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Review Article

Imaging Correlate to the Pathophysiology and Natural History of Alcohol Related Pancreatitis

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Abstract

Alcohol-induced pancreatitis (ALP) presents a growing health concern, with recent rising prevalence. According to the National Institute on Alcohol Abuse and Alcoholism, alcohol abuse is indeed a leading cause of both acute and chronic pancreatitis in the United States. A study found that alcohol accounted for nearly one-third of acute pancreatitis cases in the United States. The impact of ALP extends a substantial burden on health care systems due to the need for medical interventions, hospitalizations, and long-term management of chronic conditions. Binge drinking and high-intensity drinking, characterized by consuming large amounts of alcohol in a short period or engaging in heavy drinking episodes, respectively, exacerbate the risk of pancreatitis and complicate its management.

While the imaging characteristics of ALP may not differ significantly from other common causes of pancreatitis, such as gallstones, identifying its unique natural history and pathophysiology is essential for accurate diagnosis and management. By leveraging the capabilities of various imaging modalities and by being aware of the unique features, radiologists can contribute to the clinical management of this condition. This is a comprehensive review of the pathophysiology, natural history, and imaging of ALP for radiologists to enhance their understanding and diagnostic accuracy.

Keywords

- alcohol-induced pancreatitis
- alcoholic pancreatitis
- binge pancreatitis
- fatty acid ethyl esters
- high-intensity drinking
- pancreatic stellate cells

Introduction

Acute pancreatitis (AP) is a necroinflammatory disorder of the exocrine pancreas, potentially leading to fibrosis and chronic pancreatitis. Alcohol abuse is the leading cause of both acute and chronic pancreatitis in the United States.[1] Alcohol accounts for nearly one-third of AP cases in the United States.[2] Chronic alcohol consumption is the second most common cause of AP after gallstones, accounting for 17 to 25% of cases.[3] In the United States, the annual incidence of AP is estimated to be approximately 40/100,000 persons, making it a significant cause of hospital admissions.[4] The incidence is proportionally highest in males between 35 and 54 years old. Although a single episode of alcohol consumption can induce alcohol-related AP, chronic consumption is a major risk factor for the

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development of pancreatitis. The single most common etiology of chronic pancreatitis (CP) is alcohol-induced CP (ACP), responsible for up to 49.0% of cases.[5]

Research by Yang et al indicates a rise in AP diagnoses despite stable alcohol consumption rates, suggesting drinking patterns as contributors.[6] Binge drinking episodes have increased since 1995, with alcohol consumption in the week before symptom onset affecting AP severity. Alcoholic AP is strongly associated with organ failure and pancreatic necrosis (PNEC), with higher mortality rates than nonalcoholic AP. Patients with alcoholic pancreatitis have a 36% higher mortality rate than the general population, with about half dying within 20 years postonset.[7] According to the Centers for Disease Control and Prevention, alcohol-related deaths have increased over the past 20 years. It has been reported that alcohol-related death numbers increased by 25.5% between 2019 and 2020, the first year of the pandemic.[8]

AP manifests in various ways, including acute attacks, PNEC, recurrent episodes, and eventual progression to CP. Smoking alongside heavy alcohol use increases the risk of malignancy.[9] Pathophysiological mechanisms involve premature enzyme activation, protein plug formation, acinar cell damage from alcohol byproducts, and stellate cell-induced fibrosis.[10,11] Smoking can be an additional trigger for pancreatic injury.[12]

Pathophysiology of Alcohol-Related Acute and Chronic Pancreatitis

According to the American College of Gastroenterology guidelines, alcohol can be considered to be the cause of AP, only if a patient has a history of over 5 years of heavy alcohol consumption ($>$ 50 g/per day).[13] The risk of developing pancreatic injury/pancreatitis appears to be directly proportional to the amount and duration of alcohol intake.[14] Since only 5% alcoholics develop pancreatitis, a search for additional insult (trigger) or individual susceptibility is being explored like genetic and metabolic factors.[15] Complete pathophysiology is not fully understood. More recent evidence suggests that combination of remote events like increased gut permeability to bacterial products such as lipopolysaccharide and more proximal effects like altered pancreatic cholinergic inputs and direct toxic effects of alcohol or the products of its metabolism play a major role in alcoholic pancreatitis.[14,16] The major sites of alcohol-induced injury are acinar cells, pancreatic stellate cells, and small ducts.

Pancreatic Acinar Cell and Function

The pancreatic acinar cell is a major functional unit of the exocrine pancreas.[17] It is a highly specialized structure developed for synthesis, storage, and secretion of digestive enzymes.[18] To protect it from digesting itself, the enzymes are synthesized as inactive precursors (zymogens). These are secreted into small ducts, leading into the main pancreatic duct (MPD). Under normal physiological conditions, digestive enzymes are activated only once they have reached the duodenum.[17]

Alcohol Metabolism and Its Effect on the Pancreas

Pancreatic Acinar Cells

Alcohol metabolism in the pancreas induces acinar cell toxicity and triggers inflammation. Chronic alcohol intake leads to enzyme activation within cells, increasing the risk of autodigestive damage.[15] Metabolism generates acetaldehyde, acetate, and reactive oxygen species, while nonoxidative pathways produce fatty acid ethyl esters (FAEEs). These metabolites disrupt intracellular processes, causing mitochondrial dysfunction, impaired autophagy, and cell death.[19] Elevated FAEE levels contribute to sustained calcium elevations and acinar cell injury. Necrotic cell death exacerbates inflammation, worsening pancreatic injury. Alcohol also affects pancreatic ducts by reducing secretions, increasing viscosity, and forming protein plugs, potentially leading to ductal blockage and calcification.[7]

Pancreatic Stellate Cells

Pancreatic stellate cells (PSCs) are key in pancreatic fibrogenesis and remodeling.[20] They are activated by alcohol, its metabolites, and cytokines released during alcohol-induced pancreatic necroinflammation. Activated PSCs transform into myofibroblast-like cells, triggering inflammatory responses and releasing excessive extracellular matrix proteins, which create a proinflammatory microenvironment that promotes pancreatic fibrosis.[11] PSCs also play a role in regeneration after necrotizing pancreatitis. ►**Table 1** and ►**Flowchart 1** show the changes happening.

Natural History of Pancreatitis

Pancreatitis is clinically diagnosed by severe abdominal pain and elevated blood amylase levels. The disease can progress from an initial AP event (sentinel acute pancreatitis event hypothesis) to recurrent or chronic inflammation, leading to fibrosis.[21] A significant delay typically occurs between the start of heavy drinking and the first manifestation of alcoholic pancreatitis, often requiring more than 80 g of alcohol per day for 6 to 12 years.[22] Abstinence after the first episode can prevent recurrent attacks.[23]

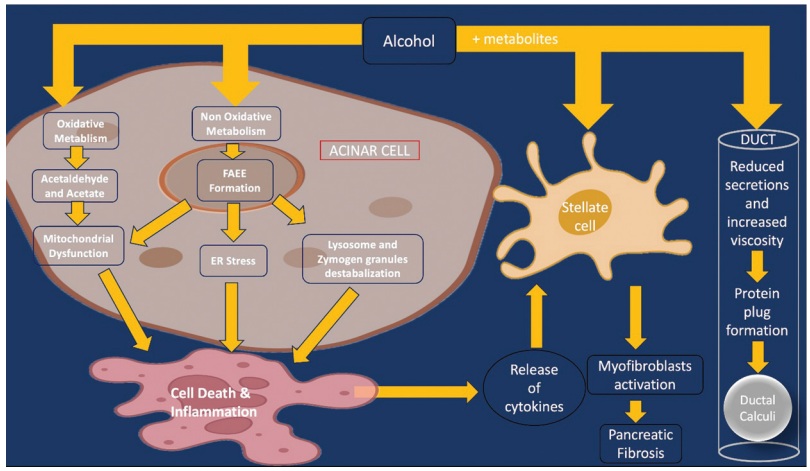
Progression of Alcoholic Pancreatitis

After the first episode of alcoholic pancreatitis, 25 to 50% of patients develop acute recurrent pancreatitis (ARP), with 42 to 80% of those progressing to ACP.[24] Mild initial attacks result in fewer long-term changes, but even a single episode can cause chronic changes. A meta-analysis found a 10% prevalence of CP after an initial acute episode, rising to 36% for those who experience recurrent AP (RAP).[25] The risk is higher among smokers, alcoholics, and men.[26] ►**Flowchart 2** depicts the natural history of alcoholic pancreatitis and its progression to CP.

