Serum C-reactive protein on the seventh day after pancreatitis could add value in predicting the course of disease progression

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Background
The incidence of acute pancreatitis (AP) has increased recently. Although most cases follow a mild course, some cases follow a severe course that may lead to death. Different scoring systems are used for the assessment of the severity of the attack such as Acute Physiology and Chronic Health Examination, Ranson, and modified computed tomography severity index. The most popular method of grading is based on contrast-enhanced computed tomography imaging. The computed tomography severity index (CTSI), developed by Balthazar and Ranson, clarifies the degree of pancreatic and peripancreatic inflammation, extent of parenchyma necrosis, and fluid collection measured by the computed tomography. C-reactive protein (CRP) is an acute-phase reactant that is synthesized by hepatocytes. This synthesis is induced by the release of IL–1and IL–6. CRP is one of the most sensitive markers for inflammation used today.
Patients and methods
A prospective observational comparative study was done on 70 patients with AP; they were followed up by a correlation between CTSI and CRP levels on day 2 and day 7 after presentation.
Results
It was found that there is a statistically significant increase in CRP levels in correlation with CTSI. Results showed that CRP levels rise significantly in severe and in necrotizing pancreatitis.
Conclusion
CRP is a straightforward way to predict severity for patients with AP. Based on this study, CRP levels are useful in patients who have contraindications for computed tomography with intravenous contrast such as patients with renal failure and pregnant women.

Keywords:
computed tomography severity index, C-reactive protein, pancreatitis

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Introduction

The incidence of acute pancreatitis (AP) is increasing, with incidence ranging from 5 to 80 per 100 000 persons [1]. It ranges from a self-limiting mild parenchymatous pancreatic inflammation to critical disease with infected pancreatic necrosis, multiple organ failure, and a considerable risk of mortality [2]. Although most cases follow a mild course, ~20% of patients develop severe acute pancreatitis (SAP) [3]. The overall mortality of patients with pancreatitis is less than 5% with proper management; however, SAP leads to prolonged hospitalization and higher mortality. Early identification of patients with SAP is especially important because the earlier the therapeutic interventions, the better the outcome [4].

Different scoring systems are used to measure the degree of severity of the attack as Acute Physiology and Chronic Health Examination II, bedside index for severity of acute pancreatitis (BISAP), Ranson, modified Glasgow score, and modified computed tomography severity index [5].

The most popular method of grading is based on contrast-enhanced computed tomography imaging. The computed tomography severity index (CTSI), developed by Balthazar and Ranson, is defined by the degree of pancreatic and peripancreatic inflammation, extent of parenchyma necrosis, and fluid collection measured by the computed tomography (CT) [6] (Table 1).

Hepatocytes, Hep-3B cells, synthesize C-reactive protein (CRP) as an acute-phase reactant, the first

Table 1 Computed tomography severity index [7,8]

Normal gland	0 point
Gland enlargement	1 point
Peripancreatic inflammation	2 points
Single fluid collection	3 points
Multiple fluid collection	4 points
Necrosis less than 30%	2 points
Necrosis from 30 to 50%	4 points
Necrosis more than 50%	6 points

acute-phase reactant to be described in 1930. This synthesis is induced by IL–1 and IL–6 release during the inflammatory process. It is produced in an extremely limited amount by nonhepatic cells like monocytes, Kupffer cells, lymphocytes, neurons, atherosclerotic plaques, epithelial cells of both renal epithelium and respiratory tract in certain situations, and human coronary artery smooth muscle cells [9,10].

It was found that the CRP has many functions in the inflammatory process as it serves as a chemotactic factor for monocytes and macrophages. It also activates the complement pathway and enhances phagocytosis, amplifying the inflammatory response [11,12].

CRP is considered one of the main predictors for inflammation, but it also increases in cases of tissue injury or tissue death. It is commonly used in clinical practice to assess, diagnose, and follow-up the prognosis of inflammation [13]. In this study, CRP was done after 48 h and on the seventh day after presentation, and CRP levels were correlated with the CT severity index.

