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THE DEGREE OF AGREEMENT BETWEEN LDH/AST RATIO AND CT SCAN IN DETECTION OF PANCREATIC NECROSIS IN ACUTE BILIARY PANCREATITIS

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ABSTRACT

Introduction: Pancreatitis is inflammatory disease of pancreas which may be acute or chronic. Acute pancreatitis can present with mild, moderate or severe forms. Acute severe pancreatitis may lead to pancreatic necrosis and organ dysfunction. Pancreatic necrosis is the most severe form of inflammation in setting of pancreatitis and results from cellular death of parenchyma of pancreas. Different biochemical markers are being used to predict and detect pancreatic necrosis. Lactate dehydrogenase/Aspartate aminotransferase (LDH/AST) Ratio has been found to be one of the useful markers in detection of pancreatic necrosis. **Objective:** Objective of this study was to determine the degree of agreement between LDH/AST ratio and CT scan in detection of pancreatic necrosis in acute biliary pancreatitis. **Study design:** Cross-sectional study **Setting:** Services Hospital, Lahore. **Duration of study:** Six months from 18th October 2015 to 17th April 2016. **Materials and Methods:** A total of 270 patients with pancreatitis between ages 20-75 were included in the study. Data of the patients was collected by a pre-designed Performa. LDH/AST ratio was measured on 7th post admission day. Pancreatic necrosis was labelled on LDH/AST ratio if ratio was greater than 20. CT scan of the patients was done on 7th post admission day to confirm the diagnosis. Data was analyzed using SPSS version 22. Degree of agreement between pancreatic necrosis as suggested by LDH/AST Ratio and that found on CT scan was calculated. Kappa statistics were calculated and chi-square test was applied. **Results:** Agreement between pancreatic necrosis on LDH/AST Ratio and CT scan was found to be 98.9%. Kappa coefficient was 0.985 which showed strong strength of agreement. **Conclusion:** LDH/AST Ratio >20 on 7th post-admission day is strongly associated with the development of pancreatic necrosis and can be used as a biochemical marker of pancreatic necrosis.

KEYWORDS: *Acute Pancreatitis, Pancreatic Necrosis, LDH/AST Ratio.*

INTRODUCTION

Pancreatitis is nonbacterial inflammatory disease caused by activation, interstitial liberation, and digestion of the pancreatic parenchyma by its own enzymes.[1] The annual incidence of acute pancreatitis around the globe is estimated to range from 5-50/100000[2]. About 70%-80% of acute pancreatitis takes a mild course and is associated only with minimal organ dysfunctions. In remaining 15 to 25% of patients with acute pancreatitis take severe course characterized by organ dysfunction and local (pancreatic parenchymal) complications like pancreatic necrosis.[3] Overall, the mortality rate from acute pancreatitis is low (< 1% for acute edematous pancreatitis), but it depends upon the proportion of patients in the group with severe pancreatitis complicated by multi organ dysfunction (MODS), with or without associated sepsis. The mortality rate from sterile pancreatic necrosis is 10% and rises to 30% with infection in the necrotic area.[4]

Pancreatic necrosis refers to a diffuse or focal area of non-viable parenchyma that is associated with peri-pancreatic fat necrosis. Necrotic areas can be identified on CT scan as absence of contrast enhancement on CT scan.[2] Pancreatic necrosis is observed in about 20% of patients with acute pancreatitis and takes place in the first week after onset[3]. Revised Atlanta classification has recommended CT scan as the modality of choice for diagnosis of complications of pancreatitis.[2] CT has shown an overall accuracy of 87% with a sensitivity of 100% for the detection of extended pancreatic necrosis and a sensitivity of 50% if only minor necrotic areas were present at surgery. CT scan yields a specificity of 100%.[5]

Several scoring systems and biochemical markers have been developed to assess and predict the severity of pancreatitis. Early prediction of the severity of disease can help in modifying the patient management and preventing complications.

Lactate Dehydrogenase (LDH) is a sensitive indicator of pancreatic necrosis with sensitivity, 88%; specificity, 100%; accuracy, 91% on 5th day of acute pancreatitis.[5] Serum transaminases especially Aspartate Aminotransferase (AST) elevation in biliary pancreatitis reflects acute hepatocellular injury caused by impacted bile duct stones.[5-7] However Isogai and his coworkers in Japan showed that LDH/AST ratio is better indicator of pancreatic necrosis in biliary pancreatitis. They found that LDH to AST ratio had a high predictive value for pancreatic necrosis especially after third day of admission.[8] In this study, out of 22 patients with acute biliary pancreatitis 5 patients developed pancreatic necrosis which was confirmed by CT scan. Among 5 patients with pancreatic necrosis, 4 patients had LDH/AST ratio greater than 20 on 7th post admission day. Remaining 17 patients did not develop pancreatic necrosis and had LDH/AST ratio less than 20 on 7th post admission day. Hence the Agreement between LDH/AST ratio and CT scan in detection of pancreatic necrosis was 95.4%.[8]

The rationale of this study was to find the agreement between LDH/AST ratio and CT scan in detection of pancreatic necrosis in acute biliary pancreatitis. As there was only one international study available on diagnostic accuracy of LDH/AST ratio in detection of necrosis in acute biliary pancreatitis on inadequate sample size that was 22 patients, so I wanted to conduct the research on this topic to generate substantial evidence with sample size of 270 patients in local community (Pakistan).

LITRERATURE REVIEW

Anatomy

The name pancreas is derived from the Greek "pan" (all) and "kreas" (flesh).[2] It 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. Due to its retroperitoneal location, pain associated with pancreatitis often is characterized as penetrating through to the back.[9]

Gross Anatomy

Pancreas is divided into head, body and tail.

- **Head**

The head of the pancreas lies to the right of the midline, anterior and to the right side of the vertebral column, within the curve of the duodenum.

The **anterior surface** of the head is covered in peritoneum and is related to the origin of the transverse mesocolon.

The **posterior surface** of the head is related to the inferior vena cava.

- **Neck**

The neck of the pancreas is approximately 2 cm wide and links the head and body. It is often the most anterior portion of the gland and is defined as the portion of the pancreas that lies anterior to the portal vein.

- **Body**

The body of the pancreas is the longest portion of the gland and runs from the left side of the neck to the tail. The body is described as having three surfaces, anterosuperior, posterior and anteroinferior.

- **Tail**

The tail of the pancreas is the narrowest, most lateral portion of the gland and lies between the layers of the splenorenal ligament. The tip of the tail may lie in contact with the splenic hilum.[10] (Fig. 1).

Pancreatic Duct Anatomy

The main pancreatic duct begins in the tail of the pancreas and runs through the parenchyma of the gland to the pancreatic head: here it turns inferiorly and is closely related to the bile duct. The main pancreatic duct and bile duct usually unite to form the short, dilated hepatopancreatic ampulla (of Vater), which opens into the descending part of the duodenum at the summit of the major duodenal papilla. At least 25% of the time, the ducts open into the duodenum separately.

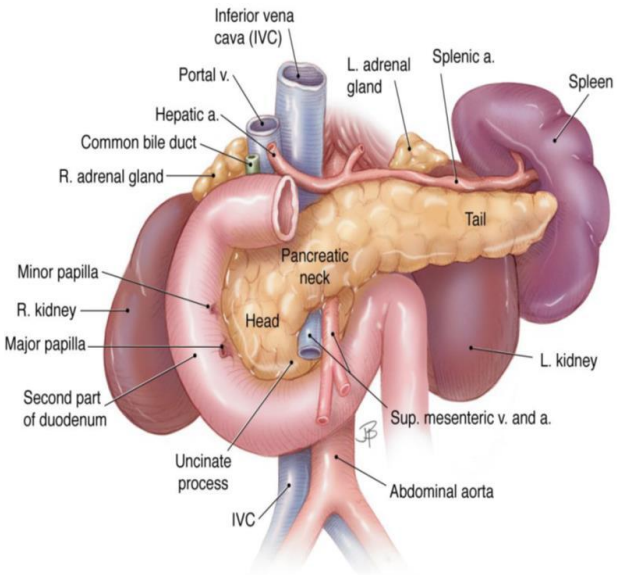

Figure 1: Anatomy of Pancreas.

