failure (12.3%), and other causes. 6 deaths are due to renal failure, and 3 percent are caused by disseminated intravascular coagulation.[6] The mortality rate is about 30% among patients with severe disease (organ failure), who make up about 20% of presentations.[7]

A good or poor prognosis can be determined by measuring the C-reactive protein level 24 to 48 hours after presentation. Since organ failure is associated with higher levels. When a patient has a CRP level of 10 mg/dL or higher, it is considered to have severe pancreatitis. This diagnosis can be made within 48 hours of the onset of symptoms, with a sensitivity of 80–86% and specificity of 61–84%. A CRP level of 150 mg/dL or higher strongly suggests multi-organ failure and severe pancreatitis, with 81.4% specificity and 100% sensitivity.[8] The goal of this study was to measure CRP because it is the most commonly used noninvasive biomarker for assessing the severity of acute pancreatitis, although different studies have found different cutoff values for predicting acute severe pancreatitis. Second, compared to CT scans, it is less expensive, places less of a financial strain on patients, is easily measured, and does not expose them to large amounts of radiation. Therefore, we not only lessen the financial burden on patients but also make diagnostic accuracy easily accessible by measuring its sensitivity and specificity.

Methodology

A cross-sectional validation study was carried out at the Department of General Surgery, Pakistan Institute of Medical Sciences, Islamabad, spanning six months from May 2019 to December 2019. The study aimed to assess the prevalence of acute pancreatitis using a sensitivity and specificity calculator, with assumptions based on a prevalence of 35.8% and a 95% confidence interval. Sensitivity was set at 95.8%, specificity at 81.4%, with a precision of 5% for sensitivity and 10% for specificity. The study enrolled a sample size of 150 patients through non-probability consecutive sampling. All individuals, irrespective of gender, aged between 20 and 80 years, who were admitted with suspected cases of severe acute pancreatitis within 48 hours, were included. Suspected cases were identified based on symptoms such as epigastric pain, nausea, and vomiting.

Exclusion criteria were applied to refine the study group and excluded patients with acute gastritis, diagnosed through clinical history and presentation, acute pyelonephritis determined by history, clinical findings, and urine examination, acute cholecystitis diagnosed through history, clinical findings, and abdominal ultrasonography, and renal stone disease identified through history, clinical findings, and ultrasound of the kidneys, ureters, and bladder (KUB). This meticulous approach ensured a focused and relevant study population for the investigation of acute pancreatitis.

Prior to patient enrollment, the hospital committee granted ethical approval for the study. After gaining informed consent, patients who fit the inclusion criteria were chosen from the emergency room and

out-of-patient departments and enrolled in the research.

A specially designated Performa recorded all the study data, including a thorough history and examination. Blood was aseptically drawn, labelled with the patient's information, and sent to the hospital laboratory so that a consultant biochemist could measure the C-reactive protein level. Concurrently, a CT scan of the abdomen was performed to verify the severity of acute pancreatitis, and the consultant radiologist provided the report. The proforma was used to record the results of the CT scan and CRP levels for thorough record-keeping.

The statistical software SPSS (Statistical Package for the Social Sciences) version 25.0 was utilized for data analysis on a computer. Frequencies and percentages for categorical variables were computed, including gender, true positive, true negative, false positive, and false negative. The continuous numerical variables, such as age, have their means and standard deviations calculated. Tables and graphs were used to explain and display the findings. A 2x2 Table (Table 1) was used to calculate the serum CRP levels' sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for a thorough evaluation.

Sensitivity = TP / (TP + FN) * 100 is one of the standard formulas used to calculate sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for CRP level assessment. ROC and the likelihood ratio were also calculated. For a thorough assessment, stratification was used to control age and gender, two possible effect modifiers. Post-stratification diagnostic accuracy was then assessed.