Patients and methods

Our study included 70 patients admitted to ER Department at Kasr Al-Ainy Hospital of Cairo University from April 2020 to October 2020 with an acute abdomen that proved to be pancreatitis. We excluded patients with elevated kidney functions (as intravenous contrast is hazardous to the patient). We also excluded patients with other associated pathologies that might increase CRP such as associated malignancy, patients with infections (e.g. tuberculosis and pneumonia), and other inflammatory diseases such as inflammatory bowel disease and rheumatoid arthritis. Patients on medications causing low CRP such as statins, steroids, and nonsteroidal anti-inflammatory drugs were also excluded from our study.

Sample size calculation: it was calculated based on evidence from previous similar studies and by considering CRP% in nonsurvivors as a primary outcome. Epi-calc 2000 was used to calculate the sample size of this prospective observational comparative study. Assuming 80% power, 0.05 level of significance, 75% null hypothesis value and estimated proportion of 89%, the sample size was 63 participants. Considering a dropout rate of 10%, the final sample size was 70 participants.

Methodology in details: patients presenting to the emergency surgical department at Kasr Al-Ainy Hospital, Cairo University, with acute abdomen were enrolled after being diagnosed with AP by proper history taking, which included upper abdominal pain that radiates to the back, increases after meals, and decreases when leaning forward, associated with nausea and vomiting. Clinical examination included epigastric tenderness. Complementary abdominal ultrasound was performed to detect gall bladder stones as the most common etiology. Full laboratory investigations were performed, including lipase and amylase, which should be at least three times the normal serum level.

CT abdomen and pelvis with intravenous contrast enhancement was done on presentation. Overall, 70–100 ml contrast material (at a dose of 1.5 ml/kg) was administered intravenously by using a pressure injector at a rate of 3 ml/s follow it bias align chase off 20 ml normal saline at the rate of 2.5 ml/s.

CT severity index measurements were done by a radiologist. Serum CRP was assessed at 48 h and on the seventh day after presentation for further correlation (Table 1).

The clinical deterioration of any patient indicates reassessment of the parameters of the severity of pancreatitis to check if the patient is in worst severity index or not.

Statistical analysis

Microsoft Excel 2013 was used for data entry, and the Statistical Package for Social Sciences (SPSS, version 24, Norman H. Nie, Dale H. Bent, C. Hadlai Hull, Armonk, New York) was used for data analysis. Simple descriptive statistics such as arithmetic mean and SD were used for summary of normal quantitative data, median and range were used for summary of abnormal quantitative data, and frequencies were used for qualitative data. Pearson correlation was used to compare normally distributed quantitative data and Spearman ρ correlation for skewed data. *P* value was calculated to assess statistical significance. A value less than 0.05 was considered statistically significant. Logistic regression models were applied to assess the change of CRP on relation to the severity of pancreatitis. The ability of these models to discriminate and predict the outcomes

was analyzed by the area under the receiver operating characteristic curve (AUC).

Results

A total of 70 patients with AP according to the CTSI were included: 61 patients with mild AP and nine patients with moderate pancreatitis. All of the patients with mild pancreatitis showed complete resolution with conservative treatment. Three patients of the nine cases with moderate AP were monitored in the ICU owing to local and/or systemic complications (necrosis of greater than 50% in two and respiratory failure in one patient). These three cases showed increased serum CRP level on the seventh day compared with the sample withdrawn after 48 h. One patient with severe necrotizing pancreatitis died after multiple organ failure. Biliary pancreatitis was the leading cause in both of AP groups (85.71%) (Table 2).

The serum CRP at 48 h and on seventh day was found to be positively correlated with the CTSI, with correlation coefficient R^2=0.611 for CRP at 48 h and R^2=0.5113 for CRP on the seventh day (Figs. 1 and 2). Every unit increase within the CRP is related to an increase in CT severity index using Spearman's ρ (P<0.001), with r=0.0685 and 0.726 at 48 h and seventh day, respectively.