The sphincter of the pancreatic duct (around the terminal part of the pancreatic duct), the sphincter of the bile duct (around the termination of the bile duct), and the hepatopancreatic sphincter (of Oddi)—around the hepatopancreatic ampulla—are smooth muscle sphincters that control the flow of bile and pancreatic juice into the ampulla and prevent reflux of duodenal content into the ampulla. The accessory pancreatic duct opens into the duodenum at the summit of the minor duodenal papilla. Usually, 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 may not be

connected. In such cases, the accessory duct carries most of the pancreatic juice.[11] (fig. 2)

Vascular Supply of Pancreas

Arterial Supply of the Pancreas The pancreas is supplied with blood from branches arising from both the celiac trunk (through splenic artery and pancreaticoduodenal arteries) and the superior mesenteric artery (SMA).

Venous Drainage of the Pancreas

In general, the veins of the pancreas parallel the arteries and lie superficial to them. Both lie posterior to the ducts in the body and tail of the pancreas. The drainage is to the portal vein, the splenic vein, and the superior and inferior mesenteric veins.[12]

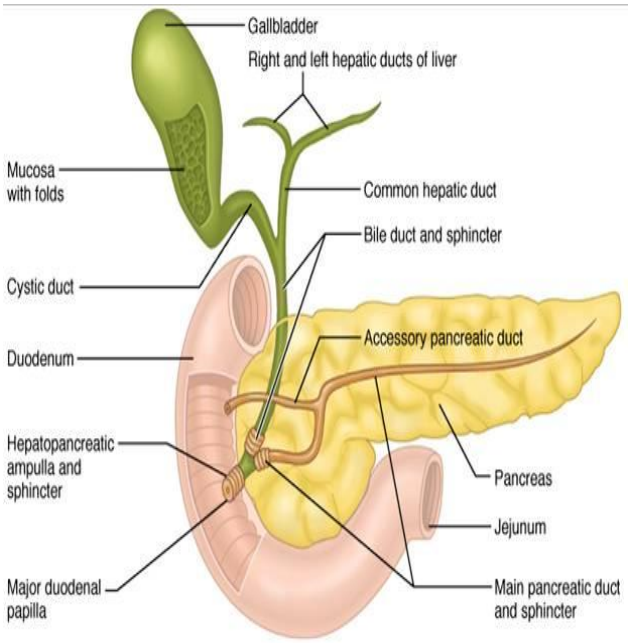

Figure 2: Ductal System of Pancreas

Lymphatics of Pancreas

The lymphatic drainage of the pancreas is extensive; multiple groups of nodes may receive drainage from each region of the gland which in part explains the poor prognosis following resection of pancreatic tumors. Lymph capillaries commence around the pancreatic acini. The larger lymph vessels follow the arterial supply and drain into the lymph nodes around the pancreas and adjacent node groups. Lymphatics from the tail and body drain mostly into the pancreaticosplenic nodes, although some drain directly to pre-aortic nodes. Lymphatics from the neck and head drain more widely into nodes along the pancreaticoduodenal, superior mesenteric and hepatic arteries, and some also drain to the pre-aortic nodes and coeliac axis nodes. There is no evidence of lymphatic channels within the pancreatic islets.[9]

Nerve supply of Pancreas

Parasympathetic vagal fibers, which are capable of stimulating exocrine secretion, reach the gland mainly from the posterior vagal trunk and coeliac plexus, but, as with the gallbladder, hormonal control is more important than the neural. Sympathetic vasoconstrictor impulses are derived from spinal cord segments T6–10 via splanchnic nerves and the coeliac plexus, the postganglionic fibers running to the gland with its blood vessels. As with other viscera, pain fibers accompany the sympathetic supply, so that pancreatic pain may radiate in the distribution of thoracic dermatomes 6–10.[13]

Histology of Pancreas

The pancreas is composed of two different types of glandular tissue. The main tissue mass is exocrine, in which pancreatic islets of endocrine cells are embedded.

Exocrine pancreas

The exocrine pancreas is a branched acinar gland, surrounded and incompletely lobulated by delicate loose connective tissue. It is formed of pyramidal, secretory cells arranged mainly as spherical clusters, or acini.

Acinar cells Acinar cells of the exocrine pancreas have a basal nucleus and, in their basal cytoplasmic domain, abundant rough endoplasmic reticulum which results in their basophilic staining characteristics. Dense secretory zymogen granules stain deeply with eosin in the apical region.

Stellate cells: PaSCs are myofibroblast-like cells and are found in the periacinar space, where their long cytoplasmic processes encircle the base of the acinus, and in perivascular and periductal regions of the pancreas. They have been implicated as key players in the pathobiology of the major disorders of the exocrine pancreas, including chronic pancreatitis and pancreatic necrosis.

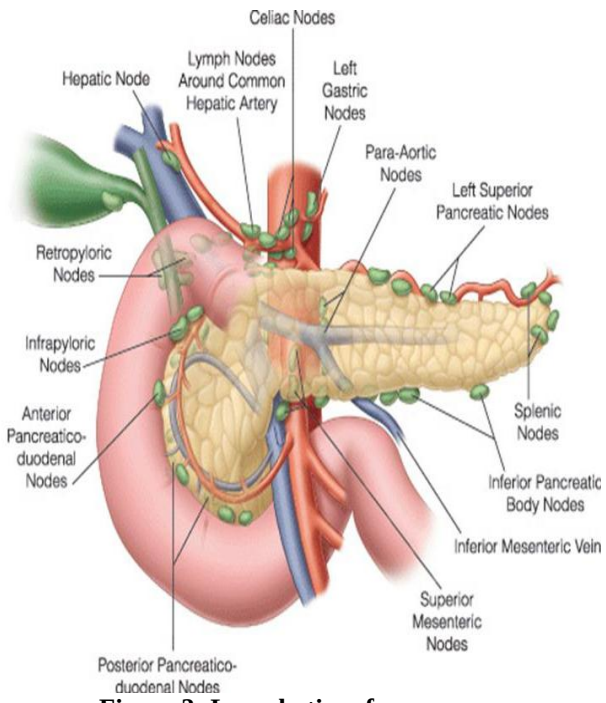

Figure 3: Lymphatics of pancreas.

Endocrine pancreas

The endocrine pancreas consists of pancreatic islets of Langerhans, composed of spherical or ellipsoid clusters of cells embedded in the exocrine tissue. Specialized staining procedures or immunohistochemical techniques are necessary to distinguish the three major types of cell, designated alpha, beta and delta. The most numerous cells namely alpha and beta cells secrete glucagon and insulin respectively. Alpha cells tend to be concentrated at the periphery of islets, and beta cells more centrally. A third type, the delta cell, secretes somatostatin and gastrin, and like alpha cells, is peripherally placed within the islets. A minor cell type, the F cell, secretes pancreatic polypeptide (PP), which is stored in smaller secretory granules. The autonomic neurotransmitters acetylcholine (ACh) and noradrenaline affect islet cell secretion: ACh augments insulin and glucagon release, noradrenaline inhibits glucose-induced insulin release, and they may also affect somatostatin and PP secretion.[10]

Embryology of Pancreas

The pancreas is formed by two buds, dorsal and ventral, originating from the endodermal lining of the duodenum. Whereas the dorsal pancreatic bud is in the dorsal mesentery, the ventral pancreatic bud is close to the bile duct. Later, the parenchyma and the duct systems of the dorsal and ventral pancreatic buds fuse. The ventral bud forms the uncinate process and inferior part of the head of the pancreas. The remaining part of the gland is derived from the dorsal bud. The main **pancreatic duct** (of **Wirsung)** is formed by the distal part of the dorsal pancreatic duct and the entire ventral pancreatic duct. The proximal part of the dorsal pancreatic duct either is obliterated or persists as a small channel, the **accessory pancreatic duct** (of **Santorini)**.

In the third month of fetal life, **pancreatic islets** (of **Langerhans)** develop from the parenchymatous pancreatic tissue and scatter throughout the pancreas. **Insulin secretion** begins at approximately the fifth month. Glucagon- and somatostatin-secreting cells also develop from parenchymal cells. Visceral mesoderm surrounding the bud form the pancreatic connective tissue.[14]

Anomalies of Pancreas

- **Annular Pancreas**

In annular pancreas, the ventral pancreatic bud becomes fixed so that, when the stomach and duodenum rotate, the ventral bud is pulled around the right side of the duodenum to fuse with the dorsal bud of the pancreas, thus encircling the duodenum.