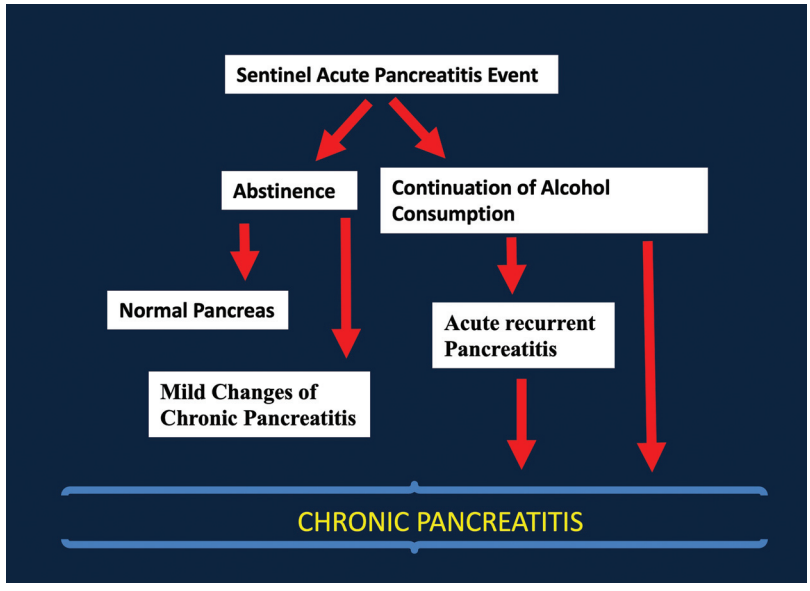
Table 1 Various events seen at the microscopic level in the pancreatic gland

Key sites of injury and events		
Acinar cell	**Duct level**	**Stellate cell activation**
Mitochondrial dysfunction	Increased viscosity of secretions	Conversion to myofibroblast-like cells
Decreased cellular NAD +/NADH balance	Precipitation and formation of protein plugs	Release of extracellular matrix proteins
Increased Ca2+ Levels	Calcification	Initiate pancreatic fibrosis
Premature activation of zymogens		
Reduced ATP ER stress Altered autophagy		

Abbreviations: ATP, adenosine triphosphate; ER, endoplasmic reticulum; NAD +, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydrogen.



Flowchart 1 Pathophysiology of alcoholic pancreatitis at cellular and ductal levels.



Flowchart 2 Natural history of alcoholic pancreatitis.

Drinking Pattern

A standard drink has been defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as one that contains 14 g of pure alcohol (about 0.6 fluid oz or 1.2 tablespoons), as is found in one 12-oz beer, one 5-oz glass of wine, or one 1.5-oz shot of distilled spirits.[27,28]

Typically, alcohol use disorder (AUD) is a long-term pattern of alcohol use that becomes difficult to control. However, the number of drinks a person consumes and the rate at which they consume can influence the outcome. Episodic drinking can escalate the blood alcohol content to dangerous, even life-threatening levels.

Though there is no seasonal association, it has been shown to increase significantly during the holidays, including Christmas and New Year's.[29] Adolescents, although they may drink less often, tend to consume higher quantities of alcohol on these occasions compared with adults.[30–32]

Binge Drinking

NIAAA defines binge drinking as a pattern of drinking that brings blood alcohol concentration to 0.08 g per deciliter (0.08%) or higher. This typically occurs after a woman consumes 4 drinks or a man consumes 5 drinks in a 2-hour time frame.[33]

It is uncertain if and how much alcohol is necessary during a binge to induce an attack of "AP" in persons with established or without chronic alcoholic pancreatitis, but there is evidence that bingeing or acute withdrawal after bingeing precipitates an attack.[34] Typically, and particularly in binge drinkers, an attack begins 12 to 48 hours after cessation of drinking ("the afternoon after the night before") (►**Fig. 1**).

Multiple studies indicate that patients who develop alcohol-induced pancreatitis (ALP) frequently report short-term heavy drinking or bingeing. In a Swedish study by Sadr Azodi et al, it was found that there was a 52% increased risk of AP for every increment of five standard drinks of spirits consumed on a single occasion.[35]

The risk of AP was associated with the amount of spirits consumed on a single occasion but not with wine or beer consumption. In a multicenter prospective study done in Munich during Oktoberfest, despite a sale of 6.6 million liters of beer in 16 days, the incidence of acute attacks of alcoholic pancreatitis did not increase.[36]

Extreme Binge Drinking or High-Intensity Drinking

Research indicates that a substantial portion of binge drinkers often drink at levels two or three times the binge threshold, resulting in high peak blood alcohol concentrations. There is no common consensus, and is defined as at least twice the typical binge drinking threshold (i.e., 10+ drinks) or twice the gender-specific binge threshold (i.e., 8+ for women/10+ for men).[37] High-intensity drinking is of particular concern because of the adverse consequences associated with it (►**Fig. 2**).

The causal relationship between single instances of high-intensity drinking in the absence of chronic alcohol consumption and the onset of AP remains unclear. Cubillan and Raphael

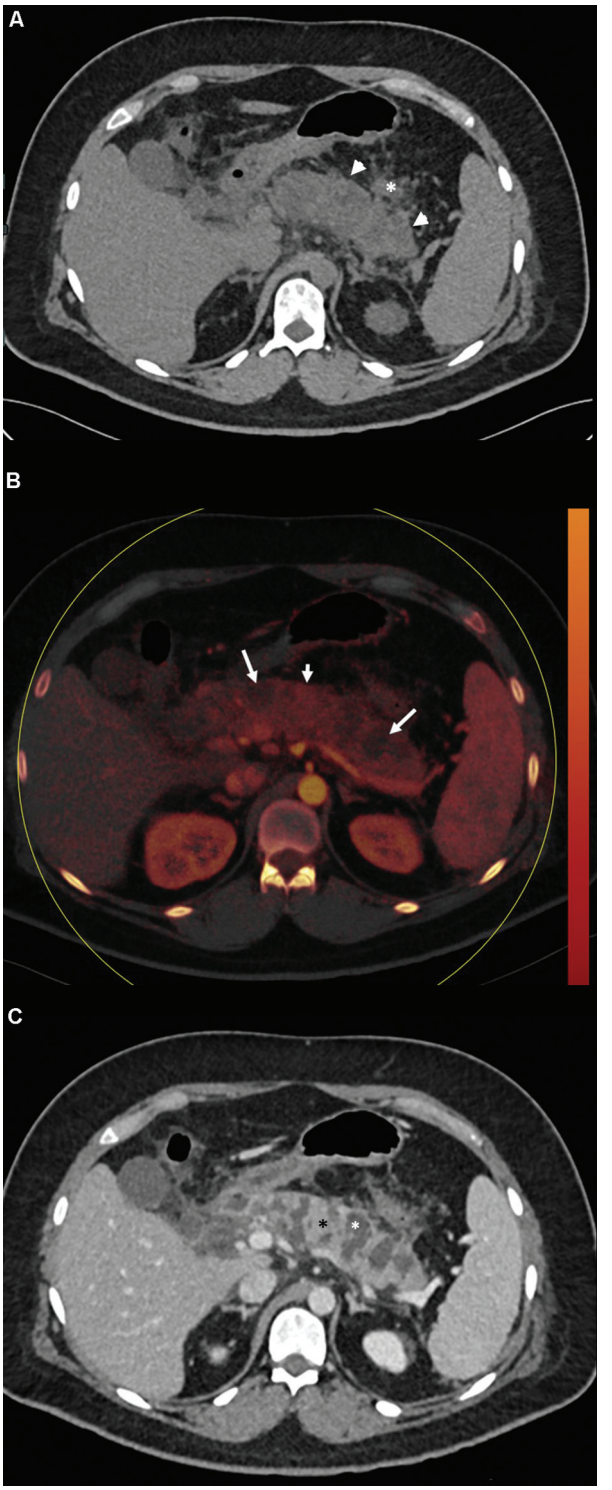


Fig. 1 Dual-energy computed tomography (CT) in a 27/M with acute alcohol-related necrotizing pancreatitis due to binge drinking. (**A**) Noncontrast-enhanced CT (NECT) in axial plane done 72 hours after acute pain following alcohol binge with a history of alcohol abuse, shows bulky pancreas (white arrowhead) with heterogeneity. The white star represents peripancreatic edema. (**B**) Dual-energy iodine image (late arterial phase) showing multiple focal areas of lack of iodine/enhancement (long white arrow). The short white arrow represents iodine/enhancement in the intervening areas. (**C**) Contrast-enhanced CT (CECT) (portovenous phase) at the same level as B shows bulky pancreas with multiple necrotic areas (white star) alternating with enhancing areas (black star) corresponding to image B.

