



RISK FACTORS ASSOCIATED WITH WORSENING OF ACUTE PANCREATITIS.

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Abstract:

Background: The aim of the present study was to investigate risk factors for developing more severe pancreatitis, including moderately severe (MSAP) and severe acute pancreatitis (SAP), in patients admitted with mild acute pancreatitis (MAP).

Material/Methods: This was a hospital based retrospective and prospective study conducted in the Department of Gastroenterology, SKIMS Soura, Srinagar, Kashmir for a period of 2 years w.e.f. September 2017 to September 2019 on patients of all age groups with clinical/Laboratory/imaging findings suggestive of acute pancreatitis. The protocol of the study was approved by the Institutional Ethical Committee. Patients admitted with MAP to our hospital were included and prospectively evaluated. Possible risk factors for developing MSAP or SAP were Evaluated.

Results: Risk factors like BMI >25kg/m² was observed in 61 (19.3%) patients with mild pancreatitis and 142 (42.5%) patients with moderate to severe pancreatitis. Waist circumference >100cm was observed in 23 (7.3%) and 129 (38.6%) patients of mild and moderate to severe pancreatitis. High blood sugar >200mg/dl was observed in 37 (11.7%) patients with mild pancreatitis and 152 (45.2%) patients with moderate to severe pancreatitis. 27 (8.5%) and 167 (50%) patients of mild and moderate to severe pancreatitis had hematocrit >44 whereas 13 (4.1%) patients with mild pancreatitis and 140 (41.9%) patients with moderate to severe pancreatitis had CRP >150mg/dl. This table concluded that there is statistically significant association between high BMI >25 Kg/m², waist circumference >100 cm, high blood sugar >200 mg /dl, hematocrit >44, CRP >150 mg/d and worsening of AP.

Conclusions: Significant risk factors for developing MSAP or SAP in patients admitted with MAP included BMI (≥25 kg/m²), APACHE-II (≥5), and blood glucose level on admission (>11.1 mmol/L). These factors should be used in the prediction of more severe pancreatitis in patients admitted with MAP.

Keywords: Obesity, Pancreatitis, Risk Factors

Introduction:

Acute pancreatitis is an inflammatory disease of the pancreas. The etiology and pathogenesis of acute pancreatitis have been intensively investigated for centuries worldwide. It can be initiated by several factors, including gallstones, alcohol, trauma, infections and hereditary factors. About 75% of pancreatitis is caused by gallstones or alcohol¹. The overall mortality rate of acute pancreatitis was 3.8%, mortality rate of severe acute pancreatitis was high as 16.3% and mortality rate of moderately severe acute pancreatitis as 4.08%².

The diagnosis of acute pancreatitis requires two of the following three³:

Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)

Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or trans abdominal ultrasonography⁴.

Acute pancreatitis is a relatively common disease that affects about 300,000 patients per annum in America with a mortality of about 7%. Acute pancreatitis is mild and resolves itself without serious complications in 80% of patients, but it has complications and a

substantial mortality in up to 20% of patients despite the aggressive intervention⁵. The incidence of alcoholic pancreatitis is higher in male, and the risk of developing acute pancreatitis in patients with gallstones is greater in male. However, more women develop this disorder since gallstones occur with increased frequency in women⁶.

The pathogenesis of acute pancreatitis has not been fully understood. The general belief today is that pancreatitis begins with the activation of digestive enzymes inside acinar cells, which cause acinar cell injury. The risk factors in acute pancreatitis can be classified as¹:

Metabolic

Alcoholism,Hypertriglyceridemia,Hypercalcemia,Drugs (e.g., thiazide diuretics),Genetic,Scorpion poison

Mechanical

Trauma,Gallstones,Iatrogenic injury, Perioperative injury, Endoscopic procedures with dye injection (ERCP), Pancreas divisium, Pancreatic duct obstruction (tumors, ascariasis, ampullar stenosis), Pancreatic duct bleeding, Duodenal obstruction

Vascular

Shock, Atheroembolism, Vasculitis (Polyarteritis nodosa)