- **Ectopic Pancreas**

Ectopic pancreatic tissue may be found in the submucosa of the stomach, duodenum, small intestine (including Meckel's diverticulum), and gallbladder, and in the spleen. It is important in that it may protrude into the lumen of the gut and be responsible for causing intussusception.

- **Congenital Fibrocystic Disease**

Basically, congenital fibrocystic disease in the pancreas is caused by an abnormality in the secretion of mucus. The mucus produced is excessively viscid and obstructs the pancreatic duct, which leads to pancreatitis with subsequent fibrosis. The condition also involves the lungs, kidneys, and liver.[15]

Physiology of Pancreas

The pancreatic digestive enzymes are secreted by pancreatic acini, and large volumes of sodium bicarbonate solution are secreted by the small ductules and larger ducts leading from the acini. The combined product of enzymes and sodium bicarbonate then flows through a long pancreatic duct that normally joins the hepatic duct immediately before it empties into the duodenum through the papilla of Vater, surrounded by the sphincter of Oddi. The pancreas also secretes insulin, but it is not secreted by the same pancreatic tissue that secretes intestinal pancreatic juice.

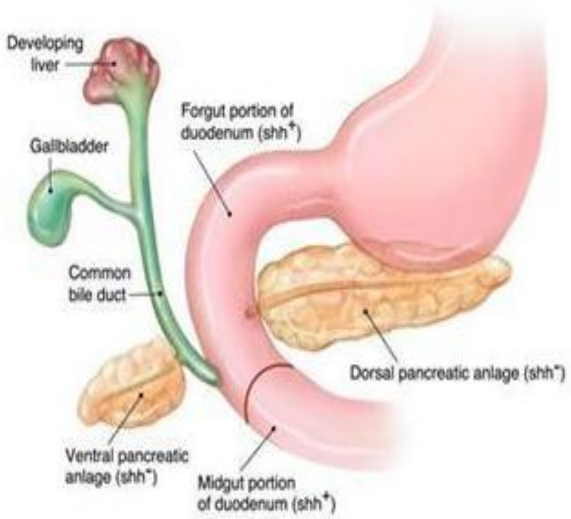

Figure 4: Embryology of Pancreas.

Instead, insulin is secreted directly into the blood—not into the intestine— by the islets of Langerhans that occur in islet patches throughout the pancreas.

Pancreatic digestive enzymes

Pancreatic secretion contains multiple enzymes for digesting all of the three major types of food: proteins, carbohydrates, and fats. It also contains large quantities of bicarbonate ions, which play an important role in neutralizing the acidity of the chyme emptied from the stomach into the duodenum.

The most important of the pancreatic enzymes for digesting proteins are trypsin, chymotrypsin, and carboxypolypeptidase. By far the most abundant of these is trypsin.

Trypsin and **chymotrypsin** split whole and partially digested proteins into peptides of various sizes but do not cause release of individual amino acids. However, **carboxypolypeptidase** splits some peptides into individual amino acids, thus completing digestion of some proteins all the way to the amino acid state. The pancreatic enzyme for digesting carbohydrates is **pancreatic amylase**, which hydrolyzes starches, glycogen, and most other carbohydrates (except cellulose) to form mostly disaccharides and a few trisaccharides. The main enzymes for fat digestion are;

(1) **Pancreatic lipase**, which is capable of hydrolyzing neutral fat into fatty acids and monoglycerides;
(2) **Cholesterol esterase**, which causes hydrolysis of cholesterol esters; and
(3) **Phospholipase**, which splits fatty acids from phospholipids.

When first synthesized in the pancreatic cells, the proteolytic digestive enzymes are in their enzymatically inactive forms trypsinogen, chymotrypsinogen, and procarboxypolypeptidase. They become activated only after they are secreted into the intestinal tract. Trypsinogen is activated by an enzyme called **enterokinase,** which is secreted by the intestinal mucosa when chyme comes in contact with the mucosa.

It is important that the proteolytic enzymes of the pancreatic juice not become activated until after they have been secreted into the intestine because the trypsin and the other enzymes would digest the pancreas. Fortunately, the same cells that secrete proteolytic enzymes into the acini of the pancreas simultaneously secrete another substance called **trypsin inhibitor**. This substance, which is formed in the cytoplasm of the glandular cells, prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas. In addition, because it is trypsin that activates the other pancreatic proteolytic enzymes, trypsin inhibitor prevents activation of the other enzymes as well.

When the pancreas becomes severely damaged or when a duct becomes blocked, large quantities of pancreatic secretion sometimes become pooled in the damaged areas of the pancreas. Under these conditions, the effect of trypsin inhibitor is often overwhelmed, in which case the pancreatic secretions rapidly become activated and can literally digest the entire pancreas within a few hours, giving rise to the condition called **acute pancreatitis**. This condition is sometimes lethal because of accompanying circulatory shock; even if it is not lethal, it usually leads to a subsequent lifetime of pancreatic insufficiency.

Secretion of bicarbonate ions

Although the enzymes of the pancreatic juice are secreted entirely by the acini of the pancreatic glands, the other two important components of pancreatic juice, bicarbonate ions and water, are secreted mainly by the epithelial cells of the ductules and ducts that lead from the acini.

The basic steps in the cellular mechanism for secreting sodium bicarbonate solution into the pancreatic ductules and ducts are as follows:

1. Carbon dioxide diffuses to the interior of the cell from the blood and, under the influence of carbonic anhydrase, combines with water to form carbonic acid (H2CO3). The carbonic acid dissociates into bicarbonate ions and hydrogen ions (HCO3− and H+). Additional bicarbonate ions enter the cell through the basolateral membrane by co-transport with sodium ions (Na+). The bicarbonate ions are then exchanged for chloride ions (Cl−) by secondary active transport through the luminal border of the cell into the lumen of the duct. The chloride that enters the cell is recycled back into the lumen by special chloride channels.

2. The hydrogen ions formed by dissociation of carbonic acid inside the cell are exchanged for sodium ions through the basolateral membrane of the cell by secondary active transport. Sodium ions also enter the cell by co-transport with bicarbonate across the basolateral membrane. Sodium ions are then transported across the luminal border into the pancreatic duct lumen. The negative voltage of the lumen also pulls the positively charged sodium ions across the tight junctions between the cells.

3. The overall movement of sodium and bicarbonate ions from the blood into the duct lumen creates an osmotic pressure gradient that causes osmosis of water also into the pancreatic duct, thus forming an almost completely isosmotic bicarbonate solution.

Regulation of pancreatic secretion

Three basic stimuli are important in causing pancreatic secretion

1. **Acetylcholine**, which is released from the parasympathetic vagus nerve endings and from other cholinergic nerves in the enteric nervous system
2. **Cholecystokinin,** which is secreted by the duodenal and upper jejunal mucosa when food enters the small intestine
3. **Secretin**, which is also secreted by the duodenal and jejunal mucosa when highly acidic food enters the small intestine.

The first two of these stimuli, acetylcholine and cholecystokinin, stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes. Without the water, most of the enzymes remain temporarily stored in the acini and ducts until more fluid secretion comes along to wash them into the duodenum. Secretin, in contrast to the first two basic stimuli, stimulates secretion of large quantities of water solution of sodium bicarbonate by the pancreatic ductal epithelium.

The presence of food in the upper small intestine also causes a second hormone, **cholecystokinin** *(*CCK), a polypeptide containing 33 amino acids, to be released from yet another group of cells, the I cells, in the mucosa of the duodenum and upper jejunum. This release of CCK results especially from the presence of proteoses and *peptones* (products of partial protein digestion) and long-chain fatty acids in the chyme coming from the stomach.

CCK, like secretin, passes by way of the blood to the pancreas, but instead of causing sodium bicarbonate secretion, it mainly causes secretion of much more pancreatic digestive enzymes by the acinar cells. This effect is similar to that caused by vagal stimulation but is even more pronounced, accounting for 70 to 80 percent of the total secretion of the pancreatic digestive enzymes after a meal.[16,17]

Pancreatitis

Pancreatitis is a common nonbacterial inflammatory disease caused by activation, interstitial liberation, and auto digestion of the pancreas by its own enzymes. The process may or may not be accompanied by permanent morphologic and functional changes in the gland.[1]

Pancreatitis can be divided into acute form and chronic form.

