زانکۆی سەلاحەدین - هەولێر
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Determination of Acute pancreatitis in patients with Pancreatic cancer

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2022-2023

Abstract

The pancreas is a glandular organ that is responsible for the proper functioning of the digestive and endocrine systems, and therefore, it affects the condition of the entire body. Consequently, it is important to effectively diagnose and treat diseases of this organ. According to clinicians, pancreatitis—a common disease affecting the pancreas—is one of the most complicated and demanding diseases of the abdomen. The classification of pancreatitis is based on clinical, morphologic, and histologic criteria.

Acute pancreatitis is an acute inflammation of the pancreas. The clinical classification of the disease recognizes the mild acute pancreatitis, characterized by the absence of local and/or systemic complications, and the severe disease, characterized by the presence of local complications such as necrosis, abscess or pseudo cysts and/ or distant organ failure. Gallstones constitute the predominant etiological factor. The severity assessment is essential for proper initial treatment of the disease. Primary objectives to achieve in the treatment of acute pancreatitis essentially are: pain control, electrolyte support and energy intake, removal of the causal agent, attenuation of the inflammation, and prevention and eventual treatment of local and systemic complications of necrotizing forms.

Pancreatic cancer remains a major cause of cancer related death worldwide and is associated with a dismal prognosis. Curative-intent surgery offers the only chance of survival from pancreatic cancer. However, fewer than 20% of patients are eligible for resection at the time of diagnosis due to locally advanced or metastatic disease.

Acute pancreatitis (AP) is a rare manifestation of pancreatic cancer (PC). The relationship between AP and PC remains less distinct.

Keywords: pancreas, acute pancreatitis, Pancreatic cancer.

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1.Introduction

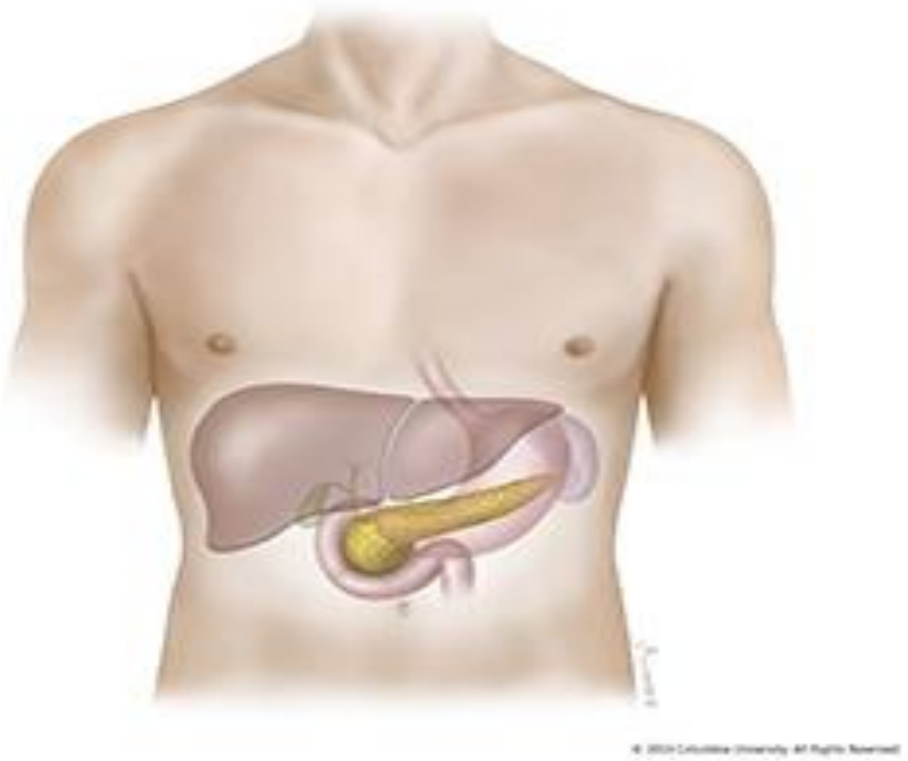
Pancreatic cancer is the fourth leading cause of cancer-related mortality in the western world and is projected to increase.[1, 2] About 15% of pancreatic tumors are resectable at diagnosis, limiting five-year survival to 8%.[2, 3] To improve pancreatic cancer prognosis, early detection when the tumor is resectable is essential. This is difficult due to a lack of early disease-specific symptoms.[4]

Acute pancreatitis may constitute an early and symptom of pancreatic cancer, as around 1% of acute pancreatitis admissions are due to pancreatic cancer.[5] Many of these patients are diagnosed with pancreatic cancer within few months after acute pancreatitis diagnosis,[6, 7] but some patients experience longer diagnostic delays because of initial misdiagnosis, impeding survival.[6, 8] However, the prognostic value of acute pancreatitis on pancreatic cancer prognosis is unclear. Studies have suggested that pancreatic cancer patients with acute pancreatitis may have lower tumor stage,[9–11] higher resection frequencies,[9, 11] and improved prognosis[9, 12] compared with patients without acute pancreatitis. Another study found no differences in tumor stage, treatment, or survival.[13] However, all studies had substantial limitations – failing to distinguish between acute and chronic pancreatitis,[9] including patients with self-reported pancreatitis,[9] or provided imprecise estimates.[10–13]

1.1 what is pancreas

The pancreas is an organ located in the abdomen. It plays an essential role in converting the food we eat into fuel for the body's cells. The pancreas has two main functions: an exocrine function that helps in digestion and an endocrine function that regulates blood sugar.

