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ROLE OF MDCT IN PATIENTS OF SUSPECTED ACUTE PANCREATITIS WITH LESS THAN THREE FOLD RISE IN SERUM LIPASE LEVEL

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ABSTRACT

Background: Role of amylase and lipase in the diagnosis and prognosis of acute pancreatitis has frequently been the subject of confusion and controversy. A three fold rise in serum amylase and lipase is required for diagnosis of acute pancreatitis. However acute pancreatitis can occur with normal levels of amylase and lipase confirmed by computed tomography. **Methods:** In this study, total 40 patients were included who presented with clinical suspicion of acute pancreatitis. These patients were evaluated clinically, biochemical analysis was done and then CECT was done in all cases after 72 hours. CECT findings were evaluated in all the patients. Modified CT severity index was calculated in each patient and its correlation between serum amylase and lipase values was evaluated. CECT findings in lipase negative and lipase positive patients were compared. Patients were followed up for complications at two months interval. **Results:** 29.8% of the study population (Lip−) had less than three fold rise in serum lipase levels at presentation despite abdominal pain and signs of Acute pancreatitis on CECT. Extra-pancreatic findings such as pleural effusion and Ascites were more in lipase positive patients. On follow up, complications were significantly more in lipase positive group as compared to lipase negative group (19.2% vs 9.1%). **Conclusion:** A significant subset of patients with clinically suspected acute pancreatitis, without threefold increase in lipase levels on admission can also have evidence of acute pancreatitis on imaging. Without CECT, this substantial subset of patients would remain under-diagnosed. CECT is absolutely mandatory in subset of patients with less than three fold rise in serum lipase for correct early diagnosis of acute pancreatitis and thereby reducing mortality and morbidity.

KEYWORDS: MDCT; Acute pancreatitis; serum lipase; less than three fold rise.

1. INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory state involving the pancreas and is potentially life threatening condition. Majority of patients with acute pancreatitis (approximately 80% to 85%) will have the mild form, with a clinical course which has no complications. On the other hand, 15% to 20% will develop a complicated clinical course characterized by organ failure and or local complications.[1]

Classical clinical features include acute severe epigastric pain exacerbated by supine position, radiating to back in 50% of patients, nausea, vomiting and poorly localized tenderness.[2] Gallstone and alcohol abuse are the most common causes of acute pancreatitis.[3] Despites of its various causes, the clinical course of acute pancreatitis involves inflammatory events within the pancreas which leads to a systemic inflammatory response. The mortality and morbidity is influenced by events leading to the pancreatic injury as a result of release of cytokines and other inflammatory mediators.[4]

Acute pancreatitis is clinically defined by at least two of three features

(a) Abdominal pain suggestive of pancreatitis (epigastric pain radiating to the back).
(b) Serum amylase and lipase levels three or more times of upper limit of normal(imaging is to be used if the elevated values are, 3 times normal i;e more than 180 U/L).
(c) Findings suggestive of acute pancreatitis on CT, MRI, or ultrasonography (USG).

An assay of serum amylase and lipase has to be performed in all patients of suspected acute pancreatitis.[5] Normal values of serum lipase ranges from 20-60 U/L. A three-fold rise of serum lipase and amylase from the upper limit of normal (>180 U/L) is

required for the diagnosis of acute pancreatitis. Serum lipase concentration more than three times the upper limit of laboratory reference range has sensitivity and specificity of 64% and 97% respectively, for the diagnosis of acute pancreatitis when compared with corresponding values of 50% and 99% for serum amylase.[6]

When it comes to the diagnosis of acute pancreatitis, there is no doubt that serum amylase and lipase are the most important biochemical tests to diagnose acute pancreatitis.[7] Due to their technical simplicity and easy availability combined with high sensitivity, amylase and lipase estimation remains the most frequently requested tests when the diagnosis of AP is considered. Till date more than three fold rise in serum amylase and lipase is required for diagnosis of acute pancreatitis.