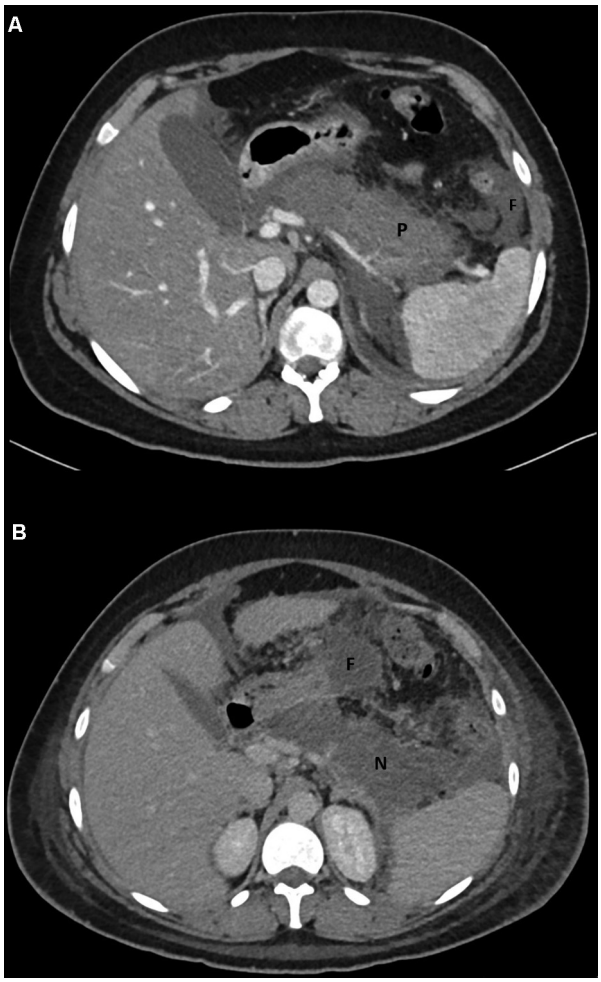


Fig. 2 Computed tomography (CT) in a 20/M with acute alcohol-related necrotizing pancreatitis due to high-intensity drinking. (**A**) Contrast-enhanced CT (CECT**)** in axial plane shows bulky pancreas (P) and hypoenhancement of the parenchyma. No definite necrotic areas could be identified. F represents peripancreatic acute fluid collection. (**B**) CECT done at 1 week follow-up, shows necrosis of the entire body and tail with nonenhancement (N). F represents peripancreatic acute fluid collections.

documented a case of acute necrotizing pancreatitis following transcoronary alcohol infusion during cardiac ablation for recurrent atrial fibrillation.[38] The patient reported lifelong abstinence from alcohol and tobacco use, with no other identifiable cause of pancreatitis. Approximately 9 mL of pure alcohol was administered during the procedure, equivalent to the blood alcohol level typically resulting from 8 to 9 drinks in an average man. Further investigation is required to corroborate or refute this association.

Role of Imaging

There are no specific imaging features in the pancreatic gland to distinguish alcoholic pancreatitis from other etiology. Diagnosis relies on a clinical history of chronic alcohol use. Due to the lack of distinct imaging features, it is important to use a comprehensive diagnostic approach, integrating clinical, laboratory, and imaging data to accurately identify and manage alcoholic pancreatitis. Multiple imaging modalities are available including ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS).

Ultrasound

Sonography in patients with AP plays a role in the initial evaluation of suspected or confirmed AP.[39] However, it can be challenging due to difficulties in visualizing the pancreas caused by ileus and bowel gas interference. Sick patients may not cooperate, further limiting its role. Its primary role in imaging AP is limited to detecting cholelithiasis and choledocholithiasis.

CT Scan

Contrast-enhanced CT (CECT) is the most used imaging modality for the diagnosis and staging of AP.[40] CT can visualize characteristic findings like pancreatic enlargement, peripancreatic inflammation, and fluid collection. CT is the most accurate to detect calcifications. The protocol has been outlined in ►**Table 2**.

Table 2 CT scan protocols to be used for evaluation of pancreatitis

CT scan protocol (64-slice scanner)		
Sequence	**Timing from tigger[a]**	**Purpose**
NECT		Look for calcification
Portovenous phase	65 seconds	Look for contrast enhancement in the gland and vessels
Optional sequences		
Early arterial phase	6 seconds	Suspected bleed
Late arterial phase	15 seconds	When you suspect necrosis or vascular complications
Dual energy (iodine image)	Can be used during late arterial or venous phase	When you suspect necrosis

Abbreviations: CT, computed tomography; NECT, noncontrast-enhanced computed tomography.
[a]Trigger is based on 100 HU achieved in the aorta after contrast injection for a 64-slice CT scanner independent of the vendor.

Table 3 MRI protocols to be used for evaluation of pancreatitis

MRI and MRCP sequences	
T2W	Single-shot fast spin-echo/HASTE
MRCP	Thick-slab high TE T2-weighted half-Fourier RARE Thin high-resolution high TE T2W 3D FS
T1W	DIXON T1W FS
Diffusion	B 50-800 and ADC
Post-gadolinium	Dynamic T1W FS 3D gradient echo Delayed 2D T1W FS axial

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; ADC, apparent diffusion coefficient; FS, fat-suppressed; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; T1W, T1-weighted; T2W, T2-weighted.

MRI

MRI offers diagnostic capabilities similar to those of CT, with additional intrinsic advantages including lack of ionizing radiation and exquisite soft tissue characterization.[41] MRI emerges as an alternative imaging modality in patients with severe renal dysfunction during the acute phase. It has the added advantage of evaluating pancreatic and biliary ductal systems. Magnetic resonance cholangiopancreatography (MRCP) and secretin MRCP (S-MRCP) are especially useful in CP. It is superior to a CT scan in detecting a mild form of pancreatitis than CECT.[42] The typical sequences used in MRI/MRCP have been outlined in ►**Table 3**.

Mild Acute Pancreatitis

In 85% of patients, the inflammation is mild and self-limiting and typically resolves within a week. The initial episode of alcoholic pancreatitis typically presents as acute interstitial edematous pancreatitis, seen as an enlarged pancreas and peripancreatic fat stranding and fluid on imaging.

On ultrasound, AP typically presents as an enlarged hypoechoic gland, with the ability to visualize peripancreatic acute fluid collections. However, ultrasound imaging lacks sensitivity in detecting necrosis.

On CT, the pancreas may appear enlarged and hypodense on the noncontrast images, usually with diffuse involvement, although focal manifestations are occasionally observed (►**Fig. 3**).

On MRI, T2-weighted images typically show an enlarged pancreas with hyperintensity. T1-weighted images with fat suppression may exhibit normal signal intensity or more hypointense. Peripancreatic fat stranding, a hallmark feature of AP, is optimally visualized using T1 gradient-echo and T2 fat-suppressed sequences. Diffusion-weighted imaging (DWI) shows greater diffusion restriction in AP patients compared to healthy individuals.[43]

Upon administration of contrast agents, both CT and MRI typically demonstrate homogeneous enhancement of the viable edematous parenchyma, albeit less intense than normal. However, the presence of edema may induce slight heterogeneity in enhancement patterns.

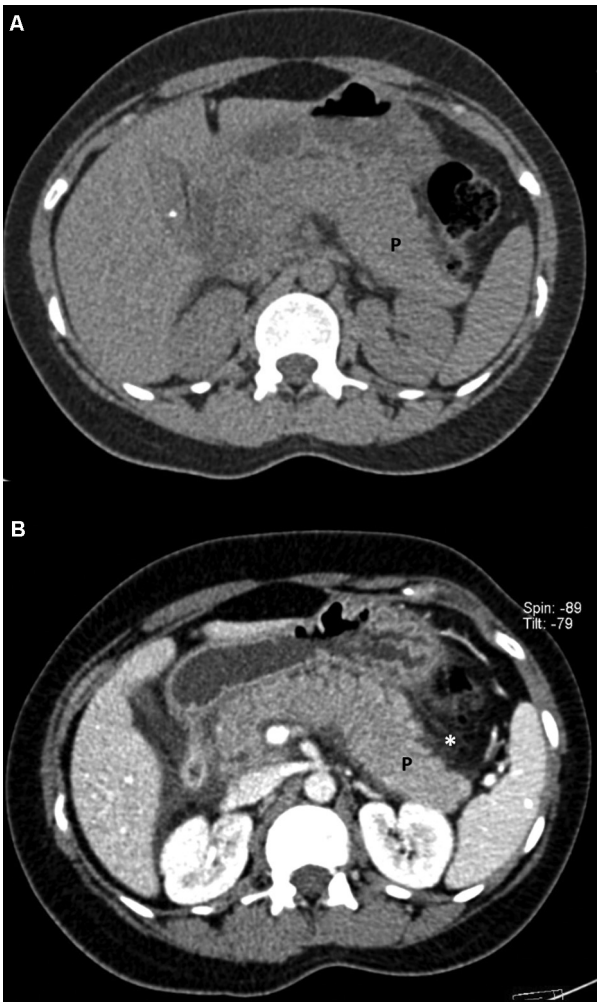


Fig. 3 Computed tomography (CT) in acute alcohol-related interstitial pancreatitis with history of alcohol abuse. (**A**) Noncontrast-enhanced CT (NECT) in axial plane shows a bulky pancreas [P] with normal density. White arrow is a gallstone in a partially distended, normal-looking gallbladder. (**B**) Contrast-enhanced CT (CECT) at the same levels shows bulky and edematous pancreatitis (P) with parenchymal enhancement. White star (*) represents peripancreatic fat stranding and edema.