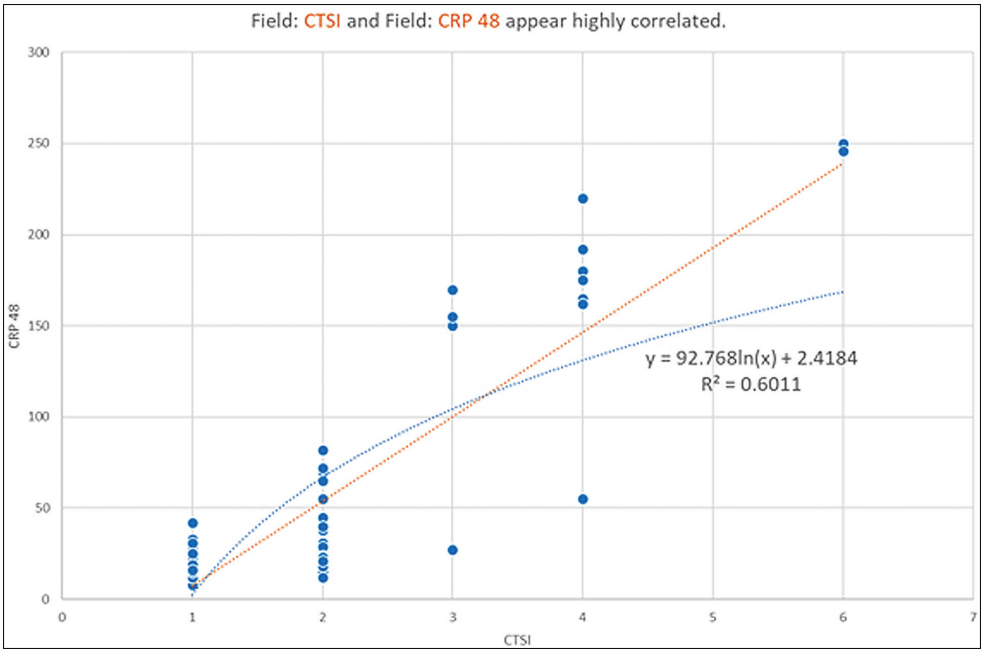
In almost all patients, the CRP level on the seventh day is lower than that at 48 h after presentation, except for three patients, where two had CTSI of six and one

Table 2 Patient features

	Severity		Total	*P* value
	Mild (*N*=61) CTSI '1–3'	**Moderate (*N*=9) CTSI '4–6'**		
Sex [*n* (%)]				
Male	14	5	19 (27.1)	0.054419
Female	47	4	51 (72.9)	
Age (years) 'range (mean±SD)'	21–73 (39±13.3)	27–64 (46±9)		0.216139
Etiology [*n* (%)]				
Biliary	55	5	60 (85.7)	0.005610
Nonbiliary	6	4	10 (14.3)	
Amylase on admission 'range (mean±SD)'	430–2600 (1085±554)	420–2570 (1269±803)		0.381768
TLC 'range (mean±SD)'	4.7–16.2 (8.77±2.7)	9–35.2 (22±7.8)		0.002808
CRP 48 'range (mean±SD)'	8–170 (34±32)	55–250 (183±58)		0.000243
CRP seventh day 'range (mean±SD)'	4–142 (19±22)	43–280 (158±91)		0.000971
Cases progressed to severe pancreatitis	0	3 (33.3)		

