The Importance of Structural Changes and Imaging in Chronic Pancreatitis

Ingrid Kvåle Nordaas

Thesis for the degree of Philosophiae Doctor (PhD)
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"What I love about science is that as you learn, you don't really get answers. You just get better questions."

John Green

Scientific environment

The research in this dissertation was carried out at the National Centre for Ultrasound in Gastroenterology (NCUG) and the Section for Gastroenterology at Department of Medicine, Haukeland University Hospital, Bergen, Norway, with funding from the Western Norway Regional Health Authority (Helse Vest RHF).

The Bergen Research Group for Ultrasound in Gastroenterology (BRUSE) at the Department of Clinical Medicine, University of Bergen is headed by Professor Odd Helge Gilja. BRUSE aims to develop and validate clinical ultrasound methods in gastroenterology. BRUSE has been widely internationally recognized and has broad collaborations in the fields of transabdominal and endoscopic ultrasonography. The Pancreas group within BRUSE is led by Professor Georg Dimcevski and Dr. Trond Engjom, and the group has provided excellent guidance and a stimulating environment.

NCUG was established by the Norwegian Health Authorities in 2001 and has a national function as a center of excellent competence for educating and teaching in clinical ultrasound to gastroenterologists in Norway. In 2014, NCUG was accredited as a European Learning Centre for Gastrointestinal Ultrasound.

Over 375 peer-reviewed publications and 25 completed dissertations have emerged from the NCUG/BRUSE environment, and 5 are currently ongoing.

Acknowledgements

This thesis is not just my own, it is a result of the joint efforts of my supervisors, fellow researchers and pancreas enthusiasts, friends, and family.

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Abbreviations

AUROC	Area under the receiver operating characteristic curve
BMI	Body mass index
CCK	Cholecystokinin
CI	Confidence interval
CP	Chronic pancreatitis
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
FE-1	Fecal elastase 1
IQR	Interquartile range
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
OR	Odds ratio
PEI	Pancreatic exocrine insufficiency
ROC-curve	Receiver operating characteristic curve
SBPC	Scandinavian Baltic Pancreatic Club
S-MRCP	Secretin stimulated magnetic resonance cholangiopancreatography
US	Transabdominal ultrasound

Abstract

Background: Chronic pancreatitis (CP) is diagnosed using combinations of symptoms, patient history, pancreatic function tests, and imaging. Imaging is also important in follow-up, for instance, if complications are suspected.

Aims: The overall objective was to evaluate the importance of diagnostic imaging modalities and different structural pancreatic changes in CP. In the first study, we aimed to evaluate the diagnostic accuracy of computed tomography (CT) scores, and in the second study, we aimed to compare the diagnostic accuracy of CT and ultrasound (US). In the third study, we aimed to explore the associations between key structural pancreatic changes and common complications related to CP.

Material and methods: Using a local database with registrations on patients with suspected CP, we evaluated the diagnostic accuracy of CT (n = 118). In patients who had been examined with CT and US (n = 73), we compared diagnostic performance of CT versus US. Using data registrations from 959 patients with CP included in an international multicenter database, we performed multiple logistic regression analyses to assess the relationships between structural pancreatic changes and clinical complications (pancreatic exocrine insufficiency, diabetes, underweight, and pain).

Results: For CT, we found sensitivities ranging from 63% to 72% and specificities from 75% to 91%. US had sensitivities between 64% and 72% and specificity of 85%. The differences between CT and US were not statistically significant. Patients with ductal obstruction, ≥15 calcifications, pancreatic atrophy, or parenchymal changes involving the entire pancreas were more likely to have CP related complications.

Conclusions and consequences: CT and US had similar, moderate diagnostic accuracy for CP. Our findings point to the importance of a multimodal workup and the weaknesses in the current imaging scoring systems. Structural imaging changes that are associated to complications may be used in the development of severity scoring systems. If these structural changes are detected in CP patients, closer monitoring for the development of complications is warranted.

List of Publications

1. Nordaas IK, Dimcevski GD, Gilja OH, Havre RF, Haldorsen IS, Engjom T. Diagnostic Accuracy of Computed Tomography Scores in Chronic Pancreatitis. Pancreas. 2021 Apr 1;50(4):549-555.

2. Nordaas IK, Engjom T, Gilja OH, Havre RF, Sangnes DA, Haldorsen IS, Dimcevski GD. Diagnostic Accuracy of Transabdominal Ultrasound and Computed Tomography in Chronic Pancreatitis: A Head-to-Head Comparison. Ultrasound International Open. 2021 Aug 24;07(01):E35-E44.

3. Nordaas IK, Tjora E, Dimcevski G, Haldorsen IS, Olesen SS, Drewes AM, Zviniene K, Barauskas G, Bayram BK, Nørregaard P, Borch A, Nøjgaard C, Jensen AB, Kardasheva SS, Okhlobystin A, Hauge T, Waage A, Frøkjær JB, Engjom T, the Scandinavian Baltic Pancreatic Club. Structural Imaging Findings are Related to Clinical Complications in Chronic Pancreatitis. *Submitted to United European Gastroenterology Journal on August 30th 2021.*

Contents

2. Introduction

Chronic pancreatitis (CP) is a progressive and multifaceted disease of the pancreas which may present and develop as a manifold of phenotypes. Therefore, CP can be difficult to diagnose, and a variety of imaging modalities and scoring systems are applied. Over the past two decades, imaging technology and hence quality have significantly improved, increasing the potential applications of imaging in CP. Understanding the strengths and limitations of the imaging modalities and associated scoring systems is necessary for both clinicians and researchers working with CP.

Throughout this thesis, I hope to add to the knowledge on the value of diagnostic imaging and imaging scores in CP, with a particular focus on two fundamental imaging modalities: computed tomography (CT) and transabdominal ultrasound (US). I also explore the potential diagnostic and clinical importance of the structural pancreatic changes that can be depicted on imaging in patients with CP.

2.1 The healthy pancreas

2.1.1 Gross anatomy

The pancreas is an organ positioned in the retroperitoneal, upper abdomen. It reaches from the inner curvature of the duodenum, behind the stomach, and towards the hilum of the spleen. The pancreas varies in size between individuals [1] and weighs around 80 g [2]. It is lobulated, soft, and non-capsulated. It consists of four segments: the head, neck, body, and tail (Figures 1 and 2). The pancreatic head also includes the uncinate process.

The arterial supply for the pancreas is complex and includes different branches from the gastroduodenal, mesenteric superior, and splenic arteries [3; 4]. The venous drainage of the pancreas is through the superior mesenteric vein and the splenic vein, which both drains to the portal vein [2]. The sympathetic and parasympathetic nervous systems innervate the pancreas. The sympathetic innervation derives from the lateral grey matter of the lumbar and thoracic spinal cord [2]. The sympathetic nervous system innervates pancreatic blood vessels. The parasympathetic branches derive from the

vagus nerve, and synapse with intrapancreatic ganglia, which again innervate endocrine and exocrine structures [2].

The pancreas is comprised of exocrine tissue, endocrine tissue, and interstitial tissues including connective tissue and fat. Key functions of the pancreas are to contribute to digestion and glucose homeostasis.

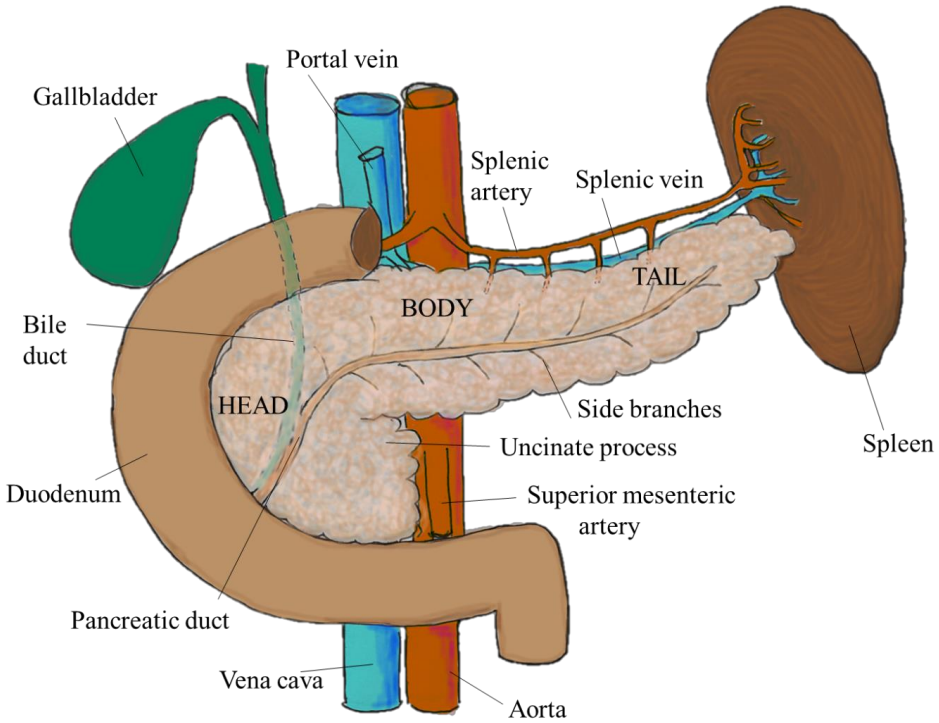

***Figure 1**: Pancreatic gross anatomy and relations to surrounding structures.*
Illustration: IK Nordaas

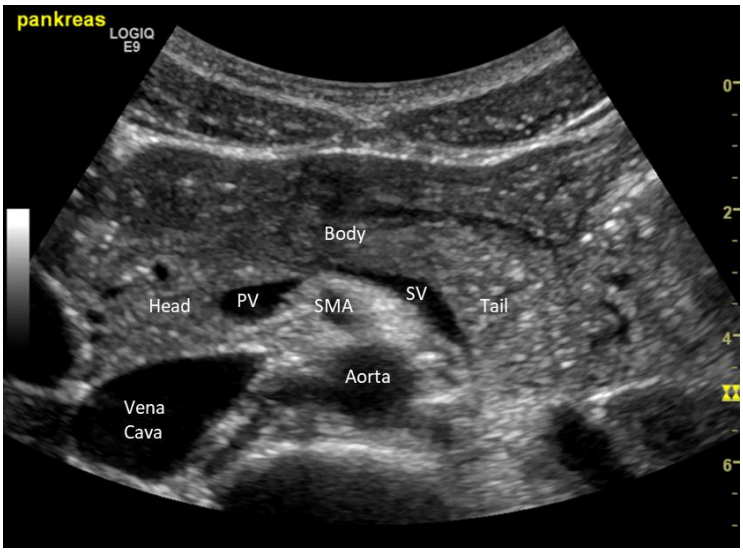

***Figure 2**: US image showing the head, body, and tail of the pancreas and surrounding structures. Abbreviations: PV = portal vein. SMA = superior mesenteric artery. SV = splenic vein. Adapted from Dr. Trond Engjom.*

2.1.2 The exocrine pancreas

As much as 95% of the pancreas consists of exocrine tissue: pancreatic acini and ductal systems [2; 5]. The exocrine pancreas synthesizes, stores and secretes pancreatic enzymes in the acini before water and electrolytes are added in the acinar tubules and ducts. The final product is pancreatic juice, which is secreted into the duodenum in response to meals [2].

The pancreatic ductal system handles pancreatic juice and consists of the main pancreatic duct (MPD) and the pancreatic side ducts (Figure 3). The MPD reaches from the pancreatic tail to the head. Pancreatic juice runs from the small ducts to the MPD and towards the pancreatic head. In the pancreatic head, the MPD and the common bile duct join and run through the sphincter of Oddi and the major papilla. In addition, some patients have a patent accessory pancreatic duct with a separate outlet to the duodenum through the minor duodenal papilla [6].

