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RESPONSIBLE EDITORS FOR THIS ISSUE

Comprehensive review of diagnostic modalities for early chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is a progressive condition caused by several factors and characterised by pancreatic fibrosis and dysfunction. However, CP is difficult to diagnose at an early stage. Various advanced methods including endoscopic ultrasound based elastography and confocal laser endomicroscopy have been used to diagnose early CP, although no unified diagnostic standards have been established. In the past, the diagnosis was mainly based on imaging, and no comprehensive evaluations were performed. This review describes and compares the advantages and limitations of the traditional and latest diagnostic modalities and suggests guidelines for the standardisation of the methods used to diagnose early CP.

Key Words: Chronic pancreatitis; Pancreatic fibrosis; Early diagnosis; Ultrasound endoscopy; Endosonography; Elastography; Confocal laser endomicroscopy

Core Tip: Chronic pancreatitis (CP) is a progressive disease that is difficult to diagnose at an early stage. This review evaluates the characteristics, strengths, and limitations of modalities for the diagnosis of early CP. This paper will be of interest to the readership

because the information presented here highlights multiple novel strategies, such as elastography and confocal laser endomicroscopy, some of which require further research and development to improve the diagnostic efficiency. This review will be highly beneficial for researchers and clinicians focusing on the management of this condition.

INTRODUCTION

Chronic pancreatitis (CP) is a multifactorial inflammatory syndrome characterised by recurring epigastric pain and progressive fibrosis that eventually leads to pancreatic atrophy and calcification, ductal distortion, and exocrine and endocrine dysfunction[1, 2]. In early pancreatitis, clinical features of the disease are mild and non-specific[3,4]. The global incidence of CP is 10 per 100000 persons per year, and significantly more men than women are affected. In Japan, the overall prevalence of early CP is 4.2 per 100000 persons, and the annual incidence is 1.0 per 100000 persons[5-7]. Several classifications and diagnostic recommendations for CP have recently been proposed[3,4,8-10]. For advanced or end-stage CP, morphologic changes characteristic of fibrosis, duct dilation, calcifications, or atrophy can be detected with imaging modalities and functional failures can be evaluated through functional tests. However, there is no universally accepted diagnostic method for CP[4]. Furthermore, due to a lack of specific clinical presentation or morphologic features, diagnosing CP at an early stage is challenging[11]. Thus, it is critical to combine what is known about the aetiology, risk factors, clinical symptoms, imaging features, and pancreatic function test results to paint a clinical picture[12]. In this review, we compare different diagnostic modalities including several recently developed testing approaches such as endoscopic ultrasound (EUS)-elastography and EUS-guided needle-based confocal laser endomicroscopy (nCLE). We also suggest the development of standardised guidelines for the early diagnosis of CP, which will resolve the challenge of diagnosing early CP.

AETIOLOGY AND CLINICAL PRESENTATION

CP is a fibro-inflammatory disease with various aetiologies that is typically diagnosed using the TIGAR-O criteria[13] (Table 1) and M-ANNHEIM classification system[9]. These international classification systems incorporate common aetiological risks including alcohol and nicotine consumption, genetic mutations and polymorphisms, metabolic disorders, ductal obstruction, immunological factors, and idiopathic pancreatitis[14-16]. Among these factors, alcohol abuse is the most common aetiology of CP and is diagnosed in 42%-77% of patients with CP[17,18]. A prospective study reported that lifestyle-related factors such as alcoholism or smoking are closely associated with the occurrence and progression of CP[19,20]. Ethanol and nicotine are associated with oxidative stress, which activates quiescent pancreatic stellate cells that play an essential role in the inflammatory response and pathological progression of CP, eventually leading to irreversible pancreatic parenchyma damage and fibrosis[21-25]. Chronic alcohol consumption is also thought to increase gut permeability and decrease the phagocytic capacity of Kupffer cells, rendering them unable to detoxify circulating endotoxins; thus, heavy drinkers (> 80 g alcohol/d or more than 5 drinks/d) are susceptible to pancreatic diseases[26,27]. The revised TIGAR-O criteria[13] are used as a grading system for alcohol and nicotine consumption and are preferred to the exposure assessment (Table 1). Furthermore, genetic mutations are usually associated with CP onset, and different genotypes may lead to different effects and disease outcomes. A large Chinese cohort study focusing on four CP-associated genes (*SPINK1*, *PRSS1*, *CTRC*, and *CFTR*) found that patients with gene mutations had earlier disease onset than patients without. The study also found that genetic mu-

Table 1 Revised TIGAR-O aetiology criteria

Toxic-metabolic

Alcohol-related

0 to < 1 drinks/d

1-2 drinks/d

3-4 drinks/d

5 or more drinks/d

Smoking

Non-smoker (< 100 cigarettes in lifetime)

Past smoker

Current smoker (patients undergoing both past and ongoing cigarette exposure)

Other, not otherwise specified

Hypercalcaemia (total calcium levels > 12.0 mg/dL or 3 mmol/L)

Hypertriglyceridemia

Hypertriglyceridemia risk (fasting glucose > 300 mg/dL; non-fasting glucose > 500 mg/dL)

Hypertriglyceridemia in acute pancreatitis (history of glucose > 500 mg/dL in first 72 h of AP onset)

Medications

Toxins, other

Chronic kidney disease [CKD Stage 5: end-stage renal disease (ESRD)]

Other, not otherwise specified

Idiopathic

Early-onset (< 35 yr of age)

Late-onset (> 35 yr of age)

Genetic

Suspected; no or limited genotyping available

Autosomal dominant (Mendelian inheritance-single gene syndrome)

PRSS1 mutations (hereditary pancreatitis)

Autosomal recessive (Mendelian inheritance-single gene syndrome)

CFTR, 2 severe variants in trans (cystic fibrosis)

CFTR, < 2 severe variants in trans (CFTR-RD)

SPINK1, 2 pathogenic variants in trans (SPINK1-associated familial pancreatitis)

Complex genetics (non-Mendelian, complex genotypes +/- environment)

Modifier Genes (pathogenic genetic variants)

PRSS1-PRSS1 locus

CLDN2 locus

Others

Hypertriglyceridemia

Other, not otherwise specified

Autoimmune pancreatitis (AIP)/ steroid responsive pancreatitis

AIP Type 1—IgG4-related disease

AIP Type 2

Recurrent acute pancreatitis (RAP) and severe acute pancreatitis (SAP)

Acute pancreatitis (single episode, including date of event if available)

AP aetiology—Extra-pancreatic (excluding alcoholic, HTG, hypercalcaemia, genetic)
Biliary pancreatitis
Post-ERCP
Traumatic
Undetermined or not otherwise specified
Recurrent acute pancreatitis (number of episodes, frequency, and dates of events if available)
Obstructive
Pancreas divisum
Ampullary stenosis
Main duct pancreatic stones
Widespread pancreatic calcifications
Main pancreatic duct strictures
Localized mass causing duct obstruction

From the short form of TIGAR-O version 2 risk/aetiology checklist (2019)[13]. AP: Acute pancreatitis; CKD: Chronic kidney disease; HTG: Hypertriglyceridemia; ERCP: Endoscopic retrograde cholangiopancreatography.

tations were most common in patients with idiopathic chronic pancreatitis (ICP) than in patients with alcoholic chronic pancreatitis (ACP) or smoking-associated chronic pancreatitis (SCP)[28]. Patients with inherited *PRSS1* mutations have reportedly presented with specific imaging features including pancreatic atrophy, calcification, and main pan-creatic duct (MPD) dilatation, which have been termed the PRSS1 imaging triad[29]. Patients with *CFTR* gene mutations have presented with pancreatic atrophy.

An early diagnosis of CP is challenging due to nonspecific clinical presentation. Recurrent abdominal pain with radiation to the back is the most common symptom, with Wilcox *et al*[30] reporting that constant, mild pain with intermittent episodes of severe pain is described by 45% of patients. A history of acute pancreatitis (AP), especially recurrent AP, is a significant risk factor for early CP[4]. However, in some patients, CP is asymptomatic during the early stage, and steatorrhea or diabetes secondary to exocrine/endocrine dysfunction may be the first clinical manifestation of CP without pain[31]. If patients with CP are not diagnosed at an early stage, they have a higher risk of progressing to advanced or end-stage CP, which is characterised by multiple complications including severe pain, pancreatic insufficiency (endocrine or exocrine), metabolic bone disease, and pancreatic ductal adenocarcinoma (PDAC)[19,32,33]. It is currently accepted that an early or suggestive CP diagnosis can be made when three or more of the following clinical features are present: Abnormal serum or urine pancreatic enzyme concentrations; recurring upper abdominal pain; continuous heavy alcohol consumption (> 80 g alcohol/d); family history of hereditary CP or known sporadic high-risk mutations; and abnormal exocrine function (Table 2)[1,4,33,34]. Genetically mediated pancreatitis is likely in a young patient with clinical features of CP but without a history of risk factors such as smoking or alcohol consumption. However, early CP cannot be diagnosed using clinical manifestations alone.

IMAGING MODALITIES

The progression from normal pancreatic status to severe inflammation is typically subtle during which the patient experiences few specific symptoms. Thus, the majority of CP diagnoses are based on imaging features[1,4]. Imaging and radiographical evaluations of a patient with suspected CP should progress from a non-invasive approach to an invasive approach.