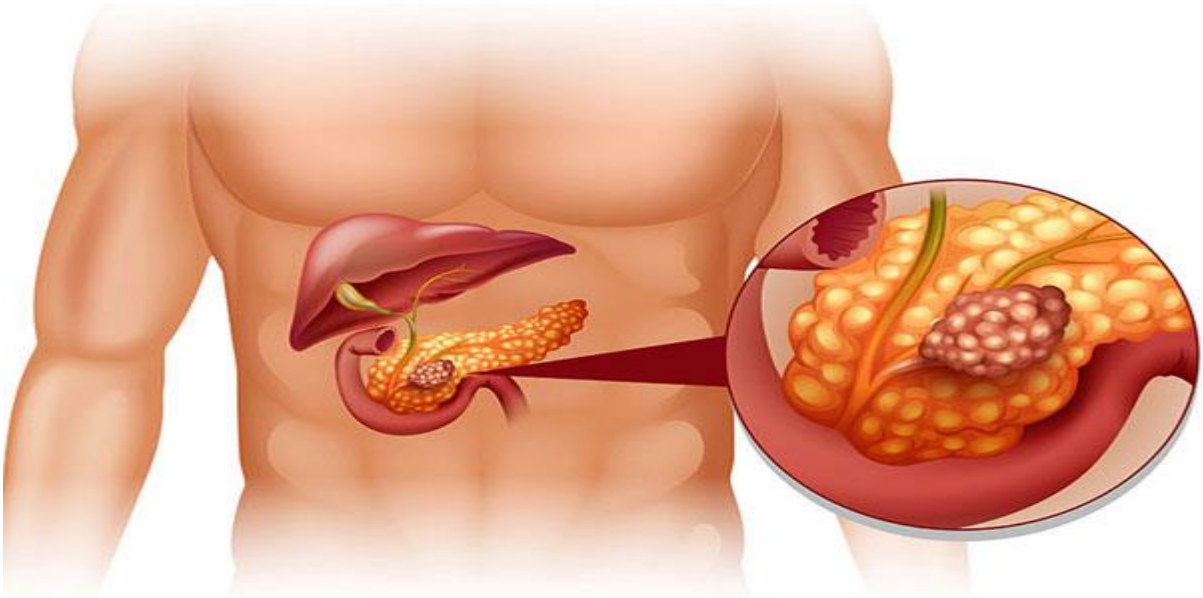
The pancreas is a glandular organ that affects the functioning of the entire body. The emerging pancreatic insufficiency is the inability of the pancreas to biosynthesize and/or secrete digestive enzymes in an amount sufficient to digest and absorb food components in the intestines. Insufficiency usually occurs as a result of damage to the pancreas, which can be caused by a variety of clinical conditions, e.g., recurrent acute pancreatitis, chronic pancreatitis, diabetes, autoimmune diseases, after pancreatectomy surgery. It happens that such failure is the result of pancreatic or gastrointestinal cancer.



1.2 What is acute pancreatitis

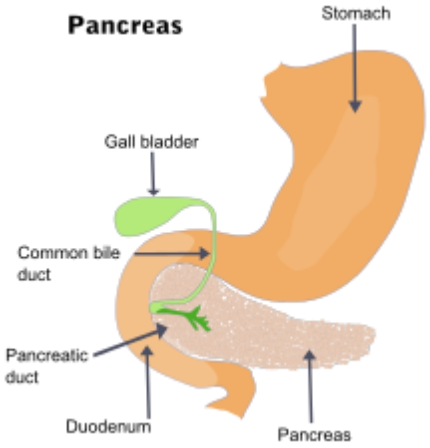
Acute pancreatitis (AP) caused approximately 275,000 hospitalization's in 20091 (an increase of more than 2-fold since 19882) and is the single most frequent gastrointestinal cause of hospital admissions in the United States. Although the incidence and prevalence of chronic pancreatitis (CP) is lower than that of AP, CP significantly affects patients' quality of life; it is characterized by chronic abdominal pain, frequent disease exacerbations, and exocrine and/or endocrine insufficiency. The incidence of pancreatic cancer is lower than that of many other types of cancer, but it is the fourth most common cause of death from cancer. We review the epidemiology and risk factors for pancreatitis and pancreatic cancer.

[1] Hidalgo, M., 2010. Pancreatic cancer. *New England Journal of Medicine*, *362*(17), pp.1605-1617.



1.3 Pathology[edit]

Pathogenesis[edit]



Acute pancreatitis occurs when there is abnormal activation of digestive enzymes within the pancreas. This occurs through inappropriate activation of inactive enzyme precursors called zymogens (or proenzymes) inside the pancreas, most notably trypsinogen. Normally, trypsinogen is converted to its active form (trypsin) in the first part of the small intestine (duodenum), where the enzyme assists in the digestion of proteins. During an episode of acute pancreatitis, trypsinogen comes into contact with lysosome enzymes (specifically cathepsin), which activate trypsinogen to trypsin. The active form trypsin then leads to further activation of other molecules of trypsinogen. The activation of these digestive enzymes lead to inflammation, edema, vascular injury, and even cellular death. The death of pancreatic cells occurs via two main mechanisms: necrosis, which is less organized and more damaging, or apoptosis, which is more controlled. The balance between these two mechanisms of cellular death is mediated by caspases which regulate apoptosis and have important anti-necrosis functions during pancreatitis: preventing trypsinogen activation, preventing ATP depletion through inhibiting polyADP-ribose polymerase, and by inhibiting the inhibitors of apoptosis (IAPs). If, however, the caspases are depleted due to either chronic ethanol exposure or through a severe insult then necrosis can predominate.

Pathophysiology[edit]

The two types of acute pancreatitis are mild and severe, which are defined based on whether the predominant response to cell injury is inflammation (mild) or necrosis (severe). In mild pancreatitis, there is inflammation and edema of the pancreas. In severe pancreatitis, there is necrosis of the pancreas, and nearby organs may become injured.

As part of the initial injury there is an extensive inflammatory response due to pancreatic cells synthesizing and secreting inflammatory mediators: primarily TNF-alpha and IL-1. A hallmark of acute pancreatitis is a manifestation of the inflammatory response, namely the recruitment of neutrophils to the pancreas. The inflammatory response leads to the secondary manifestations of pancreatitis: hypovolemia from capillary permeability, acute respiratory distress syndrome, disseminated intravascular coagulations, renal failure, cardiovascular failure, and gastrointestinal hemorrhage.