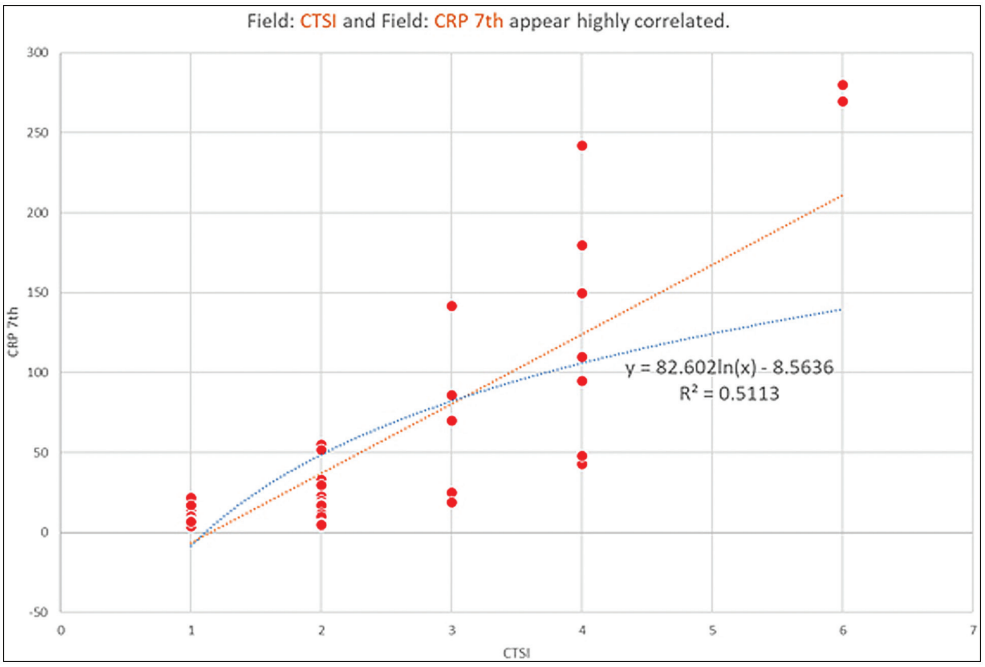
CRP, C-reactive protein; CTSI, computed tomography severity index; TLC, Total Leucocytic Count.

Figure 1



Correlation between CRP at 48 h and the CTSI. CRP, C-reactive protein; CTSI, computed tomography severity index.

Figure 2



Correlation between CRP at seventh day and the CTSI. CRP, C-reactive protein; CTSI, computed tomography severity index.

had CTSI of four. These three patients developed acute severe pancreatitis and required admission to the ICU for further monitoring (Fig. 3).

Further analysis of the data showed a suggested cutoff point of serum CRP level in correlation with the CTSI, showing high sensitivity with AUC with serum CRP at 48 h=0.982696 and AUC with serum CRP at seventh day=0.978142. The receiver operating characteristic curve analysis demonstrated a serum CRP level greater than equal to 152 at 48 h after presentation would be suggestive of CTSI greater than equal to 4 (Fig. 4). Moreover, a serum CRP level greater than equal to 90 at seventh day after presentation would be suggestive of initial CTSI greater than equal to 4 (Fig. 5).