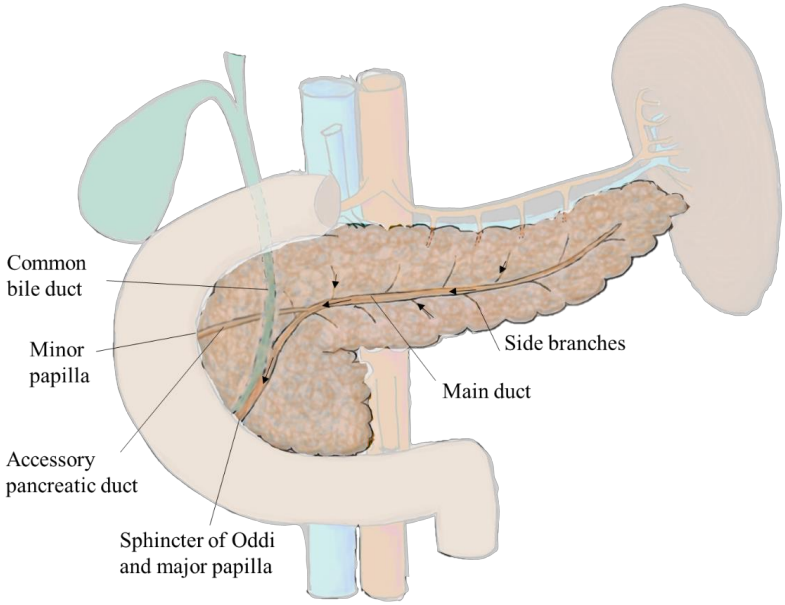

***Figure 3**: The pancreatic ductal system including a patent accessory pancreatic duct. Arrows indicate pancreatic juice flow direction. Illustration: IK Nordaas*

The pancreatic exocrine functions are regulated by two hormones in particular, secretin and cholecystokinin (CCK). Secretin and CCK are released in response to meals, specifically by acid, bile, protein, and fat in the duodenum [7].

When stimulated through secretin and CCK, the exocrine pancreas secretes digestive enzymes and proenzymes. The most important enzymes include proteases (trypsin, chymotrypsin, carbopepdidases, and elastase), lipases (colipase, phospholipase), amylases (α-amylase), and nucleases (ribonuclease, deoxy ribonuclease) [8]. They split nutrients (proteins, amino acids, fatty acids, glycerides, cholesterol, starch, DNA, and RNA) into splitting products which can be absorbed, and thus are vital for maintaining a normal nutritional status.

In addition to digestive enzymes, pancreatic juice is rich in bicarbonate which helps optimize the environment for the actions of pancreatic enzymes and avoid damage to the intestinal mucosa through neutralization of acidic contents from the stomach and inactivation of pepsin [2].

2.1.3 The endocrine pancreas

Islets of Langerhans were described in 1869 by Paul's Langerhans [9] and can be found situated amongst the exocrine tissue (Figure 4). This endocrine tissue only constitute a small portion of the pancreas, about 2% [10], but its function is highly critical in human health.

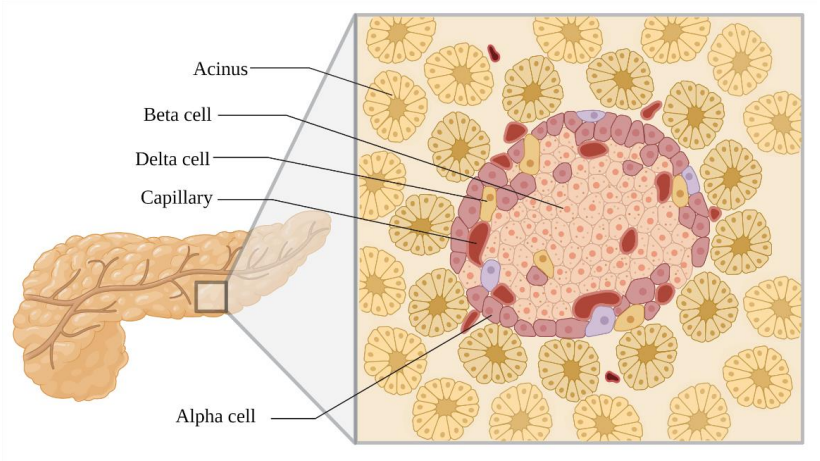

***Figure 4**: An Islet of Langerhans closely surrounded by exocrine acini.*
Illustration: IK Nordaas, created with BioRender.com.

The islets are comprised of cells with different functions in regulating glucose homeostasis; alfa-, beta-, delta-, and pp-cells [11]. The glucose homeostasis is complex, but in short, beta cells produce insulin in response to high glucose levels resulting in increased cellular glucose uptake [11; 12], whilst glucagon is produced by alpha cells in response to hypoglycemia and mobilizes glucose release from the liver [11]. Delta cells produce somatostatin which acts predominantly as an inhibitor on numerous processes in the central nervous system and in endocrine and exocrine systems throughout the body. Pancreatic polypeptide is produced by the pp-cells, and one of its functions is inhibiting pancreatic exocrine activity [13].

The hormones are released directly into the bloodstream, which passes through the exocrine pancreas, allowing the hormones to function locally [2; 14-16].

2.1.4 Interstitial tissues of the pancreas

Interstitial tissue surrounds the pancreatic exocrine and endocrine tissue, and contains blood and vessels, lymphatics, nervous tissue, and pancreatic stellate cells. The stellate cells are connective tissue cells with star-like shape [17; 18]. Stellate cells comprise about 4% of pancreatic cells and are responsible for producing extracellular matrix components, growth factors and cytokines [19]. These cells have been found to have a key role in pancreatic inflammation and the development of fibrosis in pancreatic cancer and chronic pancreatitis (CP) [19].

2.2 Evaluating pancreatic function

2.2.1 Evaluating exocrine function

Pancreatic exocrine insufficiency (PEI) is defined as insufficient activity of the pancreatic digestive enzymes as a result of inadequate enzyme production, inadequate enzyme activation or early enzyme degradation [20]. In CP, PEI is mainly caused by inadequate enzyme production from the acini due to loss of healthy exocrine parenchyma, in addition to insufficient secretion of sodium bicarbonate by the pancreatic ductal system [21].

Steatorrhea, meaning fatty stools due to fat malabsorption, occurs when less than approximately 10% the exocrine function remains [22; 23]. Steatorrhea is a hallmark of severe PEI. Consequences of PEI can be abdominal discomfort and bloating, underweight, malnutrition with fat-soluble vitamin deficiencies (A, D, E, and K), and deficiencies of folic acid, thiamine, magnesium, calcium, and zinc [24-27]. Vitamin D deficiency may cause decreased bone mass [28].

When evaluating exocrine function, non-invasive function tests are recommended as the first-line test in clinical settings [21], and the fecal elastase-1 (FE-1) test is widely used. Tests can be categorized as direct or indirect. Direct tests involve collection of pancreatic fluids in the duodenum after intravenous secretin stimulation (with or without CCK), and measure ions and enzymes. Indirect tests measure the effects of the

pancreatic function, enzymes in stool, or ions and enzymes in duodenal juice after meal ingestion [29].

Stimulated direct exocrine function tests

The secretin stimulated tube test and the secretin stimulated endoscopic short tests are invasive, but these direct tests are considered gold standards for detecting PEI due to their ability to detect mild insufficiencies [21; 30]. Whilst the secretin stimulated tube test is performed either by a double-lumen or a double-balloon nasoduodenal tube, the endoscopic short test uses an endoscope. The objective is to isolate and aspirate the pancreatic fluids secreted to the duodenum following secretin stimulation [31; 32]. Pancreatic secretion volume and concentrations of bicarbonate can then be determined. A limitation to secretin stimulated tests is that secretin mainly stimulates the ductal system and not the acini. Despite their high accuracy, these procedures are complex and time-consuming. Endoscopic short tests are rarely performed outside specialized centers [21; 33; 34].

Fecal elastase

The FE-1 test is widely used due to availability and feasibility [21; 35]. It only requires a small stool sample, is stable at room temperature for several days, and results are not affected by pancreatic enzyme replacement therapy. The FE-1 test estimates the fecal concentration of elastase using antibodies against pancreatic elastase through a monoclonal ELISA test [36]. Consensus regarding the cut-off for PEI is lacking, and diagnostic accuracy varies depending on the applied cut-off; while the commonly used cut-off of <200 μg/g is sensitive for moderate and severe PEI, the sensitivity for mild PEI is poor. A meta-analysis showed pooled sensitivities of 47% for mild PEI, 67% for moderate PEI, and 97% for severe PEI [37]. False positives can occur in patients with loose stools due to sample dilution [37; 38].

Fecal fat output

The gold standard for evaluating fat absorption is collection of stools for quantification of fecal fat output, but despite suggested modifications, the method is still inconvenient and rarely used [37; 39-41].

C13 mixed triglyceride breath test

For this test, the patient consumes a standardized meal containing C^{13}-labeled fatty substrates, and the recovered C^{13} isotope is measured in the exhaled air [42; 43]. The test correlates with fecal fat excretion and duodenal lipase output [44; 45] and has high diagnostic accuracy for PEI in CP [42; 43]. Results on reproducibility vary [46-48]. It is without risk to patients, but it is time-consuming despite of shortened protocols [43].

Secretin stimulated magnetic resonance imaging

Secretin stimulated magnetic resonance imaging (S-MRI) provides information on pancreatic output to the duodenum, and the estimates have been shown to correlate with exocrine function [49]. Because it only measures output volume, and not enzyme or bicarbonate concentrations, the usefulness of S-MRI as a pancreatic function test is reduced in CP where the acinar axis may be more compromised than the ductal axis [49].

2.2.2 Evaluating endocrine function

Diabetes mellitus caused by diseases of the exocrine pancreas such as CP, pancreatic cancer, cystic fibrosis, and haemochromatosis is categorized as type 3c diabetes [50]. In CP, diabetes is most frequent in patients with longstanding disease [51; 52]. Pancreatic endocrine function is evaluated based on plasma glucose or glycated hemoglobin (HbA1c). Ideally, plasma glucose is measured in fasting state or after an oral glucose tolerance test. Type 3c diabetes is often misdiagnosed as type 2 diabetes [53], but this can be avoided by examining for PEI and performing pancreatic imaging. Type 1 diabetes associated autoimmunity is not present in type 3c diabetics [54].

2.3 Diseases affecting the pancreas

The most common diseases of the exocrine pancreas are acute pancreatitis, CP, and pancreatic ductal adenocarcinoma [55; 56]. Less common diseases include cystic fibrosis, autoimmune pancreatitis, cystic diseases, and other pancreatic neoplasms [57-59]. The symptoms of pancreatic disease span from none to severe, and may include abdominal pain, diabetes, and pancreatic exocrine insufficiency with malnutrition and

steatorrhea. Pancreatic function can also be disturbed in non-pancreatic diseases, for instance, PEI occurs in patients with coeliac disease and inflammatory bowel diseases [60].

Pancreatic diseases may overlap with respect to structural pancreatic changes on imaging. This is exemplified by cystic structures which can be seen in acute and chronic pancreatitis, cystic fibrosis, and pancreatic malignancies, but also occur as accidental and benign findings in healthy subjects [61]. Pancreatic calcifications are considered pathognomonic to CP [62-64], but can also be found in elderly individuals [65] and in other conditions such as cystic fibrosis, several pancreatic neoplasms and metastases, and longstanding autoimmune pancreatitis [66-68]. Vascular calcifications (*e.g.,* in the splenic artery) or calcified gallstones in the pancreatic head may mimic pancreatic calcifications [67]. A study on patients undergoing pancreatic CT scans found that 68% of patients with pancreatic calcifications had CP, whereas 32% had other pancreatic disorders [69].

2.4 Chronic pancreatitis

CP can be defined using different approaches, but the key message remains that CP is a consequence of lasting damage to the pancreatic parenchyma, which may result in pancreatic exocrine and endocrine insufficiency [21; 70]. In the traditional definition, inflammation and fibrosis are weighted [21; 30]:

"CP is a disease of the pancreas in which recurrent inflammatory episodes result in replacement of the pancreatic parenchyma by fibrous connective tissue. This fibrotic reorganization of the pancreas leads to progressive exocrine and endocrine pancreatic insufficiency."

The proposed mechanistic definition [70] also give weight to genetic, environmental, and other risk factors driving disease development.

2.4.1 Symptoms of chronic pancreatitis

Symptoms of CP include abdominal bloating, discomfort and pain, and symptoms related to PEI (malnutrition, weight loss, osteopenia) and diabetes. Patients may also be asymptomatic [21; 71; 72]. Pain is the dominating symptom in CP [73-75]. It is typically located in the upper abdomen and may radiate towards the back. Some experience extra-pancreatic pain due to maldigestion from PEI. Pain characteristics vary between patients and over time, and it may be mild or severe, intermittent, persistent, or persistent with intermittent attacks of more severe pain [76]. In CP, pain is associated with reduced quality of life [75].

2.4.2 Diagnosing chronic pancreatitis

The listed symptoms of CP are non-specific to the disease. In addition, CP is multifaceted, and patients with CP may present with none or several positive findings on imaging and pancreatic function tests. Reaching a diagnosis can be difficult because of the varying presentation, and different diagnostic scoring systems have been developed [72; 77; 78]. These systems provide a diagnosis based on findings such as symptoms (pain, history of acute pancreatitis), pancreatic function (PEI, diabetes), structural changes on imaging, and histology.