Ultrasound and computed tomography
Ultrasound (US) and computed tomography (CT) are recommended by various guidelines as the first-line non-invasive imaging approaches for evaluating patients with suspected CP[10,12]. Intraductal pancreatic calcification and parenchymal atrophy are

Table 2 Comparisons of diagnostic modalities

Modality	Diagnostic standards	Sensitivity	Specificity
Aetiology	TIGAR-O classification (version 2)[13].	-	-
Clinical presentation	Three or more of the following features: Abnormal serum or urine pancreatic enzyme concentrations; continuous heavy alcohol consumption (> 80 g alcohol/day or more than 5 drinks/day), family history of hereditary chronic pancreatitis, or known sporadic high-risk mutations; recurring epigastric abdominal pain; and abnormal exocrine function. Genetic pancreatitis should be suspected in young patients with clinical presentations but without a history of risk factors.	-	-
TA-US	Irregular main pancreatic duct with a diameter > 3 mm, hyperechoic pancreatic duct wall, or lobularity with stranding.	69% (95%CI: 54-80)	94%(95%CI: 90-100)
CT	Two or more of the following features: MPD within 2-4 mm; mild organ enlargement; irregular main pancreatic duct with ≥ 3 pathological side branches; pseudocysts ≤ 10 mm; and heterogeneous parenchyma.	75% (95%CI: 66-83)	91%(95%CI: 81-96)
MRI/MRCP	Two or more of the following features: MPD 2-4 mm; mild organ enlargement; irregular main pancreatic duct with ≥ 3 pathological side branches; pseudocysts ≤ 10 mm; and heterogeneous parenchyma.	Single-parametric: 77%; Multi-parametric: 91%	Single-parametric: 83%; Multi-parametric: 86%
ERCP	More than three pathological side branches plus a normal MPD.	82% (95% CI: 76-87)	94% (95% CI: 87-98)
EUS	More than two of the following seven criteria, including at least one of criteria 1-4: (1) Stranding; (2) Hyperechoic foci without shadowing; (3) Lobularity with honeycombing; (4) Lobularity without honeycombing; (5) Cysts; (6) Dilated side branches; (7) Hyperechoic main pancreatic duct margin.	61% (non-fibrosis); 84% (for fibrosis)	75% (non-fibrosis); 100% (for fibrosis)
EUS-EG	A strain ratio of > 10 or a mean strain histogram value of < 50 was associated with malignancy.The mean value can be used to diagnose mild or higher-grade fibrosis.	76.4%	91.7%
FE-1	Moderate EPI can be diagnosed based on an abnormal FE-1 level of < 200 μg/g, which has a high false-positive rate.	76.5%; 45.0% (mild ductal changes and insufficiency)	86.0%
ePFT	Peak bicarbonate concentration of < 80 mmol/L is considered abnormal and correlated with early fibrosis.	86% (95%CI: 67-100)	67% (95%CI: 13-100)
FNA	Ruling out malignancy and staging of CP. CEA testing: Cut-off value of 192 ng/mL. Molecular analysis: *KRAS* and *GNAS* mutations.	85% (pancreatic cancer)	98% (pancreatic cancer)
nCLE	A complementary modality for detecting subtle changes in early CP and helpful for distinguishing malignancies.	94.3% (cystic lesions); 90.3% (PDAC)	98.1% (cystic lesions); 89.5% (PDAC)

Sen: Sensitivity; Spec: Specificity; TA-US: Transabdominal ultrasound; MPD: Main pancreatic duct; CT: Computed tomography; MRI: Magnetic resonance imaging; EUS: Endoscopic ultrasound; EUS-EG: Endoscopic ultrasound elastography; FE-1: Faecal elastase-1; ePFT: Endoscopic pancreatic function test; nCLE: Endoscopic pancreatic function test; EPI: Exocrine pancreatic insufficiency; CP: Chronic pancreatitis; CEA: Carcinoembryonic antigen; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; FNA: Fine-needle aspiration; PDAC: Pancreatic ductal adenocarcinoma; AIP: Autoimmune pancreatitis; AP: acute pancreatitis; RAP: Recurrent acute pancreatitis; CKD: Chronic kidney disease; NCCP: Non-calcific chronic pancreatitis; ROC: Receiver operating characteristic; ROI: Region of interest; SD: Standard deviation; SR: Strain ratio.

considered the most specific and reliable sonographic signs of CP. However, the value of transabdominal US (TA-US) may be limited by the retroperitoneal location of the pancreas, which increases the sound wave distance to the pancreas, and by several other factors including bowel gas, obesity, and individual variations. Nevertheless, advances in US technology have significantly improved the diagnostic value of the modern abdominal US. A prospective observational cohort study reported a sensitivity of 0.69 (95%CI: 0.54-0.80) and specificity of 0.97 (95%CI: 0.90-1.0) for the detection of CP using TA-US[35]. The following US signs have been proposed for the diagnosis of early or suspected CP: An irregular main pancreatic duct > 3 mm; an hyperechoic pancreatic duct wall; or lobularity with stranding (Table 2)[1]. In addition also criteria of size, shape and mobility should also be taken into account[36,37].

CT is believed to be the best initial imaging modality for the diagnosis of CP, and some guidelines have suggested that all patients with suspected CP should undergo a baseline CT scan[10,12,38]. Ductal changes such as dilation, strictures, and contour irregularity and parenchymal or intraductal calcification, which have been deemed to constitute an independent pathophysiological process involved in the development of CP, can be identified on CT. Furthermore, baseline CT can be useful to rule out other intra-abdominal diseases, including pancreatic and upper gastrointestinal cancers,

which may present with similar symptoms of epigastric pain, weight loss, and maldigestion[38]. In addition, CT can also be used to monitor the progression of pancreatitis and its subsequent complications, such as pseudocysts and biliary obstruction. A systematic meta-analysis reported a sensitivity of 75% (95%CI: 66-83) and specificity of 91% (95%CI: 81-96) for the detection of CP using CT[39]. However, the value of CT is limited for patients with early CP as the parenchymal and ductal changes are subtle. Furthermore, both US and CT have high rates of false negatives due to their limitations. It has been recommended that the quantity, size, and location of pancreatic calcification need to be demonstrated for accurate and comprehensive fibrosis assessments[40,41]. A dilated main pancreatic duct (2-4 mm), mild organ enlargement, pseudocysts, and pathological side branches are considered to be the diagnostic signs of early CP on CT (Table 2)[1,4,33,34].

Magnetic resonance imaging

Patients with suspected pancreatitis should also undergo magnetic resonance imaging (MRI) prior to other evaluations using invasive investigations to rule out carcinoma [10]. MRI and MR cholangiopancreatography (MRCP) are recommended, especially in patients without specific changes detected on CT. MRI and MRCP are superior to CT for the identification of mild CP. For example, morphological changes such as duct dilatation and strictures and pathological side branches that are typical early CP signs are more easily detected on MRI than on CT. Furthermore, new MRI techniques have been applied to quantitatively evaluate the severity of pancreatic fibrosis and pancreatic exocrine dysfunction, including diffusion-weighted imaging (DWI), MR elastography, and T1-mapping of the pancreatic parenchyma[38,41-43]. A retrospective analysis conducted by Tirkes *et al*[44] proposed that T1-weighted MR signaling in the pancreas had a high sensitivity (77%, $P < 0.0001$) and specificity (83%, $P < 0.0001$) for detecting parenchymal abnormalities related to exocrine dysfunction and could be helpful for the assessment of suspected early CP. Another study showed that multiparametric mapping MRI (a combination of T1, T2, and apparent diffusion coefficient values) yielded a higher accuracy for the detection of CP than any sole component (sensitivity: 91.54%; specificity: 85.81%; $P < 0.001$)[45]. If a patient has a high probability of having CP but shows negative results on MRI or MRCP, secretin-stimulating MRCP (part of the exocrine function test) should be performed[38]. However, MRCP does not always detect subtle pancreatic changes, especially when compared to endoscopic retrograde cholangiopancreatography (ERCP), which can be used to diagnose early CP based on the criteria of more than three pathological side branches and a normal main pancreatic duct (MPD) with a specificity of 94%. However, ERCP is not readily available everywhere, and it is operator-dependent and challenging to conduct[46]. The revised Cambridge classification system[47] recommends the following MRCP criteria for the diagnosis and evaluation of early CP: MPD of 2-4 mm; pseudocysts ≤ 10 mm; and irregular MPD with ≥ 3 pathological side branches (Table 2)[1,35].

Endoscopic ultrasound

Endoscopic ultrasound (EUS) has been reported to be the most sensitive modality for detecting fibrosis in patients with CP[4]. EUS is also superior to non-invasive imaging tools in diagnosing parenchymal and ductal changes, especially during the early stage of the disease. Therefore, when CT and MRI show negative results in patients who are suspected of having CP, EUS should be performed[38]. The majority of the EUS diagnostic criteria are based on the Rosemont classification system published in 2009 [48], which attempted to define each EUS criterion precisely to achieve excellent interobserver agreement. Based on the Rosemont classification system, EUS can be used to detect subtle changes in the structure of the pancreatic parenchyma and ducts even before traditional imaging and functional testing. EUS can also be used to treat pancreatitis-related symptoms or complications such as peripancreatic fluid and pseudocyst drainage[49,50]. Standard EUS findings include changes in the parenchyma (hyperechoic foci with or without shadowing, lobularity with or without honeycombing, pseudocysts, and hyperechoic stranding) and ducts (MPD irregularity, dilated side branches, hyperechoic main pancreatic duct wall, MPD dilation (3 mm at the head, 2 mm in the body, or 1 mm at the tail], and MPD stones)[48]. When more than two of the following pancreatic features are found on EUS, including at least one of the first three criteria, the patient is diagnosed with early CP: Lobularity with or without honeycombing, hyperechoic foci without shadowing, stranding, cysts, dilated side branches, and hyperechoic main pancreatic duct margins (Table 2)[1,34].