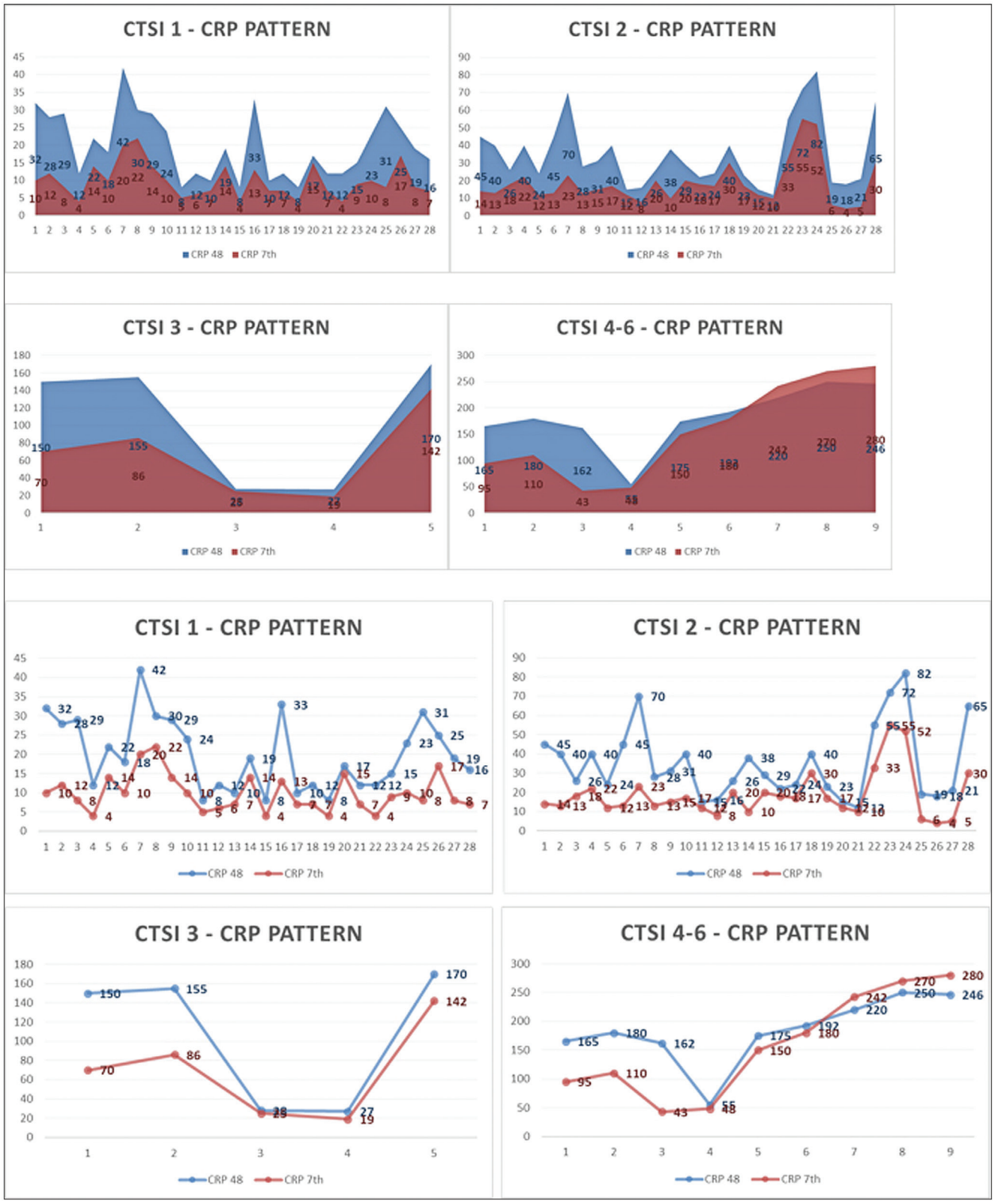
Discussion

The grading of AP and assessment of severity have been an issue for many years to delineate the outcome of each case and the proper unique management according to the stage of the disease. Morphologically, the severity of AP was categorized according to the CTSI into mild (0–3 points), moderate (4–6 points), or severe (7–10 points) [7,14].

Multiple scoring systems have been studied for assessment of the severity of AP. Some of them depend on the clinical and laboratory outputs of the patient, such as Ranson criteria, BISAP, Acute Physiology and Chronic Health Examination II, and CRP. However, the anatomical and local pathological ongoing process was assessed by Atlanta classification, CTSI, and the modified computed tomography severity index. CTSI can identify the extent of inflammation, pancreatic necrosis (PNec), and other related complications such as splenic vein thrombosis [7]. Unluckily CTSI cannot be used in all patients because it is contraindicated in some cases such as pregnant women and patients with compromised renal functions. Many studies and meta-analyses compared the different scoring systems and their sensitivity to detect the progression of the disease into SAP. Moreover, these systems were compared with other inflammatory markers, especially serum CRP, IL–1, and IL–6, and they were found to be clinically relevant in the differentiation of mild and nonmild AP [15]. A predictive accuracy meta-analysis included 30 studies and compared CTSI with other indices in the prediction of severity and mortality in AP. The meta-analysis showed that there was no statistical difference between the severity predicting values of the different scoring systems [8]. Another multicentric, international cohort analysis of 1435 cases showed that the changes in serum CRP level would predict the progression of the disease. Increased event rates of severe AP and mortality correlate with increased CRP level on presentation. This study pointed to the importance of the follow-up of the serum CRP levels over the course of disease to assess severity and morbidity rather than the timing only [16].

In our study, there were 70 patients, where 72.9% were females and 27.1% were males, with a mean age of 40 ± 13.5 years. A total of 60 (85.7%) patients had