2.4.3 Epidemiology

Estimates on the frequencies of CP vary, and studies report prevalence ranging from 14 to 143 per 100 000 and incidences between 4 and 14 new cases per 100 000 per year [55; 79-84]. The incidence of CP seems to increase, perhaps due to improvements in CP diagnostics. The disparity in prevalence and incidence estimates might be caused by differences in disease definitions and health care organization, but underestimation of CP is also likely [21; 71; 81; 85]. Factors contributing to underdiagnosing may include the variation in presenting symptoms, inadequate methods/scores for diagnosing CP, and patient compliance.

2.4.4 From risk factors to chronic pancreatitis

Risk factors associated to CP are commonly classified by the M-ANNHEIM or the TIGAR-O classifications [77; 86; 87]. Alcohol consumption, smoking, genetic, and idiopathic etiologies may be the most common [88].

We still do not completely understand how some etiological risk factors infer damage and start the process towards CP. A current opinion is that in the majority of patients, more than one factor contributes to the development of CP [71]. Repeated or prolonged injury to the pancreatic parenchyma and activation of interstitial stellate cells are key elements. Several hypotheses for the CP pathogenesis have been described, possibly interacting in driving disease progression [89]. These hypotheses include repeated pancreatic damage inferred by recurrent acute pancreatitis, metabolic-toxic effects from environmental factors such as alcohol and smoking, oxidative stress due to free radicals, and ductal dysfunctions [29; 85; 89]. At last, the sentinel acute pancreatitis event hypothesis or two-hit hypothesis [90; 91] proposes that after an initial pancreatic inflammation sparked by a risk factor to acute pancreatitis, sustained inflammation due to additional risk factors can result in progression towards CP.

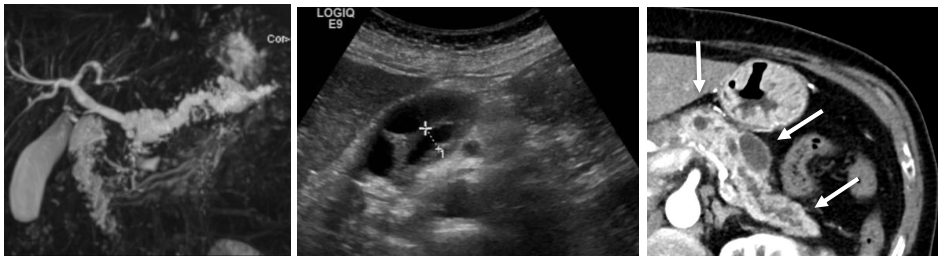

Figure 5*: MRI, US, and CT scans from a patient with CP and branch duct intraductal papillary mucinous neoplasms (IPMN). Symptoms included diabetes and episodes of acute pancreatitis. Imaging showed an atrophic pancreas with multiple cysts, several punctate calcifications, intraductal calculi, duct dilatation, pathological side ducts, and ductal irregularities. The branch duct IPMN may have caused obstruction and thus triggered acute inflammation and CP development. Contributing risk factors included smoking and alcohol abuse. This casus illustrates an overlap in structural features between pancreatic diseases, and how multiple risk factors may result in CP development. Sources: Dr. Trond Engjom and Dept. of Radiology, Haukeland University Hospital.*

2.4.5 Treatment and follow-up

There is no cure for CP [21]. Still, establishing a correct diagnosis is important to give patients an opportunity to understand and manage their symptoms, and for health care professionals to provide correct advice, treatment, and follow-up [92]. Patients with CP should be encouraged to smoking and alcohol cessation [21; 92-94], and medical treatment include pain management and treatment for diabetes and PEI [21]. Endoscopic and surgical interventions are options for patients with intractable pain, local complications or suspected malignant lesions [95]. Early intervention increases chance of successful outcome in CP patients undergoing surgical intervention [96]. It is recommended to monitor patients for development of diabetes, malnutrition, and PEI [21; 30; 97]. Screening for pancreatic cancer is not generally recommended [92; 98], but may be considered in individuals with particularly high risk (*e.g.,* hereditary CP) [21; 30].

2.4.6 Prognosis and severity scoring

In CP, mortality rates are 1.7 to 4.5 times higher compared to the general population [99-101]. Factors that predict increased mortality in CP patients include smoking, drinking, age at time of diagnosis, diabetes, PEI, and poor nutritional status [99; 101].

In a recent systematic review, Rahman et al. [102] evaluated current CP classifications and severity scoring systems, and advocated for the development of a new, comprehensive severity and prognostic score for CP. They recommend that such a score should include etiology, presence of structural changes, and presence of clinical complications (PEI, diabetes, pain).

To our knowledge, the Chronic Pancreatitis Prognosis Score (COPPS) [103] is the only validated prognostic score for CP. It predicts the short-term (1 year) risk of hospitalization, but it does not provide any suggestions of long-term risk.

2.5 Imaging in chronic pancreatitis

In CP, imaging is drawn on for diagnostics, follow-up, and detection of complications. Computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), transabdominal ultrasound (US), and endoscopic retrograde cholangiopancreatography (ERCP) are relevant imaging modalities [104].

Most guidelines recommend cross-sectional imaging (CT or MRI) for the initial workup for CP [71; 105]. Cross-sectional imaging is available worldwide and works excellent as a baseline examination if structural complications are encountered later in the disease course. The role of US in CP diagnostics is debated [21; 30; 106-108], but because US is a first line modality for patients with upper abdominal pain [21; 109], exploring its diagnostic value is important. EUS reportedly has high diagnostic accuracy for CP and is sensitive to subtle parenchymal and ductal changes which may relate to early CP [110], but it is invasive. Due to risk of complications, use of ERCP should be limited to therapeutic applications [21; 30; 111; 112]. For more details on each modality, see *Section 2.5.2*.

The diagnostic performance of different imaging modalities in CP was summarized in a systematic review and meta-analysis [104]. They found that CT, MRI, EUS, and ERCP had similar, high accuracies for the diagnosis, whilst US had the lowest accuracy (Table 1). Several of the included studies were published >20 years ago, particularly those evaluating ERCP, CT or US. They concluded that the choice of modality should be based on invasiveness, costs, local availability, and experience.

Estimated overall diagnostic performance for CP		
Modality	Sensitivity (95% CI), %	Specificity (95% CI), %
EUS	81 (70 – 89)	90 (82 – 95)
ERCP	82 (76 – 87)	90 (82 – 95)
MRCP	78 (69 – 85)	94 (87 – 98)
CT	75 (66 – 83)	96 (90 – 98)
US	67 (53 – 78)	91 (81 – 96)

***Table 1**: Estimated overall sensitivity and specificity for diagnosing CP. Modified from: Issa Y. et al., European Radiology 2017 [104].*

2.5.1 Structural pancreatic changes

Structural pancreatic changes in CP may be progressive and originate from pathologic inflammation and repair processes [71]. Changes corresponding to acute pancreatic inflammation may be present, particularly in the early phases of the disease. As the disease progresses, histopathological changes cause loss of healthy tissue and deterioration of the architectural structure of the gland as the disease progresses [85], and chronic features become more prevalent on imaging [113]. It is common to categorize structural changes as ductal or parenchymal (Table 2), and the changes may occur in only segments of the pancreas or throughout the organ (*continuous organ involvement*). Tirkes et al. [114] suggested that reporting the distribution of findings may be of importance because of relations between distribution and pancreatic function.

Structural pancreatic changes	
Parenchymal	**Ductal**
Parenchymal calcifications	Intraductal calculi/stones
Fibrosis / stranding	MPD dilatation
Gross structural derangement / lobulation	Duct obstruction
Pancreatic atrophy	Duct irregularities
Pseudocysts	Dilated side branches
(Acute inflammation)	

Table 2*: Summary of structural pancreatic changes observed on imaging in patients with CP. The changes are often categorized as parenchymal or ductal.*

Calcifications are pathognomonic for CP [62-64] and may occur both in the pancreatic ducts and in the parenchyma. Calcifications are hyperdense foci on CT and hyperechoic foci with or without posterior shadows on EUS and US [115]. Intraductal stones present on US as echogenic structures with posterior shadows in the pancreatic duct [115]. On US, smaller calcifications may be distinguished from irregular pancreatic parenchyma by applying color Doppler to detect twinkling artifacts [116; 117]. MRI has low sensitivity for calcifications [118]. Calcifications have been associated to PEI and diabetes [119; 120]. Patients with CP due to smoking or alcohol abuse are more likely to have calcifications, and patients with smoking etiology may have a higher number of calcifications [113]. A study found number of calcifications to be negatively

correlated to BMI, but they found no significant correlation to structural pancreatic changes or other clinical patient characteristics [121].

Pancreatic atrophy is a common feature in CP, but it is not included in most diagnostic/imaging scoring systems [77; 78; 110; 122]. The normal range for pancreatic diameter is broad [1] and there is no consensus regarding the cut-off for atrophy [105]. Additionally, pancreatic size is known to decrease in high age [1; 123; 124], and females have been found to have smaller glands compared to men [1]. Estimating pancreatic volume can be done using 3D rendering based on CT and MRI [125; 126]. This may be more accurate than anteroposterior diameters for assessing pancreatic size, but the necessary post-processing is time-consuming [114]. Use of anteroposterior diameters was suggested in a recently proposed CP imaging scoring system [127] and in reporting standards for pancreatic imaging in CP [114]. Studies have found pancreatic size to be associated with impaired pancreatic function [127; 128].

Ductal changes. The normal MPD is wider in the pancreatic head compared to body and tail, and duct diameters are increased elderly patients [129; 130]. The cut-off for duct dilatation varies slightly depending on the definition applied, but the duct is generally considered dilated when it measures >3–4 mm in the head or body, and >1.5 mm in the tail [110; 122; 131]. Dilatation can be caused by ductal calculi or strictures causing obstruction with upstream duct dilatation, but also occurs without visible obstruction. Other ductal changes include irregular ducts and dilated side ducts. Ducts are categorized as irregular if a caliber variation >1 mm is present, or severely irregular if >2 mm. Dilated side ducts can be seen as tubular structures that communicate with the MPD and are best visualized using MRI/MRCP or ERCP.

Pancreatic pseudocysts are oval or round fluid filled cystic lesions and occur in or close to the pancreas in 20-40% of patients with CP [131; 132]. On US and EUS they are anechoic with posterior enhancement. Pseudocysts present with high intensity signal on T2-weighted MRI. MRI, CT, EUS, and US all have reported high sensitivity and specificity for detecting pseudocysts [132]. Patients with pseudocysts may have no

associated symptoms, or they may experience acute or chronic complications, for instance pain, pancreatitis, infection, bleeding, ruptures, and compression of the common bile duct, duodenum or stomach [133].

Fibrosis is a hallmark of CP [134], but grading fibrosis on imaging can be complicated. Irregular ductal contour on CT and reduced ductal compliance on S-MRCP imply periductal fibrosis [135]. On EUS, hyperechoic foci or bands without shadowing are proposed to represent parenchymal fibrosis, whilst ductal fibrosis can be seen as hyperechoic MPD margins [110]. New MRI based methods for detecting parenchymal fibrosis (*e.g.,* apparent diffusion coefficient from diffusion-weighted MRI, T1-weighted signal intensity ratio, elastography) are also being explored [136; 137]. Because fibrosis starts to develop early in the disease course, such methods may be useful in diagnosing early CP [136].

2.5.2 The imaging modalities

Abdominal radiography

Abdominal radiography, or abdominal X-ray, can depict pancreatic calcifications [138] and was used CP diagnostics before cross-sectional imaging was available. The method has low sensitivity, and is no longer used for diagnosing CP [138].

Endoscopic retrograde cholangiopancreatography

ERCP was previously considered the gold standard for diagnosing CP, but as stated, it is not currently applied in diagnostics due to invasiveness and risk of complications [21; 30; 71; 139]. ERCP has high diagnostic accuracy, but a meta-analysis from 2017 [104] showed that other modalities, namely EUS, MRI, and CT, had similarly high diagnostic accuracy. A benefit with ERCP is that it may dilate the pancreatic ductal system, making subtle ductal changes more apparent [105]. On the other hand, ERCP does not depict the pancreatic parenchyma, and ERCP is subject to operator dependency and interobserver variability [140].

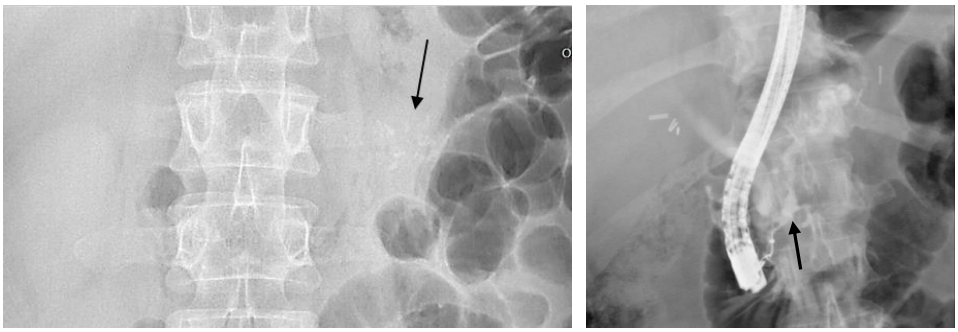

Figure 6: *Left panel: Abdominal radiography showing multiple calcifications in the pancreatic region. Image: Department of Radiology. Right panel: ERCP image showing an irregular and dilated pancreatic duct with obstructing chalk stones.*
Source: Dept. of Surgery, Haukeland University Hospital.