However, normal levels of serum amylase and lipase have been reported in 18-27% of total AP cases. Many authors have observed less than three fold rise in serum lipase levels in suspected AP patients.[8,9,10] Multiple factors may contribute to the absence of increased enzyme levels on admission. They may include either the inability of inflamed pancreas to produce these enzyme, or return of enzyme levels to normal before hospitalization. Moreover, the natural history of acute pancreatitis including renal impairment, need for dialysis and artificial ventilation, development of pseudocysts, necessity for surgery, and mortality rates in these patients are the same as in patients with an at least threefold serum lipase increase.[11]

The local complications of acute pancreatitis are assessed by computed tomography between 48–72 hours after the onset of symptoms. After the patients are adequately fluid replenished and normovolemia is restored, contrast enhanced computed tomography should be performed to assess for pancreatic necrosis unless contraindicated (e.g., renal dysfunction, pregnancy). Interestingly, AP does not appear to behave differently whether serum amylase or lipase were normal or elevated, and treatment principles remains the same in either subset.[12]

The spectrum of acute pancreatitis is wide ranging. The mild attacks of AP are often undiagnosed which predisposes to a severe second attack. The mortality of acute pancreatitis is 1 to 2% in mild cases, raises to 10 to 30% in severe acute pancreatitis. Early diagnosis of acute pancreatitis is therefore important to start immediate and proper treatment.

Till date there is not enough documented literature about CT findings in patients with serum lipase less than three fold rise of normal(<180 U/L). So a subset of patients with acute pancreatitis may have less than three fold rise in serum lipase level and may be under diagnosed. CECT may be necessary in these patients for correct diagnosis and thereby helping in further management of patient.

II. MATERIAL AND METHODS

This study was aimed to compare CT findings and complications in patients with and without three fold rise in serum lipase level and was carried out on patients referred to the Department of Radio-diagnosis from various clinical departments of Indira Gandhi Medical College and Hospital, Shimla. Patients with clinical suspicion of acute pancreatitis were admitted to the hospital.

The research procedure was in accordance with the approved ethical standards of Indira Gandhi Medical College and Hospital, Shimla, Ethics Committee.
Study Design: Analytical cross sectional study.
Study location: This was a tertiary care teaching hospital based study done in Department of Radio-diagnosis, Indira Gandhi Medical collage Shimla, Himachal Pradesh, India.
Study duration: July 2018 to June 2019.
Sample size: 40 patients.

Inclusion Criteria

1. Age ≥ 18 years.
2. Admitted patients in various clinical departments having clinical, and/or biochemical (or both) suspicion of acute pancreatitis after 72 hours of onset of symptoms.
3. All patients with CT findings suggestive of acute pancreatitis irrespective of serum lipase level.
4. Willingness to participate in prospective study.

Exclusion Criteria

1. Patients who had allergy to Iodine CT-contrast agents.
2. Impaired creatinine clearance.
3. Pregnant patients.
4. Patients with signs of chronic pancreatitis.
5. Absence of peripheral venous access.
6. Who were not willing to participate in the study.

Steps of Study

1. Serum lipase level less than 180 units/L was referred as Lipase negative patient and lipase level more than 180 units/L was referred as Lipase positive patient.
2. CECT abdomen was performed after 72 hours in all patients of suspected acute pancreatitis (lipase -) and patients of acute pancreatitis(lipase +).
3. CECT findings were interpreted and compared to see how do CT findings differ across lipase negative and positive patients. Modified CT severity index was calculated in each case.
4. Patients were followed up for complications of acute pancreatitis and also for morbidity and mortality for a period of two months.
5. Statistical analysis and conclusions were derived on completion of the study.

PROCEDURE METHODOLOGY

CT acquisition and image reconstruction

CECT was done in all patients of suspected acute pancreatitis after 72 hours after onset of symptoms using a MDCT 64 slice MODEL VCT XTE GE Medical System CT scanner. All patients were given omnipaque (Iohexol) 1.5 ml/kg body weight with concentration of 350 miligram iodine/millilitre intravenously (i.v.) at a rate of 3 ml/second via the antecubital vein. No enteric i;e oral or rectal contrast material was given. Imaging was performed in the portal venous phase starting 60 seconds after intravenous contrast agent injection. The scanning was done covering the area from the diaphragm to the pubic symphysis.

