COMPARISON OF THE EFFICACY OF 5 SCORING SYSTEMS AND 5 BIOCHEMICAL MARKERS IN PREDICTING THE SEVERITY OF ACUTE PANCREATITIS IN THE INDIAN POPULATION

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CERTIFICATE

This is to certify that **Dr. PRIYANKHA BALASUNDARAM,** postgraduate student (2009-2012) in the department of General Surgery, PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH, Coimbatore, has done this dissertation titled **"COMPARISON OF THE EFFICACY OF 5 SCORING SYSTEMS AND 5 BIOCHEMICAL MARKERS IN PREDICTING THE SEVERITY OF ACUTE PANCREATITIS IN THE INDIAN POPULATION"** under the direct guidance and supervision of guide **Dr.T.S.BALASHANMUGAM** in partial fulfillment of the regulations laid down by The Tamilnadu Dr.M.G.R. Medical University, Chennai, for M.S., Branch – I General Surgery degree examination.

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DECLARATION

I, **Dr. PRIYANKHA BALASUNDARAM,** solemnly declare that this dissertation **"COMPARISON OF THE EFFICACY OF 5 SCORING SYSTEMS AND 5 BIOCHEMICAL MARKERS IN PREDICTING THE SEVERITY OF ACUTE PANCREATITIS IN THE INDIAN POPULATION"** is a bonafide record of work done by me in the Department of General Surgery, PSG institute of Medical Sciences & Research, Coimbatore, under the guidance of **Dr. T.S. BALASHANMUGAM,** Professor of Surgery.

This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the University regulations for the award of MS Degree (General Surgery) Branch-I, Examination to be held in April 2012.

Place: Coimbatore

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Priyankha Balasundaram

CONTENTS

INTRODUCTION

Acute pancreatitis is a common emergency with potentially devastating consequences (1). It is protean in nature and presents across a wide spectrum of severity ranging from a mild, self-limiting disease to severe disease with fatal outcome (1, 2).

About 20 to 30 percent of patients with acute pancreatitis develop complications of necrosis, organ failure, or both. Unfortunately, the serum amylase level and the lipase level are not specific enough measures of disease activity to be used prognostically.

Clinical monitoring is inadequate for determining severity and predicting the course of pancreatitis because it only detects about 40 percent of severe cases. Thus, assessment of progress requires careful monitoring of clinical signs and symptoms, including pain and nausea, fever (greater than 38.6°C [101.5°F]), ascites, ecchymosis, laboratory assessments (specifically, C-reactive protein level) and the use of severity classifications systems.

Several systems have been developed in an attempt to provide reliable prognostic classification for patients with acute pancreatitis.

Most complications of acute pancreatitis and subsequent deaths occur within two weeks of onset of pain. Secondary pancreatic infection is the most common cause of death in acute pancreatitis, accounting for 70 to 80 percent of deaths. Complications frequently manifest as necrosis and organ failure, which often includes the cardiovascular, pulmonary and renal systems. Cardiovascular complications may reflect bleeding into the retroperitoneal space and decreased vascular resistance. Pulmonary insufficiency may range from mild atelectasis to life-threatening adult respiratory distress syndrome. Acute renal failure defined as a twofold creatinine rise may ensue secondary to cardiovascular collapse and hypotension, resulting in acute tubular necrosis.

CT scanning may detect late complications of pancreatitis. Complications that usually occur after three weeks include pseudocysts and abscess formation. Pseudocysts occur in about 1 to 8 percent of cases. Abscesses occur in 1 to 4 percent of patients

Identification of patients at risk for severe disease early in the course of acute pancreatitis (AP) is an important step to guiding management and improving outcomes. The decision to undertake interventional or surgical treatment is a complex task requiring both clinical judgment and meticulous monitoring of the patient. Although a

plethora of evidence exists that justifies the use of scoring systems and biochemical markers in the stratification and prediction of severe acute pancreatitis, there is paucity of data concerning their validity, sensitivity and specificity in the Indian population. My study aims to evaluate the efficacy and validity of 5 scoring systems and 5 individual biochemical markers of predicting the progression of acute pancreatitis to mild or severe disease in the Indian patient population typically seen in our South Indian tertiary care centre.

AIMS AND OBJECTIVES

Aims and Objectives:

- To assess and compare the validity, specificity and sensitivity of 5 commonly used scoring systems and 5 biochemical markers in their ability to predict the outcome of acute pancreatitis in the Indian population presenting at our institution during the course of the study period.

- To generate an algorithm which will help stratify patients admitted with acute pancreatitis into severe or mild forms of acute pancreatitis in the most effective way based on the collected data validating the scoring and biochemical markers.

- To formulate a management plan based on the above algorithm, which will help distribute available resources with maximum efficiency.

Rationale / Justification for the study:

Although a plethora of evidence exists that justifies the use of scoring systems and biochemical markers in the stratification and prediction of severe acute pancreatitis, there is paucity of data concerning their validity, sensitivity and specificity in the Indian population.

Hypothesis:

Due to patient, environmental, cultural, social, and economic factors the incidence and etiology of acute pancreatitis, the subsequent development of severe acute pancreatitis and various complications are different in the Indian population when compared to the western one. Thus there will be a difference in the validity, specificity and sensitivity of the commonly used scoring systems and biochemical markers.

REVIEW OF LITERATURE

History

Acute pancreatitis is a common emergency with potentially devastating consequences (1). It is protean in nature and presents across a wide spectrum of severity ranging from a mild, self-limiting disease to severe disease with fatal outcome (1, 2).

Bradley EL, 3rd. et al. in their article ***"A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13", 1992. Arch Surg. 1993 May; 128(5):586-90*** (14) comprehensively aggregated the consensus statement issued at the Atlanta conference that standardized the series of definitions of acute pancreatitis, and helped evolve a universally accepted, clinically based classification. According to the Atlanta system of classification, severe acute pancreatitis (SAP) is associated with multiple organ failure and may additionally include local complications such as necrosis, abscess or pseudocyst formation.

Ranson JH et al. (15) note in their sentinel paper, ***"Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. Surg***

Gynecol Obstet." 1976 Aug;143(2):209-19 that an ideal or desirable detection system should

(a)have high sensitivity and PPV, (b) be able to predict necrosis early (< 48 h), (c) be performed rapidly (<48 h), (d) be available in most hospitals, (e) be relatively inexpensive, and (f) be objective and not observer-dependent.

In their systemic review of current literature, Gravante G. et al ***"Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. "Pancreatology. 2009;9(5):601-14***(4) find that there are a plethora of different prognostic variables, biochemical markers and scoring systems currently in use that attempt to predict severity and help identify patients at increased risk for morbidity and mortality, thereby assisting in appropriate triage and selection of patients for specific interventions. They conclude that no single factor (e.g C-reactive protein which in their review showed a sensitivity of 40%, specificity 100%, PPV 67% and NPV of 79%) can reliably predict outcome and mortality. They demonstrated that the APACHE II seemed to have the highest positive predictive value (69%). In their review they state that other scores and indexes do not have a high degree of sensitivity, specificity and predictive values.

On the other hand, a recent study by Papachristou GI et al. ***"Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis." Am J Gastroenterol. 2010 Feb;105(2):435-41***(16) comparing BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis, reports that a meta-analysis encompassing 1,300 patients demonstrated that the Ranson's score has an overall sensitivity of 75 % , specificity 77%, PPV of 49%, and NPV of 91 % (13). They note that on stepwise comparison, Ranson's, APACHEII and BISAP scores perform similarly as reported in previous studies (17). They conclude that the above multifactorial clinical scoring systems have been very helpful in evaluating the severity of AP. However, the overall disadvantage of such scoring systems is that they are not designed to predict potentially preventable complications in AP, and are least useful in the middle prediction range where the clinician needs most guidance. Therefore, their use seems to be confined in medical decision-making at the extreme of the prediction range, such as triaging intensive care unit admission and as enrolment criteria for clinical trials.

The Japanese have been active in the quest for identifying individual biochemical markers and for formulating an ideal, efficient

scoring system for predicting outcome accurately in acute pancreatitis. Takada et al. ***"Cutting-edge information for the management of acute pancreatitis." J Hepatobiliary Pancreat Sci. 2010 Jan; 17(1):3-12.*** (7) published the revised version of the Japanese (JPN) guidelines for the management of acute pancreatitis and confidently assert that universal adoption of these algorithms will improve the quality of management patients presenting with acute and severe acute pancreatitis.

Kandasami P. et al. ***"Acute pancreatitis in a multi-ethnic population." Singapore Med J. 2002 Jun; 43(6):284-8*** (11) rightly state that there is very little information in literature describing ethnic variations in etiologic and clinical outcome of acute pancreatitis. 133 consecutive patients were incorporated into their study. The demographic, etiologic and clinical course of acute pancreatitis among the three main races in Malaysia-Malays, Chinese and Indians were statistically reviewed. They conclude that there are differences in the characteristics of acute pancreatitis among the three major races in the country and this divergence is primarily due to socio-cultural habits.

Anatomy

Embryology

The embryogenesis of the human pancreas is more complicated than of most other tissue.

Its embryological origin reveals two buds:

- dorsal bud, described by His in 1885 and cited by Odgers (18)
- and the ventral bud first described by Phisalix 1888 (16)

Both develop on the opposite side of the duodenum at the point of contact between the endoderm and the vasculature (19-21).

Furthermore, two morphologically distinct tissue types must derive from one simple epithelium.

These two tissue types are:

- Exocrine (including acinar cells, centro-acinar cells, and ducts)
- Endocrine cells

The two tissue types serve disparate functions, and have entirely different morphology.

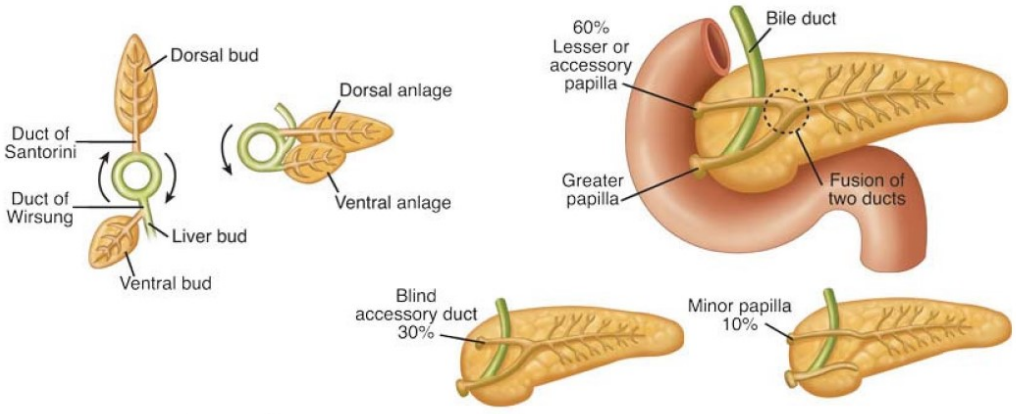
In addition, the endocrine tissue must become disconnected from the epithelial lining during its development.(20)

4th Week Of Embryologic Growth

Ventral (caudal) and dorsal (cranial) outpouchings develop at the junction of the foregut and midgut. The gallbladder, extrahepatic bile ducts (EBDs), central intrahepatic bile ducts (IBDs), and ventral pancreas with its ductal network are derived from the ventral outpouching-the hepatic diverticulum.

Fig - 1

(Embryology of the pancreas and duct variations. The duct of Wirsung from the ventral bud connects to the bile duct, while the duct of Santorini arising from the larger bud connects to the duodenum. With gut rotation, the two ducts fuse in most cases such that the majority of the pancreas drains through the duct of Wirsung to the major papilla. The duct of Sartorini can persist as a blind accessory duct or drain through the lesser papilla. In a minority of patients, the ducts remain separate and the majority of the pancreas drains through the duct of Santorini, a condition called pancreatic divisum.)



The dorsal bud arises from the dorsal mesogastrium and is the precursor of the dorsal pancreas and its ductal system.

At about this time, the developing ventral pancreas, gallbladder, and bile duct rotate clockwise (when viewed from the top) posterior to the duodenum and join the dorsal pancreas in the retroperitoneum.

The ventral pancreatic duct and the CBD are, therefore, linked by their embryologic origins, resulting in the adult configuration of their common entrance into the duodenum at the major duodenal papilla. (22, 23).

7th Gestational Week

The dorsal and ventral pancreatic ducts fuse in the region of the neck.

The territory drained by each system can vary, but in general:

- the dorsal pancreatic ductal system drains the
    - tail
    - body
    - anterior portion of the pancreatic head
- the ventral component drains the
    - posterior aspect of the pancreatic head.

Both dorsal and ventral ducts variably drain the uncinate process of the pancreatic head.

The portion of the ventral duct between the dorsal-ventral fusion point and the major papilla is termed the duct of Wirsung.

The portion of the dorsal duct proximal to the dorsal-ventral fusion point is called the main pancreatic duct (MPD).

If a segment of the dorsal duct persists distal to the dorsal-ventral fusion point, it is termed the duct of Santorini, or accessory duct. In 30% of individuals, however, the duct of Santorini loses its communication with the minor duodenal papilla and persists only as a branch of the MPD (22, 23)

Surgical (Gross) Anatomy

The pancreas is a retroperitoneal organ that lies in an oblique position, sloping upward from the C-loop of the duodenum to the splenic hilum. In an adult, the pancreas weighs 75 to 100 g and is about 15 to 20 cm long.

Regions of the Pancreas

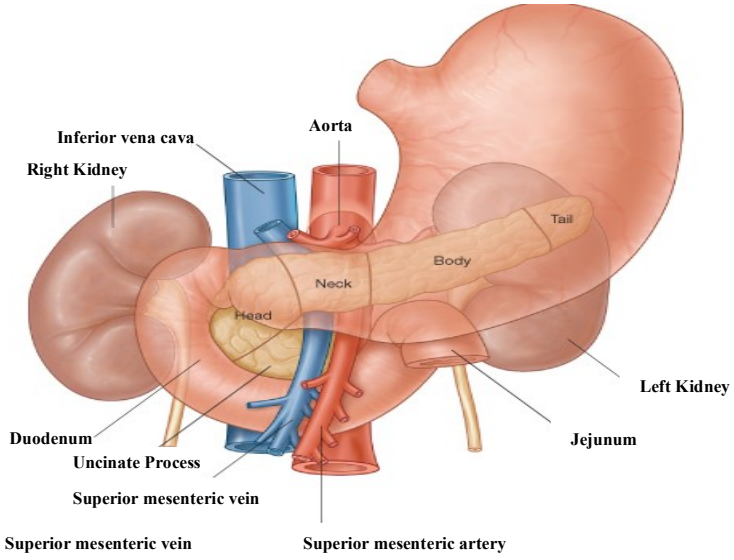
Surgeons typically describe the location of pathology within the pancreas in relation to four regions: the head, neck, body, and tail.

Head and Uncinate Process

The head of the pancreas is the expanded part of the gland in the C shaped curve of the duodenum. It is flattened structure, 2- 3 cm thick and is attached to the 2nd and 3rd portions of duodenum on the right. It rests posteriorly on the IVC, right renal artery and vein, and the left renal vein. On its way to opening into the descending part of the duodenum, the bile duct lies in a groove on the posterosuperior surface of the head or is embedded in its substance.

The Uncinate process is a projection from the inferior part of the pancreatic head. It extends medially to the left, posterior to the superior mesentery artery.

Fig-2
Surgical anatomy of the Pancreas



Neck

The neck of the pancreas is short, about 2.5 cm in length and overlies the superior mesenteric vessels, which form a groove in its posterior aspect. The anterior surface of the neck, covered with peritoneum, is adjacent to the pylorus of the stomach. Posteriorly to the neck, the superior mesentric vein and the splenic vein confluence to form the portal vein.

Body

The Body of pancreas continues from the neck and lies to the left of the superior mesenteric vessels, passing over the aorta and L2 vertebra, posterior to the omental bursa. The anterior surface of the body of the pancreas is covered with peritoneum and lies in the floor of the omental bursa and forms part of the stomach bed. The posterior surface of the pancreatic body is devoid of peritoneum and is in contact with the aorta, superior mesentery artery, left suprarenal gland, and left kidney and renal vessels.

Tail

The tail of the pancreas lies anterior to the left kidney, where it is closely related to the splenic hilum and the left colic flexure. The tail is relatively mobile and passes between the layers of the splenorenal

ligament with the splenic vessels. The tip of the tail is usually blunted and turned superiorly

Pancreatic Ducts

The main pancreatic duct of Wirsung runs the entire length of pancreas and joins the common bile duct at the ampulla of Vater. It is 2-4 mm in diameter and has approximately 20 or more secondary branches. Ductal pressure is 15-30 mm Hg (vs. 7-17 in CBD) thus preventing damage to the pancreatic duct.

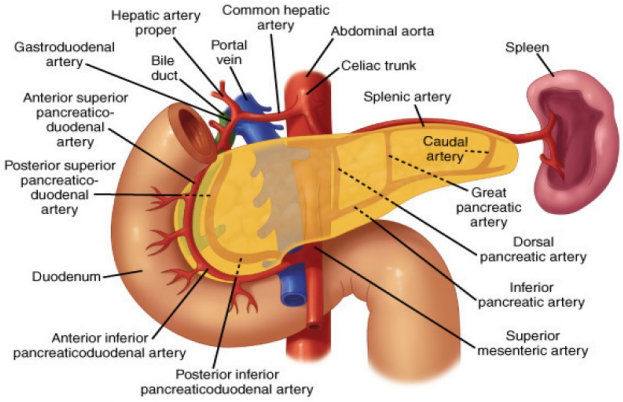
The lesser duct of Santorini drains the superior portion of head and empties separately into the 2nd portion of duodenum at the summit of the accessory papilla. Usually (60% of the time), the accessory duct communicates with the main pancreatic duct. In some cases, the main pancreatic duct is smaller than the accessory pancreatic duct and the two are not connected.

Blood and Lymphatic Supply to the Pancreas

The pancreatic arteries derive mainly from the branches of the splenic artery, which form several arcades with the pancreatic branches of the gastroduodenal and superior mesenteric arteries.