Histopathology[edit]

The acute pancreatitis (acute hemorrhagic pancreatic necrosis) is characterized by acute inflammation and necrosis of pancreas parenchyma, focal enzymic necrosis of pancreatic fat and vessel necrosis (hemorrhage). These are produced by intrapancreatic activation of pancreatic enzymes. Lipase activation produces the necrosis of fat tissue in pancreatic interstitium and peripancreatic spaces as well as vessel damage. Necrotic fat cells appear as shadows, contours of cells, lacking the nucleus, pink, finely granular cytoplasm. It is possible to find calcium precipitates (hematoxylinophilic). Digestion of vascular walls results in thrombosis and hemorrhage. Inflammatory infiltrate is rich in neutrophils. Due to the pancreas lacking a capsule, the inflammation and necrosis can extend to include fascial layers in the immediate vicinity of the pancreas.

The pancreas is able to protect itself from auto-digestion in a number of ways. First, some digestiveenzymes are stored in the acinar cells as inert zymo-gens, and theoretically are only activated after secre-tion into the lumen of the duodenum.5Second, withinthe acinar cell, the zymogen granules remain physicallyseparate from the lysosomal granules enclosed inmembrane-bound organelles.20Lysosomal enzymes areproduced on ribosomes attached to rough endoplasmicreticulum in the same manner that zymogens are pro-duced, but additionally are glycosolated and phosphor-ylated as they pass through the Golgi complex.20,21Studies have shown that these 2 enzyme groups arekept physically apart throughout all stages of theirproduction.22Third, location of pancreatic secretorytrypsin inhibitor (PSTI) within the acinar cells allowsfor immediate inhibition of trypsin should it be acti-vated within the acinar cells. PSTI is produced andstored in the same cellular location as the digestiveenzymes.5,23Finally, should any activated trypsin bereleased into the circulation, larger antiproteases in theblood theoretically have the capacity to deactivatesome circulating trypsin.

Pathophysiology

Cellular events central to the pathogenesis of acute pancreatitis include pathological calcium signalling2,20,31,32, mitochondrial dysfunction19,33,34, premature trypsinogen activation within the acinar cells and macrophages35–41, endoplasmic reticulum (ER) stress, impaired unfolded protein response (UPR)33,42–44 and impaired autophagy33,45. These events are triggered by common acinar cell toxins, such as alcohol, nicotine and bile acids. Intraductal events, such as increased pressure caused by ductal obstruction, luminal acidification and ductal cell exposure to bile acid, can also indirectly trigger these events. The crosstalk between acinar cells and the immune system perpetuates an inflammatory response46–48. At a locoregional level, the mediatory role of intrapancreatic and peripancreatic fat saponification and ischaemiaconditioned mesenteric lymph in acute pancreatitis severity has been recognized23,24,49–52.

Lee, P.J. and Papachristou, G.I., 2019. New insights into acute pancreatitis. *Nature reviews Gastroenterology & hepatology*, *16*(8), pp.479-496.

Pathogenesis and Etiology

Acute pancreatitis is characterized by damage to the acinar cells, the functional units of theexocrine pancreas, precipitating inappropriate release and activation of trypsinogen to trypsin within the acini. This triggers the activation of other digestive enzymes, the kinin system, and thecomplementcascade resultinginautodigestion of thepancreaticparenchyma.8,9Pancreaticductobstruction (eg, gallstonepancreatitis) is one of themore common causes ofacinar damage, causingan increase in ductal pressure, interstitial edema, and accumulation of enzyme-rich fluidwithin thepancreatic tissue.10Alternatively,primary acinar injury may be caused by a variety of other factors, such as calcium, which regulates trypsin activation. Inappropriate release of intracellularcalcium,enhancedentryofextracellularcalcium,ordefective calcium extrusion/reuptake mechanisms causes a sustained increase in cytosolic calcium in the acini. This elevation leads to premature activation of trypsinogen to trypsin, resulting in acinar injury and death.11,12 Ethanol is a common cause of acute pancreatitis, but its pathogenesis remains unknown; there isevidence that itmay disrupt multiple biochemical pathways within acinar cells.

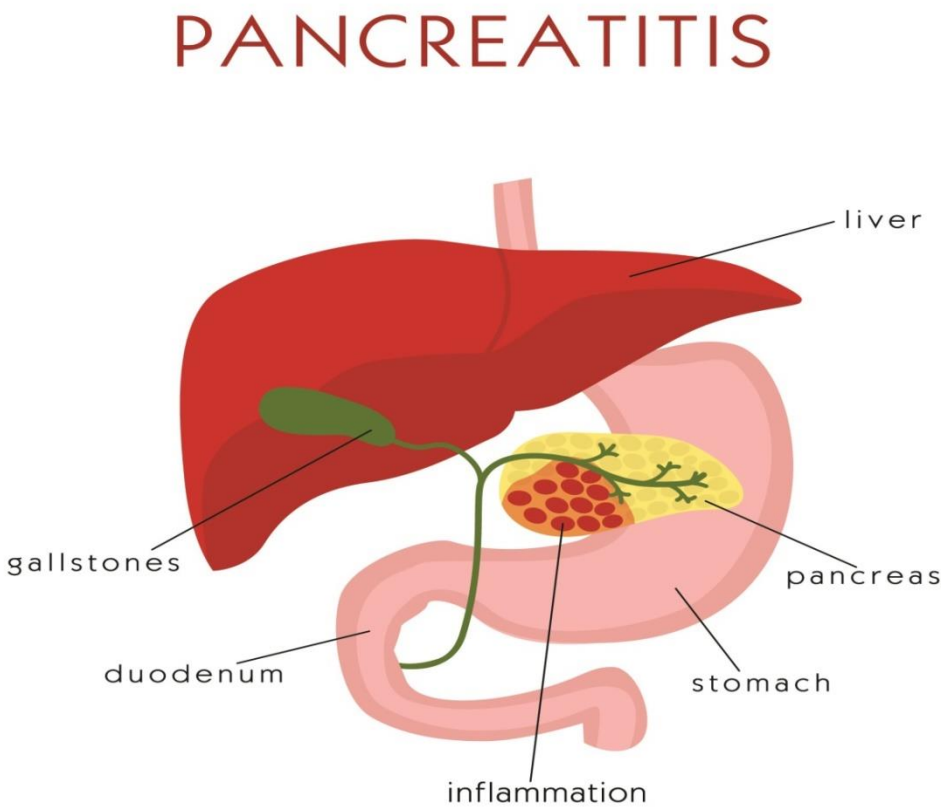
Mederos, M.A., Reber, H.A. and Girgis, M.D., 2021. Acute pancreatitis: a review. *Jama*, *325*(4), pp.382-390.