Acute Pancreatitis

It is defined as upper abdominal pain often radiating to the back with serum amylase or lipase level >3 times than normal and inflammation of gland parenchyma of the pancreas on imaging.[5]

Chronic Pancreatitis

Chronic pancreatitis is characterized by chronic pain, pancreatic calcification on x-ray, and exocrine (steatorrhea) or endocrine (diabetes mellitus) insufficiency. Attacks of acute pancreatitis often occur in patients with chronic pancreatitis.[1]

Pancreatitis can also be classified as

- ✓ **Acute relapsing pancreatitis** is defined as multiple attacks of pancreatitis without permanent pancreatic scarring, a picture most often associated with biliary pancreatitis.
- ✓ **Chronic relapsing pancreatitis,** denoting recurrent acute attacks superimposed on chronic pancreatitis, is not used in this chapter. Alcoholic pancreatitis often behaves in this way.
- ✓ **Subacute pancreatitis** has also been used by some to denote the minor acute attacks that typically appear late in alcoholic pancreatitis.[1]

Acute Pancreatitis

The annual incidence of acute pancreatitis has ranged from 4.9 to 35 per 100,000 population in various reports,[19] but may be on the rise in many European and Scandinavian countries due to increased alcohol consumption and better diagnostic capability.[20] Advances in diagnostic and therapeutic interventions have led to a decrease in mortality from acute pancreatitis, especially in those with severe, often necrotizing pancreatitis. While the overall mortality in all hospitalized patients with acute pancreatitis is approximately 10 percent (range 2 to 22 percent), the mortality in the subset with severe acute pancreatitis may be as high as 30 percent.[18] The mortality in the first two-week period is usually due to systemic inflammatory response syndrome and organ failure, while after two weeks it is usually due to sepsis and its complications. The frequency of early (<two weeks after onset) death has been to reported vary from 0 to 50 percent of all deaths due to acute pancreatitis.[21,22]

Pathogenesis of Acute Pancreatitis

Acute Pancreatitis occurs when all the protective mechanisms to prevent intracellular activation of pancreatic enzymes fail due to any cause. Both extracellular (neural and vascular response) and intracellular (intracellular enzyme activation, increased serum calcium levels) factors are involved in initiating acute pancreatitis.

Intraacinar activation of proteolytic enzymes: One of the earliest events in different models of acute pancreatitis is blockade of secretion of pancreatic enzymes while synthesis continues.[23] It is becoming increasingly apparent that the central requirement for induction of acute pancreatitis is the intraacinar activation of these proteolytic enzymes, which ultimately leads to an 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:[23]

- A devastating event occurs very early which allows generation of large amounts of active trypsin within the pancreas. Colocalization of lysosomal enzymes, such as cathepsin B and digestive enzymes, including trypsinogen, occurs in unstable vacuoles within the acinar cell.[24]
- The vacuoles then rupture, releasing the active trypsin.
- 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, setting up a vicious cycle of active enzymes damaging cells, which then release more active enzymes.

Trypsinogen activation within the pancreas occurs within 10 minutes of infusing rats with a maximally stimulating dose of the cholecystokinin analogue cerulein, a common agent used to induce pancreatitis in animals.[25]

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.[26] This observation supports the significance of cathepsin B activation of trypsinogen, and the importance of colocalization 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.

Microcirculatory injury

The release of pancreatic enzymes damages the vascular endothelium and the interstitium as well as the acinar cells.[27,29] 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.

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.[29]

Leukocyte chemoattraction, release of cytokines, and oxidative stress

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.[30-32] Activation of complement and the subsequent release of C5a have a significant role in the recruitment of these inflammatory cells.[33]

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.

Heat shock protein, angiotensin II, substance P, and cyclooxygenase 2 are the other recently described candidate pathogenetic factors in experimental pancreatitis, heat shock proteins being the only protective factor.[34]

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.[35,36] 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.

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.[36] One study suggested that an increased tissue concentration of macrophage migration inhibitory factor was a critical factor in the pathogenesis of severe acute pancreatitis.[37]

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.[38] The breakdown in the gut barrier is thought to be a consequence of ischemia due to hypovolemia and pancreatitis-induced gut arteriovenous shunting.[39,40]

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. As a result, attempts to maintain the gut barrier function of the gut continue to be studied. Among the best studied interventions is enteral feeding, which is associated with decreased bacterial translocation in animal models of acute pancreatitis and may be beneficial in humans with acute pancreatitis.

Etiology of Acute Pancreatitis

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, which account for 35 to 40 percent of cases.[41,42]

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: reflux of bile into the pancreatic duct due to transient obstruction of the ampulla during passage of gallstones,[43] or obstruction at the ampulla secondary to stone (s) or edema resulting from the passage of a stone.[44]

Acute pancreatitis is associated with a stone diameter of less than 5 mm. Smaller stones or microlithiasis are more likely than larger stones to pass through the cystic duct and cause obstruction at the ampulla by the mechanisms mentioned above.[46,47]

Biliary sludge and Microlithiasis

Biliary sludge is a viscous suspension in gallbladder bile that may contain small stones (<5 mm in diameter).[49] It is formed by modification of hepatic bile by gallbladder mucosa; thus hepatic bile samples may be insufficient for its diagnosis.[50]

Most patients with biliary sludge are asymptomatic. 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.[51]

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, ceftriaxone can complex with bile to form sludge within the biliary system when its solubility in bile is exceeded; stone formation can rarely occur.[52,53]

Others

Other conditions causing obstruction of the ampulla that have been associated with pancreatitis include;

- Biliary ascariasis,[56]
- Periampullary diverticula,[57] and,
- Pancreatic and periampullary tumors.[58]

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

Approximately 10 percent of chronic alcoholics develop attacks of clinically acute pancreatitis that are indistinguishable from other forms of acute pancreatitis. Alcohol may act by increasing the synthesis of enzymes by pancreatic acinar cells to synthesize the digestive and lysosomal enzymes that are thought to be responsible for acute pancreatitis or over-sensitization of acini to cholecystokinin.[60,61]

Smoking

It has been suggested that cigarette smoking is an independent risk factor for acute and chronic pancreatitis by mechanisms that are unclear.[65-67]

Hypertriglyceridemia

Serum triglyceride concentrations above 1000 mg/dL (11mmol/L) can precipitate attacks of acute pancreatitis, although the pathogenesis of inflammation in this setting is unclear. Hypertriglyceridemia may account for 1.3 to 3.8 percent of cases of acute pancreatitis.[68,69]

The incidence of this form of pancreatitis in hypertriglyceridemic subjects has been best defined in children with inherited disorders of lipoprotein metabolism that are associated with severe hypertriglyceridemia.[70-72] Acquired causes of hypertriglyceridemia include obesity, diabetes mellitus, hypothyroidism, pregnancy, estrogen or tamoxifen therapy, glucocorticoid excess, nephrotic syndrome, and beta blockers.[72,73]

The mechanism behind hypertriglyceridemia-induced pancreatitis is unclear. One hypothesis is that impairment of microcirculation in the pancreas due to high levels of chylomicrons (triglyceride-rich lipid particles) disturbs acinar structure and exposes chylomicrons to pancreatic lipase. The proinflammatory, non-esterified free fatty acids generated from degradation of chylomicrons may lead to further damage to pancreatic acinar cells and microvasculature leading to pancreatitis. Mutations in the enzyme lipoprotein lipase (responsible for metabolizing lipoproteins) have also been described in patients with hypertriglyceridemia-induced pancreatitis.[75]

Hypercalcemia

Hypercalcemia can cause can lead to acute pancreatitis.[76] Proposed mechanisms include deposition of calcium in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma.[77-79]

Genetic Mutations

Some genetic disorders are associated with a high-penetrance (e.g., 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 (e.g., 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 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.[82]

Drugs

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

- 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.[84-86]
- Others – calcium, estrogen, tamoxifen as noted above, estrogen and tamoxifen may act via the induction of hypertriglyceridemia.[73,74]

The pathogenesis of drug-induced pancreatitis may be due to an idiosyncratic response in some cases (e.g., 6-mercaptopurine, aminosalicylates, sulfonamides) or to a direct toxic effect (e.g., diuretics, sulfonamides). Pancreatitis associated with angiotensin converting enzyme inhibitors is thought to reflect angioedema of the gland.