INFECTIOUS

Viral, Mumps, Coxsackievirus, EBV, HIV (Human Immunodeficiency Virus),Bacterial, Mycoplasma pneumonia, Campylobacter, Legionella, Parasites, Ascaris, Clonorchis sinensis Of note, 10% to 20% of patients with acute pancreatitis have no known associated processes. Although this condition is currently termed idiopathic. The underlying reason of gallstone disease and other conditions causing acute pancreatitis is ductal hypertension resulting from ongoing exocrine secretion into an obstructed pancreatic duct. Elevated intraductal pressure, due to ongoing exocrine secretion, causes rupture of the smaller ductules and leakage of pancreatic juice into the parenchyma. Pancreatic tissue favors activation of proteases when transductal extravasation of fluid occurs. in response to ductal obstruction, hypersecretion, or a cellular insult, these two classes of substances become improperly colocalized in a vacuolar structure within the pancreatic acinar cell. Coalescence of zymogen granules with lysosome vacuoles resulting in intrapancreatic activation of proteolytic enzymes. Small amounts of trypsin can be

countered by endogenous pancreatic trypsin inhibitor. However, large amounts of trypsin release can overwhelm the serological defense mechanism (α -1-antitrypsin and α -2-macroglobulin) and activate other enzymes resulting in destruction of acinar cells, local and systemic complications commonly seen in the course of the disease. Activation of the enzyme phospholipase A2 has important consequences like destruction of pulmonary surfactant that can result in ARDS and liberation of prostaglandins and leucotrienes that may be important in the pathogenesis of the systemic inflammatory response which can lead to multi organ failure. More than that, inflammatory mediators may be used as predictors of disease severity in the near future. Also, trypsin activates and complements kinin, kallikrein, possibly playing a part in disseminated intravascular coagulation, shock, renal failure and vascular instability^{7,8}.

The diagnosis of gallstone pancreatitis should be suspected if the patient has a prior history of biliary colic^{9,10}. With increasing severity of disease, the intravascular fluid loss may become life-threatening as a result of sequestration of edematous fluid in the retroperitoneum.

Due to the destruction of acinar cells, the levels of the enzymes that they contain (e.g., amylase, lipase, trypsinogen, and elastase) are found elevated in the serum of most pancreatitis patients There is no significant correlation between the magnitude of serum amylase elevation and severity of pancreatitis^{11,12}.

Lipase is more specific for pancreatitis. Several tests can help differentiate biliary pancreatitis from other causes of pancreatitis. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-Transpeptidase (GGT), alkaline phosphatase and serum bilirubin are the so-called liver function tests; they should be reviewed before making a confident diagnosis. Several recent research studies have suggested additional markers that may have prognostic value, including C-reactive protein (CRP), alpha2-macroglobulin, polymorphonuclear neutrophil-elastase, alpha1-antitrypsin, and phospholipase A2.^{13,14} Although The measurement of IL-6 has recently been shown to distinguish patients with mild or severe forms of the disease. Another prognostic marker under evaluation is urinary-trypsinogen activation peptide (TAP). It has a good correlation between the severity of pancreatitis and concentrations of TAP in urine.

Ultrasound: Abdominal ultrasound (US) examination is the best way to confirm the presence of gallstones in suspected biliary pancreatitis. Computed Tomography Scan (CT): A CT allows severity of pancreatitis to be graded. CT has become the gold standard for detecting and assessing the severity of pancreatitis. Magnetic Resonance Cholangiopancreatography (MRCP): MRCP has been found to be as accurate as contrast-enhanced CT in predicting the severity of pancreatitis.

A variety of scoring systems have been proposed for accurate assessment of the severity of acute pancreatitis. These include the clinical scoring scales as Ranson's criteria, Glasgow scales, simplified acute physiology (SAP), score and acute physiology and chronic health evaluation II (APACHE II) score. The CT severity index (CTSI) derived by Balthazar grading of pancreatitis and the extent of pancreatic necrosis is now widely used in describing CT findings of acute pancreatitis and serves as the radiological scoring system.

Material and Methodology

This was a hospital based retrospective and prospective study conducted in the Department of Gastroenterology, SKIMS Soura, Srinagar, Kashmir for a period of 2 years w.e.f. September 2017 to September 2019 on patients of all age groups with clinical/Laboratory/imaging findings suggestive of acute pancreatitis. The protocol of the study was approved by the Institutional Ethical Committee.

Inclusion criteria

All patients with a diagnosis of acute pancreatitis presenting to our accidental emergency were enrolled. Presence of at least two of the following:

1. Acute abdominal pain and tenderness suggestive of pancreatitis.
2. Serum amylase/lipase ≥ 3 times the normal.
3. Imaging findings (USG and/or CT) suggestive of acute pancreatitis.

Sixty patients of acute pancreatitis who presented to the emergency department as acute abdomen were included in the study. Informed consent was obtained from all the patients prior to enrolment in the study and were given standard medical care throughout the study period as approved by the Ethical Committee SKIMS Soura. The study period included, total duration of stay in hospital and thereafter follow up.