Peripancreatic inflammation commonly manifests as peripancreatic fat stranding and fluid accumulation. Acute peripancreatic fluid collections are typically unencapsulated and conform to the contours of the peripancreatic fascial planes that envelop them. These collections often exhibit spontaneous resolution, with approximately 5 to 15% persisting beyond the initial 4 weeks and potentially progressing into pseudocysts.

These collections vary in size and shape, frequently clustering adjacent to the pancreas and often occupying the lesser sac or anterior pararenal space. In some cases, collections may extend to remote areas such as the pelvis or mediastinum.

Cross-sectional imaging, such as CT scans and MRI, reveal these collections as uniformly fluid-filled with a lack of

capsules. They typically appear hypodense on CT scans and demonstrate T1 hypointensity and T2 hyperintensity on MRI.

Severe Acute Pancreatitis

Approximately 20% of patients develop severe AP, in which the mortality rate is much higher due to complications from the systemic inflammatory reaction.[44]

The amount of alcohol consumed may be an important determinant of the severity of the first alcoholic AP episode. Jaakkola et al found that in patients having their first alcoholic AP episode, the reported 2-month alcohol consumption correlated significantly with the number of positive Ranson criteria, the length of the hospital stay, and more complications.[45]

In a study by Papachristou et al, alcohol consumption was identified as a significant risk factor for the development of PNEC.[46] Necrotizing pancreatitis represents the severest form of AP with a high mortality rate ranging from 15 to 30%,[47] due to complications from the systemic inflammatory reactions. Necrosis can present in three configurations: combined PNEC and peri-PNEC (75%), peri-PNEC alone (20%), and PNEC alone ($< 5\%$). Patients with peri-PNEC alone have lower morbidity and mortality rates. The various imaging findings are summarized in ►**Table 4**.

Necrotizing pancreatitis shares similarities with interstitial edematous pancreatitis, but it presents additional findings indicative of necrosis. On noncontrast-enhanced CT, the pancreas may exhibit hyperdensity or heterogeneity with hyperdense areas, often attributed to hemorrhage. The process of PNEC evolves gradually and may not become apparent until 72 hours to a week following the initial event. While imaging is typically recommended after 72 hours, CT scans are frequently performed early in cases of acute abdomen in the emergency room. In such scenarios, dual-energy CT scans can aid in detecting ischemic regions at risk of necrosis using iodine imaging. The iodine image shows reduced iodine uptake/enhancement in the area around the necrosis.[48]

Following the first week of presentation, areas of impaired perfusion and necrosis mature, appearing as confluent nonenhancing regions on imaging. Peripancreatic fat necrosis initially presents with a heterogeneous appearance on CECT, with later stages revealing disintegrating fat more prominently (►**Fig. 4**).

Out-of-phase T1-weighted imaging can demonstrate peripancreatic fat necrosis by eliciting a signal drop. On MRI, necrotic parenchyma or peripancreatic tissue is hypointense on T1-weighted images and nonenhancing on gadolinium-enhanced T1-weighted imaging. On T2-weighted images, necrotic tissue is typically hypointense, though it can be hyperintense if liquefied. Abnormal hyperintensity on T1-weighted fat-suppressed images corresponds to hemorrhage, necrosis, and is usually associated with an extremely poor prognosis (►**Fig. 5**).

Noncontrast MRI is superior to noncontrast CT for the detection of PNEC.[47] MRI can distinguish between necrotic pancreatic and peripancreatic tissues and adjacent fluid collections or hemorrhage, whereas differentiating between necrosis and adjacent fluid may be difficult with CT.

Persistent collections of fluid and necrotic material can develop in necrotizing pancreatitis and should not be called fluid collections, but rather acute necrotic collections or walled-off necrosis, because they contain solid necrotic material.[49] The necrotic collections can communicate with the pancreatic duct or may sometimes rupture or have fistulous communication with the bowel.

Pancreatic Regeneration following Necrosis

The process of pancreatic regeneration is well-known after AP. After PNEC, the morphological and functional regeneration is associated with the normalization of glycemia and the exocrine function.[50]

In normal tissue, only a few stellate cells and myofibroblasts are present around ducts and ductules. In contrast, numerous stellate cells and myofibroblasts are detected after AP exhibiting increased proliferative activity and appear to participate in regeneration.[20] ►**Fig. 6** is a case involving the phenomenon of pancreatic regeneration following necrosis. This intriguing aspect of the pancreas' capability to regenerate after experiencing necrotic damage warrants further investigation and understanding in the medical community.

Table 4 Multimodality imaging changes seen in acute pancreatitis

Imaging changes in acute pancreatitis		
Acute interstitial pancreatitis	**Acute necrotizing pancreatitis**	**Peripancreatic fat necrosis**
Pancreas: CT: Enlarged and hypodense on noncontrast T2W: Enlarged and hyperintense DWI: Restricted diffusion Peripancreatic region: - Peripancreatic fat stranding - Acute peripancreatic fluid collections	NECT: The pancreas may appear heterogeneous and slightly hyperdense due to hemorrhage MRI: T1W – hypointense Hyperintense if hemorrhage MRI T2W: Heterogeneous CECT/MR contrast: Nonenhancing regions and necrotic fluid collection later Dual-energy CT: Lack of iodine enhancement in necrotic areas	Mixed intensity depending on the degree of necrotic material Hemorrhage can be differentiated

Abbreviations: CECT, contrast-enhanced computed tomography; CT, computed tomography; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; NECT, noncontrast-enhanced computed tomography; T1W, T1-weighted; T2W, T2-weighted.

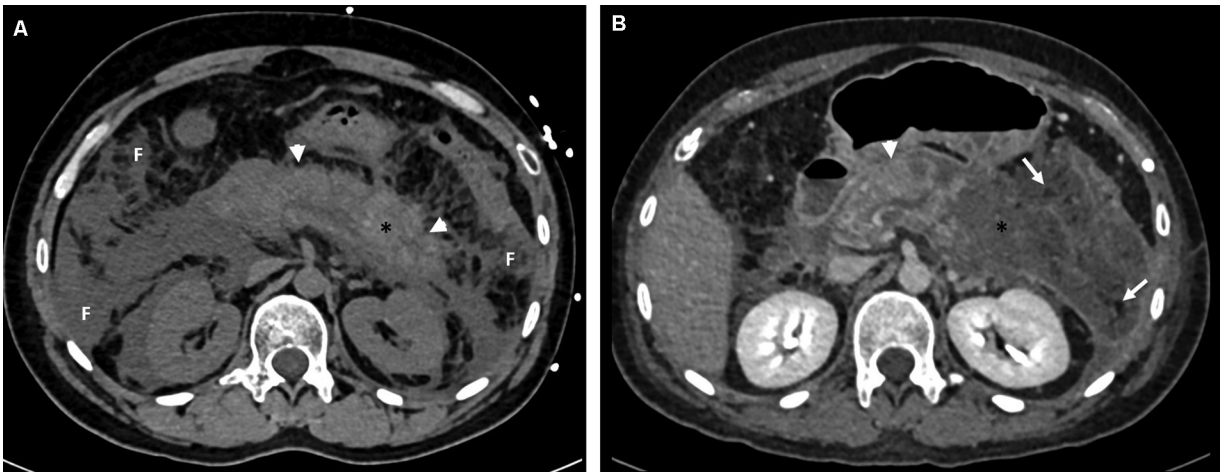


Fig. 4 Computed tomography (CT) in a 32 /M with acute alcohol-related necrotizing pancreatitis with extrapancreatic fat necrosis with history of alcohol abuse. (**A**) Noncontrast-enhanced CT (NECT) in axial plane shows a bulky pancreas [white arrowhead] and raised density in the distal body (black star). (**B**) Contrast-enhanced CT (CECT) at the same levels after a week shows necrosis in the distal body (black star), corresponding to A. Peripancreatic fluid in relation to the distal body has increased and now shows fat necrosis (white arrow). White arrowhead shows normal enhancement in the proximal body of pancreas.