Infection

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:

- Viruses – Mumps, Coxsackievirus, hepatitis B, cytomegalovirus, varicella-zoster, herpes simplex
- Bacteria – Mycoplasma, Legionella, Leptospira, Salmonella
- Fungi – Aspergillus
- Parasites – Toxoplasma, Cryptosporidium, Ascaris.[91]

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

HIV Infection: Acute pancreatitis may be associated with HIV infection, occurring in one series in 4.7 percent of 939 hospitalized patients who were seropositive for HIV. It can be part of primary HIV infection but more frequently occurs as a complication of medications taken to combat the virus (eg, didanosine) or treat opportunistic infections (eg, pentamidine) or to a number of opportunistic infections including Pneumocystis carinii and Mycobacterium avium-intracellulare.[91-94]

Trauma

Blunt or penetrating trauma can damage the pancreas, 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. Trauma can range from a mild contusion to a severe crush injury or transection of the gland; the latter usually occurs at the point where the gland crosses over the spine. This injury can cause acute duct rupture and pancreatic ascites. Healing of pancreatic ductal injuries can lead to scarring and stricture of the main pancreatic duct, with resultant obstructive pancreatitis in the gland downstream from the stricture.[95]

Pancreas Divisum

Pancreas divisum is a common anatomic variant, occurring in approximately 7 percent of autopsy series. It results from failure of the dorsal and ventral pancreas to fuse, resulting in separate pancreatic ductal systems. It can result in acute pancreatitis.[87-89]

Vascular Disease

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

- Vasculitis (systemic lupus erythematosus and polyarteritis nodosa).[96]
- Atheroembolism.[97,98]
- Intraoperative hypotension.[99]
- Hemorrhagic shock.[100]

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.[80-83,101]

Idiopathic

No obvious etiology is identifiable by history (eg, alcohol, family history), laboratory tests (eg, gallstone pancreatitis, hyperlipidemia, hypercalcemia), and gallbladder ultrasound in up to 30 percent of patients with acute pancreatitis. Some authors have preferred to use the term unexplained pancreatitis in this setting, reserving the term idiopathic pancreatitis for those who

have no cause found even after an exhaustive search for an etiology.

Celiac Disease
Another rare cause of recurrent pancreatitis is celiac disease, where duodenal inflammation and papillary stenosis may be the mechanisms for pancreatitis.[102]

Autoimmune pancreatitis
Autoimmune pancreatitis can sometimes present as acute pancreatitis, although the usual presentation is by weight loss, jaundice, and pancreatic enlargement on imaging, mimicking a neoplasm.

Diagnosis of Pancreatitis
Acute pancreatitis is an important cause of acute upper abdominal pain. Because its clinical features are similar to a number of other acute illnesses, it is difficult to base a diagnosis only on symptoms and signs.

Symptoms and Signs
The acute attack frequently begins following a large meal and consists of severe epigastric pain that radiates through to the back. The pain is unrelenting and usually associated with vomiting and retching. In severe cases, the patient may collapse from shock.

Depending on the severity of the disease, there may be profound dehydration, tachycardia, and postural hypotension. Myocardial function is depressed in severe pancreatitis, presumably because of circulating factors that affect cardiac performance.

Examination of the abdomen reveals decreased or absent bowel sounds and tenderness that may be generalized but more often is localized to the epigastrium.

Temperature is usually normal or slightly elevated in uncomplicated pancreatitis. Clinical evidence of pleural effusion may be present, especially on the left.

If an abdominal mass is found, it probably represents a swollen pancreas (phlegmon) or, later in the illness, a pseudocyst or abscess. In 1–2% of patients, bluish discoloration is present in the flank (**Grey Turner sign**) or periumbilical area (**Cullen sign**), indicating hemorrhagic pancreatitis with dissection of blood retroperitoneally into these areas.[1]

Laboratory Findings and Biochemical Markers

- The **hematocrit** may be elevated as a consequence of dehydration or low as a result of abdominal blood loss in hemorrhagic pancreatitis.
- There is usually a moderate **leukocytosis**, but total white blood cell counts over 12,000/L are unusual in the absence of suppurative complications.
- **Liver function studies** are usually normal, but there may be a mild elevation of the serum bilirubin concentration (usually < 2 mg/dL).
- **The serum amylase** concentration rises to more than 2½ times normal within 6 hours after the onset of an acute episode and generally remains elevated for several days. Values in excess of 1000 IU/dL occur early in the attack in 95% of patients with biliary pancreatitis and 85% of patients with acute alcoholic pancreatitis. Those with the most severe disease are more apt to have amylase levels below 1000 IU/dL.
- **Elevated serum lipase** is detectable early and for several days after the acute attack. Since the lipase level tends to be higher in alcoholic pancreatitis and the amylase level higher in gallstone pancreatitis, the lipase/amylase ratio has been suggested as a means to help distinguish the two.

Elevated amylase levels may occur in other acute abdominal conditions, such as gangrenous cholecystitis, small bowel obstruction, mesenteric infarction, and perforated ulcer, though levels rarely exceed 500 IU/dL. Episodes of acute pancreatitis may occur without rises in serum amylase; this is the rule if hyperlipidemia is present. Furthermore, high levels may return to normal before blood is drawn.

In severe pancreatitis, the serum calcium concentration may fall as a result of calcium being complexed with fatty acids (liberated from retroperitoneal fat by lipase) and impaired reabsorption from bone owing to the action of calcitonin (liberated by high levels of glucagon). Relative hypoparathyroidism and hypoalbuminemia have also been implicated.

Imaging Studies
In about two thirds of cases, a **plain abdominal film** is abnormal. The most frequent finding is isolated dilation of a segment of gut (sentinel loop) consisting of jejunum, transverse colon, or duodenum adjacent to the pancreas. Gas distending the right colon that abruptly stops in the mid or left transverse colon (colon cutoff sign) is due to colonic spasm adjacent to the pancreatic inflammation. Both of these findings are relatively nonspecific. Glandular calcification may be evident, signifying chronic pancreatitis. An upper gastrointestinal series may show a widened duodenal loop, swollen ampulla of Vater, and, occasionally, evidence of gastric irritability. Chest films may reveal pleural effusion on the left side.

Ultrasound
All patients with pancreatitis should undergo an ultrasound of the biliary tree. On ultrasound we aim to find out any gallstones, common bile duct stones, swelling of pancreas and any fluid around pancreas. Although the role of ultrasound may be limited in emergency due to bowel gas shadows it should be repeated to rule out gallstones.[45]

ERCP
Several weeks after the pancreatitis has subsided, ERCP may be of value in patients with a tentative diagnosis of

idiopathic pancreatitis. This examination demonstrates gallstones or changes of chronic pancreatitis in about 40% of such patients.[45]

Computed Tomography Scan (CT Scan)

Computed tomography scan (CT scan) is a very useful investigation for acute pancreatits.[46] It main indications are:

- When there is diagnostic uncertainty especially in patients of multiple organ dysfunction to rule out other causes such as intestinal perforation and mesenteric ischemia.
- To determine disease severity and predict complications.

CT scan is a very useful investigation particularly for pancreatic necrosis and other local complications including simple cysts, abscesses and pseudocyst.

CT Severity Index (CTSI): CT severity index is based on the CT findings about severity of pancreatitis and its complications. It is related to the clinical prognosis. This score was primarily developed by Balthazar and then later modified.[5]

Magnetic Resonance Imaging

Abdominal magnetic resonance imaging (MRI) is also useful to evaluate the extent of necrosis, inflammation, and presence of free fluid. However, its cost and availability, and the fact that patients requiring imaging are critically ill and need to be in intensive care units, limit its applicability in the acute phase. Although magnetic resonance cholangiopancreatography (MRCP) is not indicated in the acute setting of AP, it has an important role in the evaluation of patients with unexplained or recurrent pancreatitis because it allows complete visualization of the biliary and pancreatic duct anatomy. In addition, IV administration of secretin increases pancreatic duct secretion, which causes a transient distention of the pancreatic duct.

Endoscopic Ultrasound

In the setting of gallstone pancreatitis, endoscopic ultrasound (EUS) may play an important role in the evaluation of persistent choledocholithiasis. Several studies have shown that routine ERCP for suspected gallstone pancreatitis reveals no evidence of persistent

Table 1: Modified CT Severity Index.

Modified ct severity index	
Pancreatic inflammation	
Normal pancreas	0
Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat	2
Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis	4
Pancreatic necrosis	
None	0
30% or less 2	2
More than 30%	4
Extrapancreatic complications	
One or more of pleural effusion, ascites, vascular complications, parenchymal complications and or gastrointestinal involvement	2
Total Score	10

0-2: mild 4-6: moderate 8-10: severe

Figure 5: CT scan of abdomen revealing pancreatic inflammation and peripancreatitis.