1.4 signs and symptoms

Acute pancreatitis usually begins with gradual or sudden pain in the upper abdomen that sometimes extends through the back. The pain may be mild at first and feel worse after eating. But the pain is often severe and may become constant and last for several days. A person with acute pancreatitis usually looks and feels very ill and needs immediate medical attention. Other symptoms may include

- A swollen and tender abdomen
- Nausea and vomiting
- Fever
- a rapid pulse

Severe acute pancreatitis may cause dehydration and low blood pressure. The heart, lungs, or kidneys can fail. If bleeding occurs in the pancreas, shock and even death may follow



1.5 Acute pancreatitis causes include

Acute pancreatitis is usually caused by gallstones or drinking too much alcohol, but sometimes no cause can be identified.

Gallstones

Gallstones are small stones that form in your gallbladder. They can sometimes trigger acute pancreatitis if they move out of the gallbladder and block the opening of the pancreas.

Alcohol consumption

It's not fully understood how alcohol causes the pancreas to become swollen (inflamed). One theory is that it causes enzymes inside the pancreas to start digesting it.

Whatever the cause, there is a clear link between alcohol use and acute pancreatitis.

Binge drinking – drinking a lot of alcohol in a short period of time – is also thought to increase your risk of developing acute pancreatitis.

Other causes

Less common causes of acute pancreatitis include:

- high blood fat levels (hypertriglyceridaemia)
- accidental damage or injury to the pancreas – for example, during a procedure to remove gallstones or examine the pancreas
- a side effect of medicine
- viruses like mumps or measles
- high blood calcium levels (hypercalcaemia)
- the immune system attacking the pancreas (autoimmune pancreatitis)

1.6 Pancreatic Cancer

Pancreatic cancer (PC) is an aggressive disease and ranks fourth in cancer-related mortality in the United States.[1] The prognosis of PC is dismal due to its asymptomatic nature in the early stages. Less than 30% of patients with PC were impossible to remove the tumors when classical clinical findings were present.[2] One approach to cure PC is early diagnosis and radical surgery. Disappointingly, there is a lack of effective intervention for early diagnosis of PC at present. Once clinical presentations of PC present with weight loss, abdominal or back pain, and jaundice, it may be a sign of late stage.

Recently, it has been described that acute pancreatitis (AP) is an early symptom of PC. Mujica et al[3] reported that 1-year overall survival rate was 28% in patients with PC presenting with AP and 20% in patients with PC. However, AP is a rare manifestation of PC. Most patients may be misdiagnosed as AP and delayed in cancer diagnosis. Little is known of the relationship between clinical features of AP and PC. The objectives of this report were to identify the clinical characteristics, the optimal timing of surgical intervention, and survival.

[1] Hidalgo, M., 2010. Pancreatic cancer. *New England Journal of Medicine*, *362*(17), pp.1605-1617.

[2] Dítě, P., Hermanová, M., Trna, J., Novotný, I., Růžička, M., Liberda, M. and Bartkova, A., 2012. The role of chronic inflammation: chronic pancreatitis as a risk factor of pancreatic cancer. *Digestive Diseases*, *30*(3), pp.277-283.

[3] Mujica, V.R., Barkin, J.S. and Go, V.L.W., 2000. Acute pancreatitis secondary to pancreatic carcinoma. *Pancreas*, *21*(4), pp.329-332.

1.7 Signs and symptoms[edit]

Since pancreatic cancer usually does not cause recognizable symptoms in its early stages, the disease is typically not diagnosed until it has spread beyond the pancreas itself.[4] This is one of the main reasons for the generally poor survival rates. Exceptions to this are the functioning PanNETs, where over-production of various active hormones can give rise to symptoms (which depend on the type of hormone).[30]

Bearing in mind that the disease is rarely diagnosed before the age of 40, common symptoms of pancreatic adenocarcinoma occurring before diagnosis include:

- Pain in the upper abdomen or back, often spreading from around the stomach to the back. The location of the pain can indicate the part of the pancreas where a tumor is located. The pain may be worse at night and may increase over time to become severe and unremitting.[24] It may be slightly relieved by bending forward. In the UK, about half of new cases of pancreatic cancer are diagnosed following a visit to a hospital emergency department for pain or jaundice. In up to two-thirds of people, abdominal pain is the main symptom, for 46% of the total accompanied by jaundice, with 13% having jaundice without pain.[12]
- Jaundice, a yellow tint to the whites of the eyes or skin, with or without pain, and possibly in combination with darkened urine, results when a cancer in the head of the pancreas obstructs the common bile duct as it runs through the pancreas.[31]
- Unexplained weight loss, either from loss of appetite, or loss of exocrine function resulting in poor digestion.[12]
- The tumor may compress neighboring organs, disrupting digestive processes and making it difficult for the stomach to empty, which may cause nausea and a feeling of fullness. The undigested fat leads to foul-smelling, fatty feces that are difficult to flush away.[12] Constipation is also common.[32]
- At least 50% of people with pancreatic adenocarcinoma have diabetes at the time of diagnosis.[2] While long-standing diabetes is a known risk factor for pancreatic cancer (see Risk factors), the cancer can itself cause diabetes, in which case recent onset of diabetes could be considered an early sign of the disease.[33] People over 50 who develop diabetes have eight times the usual risk of developing pancreatic adenocarcinoma within three years, after which the relative risk declines.[12]

Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet. 2011 Aug 13;378(9791):607-20. doi: 10.1016/S0140-6736(10)62307-0. Epub 2011 May 26. PMID: 21620466; PMCID: PMC3062508.