Fig-3

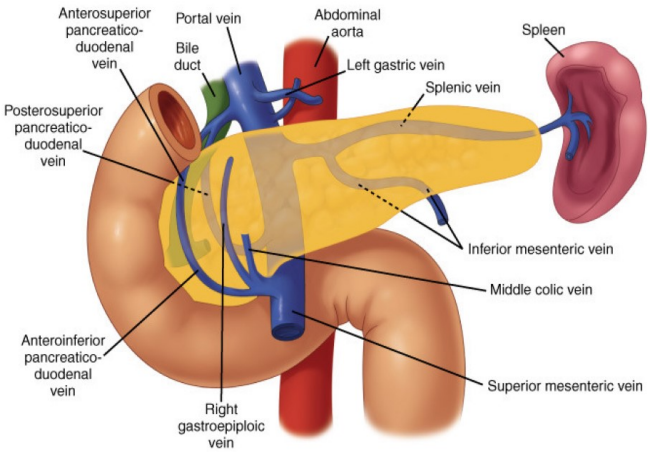
Arterial Blood Supply of the Pancreas



The superior pancreaticoduodenal arteries, branches of the gastroduodenal artery, and the inferior pancreaticoduodenal arteries, branches of the superior mesentry artery, supply the head. The body and tail are supplied by the splenic artery by about 10 branches. The three biggest branches are the dorsal pancreatic artery, the Pancreatica Magna (midportion of body) and the caudal pancreatic artery (tail).

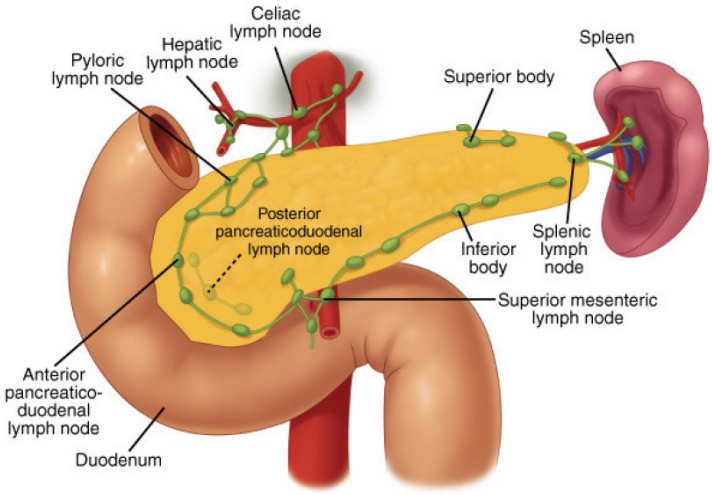
Fig-4

Veins of the Pancreas



The corresponding pancreatic veins are tributaries of the splenic and superior mesenteric parts of the portal vein; however, most of them empty into the splenic vein.

Fig-5
Lymphatic network of the Pancreas



A rich peri acinar network of lymphatics drains into 5 nodal groups: the superior nodes, the anterior nodes, the inferior nodes, the posterior pancreatic duct nodes and the splenic nodes.

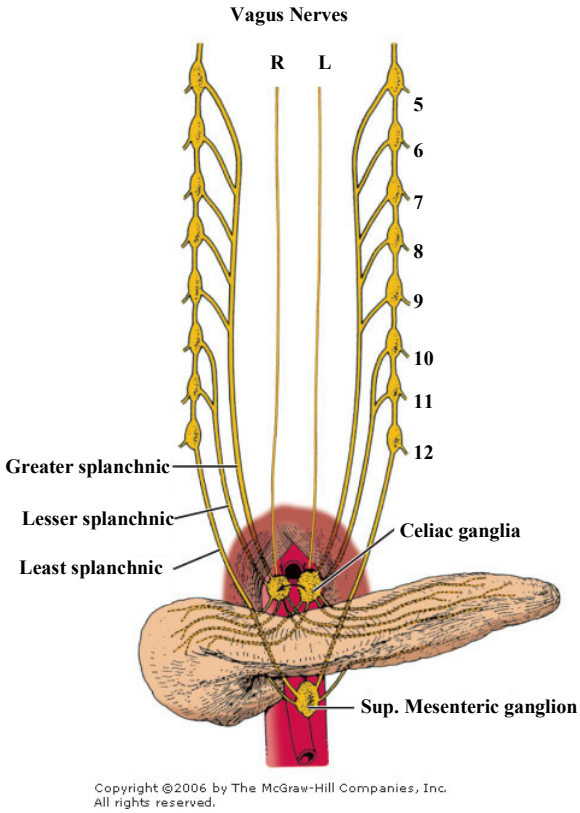
Nerve Supply of the Pancreas

Nerves of the pancreas are derived from the vagus and abdominopelvic splanchnic nerves passing through the diaphragm. The

parasympathetic and sympathetic fibers reach the pancreas by passing along the arteries from the celiac plexus and superior mesenteric plexus.

In addition to sympathetic fibers that pass to blood vessels, sympathetic and parasympathetic fibers are distributed to pancreatic acinar cells and islets.

Fig-6
Nerve Supply of the Pancreas



The parasympathetic fibers are secretomotor, but pancreatic secretion is primarily mediated by secretin and cholecystokinin, hormones formed by the epithelial cells of the duodenum and upper intestinal mucosa under the stimulus of acid contents from the stomach.

Histology and Physiology

The exocrine pancreas accounts for about 85% of the pancreatic mass.

- 10% of the gland is accounted for by extracellular matrix.
- 4% of pancreatic mass is blood vessels and the major ducts.
- The remaining 2% of the gland is comprised of endocrine tissue (24)

Exocrine Pancreas

The pancreas secretes approximately 500 to 800 mL per day of colourless, odourless, alkaline, isosmotic pancreatic juice. Pancreatic juice is a combination of acinar cell and duct cell secretions.

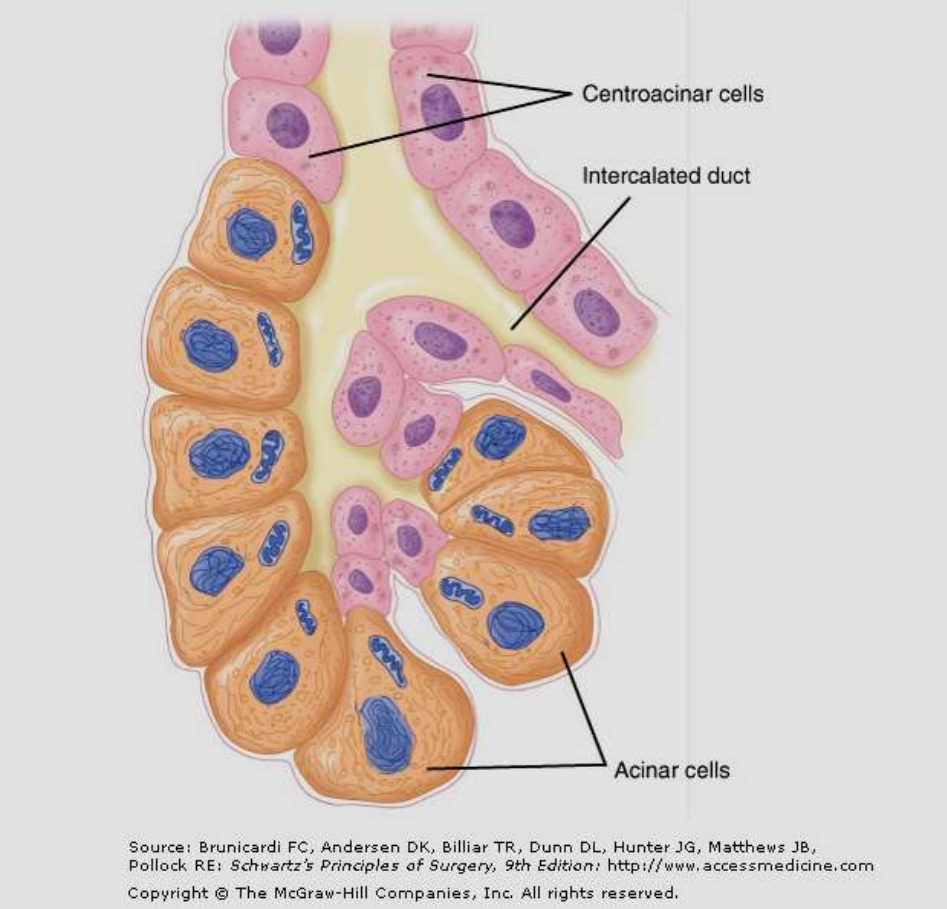
Acinar Cells

The acinar cells secrete amylase, proteases, and lipases, enzymes responsible for the digestion of all three food types: carbohydrate, protein, and fat.

The acinar cells are pyramid-shaped, with their apices facing the lumen of the acinus. Near the apex of each cell are numerous enzyme-containing zymogen granules that fuse with the apical cell membrane. Unlike the endocrine pancreas, where islet cells specialize in the secretion of one hormone type, individual acinar cells secrete all types of enzymes.

However, the ratio of the different enzymes released is adjusted to the composition of digested food through nonparallel regulation of secretion.

Fig-7
Acinar Cell of the Pancreas



Acute Pancreatitis

Definition

The International Symposium on Acute Pancreatitis (Atlanta, September 1992) defined Acute Pancreatitis as "An acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems" (14).

Acute Pancreatitis is an inflammatory disease of the pancreas that is associated with little or no fibrosis of the gland and by definition, it is reversible. It is distinguished from chronic pancreatitis by the absence of continuing inflammation, irreversible structural changes, and permanent impairment of exocrine and endocrine pancreatic function. Acute pancreatitis can be initiated by several factors, including gallstones, alcohol, trauma, and infections, and, in some cases, it is hereditary. Very often, patients with acute pancreatitis develop additional complications such as sepsis, shock, and respiratory and renal failure, resulting in considerable morbidity and mortality.

Classification of Acute Pancreatitis

A commonly used classification system (the Atlanta classification) divides AP into two broad categories. The classification was developed following 3 days of group meetings and open discussions, with unanimous consensus on a series of definitions for a clinically based classification system for acute pancreatitis by a diverse group of 40 international authorities from six medical disciplines and 15 countries. The proposed classification system was to be of value to practicing clinicians in the care of individual patients and to academicians seeking to compare inter-institutional data. (14)

The Atlanta Classification:

1. **Mild:** (edematous and interstitial) acute pancreatitis
2. **Severe:** (usually synonymous with necrotizing) acute pancreatitis

The criteria for severe AP included any of the following:

- A Ranson's score of 3 or more
- An APACHE II score of 8 or more within the first 48 hours
- Organ failure (respiratory, circulatory, renal, and/or gastrointestinal bleeding)
- Local complications (pancreatic necrosis, abscess, or pseudocyst)

Most attacks of AP are mild with recovery occurring within five to seven days. Death is unusual (less than 3 percent) in such patients. (17)

Approximately 15 to 25 percent of all cases are severe. Severe necrotizing pancreatitis is associated with a high rate of complications (local and systemic) and mortality (approximately 17 percent). (17)

As an example, one of the complications, systemic inflammatory response syndrome (SIRS), is the result of severe intra-and extrapancreatic inflammation mediated by cytokines. SIRS accounts for nearly one-half of the mortality from severe AP. Local complications from pancreatic necrosis, such as pseudocysts and abscesses, can occur from 24 hours to up to six weeks following the onset of acute pancreatitis and account for many of the deaths that occur more than two weeks after the onset of acute pancreatitis.

Severe Acute Pancreatitis as Defined by Atlanta Symposium
Early Prognostic Signs
Ranson signs ≥3
APACHE-II score ≥8
Organ Failure and/or Local Complications Necrosis Abscess Pseudocyst

However, some patients with local complications in the absence of organ failure are seen to have low mortality rates, like patients with mild acute pancreatitis, but have prolonged hospitalizations, like patients with severe acute pancreatitis. A proposal has been made to include such patients in a new subgroup called **"moderately severe acute pancreatitis"** (25).

The Atlanta classification has several deficiencies (26):

- It fails to recognize multiple and persistent (≥48 hours) organ failure, which is more predictive of severity than transient organ failure
- The nomenclature developed to describe local complications cannot be used to describe findings such as walled off pancreatic necrosis and does not allow for the differentiation of infected from sterile necrosis
- It combines predicting systems (early) and local complications (late) to define severe AP

A working group is revising the classification with input from specialists from around the world. This is expected to be published soon.

Etiology of Acute Pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood. (27, 28) In mild acute pancreatitis, the pancreas recovers its normal endocrine and exocrine histology and functions. Patients with severe acute pancreatitis can develop permanent endocrine and exocrine insufficiency depending on the extent of pancreatic injury and necrosis, irrespective of the etiology. Scarring of the pancreatic ducts can persist in some patients, mimicking the ductal changes of chronic pancreatitis. (29)

The complex pathogenesis of acute pancreatitis is still not clearly understood, although several theories based on animal model studies have been put forward. A number of conditions are suspected, with varying degrees of certainty, to induce acute pancreatitis. Gallstones and chronic alcohol abuse accounts for 75-80 % of the cases, the rest are attributed to other factors such as Hypertriglyceridemia, Hypercalcemia, drugs, smoking, genetic mutations, infection, trauma, factors causing ampullary obstruction etc. A minor subset of patients has no identifiable etiology, and the cause of pancreatitis remains undetermined. As our knowledge and understanding of the disease grows the number of so called "idiopathic" cases will decrease as our list of causes grows.

A review on the epidemiology of acute pancreatitis found an increasing incidence (especially that due to alcohol and gallstones in some areas) and decreasing case-fatality rate. (30)

Gallstones and Other Causes of Mechanical Ampullary Obstruction

Mechanical ampullary obstruction can be induced by gallstone and a variety of disorders. The most common cause of acute pancreatitis in most areas of the world is gallstones (including microlithiasis), which account for 35 to 40 percent of cases. (13) Cholecystectomy and clearing the common bile duct of stones prevents recurrence, confirming the cause-and-effect relationship. (31)

The mechanism by which the passage of gallstones induces pancreatitis is unknown.

Two factors have been suggested as the possible initiating event in gallstone pancreatitis:

1. Reflux of bile into the pancreatic duct due to transient obstruction of the ampulla during passage of gallstones (32)
2. Obstruction at the ampulla secondary to stone(s) or edema resulting from the passage of a stone (33)

Incidence of Gallstone (Biliary) Pancreatitis

Although 35 percent of attacks of acute pancreatitis are caused by gallstones, only 3 to 7 percent of patients with gallstones eventually develop pancreatitis. (31, 34) Gender and stone size may be risk factors for gallstone pancreatitis. The risk of developing acute pancreatitis in patients with gallstones is greater in men; however, more women develop this disorder since gallstones occur with increased frequency in women. It has been suggested that acute pancreatitis is associated with a stone diameter of less than 5 mm and that smaller stones or microlithiasis are more likely than larger stones to pass through the cystic duct and cause obstruction at the ampulla. (35, 36)

Management of Biliary Pancreatitis

The diagnosis of gallstone pancreatitis should be suspected if the patient has a prior history of biliary colic. In addition, all patients with a first attack of acute pancreatitis should have an abdominal ultrasound to search for gallstones, common duct stones, or signs of extrahepatic biliary tract obstruction. (34) Laboratory values obtained during the acute attack may also assist in making the diagnosis. Serum alanine aminotransferase (ALT) concentration is the most clinically useful parameter in predicting a gallstone etiology in patients with acute pancreatitis. (37)

If gallstone pancreatitis is suspected on the basis of imaging and laboratory findings and there is no history of alcohol abuse, cholecystectomy with cholangiography is recommended during the same hospitalization. ERCP is performed after laparoscopic cholecystectomy if a common duct stone is found and not removed at surgery.

Biliary sludge and Microlithiasis

Biliary sludge is a viscous suspension in the gallbladder bile that may contain small stones (<5 mm in diameter). (38) It is formed by modification of hepatic bile by gallbladder mucosa; thus hepatic bile samples may be insufficient for its diagnosis. (38)

Most patients with biliary sludge are asymptomatic. (38) Sludge appears as a mobile, low-amplitude echo on ultrasound that layers in the most dependent part of the gallbladder and is not associated with shadowing. Microscopic analysis of bile in patients with sludge often shows cholesterol monohydrate crystals or calcium bilirubinate granules. (39)

Sludge is typically found in patients with functional or mechanical bile stasis, such as those undergoing a prolonged fast, with distal bile duct obstruction, or on total parenteral nutrition. In addition, certain drugs that excreted by hepatocytes, such as ceftriaxone, can complex with bile to

form sludge within the biliary system when its solubility in bile is exceeded.

Biliary sludge is commonly found in patients with acute pancreatitis with no obvious cause. However, the association between biliary sludge and acute pancreatitis is unproven. Because of the high risk of recurrence, cholecystectomy is recommended in patients who have had an episode of pancreatitis and have biliary sludge. (40)

Other Causes of Acute Pancreatitis secondary to Ampullary Obstruction

Other conditions causing obstruction of the ampulla that have been associated with pancreatitis include biliary ascariasis, periampullary diverticula and pancreatic and periampullary tumours. Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are being recognized increasingly and may occasionally present as acute pancreatitis, especially in elderly nonalcoholic males.

Alcohol and Acute Pancreatitis

Acute alcoholic pancreatitis, along with Gallstone pancreatitis, is the most common diagnosis among patients hospitalized with pancreatic disease. (41-45) Approximately 10 percent of chronic alcoholics develop attacks of clinically acute pancreatitis. Studies have shown that not all

patients progress to chronic pancreatitis, even with continued alcohol abuse. (46)

Why only a small proportion of all alcoholics develop pancreatitis, what genetic and environmental factors influence the development of pancreatitis in alcoholics, and what is the exact mechanism of pancreatic injury by alcohol remain unanswered in spite of extensive and ongoing research.

Role of Smoking in the Etiology of Acute Pancreatitis

Until recently, smoking was thought to be a risk factor due to its association with alcohol. However, at least three large studies have suggested that cigarette smoking is an independent risk factor for acute and chronic pancreatitis by mechanisms that are unclear. (16, 47, 48)

Hypertriglyceridemia

Serum triglyceride concentrations above 1000 mg/dL can precipitate attacks of acute pancreatitis, although the pathogenesis of inflammation in this setting is unclear. (49) Hypertriglyceridemia may account for 1.3 to 3.8 percent of cases of acute pancreatitis. (50)

Hypertriglyceridemia, with concentrations severe enough to trigger attacks of acute pancreatitis, may even be present in children as part of a spectrum of inherited lipoprotein metabolism disorders. Acquired causes of

hypertriglyceridemia include obesity, diabetes mellitus, hypothyroidism, pregnancy, estrogen or tamoxifen therapy, glucocorticoid excess, nephrotic syndrome, and beta blockers. (50)

Hypercalcemia

Hypercalcemia of any cause can lead to acute pancreatitis, although actual incidence is low. Proposed mechanisms include deposition of calcium in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma. (51)

Genetic Mutations

There have been tremendous advances in the past few years in our understanding of the genetic basis of acute pancreatitis. Some genetic disorders are associated with a high-penetrance (eg, mutations at codons 29 and 122 of the serine protease 1 (cationic trypsinogen) gene (PRSS1)), while others have a low penetrance and are more frequent in the general population (eg, mutations in the serine protease inhibitor Kazal type 1 (SPINK1), which may act as a disease modifier). In addition, certain mutations in the cystic fibrosis gene (CFTR) have been associated with acute pancreatitis.