Figure 6: CT scan demonstrating pancreatic necrosis.

Obstruction in most cases and may actually worsen symptoms because of manipulation of the gland. EUS has been proven to be sensitive for identifying choledocholithiasis; it allows for examination of the biliary tree and pancreas with no risk of worsening the pancreatitis. In patients in whom persistent choledocholithiasis is confirmed by EUS, ERCP can be used selectively as a therapeutic measure.[48]

Assessment of Severity of Disease

Many scoring systems (e.g., 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 (e.g., Banks) or are invasive. (e.g., Leeds diagnostic peritoneal lavage) As a result, many of these systems are not used routinely.

Ranson criteria

The earliest scoring system designed to evaluate the severity of AP was introduced by Ranson and colleagues in 1974. It predicts the severity of the disease based on 11 parameters obtained at the time of admission and/or 48 hours later. The mortality rate of AP directly correlates with the number of parameters that are positive. Severe pancreatitis is diagnosed if three or more of the Ranson criteria are fulfilled. The main disadvantage is that it does not predict the severity of disease at the time of the admission because six parameters are only assessed after 48 hours of admission. Ranson's score has a low positive predictive value (50%) and high negative predictive value (90%). Therefore, it is mainly used to rule out severe pancreatitis or predict the risk of mortality. The original scoring symptom designed to predict the severity of the disease and its modification for acute biliary pancreatitis (table 2).

Apache II

AP severity can also be addressed using the Acute Physiology and Chronic Health Evaluation (APACHE II) score. Based on the patient's age, previous health status, and 12 routine physiologic measurements, APACHE II provides a general measure of the severity of disease. An APACHE II score of 8 or higher defines severe pancreatitis. The main advantage is that it can be used on admission and repeated at any time. However, it is complex, not specific for AP, and based on the patient's age, which easily upgrades the AP severity score. APACHE II has a positive predictive value of 43% and a negative predictive value of 89%.[48]

Systemic inflammatory response syndrome score

As noted above, 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.

Table 2: Tables of Ranson Criteria.

Ranson's Prognostic Criteria for Non gallstone Pancreatitis	
At Admission	**At 48 Hours**
Age >55 yr	Hematocrit: Decrease >10%
Blood glucose level >200 mg/dL	Serum calcium level <8 mg/dL
WBC >16,000 cells/mm3	Base deficit >4 mEq/L
Lactate dehydrogenase level >350 IU/L	Blood urea nitrogen level: Increase >5 mg/dL
Aspartate aminotransferase >250 IU/L	Fluid requirement >6 liters
	Pao2 <60 mm Hg
Ranson's Prognostic Criteria for Gallstone Pancreatitis	
At Admission	**At 48 Hours**
Age >70 yr	Hematocrit: Decrease >10%
Blood glucose level >220 mg/dL	Serum calcium level <8 mg/dL
WBC >18,000 cells/mm3	Base deficit >5 mEq/L
Lactate dehydrogenase level >400 IU/L	Blood urea nitrogen level: Increase >2 mg/dL
Aspartate aminotransferase >250 IU/L	Fluid requirement >4 liters

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. In one validation study, mortality rates were 25, 8, and 0 percent in those with persistent SIRS from admission, SIRS at admission but not persistent, and no SIRS, respectively. Another study found that the severity of AP was greater among patients with AP 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 favorably with other more complicated scores.[54]

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 are assigned 1 point for each of the following during the first 24 hours: BUN >25 mg/dL, impaired mental status, SIRS (using the same criteria as the SIRS score, (table 2)), age >60 years, or the presence of a pleural effusion. Patients with a score

of zero had a mortality of less than one percent, whereas patients with a score of five had a mortality rate of 22 percent.[55]

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, and normal serum creatinine.[59]

Organ Failure Scoring Systems

Organ failure scoring systems such as the Goris multiple organ failure score,[59] 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.[62,63,64]

CT Severity Index

Using imaging characteristics, Balthazar and associates have established the CT severity index.

Biochemical Markers

C-reactive protein (CRP) is an inflammatory marker that peaks 48 to 72 hours after the onset of pancreatitis and correlates with the severity of the disease. A CRP level 150 mg/mL or higher defines severe pancreatitis. The major limitation is that it cannot be used on admission; the sensitivity of the assay decreases if CRP levels are measured within 48 hours after the onset of symptoms. In addition to CRP, a number of studies have shown other biochemical markers (e.g., serum levels of procalcitonin, IL-6, IL-1, elastase) that correlate with the severity of the disease. However, their main limitation is their cost and that they are not widely available.[48]

Role LDH and LDH/AST Ratio in Detecting Pancreatic Necrosis;

Lactate Dehydrogenase (LDH) is a sensitive indicator of pancreatic necrosis with sensitivity, 88%; specificity, 100%; accuracy, 91% on 5th day of acute pancreatitis.[5] Serum transaminases especially Aspartate Aminotransferase (AST) elevation in biliary pancreatitis reflects acute hepatocellular injury caused by impacted bile duct stones.[5-7] However, Isogai and his coworkers in Japan showed that LDH/AST ratio is better indicator of pancreatic necrosis in biliary pancreatitis. They found that LDH to AST ratio had a high predictive value for pancreatic necrosis especially after third day of admission.[8]

Complications of Acute Pancreatitis

Once the acute phase has been survived, usually by the end of the first week, and major organ failure is under control, then local complications become pre-eminent in the management of these patients. The course of the patient should be followed carefully and, if clinical resolution does not take place or signs of sepsis develop, a CT scan should be performed. It is important to be clear about the definitions. Certain terms are confusing, such as phlegmon, which may refer to an abscess or to an inflammatory mass in the pancreas. Local complications in pancreatic disease are serious and carry a significant mortality. The management approach is conservative on the whole, with surgery restricted to situations in which conservative management has failed.[2]

Local Complications

- **Acute fluid collection**

This occurs early in the course of acute pancreatitis and is located in or near the pancreas. The wall encompassing the collection is ill defined. The fluid is sterile and most such collections resolve.

- **Sterile and infected pancreatic necrosis**

The term pancreatic necrosis refers to a diffuse or focal area of non-viable parenchyma that is typically associated with peripancreatic fat necrosis. Necrotic areas can be identified by an absence of contrast enhancement on CT. These are sterile to begin with, but can become subsequently infected, probably due to translocation of gut bacteria. Infected necrosis is associated with a mortality rate of up to 50%.

- **Pancreatic abscess**

This is a circumscribed intra-abdominal collection of pus, usually in proximity to the pancreas. It may be an acute fluid collection or a pseudocyst that has become infected.

- **Pancreatic ascites**

This is a chronic, generalized, peritoneal, enzyme-rich effusion usually associated with pancreatic duct disruption. Paracentesis will reveal turbid fluid with a high amylase level.

- **Pancreatic effusion**

This is an encapsulated collection of fluid in the pleural cavity, arising as a consequence of acute pancreatitis. Concomitant pancreatic ascites may be present, or there may be a communication with an intra-abdominal collection.

- **Hemorrhage**

Bleeding may occur into the gut, into the retroperitoneum or into the peritoneal cavity. Possible causes include bleeding into a pseudocyst cavity, diffuse bleeding from a large raw surface, or a pseudoaneurysm. The last is a false aneurysm of a major peripancreatic vessel confined as a clot by the surrounding tissues and often associated with infection. Recurrent bleeding is common, often culminating in fatal hemorrhage.

- **Portal or splenic vein thrombosis**

This may often develop silently and is identified on a CT scan. A marked rise in the platelet count should raise suspicions. In the context of acute pancreatitis, treatment is usually conservative. The patient should be screened for pro-coagulant tendencies.

If varices or other manifestations of portal hypertension develop, they will require treatment.

- **Pseudocyst**

A pseudocyst is a collection of amylase-rich fluid enclosed in a wall of fibrous or granulation tissue. Pseudocysts typically arise following an attack of acute pancreatitis, but can develop in chronic pancreatitis or after pancreatic trauma.

Formation of a pseudocyst requires 4 weeks or more from the onset of acute pancreatitis. They are often single but, occasionally, patients will develop multiple pseudocysts. If carefully investigated, more than half will be found to have a communication with the main pancreatic duct.