Computed tomography

Today, CT is widely available and considered by most to be an appropriate first-line modality in CP diagnostics [21; 92] and the preferred modality for detecting pancreatic calcifications [104; 121]. Other benefits of CT include its ability to detect structural complications (*e.g.,* vascular involvement, pseudocysts, pancreatic cancer) and rule out differential diagnoses to abdominal pain [105]. Though tissue sampling is more reliable and often necessary, both MRI and CT have a role in differentiating mass-forming CP from pancreatic cancer [141]. The use of CT should be limited in patients where ionizing radiation or intravenous iodinated contrast agents should be avoided, and when repeated use is necessary [142-144]. Because CT has low sensitivity to subtle changes in the pancreatic ducts, its usefulness is limited in early CP.

The recommended protocol for depicting the pancreas includes thin slices through the pancreas and the upper abdomen, depicted without contrast and with contrast in the late arterial phase (+40 s after contrast infusion initiation) and the portal venous phase (+70–90 s after contrast infusion initiation) [138]. If pancreatic malignancy is suspected, a delayed phase scan (3–5 min after contrast) is also indicated. A pancreatic CT allows for assessment of both the parenchyma and the ductal system. Images without contrast are best for detecting calcifications and are useful for assessing the

contours of the organ [138]. When assessing the parenchyma and ductal systems, contrast images in the late arterial and portal phase are preferred.

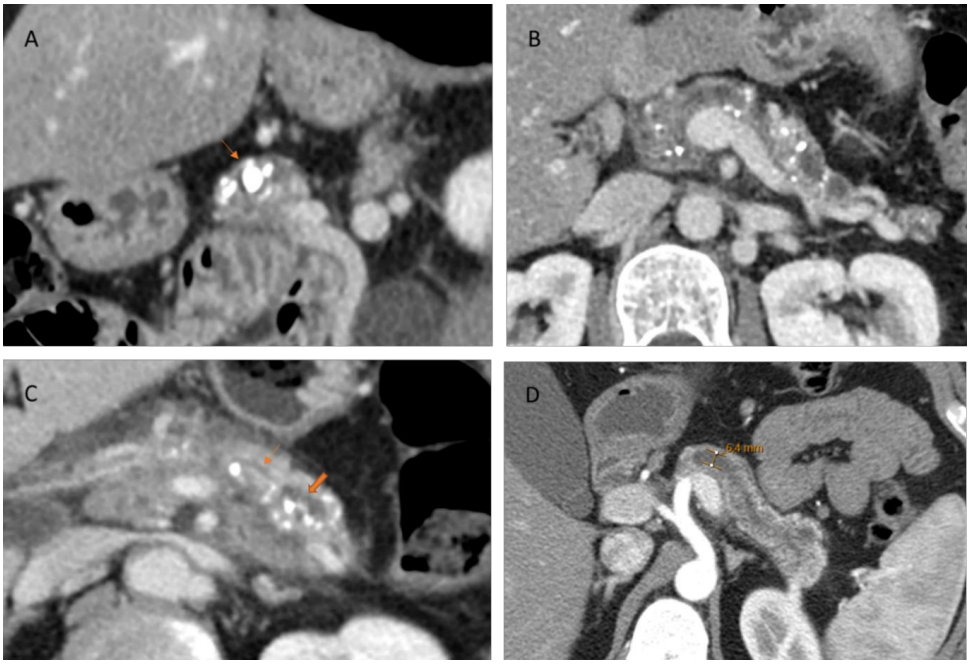

Figure 7: *Examples of structural pancreatic changes on CT in patients with CP. Panel A: parenchymal calcifications and a large, obstructing intraductal calcification (arrow). Panel B: an atrophic pancreas with severe calcifications and an irregular and dilated main duct. Panel C: calcifications and a highly irregular duct (arrows). Panel D: dilated duct. Source: Dept. of Radiology, Haukeland University Hospital.*

Magnetic resonance imaging

MRI is excellent for depicting the ductal system, parenchyma, and cystic structures, but it is not sensitive for parenchymal calcifications, and is rarely used for this purpose [114; 145]. MRI is non-invasive and does not involve radiation, which makes it a good option in young individuals and if repeated examinations are required. Pancreatic MRIs can be performed with or without contrast. When using contrast, scans are performed in arterial, portal-venous, and delayed venous phase [138].

Magnetic resonance cholangiopancreatography (MRCP) are T2-weighted MRI images that have been processed to provide a better depiction of the biliary and pancreatic ductal systems. Structural changes of the ductal system become more evident on secretin stimulated MRCP compared to traditional MRCP [146; 147]. This improves the diagnostic accuracy for anomalies and diseases of the ductal system [148; 149]. However, Issa et al. [104] found no significant differences between MRCP and s-MRCP for diagnosing CP.

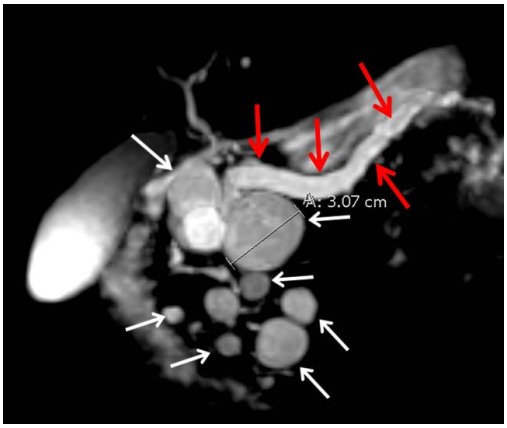

***Figure 8**: Magnetic resonance cholangiopancreatography illustrating multiple hyperintence cystic lesions (white arrows) in the pancreatic head and a dilated main pancreatic duct (white arrows) in a patient with CP. Source: Dr. Ingfrid S. Haldorsen.*

Endoscopic ultrasound

EUS is highly sensitive for CP-related features and may detect structural changes before the changes are visible on other imaging or functional tests show pancreatic insufficiencies [150-152]. This makes EUS particularly useful in patients where the diagnosis is uncertain and in patients with suspected early CP. Furthermore, it allows for real-time interventions and tissue sampling (*e.g.,* cyst drainage, needle biopsies, or fine-needle aspirations), increasing the diagnostic yield. Because the EUS probe is positioned in the stomach and the duodenum, bowel gas and obesity do not limit visualization like it does for transabdominal US. The endoluminal probe placement also brings it in close proximity to the pancreas, allowing EUS to be performed with higher frequency probes (5-12 MHz) that allow higher resolution and clearer imaging.

The drawbacks with EUS are invasiveness, and that it is mostly performed in specialized centers and requires highly experienced personnel [153].

Though EUS can detect very subtle changes in the pancreas, the diagnostic value of such findings is still debated. A large proportion of patients with minimal change CP on EUS do not progress to CP [154], and low interobserver agreement for some of these findings has been reported [153; 155].

Harmsen et al. [156] showed that contrast-enhanced high mechanical index EUS may be better than CT in discriminating between CP and pancreatic cancer. The value of contrast-enhanced EUS in diagnosing CP is undetermined.

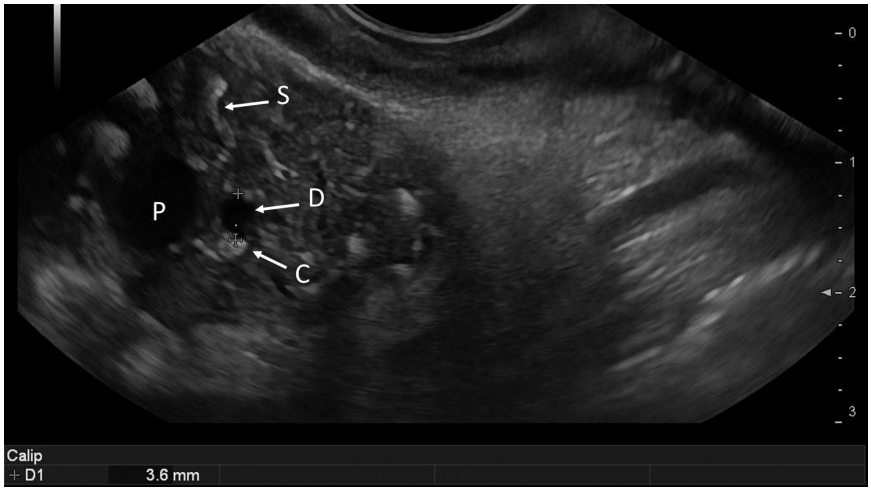

Figure 9*: EUS from a CP patient with stranding (S), duct dilatation (D), a calcification (C) in close proximity to the duct, and a pseudocyst (P). Source: Dr. Roald Flesland Havre.*

Transabdominal ultrasound

US is readily available at most medical centers; it is non-invasive and does not involve ionizing radiation. US is particularly useful in children, adolescents, and female with childbearing potential where radiation should be limited. US has a role in advanced CP and in CP patients for whom repeated examinations are required [21; 30; 71; 92]. However, the reported diagnostic accuracy for CP varies between studies [104; 108].

Under satisfactory scanning conditions, the pancreas and surrounding structures can be well visualized using US. Visualization can be compromised due to bowel gas, content in the stomach or intestines, or obesity. The experience level of the examiner is linked to the success rate of pancreatic visualization [157]. Techniques to improve the visualization include fasting in addition to changing probe position and applied pressure. The patient can also be asked to change position, hold their breath, or drink water [115].

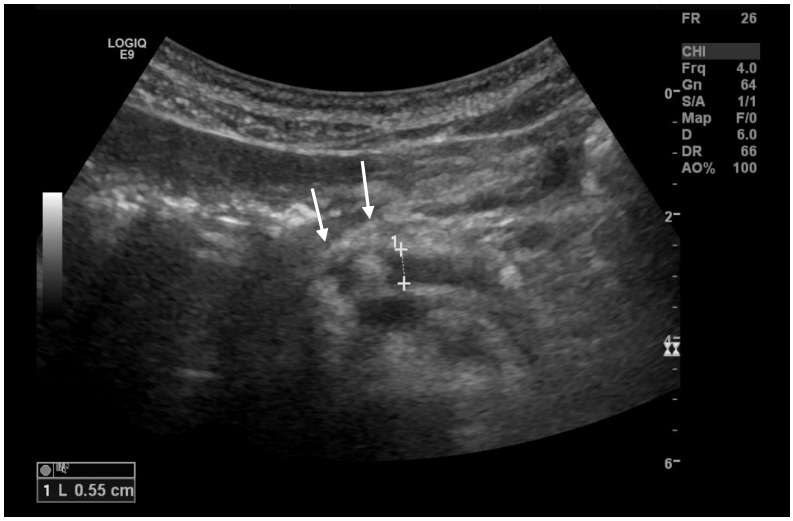

***Figure 10**: US image from a CP patient showing atrophic pancreatic parenchyma, duct dilatation (0.55 cm), and large intraductal stones (arrows). Source: Dr. Trond Engjom.*

The examination can be performed using a standard low-frequency abdominal curvilinear probe, which is good for visualizing structures in the depth of the abdomen. In slender patients, one can also use a high frequency linear probe for more detailed imaging.

Conventional B-mode US can be sufficient for evaluating most parenchymal and ductal features, and Doppler imaging is useful in detecting small calcifications (twinkling artifacts) and evaluating surrounding vasculature. As with EUS, contrast-enhanced US does not currently have a role in CP diagnostics but may be useful when pancreatic cancer is suspected [21; 158].

Advanced pancreatic imaging

Advanced and/or experimental pancreatic imaging in CP is outside the scope of this thesis, but several techniques have been and are currently being explored [159]. For instance, studies propose that elastography and pancreatic perfusion may have a future clinical relevance in CP diagnostics or characterization.

Elastography assesses tissue elasticity, or stiffness, and can be performed using different techniques on EUS, US, and MRI. The healthy pancreas is soft with high elasticity, but in CP, elasticity is focally or diffusely reduced due to tissue hardening from fibrosis, calcifications, edema or inflammation [160]. It has been suggested that elastography may help diagnose CP [161-166].