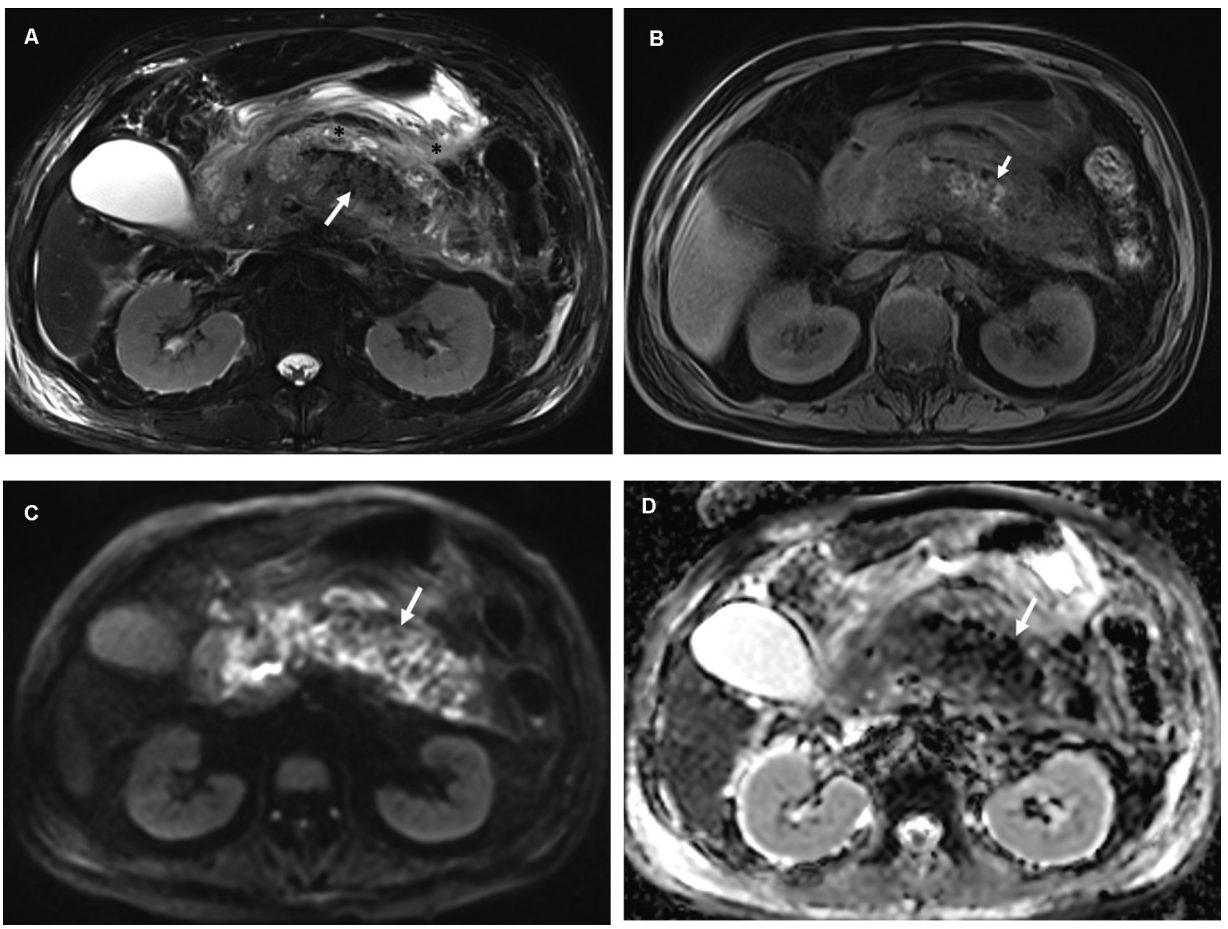


Fig. 5 Magnetic resonance imaging (MRI) in a 50/M with acute alcohol-related necrotizing pancreatitis and hemorrhage. (**A**) T2-weighted (T2W) fat-suppressed (FS) in axial plane shows a bulky pancreas with hypointense areas in the body (white arrow). The black star represents peripancreatic fluid. (**B**) T1W FS in axial plane shows hyperintense areas (white arrow), corresponding to the hypointense areas in image A. (**C**) Diffusion-weighted imaging (DWI) in axial plane shows these areas to be heterogeneous (white arrow). (**D**) Apparent diffusion coefficient (ADC) in axial plane shows these areas are hypointense (white arrow).

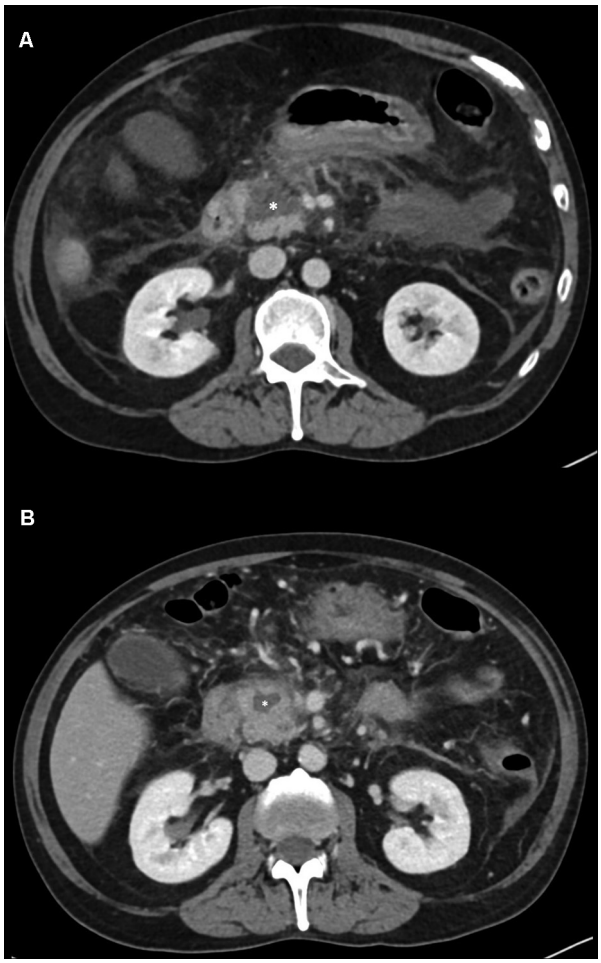


Fig. 6 Computed tomography (CT) showing pancreatic regeneration in alcohol-related necrotizing pancreatitis. (**A**) Contrast-enhanced CT (CECT) in axial plane shows a lack of enhancement in a segment of the pancreatic head (white star), consistent with pancreatic necrosis. (**B**) Follow up CECT done after a few weeks in the same patient shows an increase in areas of parenchymal enhancement and reduction of necrotic area (white star). This is due to parenchymal regeneration.

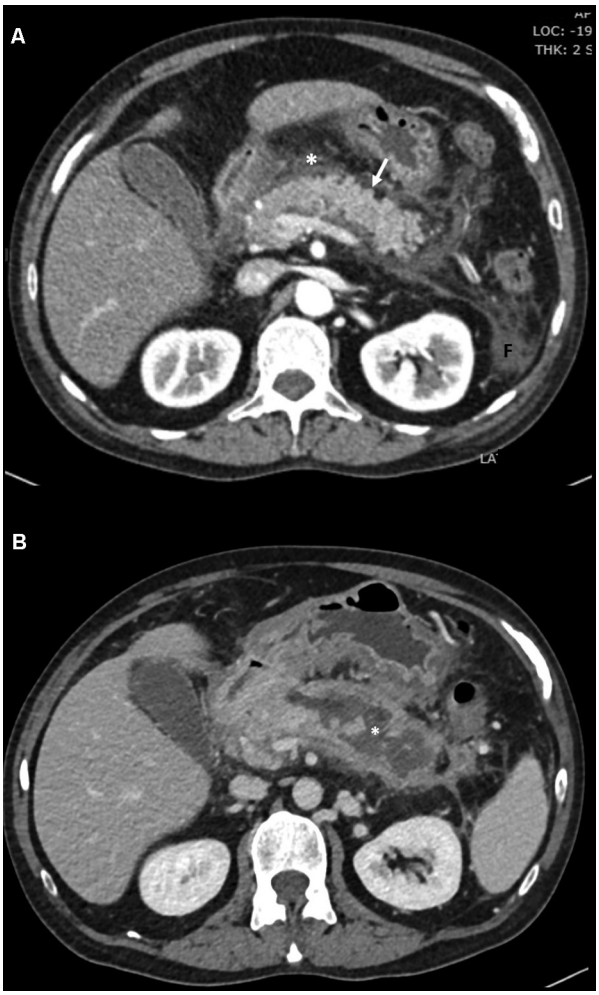


Fig. 7 Computed tomography (CT) in a 55/M with alcohol-related recurrent acute pancreatitis (RAP), due to a continuous history of alcohol abuse. (**A**) Noncontrast-enhanced CT (NECT) in axial plane shows the pancreas of normal bulk and enhancement but has peripancreatic fat stranding (white arrow) suggesting mild acute pancreatitis. (**B**) Same patient reported to the emergency room (ER) after 6 years due to acute pancreatitis. Contrast-enhanced CT (CECT) in axial plane shows necrotic regions with acute fluid collections (white star).

