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RESEARCH ARTICLE

ROLE OF INFLAMMATORY MARKERS IN PREDICTING PANCREATIC NECROSIS IN ACUTE PANCREATITIS-INSTITUTIONAL STUDY

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ABSTRACT

Acute pancreatitis is an inflammation of pancreas of variable severity and variable etiology. The severity varies from mild to severe attack like necrotising pancreatitis which portends bad prognosis on the patient and it is associated with complications which may lead to death. Many prognostic indicators were developed to prognosticate the patient. C-reactive protein is an inflammatory mediater synthesized in liver and it is rised in Acute Inflammation of Pancreatitis.CRP levels are correlated with contrast CT findings and cutt off value is estimated so that above that value one can predict pancreatic necrosis.CRP test is cheap and is easier to do. Hence in this study, CRP is tested as a tool to prognosticate the patient.25 patients admitted in the medical wards of NRI General hospital were included in the study and the study showed that CRP levels peaked at 5th day of illness and cut off 150mg/dl value can be taken, above which pancreatic necrosis can be predicted with high probability. It has specificity of 80 %. CRP values of more than 200 mg/dl had specificity of 100%.

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INTRODUCTION

Acute pancreatitis is an inflammation of pancreas of variable severity and variable etiology (Azab *et al.,* 2011). The severity varies from mild to severe attack like necrotising pancreatitis which portends bad prognosis on the patient and it is associated with complications which may lead to death. Many prognostic indicators were developed to prognosticate the patient. C-reactive protein is an inflammatory mediater synthesized in liver and it is rised in acute Pancreatitis.

MATERIALS AND METHODS

Twenty five patients admitted in Medical Wards of NRI General Hospital with features suggestive of acute pancreatitis from September-2016 to September-2018 were taken for the study. The diagnosis of cirrhosis was based on history, clinical examination, serum amylase and lipase levels, and with help of Ultrasonography and CT abdomen. Inclusion criteria included patients of any age and either sex presenting with acute pain abdomen, with fourfold elevation of S. Amylase and or lipase. Exclusion criteria was patients with Ischemic heart disease and angina, Patients with prior history of fever before onset of pain, patients with chronic infectious diseases, known cases of Collagen vascular diseases Under the study protocol CRP levels done by serum immuneelectrophoretic assay and CRP levels done on days 3, 5 & 9 because most elevations are in between 3-5 days, CT abdomen with oral and IV contrast was taken in between 5-9 days., CRP levels were compared with Contrast CT abdomen findings. The peak levels are compared with CT abdomen findings and sensitivity and specificity were calculated.

RESULTS

Among the 25 patients in the present study group the sex predominance was males are 20 (80%), females are 5 (20%). Out of the 20 males 7 developed necrotising pancreatitis (35%) and 3 out of 5 females developed necrotising pancreatitis (70%).The age predominance is that most patients presented in the age group of 20 to 50 years (21) patients and 7 developed necrotising pancreatitis (33.33%), where as 2 out of 3 patients in the age group <20 developed necrotising pancreatitis (66.66%). The aetiological predominance responsible in developing pancreatitis was first alcohol (68%), followed by gall stones (16%), then by hypertriglyceridemia (12%) and finally idiopathic cause (4%).Out of the 10 patients with necrotising pancreatitis, 7 had alcohol as the aetiological factor (70%), 2 had gall stones aetiological factor (10%), 1 had idiopathic cause (10%), none of the 10 patients had hypertri-glyceridemia as the cause. Out of the 25 patients in the present study group the serum lipase values done on the first day elevated three times the base line normal, the mean serum lipase levels are 306.52 U/L,but if the values of the mild acute pancreatitis and severe acute pancreatitis separately the value

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Table 1. Aetiology and sex predominance

Aetiology	Male	Female
Alcohol	17	0
Gall stones	2	2
Hypertriglyceridemia	0	3
Idiopathic	1	O