Inherited forms of pancreatitis, which may present as recurrent acute pancreatitis but eventually progresses to chronic pancreatitis, may

be inherited as autosomal dominant, autosomal recessive, or be a multigenic disorder as a result of mutations in these or yet unidentified genes.

Drug Induced Acute Pancreatitis

Acute pancreatitis related to drug or medication use is uncommon. The literature on drug-induced pancreatitis mostly consists of case reports and anecdotal account. Many drugs have been implicated as etiologic agents, and the list continues to grow. (52)

The following drugs were definitely associated with pancreatitis by at least two of the three reviews of this subject (52):

- AIDS therapy-didanosine, pentamidine
- Antimicrobial agents-metronidazole, stibogluconate, sulfonamides, tetracycline
- Diuretics-furosemide, thiazides
- Drugs used for inflammatory bowel disease-sulfasalazine, 5-ASA
- Immunosuppressive agents-L-asparaginase, azathioprine
- Neuropsychiatric agents-valproic acid
- Antiinflammatory drugs-sulindac, salicylates
- Others-calcium, estrogen, tamoxifen

The pathogenesis of drug-induced pancreatitis may be due to an idiosyncratic response in some cases (eg,6-mercaptopurine, aminosalicylates, and sulfonamides) or to a direct toxic effect (eg, diuretics, sulfonamides).

A high index of suspicion and careful drug history are essential for making the diagnosis. The time course of developing the disorder depends upon the drug involved.

Infectious causes of Acute Pancreatitis

There are numerous case reports of acute pancreatitis due to a wide variety of infectious agents. Cases of definite pancreatitis were associated with the following organisms (53):

- Viruses-Mumps, Coxsackievirus, hepatitis B, cytomegalovirus, varicella-zoster, herpes simplex
- Bacteria-Mycoplasma, Legionella, Leptospira, Salmonella
- Fungi-Aspergillus
- Parasites-Toxoplasma, Cryptosporidium, Ascaris

The frequency with which these infections lead to pancreatitis is not known.

Trauma

Blunt or penetrating trauma can damage the pancreas and cause acute pancreatitis, although these injuries are uncommon due to the retroperitoneal location of the gland. The diagnosis of traumatic pancreatitis is difficult and requires a high degree of suspicion. (54)

Vascular disease

Pancreatic ischemia is an uncommon cause of clinically significant pancreatitis. However, ischemia with resultant pancreatitis has been reported in the following circumstances (55):

- Vasculitis (systemic lupus erythematosus and polyarteritis nodosa)
- Atheroembolism
- Intraoperative hypotension
- Hemorrhagic shock

Acute Pancreatitis Post-ERCP

Asymptomatic hyperamylasemia occurs in 35 to 70 percent of patients undergoing ERCP. A diagnosis of post-ERCP pancreatitis is generally made if the hyperamylasemia is accompanied by persistent severe upper abdominal pain, often with nausea and vomiting. Acute pancreatitis occurs in about 3 percent of patients undergoing diagnostic ERCP, 5 percent undergoing therapeutic ERCP, and up to 25 percent undergoing sphincter of Oddi manometric studies. (56)

Idiopathic Acute Pancreatitis

No obvious etiology is identifiable by history (eg, alcohol, family history), laboratory tests (eg, gallstone pancreatitis, hyperlipidemia, hypercalcemia), and abdominal ultrasound in up to 30 percent of patients with acute pancreatitis. The term idiopathic pancreatitis is used for these who have no cause found even after an exhaustive search for an etiology. Most recommendations suggest that extensive investigation for unusual causes of pancreatitis is not required after the first episode of unexplained pancreatitis. Approximately 15 to 25 percent of patients with acute pancreatitis may be labelled as idiopathic and this figure will probably decrease in the future with better identification of different causes.

CAUSES OF ACUTE PANCREATITIS

Mechanical	Gallstones, biliary sludge, ascariasis, periampullary diverticulum, pancreatic or periampullary cancer, ampullary stenosis, duodenal stricture or obstruction
Toxic	Ethanol, methanol, scorpion venom, organophosphate poisoning
Metabolic	Hyperlipidemia (types I, IV, V), Hypercalcemia
Drugs	Didanosine, pentamidine, metronidazole, stibogluconate, tetracycline furosemide, thiazides, sulphasalazine, 5-ASA, L-asparaginase, azathioprine, valproic acid, sulindac, salicylates, calcium, estrogen
Infection	**Viruses** - mumps, coxsackie, hepatitis B, CMV, varicella-zoster, HSV, HIV
	Bacteria - mycoplasma, Legionella, Leptospira, salmonella
	Fungi - aspergillus
	Parasites - toxoplasma, cryptosporidium, Ascaris
Trauma	Blunt or penetrating abdominal injury, iatrogenic injury during surgery or ERCP (sphincterotomy)
Congenital	Cholodochocele type V, ? pancreas divisum
Vascular	Ischemia, atheroembolism, vasculitis (polyarteritis nodosa, SLE)
Miscellaneous	Post ERCP, pregnancy, renal transplantation, alpha-1-antitrypsin deficiency
Genetic	CFTR and other genetic mutations
Idiopathic	

Pathogenesis of Acute Pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood. (27, 28)The disease process can be localized or affect the whole pancreas, and is a disease with a typically unpredictable course. (57) A number of conditions are known to induce this disorder. The exact mechanisms by which diverse etiological factors induce an attack are still unclear. It is generally believed that the earliest events in acute pancreatitis occur within acinar cells. Acinar cell injury early in acute pancreatitis leads to a local inflammatory reaction. If this inflammatory reaction is marked, it leads to a systemic inflammatory response syndrome (SIRS). An excessive SIRS leads to distant organ damage and multiple organ dysfunction syndrome (MODS). MODS associated with acute pancreatitis is the primary cause of morbidity and mortality in this condition.(58)

Animal Models Demonstrate Pathogenesis of Inflammatory Response

Although a number of animal models have been developed to understand the pathogenesis of acute pancreatitis, none is strictly comparable to the human condition.(59) Alcohol abuse and gallstones are implicated in the etiopathogenesis of 90% of cases of acute pancreatitis in India(3) which is comparable to their role stated in western literature. (44, 45, 60-62).

However, none of the existing animal models duplicates these situations. In addition, the commonly used agents for inducing pancreatitis in animal models, such as cerulein and a choline-deficient ethionine-supplemented diet, are not recognized causes of human acute pancreatitis.(59)

Nevertheless, the structural and biochemical changes seen in early phases of acute pancreatitis are remarkably constant in different animal models, and similar changes have been demonstrated in human acute pancreatitis. Furthermore, the clinical and pathologic features of human acute pancreatitis, regardless of the inciting event, are very similar.(59, 63, 64)

Despite the limitations of animal models, the data suggest that a similar cascade of events occurs once pancreatitis begins independent of the inciting event or initial mechanism.(63) Animal studies have shown that this cascade cannot be halted successfully unless therapy is initiated either prophylactically or within a few hours of the inciting event. It is not clear from these studies why some individuals experience only interstitial or edematous pancreatitis, while others go on to develop the necrotizing form of the disease.(65)

Thus animal models help us understand the mechanisms and subsequent consequences of intrapancreatic digestive enzyme activation, the generation and role of cytokines and other inflammatory mediators in the pancreatic acinar cell, and the role of extra-acinar players such as inflammatory cells in pancreatic inflammation. Further, mechanistic advances have also been made in understanding the modes of cell death, including apoptosis and necrosis, and their relevance to pancreatitis.

From these experimental studies, numerous factors have been implicated in causing pancreatic injury, including intrapancreatic digestive enzyme activation (66), calcium, the cytoskeleton (67), transcription factors (67), cytokines and chemokines (68), inflammatory cells (68), peptide mediators such as substance P (69), small molecule mediators such as nitric oxide (70), reactive oxygen species (54), polyamine depletion (71), and cyclooxygenase (COX)-2 (72). While pancreatitis may be due to several of these factors acting in different ways, the disease frequently develops in severity over time and thus it is important to understand the initial events that trigger or exacerbate it, so as to design treatments that are beneficial if administered in the early stages of presentation.

Triggering event

Only a small percent of people with predisposing factors actually develop acute pancreatitis. For example, several large population based studies have drawn the conclusion that only 3-7 % with gallstones, 10% of alcoholics and <1% of patients with hypercalcemia eventually contract pancreatitis.(34, 73)

The exact mechanism of induction of acute pancreatitis is not known. However several theories have been put forward.

In alcohol induced acute pancreatitis ongoing studies are being conducted to elucidate the following possible triggering pathways (41):

- Sensitization of acinar cells to CCK-induced premature activation of zymogens
- Potentiation of the effect of CCK on the activation of transcription factors, nuclear factor kB, and activating protein-1
- Generation of toxic metabolites such as acetaldehyde and fatty acid ethyl esters
- Sensitization of the pancreas to the toxic effects of coxsackie virus B3

- Activation of pancreatic stellate cells by acetaldehyde and oxidative stress and subsequent increased production of collagen and other matrix proteins

Two factors have been suggested as the possible initiating event in gallstone pancreatitis (32, 33):

- reflux of bile into the pancreatic duct due to transient obstruction of the ampulla during passage of gallstones
- obstruction at the ampulla secondary to stone(s) or edema resulting from the passage of a stone

In hyperlipidemia it has been suggested that the triggering factor is free fatty acids that are released from serum triglycerides in toxic concentrations by the action of pancreatic lipase within pancreatic capillaries. (49)

Early Acute Changes

Intraacinar activation of proteolytic enzymes

One of the earliest events seen in different models of acute pancreatitis is blockade of secretion of pancreatic enzymes while synthesis continues.

The central requirement for induction of acute pancreatitis is intraacinar activation of these proteolytic enzymes, which ultimately leads to autodigestive injury to the gland.

A proposed mechanism by which intraacinar activation occurs and leads to pancreatic destruction in animal models of pancreatitis is as follows (74):

- A devastating event occurs very early which allows generation of large amounts of active trypsin within the pancreas.
- Collection of lysosomal enzymes such as cathepsin B and digestive enzymes including trypsinogen occurs in unstable vacuoles within the acinar cell. In the normal acinar cell, these two groups of enzymes are carefully sorted by the Golgi network.
- In early pancreatitis, however, cathepsin B cleaves the trypsinogen activation peptide from trypsinogen within the acinar vacuoles, leading to intrapancreatic activation of trypsin.
- The vacuoles then rupture, releasing the active trypsin.
- The normal defence mechanisms of the pancreas are overwhelmed by the large amounts of trypsin released.
- The intrapancreatic release of trypsin leads to activation of more trypsin, and other pancreatic enzymes such as phospholipase, chymotrypsin, and elastase.
- Trypsin also activates other enzyme cascades including complement, kallikrein-kinin, coagulation, and fibrinolysis.

- The intrapancreatic release of active pancreatic enzymes leads to pancreatic autodigestion

This sets up a vicious cycle of active enzymes damaging cells, which then release more active enzymes. The destruction spreads along the gland and into the peripancreatic tissue.

Microcirculatory injury

The release of pancreatic enzymes damages the vascular endothelium and the interstitium as well as the acinar cells. Microcirculatory changes, including vasoconstriction, capillary stasis, decreased oxygen saturation, and progressive ischemia, occur early in experimental models of acute pancreatitis. These changes lead to increased vascular permeability and swelling of the gland (edematous or interstitial pancreatitis). Vascular injury could lead to local microcirculatory failure and amplification of the pancreatic injury. (55, 75)

There is also speculation about the role of ischemia-reperfusion injury in the pancreas. Reperfusion of damaged tissues leads to the release of free radicals and inflammatory cytokines into the circulation, which could cause further injury.(75) The importance of microcirculatory injury can be appreciated by the importance of aggressive fluid replacement in the management of acute pancreatitis, which minimizes this injury.

Leukocyte chemoattraction and release of cytokines

Microscopic and radionuclide studies using Indium-111 tagged leukocytes show marked glandular invasion by macrophages and polymorphonuclear leukocytes in early stages of animal and human pancreatitis. Activation of complement and the subsequent release of C5a have a significant role in the recruitment of these inflammatory cells.

Granulocyte and macrophage activation causes the release of proinflammatory cytokines (tumor necrosis factor, interleukins 1,6, and 8), arachidonic acid metabolites (prostaglandins, platelet-activating factor, and leukotrienes), proteolytic and lipolytic enzymes, and reactive oxygen metabolites which overwhelm the scavenging capacity of endogenous antioxidant systems. These substances also interact with the pancreatic microcirculation to increase vascular permeability and induce thrombosis and hemorrhage, leading to pancreatic necrosis.

Activated pancreatic enzymes, microcirculatory impairment, and the release of inflammatory mediators lead to rapid worsening of pancreatic damage and necrosis. This interaction makes it difficult to estimate the individual roles of these factors in inducing pancreatic damage. In addition, approximately 80 percent of patients with pancreatitis develop only interstitial pancreatitis rather than necrotizing

pancreatitis; the factors involved in limiting the pancreatic damage are not well understood.

Systemic Response

Some patients with severe pancreatic damage develop systemic complications including fever, acute respiratory distress syndrome (ARDS), pleural effusions, renal failure, shock, and myocardial depression.

This systemic inflammatory response syndrome (SIRS) is probably mediated by activated pancreatic enzymes (phospholipase, elastase, trypsin, etc) and cytokines (tumor necrosis factor, platelet activating factor) released into the circulation from the inflamed pancreas.

ARDS, in addition to being secondary to microvascular thrombosis, may be induced by active phospholipase A (lecithinase), which digests lecithin, a major component of surfactant. Myocardial depression and shock are thought to be secondary to vasoactive peptides and a myocardial depressant factor. Acute renal failure has been explained on the basis of hypovolemia and hypotension. Metabolic complications include hypocalcemia, hyperlipidemia, hyperglycemia, hypoglycemia, and diabetic ketoacidosis. The pathogenesis of hypocalcemia is multifactorial and includes calcium-soap formation,

hormonal imbalances (eg, parathyroid hormone, calcitonin, glucagon), binding of calcium by free fatty acid-albumin complexes, and intracellular translocation of calcium.

These systemic complications are uncommon and much less severe in patients with interstitial pancreatitis than in those with necrotizing pancreatitis. However, only about 50 percent of patients with necrotizing pancreatitis develop organ failure, and this complication cannot be predicted from the degree of pancreatic necrosis or the presence or absence of infected necrosis. One study suggested that an increased tissue concentration of macrophage migration inhibitory factor was a critical factor in the pathogenesis of severe acute pancreatitis.

Bacterial translocation - The normal human gut prevents the translocation of bacteria into the systemic circulation through a complex barrier that consists of immunologic, bacteriologic, and morphologic components. During the course of acute pancreatitis, the gut barrier is compromised, leading to translocation of bacteria, which can result in local and systemic infection. The breakdown in the gut barrier is thought to be a consequence of ischemia due to hypovolemia and pancreatitis-induced gut arteriovenous shunting.

Most infections in acute pancreatitis are caused by common enteric organisms suggesting that they originate from the gastrointestinal tract

The consequences of bacterial translocation from the gut in acute pancreatitis can be lethal. Local bacterial infection of pancreatic and peripancreatic tissues occurs in approximately 30 percent of patients with severe acute pancreatitis, potentially resulting in multiorgan failure and its sequelae.

The Inflammatory Cascade in Acute Pancreatitis

Triggering Events

A number of situations can precipitate acute pancreatitis in humans, but only a small fraction of patients with these predisposing factors ultimately develop the disease. For example, only 3 to 7 percent of people with gallstones (34); 10 percent of alcoholics; and few patients with hypercalcemia (73) eventually develop acute pancreatitis.

Alcoholic Pancreatitis

The exact mechanism of induction of pancreatitis by these agents is not known. It is unclear, for example, why alcohol-induced pancreatitis occurs only after many years of alcohol abuse and not after a single binge in humans not habituated to alcohol use. However, several mechanisms

have been proposed for the development of acute pancreatitis in alcoholics (41):

- Sensitization of acinar cells to CCK-induced premature activation of zymogens
- Potentiation of the effect of CCK on the activation of transcription factors, nuclear factor kB, and activating protein-1
- Generation of toxic metabolites such as acetaldehyde and fatty acid ethyl esters
- Sensitization of the pancreas to the toxic effects of coxsackie virus B3
- Activation of pancreatic stellate cells by acetaldehyde and oxidative stress and subsequent increased production of collagen and other matrix proteins

Different mechanisms have been proposed for other forms of pancreatitis.

Gallstone Pancreatitis

- reflux of bile into the pancreatic duct due to transient obstruction of the ampulla during passage of gallstones (32)
- obstruction at the ampulla secondary to stone(s) or edema resulting from the passage of a stone (33).

Hyperlipidemic pancreatitis

- Release of free fatty acids from serum triglycerides in toxic concentrations by the action of pancreatic lipase within pancreatic capillaries (49)

Initial Acute Response

Once the triggering factors are initiated they ultimately cumulate in the activation of the zymogen trypsinogen to its active form trypsin. It is thought that mechanisms of inflammatory response are then triggered.

It is a well known fact that the exocrine pancreas synthesizes and secretes a variety of digestive enzymes that normally become activated only after reaching the duodenum. At times, small amounts of trypsinogen are spontaneously activated, but the pancreas has mechanisms to quickly remove activated trypsin:

- The first line of defence is the pancreatic secretory trypsin inhibitor (PSTI or SPINK1), which can bind and inactivate about 20 percent of the trypsin activity.
- The second line of defence is autolysis of prematurely activated trypsin. Absence of this mechanism is postulated to cause hereditary pancreatitis.

- Another defence mechanism involves mesotrypsin and enzyme Y, which lyses and inactivates trypsin.
- Nonspecific antiproteases such as alpha-1 antitrypsin and alpha-2-macroglobulin are present in the pancreatic interstitium.