EUS findings such as hyperechoic foci and strands, parenchymal lobularity, and a hyperechoic ductal wall are considered to be signs of pancreatic fibrosis[51]. A study conducted in 2016 using a quantitative receiver operating characteristic (ROC) curve analysis to evaluate the accuracy of EUS features revealed that four or more standard EUS features achieved the best balance of sensitivity (61%; 95%CI: 46.8-73.5) and specificity (75%; 95%CI: 42.8-94.2) (AUC = 0.68) for predicting abnormal pancreatic histopathology alterations of non-calcific pancreatitis. Nevertheless, the Spearman rank correlation coefficient (*r*) calculated in the study demonstrated a poor correlation between standard EUS features and histopathology (*r* = 0.24, *P* < 0.05), suggesting that EUS is not an independent diagnostic modality for early CP, and that other influencing factors, such as age, sex, BMI, and environmental exposure, should also be included in the diagnostic algorithm[52]. However, a different retrospective study reported that the sensitivity (84%; 95%CI: 69-100) and specificity (100%; 95%CI: 40-100) of the detection of fibrosis using EUS becomes superior as the disease progresses[53,54]. A significant advantage of EUS is its ability to image the side branches and mild contortions of the MPD in normal individuals, especially in elderly individuals. Side branches exceeding 1 mm are considered abnormal. However, by the same token, there is potential for over-diagnosis of early CP especially in elderly individuals due to the very high sensitivity. Therefore, there is potential of over-diagnosis of early CP (Figure 1) by EUS and it should be performed and interpreted in the right clinical setting. Contrast-enhanced EUS with secretin stimulation and quantitative elastography are needed to improve the diagnostic accuracy for mild or suspected CP[55].

Elastography

Fibrosis in CP generally results in increased stiffness of the pancreatic parenchyma or ducts, which can be qualitatively or quantitatively evaluated based on strain or shear wave speed using elastography[56,57]. Together, EUS and elastography have been used to quantitatively measure the severity of pathological changes in CP, including parenchymal fibrosis[58]. EUS elastography (EUS-EG) involves the compression of a target tissue with an echo-endoscopic probe. The resulting strain on the tissue depends on its hardness or softness and can be compared with that of normal surrounding tissue using a three-colour system: Red, soft tissue; green, average hardness; and blue, hard tissue[59]. The quantitative analysis is based on a strain ratio (SR) calculation. Tissue stiffness is measured in a target lesion (region of interest ROI A) and a normal reference area (ROI B), which can be located either in the surrounding normal parenchyma or the wall of the gastrointestinal tract, and the SR is calculated as the quotient A/B[60]. Specific software is used to differentiate between lesions and normal tissues based on the negative correlation between SR and tissue elasticity. Strain histogram analysis is another quantitative elastography method, involving the calculation of the average hue histogram value over several compression cycles. The mean value of the strain histogram reflects the global stiffness or elasticity of a focal lesion based on the selected ROI calculation. Standard deviation (SD) and other parameters can also be used to further describe the hue distribution within the ROI [61]. Previous studies have reported that the evaluation based on the SR and histogram obtained by quantitative EUS-EG can be used as a supplementary approach for assessing the severity of parenchymal fibrosis and making a differential diagnosis of pancreatic masses[2,4,56,57,62]. A prospective study revealed a strong linear correlation between the number of EUS criteria for CP (according to the Rosemont classification system) and the SR (*r* = 0.813; *P* < 0.0001). Additionally, the area under the ROC curve was 0.949 (95%CI: 0.916-0.982), indicating outstanding diagnostic accuracy (91.1%, *P* < 0.0001) based on a cut-off SR of 2.25[63]. Itoh *et al*[64] used quantitative EUS-EG to diagnose the grade of pancreatic fibrosis and proposed that the pancreatic fibrosis grade is significantly correlated with histogram parameters, especially the mean histogram value (*r* = -0.75). When the mean value was used to diagnose mild or higher-grade fibrosis, the area under the ROC curve exceeded 0.9 (95%CI: 0.82-0.98) with a sensitivity of 76.4% and specificity of 91.7% (Table 2). An SR > 10 or a mean strain histogram value < 50 has been associated with malignancy, suggesting that EUS elastography is a useful supplementary modality to rule out malignant lesions of the pancreas due to its high negative predictive value[65]. A correlation between elasticity and EUS criteria has also been reported when elastography evaluations are based on the shear wave, which enriches the elastography approach for CP diagnosis[66-69]. As elastography is able to efficiently and accurately assess pancreatic fibrosis, combining EUS and elastography can greatly enhance the accuracy of detecting subtle or mild changes in patients with early or higher-grade CP.
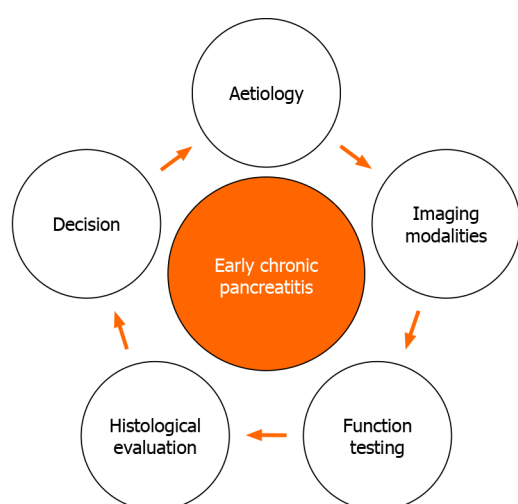
Figure 1 Outline of comprehensive diagnosis of early chronic pancreatitis.

PANCREATIC FUNCTION TESTING

Exocrine pancreatic insufficiency (EPI) is a common complication of CP mainly caused by the impairment of the production and secretion of enzymes in the pancreas. Symptoms of EPI include maldigestion of nutrients, unexpected weight loss, and steatorrhea due to fat maldigestion[32]. Pancreatic function testing (PFT) is recommended for the diagnosis of CP, especially in patients with non-specific and inconclusive morphological or imaging features of the disease[33,38]. PFT includes direct tests, which collect and analyse pancreatic secretions after a hormone stimulus, and indirect tests, which assess pancreatic function *via* faecal elastase-1(FE-1) or a breath test.

Direct PFT is conducted by determining the pancreas enzyme output after stimulation with cholecystokinin (CCK). The combination of secretin-stimulated MRI (s-MRI) and EUS-based PFT allows for the assessment of the bicarbonate concentration in the pancreatic juices as well as an improved morphological analysis[70]. S-MRI is considered to be a safe and non-invasive technique that enhances the visualisation of the ductal system by stimulating the bicarbonate-rich fluid filling the MPD and its side branches. EPI is diagnosed when the bicarbonate concentration is < 80 mmol/L after secretin stimulation[71]. Following intravenous secretin (0.2-0.3 μg/kg within 1-2 min) administration, an increase in hyperintense fluid content is observed in the small intestine 10-13 min thereafter. During the post-secretin stimulation stage, the MPD has a larger diameter and can be more easily evaluated, and pancreatic ductal compliance, which is associated with ductal stiffness or calcification, can be assessed. Healthy, nonfibrotic pancreatic parenchyma and ducts without strictures or calcification have an elastic capacity for accommodating pancreatic juice fluid without dilatation, and the diameter will not increase by more than 1 mm from the baseline value after secretin stimulation[10,23,72]. Exocrine pancreatic function can be quantitatively and semi-quantitatively evaluated by assessing the production and excretion of bicarbonate from pancreatic glands[10,73]. Thus, s-MRI can be applied to diagnose early or mild CP based on its superior ability to detect early pathological changes, such as the presence of side branches and an enlarged or restricted MPD, compared to CT or standard MRI. Several studies have reported significant differences between patients with a normal pancreas and early pancreatitis using s-MRI and correlations between s-MRI findings and the histopathological features of CP[74-76]. Similarly, EUS can be used in the endoscopic pancreatic function test (ePFT), which has been reported to have a sensitivity of 86% (95%CI: 67-100) and specificity of 67% (95%CI: 13-100) for the diagnosis of early fibrosis[53]. A retrospective study reported that a peak bicarbonate concentration of < 80 mmol/L on ePFT is considered abnormal and proposed a correlation between the peak bicarbonate concentration and fibrosis score (r = -0.57; P = 0.016). However, other studies have also claimed that the specificity and concordance for CP diagnosis were more accurate in a shortened ePFT with the use of a lower cut-off value; more prospective studies are required for further validation of the ePFT (Table 2)[77,78].

