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C-REACTIVE PROTEIN LEVELS IN ACUTE PANCREATITIS AND ITS PROGNOSTIC SIGNIFICANCE

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ABSTRACT: AIM: To measure C-reactive protein (CRP) levels in patients of acute pancreatitis and evaluate if CRP levels predict the severity of pancreatitis by correlating these levels with- 1. C T Severity Index (CTSI). 2. Presence of complications. 3. Time taken for recovery. **METHOD:** Between the years 2007 and 2009 fifty patients diagnosed to have acute pancreatitis were included in this study. Their CRP levels were sent on second day of admission and CT scan done after 72 hours of admission. **RESULTS:** CRP levels of 63mg/dl and above are significantly associated with increased time to recovery (R>7D), (p-0.004). A significant association was seen between the presence of complications and a CTSI >7, (p-0.0002). There was no significant correlation or association between the CRP levels and CTSI as indicated by a value of 0.040528 (test of correlation) and p-<0.05. **CONCLUSION:** High serum CRP levels have predicted prognosis as well as mortality in this study. CTSI can be a very accurate predictor of development of complications in a case of acute pancreatitis.

INTRODUCTION: Acute pancreatitis is major cause of acute abdominal pain. The clinical presentation of the acute pancreatitis is variable. Most of these patients recover without specific complications. Some patients however display severe complications such as pancreatic as cites and pancreatic necrosis; these patients show high morbidity and mortality.

The role of diagnostic markers (pancreatic enzymes such as amylase and lipase) as prognostic indicators has been a failure. Other biochemical markers like CRP, pro-calcitonin and the like are under evaluation as prognostic indicators. CRP estimation is cheap and easily available. In this study we have attempted to see if a single and early estimation of CRP levels is an effective predictor of morbidity and mortality in acute pancreatitis.

We have attempted association between CRP, radiological imaging, and the clinical features and outcome of acute pancreatitis.

MATERIALS AND METHODS: Between the years 2007 and 2009 fifty patients admitted in LTMGH in the departments of General Medicine and General Surgery with a diagnosis of acute pancreatitis were studied. This is an observational study to evaluate whether the C-reactive protein (CRP) levels predict the severity of pancreatitis by co-relating these levels with CT severity index. Tests of association were applied between CRP levels and presence of complications, and time taken for recovery. These patients were diagnosed on the basis of presenting symptoms and clinical signs and serum amylase & lipase levels. In patients in whom diagnosis was confirmed, serum CRP levels were sent on day 2 of admission and patients subjected to a contrast enhanced CT scan of the abdomen in 72 hours after admission. Patients were observed for development of complications, both local and

general. Their subsequent recovery, morbidity or mortality was recorded. Patients with acute exacerbation of chronic pancreatitis, any chronic inflammatory disorder and age <18 and >65 years were excluded. The Approval of the Ethics committee of Lokmanya Tilak Medical College was taken for the study.

STATISTICAL ANALYSIS: Statistical analysis was done using tests of correlation of coefficient as both parameters were unrelated entities. Correlation between CRP levels and CTSI was initially assessed. A value nearing 1 would be considered as significant.

As a significant correlation was not reached, CHI SQUARE test was used to find an association between CRP levels and CTSI. Association of each, that is CRP levels and CTSI with presence or absence of complications and time to recovery again by using CHI SQUARE test.

CHI SQUARE test to find an association between:

1. Serum CRP levels of 63mg/dl and CTSI of 3- that is whether there is association between CRP levels of 63 and above, with a CTSI of 3 and above which is significant.(a value of 63 was selected as it is the middle value about which all other values of CRP are distributed)
2. Serum CRP levels of 63mg/dl and CTSI of 7- that is whether there is association between CRP levels of 63 and above, with a CTSI of 7 and above which is significant.
3. Serum CRP levels of 63mg/dl and above and presence or absence of complications -that is whether there is a significant association of complications.
4. Serum CRP levels of 63mg/dl and above and the time to recovery- that is if higher CRP values are associated with a longer recovery period.(for ease of calculation a value of 7days or more was selected).
5. CTSI of 7 and above with presence or absence of complications that is whether a CTSI of 7 and above is significantly associated with presence of complications.
6. CTSI of 7 and above with time to recovery that is whether a CTSI of 7 and above was significantly associated with delayed recovery. (again for ease of calculation and comparison a value of 7 days or more was selected.