Results

The study encompassed 150 suspected cases of severe acute pancreatitis within 48 hours, with the age distribution depicted in Figure 1. The average age of the patients was 45.03±10.86 years (95%CI: 43.37 to 46.78), detailed in Table 1. Among the cases, 82 (54.67%) were male, and 68 (45.33%) were female, illustrated in Figure 2.

The incidence of severe acute pancreatitis, confirmed by CT, was noted in 28.7% of cases, as outlined in Table 2. Diagnostic accuracy metrics for CRP in the diagnosis of severe acute pancreatitis are presented in Tables 2 and 3, with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy reported as 81.4%, 92.52%, 81.4%, 92.52%, and 89.33%, respectively. Additional metrics, including likelihood ratio and kappa statistics, are detailed in Table 3.

Stratification analysis by age and gender revealed that CRP's diagnostic accuracy for severe acute pancreatitis was 89.47% for individuals aged 50 or below and 89.09% for those above 50, as demonstrated in Tables 4 to 7. Furthermore, the diagnostic accuracy of CRP was 86.59% for males and 92.65% for females, presented in Tables 8 and 11. The ROC curve, plotted and displayed in Figure 3, provides a visual representation of the diagnostic performance of CRP in severe acute pancreatitis.

The results of a diagnostic test evaluating the correlation between C-reactive protein (CRP) levels and the gold standard diagnostic approach—CT scans, most likely—are shown in this table. Two CRP level categories are applied to the data: greater than 150 and equal to or less than 150. The test found 8 false positive cases (incorrectly identified positives) and 35 true positive cases (correctly identified positives) for CRP levels higher than 150, accounting for 28.7% of the total cases. There were 8 false negative cases (erroneously identified negatives) and 99 true negative cases (correctly identified negatives) for CRP levels equal to or less than 150, accounting for 71.3% of the total cases. There are 150 cases in the entire dataset.

The CRP test has an estimated 81.4% sensitivity, meaning it can accurately identify people with

severe acute pancreatitis; its specificity, on the other hand, is very high at 92.52%, indicating that it can also accurately exclude people without the condition. The sensitivity and specificity of both positive and negative predictive values closely match, highlighting the dependability of CRP in confirming or ruling out severe acute pancreatitis. The CRP test's overall diagnostic accuracy of 89.33% highlights how well it performs in terms of producing precise diagnostic results. Significantly increasing the chance of severe acute pancreatitis is a positive CRP result, as indicated by the substantial likelihood ratio of a positive test of 10.89. In contrast, when the CRP test results are negative, there is a significant decrease in the likelihood of having the condition, as indicated by the likelihood ratio of a negative test, which is 0.2011.

The value of Cohen's kappa, which quantifies the degree of agreement between the gold standard CT scan and the CRP test, is 0.7392. This value supports the validity of CRP as a diagnostic marker for severe acute pancreatitis because it falls within a range that suggests substantial agreement above chance. The statistical precision of these estimates is indicated by the inclusion of 95% confidence intervals for each parameter.

The gold standard for examining the diagnostic accuracy of C-reactive protein (CRP) in severe acute pancreatitis, particularly in the female population, is a 48-hour contrast-enhanced computed tomography (CT) scan. The outcomes show that CRP has a high degree of accuracy and dependability in this situation. The estimated sensitivity of the CRP test for females is 88.24%, demonstrating the test's effectiveness in accurately diagnosing women who have severe acute pancreatitis. With a noteworthy high specificity of 94.12%, the CRP test may be able to reliably rule out the condition in female subjects. It is reported that the negative predictive value (NPV) is 96% and the positive predictive value (PPV) is 83.33% for females. A positive CRP result, therefore, suggests that there is an 83.33% possibility that the person actually has severe acute pancreatitis, whereas a negative result assures that the person does not have the illness, 96% of the time. Reliability of CRP as a diagnostic tool for severe acute pancreatitis in females is highlighted by the impressive overall diagnostic accuracy of 92.65%. In females, a positive CRP test results in a high likelihood ratio of 15 for a positive test, indicating a significant increase in the risk of severe acute pancreatitis.