Although direct PFT is generally considered to be the gold standard for EPI, indirect PFT is useful for screening patients with risk factors for CP, as it is non-invasive and convenient. Indirect PFT can be performed using faecal chymotrypsin or FE-1 assays, 72-h faecal fat measurement, bentiromide (NBT-PABA) tests, and fluorescein dilaurate tests. FE-1 assessment is the most commonly used PFT method as it is stable throughout the intestinal tract. Furthermore, EPI can be diagnosed based on an abnormal FE-1 level (< 200 μg/g), though this diagnostic method is limited by a high false-positive rate (Table 2)[79]. FE-1 has also been reported to correlate with pancreatic duct changes, with a sensitivity of 76.5% and a specificity of 86% ($P < 0.05$) for moderate to severe changes at a cut-off of 200 μg/g. However, the correlation of FE-1 with mild ductal changes and insufficiency was not as strong, with a sensitivity of 45% [80,81].Therefore, the FE-1 test is not an accurate method for the functional diagnosis of EPI and should not be used to diagnose early CP.

HISTOLOGICAL EVALUATION

EUS-guided tissue acquisition

While the histopathological examination is considered the gold standard of disease diagnosis, direct acquisition of pancreatic tissue is limited due to the retroperitoneal location of the organ. Tissue acquisition with EUS (EUS-TA) can be used to obtain pancreatic tissue samples for microscopic analysis and establish a cytopathological diagnosis of the gastrointestinal tract or adjacent lesions[82]. In patients with suspected pseudo tumoural masses or cystic lesions in the setting of CP, a histopathological examination is necessary to eliminate malignant lesions from the differential diagnosis[72,82]. EUS-TA can be achieved *via* EUS fine-needle aspiration (EUS-FNA) and EUS-fine needle biopsy (EUS-FNB), which is the current gold standard for tissue acquisition from solid masses. FNA is used to rule out malignancy from the differential or to stage CP and can provide both cytological and histological evaluations. FNA is reported to be superior to other modalities for the evaluation of cystic pancreatic lesions in patients with concurrent CP[83]. The fluid obtained by FNA can be tested for amylase and carcinoembryonic antigen (CEA). Moreover, the CEA level can be used to distinguish mucinous and non-mucinous lesions with a cut-off value of 192 ng/mL[83,84]. Additionally, the molecular analysis of mutations in the *KRAS* and *GNAS* genes using the FNA specimen can distinguish malignant lesions from benign cystic lesions[85,86]. FNA has also been reported to be useful for evaluating solid lesions and suitable for distinguishing autoimmune pancreatitis (AIP) from pancreatic cancer[87,88]. FNA has been reported to have a sensitivity of 85% and specificity of 98% for the diagnosis of pancreatic cancer (Table 2)[89]. However, according to a current retrospective analysis of multicentric databases, FNB showed a higher diagnostic sensitivity than FNA for distinguishing between inflammatory masses and malignant lesions in the setting of CP[90]. However, histopathological evaluation by FNB may cause needle tract seeding, which should be taken into consideration when conducting FNB on patients with resectable solid masses[62]. Thus, the appropriate method of tissue acquisition depends on the specific type of pancreatic lesion and the purpose of diagnosis. EUS-TA is limited by its potential complications such as bleeding and post-procedure pancreatitis, and requires an experienced operator.

Confocal laser endomicroscopy

Needle-based confocal laser endomicroscopy (nCLE) is a novel diagnostic method that allows for real-time optical biopsy at a subcellular resolution during a EUS procedure. The patient is administered with 2.5 mL of 10% fluorescein intravenously, and a confocal mini-probe with a 0.632-mm diameter is preloaded into a 19-gauge EUS needle and locked into position with 2 mm exposed beyond the tip. The images are obtained 6-8 min after fluorescein injection. In solid pancreatic masses, residual regular glandular pancreatic structures on nCLE are characteristic of CP (Table 2). In cystic lesions, the presence of villous epithelial structures on nCLE may be associated with pancreatic cystic neoplasms. A study conducted by Karia *et al*[91] compared the interobserver agreement and diagnostic accuracy of nCLE *via* FNA for pancreatic cystic lesions (PCLs) and found that the diagnostic accuracy for PCLs was low, with a mean sensitivity of 46% and an unimpressive agreement (k = 0.13). Another study found that nCLE is a safe and feasible diagnostic method for cystic neoplasms with an overall accuracy of 80% (sensitivity: 66%, specificity: 100%)[92]. Another study reported a sensitivity of 90.3% and specificity of 89.5% for the diagnosis of PDAC *via* nCLE and a sensitivity of 94.3% and specificity of 98.1% for the diagnosis of PCLs *via*

nCLE (P < 0.05; Table 2)[93]. These results suggest that nCLE is a promising method that can improve the diagnostic efficiency of EUS technology by providing better imaging accuracy and verifying EUS imaging features by combining subcellular observation with tissue acquisition. Furthermore, this method can be a complementary modality for detecting the subtle changes of early CP and distinguishing malignancies from benign lesions. Limitations of nCLE include the potential complications of infections, bleeding, and pancreatitis. Furthermore, patients with significant coagulopathy or allergy to fluorescein should not undergo nCLE and FNA.

CONCLUSION

No individual diagnostic method can be used to establish a diagnosis of early CP due to the non-specific clinical presentation and subtle morphological changes as well as the lack of globally accepted standards. Various advanced modalities have been used to improve the accuracy of the diagnostic methods for CP. It is important to consider the possible aetiologies, risk factors, and complications of the disease in patients suspected to have CP. Inflammatory complications are mainly due to alcohol consumption and fibrotic complications are mainly due to smoking. Pancreatic insufficiencies have been associated with disease duration and age at onset[94]. CP is typically diagnosed using imaging modalities that can detect morphological changes in the pancreas or detect functional insufficiency (by combining imaging and secretin stimuli). Elastography can quantitatively evaluate the stiffness of the pancreatic parenchyma. However, each imaging modality has limitations that require verification of the diagnosis using an additional modality. Furthermore, there is a lack of consistency among the features and diagnostic criteria of different imaging modalities. The diagnostic criteria of MRCP and ERCP are based on the Cambridge scoring system, which focuses on the morphology of the MPD and the appearance of its side branches; however, a lack of strong concordance between the ERCP- and MRCP-based grading systems for CP using the Cambridge criteria has been recently reported[8,95,96]. Therefore, the imaging standards for CP may need to be revised to improve the consistency of the diagnostic methods. Prospective studies are required to verify the diagnostic accuracy of these imaging modalities. However, ERCP purely for diagnostic purposes for assessing chronic pancreatitis is outdated with risks greater than benefits and should not be done. Each imaging modality has sensitive indicators for pancreatic pathological changes, and some modalities do not have a high sensitivity or specificity for pancreatitis at an early stage, as shown in Table 2. Promising tools, such as nCLE, are currently being developed and require more studies for the verification of their diagnostic efficiency and potential. Furthermore, probable biomarkers for the diagnosis of early CP or to rule out malignancy, such as metabolomic and microRNA signatures in the blood, have been investigated, but they also require further verification[97-100].

A limitation of this review is that it could not identify a single appropriate modality for the diagnosis of early CP; however, comparisons of these clinical approaches provide references for physicians to help establish a diagnosis of early CP. The modalities used may depend on the local availability of a particular test, *e.g.*, pancreatic function testing. MRCP or EUS may not be universally available at each institution. In conclusion, although several imaging modalities can elucidate specific pancreatic features, an accurate and definite diagnosis of early CP should be based on the patient's risk factors, symptoms, imaging results, and histological findings when available. There has been a renewed recent interest in the use of artificial intelligence (AI)[101] in medical imaging and application of AI to EUS images and the other modalities discussed above could potentially further increase the reliability in diagnosis of CP since medical diagnosis based on images is subject to interpretation of the reader and interobserver variability can become a greater issue even more for the diagnosis of an early stage of disease than a late one.

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REFERENCES

1   **Beyer G**, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. *Lancet* 2020; **396**: 499-512 [PMID: 32798493 DOI: 10.1016/S0140-6736(20)31318-0]

2   **Gupte A**, Goede D, Tuite R, Forsmark CE. Chronic pancreatitis. *BMJ* 2018; **361**: k2126 [PMID: 29880587 DOI: 10.1136/bmj.k2126]

3   **Shimosegawa T**, Kataoka K, Kamisawa T, Miyakawa H, Ohara H, Ito T, Naruse S, Sata N, Suda K, Hirota M, Takeyama Y, Shiratori K, Hatori T, Otsuki M, Atomi Y, Sugano K, Tanaka M. The revised Japanese clinical diagnostic criteria for chronic pancreatitis. *J Gastroenterol* 2010; **45**: 584-591 [PMID: 20422433 DOI: 10.1007/s00535-010-0242-4]

4   **Whitcomb DC**, Shimosegawa T, Chari ST, Forsmark CE, Frulloni L, Garg P, Hegyi P, Hirooka Y, Irisawa A, Ishikawa T, Isaji S, Lerch MM, Levy P, Masamune A, Wilcox CM, Windsor J, Yadav D, Sheel A, Neoptolemos JP; Working Group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. *Pancreatology* 2018; **18**: 516-527 [PMID: 29793839 DOI: 10.1016/j.pan.2018.05.008]

5   **Xiao AY**, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, Petrov MS. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. *Lancet Gastroenterol Hepatol* 2016; **1**: 45-55 [PMID: 28404111 DOI: 10.1016/S2468-1253(16)30004-8]