A pseudocyst is usually identified on ultrasound or a CT scan. It is important to differentiate a pseudocyst from an acute fluid collection or an abscess; the clinical scenario and the radiological appearances should allow that distinction to be made.[2]

Systemic

- **Pulmonary**

1. Pneumonia, atelectasis
2. Acute respiratory distress syndrome
3. Pleural effusion

- **Cardiovascular**

1. Hypotension
2. Hypovolemia
3. Sudden death
4. Nonspecific ST-T wave changes
5. Pericardial effusion

- **Hematologic**

1. Hemoconcentration
2. Disseminated intravascular coagulopathy

- **GI hemorrhage**

1. Peptic ulcer
2. Erosive gastritis
3. Portal vein or splenic vein thrombosis with varices

- **Renal**

1. Oliguria
2. Azotemia
3. Renal artery/vein thrombosis

- **Metabolic**

1. Hyperglycemia
2. Hypocalcemia
3. Hypertriglyceridemia
4. Encephalopathy
5. Sudden blindness (Purtscher's retinopathy)

- **Central nervous system**

1. Psychosis
2. Fat emboli
3. Alcohol withdrawal syndrome

- **Fat necrosis**

1. Intra-abdominal saponification
2. Subcutaneous tissue necrosis.[9]

Treatment of Acute Pancreatitis

Medical Treatment

The goals of medical therapy are reduction of pancreatic secretory stimuli and correction of fluid and electrolyte derangements.

1. Gastric Suction

Oral intake is withheld, and a nasogastric tube is inserted to aspirate gastric secretions, although the latter has no specific therapeutic effect. Oral feeding should be resumed only after the patient appears much improved, appetite has returned, and serum amylase levels have dropped to normal. Premature resumption of eating may result in exacerbation of disease.

2. Fluid Replacement

Patients with acute pancreatitis sequester fluid in the retroperitoneum, and large volumes of intravenous fluids are necessary to maintain circulating blood volume and renal function. Patients with severe pancreatitis should receive albumin to combat the capillary leak that contributes to the pathophysiology. In severe hemorrhagic pancreatitis, blood transfusions may also be required. The adequacy of fluid replacement is the single most important aspect of medical therapy. In fact, undertreatment with fluids may actually contribute to the progression of pancreatitis. Fluid replacement may be judged most accurately by monitoring the volume and specific gravity of urine.

3. Antibiotics

Antibiotics are not useful in mild cases of acute pancreatitis. However, recent studies have shown benefit of antibiotics that penetrate pancreatic tissue for patients with severe pancreatitis. Imipenem is the most commonly used antibiotic. Antibiotics should also be used for treatment of specific operative complications.

4. Calcium and Magnesium

In severe attacks of acute pancreatitis, hypocalcemia may require parenteral calcium replacement in amounts determined by serial calcium measurements. Recognition of hypocalcemia is important because it may produce cardiac dysrhythmias. Hypomagnesemia is also common, especially in alcoholics, and magnesium should also be replaced as indicated by serum levels.

5. Oxygen

Hypoxemia severe enough to require therapy develops in about 30% of patients with acute pancreatitis. It is often insidious, without clinical or x-ray signs, and out of proportion to the severity of the pancreatitis.

Hypoxemia must be suspected in every patient, and arterial blood gases should be measured every 12 hours for the first few hospital days. Supplemental oxygen therapy is indicated for PaO2 levels below 70 mm Hg. An occasional patient requires endotracheal intubation and mechanical ventilation. Diuretics may be useful in decreasing lung water and improving arterial oxygen saturation.

6. Peritoneal Lavage

Peritoneal lavage has been employed in severe refractory cases to remove toxins in the peritoneal fluid that would otherwise have been absorbed into the systemic circulation. Some patients appear to improve in response to this therapy although controlled trials have not substantiated its efficacy. Severe pancreatitis that fails to show clinical improvement after 24–48 hours of standard inpatient treatment is the usual indication for peritoneal lavage. The technique involves infusing and withdrawing 1–2 L of lactated Ringer solution through a peritoneal dialysis catheter every hour for 1–3 days. Meta-analysis of the existing data shows no benefit; this treatment is not recommended outside of a clinical trial.

7. Nutrition

Total parenteral nutrition avoids pancreatic stimulation and should be used for nutritional support in any severely ill patient who will be unable to eat for more than 1 week. Elemental diets ingested orally or given by tube into the small intestine do not avoid secretory stimulation. Neither form of nutrition directly affects recovery of the pancreas.

8. Other Drugs

Octreotide, H2 receptor blockers, anticholinergic drugs, glucagon, and aprotinin have shown no beneficial effects in controlled trials.[1]

Treatment of Biliary Pancreatitis

Gallstones are the most common cause of acute pancreatitis worldwide. The issue of when to intervene is controversial. General consensus favors either urgent intervention (cholecystectomy) within the first 48 to 72 hours of admission, or briefly delayed intervention (after 72 hours, but during the initial hospitalization) to give an inflamed pancreas time to recover. Cholecystectomy and operative common duct clearance is probably the best treatment for otherwise healthy patients with obstructive pancreatitis. However, patients who are at high risk for surgical intervention are best treated by endoscopic sphincterotomy, with clearance of stones by ERCP.

In the case of acute biliary pancreatitis in which chemical studies suggest that the obstruction persists after 24 hours of observation, emergency endoscopic sphincterotomy and stone extraction is indicated.[9]

Management of complications

Management entails more aggressive resuscitation, intensive care unit admission and vital monitoring for patients with severe pancreatitis and organ dysfunction.

- **Management of Pseudocyst**

Pseudocyst can resolve on its own. If it does not resolve than it can be drained by

- Endoscopic drainage
- Percutaneous drainage
- Open cystogastrostomy
- Laparoscopic cystogastrostomy

- **Management Of Pancreatic Necrosis**:

Sterile pancreatic necrosis is managed conservatively. But if the necrosis get infected prompt surgical treatment is required.

Management options include

- Open laparotomy and debridement accompanied by open or closed lavage and drainage.
- Minimal invasive necrosectomy.
- Endoscopic necrosectomy.

Management of pancreatitis especially severe pancreatitis requires multidisciplinary approach.[2]

OBJECTIVE

Objective of this study was to find the degree of agreement between elevated LDH/AST Ratio and CT scan for detection of pancreatic necrosis in patients presenting with acute biliary pancreatitis.

Operational Definitions

Acute biliary pancreatitis: was labeled if serum amylase and/or lipase are greater than three times their upper limit with radiological evidence of gallstones combined with abdominal pain and abdominal tenderness(less than 10 days).

Pancreatic necrosis: was labeled if there is LDH/AST ratio greater than 20 on 7th post admission day (otherwise, negative) which was then confirmed with contrast enhanced CT scan. Decreased uptake of IV contrast by pancreas in CT scan was labeled as pancreatic necrosis.

Agreement: was labeled if both LDH/AST ratio and CT scan agree for positive and negative findings of pancreatic necrosis**.**

MATERIAL AND METHODS

Study Design

Cross-sectional study

Setting
Study was conducted in Services Hospital Lahore.

Duration of Study
Six months from 18th October 2015 to 17 April 2016.

Sample Size
Sample size of 270 cases was calculated with 95% confidence level, 2.5% margin of error and taking expected percentage of degree of agreement between LDH/AST ratio and CT scan in the detection of pancreatic necrosis to be 95.4%[8] in patients with acute biliary pancreatitis.

Sampling Technique
Non-probability, consecutive sampling.

Sample Selection
- **Inclusion Criteria**: patients of both sexes and age ranging from 20 to 75 years with acute biliary pancreatitis (as per operational definition) were included in study.
- **Exclusion Criteria**: diabetic patients, smokers and patients who had causes of elevated serum transaminases such as

Acute hepatitis, (through history like pain in upper abdomen, yellow discoloration of sclera, fever vomiting and investigations like increase levels of bilirubin, AST,ALT with normal ALP and GGT and viral markers), Heart failure (history like chest pain, exertional dyspnea and echocardiography and angiography), Drug abuse (through history), were excluded from the study.