1.8Causes

We don't know what causes pancreatic cancer. But we do know many of the risk factors for this cancer (see Pancreatic Cancer Risk Factors) and how some of them cause cells to become cancerous. Some genes control when cells grow, divide into new cells, and die:

● Genes that help cells grow, divide, and stay alive are called oncogenes. Genes that help keep cell division under control or cause cells to die at the right time are called tumor suppressor genes.

● Cancers can be caused by DNA changes that turn on oncogenes or turn off tumor suppressor genes.

1.9 Risk of Pancreatic Cancer After a Primary Episode of Acute Pancreatitis

Pancreatic cancer has a 5-year relative survival rate of 6% and is 1 of the 5 most lethal malignancies.1,2 Prevention and early diagnosis of pancreatic cancer are therefore of utmost importance. A 9-fold increased risk of pancreatic cancer after acute pancreatitis has been reported.3 The pathophysiologic association between pancreatic cancer and acute pancreatitis is still under debate.3,4 It has been proposed that recurrent episodes of acute pancreatitis lead to chronic pancreatitis.5 Chronic pancreatitis is a known risk factor for pancreatic cancer.5 Another theory is that pancreatic cancer results in ductal obstruction and acute pancreatitis.6 Various studies suggest that acute pancreatitis may progress to pancreatic cancer owing to genetic alterations.7,8 The association between acute pancreatitis and pancreatic cancer is, however, contentious, and it remains questionable whether close follow-up after a first episode of acute pancreatitis is (cost-)effective and will result in earlier diagnosis of pancreatic cancer. Given the fact that acute pancreatitis is the most common gastrointestinal cause for acute hospitalization in the United States, with doubling incidence since 1988, acute pancreatitis might be an important risk factor for pancreatic cancer.5,9–11 The aim of this study was to identify those patients who develop pancreatic cancer after a first episode of acute pancreatitis and determine the risk of pancreatic cancer.

Rijkers, A.P., Bakker, O.J., Ali, U.A., Hagenaars, J.C., van Santvoort, H.C., Besselink, M.G., Bollen, T.L., van Eijck, C.H. and Dutch Pancreatitis Study Group, 2017. Risk of pancreatic cancer after a primary episode of acute pancreatitis. *Pancreas*, *46*(8), pp.1018-1022.

1.10 What are the relation between acute pancreatitis and pancreatic cancer

The relationship between acute pancreatitis and the development of pancreatic cancer is unclear. While acute pancreatitis remains common, pancreatic cancer is relatively rare, and some risk factors for acute pancreatitis are shared with pancreatic cancer (e.g., alcohol can cause acute pancreatitis but can also lead to chronic pancreatitis, a major risk factor for pancreatic cancer).

To further investigate the link between these two illnesses, researchers followed about 50,000 Swedish residents with a single prior episode of acute pancreatitis and 140,000 matched residents without prior acute pancreatitis for 1.2 million person-years (median, 5.3 years). Among the 769 people who developed pancreatic cancer, 70% had at least one prior episode of acute pancreatitis. The excess risk for pancreatic cancer was highest when temporally closest to the episode of acute pancreatitis (hazard ratio within first 2 months of acute pancreatitis diagnosis, 173), fell over time (HR at 5–10 years postdiagnosis, 2), and disappeared altogether 10 years after an episode of acute pancreatitis. Multiple episodes of acute pancreatitis were associated with increased pancreatic cancer risk.

1.11 ` Complications[edit]

Loco regional complications include pancreatic pseudo cyst (most common, occurring in up to 25% of all cases, typically after 4–6 weeks) and phlegmon/abscess formation, splenic artery pseudo aneurysms, hemorrhage from erosions into splenic artery and vein, thrombosis of the splenic vein, superior mesenteric vein and portal veins (in descending order of frequency), duodenal obstruction, common bile duct obstruction, progression to chronic pancreatitis, pancreatic ascites, pleural effusion, sterile/infected pancreatic necrosis.[5]
Systemic complications include acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome, disseminated intravascular coagulation (DIC), hypocalcaemia (from fat saponification), hyperglycemia and insulin dependent diabetes mellitus (from pancreatic insulin-producing beta cell damage), malabsorption due to exocrine failure

- **Metabolic**

Hypocalcemia, hyperglycemia, hypertriglyceridemia

- **Respiratory**

Hypoxemia, atelectasis, effusion, pneumonitis, acute respiratory distress syndrome

- **Renal**

Renal artery or vein thrombosis

Kidney failure

- **Circulatory**

Arrhythmias
Hypovolemia and shock
Myocardial infarction
Pericardial effusion
Vascular thrombosis

- **Gastrointestinal**

Gastrointestinal hemorrhage from stress ulceration
Gastric varices (secondary to splenic vein thrombosis)
Gastrointestinal obstruction

- **Hepatobiliary**

Jaundice
Portal vein thrombosis

- **Neurologic**

Psychosis or encephalopathy (confusion, delusion and coma)
Cerebral Embolism
Blindness (angiopathic retinopathy with hemorrhage)

- **Hematologic**

Anemia
Disseminated intravascular coagulation
Leucocytosis

- **Dermatologic**

Painful subcutaneous fat necrosis

- **Miscellaneous**

Subcutaneous fat necrosis
Arthalgia

1. **5** ^ *Bassi C, Falconi M, Butturini G, Pederzoli P (2001). "Early complications of severe acute pancreatitis". In Holzheimer RG, Mannick JA (eds.). Surgical Treatment: Evidence-Based and Problem-Oriented. Munich: Zuckschwerdt.*

2. DIAGNOSIS AND TESTS

How is pancreatitis diagnosed?

Pancreatitis has physical findings that affect body systems and can be diagnosed through blood test, imaging test and intervention procedure advised by doctor.

Depending on symptoms, the Gastroenterologist will ask about medical history, any family history of pancreatitis, eating and drinking habits, taking any prescription or over-the-counter medications, including vitamins and supplements.

To diagnose pancreatitis, a gastroenterologist may recommend:

1.**Blood and Stool tests:** Amylase or lipase blood test and Stool routine test for digestive enzymes of the pancreas. It will be elevated 3 times in pancreatitis from its normal range. If blood test is showing normal ranges then we need to go to further evaluation.