Table 2. Comparitive studies in determining aetiological predominance

Studies	Alcohol	Bile stones	Hypertriglyceridemia	Idiopathic	Others
Present study (n 25)	17 (68%)	4(16%)	3(12%)	1(4%)	0
Prasad H. L.*, T. R. Nagarjuna(40)	13(32%)	22(55%)	1(2.5%)	3(7.5%)	1(2.5%)
NiteshNegi *et al* (123)	73(59.3%)	40(32.5%)	5(4%)	7(5%)	2 (1%)

Table 3. Crp values in correlation with disease severity

CRP values	Pancreatic edema	Pancreatic necrosis
Less than 100 mg/dl (n-15)	13	2
Between 100 to 200 mg/dl (n-4)	2	2
More than 200 mg /dl (n-6)	0	6

Table 4. CRP and its significance to severity in study groups

Study groups	No. of SAP patients	CRP more than 150 mg/dl	CRP less than 150 mg/dl
Present study	10	8	2
Ajay K. Khanna, Susanta Meher *et al*.	29	25	4

of MAP was 230.33 U/L and that of SAP was 420.8 U/L. The CRP values where done on the days 3,5,9 and if the 5th day taken as an predictive value and were divided into 3 groups depending on the range of CRP, 1st group (n-15) CRP less than 100mg/dl, 2ndgroup CRP levels between 100 to 200 mg/dl (n-4) and 3rd group CRP levels more than 200 mg/dl (n-6). The development of necrotising pancreatitis in correlation with CRP was out of 15 patients in first group 2 (13.33%) of them developed necrotising pancreatitis, in the second group out of 4 patients 2 (50%) of them developed necrotising pancreatitis, in the third group out of the six of them 6 (100%) developed necrotising pancreatitis. If the CRP cut of value in the present study group if taken as 150 mg/dl 8 out of 10 patients fall in the group where CRP more than 150 mg/dl (80%), and 2 out of 10 had values less than 150 mg/dl(20%) .Comingto the average hospital stay in 25 patients of the present study group was 8 days, but if we divide them into two groups the patients of the mild acute pancreatitis group average was 5.4 days where as that of severe acute pancreatitis group was 11.8 days. The overall mortality rate in the 25 patients in the present study group was 8%, both these patients are of the necrotising pancreatitis group so the mortality rate was 20% in SAP.

DISCUSSION

The Acute pancreatitis is a condition characterized by a constellation of clinical symptoms, laboratory findings and radiological findings. There are many complications leading to morbidity and mortality in acute pancreatitis. Among the various complications pancreatic necrosis is one complication which is local complication which can lead to morbidity and mortality. Thus earlier diagnosis is helpful in initiating a prompt treatment. But the problem with necrotising acute pancreatitis is that the time of onset of the disease is late and the mode of diagnosis is challenging because by the time diagnosis is established the complication is already developed. So there are various inflammatory markers used in early prediction of acute pancreatic necrosis. In our study we have used CRP as the inflammatory marker as the mode of diagnosis. Crp is one of the most commonly used biomarkers as it is routinely recorded, is relatively inexpensive and has been shown to correlate well with severity (Lempinen *et al*., 2001; Azab *et al*. (2011); Conlan, 1997; Isenmann *et al*., 1999; Takeyama *et al*., 2000; Park *et al*., 2013). CRP has been established as a prognostic variable in human (Park *et al.,* 2013). C-reactive protein (CRP) is an acute phase reactant is synthesized by the hepatocytes. This synthesis is induced by the release of interleukin 1 and 6. Thus the CRP peak in serum is usually not maximal until about day three after the onset of pain, and is always later than the peak of these interleukins. CRP is the most popular single test severity marker used today. The problem is that CRP is a rather late severity marker (day 2-4) as compared to the other markers in this overview. In the 25 patients in our study 20 (80%) where male and 5 (20%) where female. Thus there is a greater degree of male predominance when compared to that of the females. However contradictory to my study the study conducted by Gunay Gurleyik, Seyfi Emir, Gamze Kilicoglu, Alper Arman, Abdullah Saglam (Gunay Gurleyik1 *et al*., 2005) in turkey on 55 patients out of which 37 were female and 18 were male. There are other studies in which though there was a male predominance bit was not as high as that of this present study, a study conducted by Giedrius Barauskas, Saulius Svagzdys, Almantas Maleckas (Giedrius Barauskas, 2004) on showed a male incidence of 56% against a female incidence of 44%. The age predominance in the present group was between 25 to 45 years of age out of the total 25 people taken for the study 21 people were of the age group's of 25-45 (84%), 3 people where of the age group of 15 to 25 (12%), in the age group of more than 65 there was only one subject (4%).