To summarize, cationic trypsin is the most abundant form of trypsin produced by the pancreas and is the primary catalyst for the conversion of pancreatic zymogens into pancreatic digestive enzymes after they are secreted into the duodenum. Premature activation of digestive enzymes in the pancreas is the major cause of pancreatic injury and immune system activation, leading to acute pancreatitis and later chronic pancreatitis. The primary defence against pancreatitis is to control trypsin activity, either through prevention of premature activation of trypsinogen to trypsin, or by the destruction, inhibition, or elimination of trypsin from the pancreas. (76)

Intra-acinar activation of proteolytic enzymes

One of the earliest events in the different models of acute pancreatitis is blockade of secretion of pancreatic enzymes while synthesis continues (74). It is becoming increasingly clear that the central event in the triggering of acute pancreatitis is the activation of these proteolytic enzymes within the acinar cells of the gland leading to auto digestive injury of pancreatic tissue.

Proposed cascade of events in Intra-acinar activation of proteolytic enzymes

Generation of large amounts of active trypsin within the pancreas is triggered by a devastating early event.

- Co localization of lysosomal enzymes, such as cathepsin B and digestive enzymes including trypsinogen, occurs in unstable vacuoles within the acinar cell (77). In the normal acinar cell, these two groups of enzymes are carefully sorted by the Golgi network. In early pancreatitis, however, cathepsin B cleaves the trypsinogen activation peptide from trypsinogen within the acinar vacuoles, leading to intrapancreatic activation of trypsin (77).
- The vacuoles then rupture, releasing the active trypsin
- The normal defence mechanisms of the pancreas are overwhelmed by the large amounts of trypsin released. In addition, the intrapancreatic release of trypsin leads to activation of more trypsin, and other pancreatic enzymes such as phospholipase, chymotrypsin, and elastase. Trypsin also activates other enzyme cascades including complement, kallikrein-kinin, coagulation, and fibrinolysis.(40)
- The intrapancreatic release of active pancreatic enzymes leads to pancreatic autodigestion, setting up a vicious cycle of active enzymes damaging cells, which then release more active enzymes.

The destruction spreads along the gland and into the peripancreatic tissue.(78)

The activation of trypsinogen occurs before either biochemical or morphological injury to acinar cells is evident.

An in vitro model found that complete inhibition of pancreatic cathepsin B activity with E-64d (a specific potent and irreversible cathepsin B inhibitor) prevented cerulein-induced trypsinogen activation (79).

This observation supports the significance of cathepsin B activation of trypsinogen, and the importance of co-localization of pancreatic digestive enzymes and lysosomal hydrolases. In addition, it suggests that complete inhibition of cathepsin B may be of benefit in either the prevention or treatment of acute pancreatitis.

Other mechanisms besides cathepsin B have also been suggested to have a role like trypsinogen autoactivation or activation by other lysosomal proteinases.

Microcirculatory Injury

The release of pancreatic enzymes damages the vascular endothelium and the interstitium as well as the acinar cells (55, 75, 80). Microcirculatory changes, including vasoconstriction, capillary stasis,

decreased oxygen saturation, and progressive ischemia, occur early in experimental models of acute pancreatitis. These changes lead to increased vascular permeability and swelling of the gland (edematous or interstitial pancreatitis). Vascular injury could lead to local microcirculatory failure and amplification of the pancreatic injury(55).

Reperfusion of damaged tissues leads to the release of free radicals and inflammatory cytokines into the circulation, which could cause further injury. The importance of microcirculatory injury can be appreciated by the importance of aggressive fluid replacement in the management of acute pancreatitis, which minimizes this injury.

Release of Inflammatory Mediators

Microscopic and radionuclide studies using Indium-111 tagged leukocytes show marked glandular invasion by macrophages and polymorphonuclear leukocytes in early stages of animal and human pancreatitis. (81-84). Granulocyte and macrophage activation causes the release of proinflammatory cytokines (tumour necrosis factor, interleukins 1, 6, and 8), arachidonic acid metabolites (prostaglandins, platelet-activating factor, and leukotrienes), proteolytic and lipolytic enzymes, and reactive oxygen metabolites which overwhelm the scavenging capacity of endogenous antioxidant systems. These substances also interact with the pancreatic microcirculation to increase

vascular permeability and induce thrombosis and hemorrhage, leading to pancreatic necrosis.(85)

Activated pancreatic enzymes, microcirculatory impairment, and the release of inflammatory mediators lead to rapid worsening of pancreatic damage and necrosis. This interaction makes it difficult to estimate the individual roles of these factors in inducing pancreatic damage. In addition, approximately 80 percent of patients with pancreatitis develop only interstitial pancreatitis rather than necrotizing pancreatitis; the factors involved in limiting the pancreatic damage are not well understood.

Predicting the Severity of Acute Pancreatitis-Scoring Systems and Biochemical Markers

Acute pancreatitis is protean in nature. It can range through a wide gamut from mild acute pancreatitis on one side of the spectrum to severely debilitating disease on the other.

Approximately 15 to 25 percent of all patients with acute pancreatitis develop severe acute pancreatitis. The ability to predict its severity can help identify patients at increased risk for morbidity and mortality, thereby assisting in appropriate early triage to intensive care units and selection of patients for specific interventions.

The severity of AP can be predicted based upon clinical, laboratory, and radiologic risk factors, various severity grading systems, and serum markers. Some of these can be performed on admission to assist in triage of patients, while others can only be obtained after the first 48 to 72 hours or later. The ideal predictor should be rapid, reproducible, inexpensive, minimally invasive and highly accurate, especially for predicting patients at low risk for complications. (86) Unfortunately, none has yet proven to be a consistently accurate predictor of the clinical course. (54)

No perfect system exists for predicting which patients will develop severe pancreatitis. In the absence of such a system, a multitude of predictive models have been developed and continue to be developed.

The problem with the predictive models overall is that they have low specificity (ie, high false positive rates), which when coupled with the fact that the prevalence of severe AP is low (15 to 25 percent) results in low positive predictive values for the various models. On the other hand, the systems have good negative predictive values, again related to the low prevalence of severe AP. The difficulties in predicting the severity of AP have been addressed in a number of studies. (87)

With the available systems lacking specificity and positive predictive value, future predictive models may depend upon new factors (eg, biomarkers, genetic polymorphisms and mutations, and proteomic and metabolic patterns) and new methods of analysis (eg, artificial neural networks, computational learning theory, systems biology, etc) (87)

Clinical Predictors

Clinical parameters that have historically been used to predict the course of pancreatitis include:

- Clinical Judgment (based on clinical and laboratory data at the time of admission)
- Older age (studies concluded that an older age portended a worse prognosis. An exact cut-off has never been established although one in study patients >75 had a 15% more chance of developing severe acute pancreatitis)

- Alcohol related pancreatitis (several reports indicate that alcohol as a cause of pancreatitis is associated with and increased risk of necrosis and the need for intubation, ventilation or hemodynamic support)
- Short time interval to admission with guarding or rigidity (A time interval between the onset of symptoms and hospital admission of less than 24 hours, as well as rebound tenderness and/or guarding were historically thought to be associated with increasing severity of pancreatitis)
- Obesity (studies have found obesity (defined as a body mass index >30) to be a risk factor for severe acute pancreatitis)
- Organ Failure (Early and persistent organ failure is a reliable indicator of a prolonged hospital stay and increased mortality. Organ failure within 72 hours of admission is associated with the presence of extended pancreatic necrosis and a mortality rate of 42 percent. Several studies have found that the evolution and clinical course of organ failure was a more accurate predictor of adverse outcomes. In one study, persistent and deteriorating (≥48 hours) organ failure were associated with mortality rates of 21 and 55 percent, respectively. On the other hand, early organ dysfunction that was not persistent (<48 hours) was associated with a mortality rate of 0 percent. Transient organ failure was associated with a mortality rate of 1.4 percent, whereas persistent organ failure had a 35 percent mortality rate. (25)

At the present time, persistent organ failure is widely accepted as a reliable criterion for severe acute pancreatitis.

Laboratory Predictors

Hemoconcentration

Acute pancreatitis results in significant third space losses, resulting in hemoconcentration and a high hematocrit. Studies evaluating the hematocrit as a predictor of the severity of AP have produced variable results. The discrepancies may be due to differences in values chosen as a cutoff and the time that they were obtained. Despite these differences, it appears that a normal or low hematocrit at admission and during the first 24 hours is generally associated with a milder clinical course.

C-reactive protein

C-reactive protein (CRP) is one of the acute phase reactants made by the liver in response to interleukin-1 and interleukin-6. Its utility for predicting the severity of pancreatitis has been studied at admission and at 24, 48, and 72 hours. A review of the literature estimated that at 48 hours, it had a sensitivity, specificity, positive predictive value, and negative predictive value of 80, 76, 67, and 86 percent, respectively, using a cutoff of 150 mg/L.

Blood Urea Nitrogen

In a large hospital-based cohort, serial blood urea nitrogen (BUN) measurements were the most reliable routine laboratory test to predict the mortality in acute pancreatitis. For every increase in the BUN of 5 mg/dL during the first 24 hours, the adjusted odds ratio for mortality was 2.2.

Serum Creatinine

An elevated serum creatinine within the first 48 hours may predict the development of pancreatic necrosis. In one study of 129 patients, a peak creatinine of greater than 1.8 mg/dL during the first 48 hours had a positive predictive value of 93 percent for the development of pancreatic necrosis.

Other Serum Markers

Multiple other serum markers have been studied for predicting the severity pancreatitis including: urinary trypsinogen activation peptide (TAP), procalcitonin, polymorphonuclear elastase, pancreatic-associated protein, amylase, lipase, serum glucose, serum calcium, procarboxypeptidase-B, carboxypeptidase B activation peptide, serum trypsinogen-2, phospholipase A-2, serum amyloid protein-A, substance P, antithrombin III, platelet activating factor, interleukins 1, 6, and 8, tumour necrosis factor-alpha or soluble tumour necrosis factor receptor, and various genetic polymorphisms

Radiologic Predictors

Chest radiographs

A pleural effusion and/or pulmonary infiltrates during the first 24 hours may be associated with necrosis and organ failure.

CT scan

CT scan is probably the most frequently used radiologic investigation when severe acute pancreatitis is suspected. It is used to look for pancreatic necrosis and extrapancreatic inflammation. Intravenous contrast-enhanced CT distinguishes between edematous and necrotizing pancreatitis, since areas of necrosis and exudates do not enhance. CT is more accurate than ultrasonography for the diagnosis of severe pancreatic necrosis.

MRI and MRCP

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are being used increasingly to diagnose acute pancreatitis and to assess its severity. MRI appears to be comparable to CT, if not better, in providing precise information regarding the severity of the disease. MRI is as effective as CT in demonstrating the presence and extent of pancreatic necrosis and fluid collections, and is probably superior for indicating the suitability of such collections for nonsurgical drainage. But high cost, lack of infrastructure

and experienced personnel have prevented the adoption of MRI and MRCP as a first line investigation of acute pancreatitis.

Scoring Systems

Many scoring systems have been reported but none has proven to be perfect. While they can be useful to group patients for the purpose of inter-institutional comparisons and reporting, none has high accuracy in predicting the severity of acute pancreatitis in a given patient at the bedside. On the other hand, they are superior to clinical judgment for triaging patients to more intensive care and aggressive therapy.

Many scoring systems (eg, Ranson, Glasgow, Banks, and Agarwal and Pitchumoni take 48 hours to complete, can be used only once, and do not have a high degree of sensitivity and specificity. In addition, some have limited utility since they focus on specific complications (eg, Banks) or are invasive (eg, Leeds diagnostic peritoneal lavage). As a result, many of these systems are not used routinely.

Ranson's criteria

A score based upon Ranson's criteria is one of the earliest scoring systems for severity in acute pancreatitis. Ranson's criteria consist of 11 parameters. Five of the factors are assessed at admission and six are assessed during the next 48 hours. A later modification for biliary

pancreatitis included only 10 points. Mortality increases with an increasing score. Using the 11 component score, mortality was 0-3% when the score was <3, 11-15% when the score was ≥3, and 40% when the score was ≥6. Although the system continues to be used, a meta-analysis of 110 studies found the Ranson score to be a poor predictor of severity.

Modified Ranson's Criteria

At admission:

At ADMISSION	
1.	age in years > 55 years
2.	white blood cell count > 16000 cells/mm3
3.	blood glucose > 10 mmol/L (> 200 mg/dL)
4.	serum AST > 250 IU/L
5.	serum LDH > 350 IU/L
At 48 Hours	
6.	Calcium (serum calcium < 2.0 mmol/L (< 8.0 mg/dL)
7.	Hematocrit fall > 10%
8.	Oxygen (hypoxemia PO2 < 60 mmHg)
9.	BUN increased by 1.8 or more mmol/L (5 or more mg/dL) after IV fluid hydration
10.	Base deficit (negative base excess) > 4 mEq/L
11.	Sequestration of fluids > 6L

One point is assigned for every criteria present.

Interpretation:

- If the score ≥ 3, severe pancreatitis likely.
- If the score < 3, severe pancreatitis is unlikely

Or

- Score 0 to 2 : 2% mortality
- Score 3 to 4 : 15% mortality
- Score 5 to 6 : 40% mortality
- Score 7 to 8 : 100% mortality

The APACHE II score

The acute physiology and chronic health examination (APACHE) II score was originally developed for critically ill patients in intensive care units.

It has 12 physiologic measures and extra points based upon age and presence of chronic disease. It is probably the most widely studied severity scoring system in acute pancreatitis. It has good negative predictive value and modest positive predictive value for predicting severe acute pancreatitis and can be performed daily. Decreasing values during the first 48 hours suggest a mild attack, while increasing values suggest a severe attack. Studies suggest that mortality is less than 4% with a score <8 and is 11 to 18 % with a score >8.

Some limitations of the APACHE II score are that is complex and cumbersome to use, it does not differentiate between interstitial and

necrotizing pancreatitis, and it does not differentiate between sterile and infected necrosis. Finally, it has a poor predictive value at 24 hours.

The addition of a body mass index (BMI) score to APACHE II (known as APACHE O) improved the prediction of severe pancreatitis compared with the conventional APACHE II score in one study. A simplified Acute Physiology Score II developed in ICU patients may be comparable to APACHE II.

Several additional variables were added to APACHE II to improve its accuracy leading to the development of APACHE III. Both APACHE II and III scores use physiology, age, and chronic health to calculate prognosis; they differ in total score, the number of physiologic variables (12 for APACHE II versus 17 for APACHE III), and the assessment of chronic health status. However, the APACHE III system does not appear to be as useful as APACHE II for distinguishing mild from severe attack.

The Glasgow-Imrie score

The Glasgow system is a simple prognostic system that uses age, and 7 laboratory values collected during the first 48 hours following admission for pancreatitis, to predict severe pancreatitis. It is applicable to both biliary and alcoholic pancreatitis.

A point is assigned if a certain breakpoint is met at any time during that 48-hour period.

Glasgow-Imrie Criteria

The data is collected during the first 48 hours following an admission for pancreatitis.

Parameters and Break Points :

DATA COLLECTED WITHIN FIRST 48 HRS	
Age	> 55 years (1) ≤ 55 years (0)
Serum Albumin	< 3.2 g/dL (1) ≥ 3.2 g/dL(0)
Arterial pO2 on room air	< 60 mm Hg (1) ≥ 60 mm Hg (0)
Serum Calcium	< 8 mg/dL (1) ≥ 8 mg/dL (0)
Blood Glucose	> 180 mg/dL (1) ≤ 180 mg/dl (0)
Serum LDH	> 600 U/L (1) ≤ 600 U/L (0)
Serum urea nitrogen	> 45 mg/dL (1) ≤ 45 mg/dL (0)
WBC count	> 15,000 per L (1) ≤ 15,000 per L (0)

Modified Glasgow prognostic criteria = SUM (points for all 8 parameters)

Interpretation:

- Minimum score 0, maximum score 8
- If the score >=3, severe pancreatitis likely.
- If the score < 3, severe pancreatitis is unlikely.

Systemic Inflammatory Response Syndrome Score

The presence of the systemic inflammatory response syndrome (SIRS) is associated with increased mortality. A score based upon the systemic inflammatory response syndrome has been developed. Initial studies suggest it can reliably predict the severity of pancreatitis and has the added advantage that it can be applied easily at the bedside every day. The severity of acute pancreatitis was greater among patients with acute pancreatitis and SIRS on day one, particularly in those with three or four SIRS criteria, compared with those without SIRS on day one. Thus, it appears that the SIRS score is inexpensive, readily available, and compares favourably with other more complicated scores.

Systemic Inflammatory Response Syndrome (SIRS)

Defined by Two or More of the Following Criteria
Pulse >90 beats/min
Respiratory rate >20/min or PCO2 <32 mmHg
Temperature <36◦C or >38◦C
White blood count <4,000 or >12,000/mm3

BISAP Score

Development of the bedside index of severity in acute pancreatitis (BISAP) score was based upon 17,922 cases of AP from 2000 to 2001 and validated in 18,256 cases from 2004 to 2005. Patients with a score of zero had a mortality of less than 1%, whereas patients with a score of five had a mortality rate of 22%. In the validation cohort, the BISAP score had similar test performance characteristics for predicting mortality as the APACHE II score. The BISAP has not been validated for predicting outcomes such as length of hospital stay, need for ICU care, or need for intervention.

A validation study of the BISAP score that included 185 patients found that its performance was similar to APACHE II, Ranson's criteria, and the CT severity index system. While the BISAP score is meant to be easily calculated at the bedside, it has been noted that to do so is not as simple as was initially reported because four variables need to be considered to determine if SIRS is present.

BISAP (Bedside Index for Severity in Acute Pancreatitis)

Patients are assigned 1 point for each of the following during the first 24 hours:
BUN >25 mg/dL
Impaired mental status
SIRS
Age >60 years
Presence of a pleural effusion

(ie, the acronym BISAP)

Impaired mental status - defined as any record of disorientation, lethargy somnolence, coma or stupor in the medical record.

Interpretation-A score greater than 3 indicates Severe Acute Pancreatitis.

Harmless Acute Pancreatitis Score

The harmless acute pancreatitis score can typically be calculated within 30 minutes of admission and takes into account three parameters:

- Lack of rebound tenderness or guarding
- Normal hematocrit
- Normal serum creatinine

It was derived on a cohort of 394 patients and validated in a cohort of 452 patients. This score correctly identified 200 of 204 patients (98 percent) with a harmless course. Patients were considered likely to have a harmless course if none of the three parameters were present.