In contrast, when the CRP test is negative in this population, there is a notable decrease in the likelihood of having the condition, as indicated by the likelihood ratio of a negative test of 0.125 for females, the value of Cohen's kappa, which gauges the degree of agreement between the CRP test and the gold standard CT scan, is 0.8077. The validity of CRP as a diagnostic marker for severe acute pancreatitis in women is strengthened by the fact that this value falls within a range that shows substantial agreement above and beyond chance. The statistical precision of these estimates is indicated by the inclusion of 95% confidence intervals for each parameter.

Figure 1: Age distribution of the patients of the patients

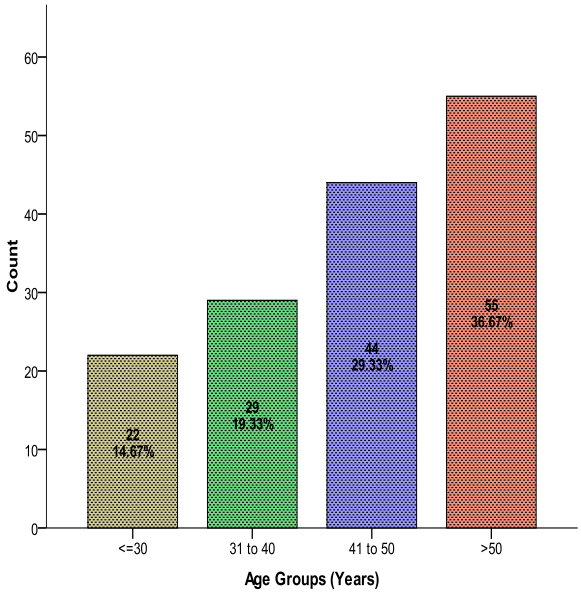


Table 1: Descriptive Statistics of Age

Statistics		Age (Years)
Mean		45.03
Std. Deviation		10.86
95% Confidence Interval for Mean	Lower Bound	43.27
	Upper Bound	46.78
Median		46
Inter quartile Range		20
Minimum		21
Maximum		60

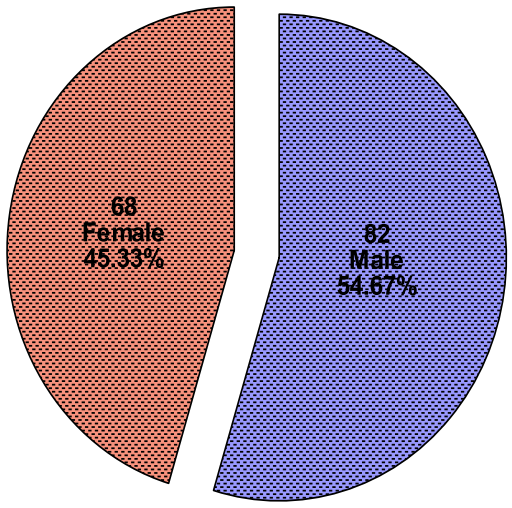


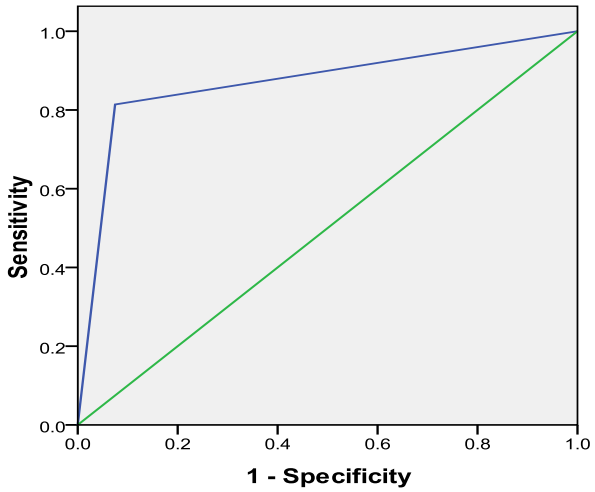
Fig. 2 Gender distribution of the patients