The following parameters were used:

Pitch	Not Applicable
Kvp	120
Ma	80-160
Slice thickness	5mm
Scan Delay	70 sec
Reconstruction	0.625mm

Automatic exposure control (AEC) factor was used to adjust the radiation dose according to the patient's body size and shape. Images were reconstructed in axial, sagittal, and coronal planes were recofrom isotropic voxels with a slice thickness of 3 mm.

CECT Diagnosis of acute pancreatitis

Acute pancreatitis was diagnosed on the basis of presence of at least one of the following findings:-

1. Enlarged edematous pancreas indicated by the increase in size of pancreas. (Normally maximum anteroposterior diameter of head, body, tail of pancreas measures 2.7cm, 2.5cm, 2.8cm respectively).
2. Peripancreatic fat stranding or fluid collection.
3. Parenchymal and/or peripancreatic necrosis.

Necrosis was indicated by absent post contrast enhancement of pancreatic parenchyma and/or heterogeneous peri-pancreatic fluid collection containing both liquefied and solid necrotic material with CT attenuation value more than 20 HU (Hounsfield unit).

Depending upon the presence or absence of necrosis Acute pancreatitis was classified into two types-

1. Acute interstitial edematous pancreatitis (AIEP)-no necrotic component present.
2. Acute necrotizing pancreatitis (ANP)-pancreatic or peripancreatic necrosis or both present.

Pancreatic and peripancreatic fluid collections were classified according to Revised Atlanta classification[13].

Analysis of serum lipase

A serum lipase level of ≥180 U/L on admission was regarded as a threefold increase of the normal and indicated the presence of AP according to the Revised Atlanta classification. All patients were grouped into a lipase positive group (Lip+) with an at least threefold serum lipase level and a lipase negative (Lip−) group with a serum lipase less than three fold of normal(<180 U/L).

Statistical Analysis

We had analyzed data using EPI-INFO 7.2.2.6 version for windows. Patients were divided into two groups i;e lipase negative and lipase positive. Each group was further divided into AIEP and ANP groups. Data was entered in Microsoft excel spreadsheet. It was presented in form of percentages, means, median, standard deviation and interquartile range. The means of two groups were compared using independent t' test for normally distributed data and Mann Whitney test for skewed data. Categorical data was analyzed using Chi square test or Fisher exact test where appropriate. P value of < 0.05 was taken as statistically significant.

III. OBSERVATIONS AND RESULTS

In this study, total 40 patients were included who presented with clinical suspicion of acute pancreatitis to the various Departments of at IGMC, Shimla. These patients were evaluated clinically, biochemical analysis was done and then CECT was done in all cases after 72 hours. CECT findings were evaluated in all the patients. Modified CT severity index was calculated in each patient and its correlation between serum amylase and lipase values was evaluated. CECT findings in lipase negative and lipase positive patients were compared. Patients were followed up for complications at two months interval.

Patients were divided into two groups- Lipase Negative and Lipase Positive. Each group was further divided into Acute Interstitial Edematous Pancreatitis (AIEP) and Acute Necrotizing Pancreatitis (ANP) groups.

Of total 14 patients in lipase negative group, 3 patients 14 had pathology other than acute pancreatitis and these patients were excluded from the statistical analysis. Actual study sample now comprised of 37 patients.

Eleven out 37 (29.8%) patients were lipase negative and 26 out of 37 patients (70.2%) were lipase positive. Of total 11patients in lipase negative group, 10(91%) patients had AIEP and only one(9%) had ANP. Of total 26 patients in lipase positive group, 18(69.2%) had AIEP and remaining 8 (30.2%) patients had ANP. This has been summarized in Table no 1.