RESULTS:
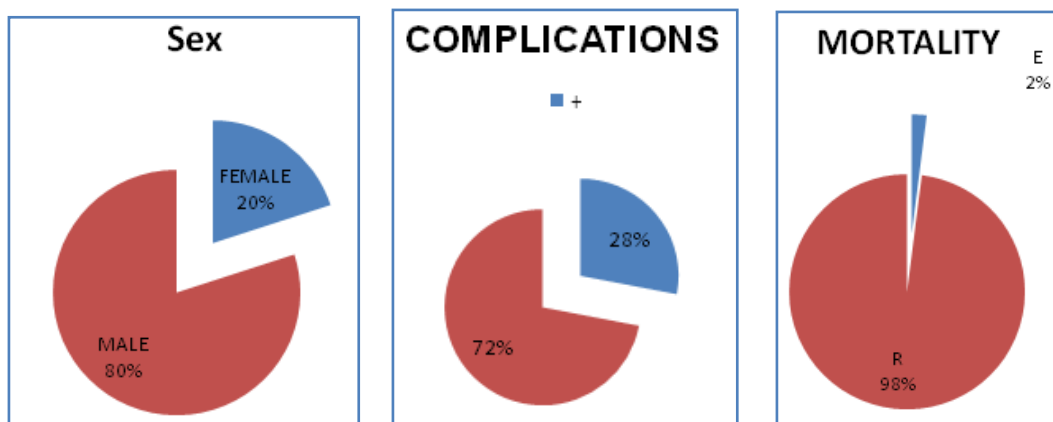
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The test of correlation was used to see if there was significant correlation between CT severity index and serum CRP levels. There was no significant correlation between the two variables as indicated by a value of 0.040528.

	CRP	CTSI
CRP	1	
CTSI	0.04528	1

The application of CHI SQUARE test to the parameters mentioned above shows the following result
1. There was no association between CRP levels of 63mg/dl and above with a value of CTSI of 3 or more or even a CTSI of 7 or more. Their CHI values were much below the required CHI value of 3.84 both before and after YATES correction. Hence the P-value was also not significant (<0.05).
2. There was no association between CRP levels of 63mg/dl and above with complications of acute pancreatitis (CHI values below 3.84 and P-value was not significant).
3. However CRP levels of 63mg/dl and above are significantly associated with increased time to recovery(R>7D). The CHI value was 8.15 with a YATES correction 6.55. This corresponded to a P-value of 0.004 and 0.01 respectively.
4. .An evaluation of CTSI of >7 with presence or absence of complications showed a significant association of the presence of complications with a CTSI >7. The CHI value was 13.45 and after YATES correction 10.33. This corresponded with a significant P-value of 0.0002 and 0.001 respectively.
5. A CTSI of >7 was however not significantly associated with an increased hospital stay. The CHI values are significantly lower than the value of 3.84 corresponding to a significant P-value of 0.05.

The above results show that while CTSI >7 can predict complications it cannot indicate the time that may be required for recovery. While CRP levels >63mg/dl can predict the time to recovery but cannot predict the complications.

CTSI and CRP levels as such are two different parameters which show no correlation and no association.

DISCUSSION: All data and studies to date are of the conclusion that early prediction of severity of acute pancreatitis will help to modify treatment/management in a way as to alter morbidity and mortality of patients. C-reactive protein-it is an acute phase reactant secreted by liver cells in large amounts on stimulation by IL6, TNF-ALPHA, IL-1BETA.It was first discovered in 1930 and has since been used as:
1. Early indicator of infectious or inflammatory conditions.
2. Screening device for inflammation.
3. Marker of disease activity.
4. Diagnostic adjunct in severe acute abdominal diseases, acute pancreatitis.