Pancreatic perfusion can be evaluated using CT, MRI, and contrast-enhanced EUS and US. Compared to healthy individuals, perfusion rates on CT are lower in patients with CP, particularly in those with PEI [167]. However, the increased radiation load limits the utility of pancreatic perfusion CT examinations [167]. Pancreatic perfusion may help distinguish between pancreatic cancer and mass-forming CP [168; 169].

2.5.3 Chronic pancreatitis imaging scoring systems

Most imaging scoring systems for CP are weighted, meaning that some factors (*e.g.,* calcifications) contribute with more points to the sum score or are classified as "major criteria" as opposed to "minor criteria". However, many of these systems have been designed based on expert opinion and/or consensus, and validation is lacking.

The Cambridge classification has applications for CT, MRI, US, and ERCP [122; 170]. The system has not been validated, and due to its complexity, it is rarely used in clinical practice [127]. A modification to the Cambridge classification for CT was recently proposed by Dasyam et al. [127], using the standardized reporting systems for imaging in CP [114]. The updated scoring system grades the severity of parenchymal calcifications, atrophy, and ductal features, in addition to the distribution of atrophy and calcifications [127].

EUS can be scored using the weighted Rosemont classification [110] or the unweighted standard criteria [171]. Interobserver agreement analyses for the CP-diagnosis and for the individual Rosemont features vary [153; 155; 172; 173]. Because of this, it has been suggested that modifications are warranted [155]. The Rosemont classification is also used for US scoring [108; 174].

A new scoring system for US was recently proposed: the Gemelli USCP score for assessment and follow-up of CP [107]. It evaluates pancreatic dimensions (globosity and atrophy), echostructure, changes of the MPD, and calcifications/plugs. The score correlates with the Cambridge classification and vitamin deficiencies [107].

The M-ANNHEIM pancreatic imaging criteria [77] also originate from the Cambridge classification and can be used for CT, US, MRI/MRCP, and EUS. The M-ANNEHIM system was originally presented as a multicomponent tool, but, perhaps because of its complexity, most studies only use single components [102].

The Japanese clinical diagnostic criteria for CP [78; 175] applies a combination of symptoms, pancreatic function tests and imaging. The Japanese criteria also includes a score for early CP that can be used for EUS, ERCP, or MRCP.

The literature review for this thesis was concluded on September 5th, 2021.

3. Aims and Hypotheses

3.1 Aims

The overall aim of this thesis was to evaluate the importance of diagnostic imaging and different structural pancreatic changes for future use in diagnostics, severity scoring, and prognostics.

Aims of paper 1: We aimed to determine the diagnostic accuracy of CT imaging scores for CP in a cohort of patients with suspected CP, and to assess the differences in frequency of CP-related structural changes in the CP and non-CP group. We further aimed to assess the interobserver agreement for different structural changes on CT between an experienced and inexperienced observer.

Aims of paper 2: We aimed to compare the diagnostic accuracy of CT and US in a cohort of patients with suspected CP, and to assess the agreement on different features between CT, EUS and US.

Aims of paper 3: We aimed to explore the associations between key structural pancreatic changes and common complications related to CP in a large cohort of patients with definite or probable CP.

3.2 Hypotheses

H1: The diagnostic accuracy of CT for diagnosing CP is higher when using a weighted scoring system (the modified Cambridge classification) compared to an unweighted score.

H2: The interobserver agreement for structural pancreatic changes on CT is high for marked and/or objective features (*e.g.*, calcifications, gross duct dilatation, large pancreatic cysts), but low for subtle and/or subjective features (*e.g.*, heterogeneous parenchyma, slight duct dilatation).

H3: The diagnostic accuracy of US for diagnosing CP is comparable to that of CT.

H4: The frequencies of all structural pancreatic changes on CT and US are higher in the CP group compared to the non-CP group.

H5: Associations between structural pancreatic changes and complications in CP exist.

4. Materials and methods

4.1 Study design and study population

4.1.1 Papers 1 and 2

Papers 1 and 2 include patients from the Bergen Pancreas database which holds registrations on a cohort of adult patients referred to our outpatient clinic due to suspected CP from 2009 to 2016. Both papers are cross-sectional cohort studies.

In paper 1, patients were eligible if their dataset contained all the necessary registrations for the diagnostic standard (Mayo score) and excluded if they had not completed a CT examination or if the CT image quality was too poor.

In paper 2, patients were eligible if they had completed examinations with all three imaging modalities (CT, EUS, and US) and excluded if US visualization or CT image quality was too low.

In both papers, patients were categorized as CP or non-CP according to their modified Mayo score, see section 4.2.1.

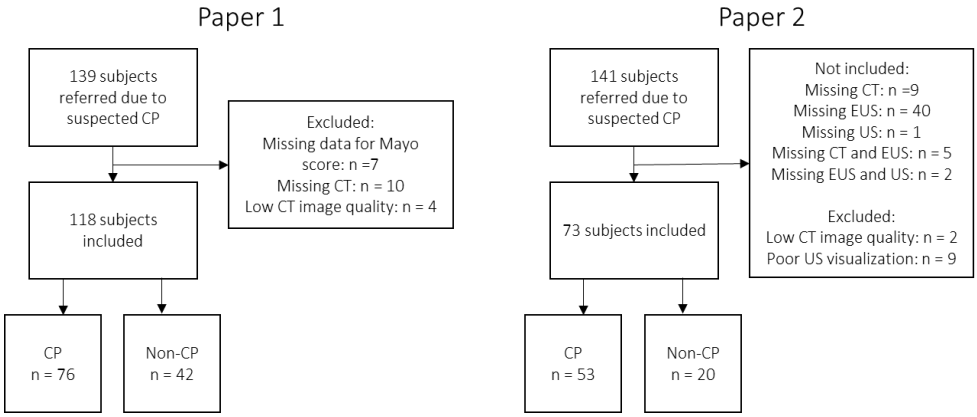

Figure 11: *Inclusion flow diagram for Papers 1 and 2, with patients from the Bergen Pancreas database.*

4.1.2 Paper 3

Paper 3 is a cross-sectional cohort study based on data from the Scandinavian Baltic Pancreas Club (SBPC) database [74]. The SBPC database includes adult patients with definite or probable CP according to M-ANNHEIM diagnostic criteria [77]. Patients with CP of all causes are included.

At the time of data extraction, 1st of July 2019, the database held registrations on 2208 patients. We included patients from the nine centers which had completed registrations in the comprehensive imaging module for the majority of patients (n = 1509). We excluded patients with incomplete datasets or whose imaging module had not been completed. In total, 959 patients were included for analysis in paper 3. Figure 12 shows a flow chart of the patient inclusion.

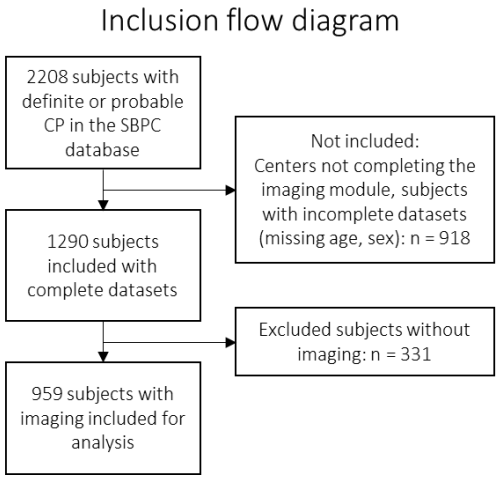

***Figure 12**: The inclusion flow diagram for paper 3, with patients from the SBPC database.*

4.2 Diagnostic standards

4.2.1 Papers 1 and 2: The modified Mayo score

We applied a modified version of the Mayo score as diagnostic standard in papers 1 and 2, see Table 3 below. Patients were categorized as CP if they had a score ≥4 points, and non-CP if the score was <4 points.

Others have used the Mayo score with different imaging modalities. To avoid interference between the reference standard and the evaluated modalities, CT was removed from the score in paper 1, and CT and US were removed in paper 2.

	The modified Mayo score: The CP diagnosis requires ≥4 points
Points	**Criteria**
4	Pancreatic calcifications on imaging, or typical histologic findings
3	Moderate or marked morphologic changes on imaging
2	Reduced exocrine pancreatic function
2	History of acute pancreatitis or upper abdominal pain
1	Diabetes mellitus, glycated hemoglobin ≥48 mmol/mol

Table 3*: The modified Mayo scores for papers 1 and 2. Adapted from: Layer P et al., Gastroenterology 1994 [72].*

Fecal elastase 1 <200 µg/g and endoscopic short tests with peak bicarbonate concentration <80 mmol/L were used as cut-offs for PEI. Histology was not available for any of our study participants.

See also section 4.6.1 about methodological considerations related to our modifications to the Mayo score.

4.2.2 Paper 3: The M-ANNHEIM diagnostic criteria

The diagnostic standard for CP in the SBPC database is the M-ANNHEIM diagnostic criteria [77], a consensus-based weighted system. All patients in the database fulfil the criteria for definite or probable CP, see Table 4.

M-ANNHEIM diagnostic criteria
The diagnosis of CP requires a typical clinical history of CP, such as recurrent pancreatitis or abdominal pain, and one or more of the following criteria:
Definite CP: Calcifications Moderate or marked ductal lesions Marked and persistent pancreatic exocrine insufficiency Histology
Probable CP: Mild ductal alterations Pseudocysts Pathological test of pancreatic exocrine function Diabetes

Table 4: *The M-ANNHEIM diagnostic criteria as applied in the SBPC database. Reproduced from: Schneider A et al., J Gastroenterol. 2007 [77]. Ductal changes were scored according to the Cambridge classification. Marked and persistent PEI was defined as steatorrhea reduced by pancreatic enzyme replacement therapy.*

4.3 Imaging and imaging scoring systems

4.3.1 Imaging in papers 1 and 2

The Bergen Pancreas database holds registrations from CT, US, and EUS. In paper 1, we included patients with CT plus US and/or EUS. In paper 2, all three modalities had to have been performed for the patient to be included.

US and EUS examinations were performed by two experienced observers (T.E. and R.H.F., respectively). Visualization of the head, body, and tail of the pancreas on US was scored from 1 to 4 (good, adequate, poor, and not visible), and patients were excluded if the visualization score was ≥3 in all segments. Detailed descriptions of the scanning systems, scanner settings, and patient positions can be found in the methods section of paper 2.

Structural findings from US and EUS were scored according to the Rosemont classification [110] directly after the procedure, see Table 5. We also applied an unweighted US-score, where the score equaled the number of positive single features from the Rosemont classification.

The Rosemont classification for EUS and US		
Parenchymal features		
Hyperechoic foci with shadowing		Major A
Lobularity		
A: without honeycombing		Minor
B: with honeycombing		Major B
Hyperechoic foci without shadowing		Minor
Cysts		Minor
Stranding		Minor
Ductal features		
MPD calculi		Major A
Irregular MPD contour		Minor
Dilated side branches		Minor
MPD dilatation		Minor
Hyperechoic MPD margin		Minor
1 - Consistent with CP	A. 1 major A feature + ≥3 minor features	
	B. 1 major A feature + 1 major B feature	
	C. 2 major A features	
2 - Suggestive of CP	A. 1 major A feature + <3 minor features	
	B. 1 major B feature + ≥3 minor features	
	C. ≥5 minor features (any)	
3 - Indeterminate for CP	A. 3 to 4 minor features, no major features	
	B. Major B feature alone or with <3 minor features	
4 - Normal	≤2 minor features, no major features	

Table 5*: The Rosemont classification for EUS and US, as applied in paper 2. For feature definitions, see Catalano et al. [110]. Adapted from Catalano M.F. et al., Gastrointestinal Endoscopy 2009 [110].*

CT scans were performed using clinical scanning protocols (abdominal or pancreatic), and most scans were performed with intravenous contrast. All scans were individually evaluated by two observers: one experienced (T.E.) and one with limited experienced (I.K.N.). The limited experience of I.K.N. allowed for analyses on the agreement between experienced and inexperienced observers for scoring CT examinations. I.K.N. was trained by T.E. prior to scoring, but scored the examinations independently and blinded to scoring by T.E. Patients were excluded if both observers deemed the image

quality as poor, most commonly because the scans were performed without intravenous contrast.

Standardized reading instructions were applied [131], and structural changes were scored according to the modified Cambridge classification for CT [122], see Table 6. We did not apply the feature "slight enlargement of the pancreas", both because of the lacking definition of the feature, and because organ enlargement is more typical for autoimmune pancreatitis [68]. In addition to the modified Cambridge score, we applied an unweighted CT-score, where the score was equal to the number of positive single features from the modified Cambridge classification.