Table no 1:

Group	No. of patients	Type of pancreatitis n(%)
Lipase Positive	26	AIEP- 18 (69.2%)
		ANP-8 (30.2%)
Lipase Negative	11	AIEP- 10 (91%)
		ANP-1 (9%)

Gender Distribution

In our study of 37 patients, there was male predominance, as twenty three (62.2%) were male patients and 14(37.8%) were females. In lipase negative group, 63.6% were males (7 out of 11) and 36.4% were females (4 out of 11).In lipase positive group 16 (61.5%) were male (out of 26 patients) and 10 were females (38.5%). The gender distribution in two groups been summarized in Table no 2.

Table no 2: Cross tabulation between Gender and lipase levels.

Gender	<180 x increased lipase (Lip−)		>180 x increased lipase (Lip+)		Total		P value
	N	%	N	%	N	%	
Male	7	63.6	16	61.5	23	62.2	**0.521 NS**
Female	4	36.4	10	38.5	14	37.8	
Total	11	100.0	26	100.0	37	100.0	

Statistical Analysis: Fisher's exact test. P≤0.05: Statistically significant

AGE DISTRIBUTION

The age group varied from 19-90 years in this study. In age wise distribution, the highest number of patients were in age group 30-60 years. The age wise distribution in lipase positive (65.4%) and lipase negative (45.6%) groups has been summarized in Table no 3 and figure A.

Table no 3: Cross tabulation between Age and lipase levels.

Age (in years)	<180 x increased lipase (Lip−)		>180 x increased lipase (Lip+)		Total		Chi-square value	P value
	N	%	N	%	N	%		
10-30	2	18.1	3	11.5	5	13.5	1.925	0.382 NS
30-60	5	45.6	17	65.4	22	59.5		
60-90	4	36.3	6	23.1	10	27		
Total	11	100.0	26	100.0	37	100.0		

Statistical Analysis: Pearson's Chi-square test. P≤0.05: Statistically significant

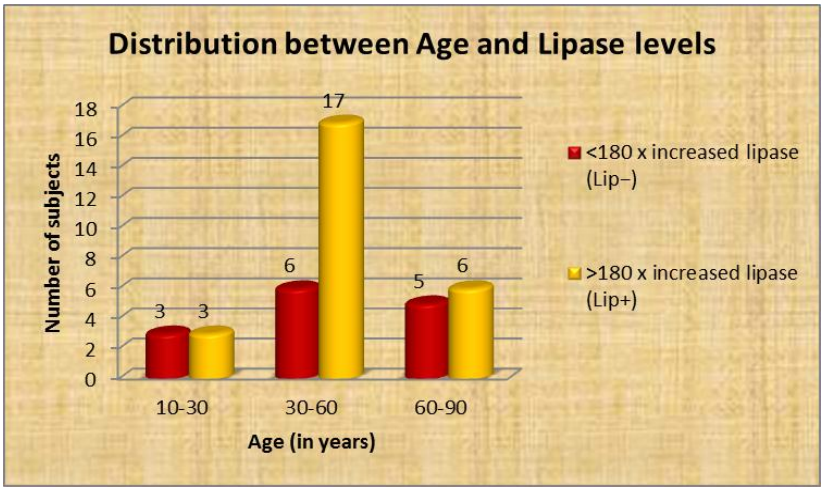


Figure A: Bar chart showing age wise distribution in lipase + and – groups.

Etiology

In the lipase negative group, 8 out of 11 patients (72.7%) had gall stones as the etiological factor and in 18.1% % of these patients (2 out of 11), alcohol was identified as the etiological factor. In lipase positive group- 50% (13 out of 26) of the patients had gall stones and 46.2 % (12 out of 26) had alcohol as etiological factor. In 2.7% patients (1 out of 37) the cause of pancreatitis could not be ascertained. One patient (2.7%) etiology was post ERCP. It has been summarized in Table no 4.

Table no 4: Cross tabulation of etiology in two groups.