2. Imaging tests: To understand pancreatitis and figure out what's the cause. Doctor may recommend X-rays with a barium meal and Ultrasound imaging: specifically evaluate the gallbladder for stones

3.Endoscopic ultrasound (EUS): Endoscopic examination to evaluate pancreatic masses and tumors, pancreatic cysts, small stone in bile duct and gall bladder not identified during ultrasound. This procedure is performed to collect small tissues of pancreas using FNA needle through the wall of the stomach or intestine directly into the pancreas.

4.Biopsy or Tissue analysis: a tissue sample (biopsy) from pancreas may help diagnose pancreatitis and further look for signs of pancreatitis.

5.Endoscopic retrograde cholangiopancreatography (ERCP): to view the bile duct and pancreatic duct. It helps to remove gallstones from the bile duct gallstones that are causing a blockage.

6.Abdominal ultrasound. Sound waves are sent toward the pancreas through a handheld device that a technician glides over the abdomen. The sound waves bounce off the pancreas, gallbladder, liver, and other organs, and their echoes make electrical impulses that create a

picture—called a sonogram—on a video monitor. If gallstones are causing inflammation, the sound waves will also bounce off them, showing their location.

7. **Computerized tomography (CT) scan.** The CT scan is a noninvasive x ray that produces three-dimensional pictures of parts of the body. The person lies on a table that slides into a donut-shaped machine. The test may show gallstones and the extent of damage to the pancreas.

8. **Endoscopic ultrasound (EUS).** After spraying a solution to numb the patient's throat, the doctor inserts an endoscope—a thin, flexible, lighted tube—down the throat, through the stomach, and into the small intestine. The doctor turns on an ultrasound attachment to the scope that produces sound waves to create visual images of the pancreas and bile ducts.

9.Magnetic resonance cholangiopancreatography (MRCP). MRCP uses magnetic resonance imaging, a noninvasive test that produces cross-section images of parts of the body. After being lightly sedated, the patient lies in a cylinder-like tube for the test. The technician injects dye into the patient's veins that helps show the pancreas, gallbladder, and pancreatic and bile ducts.

2.1 Biochemical Test

α_2- macroglobulin, α-amylase, C-reactive protein, lipase, non-esterified fatty acids, pancreatic α-amylase and phospholipase A in the diagnosis and prognosis of acute pancreatitis.

Serum amylase concentration increases almost immediately with the onset of disease and peaks within several hours. It remains elevated for 3 to 5 days before returning to normal. There is no significant correlation between the magnitude of serum amylase elevation and severity of pancreatitis. 8 Acute Pancreatitis Lipase is more specific for pancreatitis. Serum lipase has a longer half-life than amylase and therefore tends to remain elevated for longer. Urinary clearance of pancreatic enzymes from the circulation increases during pancreatitis; therefore, urinary levels may be more sensitive than serum levels. Several tests can help differentiate biliary pancreatitis from other causes of pancreatitis.

- Aspartate aminotransferase (AST),
- alanine aminotransferase (ALT),
- gamma-glut amyl Trans peptidase (GGT),
- alkaline phosphatase
- serum bilirubin are the so-called liver function tests; they should be reviewed before making a confident diagnosis. Several recent research studies have suggested additional markers that may have prognostic value,

- including C-reactive protein (CRP),
- alpha2-macroglobulin,
- polymorph nuclear neutrophil–lactase,
- alpha1-antitrypsin,
- and phospholipase A2.
- The measurement of IL-6
- urinary–trypsinogen activation peptide (TAP

[9],[10] Although CRP measurement is commonly available, many of the others are not. Therefore, at this time, CRP seems to be the marker of choice in clinical settings. The measurement of IL-6 has recently been shown to distinguish patients with mild or severe forms of the disease. Another prognostic marker under evaluation is urinary–trypsinogen activation peptide (TAP). It has a good correlation between the severity of pancreatitis and concentrations of TAP in urine. Currently, these new markers have limited clinical availability, but there is significant interest in better understanding markers of immune response and pancreatic injury because these could be valuable tools for reliably predicting the severity of acute pancreatitis and supplementing imaging modalities.

- Matull, W.R., Pereira, S.P. and O'donohue, J.W., 2006. Biochemical markers of acute pancreatitis. *Journal of clinical pathology*, *59*(4), pp.340-344.

3. Treatment

Treatment for acute pancreatitis depends on its severity. For people with mild cases, the risk of complications is low, and the symptoms may resolve after a few daysTrusted Source of rest and treatment. In severe cases, the risk is significant.

3.1Treatment for mild acute pancreatitis

The aim is to maintain bodily functions and ease the symptoms while the pancreas heals itself. The treatment may include:

- **Painkillers:** Mild acute pancreatitis can be moderately or severely painful.
- **Nasogastric tubes:** These can remove excess liquid and air to relieve nausea and vomiting.
- **Bowel rest:** The gastrointestinal tract needs to rest for a few days, so the person will not have any food or drink by mouth until their condition improves.
- **Preventing dehydration:** Dehydration often accompanies pancreatitis, and it can worsen the symptoms and complications. Healthcare professionals usually provide fluid intravenously for the first 24–48 hours.
- **Fluid replacement**[edit]

Aggressive hydration at a rate of 5 to 10 mL/kg per hour of isotonic crystalloid solution (e.g., normal saline or lactated Ringer's solution) to all patients with acute pancreatitis, unless cardiovascular, renal, or other related comorbid factors preclude aggressive fluid replacement. In patients with severe volume depletion that manifests as hypotension and tachycardia, more rapid repletion with 20 mL/kg of intravenous fluid given over 30 minutes followed by 3 mL/kg/hour for 8 to 12 hours.[26][27]

Fluid requirements should be reassessed at frequent intervals in the first six hours of admission and for the next 24 to 48 hours. The rate of fluid resuscitation should be adjusted based on clinical assessment, hematocrit and blood urea nitrogen (BUN) values.