Acute Recurrent Pancreatitis

Clinically, ACP is a multifaceted disease characterized in most instances chronologically by two phases, (1) an early stage of ARP, characterized by episodes of AP that occurs on more than one occasion, due to continued drinking (►**Fig. 7**), and (2) a late stage of CP, dominated by steatorrhea and diabetes pancreatic calcification.[51] In the clinical course, a phase comes, when patients develop early changes of CP with pancreatic insufficiency. If the patient continues the alcohol abuse, the deterioration can be marked with rapid progression to advanced changes.[52]

Alcohol-Related Chronic Pancreatitis

ACP arises from multiple factors, with disease progression risk closely tied to the continuation of alcohol and tobacco use.[24] Spicak et al, in their study, identified sociobehavioral factors influencing the development of ACP, including early initiation of drinking and smoking, high alcohol consumption at a young age, and lower educational attainment.[53]

Observations by Lankisch et al revealed that CP predominantly occurred in individuals with a history of alcoholism, irrespective of the severity of the initial pancreatitis episode or cessation of alcohol and nicotine intake.[54] Furthermore, they noted that 38% of patients developed CP within 2 years following survival of a second pancreatitis attack, with smoking significantly heightening the risk of progression from acute to chronic alcoholic pancreatitis.

Histologically, chronic alcoholic pancreatitis is characterized by fibrosis, chronic inflammation, and acinar cell depletion. Early changes in CP are reversible but can progress to irreversible and advanced stages. Notable features of established and advanced CP include pancreatic atrophy, fibrosis, ductal distortion and strictures, calcifications, and dysplasia.[55] Clinically, patients typically present with pain

syndromes, pancreatic exocrine dysfunction, and pancreatic endocrine dysfunction. Alcohol consumption accelerates the progression of pancreatic duct stones (PDS) formation in patients with CP. Shorter periods between diagnosis of CP and PDS formation were found in ACP patients than in non-ACP patients[56] (►**Fig. 8**).

There are multiple classifications to evaluate CP like Cambridge and M-ANNHEIM.[57] The Cambridge classification was developed for endoscopic retrograde cholangiopancreatography (ERCP) and has been used in MRCP. However, it only considers ductal changes and parenchymal observations are lacking. Currently, no standardized reporting system for CT, MRI, or MRCP is universally used. Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) has proposed a new reporting standard to promote standardized reporting for CT and MRI.[58]

MRI combined with MRCP is an excellent modality for assessing clinically suspected CP.[59] The changes have been summarized in ►**Table 5**. MRI demonstrates parenchymal abnormalities like atrophy and reduced signal intensity (►**Fig. 9**). Normal pancreas has high signal intensity on fat-suppressed T1-weighted images due to excess protein. Chronic inflammation and fibrosis diminish the proteinaceous fluid content of the pancreas, resulting in the loss of the usual high signal intensity on T1-weighted fat-suppressed images. The signal change can be segmental or diffuse. Volume depletion reduces the pancreas anterior-posterior diameter.[60]

DWI gives MRI a distinct benefit over other imaging modalities for evaluating functional information. The presence of parenchymal fibrosis in CP causes diffusion restriction and results in lower apparent diffusion coefficient (ADC) values on baseline DWI. The ADC values reveal either delayed peak after secretin stimulation or lower peak values in patients with early CP, which may help depict CP in its earliest stage.[61–63] ADC values further reduce with acute attacks in the background of CP (►**Fig. 10**).

Contrast dynamic MRI has been found useful in evaluating CP. The pancreas has a rich arterial capillary blood supply. Serial contrast-enhanced MRI reveals arterial peak enhancement and diminished early venous enhancement in the normal population. Arteriolar damage during AP attacks and pancreatic fibrosis is responsible for the reduced blood vessel density. In cases with CP, pancreatic parenchymal enhancement is delayed. Progressive enhancement, peaking on the portal venous phase, indicates fibrosis.[64,65]

MRCP provides a noninvasive means of visualizing the pancreatic and biliary ductal system. MRCP leverages the extended T2 relaxation time of pancreatic secretions or bile to delineate ductal structures, offering a safer and more accessible alternative to ERCP. MRCP is accurate in depicting strictures of the pancreatic duct or biliary tract.

Chronic alcoholic pancreatitis leads to initial abnormalities affecting the side branches before involving the MPD. Periductal fibrosis can cause a dilated MPD (►**Fig. 10**).

As the disease progresses, various changes are seen. The presence of a solitary stricture in the MPD prompts consideration of neoplasm or pseudocyst in the differential

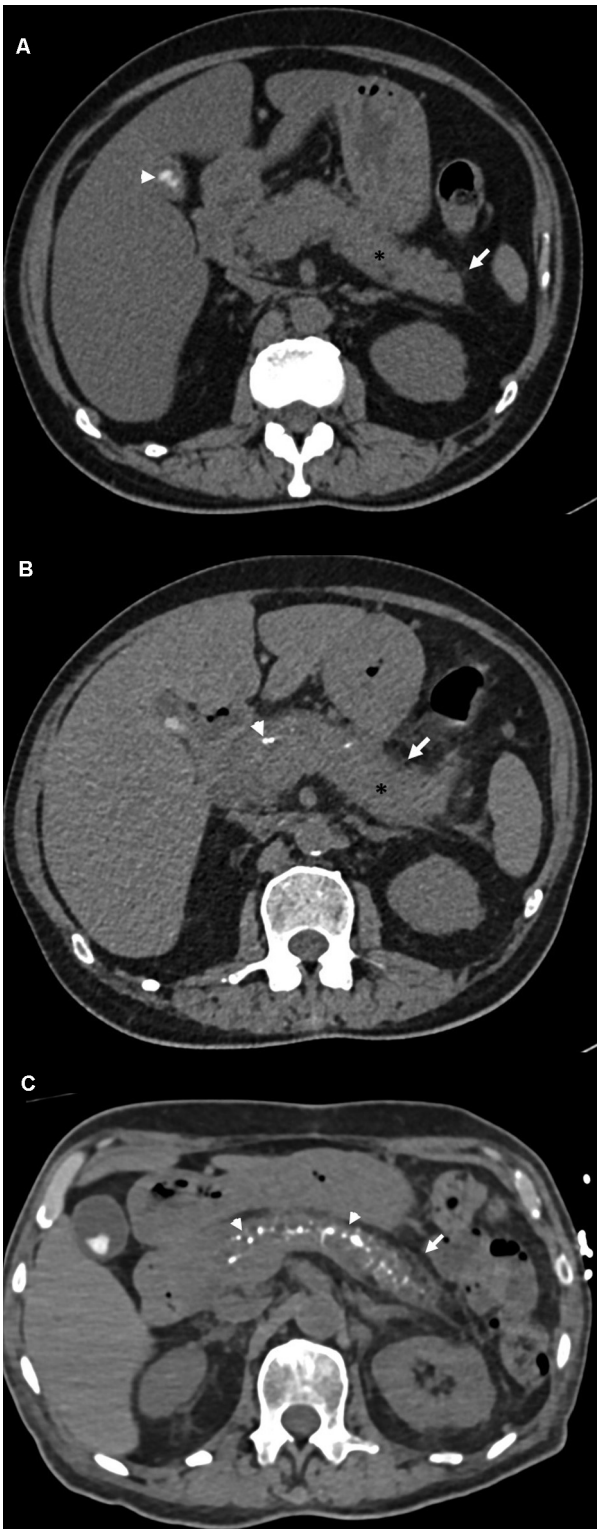


Fig. 8 Computed tomography (CT) in 62/M showing alcohol-related rapid progression to chronic pancreatitis in 2 years, due to a continuous history of alcohol abuse. (**A**) Noncontrast-enhanced CT (NECT) in axial plane shows the pancreas of normal bulk but has peripancreatic fat stranding (white arrow) suggesting mild acute pancreatitis. (**B**) NECT of the same patient done after 1 year following a binge, shows increased bulk of the pancreas (black star) with significant peripancreatic fat stranding (white arrow). New calcification is seen (white arrowhead). (**C**) NECT of the same patient done after 18 months shows reduced bulk of the pancreas and significantly increased calcifications (white arrowhead).