So the age suggests that the predominance of the disease is mostly in the mid second to late fourth decade, this can also attribute to the fact that most acute pancreatitis are due to an acquired cause rather than that of a congenital or a hereditary cause. Coming to the aetiological factors contributing to the cause of acute pancreatitis. The most common aetiological factor in case of males are alcohol induced and most common in females are bile stones. In our study put of the 25 cases the commonest aetiological factor is alcohol followed by gall stones and hypertriglyceridemia. The causes of acute pancreatitis may vary depending upon the age, sex, socio-economic status. The occurrence of acute pancreatitis in our group is as follows. In the present study group the patients who

develop acute pancreatitis due to alcohol where 17 out of 25 which constitutes to 68%, the occurrence of gall stones as the aetiological factor for acute pancreatitis where 4 out of 25 which constitutes to 16%, the occurrence of hypertriglyceridemia as the aetiological factor for acute pancreatitis is 3 out of 25 which constitutes 12%, the occurrence of idiopathic pancreatitisas aetiological factoris only onecase and constitutes 4%. This finding was consistent with article published by Nitesh Negi, Jatinder Mokta, Brij Sharma, Rajesh Sharma, Anupam Jhobta, Vishal Bodh, Asha Ranjan. In which alcohol was the most common cause of acute pancreatitis out of the 123 people enrolled in the study 73 (60%) had acute pancreatitis secondary to alcohol consumption, followed by gall stones 32%, followed by idiopathic 5% and hypertriglyceridemia which amounts to 2.44%. However the study conducted by Prasad and Nagarjuna showed that bile stones (55%) are the leading cause of acute pancreatitis, followed by alcohol (32.5%), followed by idiopathic (7.5%) and lastly hypertriglyceridemia (2.5%). This shows that the aetiological factors and alcohol go head on head as the cause for acute pancreatitis. But alcohol has more predominance to cause acute pancreatitis. Hypertrigly-ceridemia has shown 12% predominance in the present study but low occurrence in other studies, where as idiopathic cause was predominant in other studies when compared to the present study. Coming to the clinical presentation most patients of acute pancreatitis present with two symptoms they are pain abdomen and nausea with / without vomiting's. Out of the 25 patients in our group all the patients have same complaints. The clinical presentation is one of the important findings to define pancreatitis according to modified Atlanta criteria. As mentioned earlier the main basis of the present study is to predict necrotising pancreatitis as earlier as possible. In the present we have used inflammatory markers such as CRP done by immunoelectophoretic methods on the 3rd, 5th, 9th from the day of admission. The CRP values which was picked in the present study group was on 5th day as the levels of CRP peeked during this time. The CRP in the present study was divided into 3 divisions.

- CRP levels less than 100 (mg/l)
- CRP levels between 100 to 200 (mg/l)
- CRP levels more than 200 (mg/l)