In the initial stages (within the first 12 to 24 hours) of acute pancreatitis, fluid replacement has been associated with a reduction in morbidity and mortality.[28][29][30][31]

- **Pain control**[edit]

Abdominal pain is often the predominant symptom in patients with acute pancreatitis and should be treated with analgesics.
Opioids are safe and effective at providing pain control in patients with acute pancreatitis.[32] Adequate pain control requires the use of intravenous opiates, usually in the form of a patient-controlled analgesia

pump. Hydromorphone or fentanyl (intravenous) may be used for pain relief in acute pancreatitis. Fentanyl is being increasingly used due to its better safety profile, especially in renal impairment. As with other opiates, fentanyl can depress respiratory function. It can be given both as a bolus as well as constant infusion. Meperidine has been historically favored over morphine because of the belief that morphine caused an increase in sphincter of Oddi pressure. However, no clinical studies suggest that morphine can aggravate or cause pancreatitis or cholecystitis.[33] In addition, meperidine has a short half-life and repeated doses can lead to accumulation of the metabolite normeperidine, which causes neuromuscular side effects and, rarely, seizures.

- **Nutritional support**[edit]

Recently, there has been a shift in the management paradigm from total parenteral nutrition (TPN) to early, post-pyloric enteral feeding (in which a feeding tube is endoscopically or radiographically introduced to the third portion of the duodenum). The advantage of enteral feeding is that it is more physiological, prevents gut mucosal atrophy, and is free from the side effects of TPN (such as fungemia). The additional advantages of post-pyloric feeding are the inverse relationship of pancreatic exocrine secretions and distance of nutrient delivery from the pylorus, as well as reduced risk of aspiration.
Disadvantages of a naso-enteric feeding tube include increased risk of sinusitis (especially if the tube remains in place greater than two weeks) and a still-present risk of accidentally intubating the trachea even in intubated patients (contrary to popular belief, the endotracheal tube cuff alone is not always sufficient to prevent NG tube entry into the trachea).

- **Oxygen**[edit]

Oxygen may be provided in some patients (about 30%) if Pao2 levels fall below 70mm of Hg.

- **Antibiotics**[edit]

Up to 20 percent of people with acute pancreatitis develop an infection outside the pancreas such as bloodstream infections, pneumonia, or urinary tract infections.[35] These infections are associated with an increase in mortality.[36] When an infection is suspected, antibiotics should be started while the source of the infection is being determined. However, if cultures are negative and no source of infection is identified, antibiotics should be discontinued.

Preventative antibiotics are not recommended in people with acute pancreatitis, regardless of the type (interstitial or necrotizing) or disease severity (mild, moderately severe, or severe)[11][37]

A person can usually return from the hospital after about 5–7 days.

3.2 Treatment for severe acute pancreatitis

Severe cases often involve some tissue death, or necrosis. This increases the risk of sepsis, a severe bacterial infection that can affect the whole body. Sepsis can lead to multiorgan damage or failure.

Severe acute pancreatitis can also cause hypovolemic shock. This involves severe blood and fluid loss leaving the heart unable to pump enough blood to the body. If this

happens, parts of the body can rapidly become deprived of oxygen. This is a life threatening situation.

Treatment for this kind of pancreatitis includesTrusted Source:

- **Treatment in the intensive care unit (ICU):** There, injected antibiotics can help prevent an infection from developing in the dead tissue.
- **Intravenous fluids:** These help maintain hydration and prevent hypovolemic shock.
- **Feeding tubes:** These provide nutrition, and taking this course early may improve the outcome.
- **Surgery:** In some cases, the medical team may recommend surgical removal of the dead tissue.

The patient will stay in the ICU until there is no longer a risk of organ failure, hypovolemic shock, or sepsis.

3.3 Treating gallstones

If gallstones are responsible for acute pancreatitis, a doctor may recommend surgery or endoscopic retrograde cholangiopancreatography (ERCP)Trusted Source after the pancreatitis improves. ERCP involves using imaging to diagnose and treat health conditions that affect the bile and pancreatic ducts.

After surgery to remove gallstones, a person may need to have a diet that helps reduce blood cholesterol. This is because excess cholesterol encourages the growth of gallstones.

Also, when gallstones have caused pancreatitis, the American Gastroenterological

Association recommends considering surgery to remove the gallbladder to prevent future attacks.

3.4 Treating alcohol misuse

If doctors determine that alcohol misuse has caused acute pancreatitis, they may recommend a treatment program for alcohol misuse.

Endoscopic retrograde cholangiopancreatography[edit]

In 30% of those with acute pancreatitis, no cause is identified. Endoscopic retrograde cholangiopancreatography (ERCP) with empirical biliary sphincterotomy has an equal chance of causing complications and treating the underlying cause, therefore, is not recommended for treating acute pancreatitis.[38] If a gallstone is detected, ERCP, performed within 24 to 72 hours of presentation with successful removal of the stone, is known to reduce morbidity and mortality.[39] The indications for early ERCP are:

- Clinical deterioration or lack of improvement after 24 hours
- Detection of common bile duct stones or dilated intrahepatic or extrahepatic ducts on abdominal CT

The risks of ERCP are that it may worsen pancreatitis, it may introduce an infection to otherwise sterile pancreatitis, and bleeding.

Surgery[edit]

Surgery is indicated for (i) infected pancreatic necrosis and (ii) diagnostic uncertainty and (iii) complications. The most common cause of death in acute pancreatitis is secondary infection. Infection is diagnosed based on 2 criteria

- Gas bubbles on CT scan (present in 20 to 50% of infected necrosis)
- Positive bacterial culture on FNA (fine needle aspiration, usually CT or US guided) of the pancreas.