The modified Cambridge classification for CT	
Cambridge grade	**CT features**
0 - Normal	None
1 - Equivocal	Cannot be delimited in CT with current methods
2 - Mild	2 or more of the following changes: - Pancreatic duct between 2 and 4 mm in the body of the pancreas [a] - Heterogeneous parenchymal structure - Small cystic changes (<10 mm) - Duct irregularities (1-2 mm variation) - 3 or more pathological side ducts - (Excluded criteria: slight enlargement of the pancreas)
3 - Moderate	All changes specified in 2 plus pathological main duct (>4 mm).
4 - Marked	One of the changes specified in 2 and 3 plus one or more of the following: - Cystic structures (≥10 mm) - Parenchymal calcifications - Intraductal filling defects (chalk stones) - Duct obstruction (strictures) - Severe duct irregularities (>2 mm variation)

***Table 6**: The modified Cambridge classification for CT, as applied. [a)] The typical definition of duct dilatation in the body of the pancreas uses a cut-off ≥3 mm. Patients scored positive if duct diameter was ≥3 mm and ≤4 mm. Adapted from Schreyer A.G. et al., RöFo 2014 [122].*

4.3.2 Imaging in paper 3

In paper 3, we used registrations from the imaging module of the SBPC database. Imaging modalities included CT, MRI, EUS, and US, and were assessed and scored by radiologists or gastroenterologists with special interest in pancreatic imaging at each participating center. Predefined standards for reading and scoring were distributed to all centers. These standards have been evaluated in interobserver analyses [131]. They were developed prior to publication of the reporting standards for CP by Tirkes *et al*. [114], but hold some similarities.

The registered imaging parameters used in paper 3 included MPD dilatation, MPD obstruction, the presence and the number of pancreatic calcifications, pseudocysts, focal acute pancreatitis, and continuous organ involvement (parenchymal changes throughout the pancreas). The anteroposterior diameter of the pancreatic head and body was measured in order to assess pancreatic atrophy.

4.4 Statistical methods

IBM SPSS statistical software was used for all papers. In all papers, data are presented as mean with standard deviation or as median with interquartile range, depending on normality distribution. A significance level of $p < 0.05$ was applied.

4.4.1 Statistical methods in papers 1 and 2

Independent samples t-test and Mann-Whitney U test were used for parametric and non-parametric data, respectively. Binary and categorical data was analysed using Pearson's χ^2-test. Fishers Exact Test was used if the expected count of any cell in the 2x2 tables were 5 or lower.

Diagnostic performance indices are presented as area under the receiver operating characteristic curve (AUROC), sensitivity, and specificity with 95% confidence intervals (CIs). We also presented negative and positive predictive values in paper 1, but because these are highly dependent on the prevalence of the disease, such indices were not included in paper 2. A paired-samples AUROCs comparison in SPSS was

applied when comparing AUROCs. Interobserver (experienced *vs.* inexperienced observer) and intermodality (CT *vs.* US *vs.* EUS) agreement was evaluated using Cohens kappa (κ) for binary variables and weighted kappa for ordinal variables.

4.4.2 Statistical methods in paper 3

For this paper, we applied a four-step multiple logistic regression analysis to assess the associations between structural pancreatic changes and complications. We used a threshold of $p \leq 0.1$ to decide which variables should be included in the final model. We also included variables based on predetermined assumed clinical relevance. The model adjusts for the covariates age, sex, disease duration, current smoking, and current excessive alcohol use. Results were presented as odds ratios (ORs) with 95% CIs. See paper 3 for a detailed description of the statistical method.

4.5 Ethics

All patients received oral and written information and signed written consents. The studies were conducted according to the Helsinki Declarations and approved by the Regional Committees for Medical and Health Research Ethics, Western Norway (REK Vest). Papers 1 and 2 are approved under registration numbers 2011/590 and 2019/1037, and paper 3 under registration number 2019/1037. The SBPC database is coordinated by the center at Aalborg University Hospital (200858-0028, project ID 2018-19), and our group at Haukeland University Hospital coordinated the study in paper 3. Permissions for collection and sharing of data have been obtained from the institutional review boards at each center participating in the SBPC. Papers 1 and 2 adhere to the Standards for Reporting of Diagnostic Accuracy (STARD) [176], and paper 3 was reported following the TRIPOD statement [177].

4.6 Methodological considerations

Additional methodological considerations/study limitations are addressed in the discussion and the individual papers.

4.6.1 Methodological considerations: Study design, study population and diagnostic standard

Papers 1 and 2

Rather than including healthy controls, the patients in the reference group were patients referred due to suspected CP, meaning they presented with symptoms or imaging related to CP. Because of this, the boundaries between CP and non-CP may be more diffuse, causing a reduction in the diagnostic accuracy. However, including patients with suspected CP provided an advantage as the results may be closer to real-world diagnostic situations.

A limitation in papers 1 and 2 is the lack of a highly validated diagnostic standard, which is not available for CP. We applied a modified version of the Mayo score, which combines endocrine and exocrine function, imaging, and patient history (pain, previous acute pancreatitis). The Mayo score also include histology, and though including histology in our studies would likely improve the accuracy of the reference standard, the benefits did not outweigh the risks associated to pancreatic tissue sampling in this patient population. ERCP was avoided due to risk of complications, and so, EUS and/or US were used in the place of ERCP. The reported diagnostic accuracy of EUS is similar to that of ERCP [104]. In the original Mayo score [72], exocrine function is assessed using fecal fat excretion or cholecystokinin test, but these are rarely used at our hospital. We applied a combination of fecal elastase and secretin-stimulated shortened endoscopic test. As discussed in the introduction, both tests have limitations. However, combining these tests may have increased our precision. Evaluating pain is complex, and patients with non-pancreatic pain may have been miscategorized despite our best efforts.

Other options, aiming for a more accurate reference standard, could have been to use both MRI and EUS, and longitudinal observations would also have provided increased accuracy.

In paper 2, about half of the patients in the Bergen Pancreatic database were excluded due to an eligibility criteria being registrations on all three imaging modalities (CT, EUS, US). The database was not originally established for this particular study and applied an intention-to-diagnose design. This infers a risk of selection bias in this paper, where patients were more likely to be included if they had more subtle structural changes or if there was suspicion of complications requiring multiple examinations to secure the diagnosis.

Paper 3

The study population was comprised of patients who had definite or probable CP according to the M-ANNHEIM criteria. Thus, patients with early CP are not included in the SBPC database, and results does not translate to such individuals. Similarly, the results do not apply to non-CP individuals with structural pancreatic changes due to other conditions.

Participants were included from tertiary centers with particular interest in CP. This may have caused a selection bias where included patients have a more severe disease compared to the general CP patient population.

We excluded patients with no registrations in the imaging module. We have previously shown that the patients excluded due to missing imaging registrations were older and more frequently had complications such as PEI and diabetes [113]. Because of this selection bias, the frequency of patients with these complications, and perhaps also severe structural pancreatic changes, in our cohort may be reduced.

The cross-sectional study design limits us from drawing conclusions on causality and/or prognostics, and a longitudinal study design would have been preferable.

4.6.2 Methodological considerations: Imaging

Papers 1 and 2

We found that the Cambridge classification did not perform well in distributing patients to the different categories; no patients obtained the moderate score. Using the M-ANNHEIM modified version of the Cambridge classification (see Table 7 in the paper by Schneider et al., [77]) rather than the version from the S3 guideline [122], could have slightly improved our findings on ability to evaluate disease severity. One difference between the two versions can be found in the criteria for the moderate CP. Here, the S3 guideline version require *all* the changes from the mild category in addition to a marked duct dilatation. The M-ANNHEIM version only require *two* abnormal features, one of which must be a MPD abnormality. However, this could only have impacted the outcome for the few patients categorized with mild CP.

There were differences in the degree of standardization between modalities. US and EUS examinations were standardized with respect to imaging protocols and system settings. CT examinations were performed on different hospital scanners. The CT protocols were not completely uniform, but performed according to local, standardized CT protocols (abdominal and pancreatic protocols). Most scans included intravenous contrast.

In paper 2, we compared the diagnostic performance of CT and US. However, due to differences, neither the modalities nor the scores are directly comparable. The scoring systems include different criteria and apply different definitions (*e.g.*, ductal dilatation). Another difference is that while the Rosemont classification scores how certain the diagnosis is, the Cambridge classification suggests severity.

Paper 3

Different imaging modalities were used in the study, but only registrations from one modality per patient were analysed. As discussed in paper 3, the modalities have inherent strengths and weaknesses for detecting different features. This may have affected our results. Imaging protocols were not standardized, only interpreted according to predefined standards. Local differences in interpretation may still have

occurred. The high number of patients hopefully reduced the consequences of these limitations.

Not all structural pancreatic changes registered in the database were included in the logistic regression analyses. We prioritized features based on expected clinical relevance, and whether they could be scored objectively or with high interobserver agreement. To avoid compromising the analyses by including several correlating features, only two ductal features (dilatation and obstruction) were included. We recognize that some of the structural changes we did not include may yet be associated to clinical complications.

When assessing pancreatic atrophy, anteroposterior diameters were measured, but MPD diameters were not subtracted from parenchymal diameter. Because of this, patients with both atrophy and severe duct dilatation may have been wrongly categorized as not having pancreatic atrophy.

4.6.3 Methodological considerations: Defining clinical complications

The outcome variables in paper 3, namely PEI, underweight, diabetes, and pain, all have related limitations. In addition to the high count of missing data, using FE-1 to define PEI infers limitations related to cut-offs and risk of false positive. Though recommended due to availability, feasibility, and non-invasiveness, FE-1 is an indirect pancreatic function test and not the gold standard for detecting PEI.

We used underweight as a proxy for malnutrition, though underweight can be caused by a multitude of different factors. Underweight and malnutrition can be treated, but this was not accounted for in our analyses. Using BMI to define underweight carries limitations due to differences in body composition between individuals. Another option could have been vitamin D levels, however this would also imply limitations, such as variations related to sun exposure, vitamin supplements, and the lacking consensus regarding cut-off for vitamin D deficiency.

Diabetes was scored as present or not present by the clinicians at the participating centers, following definitions from the American Diabetes Association guideline. The

database does not discriminate between type 1, 2 or 3c diabetes, and it is fair to assume that some patients in fact had type 1 or 2 diabetes unrelated to their CP. This may be part of the explanation why we found few associations between structural changes and diabetes.

Pain, both in CP and in general, is complex and exposed to a wide range of biases (*e.g.,* reporting bias, recall bias, gender and racial bias, attentional bias). Pain is context dependent, patient dependent, and time dependent. Thus, by reducing pain to a dichotomous variable (pain/no pain), important information was likely lost. As in papers 1 and 2, patients with non-pancreatic pain may have been miscategorized.

4.6.4 Methodological considerations: Statistical methods

Papers 1 and 2

As a consequence of ensuring that the same diagnostic standard (modified Mayo score with EUS imaging) was used for all patients in paper 2, a large proportion of patients were excluded. This reduced the statistical power of some analyses, particularly in testing for differences in feature frequencies between groups. In such cases, we applied Fishers Exact test to reduce the risk of error, but still, not rejecting the null hypothesis of equal proportions between the two groups may represent type II errors. Similar limitations may apply to interobserver agreement analyses for the structural changes that were only observed in a limited number of patients. We did not use Bonferroni or other means to adjust for multiplicity.

In the diagnostic accuracy papers, we used the Youden index [178] to determine the optimum cut-offs for each scoring system. The Youden index has a benefit in providing an objective cut-off, but it does not take into account the clinical benefit of either having a high sensitivity or specificity at the cost of lowering the other.

Paper 3

In paper 3, statistical limitations are largely related to the multiple logistic regression analyses. Such analyses are sensitive to multicollinearity, *i.e.,* relationships between the independent variables. We performed correlation analyses to assess covariance and found that there was significant covariance between calcifications and severe

calcifications, and also some covariance between MPD dilatation and MPD obstruction. We explored different solutions including running separate analyses or introducing an interaction effect between the MPD variables, but these analyses did not yield any new information.

We chose to dichotomize most variables, leaving age and disease duration as the only continuous variables. This makes the results more understandable, but some information may also have been lost.

The cut-off for severe calcifications may seem arbitrary, but in the SBPC imaging module, registrations on the number of calcifications are continuous up to 14 calcifications, while higher numbers are registered as ≥15. In hindsight, it would have been interesting to further explore different cut-offs for severe calcifications or to evaluate calcifications as an ordinal variable (*e.g.,* no calcifications, 1-7 calcifications, 8-14 calcifications, and ≥15 calcifications).

Missing data in the dataset may have caused bias. The variable with the highest count of missing data was FE-1 value, which was used to assess presence of PEI. Not all centers use FE-1, and this may have caused a selection bias. Furthermore, if physicians assumed that the pretest risk of PEI was low, for instance due to normal imaging, and thus decided not to test for PEI, this may also have resulted in a selection bias in centers where FE-1 were used.