The New Japanese Scoring System for Acute Pancreatitis. The Japanese severity score for acute pancreatitis was revised in 2008.

New Japanese Severity Score In Acute Pancreatitis

Prognostic factor I (2 points for each positive factor)	**Prognostic factor II (1 point for each positive factor)**	**Prognostic factor Ⅲ**
Clinical signs	**Laboratory data**	SIRS score ≥ 3 (2 points)
Shock	PaO2 ≤ 60 mmHg (room air)	Age≥ 70 yr (1 point)
Respiratory failure	FBS ≥ 200 mg/dL	
Mental disturbance	Total protein ≤ 60 g/L	
Severe infection	LDH ≥ 700 IU/L	
Hemorrhagic diathesis	Ca ≤ 7.5 mg/dL	
Laboratory data	Prothrombin time ≥ 15 s	
BE ≤ -3 mEq/L	Platelet count ≤ 1 × 105 /mm3	
Ht ≤ 30% (after hydration)	CT grade IV or V1	
BUN ≥ 40 mg/dL		
creatinine ≥ 2.0 mg/dL		

Interpretation:

- 0 points Mild – Mortality 0%
- 1 point Moderate – Mortality 1%
- 2-8 points Severe I – Mortality 4%
- 9-14 points Severe II – Mortality 25%
- >= 15 points Most Severe – Mortality 60%

Organ Failure-Based Scores

Organ failure is a marker of the severity of pancreatitis. While there are several scoring systems for organ failure, they do not directly measure the severity of acute pancreatitis, but rather measure the severity of the organ failure itself.

This distinction is potentially important as reflected in the limitations of Atlanta classification system. Organ failure was listed as being present or absent, without specifying the number of organs failing or the severity of each organ failure, issues that are potentially clinically relevant.

Organ failure scoring systems such as the Goris multiple organ failure score , the Marshall (or multiple) organ dysfunction score, the Bernard score, the sequential organ failure assessment (SOFA), and the logistic organ dysfunction system score have been described. All these scores take into account the number of organ systems involved and the degree of dysfunction of each individual organ. Some also include the use of inotropic or vasopressor agents, mechanical ventilation, or dialysis. The presence of persistent organ failure lasting for more than 48 hours appears to be important.

CT Severity Index

A CT severity score (the Balthazar score) has been developed based upon the degree of necrosis, inflammation, and the presence of fluid collections. In an initial validation study, mortality was 23% with any degree of pancreatic necrosis and 0% with no necrosis. In addition, there was a strong association between necrosis >30 percent and morbidity and mortality.

Management of Acute Pancreatitis

Acute pancreatitis can be divided into two broad categories:

- Edematous or mild acute pancreatitis
- Necrotizing or severe acute pancreatitis

Treatment of acute pancreatitis is based upon the severity of the condition, which is determined by the clinical, laboratory and a severity scoring system. Most attacks of acute pancreatitis are mild with recovery occurring within five to seven days. Death is unusual in such patients. In contrast, severe necrotizing pancreatitis is associated with a high rate of complications and significant mortality. One study characterized an intermediate group called "moderately severe acute pancreatitis", which comprised patients with local complications but no organ failure. These patients had low mortality like mild acute pancreatitis but morbidity (requiring prolonged hospital stay and interventions) like severe acute pancreatitis. A subgroup of patients has early severe acute pancreatitis characterized by extended pancreatic necrosis with organ failure at admission called fulminant acute pancreatitis because of organ failure either at admission or within 72 hours (mortality 90 percent).

Treatment of acute pancreatitis is aimed at correcting any underlying predisposing factors and at the pancreatic inflammation itself.

Supportive Care

The first step in managing patients with acute pancreatitis is determining whether the pancreatitis is likely to be mild or severe.

Mild acute pancreatitis is treated with supportive care including pain control, intravenous fluids, and correction of electrolyte and metabolic abnormalities. The majority of patients require no further therapy, and recover and eat within three to seven days.

In severe acute pancreatitis, intensive care unit monitoring and support of pulmonary, renal, circulatory, and hepatobiliary function may minimize systemic sequelae.

Vital signs and urine output should be monitored every few hours in the first 24 to 48 hours. Patients with severe pancreatitis will need ongoing monitoring for other complications that might arise. Fluid replacement is important because patients with necrotizing pancreatitis accumulate vast amounts of fluid in the injured pancreatic bed. Inadequate hydration can lead to hypotension and acute tubular necrosis. In addition, fluid depletion damages pancreatic microcirculation and results in pancreatic necrosis. At least one report suggested that inadequate fluid replacement (as evidenced by persistent hemoconcentration at 24 hours) was associated with development of necrotizing pancreatitis.

The exact amount and composition of fluid resuscitation that is required has not been extensively studied but several approaches have been published. Adequate fluid replacement can be assessed by improvement in vital signs and urine output and reduction in hematocrit and blood urea nitrogen over 24 hours, particularly if they were high at the onset. Monitoring the blood urea nitrogen may be particularly important, as both the BUN at the time of admission and the change in BUN during the first 24 hours of hospitalization predict mortality. Increased fluid resuscitation should be considered in patients whose BUN levels stay the same or increase.

Fluids should be titrated to maintain urine output of greater than 0.5 cc/kg/hour [12]. A low urine output may already reflect the development of acute tubular necrosis rather than persistent volume depletion. In this setting, aggressive fluid replacement can lead to peripheral and pulmonary edema without improving the urine output.
Oxygen saturation needs to be assessed routinely and supplemental oxygen administered to maintain arterial oxygen saturation of greater than 95 percent.

Deep vein thrombosis prophylaxis should be considered in bedridden patients.

Pain Management

Abdominal pain is often the dominant symptom. Uncontrolled pain can contribute to the hemodynamic instability. Adequate pain control is mandatory.

Nutrition

Patients with mild pancreatitis can often be managed with intravenous hydration alone since recovery often occurs rapidly, allowing patients to resume an oral diet. Nutritional support is often required in patients with severe pancreatitis.

Nutritional support should be provided to those likely to remain fasting for more than seven days. Nasojejunal tube feeding (using an elemental or semi-elemental formula) is preferred to total parenteral nutrition.

Enteral

A benefit of early enteral nutrition is its ability to maintain the intestinal barrier. Bacterial translocation from the gut is probably a major cause of infection.

Radiologic or endoscopic placement of a jejunal feeding tube beyond the ligament of Treitz and enteral feeding should be attempted. If not possible, nasogastric feeding has been proposed as an easier alternative.

The presence of fluid collections or elevated pancreatic enzymes is not necessarily a contraindication to oral or enteral feeding. However, in a subgroup of patients there is clear correlation of pain, recurrence of pancreatitis, or worsening of fluid collections to feeding, either oral or enteral. These patients often have disrupted pancreatic ducts with fluid collections. Drainage of fluid collections may allow resumption of oral intake. If the fluid collections are not considered suitable for drainage, total parenteral nutrition will be needed to maintain nutrition. If the target rate of enteral feeding is not achieved within 48 to 72 hours, supplemental parenteral nutrition should be provided.

Parenteral

Parenteral nutrition should be initiated in patients who do not tolerate enteral feeding or in whom nutritional goals cannot be reached within two days.

Control of Infection

The occurrence of pancreatic infection is a leading cause of morbidity and mortality in acute necrotizing pancreatitis. Approximately one-third of patients with pancreatic necrosis develop infected necrosis. Patients who develop infection tend to have more extensive necrosis. Although infection can occur early in the course of necrotizing

pancreatitis, it is more often seen late in the clinical course (after 10 days).

The important organisms causing infection in necrotizing pancreatitis are predominantly gut-derived, including Escherichia coli, Pseudomonas, Klebsiella, and Enterococcus. The majority of infections (about 75 percent) are monomicrobial. Fungal infection and infection with gram-positive organisms are uncommon but occur more frequently in the setting of prophylactic antibiotic use for severe acute pancreatitis, especially when used for more than 10 to 14 days. Fungal infections occur in approximately 9 percent of necrotizing pancreatitis and it is not clear if they are associated with higher mortality.

Approaches taken to decrease bacterial infections in acute necrotizing pancreatitis include enteral feeding, systemic antibiotics, percutaneous computerized tomography (CT) guided aspiration, and necrosectomy.

Role of Systemic antibiotics

The role of prophylactic systemic antibiotics in acute pancreatitis is unsettled since studies evaluating its benefits and harms have produced contradictory results. Guidelines have been issued by multiple societies and differ in their recommendations.

Percutaneous CT-guided aspiration

CT-guided percutaneous aspiration with Gram's stain and culture is recommended when infected pancreatic necrosis is suspected. Sterile necrosis does not usually require antibiotics and acute fluid collections do not require therapy in the absence of infection or obstruction of a surrounding hollow viscus.

Necrosectomy

Surgical debridement of infected necrosis (necrosectomy) can be accomplished by open surgery or a minimally invasive approach (endoscopic or percutaneous radiologic). Indications for necrosectomy include a failure to improve after antibiotics and CT-guided aspiration or if the patient becomes unstable from pulmonary, cardiovascular, or renal complications.

Because of the high mortality and morbidity associated with early necrosectomy, patients may benefit from continued conservative management.

Treatment of Associated Conditions

In addition to the above treatment for pancreatic inflammation, treatment of acute pancreatitis is aimed at correcting any underlying

predisposing factors, such as gallstones, hypertriglyceridemia, and complications of splenic vein thrombosis.

Gallstone Pancreatitis

Gallstone pancreatitis requires specific therapeutic considerations. In this disorder, obstructive stones in the biliary tract or ampulla of Vater are responsible for the pancreatitis.

Endoscopic retrograde cholangiopancreatography

Early endoscopic retrograde cholangiogram (ERCP) with papillotomy or surgical intervention to remove bile duct stones may lessen the severity of gallstone pancreatitis. Multiple studies suggest that early endoscopic papillotomy is of benefit in humans with acute biliary pancreatitis.

ERCP should be performed within 24 hours if there is concomitant cholangitis. In general, ERCP should be performed within 72 hours in those with a high suspicion of persistent bile duct stones (ie, visible common bile duct stone on noninvasive imaging, persistently dilated common bile duct, jaundice).

Early ERCP in those with predicted or actual severe gallstone pancreatitis in the absence of cholangitis or a high suspicion of a persistent common bile duct stone is controversial.

Cholecystectomy

Cholecystectomy should be performed after recovery in all patients with gallstone pancreatitis prior to hospital discharge. It is indicated only after an attack of acute pancreatitis since the incidence of pancreatitis from gallstones is only 3 to 7 percent. Failure to perform cholecystectomy is associated with a 25 to 30 percent risk of recurrent acute pancreatitis, cholecystitis, or cholangitis within 6 to 18 weeks. The risk is highest in patients who did not undergo a sphincterotomy.

In patients who have had mild pancreatitis, cholecystectomy can usually be performed safely within seven days after recovery. On the other hand, in patients who have had severe necrotizing pancreatitis, delaying cholecystectomy for at least three weeks may be reasonable because of an increased risk of infection. There is some controversy about cholecystectomy after sphincterotomy in elderly and sick patients.

Pancreatitis occurring in patients with gallstones suggests that there has been migration of stones into the common bile duct. Thus, a cholangiogram and clearance of the common bile duct of stones either before or during surgery is mandatory to prevent recurrence after cholecystectomy. If the clinical suspicion of common bile duct stones is high (eg, in those with persistent or worsening liver test abnormalities or cholangitis), a preoperative ERCP is the best test as there is a high

likelihood that therapeutic intervention (sphincterotomy, stone extraction) will be required. On the other hand, if the suspicion of persistent common bile duct stone is low (eg, if liver tests normalize), an intraoperative cholangiogram during cholecystectomy may be preferable to avoid the morbidity associated with ERCP.

Magnetic resonance cholangiopancreatography and endoscopic ultrasound are other imaging options that can exclude common bile duct stones. A preoperative ERCP can then be performed only in those with stones or sludge in the common bile duct.

Splenic Vein Thrombosis

Splenic vein thrombosis is seen in up to 19 percent of patients. Treatment should focus on the underlying pancreatitis since the effective treatment may be associated with spontaneous resolution of the thrombosis. Anticoagulation may be needed if there is extension of the clot into the portal or superior mesenteric vein resulting in hepatic decompensation or compromise of bowel perfusion. However, this needs to be considered along with the theoretical possibility of hemorrhage into pancreatic necrosis or fluid collections.

MATERIALS AND METHODS

Type of Data: Primary

Study Population: Patients diagnosed with acute pancreatitis presenting to the hospital within 72 hrs of onset of symptoms.

Study Locale: Coimbatore, and surrounding localities, South India

Study Design: Prospective Observational

Sample Size: 30

Patients diagnosed with acute pancreatitis admitted consecutively within the designated study period

Inclusion Criteria:

Patients diagnosed to have acute pancreatitis based on the following 2 criteria:

1. Abdominal pain characteristic of ap
2. Serum amylase and / or lipase ≥ 3 times the upper limit of normal

Exclusion Criteria: Patients symptomatic for more than 72 hrs prior to admission

Tool(s) of data collection: collection of demographic, clinical and laboratory data while the patient is admitted to the hospital within 24 hrs and 48 hrs.

Duration of the study : 1 yr

Proposed date of commencement of the study: January 1St 2010

How the study was carried out

Step 1: At admission, confirm that the patient has been symptomatic for less than 72hrs and has acute pancreatitis using the 2 established inclusion criteria.: (i) abdominal pain characteristic of acute pancreatitis (ii) serum amylase and / or lipase ≥ 3 times the upper limit of normal.

Step 2: Fill the attached data form containing demographic, clinical and laboratory data and calculate scores within the first 24 and 48 hrs

Step 3: Evaluate the patient at 48, 72 hrs then 1 week. and classify as mild or severe as per the atlanta criteria

Step 4: Initiate appropriate management/intervention as per study algorithm

Step 5: At discharge, evaluate if the severity and clinical course of the episode of acute pancreatitis was correctly predicted.

Step 6: Calculate the specificity and sensitivity, predictive value, and statistically analyse the biochemical tests and scoring systems

Evaluation Plan:

The study is a prospective observational study

- Statistical analysis of data collected during the study will provide evidence of the validity and efficacy of the 5 scoring systems and 5 individual biochemical markers for predicting the progression of acute pancreatitis to mild or severe forms in the indian population.

- The study will be considered successful if patients at risk for severe acute pancreatic disease are identified early in the course of acute pancreatitis (ap) thus guiding management and improving outcomes

Criteria for Assessing Severity in Acute Pancreatitis

Assessing severity in patients with acute pancreatitis is essential for appropriate triage and management as patients with severe disease are at greatest risk of death. The basis for the classification, severity, and complications of acute pancreatitis was established at the International Symposium held in Atlanta in 1992.

The criteria for severe acute pancreatitis were defined as:

Organ failure of at least one organ system

- CVS

  systolic blood pressure < 90 mm Hg

- RS

  PaO2 < 60 mm Hg

- Renal
  creatinine > 2.0 mg/dL after rehydration
- GI
  gastrointestinal bleeding > 500 mL/24 h

AND/ OR

The presence of local complications such as:

- Necrosis
- Pseudocyst
- Abscess

A pseudocyst was defined as a collection of pancreatic fluid enclosed by a nonepithelialized wall that occurs due to trauma, acute pancreatitis, or chronic pancreatitis.

An infected pseudocyst is an abscess. An abscess can also form if an area of necrosis undergoes liquefaction and becomes secondarily infected.

Early predictors of severity at 48 hours included three or more Ranson signs and an APACHE II score of 8 or higher

Method of Analysis

Over a time period of 1 year from January 2010 to December 2010, all patients who were admitted to our hospital, a tertiary care center in Tamil Nadu, with a diagnosis of acute pancreatitis on admission, were

screened for inclusion into my study. 123 patients were admitted over this time period. The first 30 suitable patients who fulfilled all inclusion criteria were incorporated. Acute pancreatitis was diagnosed on the basis of characteristic signs and symptoms (upper abdominal pain with or without guarding and/or rebound tenderness), increased serum enzyme levels, and abnormal findings on diagnostic imaging (ultrasound and/or contrast-enhanced computed tomography.

The 30 patients were assessed on admission, at 24 hours and once again at 48 hours. All patients were followed up till the time of discharge. All blood work, investigations and imaging were done systematically as per the protocol laid out in the proforma. Five scoring systems, 3 conventional and established (APACHE, Ranson and Glasgow-Imrie) and 2 new (BISAP and Modified Japanese), were calculated and compared. 5 biochemical markers, taken on admission were also compared.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS software (version 20, SPSS inc, Chicago IL). The results are expressed as mean (average), sensitivity, specificity and positive predictive values rounded to 2 decimal places. Graphs and charts were analyzed and drawn using SPSS software and Microsoft Word 2007.