Etiology	<180 x increased lipase (Lip−)		>180 x increased lipase (Lip+)		Total		Chi-square value	P value
	N	%	N	%	N	%		
Alcohol	2	18.1	12	46.2	14	37.8	**7.179**	**0.028 S**
Gall Stones	8	72.7	13	50.0	21	56.8		
Post ERCP or idiopathic	1	9.2	1	3.8	2	5.4		
Total	11	100.0	26	100.0	37	100.0		

Statistical Analysis: Pearson's Chi-square test. P≤0.05: Statistically significant

CECT findings of patients with acute pancreatitis in (Lip+) and (Lip−) groups

In our study, 75.7% of patients had AIEP and 24.3% had ANP. In lipase positive group, 69.2% had AIEP and 30.8% had ANP. In lipase negative group,91% had AIEP and 9% had ANP**.**

CECT findings in two groups has been summarized in Table no 5.

Table no 5.

	Total number of patients	**≥3× increased lipase**	**< 3× increased lipase**
		(Lip+)	(Lip−)
	n = 37 (%)	n = 26 (70.2%)	n = 11 (29.8%)
CECT findings			
Morphology, n (%)			
Acute interstitial pancreatitis	28 (75.7)	18 (69.2)	10 (91)
Acute necrotizing pancreatitis	9(24.3)	8 (30.8)	1 (9)
Pancreatic findings, n(%)			
Edematous organ swelling	34 (91.9)	24 (92)	10(90)
Peripancreatic fat stranding	34(91.9)	25(57.5)	9(64.3)
Acute peripancreatic collection	18 (48.5)	15 (59)	3 (21.4)
Parenchymal or extra pancreatic necrosis	8 (21.6)	7 (26.9)	1 (7.1)
Extrapancreatic findings, n (%)			
Pleural effusion	22 (59.5)	17 (65.4)	5 (35.7)
Ascites	19 (51.3)	16 (61.5)	3 (21.4)
Mesenteric inflammation	29 (78.4)	21 (80.8)	8(57.1)

Complications on follow up between two groups

In lipase negative group -On follow up after 2 month interval, only one of 11(9.1%) patient had complication in the form of pseudocyst formation. On other hand, complications were present in 5 out of 26(19.2%) patients in lipase positive group. One patient(3.8%) died in this group. This has been summarized in Table no 6.

Table no 6: Cross tabulation between Follow up complications in two groups.

Follow up	**<180 x increased lipase (Lip−)**		**>180 x increased lipase (Lip+)**		**Total**		**P value**
	N	**%**	**N**	**%**	**N**	**%**	
Eventful	1	9.1	5	19.2	6	16.2	**0.399 NS**
Uneventful	10	90.9	21	80.8	31	83.8	
Total	11	100.0	26	100.0	37	100.0	

Statistical Analysis: Fisher's exact test. P≤0.05: Statistically significant.

Correlation between serum amylase and lipase with modified ct severity index:

There was significant correlation (P value -0.009 and correlation coefficient-0.407 and 0.409 respectively) between both serum amylase and lipase with Modified CT severity Index. Higher the values of serum amylase and lipase, Modified CT severity index was also high. It is shown in Table no 7.