5. Results and summary of the papers

Paper 1

From the Bergen Pancreas database, we included 118 patients referred due to suspected CP. Using a modified Mayo score, patients were categorized as CP (n = 76) or non-CP (n = 42). We found that the modified Cambridge classification for CT had a moderate performance in diagnosing CP, with sensitivity 63%, specificity 91% and AUROC 0.79. The unweighted CT-score yielded similar diagnostic performance indices. The distribution of CP patients within the different severity grades (0 to 4) of the modified Cambridge classification indicated an unsatisfactory performance as a severity scoring tool.

All structural pancreatic changes, minus slight duct dilatation, small cystic changes, and pathological side ducts, were significantly more frequent in the CP group compared to the non-CP group. The interobserver analyses showed very good agreement for parenchymal calcifications, and good agreement for gross duct dilatation, large cystic structures, intraductal filling defects, heterogeneous parenchymal structure, and ductal obstruction. Other structural changes yielded lower levels of interobserver agreement (moderate: severe duct irregularities, fair: ductal irregularities, slight duct dilatation, poor: small cystic changes and pathological side ducts).

Paper 2

Seventy-three patients referred due to suspected CP were included from the Bergen Pancreas database. They were categorized as CP (n = 53) or non-CP (n = 20) according to the modified Mayo score. Using the modified Cambridge classification and the Rosemont classification, CT and US yielded similar diagnostic performance indices, with sensitivities of 68% and 64%, specificities of 75% and 85%, and AUROCs of 0.75 and 0.81, respectively. The unweighted scores also demonstrated similar results, and

the only difference was a marginally reduced AUROC for the modified Cambridge classification compared to the unweighted CT-score.

Due to differences between the imaging scoring systems, it was not feasible to assess all structural pancreatic changes in intermodality agreement analyses. However, the highest agreements were found for calcifications, while pseudocysts and duct dilatations only yielded fair to moderate agreement. Both on CT and US, the frequencies of several structural changes did not significantly differ between the CP and non-CP groups.

Paper 3

In this paper, we included 959 patients with CP from the SBPC database. Through multivariate logistic regression, we explored the associations between structural pancreatic changes and key complications related to CP (PEI, diabetes, underweight, and pain). Ductal obstruction, continuous organ involvement, severe calcifications, and pancreatic atrophy were positively associated to PEI. While continuous organ involvement was positively associated to diabetes, pseudocysts showed a negative association. Pancreatic atrophy and severe calcifications were positively associated to underweight. Patients with severe calcifications were less likely to report pain compared to patients with few or no calcifications. Thus, we found distinct associations between structural pancreatic changes and complications. The associations may all be explained through pathophysiology or other known associations.

6. Discussion

"Just because you can't see something, doesn't mean it's not there."

Just like this phrase applies to wind and gravity, it also seems to apply to CP; the disease may be present despite negative imaging or low scores from imaging scoring systems. There is no arguing that imaging is relevant in CP. Imaging is important for diagnosing CP and in follow-up when structural complications are suspected. However, efforts are still needed to ensure that we extract all the information we need from the performed imaging, and to fully understand the implications of different imaging findings.

6.1 Structural changes, imaging and diagnostics

In paper 1, we revisited the diagnostic accuracy of CT, hypothesizing that the accuracy would be increased compared to previous data due to technological improvements. In contrast to our expectations, we found that the accuracy was comparable what has been reported by others. This was probably the result of several factors including weaknesses associated to CT imaging itself and to the use of the modified Cambridge classification for CT. In paper 2 we aimed to compare CT and US for diagnosing CP and found that they had similar and moderate diagnostic accuracies. We explored the use of unweighted scoring systems, but these did not differ in diagnostic accuracy compared to the weighted systems. Importantly, the specificities we found for CT and US suggest that neither modality should be used alone in the diagnostic workup for CP. Despite the limitations of these papers, our results point to some of the strengths and weaknesses of CT and US imaging, the importance of correct and conscious use of imaging, and a need for improved imaging scoring systems.

Comparing computed tomography and transabdominal ultrasound

Two major benefits with CT are availability and reproducibility, whilst limitations include radiation and risk associated to intravenous contrast agents. We showed that CT scans could be evaluated for the presence of CP by an inexperienced observer without significant loss of diagnostic accuracy. For pancreatic US, it may be the opposite. The examination is radiation-free and contrast agents are not required. US

machines are available at most centers, but not all centers have personnel skilled enough to perform high quality pancreatic US.

Moreover, CT and US differ with respect to risk of poor visualization and image quality. Image quality on CT is typically sufficient as long as the correct scanning protocols are applied and the patient is cooperative and without *e.g.*, metal implants disturbing the scan [179]. The risk of not visualizing the pancreas is higher on US. However, if the pancreas is well visualized on US, the high temporal and spatial resolution of US can be favorable in small lesions. In our material, the entire pancreas was not visualized on US in 38% of patients and nine patients were excluded due to inadequate visualization. In patients with known risk factors or clinical suspicion of pancreatic cancer, visualization is key, and CT should be preferred over US. However, despite its advantages compared to US, CT should not be used alone to rule out cancer in such cases, both because lesions may be too small to be detected and because differentiating CP related structural changes from cancer is difficult [21; 30]. Thus, a multimodal approach is recommended [30].

Parenchymal features in diagnostics

As mentioned, CT is the gold standard for detecting pancreatic calcifications. We found that both parenchymal calcifications and intraductal stones were more common on US and on CT in CP patients compared to non-CP patients. On CT, interobserver agreement for calcifications was good to very good, similar to what others have demonstrated [131; 180]. The agreement between modalities was also high, suggesting that CT, US, and EUS may all be good modalities for evaluating calcifications. Others have shown high kappa values for calcifications on US [107], while agreement levels using EUS have varied [153; 155; 172; 173; 181]. Overall, our findings support the established conception that calcifications are important in diagnosing CP. Our interpretation could theoretically be biased because calcifications alone are sufficient to obtain the CP diagnosis from the modified Mayo score used as diagnostic standard.

In the modified Cambridge classification, cysts are scored dependent on size. Large cysts (>10 mm) were more frequent in CP patients, but because of low frequency of

cysts, insufficient statistical power was an issue in assessing the frequency of small cysts. Interobserver agreement and intermodality agreement for cysts range from moderate to very good [108; 131; 174; 181]. Despite pseudocysts being an important clinical feature with large potential consequences for patients with CP, they are not specific to CP.

Heterogeneous parenchymal structure was the most common feature seen on CT, but it was also present in >10% of non-CP patients. Surprisingly, we found good interobserver agreement despite the feature's subjective nature. Thus, parenchymal heterogeneity may add to the sensitivity of a diagnostic score, but as it may reduce the specificity, it should not be heavily weighted.

The corresponding features for ultrasound modalities are lobularity and stranding. Lobularity was very infrequently observed on US. Stranding was observed more frequently and dominantly in the CP group, and may be of more use in CP diagnostics compared to lobularity when using US.

We did not assess the diagnostic value of pancreatic atrophy or continuous organ involvement (parenchymal changes throughout the pancreas). Because both features have potential relevance in severity scoring, exploring their diagnostic value through studies on patients with suspected CP is warranted. Dasyam et al. [127] suggested graded scoring of both features, providing supplementary information that may be of relevance in severity scoring and prognostics.

Ductal features in diagnostics

Gross MPD dilatation (>4 mm) was more frequent on CT in patients with CP compared to non-CP patients, but slight MPD dilatation was not. The interobserver agreement was also much higher for gross MPD dilatation compared to slight dilatation. On US, only CP patients had dilated ducts. Our findings indicate that a higher cut-off is required for use in CT diagnostic imaging scores, particularly if duct dilatation is heavily weighted.

Ductal obstructions were also more frequent in CP compared to non-CP, and agreement between observers was good, both indicating that obstructions are well suited for use in diagnostic scores.

Pathological side ducts were detected on CT-scans in very few cases, while 32% of CP patients had dilated side ducts on US. The difference in frequency between CP and non-CP groups was significant on US. Another study found pathological side ducts in 37% of CP patients on CT [131]. This suggest that we may have failed to detect pathological side ducts on CT in our study. Still, CT yields lower sensitivity compared to other modalities, and the recent MRI and CT reporting standards only recommend evaluation of side branches on MRI [114].

Ductal irregularities were more frequent in CP compared to non-CP in both modalities. CT had better interobserver agreements for severe ductal irregularities on CT compared to mild ductal irregularities, in line with claims that CT is not ideal for subtle ductal changes. Still, ductal irregularity is of use in CP diagnostics using both CT and US.

A hyperechoic MPD margin was rarely detected on US, and Engjom et al. [174] found very poor agreement for this feature between EUS and US. Thus, hyperechoic MPD margin may be a poor US criteria for CP diagnostics.

Challenges with the imaging scoring systems

We found several reasons why an updated imaging scoring systems for CT and US are warranted.

The modified Cambridge classification for CT is heavily oriented around ductal changes, despite CT having low sensitivity and reliability for subtle ductal changes [105; 127; 131]. We also found that the modified Cambridge classifications categorized very few patients as mild CP, and none as moderate CP. This suggests the scoring system does not correctly classify patients according to severity. Though the diagnostic value of pancreatic atrophy is unknown, it may improve the severity scoring abilities of the modified Cambridge classification. We chose to exclude the criteria slight organ enlargement; a study found that though patients with CP have a marginally larger

pancreas compared to healthy individuals, the difference was not sufficiently large to suggest gland enlargement should be used as a diagnostic criteria [182]. We have also showed that some features (*e.g.,* slight duct dilatation and heterogeneous parenchymal structure) may be present in a proportion of non-CP patients.

The Rosemont classification for US performed better than the modified Cambridge classification for CT in distributing patients along the different classifications (normal, indeterminate for CP, suggestive of CP, consistent with CP). US detects fewer structural changes, particularly subtle changes, compared to EUS [174]. Because of differences in technology, some features present differently on US compared to on EUS. This has implications when applying EUS scoring system for transabdominal US. An example is hyperechoic foci without shadowing, which on EUS may be the result of small calcifications or fibrotic changes. This feature has been observed less commonly in US, perhaps due to lower frequency probes and other differences in acoustic beam properties [174]. EUS has been shown to be superior to US in detecting lobulation, stranding, hyperechoic ductal walls, pathological side ducts, and minor duct caliber variations, and EUS also outperformed US in differentiating between extra- and intraductal calcifications [174]. The differences in feature detection and low agreement between EUS and US suggest that there is a need for a dedicated and less complex US scoring system for CP.

6.2 Structural changes and clinical complications

PEI, diabetes, and underweight have been linked to increased mortality in patients with CP [99; 100; 183]. Increasing the knowledge about how structural changes on imaging links to these complications is necessary to understand which imaging findings suggest severe disease and potentially increased risk of mortality.

In a recent publication, we showed associations between disease etiology and specific patterns of structural pancreatic changes [113]. When categorizing complications to clusters characterized by fibrosis, inflammation or pancreatic insufficiencies, clusters were found to differ in their association to smoking and alcoholic etiologies [52]. Both

studies infer differences in the underlying disease mechanisms between etiologies. However, in paper 3, we showed distinct associations between patterns of structural pancreatic changes and concomitant CP-related complications, even after adjusting for smoking and alcohol abuse. This suggests that though there are differences in phenotypes between the etiologies, the structural changes also influence how the disease develops and presents with regard to clinical complications. Thus, both imaging and knowledge about etiology may be useful in understanding disease development and predicting long-term outcome.

PEI and underweight

We showed that severe calcifications are associated to clinical outcome, specifically that patients with severe calcifications had higher risk of having PEI and being underweight. Others have linked calcifications to PEI [119], and BMI has been shown to be reduced as the number of calcifications increase [121]. A proposed mechanism is that multiple small calcifications can cause PEI through plugging the acini and the small ducts [121]. Another possibility may be that calcifications are linked to fibrosis and tissue destruction, which then causes PEI. Sinha et al. [184] found that having >10 parenchymal calcifications was a good predictor for severe fibrosis, while Andersen et al. [121] found no such correlation. As we did not find any associations for the variable "any calcifications", our results show that the *extent* of calcifications may play a role in severity scoring and potentially CP prognostics.

We showed that patients with pancreatic atrophy and continuous organ involvement were more likely to have PEI, probably due to the reduction in functional exocrine pancreatic tissue. The applied gender adjusted cut-offs for pancreatic atrophy were established in our previous publication [113]. Others have suggested only using measurements from the pancreatic body to increase standardization, and scoring of varying degrees of atrophy [114; 127]. Further studies on PEI, pancreatic atrophy, and alternative cut-offs are warranted, but so far, our findings indicate that pancreatic atrophy may be a relevant factor in CP severity scoring and prognostics.