6   **Pendharkar SA**, Mathew J, Petrov MS. Age- and sex-specific prevalence of diabetes associated with diseases of the exocrine pancreas: A population-based study. *Dig Liver Dis* 2017; **49**: 540-544 [PMID: 28110921 DOI: 10.1016/j.dld.2016.12.010]

7   **Masamune A**, Kikuta K, Nabeshima T, Nakano E, Hirota M, Kanno A, Kume K, Hamada S, Ito T, Fujita M, Irisawa A, Nakashima M, Hanada K, Eguchi T, Kato R, Inatomi O, Shirane A, Takeyama Y, Tsuji I, Shimosegawa T; Research Committee of Intractable Pancreatic Diseases in Japan. Nationwide epidemiological survey of early chronic pancreatitis in Japan. *J Gastroenterol* 2017; **52**: 992-1000 [PMID: 28130705 DOI: 10.1007/s00535-017-1311-8]

8   **Sarner M**, Cotton PB. Classification of pancreatitis. *Gut* 1984; **25**: 756-759 [PMID: 6735257 DOI: 10.1136/gut.25.7.756]

9   **Schneider A**, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol* 2007; **42**: 101-119 [PMID: 17351799 DOI: 10.1007/s00535-006-1945-4]

10   **Conwell DL**, Lee LS, Yadav D, Longnecker DS, Miller FH, Mortele KJ, Levy MJ, Kwon R, Lieb JG, Stevens T, Toskes PP, Gardner TB, Gelrud A, Wu BU, Forsmark CE, Vege SS. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas* 2014; **43**: 1143-1162 [PMID: 25333398 DOI: 10.1097/MPA.0000000000000237]

11   **Duggan SN**, Ní Chonchubhair HM, Lawal O, O'Connor DB, Conlon KC. Chronic pancreatitis: A diagnostic dilemma. *World J Gastroenterol* 2016; **22**: 2304-2313 [PMID: 26900292 DOI: 10.3748/wjg.v22.i7.2304]

12   **Gardner TB**, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG Clinical Guideline: Chronic Pancreatitis. *Am J Gastroenterol* 2020; **115**: 322-339 [PMID: 32022720 DOI: 10.14309/ajg.0000000000000535]

13   **Whitcomb DC**; North American Pancreatitis Study Group. Pancreatitis: TIGAR-O Version 2 Risk/Etiology Checklist With Topic Reviews, Updates, and Use Primers. *Clin Transl Gastroenterol* 2019; **10**: e00027 [PMID: 31166201 DOI: 10.14309/ctg.0000000000000027]

14   **Weiss FU**, Laemmerhirt F, Lerch MM. Etiology and Risk Factors of Acute and Chronic Pancreatitis. *Visc Med* 2019; **35**: 73-81 [PMID: 31192240 DOI: 10.1159/000499138]

15   **Mayerle J**, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Tóth M. Genetics, Cell Biology, and Pathophysiology of Pancreatitis. *Gastroenterology* 2019; **156**: 1951-1968.e1 [PMID: 30660731 DOI: 10.1053/j.gastro.2018.11.081]

16   **Yadav D**, Eigenbrodt ML, Briggs MJ, Williams DK, Wiseman EJ. Pancreatitis: prevalence and risk factors among male veterans in a detoxification program. *Pancreas* 2007; **34**: 390-398 [PMID: 17446836 DOI: 10.1097/mpa.0b013e318040b332]

17   **Singh VK**, Yadav D, Garg PK. Diagnosis and Management of Chronic Pancreatitis: A Review. *JAMA* 2019; **322**: 2422-2434 [PMID: 31860051 DOI: 10.1001/jama.2019.19411]

18   **Petrov MS**, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 175-184 [PMID: 30482911 DOI: 10.1038/s41575-018-0087-5]

19   **Masamune A**, Nabeshima T, Kikuta K, Hamada S, Nakano E, Kume K, Kanno A, Sato A, Tachibana Y, Inatomi O, Yamamoto S, Ikeura T, Futagami S, Taguchi M, Hanada K, Shimizu K, Kageoka M, Saito T, Eguchi T, Kubota K, Takenaka M, Mima A, Irisawa A, Ito T, Andoh A, Inui K, Takeyama Y, Yamaue H, Okazaki K, Shimosegawa T. Prospective study of early chronic pancreatitis diagnosed based on the Japanese diagnostic criteria. *J Gastroenterol* 2019; **54**: 928-935 [PMID: 31270692 DOI: 10.1007/s00535-019-01602-9]

20   **Muniraj T**, Yadav D, Abberbock JN, Alkaade S, Amann ST, Anderson MA, Banks PA, Brand RE,

Conwell D, Cote GA, Forsmark CE, Gardner TB, Gelrud A, Guda N, Lewis MD, Romagnuolo J, Sandhu BS, Sherman S, Singh VK, Slivka A, Tang G, Whitcomb DC, Wilcox CM. Increased awareness enhances physician recognition of the role of smoking in chronic pancreatitis. *Pancreatology* 2019; **19**: 500-506 [PMID: 30910452 DOI: 10.1016/j.pan.2019.02.009]

21   **Andriulli A**, Botteri E, Almasio PL, Vantini I, Uomo G, Maisonneuve P; ad hoc Committee of the Italian Association for the Study of the Pancreas. Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis. *Pancreas* 2010; **39**: 1205-1210 [PMID: 20622705 DOI: 10.1097/MPA.0b013e3181df27c0]

22   **Bynigeri RR**, Jakkampudi A, Jangala R, Subramanyam C, Sasikala M, Rao GV, Reddy DN, Talukdar R. Pancreatic stellate cell: Pandora's box for pancreatic disease biology. *World J Gastroenterol* 2017; **23**: 382-405 [PMID: 28210075 DOI: 10.3748/wjg.v23.i3.382]

23   **Xue J**, Sharma V, Hsieh MH, Chawla A, Murali R, Pandol SJ, Habtezion A. Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. *Nat Commun* 2015; **6**: 7158 [PMID: 25981357 DOI: 10.1038/ncomms8158]

24   **Xue R**, Jia K, Wang J, Yang L, Wang Y, Gao L, Hao J. A Rising Star in Pancreatic Diseases: Pancreatic Stellate Cells. *Front Physiol* 2018; **9**: 754 [PMID: 29967585 DOI: 10.3389/fphys.2018.00754]

25   **Hu F**, Lou N, Jiao J, Guo F, Xiang H, Shang D. Macrophages in pancreatitis: Mechanisms and therapeutic potential. *Biomed Pharmacother* 2020; **131**: 110693 [PMID: 32882586 DOI: 10.1016/j.biopha.2020.110693]

26   **Rao R**. Endotoxemia and gut barrier dysfunction in alcoholic liver disease. *Hepatology* 2009; **50**: 638-644 [PMID: 19575462 DOI: 10.1002/hep.23009]

27   **Bull-Otterson L**, Feng W, Kirpich I, Wang Y, Qin X, Liu Y, Gobejishvili L, Joshi-Barve S, Ayvaz T, Petrosino J, Kong M, Barker D, McClain C, Barve S. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. *PLoS One* 2013; **8**: e53028 [PMID: 23326376 DOI: 10.1371/journal.pone.0053028]

28   **Zou WB**, Tang XY, Zhou DZ, Qian YY, Hu LH, Yu FF, Yu D, Wu H, Deng SJ, Lin JH, Zhao AJ, Zhao ZH, Wu HY, Zhu JH, Qian W, Wang L, Xin L, Wang MJ, Wang LJ, Fang X, He L, Masson E, Cooper DN, Férec C, Li ZS, Chen JM, Liao Z. SPINK1, PRSS1, CTRC, and CFTR Genotypes Influence Disease Onset and Clinical Outcomes in Chronic Pancreatitis. *Clin Transl Gastroenterol* 2018; **9**: 204 [PMID: 30420730 DOI: 10.1038/s41424-018-0069-5]

29   **O'Brien CM**, O'Brien AC, Gleeson L, Conlon K, Feeney J, Malone DE. Imaging of genetically-mediated pancreatitis. *Clin Imaging* 2020; **65**: 113-118 [PMID: 32387800 DOI: 10.1016/j.clinimag.2020.04.005]

30   **Wilcox CM**, Yadav D, Ye T, Gardner TB, Gelrud A, Sandhu BS, Lewis MD, Al-Kaade S, Cote GA, Forsmark CE, Guda NM, Conwell DL, Banks PA, Muniraj T, Romagnuolo J, Brand RE, Slivka A, Sherman S, Wisniewski SR, Whitcomb DC, Anderson MA. Chronic pancreatitis pain pattern and severity are independent of abdominal imaging findings. *Clin Gastroenterol Hepatol* 2015; **13**: 552-60; quiz e28-9 [PMID: 25424572 DOI: 10.1016/j.cgh.2014.10.015]

31   **Giger U**, Stanga Z, DeLegge MH. Management of chronic pancreatitis. *Nutr Clin Pract* 2004; **19**: 37-49 [PMID: 16215095 DOI: 10.1177/011542650401900137]

32   **Ramsey ML**, Conwell DL, Hart PA. Complications of Chronic Pancreatitis. *Dig Dis Sci* 2017; **62**: 1745-1750 [PMID: 28281169 DOI: 10.1007/s10620-017-4518-x]