OBSERVATIONS, ANALYSIS AND RESULTS

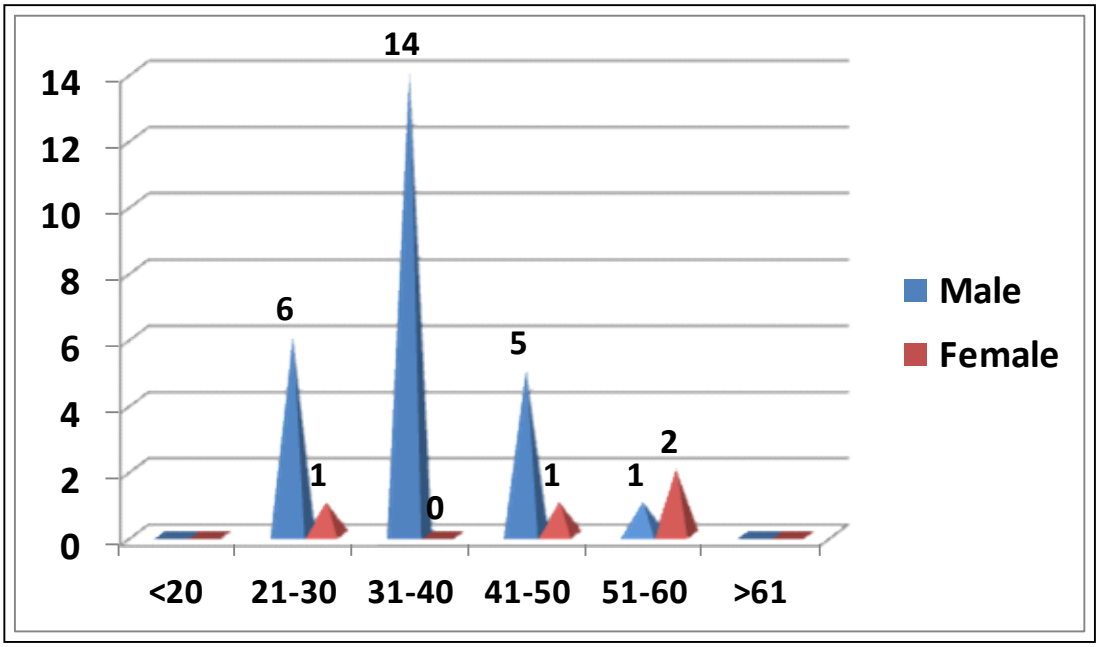
Introduction

Early and accurate identification of patients with Severe Acute Pancreatitis is essential for adequate patient care and decision making. Correctly assessing and stratifying patients based on severity will enable us to make important evidence- based judgments on treatment options, the need for intensive care treatment, and/or special therapies that may alter the clinical course and finally the outcome. In my study on the validity of newer and older scoring systems and individual biochemical markers in our Indian population, there is a linear progression between the APACHE score, Ranson's, the Glasgow-Imrie, BISAP and Modified Japanese Scoring systems which correlates with the severity of acute pancreatitis on initial presentation. The biochemical markers also correlated with severity of the disease, with BUN levels being the most accurate, while total lymphocyte count was the least accurate. This is in line with larger population based international studies. There was no correlation between amylase and lipase levels and the severity of the acute pancreatitis. The scoring systems outdid the individual clinical markers in sensitivity, specificity and positive predictive values. The BISAP score is the simplest to perform, is easily done at the bedside, easily reproducible and can be done on admission and it sensitivity, specificity and positive predictive value is on par with the present gold

standard scoring systems. On the other hand, the Gold Standard scores-the Ranson's criteria and APACHE are more complicated to perform and require (in the case of Ranson's) repeated data collection at specific time intervals.

Data Analysis

Fig-8
Sex Distribution Correlation of severity with Age



In my study, 4 out of the 30 patients presenting with acute pancreatitis were women.

All 4 female patients had a mild form of acute pancreatitis.

3 were due to gallstone pancreatitis and one was drug induced.

The mean age was 43.2 and the mean number of days admitted was 5.25.

Fig-9
Sex Distribution

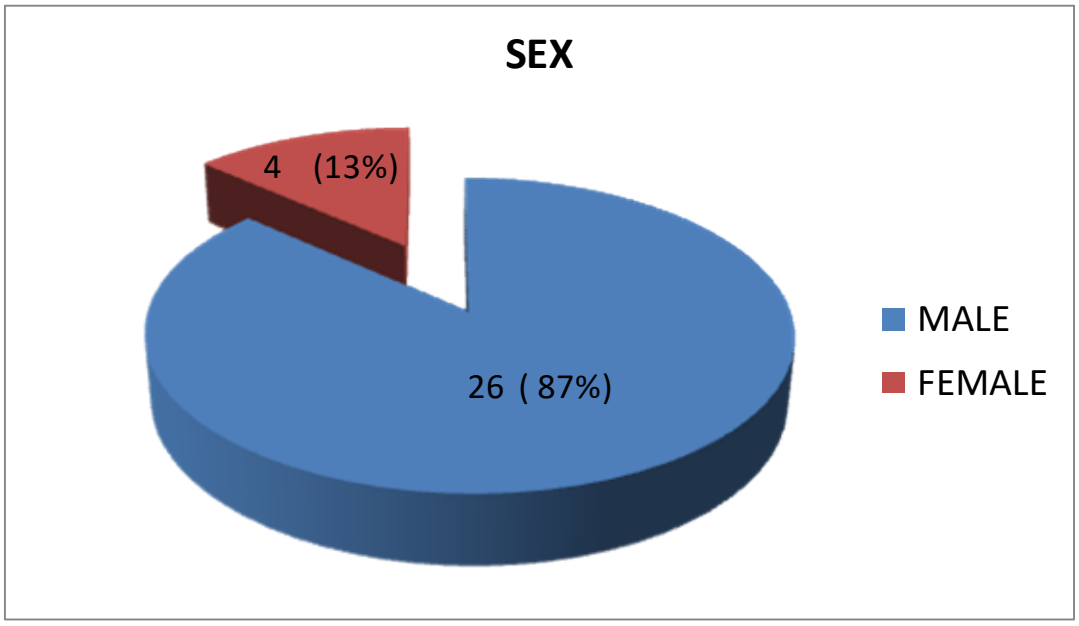
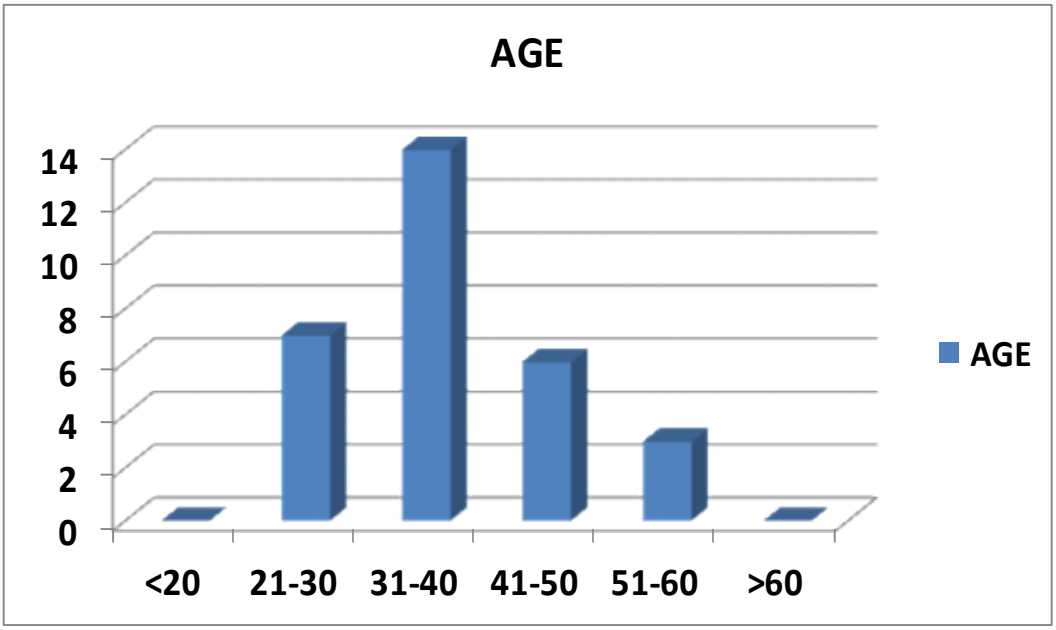


Fig-10
Age Distribution



Out of the 26 Male patients

Average age was 35.54

All 9 patients who presented with severe acute pancreatitis were male.

9 of the 26 male patients presented with severe acute pancreatitis, correlated by clinical, scoring systems and biochemical markers.

The majority of cases (19) were alcohol induced. 6 male patients had biliary pancreatitis while only one case of acute pancreatitis was drug induced.

In my study, increasing age did not correlate with increasing severity of the pancreatitis.

The mean age of the patients with severe acute pancreatitis was 37.33, the youngest was a 25 year old while the oldest patient with severe acute pancreatitis was a 47 year old male.

Average days in the hospital for male patients presenting with acute pancreatitis was 8.56.

Of the severe cases of acute pancreatitis, all of them had organ failure and required intubation and ventilatory support.

3 of the patients with SAP were taken AMA within a week due to monetary and personal reasons. Of the remaining 6 patients, the average hospital stay was 22.88 days, with a mean of 16.7 days in the ICU.

All the patients recovered completely, except the 3 patients who left AMA, and were stable at discharge.

There was no mortality in my series of patients.

Fig-11

Severity of Acute Pancreatis

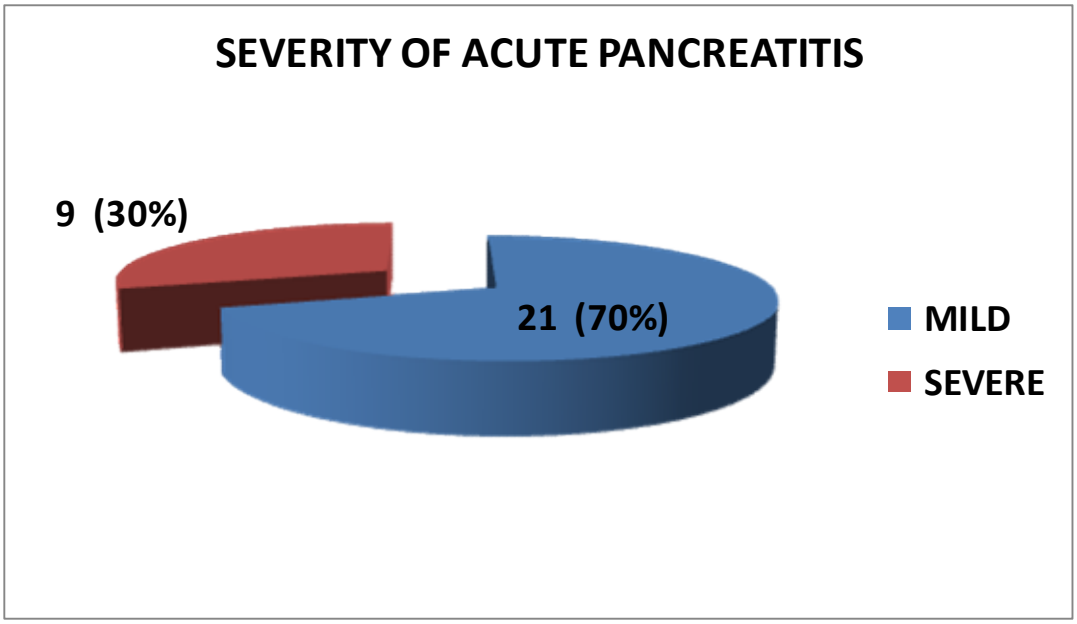


Table – 1
Age Distribution

Age	Sex		Total
	Male	Female	
<20	0	0	0
21-30	6	1	7
31-40	14	0	14
41-50	5	1	6
51-60	1	2	3
>61	0	0	0

Fig-12

Correlation of the Severity of Acute pancreatis with the Age

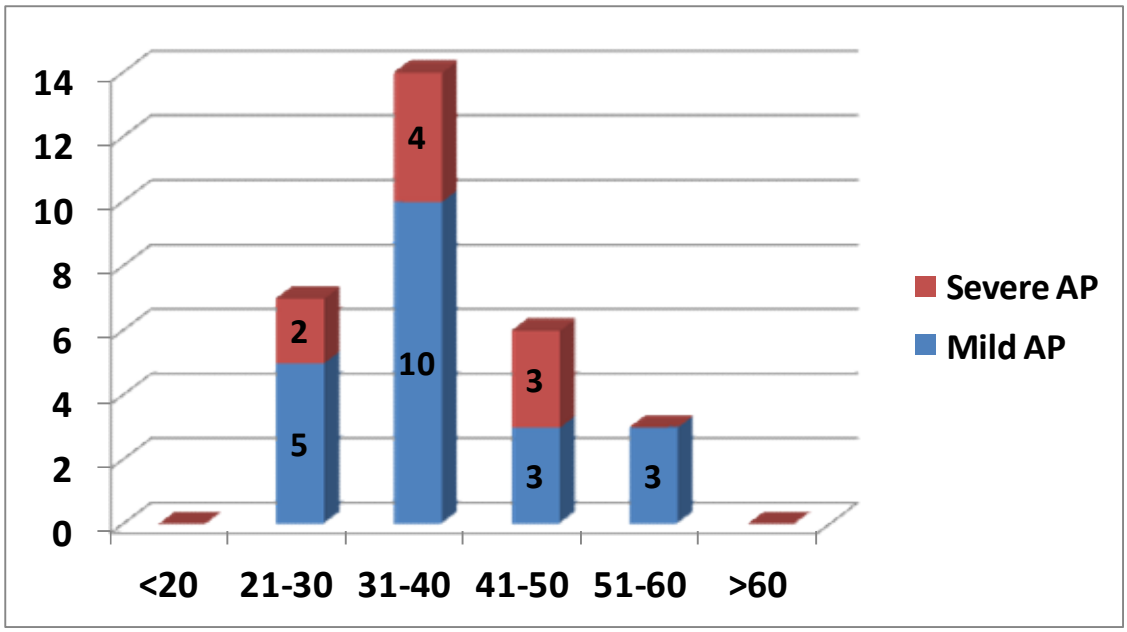
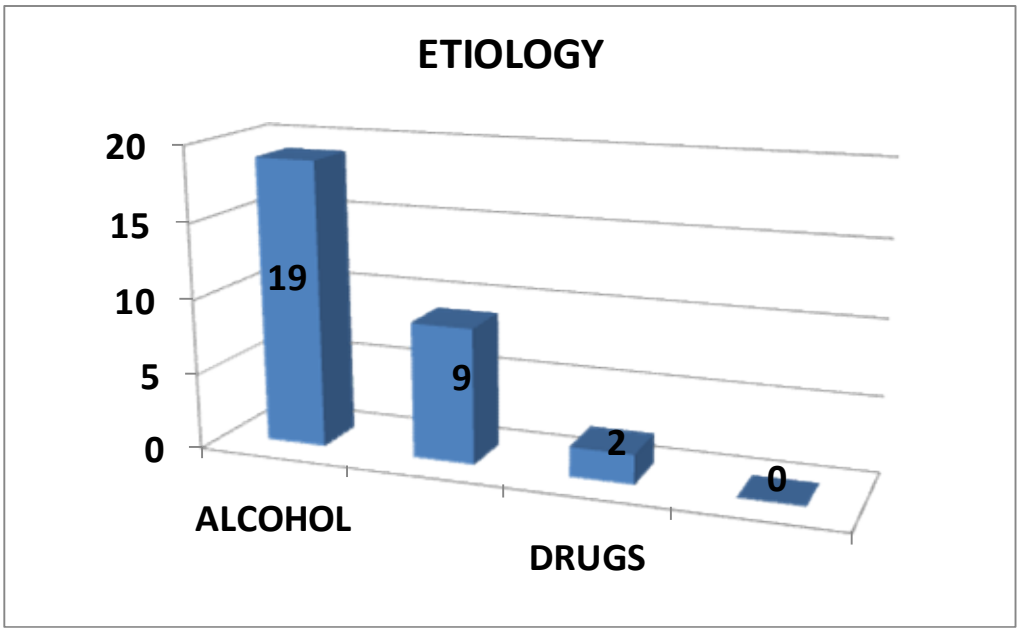


Fig-13

Etiology of Acute Pancreatis



In my study of 30 patients, 9 presented with severe acute pancreatitis.

All patients with severe acute pancreatitis were male.

7 (78%) were alcohol induced while one was biliary and one drug induced.

The remaining 21 patients presented with mild acute pancreatitis.

The average hospital stay for the patients with mild acute pancreatis was 7.62 days, with a mean of 3 days in the ICU.

Of the 2 cases of drug induced acute pancreatitis, one was female and one was male. The female patent had a single episode of clinically mild pancreatitis and was discharged in 4 days. The male on the other hand had severe acute pancreatitis and spent 21 days in the hospital.

Fig-14

Correlation of Severity Acute Pancreatis with the Etiology

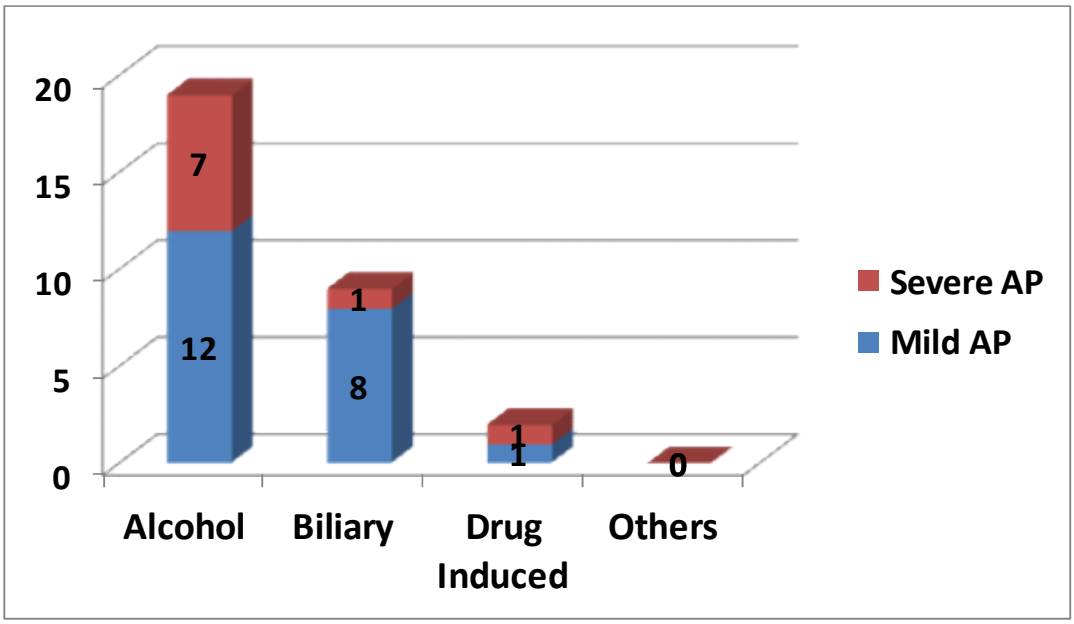
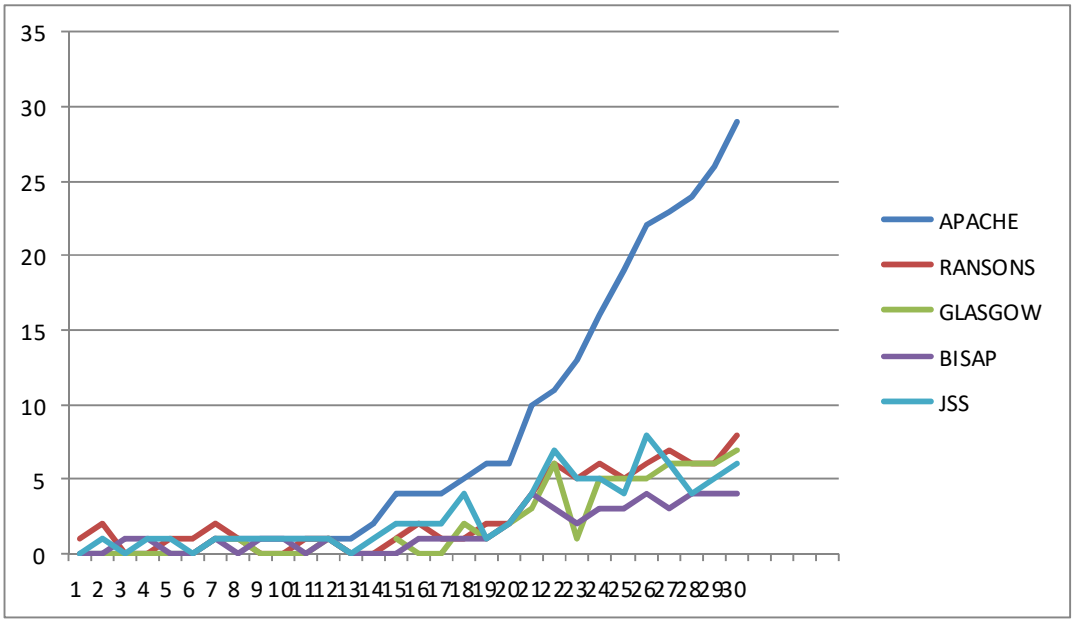


Table – 2
Statistical Analysis of Scoring System

Scoring System	Cut of Value	Sensitivity	Specificity	Positive Predictive value	Negative Predictive Value
APACHE II	7	98.2	95.2	87.3	89.2
Ranson	3	93.6	88.9	81.2	91.3
Glasgow-Imrie	3	88.7	72.6	85.6	89.1
BISAP	3	98.3	88.4	87.6	82.8
New JSS	5	96.4	89.1	89.3	87.1

Fig-15

Statistical Analysis of scoring System predicting the Severity of Acute Pancreatis



On analyses of the data, the New JSS tended to over predict the severity of the acute pancreatitis.