Table 2: True positive, true negative, false positive and false Negative Results of C-Reactive Protein after 48 Hours keeping the CT- Scan

CRP Level	CT (Gold Standard)		Total
	Positive	Negative	
>150	35 (TP)	8 (FP)	43 (28.7%)
≤150	8 (FN)	99 (TN)	107 (71.3%)
Total	**43 (28.7%)**	**107 (71.3%)**	**150**

Table 3: Diagnostic accuracy of C-Reactive Protein in Severe Acute Pancreatitis After 48 Hours Keeping the CT-Scan as a Gold Standard for Female

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	88.24%	(65.66, 96.71)
Specificity	94.12%	(84.08, 97.98)
Positive Predictive Value	83.33%	(60.78, 94.16)
Negative Predictive Value	96%	(86.54, 98.9)
Diagnostic Accuracy	92.65%	(83.91, 96.82)
Likelihood ratio of a Positive Test	15	(7.67 - 29.34)
Likelihood ratio of a Negative Test	0.125	(0.046 - 0.33)
Cohen's kappa	0.8077	(0.5702 - 1.045)



Diagonal segments are produced by ties.

Fig 3: ROC Curve

Discussion

Acute pancreatitis (AP) has emerged as a growing global health concern in recent decades, with approximately 20% of cases progressing to severe acute pancreatitis (SAP), resulting in prolonged hospitalization and heightened mortality.[9,11] Timely risk assessment is pivotal for optimal clinical outcomes and cost-effective treatment. C-reactive protein (CRP), an established acute-phase reactant, is widely utilized as an independent predictor of AP

due to its demonstrated ability to distinguish survivors from non-survivors in various infections.[12]

According to a study by Zhuang et al., the CRP/ALB ratio may be a new but promising non-invasive prognostic score that can be used in addition to Ranson, MCTSI, and BISAP scores to predict SAP, death, pancreatic necrosis, and organ failure in AP patients. It is easily measurable, reproducible, and non-invasive.[13]

A 2020 study led by Tian et al., revealed that assessing the levels of procalcitonin (PCT), lactate dehydrogenase (LDH), interleukin-6 (IL-6), and CRP collectively provides substantial diagnostic benefits in determining the severity of AP. Significant differences in CRP, PCT, IL-6, and LDH levels were observed between AP patients and controls ($P < 0.05$), a distinction that persisted when comparing moderately severe (MAP) and severe acute pancreatitis (SAP) groups ($P < 0.05$).[14]

In a single-center retrospective cohort analysis, Filipe S. Cardoso et al. found that 379 consecutive patients with acute pancreatitis were admitted. CRP readings were taken 24 hours after hospital admission, 48 hours after admission, and 72 hours after admission. Compared to CRP assessed at any other time, CRP measured 48 hours after hospital admission demonstrated good predictive accuracy for SAP, PNec, and IM. For SAP, PNec, and IM, the ideal CRP 48 hours after hospital admission ranged from 170 to 190 mg/l. Although CRP testing has inherent benefits, there are still questions about its predictive accuracy in AP.[15]

In a separate study by Amna et al., the modified CT severity index demonstrated high sensitivity (100%), specificity (97%), positive predictive value (81.13%), and negative predictive value (100%) in assessing severe acute pancreatitis among 43 patients, constituting 35.83% of the total cohort.[16]

A 2022 study under the direction of Karabuga et al., highlighted Red Cell Distribution Width (RDW) as the most sensitive parameter among those assessed. The study emphasized the efficacy of neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) to albumin ratio as accurate markers for determining AP severity. The developed NLR-CRP/albumin-RDW 2** scoring system exhibited exceptional performance, boasting a sensitivity of 85.71%, specificity of 66.49%, and an impressive negative predictive value (NPV) of 94.16%.[17]