33   **Dominguez-Munoz JE**, Drewes AM, Lindkvist B, Ewald N, Czakó L, Rosendahl J, Löhr JM; HaPanEU/UEG Working Group. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. *Pancreatology* 2018; **18**: 847-854 [PMID: 30344091 DOI: 10.1016/j.pan.2018.09.016]

34   **Ito T**, Ishiguro H, Ohara H, Kamisawa T, Sakagami J, Sata N, Takeyama Y, Hirota M, Miyakawa H, Igarashi H, Lee L, Fujiyama T, Hijioka M, Ueda K, Tachibana Y, Sogame Y, Yasuda H, Kato R, Kataoka K, Shiratori K, Sugiyama M, Okazaki K, Kawa S, Tando Y, Kinoshita Y, Watanabe M, Shimosegawa T. Evidence-based clinical practice guidelines for chronic pancreatitis 2015. *J Gastroenterol* 2016; **51**: 85-92 [PMID: 26725837 DOI: 10.1007/s00535-015-1149-x]

35   **Engjom T**, Sangnes DA, Havre RF, Erchinger F, Pham KD, Haldorsen IS, Gilja OH, Dimcevski G. Diagnostic Accuracy of Transabdominal Ultrasound in Chronic Pancreatitis. *Ultrasound Med Biol* 2017; **43**: 735-743 [PMID: 28108042 DOI: 10.1016/j.ultrasmedbio.2016.11.020]

36   **Dietrich CF**, Chichakli M, Hirche TO, Bargon J, Leitzmann P, Wagner TO, Lembcke B. Sonographic findings of the hepatobiliary-pancreatic system in adult patients with cystic fibrosis. *J Ultrasound Med* 2002; **21**: 409-16; quiz 417 [PMID: 11934098 DOI: 10.7863/jum.2002.21.4.409]

37   **Pirri C**, Cui XW, De Molo C, Ignee A, Schreiber-Dietrich DG, Dietrich CF. The pancreatic head is larger than often assumed. *Z Gastroenterol* 2013; **51**: 390-394 [PMID: 23585270 DOI: 10.1055/s-0033-1335175]

38   **Frøkjær JB**, Akisik F, Farooq A, Akpinar B, Dasyam A, Drewes AM, Haldorsen IS, Morana G, Neoptolemos JP, Olesen SS, Petrone MC, Sheel A, Shimosegawa T, Whitcomb DC; Working group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis. Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis. *Pancreatology* 2018; **18**: 764-773 [PMID: 30177434 DOI: 10.1016/j.pan.2018.08.012]

39   **Issa Y**, Kempeneers MA, van Santvoort HC, Bollen TL, Bipat S, Boermeester MA. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. *Eur Radiol* 2017; **27**: 3820-3844 [PMID: 28130609 DOI: 10.1007/s00330-016-4720-9]

40   **Andersen PL**, Madzak A, Olesen SS, Drewes AM, Frøkjaer JB. Quantification of parenchymal calcifications in chronic pancreatitis: relation to atrophy, ductal changes, fibrosis and clinical parameters. *Scand J Gastroenterol* 2018; **53**: 218-224 [PMID: 29231795 DOI: 10.1080/00365521.2017.1415372]

41   **Tirkes T**, Shah ZK, Takahashi N, Grajo JR, Chang ST, Venkatesh SK, Conwell DL, Fogel EL, Park W, Topazian M, Yadav D, Dasyam AK; Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Reporting Standards for Chronic Pancreatitis by Using CT, MRI, and MR Cholangiopancreatography: The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Radiology* 2019; **290**: 207-215 [PMID: 30325281 DOI: 10.1148/radiol.2018181353]

42   **Parakh A**, Tirkes T. Advanced imaging techniques for chronic pancreatitis. *Abdom Radiol (NY)* 2020; **45**: 1420-1438 [PMID: 31428813 DOI: 10.1007/s00261-019-02191-0]

43   **Tirkes T**, Yadav D, Conwell DL, Territo PR, Zhao X, Venkatesh SK, Kolipaka A, Li L, Pisegna JR, Pandol SJ, Park WG, Topazian M, Serrano J, Fogel EL; Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Magnetic resonance imaging as a non-invasive method for the assessment of pancreatic fibrosis (MINIMAP): a comprehensive study design from the consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer. *Abdom Radiol (NY)* 2019; **44**: 2809-2821 [PMID: 31089778 DOI: 10.1007/s00261-019-02049-5]

44   **Tirkes T**, Fogel EL, Sherman S, Lin C, Swensson J, Akisik F, Sandrasegaran K. Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis. *Abdom Radiol (NY)* 2017; **42**: 544-551 [PMID: 27660281 DOI: 10.1007/s00261-016-0917-2]

45   **Wang L**, Gaddam S, Wang N, Xie Y, Deng Z, Zhou Z, Fan Z, Jiang T, Christodoulou AG, Han F, Lo SK, Wachsman AM, Hendifar AE, Pandol SJ, Li D. Multiparametric Mapping Magnetic Resonance Imaging of Pancreatic Disease. *Front Physiol* 2020; **11**: 8 [PMID: 32153416 DOI: 10.3389/fphys.2020.00008]

46   **Tamura R**, Ishibashi T, Takahashi S. Chronic pancreatitis: MRCP *vs* ERCP for quantitative caliber measurement and qualitative evaluation. *Radiology* 2006; **238**: 920-928 [PMID: 16424235 DOI: 10.1148/radiol.2382041527]

47   **Schreyer AG**, Jung M, Riemann JF, Niessen C, Pregler B, Grenacher L, Hoffmeister A; German Society of Digestive and Metabolic Diseases (DGVS). S3 guideline for chronic pancreatitis - diagnosis, classification and therapy for the radiologist. *Rofo* 2014; **186**: 1002-1008 [PMID: 25122174 DOI: 10.1055/s-0034-1385005]

48   **Catalano MF**, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, Freeman M, Yamao K, Canto M, Hernandez LV. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. *Gastrointest Endosc* 2009; **69**: 1251-1261 [PMID: 19243769 DOI: 10.1016/j.gie.2008.07.043]

49   **Ge N**, Hu J, Sun S, Linghu E, Jin Z, Li Z. Endoscopic Ultrasound-guided Pancreatic Pseudocyst Drainage with Lumen-apposing Metal Stents or Plastic Double-pigtail Stents: A Multifactorial Analysis. *J Transl Int Med* 2017; **5**: 213-219 [PMID: 29340278 DOI: 10.1515/jtim-2017-0036]

50   **Theerasuwipakorn N**, Tasneem AA, Kongkam P, Angsuwatcharakon P, Ridtitid W, Navicharern P, Kitisin K, Wangrattanapranee P, Rerknimitr R, Kullavanijaya P. Walled-off Peripancreatic Fluid Collections in Asian Population: Paradigm Shift from Surgical and Percutaneous to Endoscopic Drainage. *J Transl Int Med* 2019; **7**: 170-177 [PMID: 32010603 DOI: 10.2478/jtim-2019-0032]

51   **Domínguez-Muñoz JE**, Lariño-Noia J, Alvarez-Castro A, Nieto L, Lojo S, Leal S, de la Iglesia-Garcia D, Iglesias-Garcia J. Endoscopic ultrasound-based multimodal evaluation of the pancreas in patients with suspected early chronic pancreatitis. *United European Gastroenterol J* 2020; **8**: 790-797 [PMID: 32576096 DOI: 10.1177/2050640620936810]

52   **Trikudanathan G**, Vega-Peralta J, Malli A, Munigala S, Han Y, Bellin M, Barlass U, Chinnakotla S, Dunn T, Pruett T, Beilman G, Arain M, Amateau SK, Mallery S, Freeman ML, Attam R. Diagnostic Performance of Endoscopic Ultrasound (EUS) for Non-Calcific Chronic Pancreatitis (NCCP) Based on Histopathology. *Am J Gastroenterol* 2016; **111**: 568-574 [PMID: 26952577 DOI: 10.1038/ajg.2016.48]

53   **Albashir S**, Bronner MP, Parsi MA, Walsh RM, Stevens T. Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis. *Am J Gastroenterol* 2010; **105**: 2498-2503 [PMID: 20606675 DOI: 10.1038/ajg.2010.274]

54   **LeBlanc JK**, Chen JH, Al-Haddad M, Juan M, Okumu W, McHenry L, Cote G, Sherman S, DeWitt JM. Endoscopic ultrasound and histology in chronic pancreatitis: how are they associated? *Pancreas* 2014; **43**: 440-444 [PMID: 24622076 DOI: 10.1097/MPA.0000000000000047]

55   **Chantarojanasiri T**, Hirooka Y, Kawashima H, Ohno E, Kuwahara T, Yamamura T, Funasaka K, Nakamura M, Miyahara R, Ishigami M, Watanabe O, Hashimoto S, Hirakawa A, Ratanachu-Ek T, Goto H. Endoscopic ultrasound in diagnosis of solid pancreatic lesions: Elastography or contrast-enhanced harmonic alone *vs* the combination. *Endosc Int Open* 2017; **5**: E1136-E1143 [PMID: 29124123 DOI: 10.1055/s-0043-118829]

56   **Bamber J**, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, Cantisani V, Correas JM, D'Onofrio M, Drakonaki EE, Fink M, Friedrich-Rust M, Gilja OH, Havre RF, Jenssen C, Klauser AS, Ohlinger R, Saftoiu A, Schaefer F, Sporea I, Piscaglia F. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med* 2013; **34**: 169-184 [PMID: 23558397 DOI: 10.1055/s-0033-1335205]

57   **Hirooka Y**, Kuwahara T, Irisawa A, Itokawa F, Uchida H, Sasahira N, Kawada N, Itoh Y, Shiina T.