The values in my study were on par with the data from other international studies, but the BISAP score outperformed the other scores in terms of ease of data collection and calculation.

Fig-16

Statistical Comparison of APACHE, RANSON and GLASGOW Scores

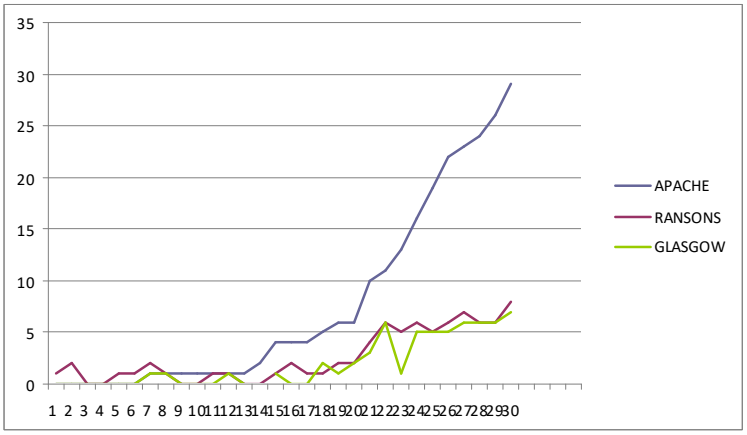


Fig-17

Statistical Comparison of APACHE, RANSON and BISAP Scores

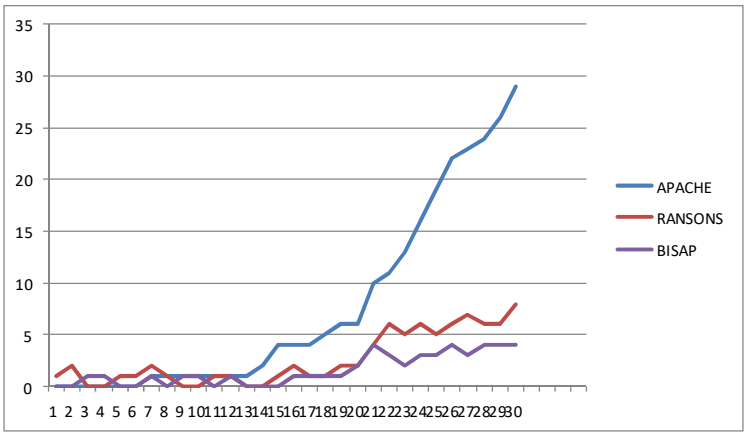


Fig-17

Statistical Comparison of APACHE, RANSON and JSS Scores

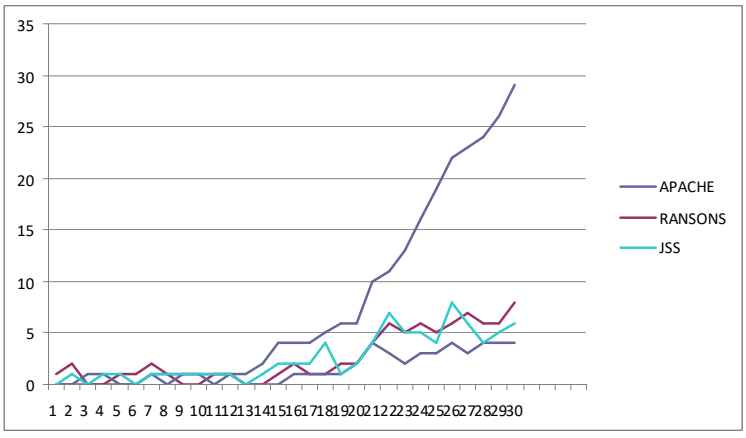


Fig-18

Statistical Analysis of Validity of BUN

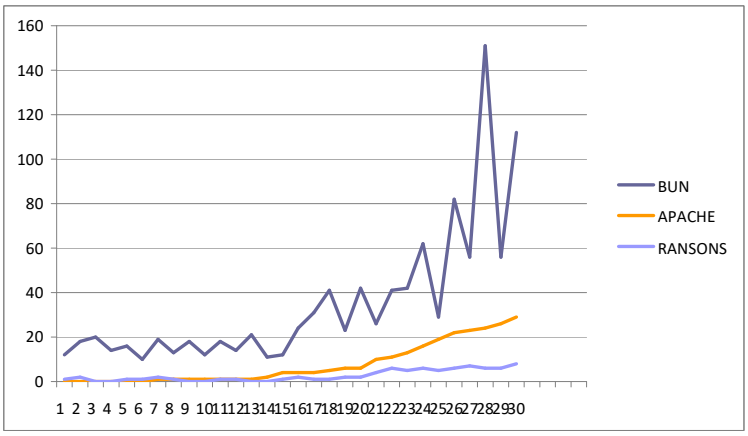


Fig-19

Statistical Analysis of Validity of Serum Calcium

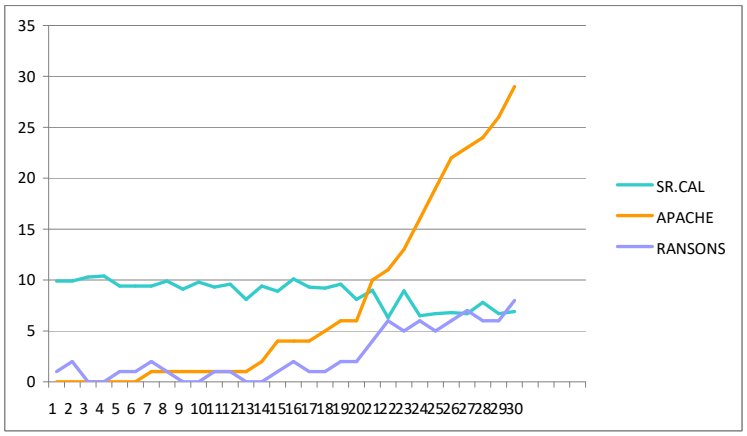


Fig-20

Statistical Analysis of Validity of Lymphocyte Level

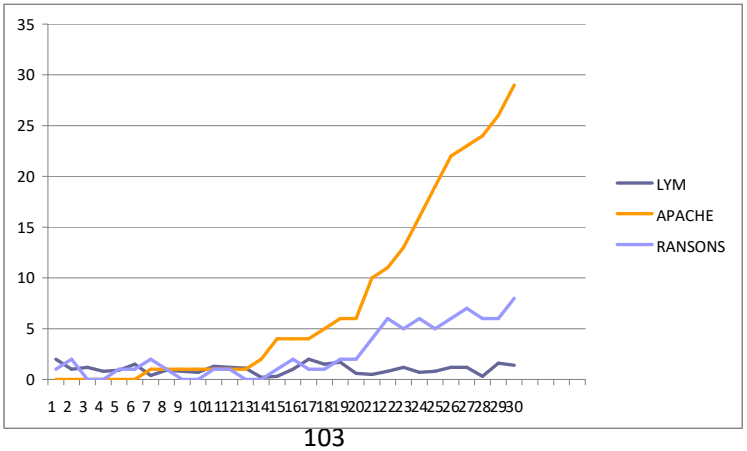


Fig-21

Statistical Analysis of Validity of HCT Level

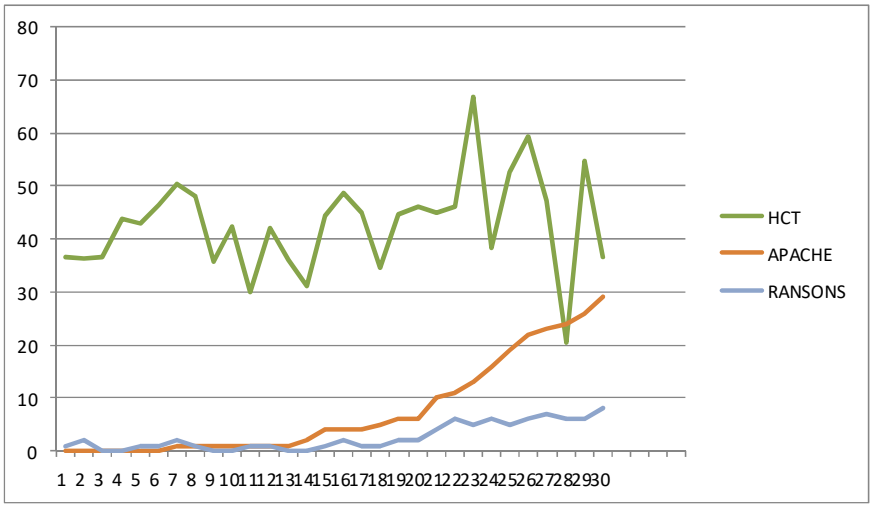
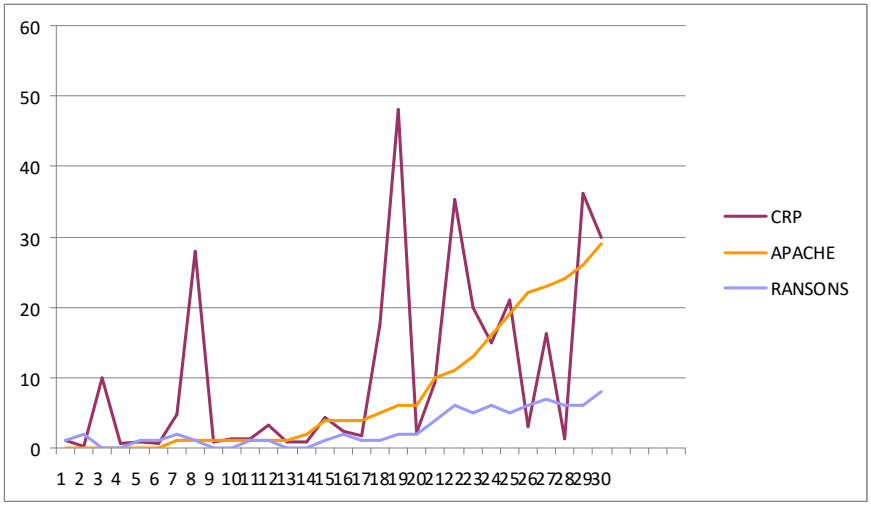


Fig-22

Statistical Analysis of Validity of CRP Level



In my study, the BUN and C-reactive protein best correlated with the Severity of Acute Pancreatitis.

Due to the parameters of the study, the rise of C-reactive protein with severity and subsequent decrease on improved prognosis was not stastically significant.

The lymphocyte levels had the lowest sensitivity, specificity and positive predictive values.

As the severity increased for patients in my study, a stastically significant decrease in the serum calcium levels was noted. As there is no established cut off, the sensitivity and specificity were calculated based on an arbitrary cut of value.

On the whole, as individual markers for predicting the severity of acute pancreatitis, all 5 biochemical markers had a significant disadvantage when compared to the scoring systems. The mean difference in sensitivity, specificity and positive predictive value was greater than 10% which is statistically significant.

Limitations of Study

My study is a small, population based study from a single institution, from among patients admitted during a brief time-frame. Larger, multi institutional studies with larger sample sizes and longer time frames are needed to confirm validity and accuracy my results.

Due to the small sample size, the positive predictive value is less accurate compared to the negative predictive value. The accuracy and validity of sensitivity and specificity of the data are also decreased in studies with small sample sizes.

Patients were followed up till the time of discharge. Further follow up; to analyze further complications of acute pancreatitis did not fall under the parameters of my study. My study dealt only with the scoring and stratification of patients early in the course of their disease and immediately on admission.

Patients who were confirmed to have acute pancreatitis, but presented more than 48 hours of developing initial symptoms were not included in the study.

Pediatric patients were not included in my study.

Serial follow up with biochemical markers are less specific after 48 hrs of admission. All Biochemical markers utilized in my study were taken serially for the first 72 hours, following which, whether the marker was taken serially or not was left to the preferences of the treating surgeon/ physician.

CT abdomen and Pelvis with IV contrast were done for all patients in my study, but the timing varied. For patients with severe acute pancreatitis, initial CT was usually done within the first 72 hours, followed by serial CT as per the treating team's discretion. For patients with mild acute pancreatitis, CT would generally be done within the first 4-5 days of admission.

46 Patients were not included in my study as all the required markers for the scoring systems or individual biochemical markers could not be done due to financial or other reasons.

DISCUSSION

Acute pancreatitis is a potentially lethal disease which varies in clinical features and severity from mild and self-limited disease to a rapidly progressive illness leading to multiple organ failure and death. The mortality rate ranges from 0% in the mild disease to 10% in sterile and 25% in infected pancreatic necrosis. Thus it is essential to accurately stratify patients in the early stage of the disease. Early identification of severely ill patients is helpful in ensuring rapid and appropriate treatment.

Determination of pancreatic enzymes in serum remains the gold standard for the diagnosis of acute pancreatitis. Amylase and lipase are both enzymes released from the pancreas during the course of the disease. The plasma levels of both enzymes peak within the first 24 hours of symptoms, but the half life of amylase in plasma is shorter than that of lipase. Amylase and lipase levels do not correlate with severity of acute pancreatitis.

Dozens of articles have reported over the past 3 decades on a wide variety of clinical parameters, single biochemical markers, scoring systems, and imaging procedures for predicting severe acute pancreatitis. Most of these parameters have found no place in clinical routine because of either low reliability or high complexity. In the 1970s, two systems

were developed to assist in the categorization of patients with acute pancreatitis. The original system proposed by Ranson was complicated by the requirement for two separate systems dependent on alcohol or gallstone etiology. The Glasgow System, and its subsequent modification, works well in all types of pancreatitis. However, both these systems require 48 hours from admission for full assessment. The advantage of APACHE II was that prediction using this system at 24 hours was as effective as the other scores at 48 hours. Due to this the APACHE score was incorporated into the ATLANTA criteria and considered the gold standard scoring system for stratifying acute pancreatitis. Currently, the best prediction of an individual's risk of complications lies in the use of a number of factors, which have been shown independently to predict a severe outcome. These include clinical features, markers of pancreatic injury, and markers of the inflammatory response.

The Ranson's prognostic criteria (1974) include 11 factors (age, white cell count, LDH, SGPT, glucose, fall in hematocrit, urea, calcium, pO_2, base deficit, fluid replacement). The Glasgow's prognostic criteria modified by Imrie (1978) includes 8 factors (white cell count, glucose, urea, pO_2, calcium, LDH, transaminases, albumin). The modified Japanese Scoring system has 9 criteria. Formerly the criteria of APACHE system acute physiology and chronic health evaluation included 34

factors (1981), which are difficult to use. This prompted a modified APACHE II (1985), which includes 12 factors and this is most widely used today. These factors include age and other coexisting diseases. APACHE III (1991) includes 18 factors whereas APACHE-O (obesity-1996) includes obesity as a factor. The APACHE II score provides a general measure of severity of disease and appears to reflect any continuing disease activity. In the Atlanta Symposium (1992) and Santorini Consensus Conference (1999), the APACHE II score was proposed as the best means for assessing the severity of acute pancreatitis.

No single biochemical marker has been shown to accurately predict severity with high sensitivity, specificity and positive predictive values although large population based studies are ongoing. Till date, C-reactive protein has proven to be the most reliable marker. The hemoconcentration, reflected by an increase in hematocrit on admission, is associated with the development of severe necrotizing pancreatitis. Thus it is considered as a simple, useful and early prognostic marker. The patients with no hemoconcentration have minimal risk to develop organ failure or death.