Out of the 25 patients taken into the present study,15 patients had a CRP value of less than 100 mg/l, where as 4 patients had a CRP value that is between 100 to 200 mg/dl, and 6 patients had a CRP value of more than 200mg/dl. According to the findings in the study we have known that 15 patients come under the category of mild acute pancreatitis. In the present study we have taken the CRP cut of value as more than 100 mg/dl which was consistent with other studies. Cut-off levels have been discussed in the literature, and levels between 120 and 210 mg/L have generally been agreed upon as distinguishing between the mild and the severe disease. Levels above 120 mg/L after one week also distinguish severity well but this is much too late for an early marker of severity. Aaron D *et al* have taken a predictive value i.e cut off value of less than 90 mg/dl as mild acute pancreatitis . Giedrius Barauskas, Saulius Svagzdys, Almantas Maleckas have taken a cut off value of 110 mg/dl. The patients in the present study with a CRP value of 100 mg/dl to 200 mg/dl and those who are above 200 mg/dl are a total of 10 people and they come under moderate to severe acute pancreatitis group. According to our study group the patients who had a CRP value of less than 100 mg/dl the patients have mostly a pancreatic edema rather than necrosis, with the exception of two patients who had pancreatic necrosis despite a CRP value less than 100 mg/dl. This says that out of the 15 patients with CRP less than 100 mg/dl, 13 (86.66%) of them had no necrosis but pancreatic edema alone on CT taken between 5 to 9 days while 2 (13.33%) had pancreatic necrosis. The patients whose CRP levels was between 100 to 200 mg/dl were 4 in number of which 2 (50%) people had pancreatic edema and the other 2 (50%) had pancreatic necrosis, how the 2 patients with pancreatic necrosis had a CRP value of more than 150 mg/dl and the patients in this group with pancreatic edema had CRP less than 150 mg/dl. This again points to the fact the cut off values for CRP to predict pancreatic necrosis is variable certain however certain articles such as Vinish *et al* have take an cut off of 150 mg/dl and the level above it as necrotising pancreatitis. The patients whose CRP was more than 200 mg/dl are 6 (100%) in number and all of them had pancreatic necrosis showing that this value was most definitive in present group. Aaron D *et al* conducted a study over 5 years on patients admitted with acute pancreatitis and have found that an absolute concentration of more than 190 mg/dl done on third day of admission stratifies severity best .

This correlates with the study done by Ajay K. Khanna, Susanta Meher, *et al* who did a study on 72 patients with acute pancreatitis, CRP levels was done on 60 patients out of which 29 patients developed severe acute pancreatitis the CRP value cut off was taken as 150 mg/dl, so out of the 29 patients 25 had a CRP value of more than 150 mg/dl. The remaining 4 people had a CRP value of less than 150 mg/dl. So according to the study the predictive percentage of patients with CRP level more than 150 g/dl in predicting severe acute pancreatitis was 100% and that of the patients developing severe acute pancreatitis whose CRP value was less than 150mg/dl was 11.4%. So if we compare the present study group with that of Ajay K. Khanna, *et al*. 2013, there where 10 people with severe acute pancreatitis in the present study group and if we divide them into SAP patients with CRP value more than 150mg/dl and those with values less than 150mg/dl. So according to this in the present study if the CRP value is more than 150mg/dl the percentage of patients developing SAP was 80%, the percentage of patients with CRP value less than 150 mg/dl developing SAP was 20%. The occurrence of necrotising pancreatitis was 10 out of 25 which amounts to 40% of total cases in the study group and that of edematous pancreatitis was 60%, with a ratio of 2:3. There were similar occurrences in other studies as well. The occurence of pancreatic necrosis was dependent of age and sex in the present study group, out of the 10 patients who presented with pancreatic necrosis in our group 7 where of male sex and 3 were of female sex so out of the 5 females in the study group 3 had necrotising pancreatitis (60%) compared to that of males 7 out of 20 (35%), coming to age predominance out of the 10 patients with NP seven patients where of age of 20 to 50 years, two patients below the age of 20 years and the only patient in the present study group above 50 years of age had developed pancreatic necrosis. Coming to the etiological predominance out of the 10 patients with necrotising pancreatitis 7 are die to consumption of alcohol and 2 due to bile stones and 1 due to idiopathic cause. Given the fact that alcohol is the common etiological factor 68% in the present study it is the tendency of this etiological factor to be the most associated with necrotising pancreatitis. This was followed by gall stones and then by 1 due to idiopathic cause. There are reports which have suggested that 5% to 10% of patients with AP develop

pancreatic necrosis .According to the study done by Kim et al., 2017 out of the 905 pancreatitis patients enrolled the number of patients who had alcohol as their aetiological factor was 72.9% which was on par and more when compared to the present study group. The next common aetiological factor for necrotising pancreatitis where gallstone, out of the 25 patients in the present study group 4 had pancreatitis secondary to gall stones, 2 of them developed necrotising pancreatitis. Out of the 25 patients in the present study group 3 of them had pancreatitis due to hypertriglyceridemia but none of them had necrotising pancreatitis. There was only one case of idiopathic pancreatitis and that patient developed necrotising pancreatitis.