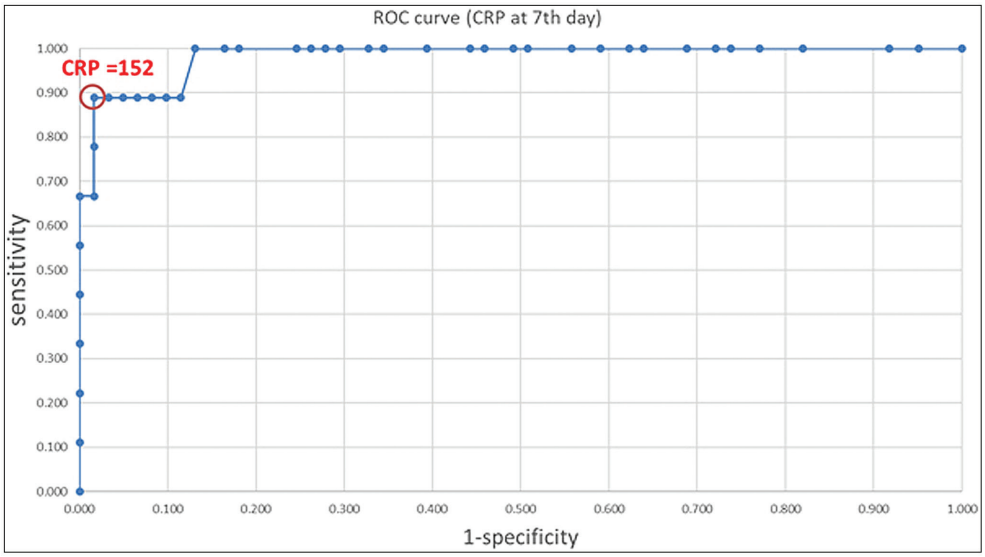
Figure 3



The pattern of serum CRP level in each patient grouped by the CTSI. The vertical axis shows the serum CRP level, whereas the horizontal axis shows the numbering of cases in each group. CRP, C-reactive protein; CTSI, computed tomography severity index.

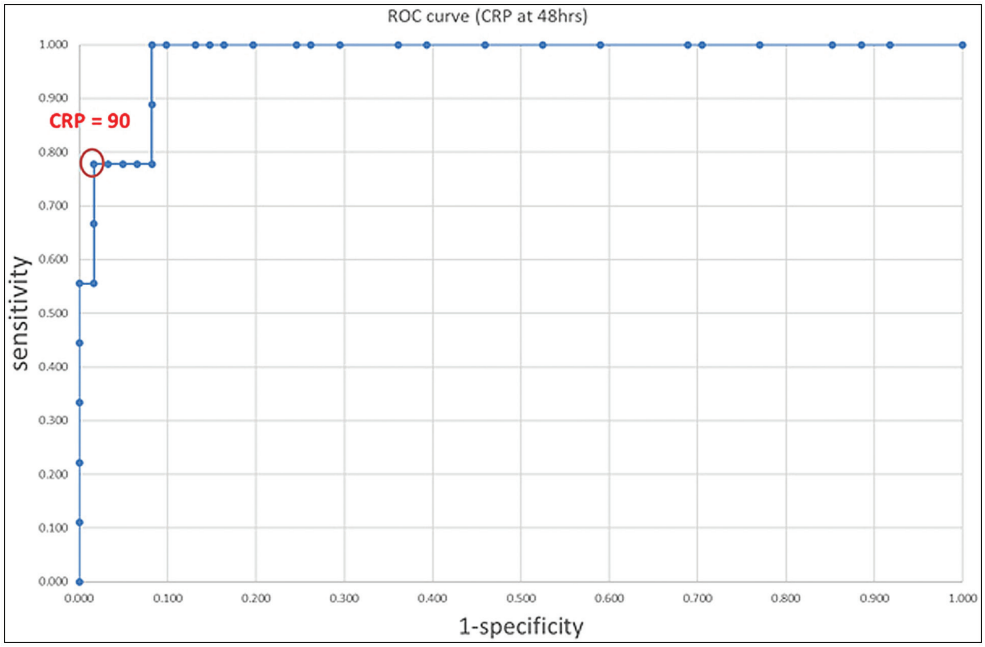
biliary pancreatitis, whereas 10 (14.3%) patients had nonbiliary pancreatitis. Overall, 87.1% had CTSI score 0–3 and 12.9% had CTSI score 4–6. Consistent with this study, there was a statistically significant association between CRP at 48 h and seventh day on one side and CTSI on the opposite side as every unit increase within the CRP is related to an increase in CT severity index using Spearman's ρ (P<0.001) (r=0.0685 and 0.726 at

Figure 4



ROC curve analysis for CRP at 48 h after admission. ROC, receiver operating characteristic.