JSUM ultrasound elastography practice guidelines: pancreas. *J Med Ultrason (2001)* 2015; **42**: 151-174 [PMID: 26576568 DOI: 10.1007/s10396-014-0571-7]

58   **Dietrich CF**, Burmeister S, Hollerbach S, Arcidiacono PG, Braden B, Fusaroli P, Hocke M, Iglesias-Garcia J, Kitano M, Larghi A, Napoleon B, Oppong KW, Rimbas M, Saftoiu A, Sahai AV, Sun S, Dong Y, Carrara S, Hwang JH, Jenssen C. Do we need elastography for EUS? *Endosc Ultrasound* 2020; **9**: 284-290 [PMID: 32675464 DOI: 10.4103/eus.eus_25_20]

59   **Dietrich CF**, Bibby E, Jenssen C, Saftoiu A, Iglesias-Garcia J, Havre RF. EUS elastography: How to do it? *Endosc Ultrasound* 2018; **7**: 20-28 [PMID: 29451165 DOI: 10.4103/eus.eus_49_17]

60   **Carrara S**, Di Leo M, Grizzi F, Correale L, Rahal D, Anderloni A, Auriemma F, Fugazza A, Preatoni P, Maselli R, Hassan C, Finati E, Mangiavillano B, Repici A. EUS elastography (strain ratio) and fractal-based quantitative analysis for the diagnosis of solid pancreatic lesions. *Gastrointest Endosc* 2018; **87**: 1464-1473 [PMID: 29329992 DOI: 10.1016/j.gie.2017.12.031]

61   **Săftoiu A**, Vilmann P, Gorunescu F, Janssen J, Hocke M, Larsen M, Iglesias-Garcia J, Arcidiacono P, Will U, Giovannini M, Dietrich C, Havre R, Gheorghe C, McKay C, Gheonea DI, Ciurea T; European EUS Elastography Multicentric Study Group. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: a multicenter study. *Endoscopy* 2011; **43**: 596-603 [PMID: 21437851 DOI: 10.1055/s-0030-1256314]

62   **Nakatsubo R**, Yamamoto K, Itoi T, Sofuni A, Tsuchiya T, Ishii K, Tanaka R, Tonozuka R, Mukai S, Nagai K, Yamaguchi H, Nagakawa Y. Histopathological evaluation of needle tract seeding caused by EUS-fine-needle biopsy based on resected specimens from patients with solid pancreatic masses: An analysis of 73 consecutive cases. *Endosc Ultrasound* 2021 [PMID: 33586689 DOI: 10.4103/EUS-D-20-00174]

63   **Iglesias-Garcia J**, Domínguez-Muñoz JE, Castiñeira-Alvariño M, Luaces-Regueira M, Lariño-Noia J. Quantitative elastography associated with endoscopic ultrasound for the diagnosis of chronic pancreatitis. *Endoscopy* 2013; **45**: 781-788 [PMID: 24019131 DOI: 10.1055/s-0033-1344614]

64   **Itoh Y**, Itoh A, Kawashima H, Ohno E, Nakamura Y, Hiramatsu T, Sugimoto H, Sumi H, Hayashi D, Kuwahara T, Morishima T, Funasaka K, Nakamura M, Miyahara R, Ohmiya N, Katano Y, Ishigami M, Goto H, Hirooka Y. Quantitative analysis of diagnosing pancreatic fibrosis using EUS-elastography (comparison with surgical specimens). *J Gastroenterol* 2014; **49**: 1183-1192 [PMID: 24026103 DOI: 10.1007/s00535-013-0880-4]

65   **Dawwas MF**, Taha H, Leeds JS, Nayar MK, Oppong KW. Diagnostic accuracy of quantitative EUS elastography for discriminating malignant from benign solid pancreatic masses: a prospective, single-center study. *Gastrointest Endosc* 2012; **76**: 953-961 [PMID: 22854060 DOI: 10.1016/j.gie.2012.05.034]

66   **Pozzi R**, Parzanese I, Baccarin A, Giunta M, Conti CB, Cantù P, Casazza G, Tenca A, Rosa R, Gridavilla D, Casella G, Conte D, Fraquelli M. Point shear-wave elastography in chronic pancreatitis: A promising tool for staging disease severity. *Pancreatology* 2017; **17**: 905-910 [PMID: 29066007 DOI: 10.1016/j.pan.2017.10.003]

67   **Ohno E**, Hirooka Y, Kawashima H, Ishikawa T. Feasibility of EUS-guided shear-wave measurement: A preliminary clinical study. *Endosc Ultrasound* 2019; **8**: 215-216 [PMID: 30924448 DOI: 10.4103/eus.eus_6_19]

68   **Yamashita Y**, Tanioka K, Kawaji Y, Tamura T, Nuta J, Hatamaru K, Itonaga M, Yoshida T, Ida Y, Maekita T, Iguchi M, Kitano M. Utility of Elastography with Endoscopic Ultrasonography Shear-Wave Measurement for Diagnosing Chronic Pancreatitis. *Gut Liver* 2020; **14**: 659-664 [PMID: 31722469 DOI: 10.5009/gnl19170]

69   **Xie J**, Liu H, Liu WS, Li JW. Quantitative shear wave elastography for noninvasive assessment of solid pancreatic masses. *Clin Hemorheol Microcirc* 2020; **74**: 179-187 [PMID: 31476148 DOI: 10.3233/CH-190665]

70   **Kwon CI**, Cho JH, Choi SH, Ko KH, Tirkes T, Gromski MA, Lehman GA. Recent advances in the diagnosis and management of chronic pancreatitis. *Korean J Intern Med* 2019; **34**: 242-260 [PMID: 30840807 DOI: 10.3904/kjim.2019.051]

71   **Madzak A**, Olesen SS, Haldorsen IS, Drewes AM, Frøkjær JB. Secretin-stimulated MRI characterization of pancreatic morphology and function in patients with chronic pancreatitis. *Pancreatology* 2017; **17**: 228-236 [PMID: 28162928 DOI: 10.1016/j.pan.2017.01.009]

72   **Boninsegna E**, Manfredi R, Negrelli R, Avesani G, Mehrabi S, Pozzi Mucelli R. Pancreatic duct stenosis: Differential diagnosis between malignant and benign conditions at secretin-enhanced MRCP. *Clin Imaging* 2017; **41**: 137-143 [PMID: 27840266 DOI: 10.1016/j.clinimag.2016.10.020]

73   **Wathle GK**, Tjora E, Ersland L, Dimcevski G, Salvesen ØO, Molven A, Njølstad PR, Haldorsen IS. Assessment of exocrine pancreatic function by secretin-stimulated magnetic resonance cholangiopancreaticography and diffusion-weighted imaging in healthy controls. *J Magn Reson Imaging* 2014; **39**: 448-454 [PMID: 23649590 DOI: 10.1002/jmri.24167]

74   **Trikudanathan G**, Walker SP, Munigala S, Spilseth B, Malli A, Han Y, Bellin M, Chinnakotla S, Dunn T, Pruett TL, Beilman GJ, Vega Peralta J, Arain MA, Amateau SK, Schwarzenberg SJ, Mallery S, Attam R, Freeman ML. Diagnostic Performance of Contrast-Enhanced MRI With Secretin-Stimulated MRCP for Non-Calcific Chronic Pancreatitis: A Comparison With Histopathology. *Am J Gastroenterol* 2015; **110**: 1598-1606 [PMID: 26372506 DOI: 10.1038/ajg.2015.297]

75   **Balci NC**, Smith A, Momtahen AJ, Alkaade S, Fattahi R, Tariq S, Burton F. MRI and S-MRCP findings in patients with suspected chronic pancreatitis: correlation with endoscopic pancreatic

function testing (ePFT). *J Magn Reson Imaging* 2010; **31**: 601-606 [PMID: 20187202 DOI: 10.1002/jmri.22085]

76   **Schlaudraff E**, Wagner HJ, Klose KJ, Heverhagen JT. Prospective evaluation of the diagnostic accuracy of secretin-enhanced magnetic resonance cholangiopancreaticography in suspected chronic pancreatitis. *Magn Reson Imaging* 2008; **26**: 1367-1373 [PMID: 18583078 DOI: 10.1016/j.mri.2008.05.007]

77   **Lee LS**, Tabak YP, Kadiyala V, Sun X, Suleiman S, Johannes RS, Banks PA, Conwell DL. Diagnosis of Chronic Pancreatitis Incorporating Endosonographic Features, Demographics, and Behavioral Risk. *Pancreas* 2017; **46**: 405-409 [PMID: 28099256 DOI: 10.1097/MPA.0000000000000768]