According to research by R Ahmad et al., CRP measured at admission or 48 hours later had virtually little bearing on CAP prediction. Its negative predictive value should be utilized in conjunction with other scoring systems to forecast cases of mild AP, as this might aid in clinical decision-making for the early discharge or management of such patients on an ambulatory care basis.[18]

Xiao Han et al., came to the conclusion that RBP had an area under the curve (AUC) of 0.821, making it more accurate in predicting acute necrotic collection (ANC) than other local problems. Additionally, in AP patients, RBP was an independent risk factor for both ANC and acute lung injury (ALI). The best cutoff value for RBP's ability to predict ALI was 30.45 mg/L, and the model's AUC was 0.829. Its sensitivity and specificity were 96.50% and 59.70%, respectively.[19]

In a study involving dogs, Keanyet et al., came to the conclusion that serum cPLI and maybe CRP could be employed as objective biomarkers for clinical changes in hospitalized dogs suffering from acute pancreatitis. To assess the broader significance of these results, more research with a greater sample size of dogs is necessary. Between the dogs that lived until discharge (n = 11) and the dogs that did not (n = 2), there was a significant difference in the MCAI scores (P =.03) but not the CAPCSI values (P = insignificant). A positive correlation was found between the levels of serum cPLI and MCAI (rho = 0.42; P =.01). There was also a positive correlation (rho = 0.42, P =.01) between the serum CRP levels and the MCAI. [20]

According to Li *et a*l., IL-6 was a better predictor of death and IPN in patients with AP than CRP. The severity of AP was significantly positively linked ($p < 0.05$) with serum CRP and IL-6 levels. Based on CRP level, the AUC for SAP prediction was 0.78 (95% CI, 0.66–0.89), and based on IL-6 level, it was 0.69 (95% CI, 0.56–0.82). CRP outperformed IL-6 in the prediction of pancreatic necrosis and organ failure (AUC 0.80 vs. 0.72 and 0.75 vs. 0.68, respectively). However, CRP's predictive power for mortality and IPN was lower than that of IL-6 (AUC 0.70 vs. 0.75 and 0.65 vs. 0.81, respectively). In comparison to systemic inflammatory response syndrome plus IL-6, systemic inflammatory response syndrome plus CRP had a higher prediction accuracy of SAP (AUC 0.79 vs. 0.72).[21] According to Behera et al., CRP/albumin is an inexpensive, readily available, and straightforward biomarker that can be used to forecast the onset of severe pancreatitis. It has also been shown to be an independent predictor of death in AP. In addition, mean ferritin and the CRP/albumin ratio were considerably greater in severe AP ($p < 0.001$) when compared to mild and moderately severe AP. In a multivariate Cox regression analysis, the CRP/albumin ratio (AOR = 1.26, 95% CI: 1.02–1.56, $p = 0.02$) was the most accurate predictor of acute pancreatitis severity, with the largest AUC. The development of necrosis in acute pancreatitis was associated with a greater AUC (0.89, 0.83–0.91, $p < 0.001$) for serum ferritin, but its efficacy as an independent predictor of mortality was not demonstrated.[22]

While the presented studies offer valuable insights, it is crucial to acknowledge limitations, including imprecise symptom onset timing, lack of information on previous pancreatic disease history, and potential biases introduced by excluding patients with pyelonephritis and cholecystitis to address CRP's non-specificity. Future research should explore these limitations to enhance our understanding of CRP's diagnostic utility in AP.

Conclusion

In conclusion, it is still very difficult to predict the severity and mortality of acute pancreatitis (AP). C-reactive protein (CRP) is a unique acute-phase reactant that the liver produces in response to interleukin-1 and interleukin-6 among the other markers. The degree of pancreatitis is correlated with its gradual elevation. Notably, CRP testing is widely available, reasonably priced, and easily quantifiable. As such, we suggest its application as a useful marker for pancreatitis severity prediction, especially during the critical 48-hour period.

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