The normal levels of CRP in plasma are less than 6mg/dl. Numerous indicators and investigations are under evaluation, foremost among them being serum CRP levels. Low levels of

CRP do not exclude any condition, hence CRP is not used in diagnosis of acute pancreatitis but as an adjunct to predict severity. CRP levels have been evaluated in terms of their ability to predict severity, necrosis, complications, mortality and morbidity in acute pancreatitis, complications in acute pancreatitis etc. A CRP level of less than or equal to 200mg/dl obtained at 72 hours is useful enough to rule out with high degree of probability the presence of necrosis in acute pancreatitis. With higher values more investigations need to be done to predict necrosis. A marked variation was seen in CRP levels of two groups of extensive pancreatic necrosis and minimal pancreatic necrosis indicating that in individual cases CRP alone is not a good indicator of necrosis. A more recent study used highly sensitive CRP (hs-CRP) levels to predict severity in patients in whom crude CRP levels were low. It found significantly raised hs-CRP levels in patients whose crude CRP levels were low suggesting that hs-CRP maybe able to predict severity early.

Moreover CRP levels are not affected by etiology, thereby proving that even clinical outcome is independent of etiology. In an evaluation of scoring systems in outcome prediction of acute pancreatitis both CRP and CTSI have been able to predict morbidity and mortality. In a study examining the value of C-reactive protein (CRP) determinations in the assessment of the severity of acute pancreatitis and the correlation of CRP with serum phospholipase A2 activity and the clinical status, it was found that CRP and S-phospholipase A2 determinations are valuable in the early assessment of the severity of acute pancreatitis, but the CRP assay is much easier to include in hospital routine.

Other markers under evaluation are lipoprotein a, SAA, TAP, poly-C avid ribonuclease, urinary trypsinogen – activator, matrix metalloproteinase 9,macrophage -migration inhibitory factor, PMN etc.

The very fact that more research continues for a better predictor indicates that serum CRP may not be the most accurate indicator. Until a more accurate indicator comes along, CRP is readily available. It will prove to be even more cost effective if single estimations will prove predictive. Therefore only single estimation of CRP is being used in this study. Even if a better marker comes along CRP will still be the reference parameter by which the other will be judged. CT-scan abdomen with IV contrast is now the gold standard for radiological diagnosis of acute pancreatitis as demonstrated by Balthazar and colleagues. It has been proved to predict severity of acute pancreatitis and pancreatic necrosis. Makela et al found a high computed tomography value and CRP value of greater than 150mg/dl on admission in ICU are valuable in predicting mortality. Patients with high CRP, respiratory and renal failure, male gender have a longer ICU stay.

Acute pancreatitis is highly variable in clinical presentation and severity. Both anatomic and physiologic criteria are used to stage the severity of acute pancreatitis. Balthazar and Ranson developed a grading system for severity based on CT findings. This computed tomography severity index (CTSI) is derived by assessing the degree of pancreatic and peri-pancreatic inflammation, fluid collection and parenchyma necrosis. The acute phase reactant C-reactive protein (CRP) is the best established and most available predictor of inflammation. The majority of patients with acute pancreatitis have mild disease and their clinical symptoms and laboratory findings resolve with supportive care within 3 to 5 days. On the contrary, severe pancreatitis is associated with organ failure and local complications such as necrosis, abscess formation and pseudo-cysts, and constitutes 15-20% of such cases. Twenty-eight percent of our cases were complicated but, in the majority of patients, the disease was self-limiting. Various scoring systems are used for predicting the severity

of acute pancreatitis. In this study, an index based on imaging method and a biochemical inflammatory parameter were prospectively used to predict the severity of disease. Therefore, the accuracy of the CTSI and serum CRP measurement were investigated for determining the severity of acute pancreatitis. In this study the highest CRP level measured was 130mg/dl and this patient had the most severe presentation of all the patients of pancreatitis studied and succumbed to his illness. However the majority of patients had CRP levels of less than 100mg/dl. In our study there was no correlation between the CRP levels and severity of pancreatitis as measured by CTSI of >7. However the severity of acute pancreatitis cannot be measured only by a radiological parameter alone due to the complexity of the disease. Radiological severity is only one aspect. The risk of infection increases with the extent of intra-pancreatic and extra-pancreatic necrosis; therefore, early recognition of necrosis is important in order to prevent a poor outcome. Contrast-enhanced computed tomography provides a better and earlier recognition of such a risk as compared to other scoring systems.

So taking into consideration the fact, that severity of pancreatitis has to be decided not on radiological or biochemical parameters, but also on clinical parameters like presence of complications and time to recovery. Here, CRP of 63mg/dl were found to be associated with a longer time to recovery but not associated with presence of complications. While CTSI score of >7 were significantly associated with presence of complications but not with increased time to recovery.