Table 5 MRI imaging changes seen in chronic pancreatitis

Changes in chronic pancreatitis on MRI	
Early changes	**Late changes**
Parenchymal: - Low-signal intensity pancreas on T1-weighted fat-suppressed images - Decreased and delayed enhancement after IV contrast administration	Parenchymal: - Parenchymal atrophy - Pseudocysts
Ductal: - Dilated side branches irregular contouring and stricture	Ductal: Main ductal changes: - Diffuse duct dilatation and loss of normal tapering - Irregularities in the duct wall - Segmental stenosis and dilatation - Communication with pseudocyst Intraductal calcifications

Abbreviations: IV, intravenous; MRI, magnetic resonance imaging.

diagnosis. Stenosis associated with pancreatitis tends to be shorter, smoother, and more symmetric compared to those seen with neoplastic conditions.[66] There can be associated stricture of common bile duct due to chronic changes in the head (►**Fig. 11**). Differentiation from malignancy in such a situation can be difficult.

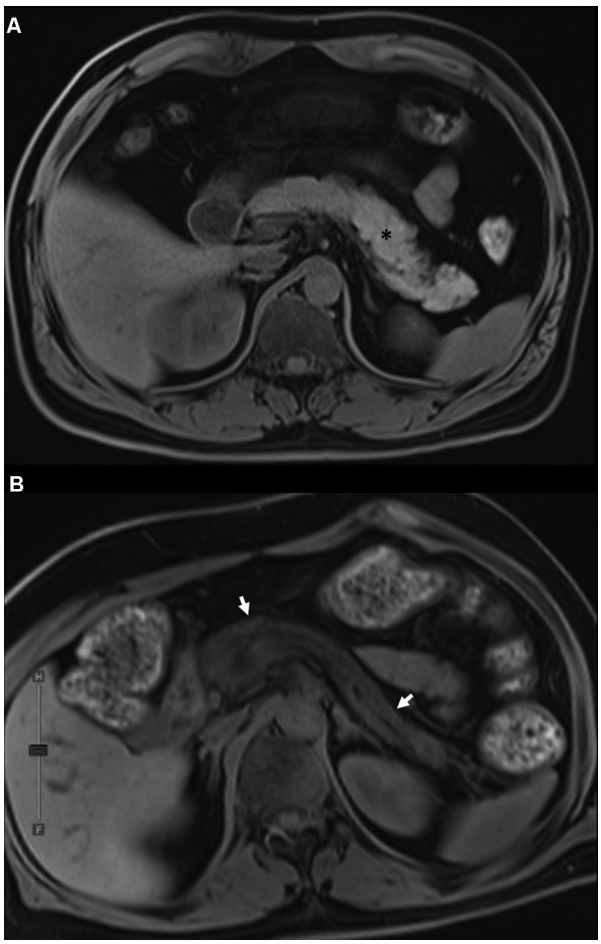


Fig. 9 Normal and abnormal appearance of the pancreas on T1-weighted (T1W) fat-suppressed (FS) magnetic resonance imaging (MRI). (**A**) Normal pancreas in axial plane shows a normal bright signal of the pancreas (black star), as compared to the spleen. (**B**) Alcohol-related chronic pancreatitis in TRA shows reduced volume of the pancreas and the gland is of low signal intensity (white arrow) as compared to the spleen.

Pancreatic calcifications can be seen on X-rays in advanced stages, which is indicative of chronic inflammation and fibrosis. CT scan is very accurate in demonstrating the stones (►**Fig. 8**). MRI can demonstrate intraductal calculi if there is fluid around them. High-resolution thin T2-weighted images are helpful for this evaluation (►**Fig. 12**).

Additional Imaging Techniques Used for Problem-Solving

S-MRCP: S-MRCP can estimate pancreatic exocrine function, and at the same time an increased number of side branch ectasia and/or decreased pancreatic duct compliance after secretin stimulation can be demonstrated as early imaging findings of CP.

EUS: The proximity of the EUS probe to the pancreas results in superior spatial resolution compared to CT scan and MRI. The normal pancreas has a homogeneous fine granular echo-pattern (salt and pepper appearance), with a thin and regular MPD. "EUS criteria" have been developed for CP. The criteria can be divided into pancreatic duct findings and parenchymal findings. Parenchymal findings include hyperechoic foci, hyperechoic strands, lobularity, heterogeneity, shadowing calcifications, and cysts. Pancreatic duct findings include dilation (>4 mm in the head, >3 mm in the body, >2 mm in the tail), irregularity, hyperechoic duct margins, and visible side branches.[67]

ERCP: Over the last 15 years, ERCP has evolved from a diagnostic tool to one that is primarily used to provide therapy. When the diagnosis of CP is sought, ERCP should be reserved for patients in whom the diagnosis is still unclear after noninvasive methods.[68] ERCP may not detect changes *in less advanced CP*. Benefits of ERCP over MRCP include evaluating communicating pseudocysts and pancreatic duct leaks.

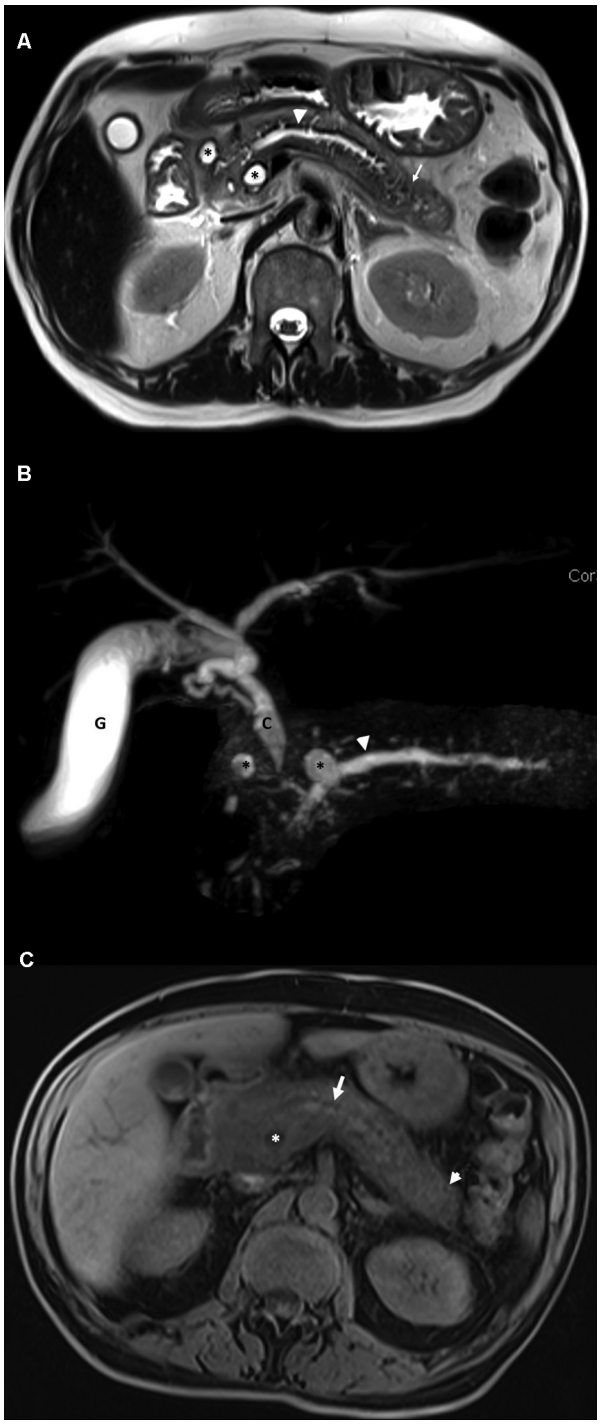


Fig. 10 Magnetic resonance imaging (MRI) in 62/M with recurrent acute alcohol pancreatitis showing early chronic changes on MRI. (**A**) T2 HASTE (half-Fourier acquired single-shot turbo spin echo) in axial plane shows bulky pancreas (white arrow) with a dilated pancreatic duct (white arrowhead) in the body. The black star represents pseudocysts. (**B**) Three-dimensional (3D) maximum intensity projection (MIP) magnetic resonance cholangiopancreatography (MRCP) shows dilated and tortuous pancreatic duct with few early dilatations of side branches (white arrowhead). C is common bile duct (CBD), G is gallbladder. (**C**) T1-weighted (T1W) fat-suppressed (FS) in axial plane shows the pancreas as low signal intensity (white arrowhead). The white arrow is the pancreatic duct. The white star is a pseudocyst.