Figure 5



ROC curve analysis for CRP on seventh day after admission. ROC, receiver operating characteristic.

48 h and seventh day, respectively). These results were in concordance with those demonstrated by other studies. Gürleyik and colleague conducted a study on 55 patients with similar demographics to the current study (mean age=57, male : female=3 : 10). There was a detailed correlation with CRP levels and therefore the CTSI. The sensitivity of serum CRP in this study was as sensitive as CTSI, with 84.6%. However, the specificity of the serum CRP at 48 h was 73.8%, which is less than the specificity of the CTSI in that study, which was 97.6%. The importance of this study was showing the positive predictive value and negative predictive value of CRP at 48 h and the CTSI, as both had high negative predictive values, with negative predictive value of 95.4% for CTSI and 93.9% for CRP. However, the CRP had high positive predictive value for patients having severe pancreatitis, and a CTSI score greater than 3 had a serum CRP level in far more than 150 mg/l (P<0.001), with positive predictive value 50.9% and accuracy of 76.4% [6]. This is concordant with our study results showing that a serum level at 48 h after presentation above 152 mg/l would suggest

SAP. Another study by Zheng and colleagues, was done on 114 cases to assess the BISAP score and CRP value in the prediction of severity and prognosis of AP. It was found that CRP was sensitive especially when not to mention the BISAP score. CRP was also positively correlated with CTSI scores (r=0.427, P<0.001) [17]. Furthermore, Cardoso and colleagues in their study on 379 patients, demonstrated similar ends regarding the relation of CRP and severity of AP and prognosis. CRP was assessed on admission and at 24, 48, and 72 h after hospital admission. CRP at 48 h showed a decent prognostic accuracy for SAP and PNec better than CRP measured at the other timing. The optimal serum CRP at 48 h after hospital admission cutoff points after receiver operating characteristic curve analysis for SAP and PNec varied from 170 to 190 mg/l. [3]. This result was just like Stirling *et al.* [18] which showed absolutely the concentration of CRP of over 190 mg/l as a sign of severity in their study, which was conducted on 373 patients. Unlike a study by Ganesh and colleagues, a study was done on 50 patients. Of the 50 patients, 30 had no local complications. A total of 14 (28%) patients had a peripancreatic collection and six (12%) had PNec. Of the 50 patients, 24 (48%) had systemic complications. Moreover, 25 patients had mild disease and 25 had severe disease as evidenced by Ranson's score. These 25 patients with severe disease also had raised CRP (P<0.05). There was no statistically significant correlation between the CTSI and CRP values. However, unlike in our study, the foremost common etiology was alcoholism, which explains the difference in demographics (mean age=37, male : female=3 : 1) [19].

Our study also studied the serum CRP levels in the seventh day after admission and the value of its measurement to assess the morbidity of the disease. Moreover, the pattern of serum CRP in our study showed a rising CRP, which would indicate a progressive disease. According to Rakesh *et al.* [20], serum CRP showed a higher prognostic sensitivity and accuracy than Ranson's scoring system and the CRP value at the end of the first week is useful in monitoring the clinical course. In the context of CRP trend and follow-up, Stirling *et al.* [18] demonstrated that interval change in CRP (ΔCRP) is an additional and comparable clinical aid in predicting severity of AP to the absolute concentration.

The low number of cases is a limitation to our study, and even if the number of cases was statistically calculated, further studies on greater scale should be accomplished for more accurate results and better understanding to the correlation between CRP level and the severity of AP.

Conclusion

CRP increases significantly in AP. There is a statistically significant association between CRP at 48 and seventh day after admission on one side and CTSI on the other side. CRP can be a proper valid alternative used in patients who have contraindication for CT such as pregnant women and patients with compromised renal functions. Moreover, it can be done repeatedly to follow-up these patients. CRP trend is more important and can be used for the assessment of AP severity and a predictor for developing complications and progression of cases.

Declaration of patient consent

This research was performed at the Department of General Surgery, Cairo University Hospitals. Ethical Committee approval and written, informed consent were obtained from all participants.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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