78   **Kothari D**, Ketwaroo G, Sawhney MS, Freedman SD, Sheth SG. Comparison of Combined Endoscopic Ultrasonography and Endoscopic Secretin Testing With the Traditional Secretin Pancreatic Function Test in Patients With Suspected Chronic Pancreatitis: A Prospective Crossover Study. *Pancreas* 2017; **46**: 770-775 [PMID: 28609365 DOI: 10.1097/MPA.0000000000000829]

79   **Vanga RR**, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic Performance of Measurement of Fecal Elastase-1 in Detection of Exocrine Pancreatic Insufficiency: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 1220-1228.e4 [PMID: 29374614 DOI: 10.1016/j.cgh.2018.01.027]

80   **Hardt PD**, Marzeion AM, Schnell-Kretschmer H, Wüsten O, Nalop J, Zekorn T, Klör HU. Fecal elastase 1 measurement compared with endoscopic retrograde cholangiopancreatography for the diagnosis of chronic pancreatitis. *Pancreas* 2002; **25**: e6-e9 [PMID: 12131782 DOI: 10.1097/00006676-200207000-00004]

81   **Domínguez-Muñoz JE**, D Hardt P, Lerch MM, Löhr MJ. Potential for Screening for Pancreatic Exocrine Insufficiency Using the Fecal Elastase-1 Test. *Dig Dis Sci* 2017; **62**: 1119-1130 [PMID: 28315028 DOI: 10.1007/s10620-017-4524-z]

82   **Guo J**, Sahai AV, Teoh A, Arcidiacono PG, Larghi A, Saftoiu A, Siddiqui AA, Arturo Arias BL, Jenssen C, Adler DG, Lakhtakia S, Seo DW, Itokawa F, Giovannini M, Mishra G, Sabbagh L, Irisawa A, Iglesias-Garcia J, Poley JW, Vila JJ, Jesse L, Kubota K, Kalaitzakis E, Kida M, El-Nady M, Mukai SU, Ogura T, Fusaroli P, Vilmann P, Rai P, Nguyen NQ, Ponnudurai R, Achanta CR, Baron TH, Yasuda I, Wang HP, Hu J, Duan B, Bhutani MS, Sun S. An international, multi-institution survey on performing EUS-FNA and fine needle biopsy. *Endosc Ultrasound* 2020; **9**: 319-328 [PMID: 32883921 DOI: 10.4103/eus.eus_56_20]

83   **Thornton GD**, McPhail MJ, Nayagam S, Hewitt MJ, Vlavianos P, Monahan KJ. Endoscopic ultrasound guided fine needle aspiration for the diagnosis of pancreatic cystic neoplasms: a meta-analysis. *Pancreatology* 2013; **13**: 48-57 [PMID: 23395570 DOI: 10.1016/j.pan.2012.11.313]

84   **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K; International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]

85   **Sawhney MS**, Devarajan S, O'Farrel P, Cury MS, Kundu R, Vollmer CM, Brown A, Chuttani R, Pleskow DK. Comparison of carcinoembryonic antigen and molecular analysis in pancreatic cyst fluid. *Gastrointest Endosc* 2009; **69**: 1106-1110 [PMID: 19249035 DOI: 10.1016/j.gie.2008.08.015]

86   **Faias S**, Duarte M, Albuquerque C, da Silva JP, Fonseca R, Roque R, Dias Pereira A, Chaves P, Cravo M. Clinical Impact of KRAS and GNAS Analysis Added to CEA and Cytology in Pancreatic Cystic Fluid Obtained by EUS-FNA. *Dig Dis Sci* 2018; **63**: 2351-2361 [PMID: 29796909 DOI: 10.1007/s10620-018-5128-y]

87   **Iglesias-Garcia J**, Dominguez-Munoz E, Lozano-Leon A, Abdulkader I, Larino-Noia J, Antunez J, Forteza J. Impact of endoscopic ultrasound-guided fine needle biopsy for diagnosis of pancreatic masses. *World J Gastroenterol* 2007; **13**: 289-293 [PMID: 17226911 DOI: 10.3748/wjg.v13.i2.289]

88   **Papanikolaou IS**, Adler A, Wegener K, Al-Abadi H, Dürr A, Koch M, Pohl H, Abou-Rebyeh H, Veltzke-Schlieker W, Wiedenmann B, Rösch T. Prospective pilot evaluation of a new needle prototype for endoscopic ultrasonography-guided fine-needle aspiration: comparison of cytology and histology yield. *Eur J Gastroenterol Hepatol* 2008; **20**: 342-348 [PMID: 18334879 DOI: 10.1097/MEG.0b013e3282f2a5cf]

89   **Hewitt MJ**, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. *Gastrointest Endosc* 2012; **75**: 319-331 [PMID: 22248600 DOI: 10.1016/j.gie.2011.08.049]

90   **Grassia R**, Imperatore N, Capone P, Cereatti F, Forti E, Antonini F, Tanzi GP, Martinotti M, Buffoli F, Mutignani M, Macarri G, Manes G, Vecchi M, De Nucci G. EUS-guided tissue acquisition in chronic pancreatitis: Differential diagnosis between pancreatic cancer and pseudotumoral masses using EUS-FNA or core biopsy. *Endosc Ultrasound* 2020; **9**: 122-129 [PMID: 32295970 DOI: 10.4103/eus.eus_75_19]

91   **Karia K**, Waxman I, Konda VJ, Gress FG, Sethi A, Siddiqui UD, Sharaiha RZ, Kedia P, Jamal-Kabani A, Gaidhane M, Kahaleh M. Needle-based confocal endomicroscopy for pancreatic cysts: the current agreement in interpretation. *Gastrointest Endosc* 2016; **83**: 924-927 [PMID: 26382051 DOI: 10.1016/j.gie.2015.08.080]

92   **Kadayifci A**, Atar M, Basar O, Forcione DG, Brugge WR. Needle-Based Confocal Laser Endomicroscopy for Evaluation of Cystic Neoplasms of the Pancreas. *Dig Dis Sci* 2017; **62**: 1346-

1353 [PMID: 28281172 DOI: 10.1007/s10620-017-4521-2]

93   **Hao S**, Ding W, Jin Y, Di Y, Yang F, He H, Li H, Jin C, Fu D, Zhong L. Appraisal of EUS-guided needle-based confocal laser endomicroscopy in the diagnosis of pancreatic lesions: A single Chinese center experience. *Endosc Ultrasound* 2020; **9**: 180-186 [PMID: 32584313 DOI: 10.4103/eus.eus_9_20]

94   **Agarwal S**, Sharma S, Gunjan D, Singh N, Kaushal K, Poudel S, Anand A, Gopi S, Mohta S, Sonika U, Saraya A. Natural course of chronic pancreatitis and predictors of its progression. *Pancreatology* 2020; **20**: 347-355 [PMID: 32107194 DOI: 10.1016/j.pan.2020.02.004]

95   **Swensson J**, Akisik F, Collins D, Olesen SS, Drewes AM, Frøkjær JB. Is Cambridge scoring in chronic pancreatitis the same using ERCP and MRCP? *Abdom Radiol (NY)* 2021; **46**: 647-654 [PMID: 32740862 DOI: 10.1007/s00261-020-02685-2]

96   **Axon AT**, Classen M, Cotton PB, Cremer M, Freeny PC, Lees WR. Pancreatography in chronic pancreatitis: international definitions. *Gut* 1984; **25**: 1107-1112 [PMID: 6479687 DOI: 10.1136/gut.25.10.1107]

97   **Wen C**, Sun H, Pan K, Zhang Z, Cao G, Wang M. Molecular Mechanism Exploration of Pancreatitis Based on miRNA Expression Profile. *Clin Lab* 2019; **65** [PMID: 30868868 DOI: 10.7754/Clin.Lab.2018.180807]

98   **Xin L**, Gao J, Wang D, Lin JH, Liao Z, Ji JT, Du TT, Jiang F, Hu LH, Li ZS. Novel blood-based microRNA biomarker panel for early diagnosis of chronic pancreatitis. *Sci Rep* 2017; **7**: 40019 [PMID: 28074846 DOI: 10.1038/srep40019]

99   **Mayerle J**, Kalthoff H, Reszka R, Kamlage B, Peter E, Schniewind B, González Maldonado S, Pilarsky C, Heidecke CD, Schatz P, Distler M, Scheiber JA, Mahajan UM, Weiss FU, Grützmann R, Lerch MM. Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis. *Gut* 2018; **67**: 128-137 [PMID: 28108468 DOI: 10.1136/gutjnl-2016-312432]

100   **Maekawa T**, Kamada Y, Ebisutani Y, Ueda M, Hata T, Kawamoto K, Takamatsu S, Mizutani K, Shimomura M, Sobajima T, Fujii H, Nakayama K, Nishino K, Yamada M, Kumada T, Ito T, Eguchi H, Nagano H, Miyoshi E. Serum Mac-2 binding protein is a novel biomarker for chronic pancreatitis. *World J Gastroenterol* 2016; **22**: 4403-4410 [PMID: 27158210 DOI: 10.3748/wjg.v22.i17.4403]

101   **Zhu M**, Xu C, Yu J, Wu Y, Li C, Zhang M, Jin Z, Li Z. Differentiation of pancreatic cancer and chronic pancreatitis using computer-aided diagnosis of endoscopic ultrasound (EUS) images: a diagnostic test. *PLoS One* 2013; **8**: e63820 [PMID: 23704940 DOI: 10.1371/journal.pone.0063820]