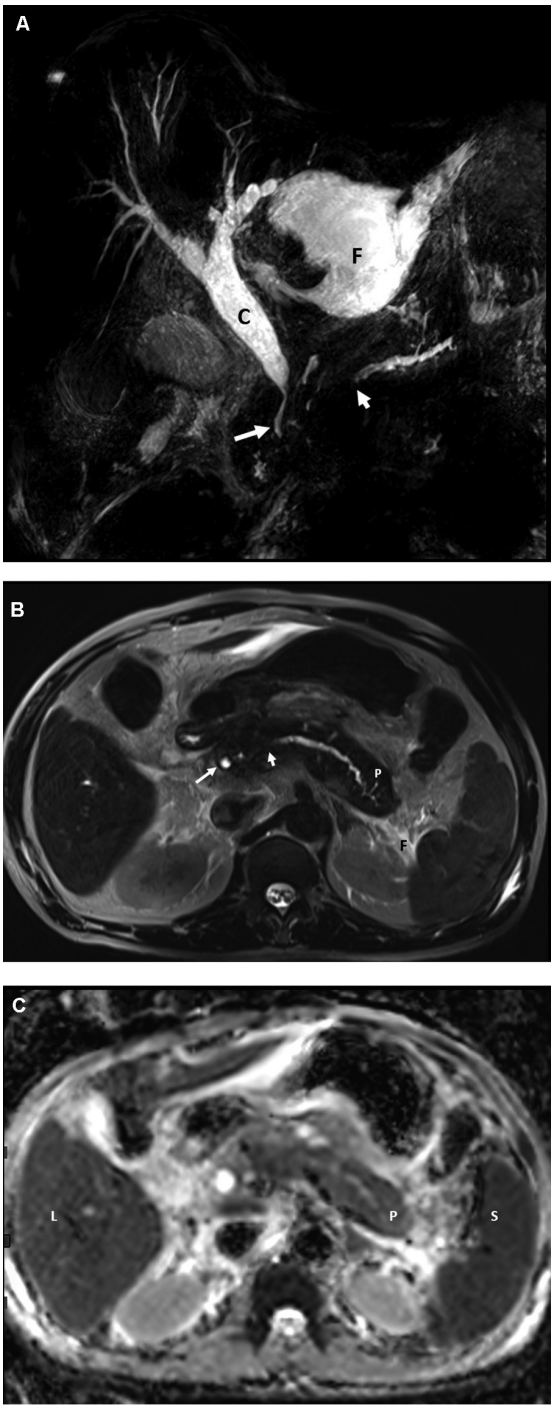


Fig. 11 Magnetic resonance (MR) in a 47/M, showing acute on chronic alcohol-related pancreatitis with common bile duct (CBD) stricture. (**A**) Three-dimensional (3D) maximum intensity projection (MIP) magnetic resonance cholangiopancreatography (MRCP) shows dilated and tortuous pancreatic duct with abrupt cutoff in the body (small white arrow). The long white arrow is CBD stricture. C is CBD and F is fluid. (**B**) Two-dimensional (2D) thin MIP high-resolution T2-weighted (T2W) image shows a bulky pancreas (P). The pancreatic duct in the body and tail is dilated with an abrupt cutoff (small white arrow). The long white arrow is CBD. (**C**) Apparent diffusion coefficient (ADC) image in axial plane shows diffuse restriction of the parenchyma (P). S is spleen and L is liver.

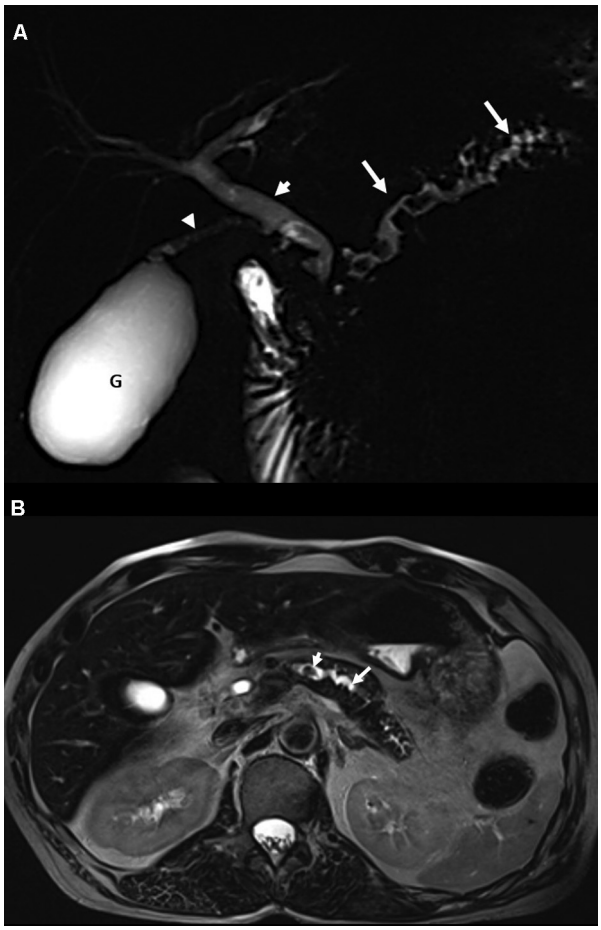


Fig. 12 Magnetic resonance (MR) in alcohol-related chronic calcific pancreatitis. (**A**) Three-dimensional (3D) maximum intensity projection (MIP) magnetic resonance cholangiopancreatography (MRCP) shows dilated and tortuous pancreatic duct with dilated side branches (white arrow). There are multiple filling defects in the duct. The short white arrow is common bile duct (CBD), the white arrowhead is cystic duct, and G is the gallbladder. (**B**) T2-weighted (T2W) SPACE thin high resolution shows an atrophic pancreatic gland with a dilated and tortuous pancreatic duct (long white arrow). Filling defects in the pancreatic duct are calculi (short white arrow).

Concomitant Liver Involvement

AUD is a disease affecting over 14 million adults in the United States.[69] Individual sensitivity to alcohol results not only in variable addiction but also in variable organ damage.

Since the liver and pancreas share development and functional attributes, they are both vulnerable to the damaging effects of alcohol.[70,71] Studies have shown varying frequencies of cooccurrence between pancreatic and liver diseases. Lowenfels et al noted no significant difference in alcohol consumption between groups with alcoholic cirrhosis and alcoholic pancreatitis, although smoking was more prevalent among men with ALP.[72]

A review of 1,022 autopsies where the cause of death was alcoholic liver disease showed that 28% had histological signs of pancreatitis, ranging from mild inflammation to moderate fibrosis.[73] A high prevalence of exocrine pancreatic insufficiency and CP was observed among patients with alcoholic liver disease. CP can exacerbate alcohol-related liver disease, leading to pancreatic insufficiency and issues with nutrient absorption that worsen liver fibrosis.

Conclusion

The imaging characteristics of ALP do not markedly differ from other pancreatitis causes like gallstones and recognizing its unique natural progression and underlying mechanisms is crucial for precise diagnosis and management. Radiologists play a pivotal role by utilizing various imaging modalities and being well-versed in ALP's distinct features, thereby significantly contributing to its clinical management.

Highlights

- Alcohol-related pancreatitis (ALP) is a spectrum of manifestations ranging from acute interstitial pancreatitis (AIP), acute pancreatic necrosis (PNEC), and recurrent acute pancreatitis (RAP), which can progress to alcohol-related chronic pancreatitis (ACP) with continued use of alcohol.
- The yearly incidence is increasing, especially in the young, and early intervention can prevent disease progression.
- The natural history of this disease is different from other causes of pancreatitis and suggesting the diagnosis on imaging can help in early detection and guide the management. CECT is usually the imaging investigation of choice in the acute setting. In a chronic setting, MRI is more sensitive to subtle changes and provides both morphological and functional information. It can also be used for monitoring the disease activity.

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Conflict of Interest
None declared.

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