Coming to the morbidity and mortality it was high in patients with necrotising pancreatitis when compared to the edematous pancreatitis patients. The average hospital stay in the present study group was 8 days, but when these patients if divided into two groups the patients in the edematous pancreatitis group had an average was 5.4 days, in comparison with the necrotising pancreatitis group whose average hospital stay was 11.8 days. So this hospital duration is both a financial fracture as well as mental trauma on patients presenting with pancreatic necrosis. This was consistent with the study conducted by Peery *et al*. (2015). The mean hospital length of stay (LOS) for AP-related hospitalizations is 4.7 days, which has improved over the past few decades from 5.8 days in 2003 and 6.4 days in 1997. The period of hospital stay could vary depending on the percentage of necrotising pancreatitis patients in the study conducted, because the more the number of necrotising pancreatitis there is an increase in duration of hospital stay. There where 2 deaths out of the 25 patients taken into the present study group. The mortality rate was 8% in the present study group, both of these patients had necrotising pancreatitis, so if said in this way out of the 10 patients with necrotising pancreatitis 2 deaths have occurred which amounts to 20%.

A study conducted by Gloor B, *et al*. (1998) on 106 necrotising pancreatitis patients 9 of them expired the percentage of mortality was 9%, half the amount when compared to that of our study group. The two patients in the present study group died secondary to respiratory failure associated with MODS. The two patient's who died had CRP values of more than 200mg/dl on the 5th day and had elevated serum lipase and amylase levels. The CT scan pf these patients revealed extensive necrosis of the pancreas, other lab findings such as serum creatinine and serum calcium where all deranged in these patients. The serum lipase value which was done on the first day of admission, because according to Atlanta criteria the serum lipase and amylase values should be elevated more than 2 times the baseline of normal, how ever lipase being more specific in comparison with amylase so we tried to correlate serum lipase levels with the severity of the disease. The 25 patients in the present study group are confirmed to have acute pancreatitis based on clinical features, laboratory parameters, radiological features. The serum lipase average of the 25 patients in the present study group was 306.52 U/L which was more than two times from base line. To consider the predictive value of serum lipase in relation to the severity of the disease the average of patients with mild acute pancreatitis and severe acute pancreatitis, so the average of 15 patients with mild acute pancreatitis (edematous pancreatitis) was 230.33 U/L which was lower than the total average taken in the 25 patients. The average of 10 patients with severe acute pancreatitis (necrotising pancreatitis) was 420.8 U/L which was higher when compared to the average taken in the 25 patients. So in this study group the serum lipase was high in the patients with severe acute pancreatitis when compared to that of mild acute pancreatitis. The 25 patients in the present study group have undergone contrast enhanced CT abdomen on the 5th to 9th day of study out of which 10 patients had necrotising pancreatitis and the remaining 15 had edematous or interstitial pancreatitis. So the predictive value of CT was superior to both the serum lipase levels or the CRP levels done on days 3,5,9. But CRP being an cheap and the risk of radiation due to CT is absent had a predictive value of 80% if CRP cut of value was taken more than 150mg/dl. So the role of CRP in predicting in pancreatic necrosis and severe acute pancreatitis cannot be ommitedeven in presence of morderninflammatory markers such as IL-6, IL-8 (as they are expensive when compared to that of CRP). So even in the present time and in view of the availability and feasibility in comparison with CT abdomen the role of CRP in predicting necrosis in acute pancreatitis is good in developing countries like India even in the primary and secondary health care center.

Conclusion

The prevalence of Acute Pancreatitis is more in males than in females and prevalence of alcoholic pancreatitis is more than G all stone pancreatitis in our study. Serum lipase levels on the first day correlated with the severity of the disease.CRP levels peaked at 5th day of illness and cut off 150mg/dl value can be taken, above which pancreatic necrosis can be predicted with high probability. It has specificity of 80 %.CRP values of more than 200 mg/dl had specificity of 100%.All complications occurred in associated with pancreatic necrosis. And the e mortality rate in pancreatitis was high among necrotising pancreatitis.

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