Exclusion criteria:

Patients having the following condition will be excluded;

1. Chronic calcific pancreatitis
 2. Those patients refusing consent for participation
- All the participants were thoroughly interviewed and subjected to clinical and laboratory examination. Hemogram, blood sugar, serum amylase, lipase, blood urea, serum creatinine, serum calcium [Serum calcium concentration (mg/dL) were calculated by correcting with $0.8 \times [4 - \text{albumin (g/dL)}]$, phosphate, lipid profile and liver function tests, HCT, CRP, BUN were done on the day of admission followed by 24 hours, 48 hours and 72 hours. Abdominal ultrasound was performed on all the patients on the day of admission. Contrast enhanced computerized tomography (CECT) of abdomen was done to stage the severity according to modified Computed Tomography Severity Index (CTSI)¹⁶ when required. MRCP was done for idiopathic pancreatitis and to confirm biliary pathology of acute pancreatitis. Grading of acute pancreatitis was done according to Revised Atlanta classification. Severity was assessed by BISAP¹⁷ scoring system at presentation and after 48 hours of admission.

Revised Atlanta classification¹⁸ for severity of acute pancreatitis:

Mild acute pancreatitis:

No organ failure

No local or systemic complications

Moderately severe acute pancreatitis:

Organ failure that resumes within 48 hours (transient organ failure) and/or

Local or systemic complications without persistent organ failure

Severe acute pancreatitis:

Persistent organ failure (>48 hours)

Single organ failure

Multiple organ failure

BISAP scoring system

Investigations:

CBC, RFT, LFT, Lipid profile, CXR (PA view), USG abdomen/pelvis, Urine R/E, BSF/BSR, Serum amylase, Serum lipase, Serum calcium Serum magnesium, Serum phosphate, LDH, ABG, 12 lead electrocardiogram, PTH USG abdomen, USG thyroid gland, CFTR/SPINK mutation, D dimer /CRP, CECT abdomen, MRCP, ERCP, Any other investigation if required

Statistical Analysis:

The data shall be recorded in n (%) or mean \pm SD, whichever is applicable and accordingly appropriate statistical test shall be applied.

Table 1:

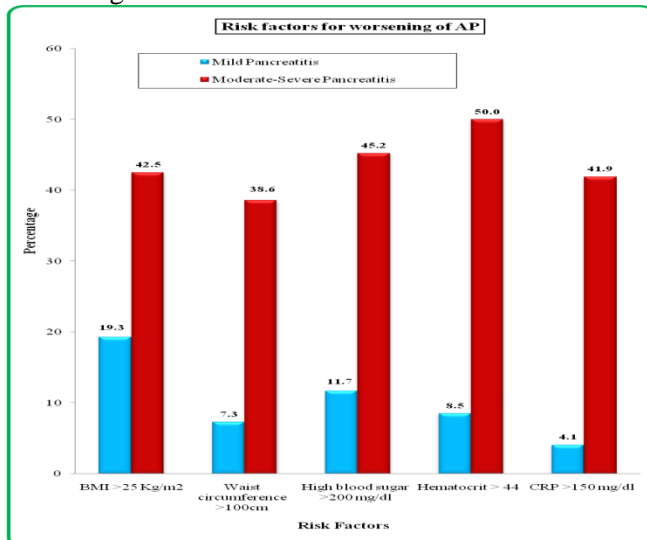
Table : Risk factors for worsening of AP

Risk Factors	Mild Pancreatitis		Moderate-Severe Pancreatitis		P-value
	No.	%age	No.	%age	
BMI >25 Kg/m ²	61	19.3	142	42.5	<0.001*
Waist circumference >100cm	23	7.3	129	38.6	<0.001*
High blood sugar >200 mg/dl	37	11.7	151	45.2	<0.001*
Hematocrit > 44	27	8.5	167	50.0	<0.001*
CRP >150 mg/dl	13	4.1	140	41.9	<0.001*

*Statistically Significant (P-value <0.05)

Risk factors like BMI >25kg/m² was observed in 61 (19.3%) patients with mild pancreatitis and 142 (42.5%) patients with moderate to severe pancreatitis. Waist circumference >100cm was observed in 23 (7.3%) and 129 (38.6%) patients of mild and moderate to severe pancreatitis. High blood sugar >200mg/dl was observed in 37 (11.7%) patients with mild pancreatitis and 152 (45.2%) patients with moderate to severe pancreatitis. 27 (8.5%) and 167 (50%) patients of mild and moderate to severe pancreatitis had hematocrit >44 whereas 13 (4.1%) patients with mild pancreatitis and 140 (41.9%) patients with moderate to severe pancreatitis had CRP >150mg/dl.

This table concluded that there is statistically significant association between high BMI >25 Kg/m², waist circumference >100 cm, high blood sugar >200 mg /dl, hematocrit >44, CRP >150 mg/d and worsening of AP.