Surgical options for infected necrosis include:

- Minimally invasive management – necrosectomy through small incision in skin (left flank) or abdomen
- Conventional management – necrosectomy with simple drainage
- Closed management – necrosectomy with closed continuous postoperative lavage
- Open management – necrosectomy with planned staged reoperations at definite intervals (up to 20+ reoperations in some cases)

Other measures[edit]

- Pancreatic enzyme inhibitors are proven not to work.[40]
- The use of octreotide has been shown not to improve outcomes.[41]

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DISCUSSION

In the present study of 50,074 pancreatic cancer patients, acute pancreatitis diagnosed within 90 days before pancreatic cancer diagnosis was associated with lower tumor stage, higher resection frequencies, and better survival. Findings were consistent in direction in both cohorts but more pronounced in Danish than US patients. Acute pancreatitis can be an early marker of pancreatic cancer. This is due to tumor obstruction of the pancreatic duct, leading to a release of digestive enzymes into the pancreatic interstitial space instead of the duct lumen.32 As acute pancreatitis is a painful condition, patients are likely to seek medical care, which could lead to a cancer diagnosis at an earlier stage. This theory is supported by the higher proportion of stage I-II cancer among patients, because Medicare is only eligible for patients aged 65+ (or with certain disabilities). This may have contributed to the higher comorbidity levels and lower resection frequencies in the US cohort. However, when restricting analyses on Danish patients to those aged 66+, there were still substantial differences in comorbidity levels between the populations. Although there were no major differences in comorbidity levels depending on the choice of comorbidity index, our findings suggest that the choice of lookback period may have contributed to the differences. However, neither the choice of comorbidity index nor lookback period had any profound effect on our risk estimates. Also, US physicians may have an incentive to record comorbidities on claims data because of their potential impacts on reimbursement. This may also have contributed to the different prevalence of acute pancreatitis in this study. The prevalence of acute pancreatitis and difference between Danish and US patients agree with previous reports.38–41 Some issues warrant consideration. First, it was unknown if acute pancreatitis was a symptom of pancreatic cancer. We used a proxy of 90 days before cancer diagnosis to capture acute pancreatitis diagnoses. This may have introduced misclassification, as acute pancreatitis in this period may have been caused by other factors. However, sensitivity analyses showed that survival estimates are unlikely to be affected by this. Also, we and others have previously shown that acute pancreatitis diagnoses in the DNPR have high validity.42–45 This mitigates concerns of exposure misclassification, although findings from these studies may not be applicable to the entire Danish population, as only diagnoses from three out of five regions were validated. However, pancreatic cancers registered in the Danish Cancer Registry have not been validated. As differentiation between pancreatic adenocarcinoma, cancer of the papilla Vateri, and distal bile duct cancers can be very difficult, some misclassification may be present. Furthermore, as these cancers can differ with respect to prognosis,46 this could have contributed to our findings. Second, information on tumor stage was missing in 20–25% of the patients, and clinical staging of pancreatic cancer is difficult, particularly when inflammation co-exists.47 Thus, tumor stage may be inaccurately determined in patients not undergoing surgery. However, we had complete information on treatment, which is closely correlated to tumor stage, mitigating this concern. Third, we lacked information on performance status, which is an important determinant of treatment allocation and prognosis.48 However, adjustment for a proxy of frailty did not affect our results. Fourth, acute pancreatitis was rare in Danish patients, limiting the precision of our estimates. Fifth, because we considered treatment to be a time-varying exposure, time-varying confounding may have been introduced. While methods exist for dealing with time-varying confounding, this would require clinical information, which is not readily available. In conclusion, acute pancreatitis diagnosed within 90 days before pancreatic cancer is

associated with lower tumor stage, higher resection frequencies, and improved survival. Our study supports that timely cancer detection in acute pancreatitis patients is important and may improve survival.

3.1 Conclusion

Our understanding of the early events which occur during the evolution of pancreatitis has been hampered by the variable and complex nature of the disease as it occurs clinically as well as the relative inaccessibility of the pancreas to morphological and biochemical monitoring. To overcome these problems, we and other investigators have turned to experimental models of acute pancreatisis which, to varying degrees, resemble the clinical disease. In addition, chronic pancreatitis has been examined in humans, but only long after the disease has become established. As noted in this review, recent findings cast doubt on the previously held concept that proteolytic enzymes are activated within the pancreatic duct or intercellular space. Rather, they suggest that early during the course of acute pancreatitis this activation may occur within the pancreatic acinar cell itself, subsequent to the mixture of digestive enzymes and lysosomal hydrolases. Chronic pancreatitis may also involve premature digestive enzyme activation by lysosomal enzymes, as evidence suggests that lysosomal enzymes and activated digestive enzymes may be released from acinar cells during this disease. Further studies will, of course, be needed to confirm these observations, evaluate their significance, and examine the intriguing possibility that drugs directed at controlling lysosomal enzyme activity may find a place in the prevention and/or treatment of pancreatitis.

There are data to indicate that AP progresses to recurrent AP and then to CP in a disease continuum.33,111–113 Overall, approximately 20% to 30% of patients with AP have a recurrence and approximately 10% develop CP. Progression from AP to CP occurs more frequently with continued exposure to alcohol or smoking and in patients with genetic causes of pancreatitis (hereditary pancreatitis). Patients with pancreatitis should receive appropriate counseling and be referred to rehabilitation services when appropriate. AP has an overall low mortality of approximately 1%.1 The risk of death increases with age, comorbidities, and severe disease; in a recent meta-analysis, the risk of death was highest among patients with both organ failure and infected necrosis.114 Proportional mortality has decreased over time, likely from better intensive and supportive care, clarity on optimal timing of interventions for complications (surgery, endoscopic, or percutaneous drainage), and increased detection of milder cases. Although data are limited, the population mortality has not decreased.10 Patients with CP have shorter survival times than the general population,7,115 but most die from nonpancreatic causes, such as other chronic diseases, cancers, or infections. Mortality is high among patients with pancreatic cancer. The number of deaths each year from pancreatic cancer is approximately equal to the number of new cases, and the 5-year survival rate is approximately 6%.9 Future Directions Much of the research on pancreatic disease has focused on identifying risk factors, clarifying the relationship between risk factors and disease, and discovering better methods for diagnosis, management, and prevention of pancreatitis. Faster, less costly methods of genetic analysis, which are rapidly becoming available, will provide much needed answers to the numerous unsolved questions concerning all types of pancreatic disorders.