Regression Equation-

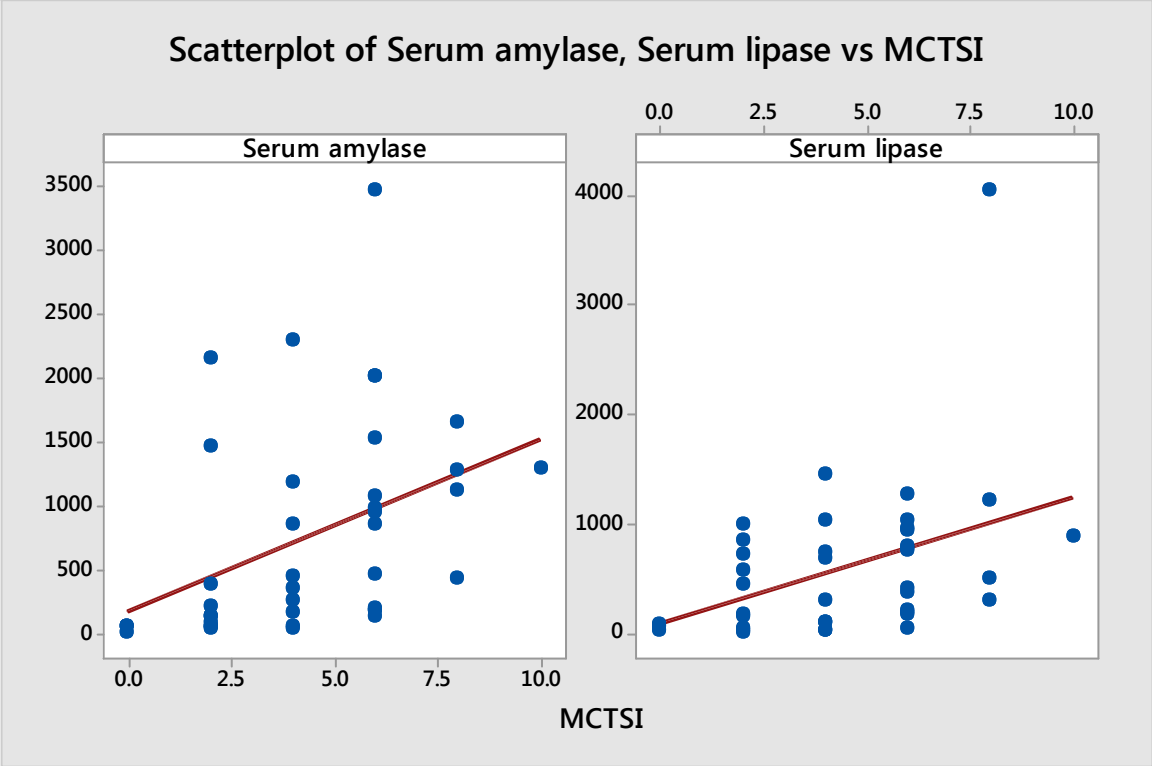
MCTSI = 3.232 + 0.000805 Serum amylase + 0.000952 serum lipase,

R^2=22.04%

Table no 7: Correlation analysis.

Correlation between	**Correlation coefficient**	**P value**
MCTSI & Serum amylase	0.407	0.009 S
MCTSI & Serum lipase	0.409	0.009 S

Statistical Analysis :Pearson's correlation analysis. P≤0.05: Statistically significant



IV. DISCUSSION

Various biliary tract diseases and alcohol intake are most common causes of acute pancreatitis. In our study, 56.8% of patients had gall stones and 39.8% patients had alcohol as the etiological factor. Majority of patients with AP show three or more fold increase in serum amylase and lipase level within 24 hours of the onset of the disease. But, the role of amylase and lipase in the diagnosis and prognosis has frequently been the subject of confusion and controversy as AP can and does occur with normal levels of amylase and lipase.[14]

Our first major finding was the presence of less than three fold increase in serum lipase levels in 14 out of 37(29.8%){with p value <0.05} of the study population (Lip−) despite abdominal pain and signs of AP on CECT. In previously published data by Lankish et al, 18% of patients with first attack of acute pancreatitis had less than three fold increase of serum lipase.[9] Another more recent study data by Avanesov et al, 27% patients of acute pancreatitis had less than three fold rise in serum lipase levels.[10] The diagnosis of AP would have been missed in these patients by serum lipase levels alone without confirming by CECT.

In our study, majority of the patients with less than three fold rise in serum lipase levels had mild form of pancreatitis on the basis of Modified CT severity index.[15] Few had moderate form of acute pancreatitis(10%). Majority of these patients i.e. 91%(10 out 11) had interstitial edematous pancreatitis. Only one patient (9%) had severe form of pancreatitis i:e necrotizing pancreatitis. This patient had few specks of calcifications within non enhancing areas in pancreas suggestive of acute on chronic pancreatitis. This explains the low serum lipase level in this patient. Otherwise, majority of lipase negative group of patients had mild form of acute pancreatitis.