SUMMARY: The study showed serum CRP levels has a weak positive correlation with CTSI, but it was not significant. Serum CRP levels have predicted prognosis as well as mortality in this study. CTSI can be a very accurate predictor of development of complications in a case of acute pancreatitis especially local complications. Moreover it shows the local extent of inflammation. Since both of these parameters, i.e. presence of complications and time taken to recovery are important in the outcome of acute pancreatitis both CRP and CTSI are important prognostic indicators of acute pancreatitis. Thus we conclude that both , CRP and CT scan should be seen as an additional tool that aids clinical observation and physical examination, to predict complication and prognosis in acute pancreatitis and should not be used as alone parameter.

REFERENCES:
1. Vermeire S, Van Assche G, Rutgeerts P: The role of C-reactive protein as an inflammatory marker in gastrointestinal diseases. Nat Clin Pract Gastroenterol Hepatol. 2005 Dec; 2(12):580-6.
2. Kaya E, Dervisoglu A, Polat C; Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. World J Gastroenterol. 2007 Jun 14; 13(22):3090-4.
3. Gürleyik G, Cirpici OZ, Aktekin A, Sağlam A: The value of Ranson and APACHE II scoring systems, and serum levels of interleukin-6 and C-reactive protein in the early diagnosis of the severity of acute pancreatitis. Ulus Travma Acil Cerrahi Derg. 2004 Apr; 10(2):83-8. Turkish.
4. Alfonso V, Gómez F, López A, Moreno-Osset E, del Valle R, Antón MD, Blanes F, Ripollés T, Ortiz I: Value of C-reactive protein level in the detection of necrosis in acute pancreatitis Gastroenterol Hepatol. 2003 May; 26(5):288-93. Spanish.
5. Imamura T, Tanaka S, Yoshida H, Kitamura K, Ikegami A, Takahashi A, Niikawa J, Mitamura K: Significance of measurement of high-sensitivity C-reactive protein in acute pancreatitis. J Gastroenterol. 2002; 37(11):935-8.

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6. Puolakkainen P, Valtonen V, Paananen A, Schröder T: C-reactive protein (CRP) and serum phospholipase A2 in the assessment of the severity of acute pancreatitis. Gut. 1987 Jun; 28(6):764-71.

7. Mayer JM, Raraty M, Slavin J, Kemppainen E, Fitzpatrick J, Hietaranta A, Puolakkainen P, Beger HG, Neoptolemos JP: Serum amyloid A is a better early predictor of severity than C-reactive protein in aute pancreatitis. Br J Surg. 2002 Feb; 89(2):163-71.

8. Kuśnierz-Cabala B, Naskalski JW, Kedra B, Panek J: Comparison of sensitivity and specificity of serum poly-C avid ribonuclease activity and C-reactive protein concentration in detection of mild and severe acute pancreatitis. Clin Chem Lab Med. 2004 May; 42(5):549-55.

9. Johnson CD, Lempinen M, Imrie CW, Puolakkainen P, Kemppainen E, Carter R, McKay C: Urinary trypsinogen activation peptide as a marker of acute pancreatitis. Br J Surg. 2004 Aug; 91(8):1027-33.

10. Chen P, Yuan Y, Wang S, Zhan L, Xu J: Serum matrix metalloproteinase 9 as a marker for the assessment of severe acute pancreatitis. Tohoku J Exp Med. 2006 Mar; 208(3):261-6.

11. Rahman SH, Menon KV, Holmfield JH, McMahon MJ, Guillou JP: Serum macrophage migration inhibitory factor is an early marker of pancreatic necrosis in acute pancreatitis. Ann Surg. 2007 Feb; 245(2):282-9.

12. Rau B, Steinbach G, Baumgart K, Gansauge F, Grünert A, Beger HG: The clinical value of procalcitonin in the prediction of infected necrosis in acute pancreatitis. Intensive Care Med. 2000 Mar; 26 Suppl 2:S159-64.

13. Yousaf M, Mc Callion K, Diamond T. Management of severe acute pancreatitis. Br J Surg 2003; 90:407-20.

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