Discussion

Acute pancreatitis (AP) is a common emergency, accounting for 3% of all patients admitted with acute pain abdomen. The spectrum of the disease is wide

ranging from mild attacks with mild epigastric discomfort to multi-organ dysfunction and death. The mild attacks often go undiagnosed predisposing to a severe second attack. Ours was a hospital based retrospective and prospective study

Majority of patients were men and the possible explanation for this is the fact that alcoholism in males, which forms a major cause of pancreatitis in the western world, is found much less often as a cause of pancreatitis in this part of the world, because of a conservative society pattern and the female sex is at more risk of gallstone formation.

There was no statistically significant association between the risk of AP in different age groups and gender.

Majority of our patients were from rural areas, probably because of higher number of referrals from peripheral hospitals due to lack of intensive care facilities in those hospitals.

Our study revealed gallstone is the major cause of AP irrespective of age and gender, although stones were more prominent in females (47.2%) as compared to males (31.5%). Compared to other studies, we observed different epidemiologies of AP in Kashmir valley with majority as gallstone(41.5%) followed by idiopathic

AP(30.2%),ascariasis(8.5%),drug(4.2%),hyperparathyroidism(3.1%),hypertriglyceridemia(3.1%),pancreaticobiliary tumor(3.1%), pregnancy(2.2%), alcohol (1.2%),trauma(1.2%),AIP(0.8%),pancreatic divisum(0.8%) and annular pancreas(0.3%).Two decades earlier parasites(ascariasis) induced AP were leading causes of AP in Kashmir valley but due to changing life style, improved hygiene, socioeconomic status, sedentary life style and obesity, parasites are now replaced by gallstones followed by idiopathic group and other causes. Alcohol which is most common etiology for AP in other studies, is least

common in Kashmir due to religious taboo. In their 2005 guidelines, the UK Working Party on Acute Pancreatitis suggested that the etiology should be determined in at least 80% of cases of acute pancreatitis. Furthermore, the classification of cases of idiopathic acute pancreatitis should be no more than 20%. Therefore, patients are subjected to extensive investigations to determine the underlying etiology. In our study idiopathic group was subjected to extensive evaluation including biochemical tests, genetic tests, imaging except EUS, as this facility was not available in our hospital. Most common drug as a cause of acute pancreatitis in our study included Azothioprine, Valproaic acid, thiazide, losartan and mesalamine. Pancreatic divisum was confirmed by MRCP and later on by ERCP. Most of our patients had type III pancreatic divisum followed by type I. Annular pancreas was confirmed by CT with oral contrast.

In our study high BMI >25Kg/m², waist circumference >100 cm, high blood sugar >200 mg/dl, hematocrit >44 and CRP > 150 mg/dl are risk factors associated with worsening of AP which was found to be statistically significant with p value 0.001.

Summary and Conclusion

Acute pancreatitis is one of the most common disease of gastrointestinal tract, leading to tremendous emotional, physical and financial burden. Acute pancreatitis is an acute inflammatory process of the pancreas i.e. associated with variable involvement of pancreas/peri-pancreatic tissues and one or more organ system in varying degrees. Evaluating the presented study we need to admit the main shortcoming, i.e., an insufficient number of patients within the groups, which seems precluded demonstrating more profound differences in course and outcomes between biliary and alcoholic SAP patients. Acute pancreatitis (AP) is a common cause of acute abdomen and alcohol and gallstone are the most common etiology

Our data revealed gallstone as most common etiological agent followed by idiopathic AP. Most of the patients were females belonging to rural population, with majority presents with mild to moderately severe pancreatitis (73.22%) with low mortality and morbidity and 26.76% patients present as severe pancreatitis with organ failure leading to higher mortality and morbidity.

Mild, moderately severe AP and SAP constitutes 48.61%, 24.61% and 26.76% of patients respectively. Both BISAP score and MCTSI were used to calculate

the severity of AP. It was found that both these scores can be used to calculate the severity equally and the difference was statistically insignificant

High BMI, increased waist circumference, high blood sugar, high hematocrit and high CRP are associated with worsening of AP.

In Kashmir valley there has been increasing number of cases of acute pancreatitis in recent years. Acute pancreatitis is one of the major cause of admission in gastroenterology ward. This, in contrast that few years back, when OCH, biliary ascariasis, UGI bleed were leading causes of admission.

The increasing incidence of acute pancreatitis in recent years is thought to be due to change in life style and food habits of patients. The sedentary life style has increased the incidence of obesity, dyslipidemia, diabetes and gall stones, all presumed to be risk factors for acute pancreatitis.

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