Data Collection
A total of 270 patients fulfilling the inclusion criteria were included in the study from Emergency department of Surgical Department of Services Hospital Lahore. Informed consent was taken and demographics (name, age, gender, contact). LDH/AST ratio was measured on 7th post admission day. Contrast enhanced CT scan with pancreatic protocol was done on 7th post admission day to confirm pancreatic necrosis. All data was recorded on the Performa (attached). Pancreatic necrosis was labelled on LDH/AST ratio and CT scan (as per operational definitions). These investigations were reported by same team of experienced staff.

Data Analysis
Data was entered analyzed using SPSS version 21. Quantitative variables like age, LDH and AST levels were calculated as mean and standard deviation. Qualitative variables like gender and pancreatic necrosis (on LDH/AST Ratio and CT) and agreement were calculated as frequency and percentage. Kappa statistics were calculated to determine the strength of agreement between LDH/AST Ratio and CT findings for presence or absence of pancreatic necrosis. Data was stratified for age and gender to address the effect modifiers. Post stratification chi-square test was applied with p value ≤ 0.05 as significant.

RESULT

A total 270 patients with acute pancreatitis were included in study. Mean age was found to be 34.57 ± 5.527 (Table 3). 93 patients were male while 177 patients were female (Table 4).

Total 43 patients were predicted to develop pancreatic necrosis on LDH/AST Ratio and among them 42 were confirmed to have necrosis (Table 5). Agreement between pancreatic necrosis prediction on peak creatinine and CT was found to be 98.9% with a kappa coefficient of 0.958 and p value of 0.001 (Table 6).

Patients were stratified for age into two groups. The Agreement of pancreatic necrosis between CT scan and LDH/AST Ratio was measured and p value and kappa coefficient was calculated. p value was significant for both groups and kappa coefficient was found to have very good strength for both groups (Table 9). Similarly, stratification for gender was calculated. p value was significant for both groups and kappa coefficient was found to have very good strength for both groups. (Table 10).

Table 3: Mean age and age in categories of patients.

Characteristics n: 270		
Mean age ± SD(years) 34.57 ± 5.527		
Age in categories	**Frequency**	**Percentage (%)**
20-39	242	89.63
40-75	28	10.37

Table 4: Gender distribution of patients.

Gender of Patient	Frequency(n)	Percentage (%)
Male	93	34.4
Female	177	65.6

Table 5: Pancreatic necrosis on LDH/AST Ratio and CT scan.

Pancreatic Necrosis	Present Frequency (%)	Absent Frequency (%)	Total
Pancreatic Necrosis on LDH/AST Ratio	43(15.93)	227(84.07)	270
Pancreatic Necrosis on CT Scan	42(15.55)	228(84.44)	270

Table 6: Degree of Agreement between Pancreatic Necrosis on LDH/AST Ratio and CT Scan.

Degree of Agreement	Frequency(n)	Percentage (%)
Yes	267	98.9
No	3	1.1

Table 7: 2x2 table showing number of patients having pancreatic necrosis on CT scan and LDH/AST Ratio.

Necrosis on CT Scan	Necrosis on LDH/AST Ratio		Total
	Present	Absent	
Present	41	1	42
Absent	2	226	228
Total	43	227	270

Table 8: Kappa statistics showing strength of agreement.

	Value	Significance P value	95% Confidence Interval(CI) Lower	Upper
Measurement of agreement: Kappa	0.958	0.001	0.911	1.00
No. of valid case	270			

Table 9: Stratification with respect to age of patients having Pancreatic Necrosis on CT Scan and LDH/AST Ratio.

Age	Necrosis on CT Scan	Necrosis on LDH/AST Ratio		Total	p value	Kappa
		present	absent			
20-39	Present	40	2	42	0.001	0.95 (CI 95%)
	Absent	1	181	182		
	Total	41	183	224		
40-75	Present	3	0	3	0.001	1.00 (CI 95%)
	Absent	0	43	43		
	Total	3	43	46		

Table 10: Stratification with respect to age of patients having Pancreatic Necrosis on CT Scan and LDH/AST Ratio.

Gender	Necrosis on CT Scan	Necrosis on LDH/AST Ratio		Total	p value	Kappa
		present	absent			
Female	Present	14	0	14	0.001	0.927 (CI 95%)
	Absent	2	161	163		
	Total	16	161	177		
Male	Present	26	1	27	0.01	0.974 (CI 95%)
	Absent	0	66	66		
	Total	26	67	93		

DISCUSSION

Acute pancreatitis which is inflammatory disease of pancreas has significant mortality and morbidity. Pancreatic necrosis occurs in setting of acute severe pancreatitis. Early prediction and detection of pancreatic necrosis and organ dysfunction can help to modify the management plan which can improve the outcomes. Different biochemical markers are being investigated as predictors of pancreatic necrosis. In our study we have investigated LDH/AST Ratio as a marker of pancreatic necrosis. We confirmed the necrosis on CT scan done on 7th Postadmission day.

A total 270 patients were enrolled in our study. We included patients from age 20-75 yrs. of age. The mean age in our study was 34.57 ± 5.527 yrs. Muddana et al.[101] found that the mean age in acute pancreatitis patients is 49.7yrs. Another study found that the mean age to be 52.5 years.[102] Another study has reported a mean age of 37.54. We had 174 (64.44%) patients in the 3rd decade of age that is age group 30-39 in our study. The mean ages in different international studies mentioned also show that acute pancreatitis is most common in third and fourth decade of life.

In our study there are 93 (34.4%) males and 177(65.6%) females. Yadav D et al.[67] report that equal proportions of male and females develop acute pancreatitis. However they also described that gender distribution is dependent on etiology with alcoholic pancreatitis more common in males and gallstone pancreatitis being more common in females. In our study acute pancreatitis is more common

in females and this can be due to the fact that in our society alcohol consumption is not common as western or other Asian societies. So gallstones are the commonest etiology in our country.

We measured LDH/AST Ratio on 7th Post-admission day. The Ratio greater than 20 was labelled as pancreatic necrosis on LDH/AST Ratio (PNec on LDH/AST Ratio). All the patients underwent a CT scan on 7th post-admission to confirm the absence and presence of pancreatic necrosis being suggested on peak creatinine levels (PNec on CT scan). A total of 43 (15.93 %) patients had LDH/AST Ratio more than 20 and hence were predicted to have pancreatic necrosis. Among these 42 were confirmed to have PNec on CT scan. While on basis of LDH/AST Ratio 227 (84.07%) patients were suggested to have no necrosis. 228 of these patients were found to be devoid of necrosis on CT scan while 42 patients had necrosis. The degree of agreement between PNec on LDH/AST Ratio and PNec on CT scan was found to be 98.9%.

Isogai and his coworkers[8] in Japan showed that LDH/AST ratio is better indicator of pancreatic necrosis in biliary pancreatitis. They found that LDH to AST ratio had a high predictive value for pancreatic necrosis especially after third day of admission. In this study, out of 22 patients with acute biliary pancreatitis 5 patients developed pancreatic necrosis which was confirmed by CT scan. Among 5 patients with pancreatic necrosis, 4 patients had LDH/AST ratio greater than 20 on 7th post admission day. Remaining 17 patients did not develop pancreatic necrosis and had LDH/AST ratio less than 20 on 7th post admission day. Hence the Agreement between LDH/AST ratio and CT scan in detection of pancreatic necrosis will be 95.4%.[8]

Thus, in nutshell the findings in our study between PNec on LDH/AST ratio and CT scan are comparable to that found in international literature. In our study Kappa statistics applied to determine the strength of agreement was found to be 98.9 with a p value 0.001. Kappa coefficient of 0.958 shows a very strong degree of agreement P value of 0.001 shows that this agreement is highly significant statistically.

Hence it shows that LDH/AST Ratio >20 measured at 7th pot-admission day has a strong correlation with pancreatic necrosis and can be used as a marker of pancreatic necrosis.

Stratification for age and gender was performed. The Degree of Agreement was calculated. p value and kappa coefficient were measured. The p value and kappa coefficient were significant in both age and gender groups. Therefore, it is be inferred that LDH/AST Ratio is a strong biochemical marker to predict and detect pancreatic necrosis. However, age and gender do not have any significant association with pancreatic necrosis. This is supported by a study in which it was found that age and gender have no statistically significant relation with pancreatic necrosis.[103]

The limitations of our study include that it was a single center study. More such multicenter studies should be conducted to validate our results.

CONCLUSION

LDH/AST Ratio >20 on 7th post- admission day is strongly associated with the development of pancreatic necrosis and can be used as a biochemical marker of pancreatic necrosis.

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