In addition, we observed, that among the different extrapancreatic inflammatory changes, the prevalence of pleural effusions, ascites, and mesenteric inflammation was significantly lower in the Lip− group in comparison with the Lip+ group (Table -5). In lipase negative group pleural effusion was present in 35.7% of patients as compared to 65.4% in lipase positive group. Ascites was present in 61.5% of patients in lipase positive group and 21.4% of patients in lipase negative patients. Mesenteric changes were seen in 57% cases in lipase negative group as compared to 80.8% patients in lipase positive group. Our findings were closely comparable to study by M. Avanesov et al.[10]

These findings are of importance as patients with abdominal pain but without threefold increase of serum lipase and without possible accompanying clinical manifestations of AP like pleural effusions and ascites are prone to be underdiagnosed without being confirmed by CECT.

In our study, among all the patients with acute pancreatitis with less than three fold rise in serum lipase 63.6 % were male. The etiological factor was alcohol in 18.2% of patients and gall stone in 72.7% of patients in lipase negative group (Table-4).These observations were in line to those in the study by Imrie CW and Whyte.[16]

Both study groups were followed up for complications. Only one of the 11(9.01%) patients with less than three fold rise serum lipase (lipase -) had pancreatic or extra-pancreatic complications on follow up. On other hand, five of 26(19.2%) patients with serum lipase positive group had pancreatic or extrapancteatic complications. One of 26(3.8%) patients in lipase positive group died (Table -6). This patient had necrotizing pancreatitis along with vascular complications in form of thrombosis of portal vein and splenic vein.

Another finding in our study was that 2 out 37 (5.4%) patients presented with first episode of pain abdomen. However on imaging, pseudocyst and walled off necrosis was present in these patients. These imaging findings are suggestive of complications of acute pancreatitis that develop after 4 weeks of an attack of acute pancreatitis. Serum lipase levels were raised in these patients. These features could imply that first episode of pancreatitis whether interstitial edematous or necrotizing type might have been of milder form causing none or negligible clinical complaints.

One of the patient (2.7%) of acute pancreatitis in our study had pseudoaneurysm of gastro-duodenal artery. Vascular complications occur in 1.2-14% patients of AP, the incidence is higher in chronic pancreatitis (7-10%) than acute pancreatitis (1-6%).[17] Direct vascular injuries are the most dreadful complications of AP. Although rare, they can cause rapid blood loss and clinical deterioration. These injuries lead to formation of pseudoaneurysm. Arterial rupture may also occur into a pancreatic pseudocyst and rarely, arterial rupture into the gut presenting with either upper or lower GI bleed.

2.7% of patients (1 out of 37) had emphysematous pancreatitis. Air foci were present within pancreatic parenchyma and not around the pancreas. There are only scattered case reports in the literature about emphysematous pancreatitis, most of them dealing with radiological features. In a study by Mendez et al[18], 2% of patients had intrapancreatic air.

Correlation of Modified CT severity Index with serum lipase and amylase was studied. There was significant positive correlation with P value -0.009 for both serum amylase and lipase and correlation coefficient 0.407 for serum amylase and 0.409 for serum lipase. Our results were closely comparable to study by MM Sharif et al in which CT severity index in acute pancreatitis had statistically significant (p-< 0.05) relation with serum amylase (0.738), lipase (0.638), SGOT (0.581) and SGPT (0.365) during admission which was found on simple linear regression test.[19]

Study limitations

Our study had its limitations. It was a small study conducted on 40 patients and thus the results need to be interpreted in a larger study for validation. Another limitation of our study was short duration of follow up so complications and recurrent episodes of acute pancreatitis beyond this duration might have been missed.

V. CONCLUSION

A significant subset of patients with clinically suspected acute pancreatitis, without threefold increase in lipase levels on admission can also have evidence of acute pancreatitis on imaging. Without confirming CECT, this substantial subset of patients would remain under-diagnosed. So CECT is absolutely mandatory in these patients also for correct early diagnosis and thereby reducing mortality and morbidity.

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