CONCLUSION

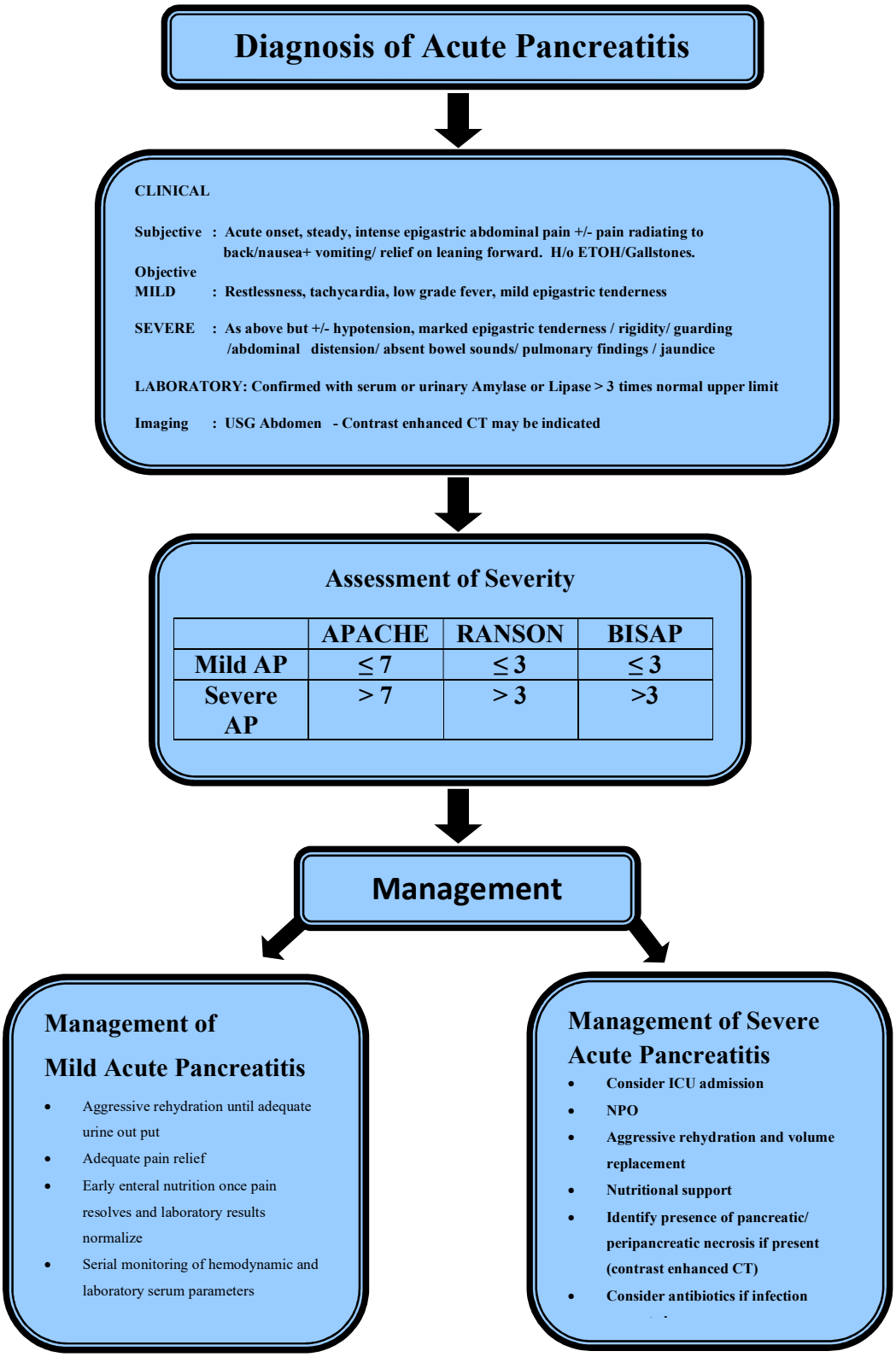
In my study I was able to validate that the BISAP scoring system is on par with the more established Ranson Criteria and APACHE II score in evaluating the severity of acute pancreatitis. The BISAP score proved to be easy to use, reliable and accurate in stratifying patients with severe disease. Although the new JSS also had similar results, which were statistically significant, the scoring system was harder gather data for as more criteria were involved in the calculations. Both the BISAP and New JSS were superior to the Glasgow- Imrie scoring system. In my study all the individual biochemical markers, although useful as adjuncts in the management and stratification of acute pancreatitis, were not as accurate as the scoring systems and were not upto par in terms of sensitivity, specificity and positive predictive value. Both the BUN and C-reactive protein proved to be valuable in predicting improvement in prognosis compared to the other three markers studied.

Based on my observations and statistical calculations, I was able to draw a conclusion that, although cumbersome. The APACHE II was the most reliable scoring system and will continue to remain the gold standard for assessing acute pancreatitis until newer, improved, accurate, and easily performed scoring systems become available.

With the conclusions drawn from my study, I was able to create the following basic algorithm which will be simple to implement in our day to day practice when faced with a case of acute pancreatitis. It will allow us to make earlier and fitting decisions, on a firm evidence-based platform. This will permit suitable allotment of resources, including management of deserving cases with poorer prognosis due to severe disease in an appropriate ICU setting.

ALGORTHIM FOR MANAGMENT OF ACUTE PANCREATITIS

BASED ON MY STUDY



SUMMARY

	Use	Advantages	Disadvantages
APACHE II	Chronic Health Score 12 physiologic measurements	Well validated score Can be done at any time Can be dome serially to measure changes in prognosis	Cumbersome Not all parameters routinely collected or assessed
Ranson	Factors measured at admission (5 criteria) And after 48 hours (6 criteria)	Well established Used for all etiologies (eg alcoholic, gallstones etc.)	Requires 48 hrs to complete Easier scoring systems are now in vogue
Glasgow-Imrie	8 prognostic factors measured over 48hrs	Straightforward and easy to use	Requires 48 hrs to complete, limiting usefulness in modern clinical practice
BISAP	5 prognostic factors to be measured within 24hrs	Straightforward Easily done at bedside Can be done at any time over initial 24hrs	Static measurement (does not incorporate changes with time) Can not be done serially
New JSS	9 factors to be measured over 24 hrs	Straight forward compared to original JSS Incorporates important prognostic factors	SIRS (4 factors) must be calculated Cannot be used serially to assess ongoing prognosis
Biochemical Markers			
Blood Urea Nitrogen	Level taken on admission or within the first 24 hrs	Accurate, inexpensive Easily available	May reflect several disease processes Low specificity
HCT	Level taken on admission	Easily Available, accurate inexpensive	May reflect dehydration due to other disease processes Low specificity
C-Reactive Protein	Levels at 48 hrs have a high level of accuracy for prediction of severe outcome	Well evaluated biochemical marker Can be done serially to evaluate ongoing improving prognosis Easily available	Peaks after 48 hrs of illness Expensive
Lymphocyte Levels	Levels measured at admission	Easily available inexpensive	Not validated in larger multi –center trials May reflect other disease processes
Serum Calcium levels	Levels to be taken at admission. Lower level indicated worse prognosis	Easily available Inexpensive Low levels correlate well with disease severity	Not validated by larger multi –center trials Cannot be measured serially to see change in prognosis

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PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH, COIMBATORE

INFORMED CONSENT

I, **DR. PRIYANKHA BALASUNDARAM,** POST GRADUATE (DEPT OF GENERAL AND G.I SURGERY) of the PSG Institute of Medical Sciences & Research (PSG IMS&R), am carrying out a study titled **The Efficacy of commonly used Scoring Systems and Biochemical markers in predicting the Severity of Acute Pancreatitis in the Indian Population** under the aegis of the Department of GENERAL AND G.I SURGERY PSG IMSR.

The objectives of this study are: To evaluate the efficacy and validity of 5 Scoring systems: BISAP, Ranson's, Imrie - Glasgow,(APACHE)-II, and JSS and 5 biochemical markers: blood urea nitrogen (BUN), c-reactive protein, hematocrit level, lymphocyte level, and serum calcium in the Indian patient population typically seen in our South Indian tertiary care centre.

The goal of the study is:

1. TO COLLECT EXTENSIVE DEMOGRAPHIC, ETIOLOGIC, CLINICAL AND LABORATORY DATA ON PATIENTS CONSECUTIVELY ADMITTED TO OUR INSTITUTION WITH ACUTE PANCREATITIS DURING THE STUDY PERIOD OF JUNE 2010 TO JUNE 2012.
2. TO FORMULATE AN ALGORITHM TO EVALUATE, MANAGE AND ACCURATELY PREDICT THE PROGRESSION OF ACUTE PANCREATITIS TO MILD OR SEVERE FORMS.
3. TO INITIATE EARLY TREATMENT OF SEVERE ACUTE PANCREATITIS.
4. TO PREVENT MORTALITY AND MORBIDITY DUE TO SEVERE ACUTE PANCREATITIS

Sample size: Minimum of 30 consecutive patients diagnosed with acute pancreatitis of 72 hrs or less duration

Population group & age group: Male and Female (Any Age Group)

Location: Coimbatore and Surrounding Localities

We request you to kindly cooperate with us in this study. We propose to collect background information and other relevant details related to this study. We will be carrying out:

Initial interview: 15 mts.

Clinical examination: To Asses Symptoms of Acute Pancreatitis

Blood sample collection: 6ml.

No. of times it will be collected: 3

Discomfort likely to be felt and side effects, if any: NIL

Final interview: 15 mts.

With the prediction of severity and outcome of patients with acute pancreatitis, timely treatment and intervention may be instituted. This in turn can prevent the complications of severe acute pancreatitis.

The results will be used to formulate an algorithm for early detection and treatment of severe acute pancreatitis

If you are uncomfortable, in answering any of our questions during the course of the interview / during blood sample collection, **you have the right to withdraw from the interview / study at anytime. You are assured that your refusal to participate or withdrawal from participation in the study WILL NOT compromise the care you receive or your access to organizational services.** You will NOT be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigators from the PSG IMS&R. Having understood the same, I hereby give my consent to them to interview me. I affixing my signature / left thumb impression to indicate my consent and willingness to cooperate in this study.

Respondent ID: _____.

Signature / Left thumb impression of the Respondent.

Signature of the Investigator with date

Signature of the witness

PRO FORMA

PATIENT DATA COLLECTION FORM

Patient No:

DEMOGRAPHIC DATA

Age (yrs): | | | Sex: Female | | Male | |

APACHE-II score	
Ranson's	
Glasgow Imrie	
BISAP	
Modified JSS	

5 BIOCHEMICAL MARKERS TO BE STUDIED

Marker	On admission
BUN	
C-Reactive Protien	
Hematocrit	
Lymphocyte Level	
Serum Calcium	

RANSON'S CRITERIA

At Admission	At 48 hr
Age > 55 yr	Hematocrit decrease > 10%
WBC > 16,000/mL	BUN increase > 5 mg/dL
LDH > 50 IU/L	Calcium < 8 mg/dL
AST > 250 IU/L	PaO2 < 60 mm Hg
Glucose > 200 mg/dL	Base deficit > 4 mg/dL (24 - HCO3)
	Fluid sequestration > 6 L (Fluid needs – IVF given)

TOTAL	

Ranson's Criteria = Sum

Glasgow Imrie

Finding at any time during 1st 48 hours

Age	serum albumin	Arterial pO2 room air	Serum Calcium
> 55 years **(1)**	< 3.2 g/dL **(1)**	< 60 mm Hg **(1)**	< 8 mg/dL **(1)**
≤55 years **(0)**	≥ 3.2 g/dL **(0)**	≥ 60 mm Hg **(0)**	≥ 8 mg/dL **(0)**
Blood Glucose	**Serum LDH**	**Serum Urea Nitrogen**	**WBC Count**
> 180 mg/dL **(1)**	> 600 U/L **(1)**	> 45 mg/dL **(1)**	>15,000 per L **(1)**
≤ 180 mg/dl **(0)**	≤ 600 U/L **(0)**	≤ 45 mg/dL **(0)**	≤ 15,000 per L **(0)**

Modified Glasgow prognostic criteria = SUM

(points for all 8 parameters)

TOTAL	

BISAP

Blood urea nitrogen level > 25 mg/dL	
Impaired mental status	
SIRS	
Age > 60 years	
Pleural effusion.	

TOTAL	

Modified JSS

Factor	Clinical signs	Laboratory data
Prognostic factor I (2 points for each positive factor)	●Shock ●Respiratory failure ●Mental disturbance ●Severe infection ● Hemorrhagic diathesis	● BE > 3 mEq/l ● Ht < 30% (after hydration) ● BUN > 40 mg/dl or creatinine > 2.0 mg/dl
Prognostic factor II (1 point for each positive factor)		● Ca < 7.5 mg/dl ● FBS >200 mg/dl ● PaO_2 < 60 mmHg (room air) ● LDH >700 IU/l ● Total protein < 6.0g/dl ● Prothrombin time > 1 5 s ● Platelet count < $1 \times 10^5/mm^3$ ● CT Grade IV or V[a]
Prognostic factor III	● SIRS score > 3 (2 points) ● Age > 70 years (1 point)	

TOTAL	

Glasgow Coma Score

BEST EYE OPENING	
SPONTANEOUS	4
TO VOICE	3
TO PAIN	2
NO RESPONSE	1
BEST MOTOR RESPONSE	
OBEYS COMMANDS	6
LOCALIZES PAIN	5
WITHDRAWS FROM PAIN	4
FLEXION (DECORTICATE)	3
EXTENSION (DECEREBRATE)	2
NO RESPONSE	1
BEST VERBAL RESPONSE	
ORIENTED	5
CONFUSED	4
INAPPROPRIATE	3
INCOMPREHENSIVE	2
NO RESPONSE	1

TOTAL	

Sirs Score

Score	1	2	3
Body temperature (°C)	> 38.0	> 38.5	> 39.0 or < 36,0
Heart beats (per min)	> 90	> 110	> 130
Respiratory rate (per min)	> 20	> 24	> 28
WBC count (x 109)	> 12000	> 16000	> 2000 or < 4000

TOTAL	

MASTER CHART

NO.	IP	NAME	ADMISSION	DOD	Total days	AGE	SEX	BUN	CRP	HCT	LYM	SR.CAL	APACHE	RANSONS	GLASGOW	BISAP	JSS	CLINICAL NOTES
1	I10000531	UDHAYA KUMAR R M	06.01.10	15.01.10	10	35	M	41	17.6	34.7	1.5	9.2	5	1	2	1	4	MAP
2	I10000836	KARTHIKEYAN D R	10.01.10	12.01.10	2	32	M	20	9.9	36.7	1.2	10.3	0	0	0	1	0	MAP
3	I10001520	BALAJI	17.01.10	24.01.10	8	22	M	12	1.1	36.7	2	9.9	0	1	0	0	0	MAP
4	I10003478	SHRUTHI SJ	06.02.10	08.02.10	3	53	F	11	0.8	31.2	0.2	9.4	2	0		0	1	MAP
5	I10005796	VIJAYARUN	16.02.10	07.03.10	20	36	M	29	21	52.8	0.8	6.7	19	5	5	3	4	SAP 60% NECROSIS
6	I10006012	GNANAPATHY	02.03.10	05.03.10	4	43	M	14	3.2	42.1	1.2	9.6	1	1	1	1	1	MAP
7	I10006593	NITHYA T	08.03.10	12.03.10	5	23	F	18	0.2	36.4	1	9.9	0	2	0	0	1	MAP
8	I10007290	ARUL RAJ	10.03.10	14.03.10	4	41	M	12	1,2	42.3	0.7	9.8	1	0	0	1	1	MAP
9	I10008343	MADHU R	25.03.10	18.4.10	25	30	M	41	35.2	46.1	0.8	6.3	11	6	6	3	7	SAP 60-70% NECROSIS
10	I10013826	JOTHIMANI	15.04.10	13.5.10	29	38	M	62	15	38.2	0.7	6.5	16	6	5	3	5	SAP 70% NECROSIS
11	I10010523	VIDHYA PRAKASH J	27.04.10	07.05.10	11	34	M	13	28	48.2	0.9	9.9	1	1	1	0	1	MAP
12	I10012185	MANIKAM	03.05.10	07.05.10	5	34	M	16	0.9	43	0.9	9.4	0	1	0	0	1	MAP
13	I10012257	SARAVANA KUMAR	04.05.10	06.05.10	3	32	M	82	3	59.3	1.2	6.8	22	6	5	4	8	SAP
14	I10013420	VELLINGARI	16.05.10	21.5.10	6	33	M	42	20	66.8	1.2	8.94	13	5	1	2	5	MAP
15	I10014087	NATARAJAN S	23.05.10	27.05.10	5	54	M	31	1.7	44.9	2	9.3	4	1	0	1	2	MAP
16	I10014542	SUNDARRAJ S	27.05.10	1.06.10	6	40	M	10	0.7	46.3	1.5	9.4	0	1	0	0	0	MAP
17	I10015129	JAMES ARUL RAJ	02.06.10	17.06.10	16	42	M	26	9.3	44.9	0.5	9	10	4	3	4	4	SAP NO NECROSIS
18	I10015525	SHAKLA BANU	07.06.10	13.06.10	7	42	F	18	1.2	30.1	1.3	9.3	1	1	0	0	1	MAP
19	I10015750	SASIKUMAR R	09.06.10	16.06.10	8	32	M	14	0.6	43.7	0.8	10.4	0	0	0	1	1	MAP 70% NECROSIS
20	I10015824	KUMAR P	10.06.10	18.06.10	9	29	M	23	48	44.6	1.7	9.6	6	2	1	1	1	MAP
21	I10019720	JAGATHEESH PRABHU M	19.07.10	27.07.10	9	30	M	19	4.7	50.3	0.4	9.4	1	2	1	1	1	MAP
22	I10020122	MOHAN KUMAR R	23.07.10	26.07,10	4	33	M	24	2.4	48.8	1	10.1	4	2	0	1	2	MAP
23	I10020330	SELVA KUMAR R	25.07.10	29.07.10 AMA	5	35	M	151	1.3	20.5	0.3	7.8	24	6	6	4	4	SAP >90% NECROSIS
24	I10026781	KUMARASAMY	03.08.10	07.08.10	5	28	M	12	4.4	44.3	0.3	8.9	4	1	1	0	2	MAP
25	I10027894	SARVANAN D	04.08.10	21.08.10	18	47	M	56	36.1	54.8	1.6	6.7	26	6	6	4	5	SAP 60-70% NECROSIS
26	I10028845	STEPHEN RAJ S	19.08.10	24.08.10 AMA	6	25	M	112	30	36,7	1.4	6.9	29	8	7	4	6	SAP HEMORRHAGIC
27	I10028976	MARRIAMUTHU	06.09.10	09.09.10	4	36	M	42	2.1	46.2	0.6	8.1	6	2	2	2	2	MAP
28	I10029678	NARAYANASAMY C	08.09.10	14.09.10	7	40	M	18	0.8	35.6	0.8	9.1	1	0	0	1	1	MAP
29	I10077842	GOVINDAMMAL	23.09.10	28.09.10	6	55	F	21	0.8	36.1	1.1	8.1	1	0	0	0	0	MAP
30	110129413	LOGANATHAN	26.09.10	2.10.10 AMA	7	43	M	56	16.2	47.3	1.2	6.7	23	7	6	3	6	SAP 60% NECROSIS