Underweight can be caused by a variety of factors, both related and unrelated to the patient's CP. The associations we found between structural changes and underweight are similar to those between structural changes and PEI, and can likely be explained by the risk of malnutrition and underweight from having PEI. This suggests that PEI, not surprisingly, is among the most important causes of underweight in patients with CP. An exception to the similarities is MPD obstruction, which demonstrated no association to underweight. It is possible that PEI from MPD obstruction can be less complete/severe compared to PEI caused by loss of functional parenchyma (atrophy, continuous organ involvement), for instance if the obstruction is situated in the pancreatic tail.

Diabetes

The sparse findings on associations between diabetes and structural changes were unexpected. Diabetes is most common in patients with longstanding disease, who expectedly would have developed more structural changes compared to patients early in the disease course. A distinct pattern can be found in the univariate analyses; features that have been associated to short or long disease duration [113], were associated to lower or higher likelihood of diabetes, respectively. It is possible that such time-related patterns causes only the strongest associated features to remain significant: pseudocysts and continuous organ involvement. See also section 4.6.3 regarding limitations in how diabetes was defined.

As discussed in previous sections, continuous organ involvement may be related to loss of functional parenchyma. A hypothesis could be that continuous organ involvement relates to a more widespread fibrosis, however, a study found that CP patients with diabetes did not have more severe fibrosis compared to non-diabetic CP patients [128].

Challenges in exploring pain-related structural changes

The only association we found between structural pancreatic changes and presence of pain was that patients with severe calcifications were less likely to report being in pain. This has also been reported by others [51]. A possible explanation for this may be the burn-out syndrome, meaning reduced pain as the disease progresses [21; 92; 185].

However, as previous studies have not succeeded in confirming the existence of burn-out [51; 76; 186], its existence is disputed. Andersen et al. [121] did not detect any correlation between pain and the number of calcifications, but their study did have a limited sample size.

MPD obstruction can theoretically and logically cause pain through increased intraductal pressure [187], and non-sham-controlled studies have shown that surgical or endoscopic interventions can reduce pain in patients with ductal obstruction [188; 189]. Still, we and others [190; 191] have failed to show increased frequency of pain in these patients. In our case, important limitations include that we did not discriminate between new or longstanding obstructions, and the location of the obstruction was not registered. Similarly, symptoms from pseudocysts are dependent on size, location, and etiology [192], and only scoring pseudocysts as present or not present may have impacted our results.

Furthermore, time between imaging and pain registration is relevant. In CP, the reported pain characteristics fluctuates [76], and so do some structural changes; particularly acute inflammatory changes and pseudocysts are likely to regress. Time between imaging and pain registrations should be reduced, and longitudinal registrations may provide knowledge about the consequences of emerging and/or regressing structural changes.

Structural changes not showing any association

In the final analyses, we found no associations between MPD dilatation or focal acute pancreatitis and any of the selected clinical complications. Acute pancreatitis is most common in the earlier course of CP [113], which may explain why there were no positive associations to complications that are more common in the later phases of CP, namely PEI and diabetes [52; 193].

In multivariate analyses, a variable may lose significance if it is strongly correlated to another. Obstructed ducts are more likely to be measured as dilated compared to non-obstructed ducts. Thus, the covariation between MPD dilatation and MDP obstruction may have masked an association between MPD dilatation and clinical complications.

Patients with pseudocysts were not more likely to have concomitant PEI, underweight or pain, and they were *less* likely to have diabetes. Whilst pseudocysts have been associated to shorter disease duration [113], PEI and diabetes are more common as the disease progresses. Longitudinal studies may provide knowledge on whether pseudocysts influence the long-term risk of developing these complications.

6.3 Study limitations

Study limitations are addressed under methodological considerations (section 4.6) and in the individual papers. To summarize, important limitations in papers 1 and 2 were weaknesses in the scoring systems and somewhat low sample sizes. Though the phrases "diagnostic accuracy of CT" and "diagnostic accuracy of US" have been used both in the papers and in this thesis, the diagnostic performance indices only reflect the performance of the modalities provided that the same imaging scoring systems are applied.

The cross-sectional study design was a key limitation of paper 3, because it restricted conclusions regarding future risk. We did not know whether the structural changes or the complications appeared first. Thus, this work was limited to being a steppingstone towards longitudinal studies and potential prognostics. In addition, dichotomization of variables (both imaging and complications) made the results easier to understand, but information was lost in the process.

7. Conclusions and future perspectives

7.1 Conclusions

Our findings on the diagnostic accuracy of CT for diagnosing CP, sensitivities 63-72% and specificities 75-91%, were comparable to the diagnostic accuracies reported in previous literature. US had similar diagnostic accuracy to that of CT, and any differences between the weighted and unweighted scores were insignificant. We have described weaknesses in the imaging scoring systems. It is possible that the diagnostic accuracy of CT and US could be improved through the use of other scoring systems. A multimodal workup may reduce the implications of suboptimal scoring systems and the inherent weaknesses related to each modality.

We found that different parenchymal and ductal features appear to have varying importance in CP diagnostics. Supporting previous literature, calcifications were central parenchymal features in diagnosing CP, and on CT, heterogeneity in the parenchyma also adds to the sensitivity. Dilatation, obstruction, and irregularity seem to be the most important ductal features. The cut-off for slight MPD dilatation applied in the Cambridge classification may be too low. Our findings support that CT and US are not ideal imaging modalities for assessing pancreatic side ducts.

Finally, we found distinct associations between structural pancreatic changes and PEI, underweight, and diabetes. Patients with ductal obstruction, severe calcifications, pancreatic atrophy or parenchymal changes involving of the entire pancreas were more likely to have CP related complications. This may suggest that these findings should be weighted when scoring the severity of CP, and patients with such findings should be monitored for the development of complications.

Most results in paper 3 are not surprising; they can be explained through pathophysiology and logic. However, some of the findings have never been demonstrated before, and to our knowledge, paper 3 was the first study to use multivariate analyses to assess the associations between a variety of structural changes and clinical complications in a large CP population.

7.2 Future perspectives

We have shown that the diagnostic accuracy of CT, the most commonly used imaging modality for CP, is not without its flaws, and that US may be a valid alternative, or even addition, in some patients. Our studies remind us of the limitations of everyday diagnostic tools, and they raise the question of how the different modalities could be combined to increase diagnostic accuracy.

Both this thesis and previous work by our group have pointed to the benefits of US in managing patients with CP. In a clinical setting, US can be performed bedside by the pancreatologist, allowing for direct integration of imaging with other clinical findings and anamnesis. This may also shorten the time between ambulatory visits and decisions regarding therapy or need for additional examinations.

Our diagnostic tools are constantly evolving, and diagnostic scores needs to be revised accordingly. The limitations of the Cambridge and Rosemont classifications have been discussed, and we call for validation of recently developed systems [107; 127] to ensure that they fit both the current definitions of CP and the inherent strengths and limitations of the different modern modalities.

The variation in how CP presents makes diagnostics complicated and reaching a standard with high sensitivity and specificity for all phenotypes of CP may be difficult, if not impossible. Our findings support that imaging should be complemented by clinical information (etiology, symptoms) and results from other testing (*e.g.,* pancreatic functions, nutrition, bone health). Including all the relevant components in a diagnostic scoring system may cause the system to become too complex, rendering it impractical. To avoid this, it is necessary to clarify which features from imaging, clinical presentation, and other testing that are most helpful in establishing the diagnosis.

In this thesis, the importance of a valid and accurate reference standard in diagnostic accuracy studies has been discussed. With histology not available in most patients, multicomponent systems and longitudinal follow-up may be good options.

The SBPC research group collects longitudinal data on a large cohort of CP patients. We intend to use this data to continue working towards understanding the roles of structural pancreatic changes, etiology, and other factors in the development of clinical complications, and hopefully towards building a system where patient factors, clinical factors, and imaging can be used to indicate a patient's long-term prognosis.

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PAPER I

I

PAPER II

II

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Original Article

Thieme

Diagnostic Accuracy of Transabdominal Ultrasound and Computed Tomography in Chronic Pancreatitis: A Head-to-Head Comparison

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ABSTRACT

Purpose Computed tomography (CT) is the most used imaging modality for diagnosing chronic pancreatitis (CP), but advances in transabdominal ultrasound (US) technology have given US a position as a viable alternative. We aimed to evaluate the diagnostic accuracy of abdominal CT and pancreatic US compared to the reference standard, a modified Mayo score.

Materials and Methods CT, US, and endoscopic ultrasound (EUS) were performed in patients referred due to suspected CP. The modified Mayo score included EUS results, clinical presentation, and results from exocrine and endocrine pancreatic function tests. We scored CT findings according to the modified Cambridge classification and US findings according to the Rosemont classification.

Results In total, 73 patients were included. 53 patients (73 %) were categorized as CP and 20 (27 %) as non-CP. CT and US yielded similar sensitivities (68 % and 64 %, respectively) and specificities (75 and 85 %, respectively) and similar areas under the receiver operating characteristic curves for diagnosing CP. We found no significant differences between the areas under the receiver operating characteristic curves (AUROCs) for CT (AUROC 0.75, 95 % CI 0.63–0.87) and US (AUROC 0.81, 95 % CI 0.71–0.91).

Conclusion We conclude that CT and US had comparable, moderate accuracy in diagnosing CP. Neither modality had high enough sensitivity to exclude the diagnosis as a standalone method.

Introduction

Chronic pancreatitis (CP) is a fibro-inflammatory syndrome in which recurrent inflammatory episodes of the pancreas result in normal pancreatic parenchyma being replaced by fibrous connective tissue [1–4]. Typical imaging features are calcifications, ductal irregularities and dilatations, increased parenchymal density or echogenicity, gland atrophy, and pseudocysts [1]. Abdominal pain is the most frequently reported symptom of CP, and pain patterns vary

from intermittent pain episodes to more prominent, continuous pain syndromes [1]. CP is further characterized by exocrine and endocrine pancreatic insufficiency, contributing to bloating, steatorrhea, underweight, malnutrition, and metabolic bone disease [1, 4, 5].

CP can be particularly difficult to diagnose in the early phases, when patients may have recurring inflammatory episodes, either silent or accompanied by non-specific symptoms, but classical structural changes or functional pancreatic insufficiencies are not yet detectable. Diagnostic guidelines [1, 2, 4–6] recommend a multimodal workup, including diagnostic imaging, pancreatic function testing and symptom evaluation, and several diagnostic criteria have been developed [7–11]. Computed tomography (CT), endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) are all recommended imaging modalities as part of the diagnostic workup for CP [1, 5, 6]. Transabdominal ultrasound (US) is widely used and recommended as a first-line modality in subjects with abdominal pain [1, 2, 12]. Although opinions on the role of US in CP diagnostics are divided, US is recommended in patients with advanced CP and when repeated examinations are warranted [1, 2, 5, 12]. The imaging modalities used to diagnose CP have inherent weaknesses related to operator and patient dependencies, and some modalities involve invasive procedures (EUS) or ionizing radiation (CT) or have limited ability to detect key features such as calcifications (MRI) or early ductal changes (CT and US) [6, 12, 13]. By combining different modalities and applying them in the appropriate clinical settings, a multimodal imaging workup may reduce the impact of modality limitations and improve diagnostic accuracy.

Image scoring systems may give more weight to important or pathognomonic features, e. g., calcifications in CP [1] than to less important features. Thus, a well-designed weighted scoring system should ideally increase the diagnostic accuracy for diagnosing CP compared to just counting the number of positive features. The Cambridge classification was originally used for endoscopic retrograde pancreatography, and later adapted to MRI and CT [14, 15]. EUS and US have often been scored by counting the number of features without any weighting [16, 17], but in recent years, the Rosemont classification [16] has proven to be a promising weighted scoring system for these modalities.

CT is the first-line imaging modality when CP is suspected, but the advances in ultrasound technology and image quality [18, 19] have strengthened the potential role of US as a first-line imaging modality. To the authors' knowledge, no studies have evaluated the diagnostic performance of CT and US for diagnosing CP against a common reference standard since the 1990s. Thus, in this head-to-head analysis in patients with suspected CP, we aimed to compare the diagnostic accuracy of modern CT and US in comparison with a multimodal diagnostic score for CP [7] based on findings from EUS, clinical presentation and results from exocrine and endocrine pancreatic function tests. We applied both unweighted scores and the most frequently used weighted scoring systems: the modified Cambridge classification for CT and the Rosemont classification for EUS and US ▶**Table 1–6**.

Materials and Methods

Study design

The Bergen Pancreas Database collected information on 141 patients referred to our outpatient clinic with symptoms or imaging findings suggestive of CP. Patients were included consecutively in the period from 2009 to 2016. Patient characteristics, results from biochemistry and pancreatic function tests, and results from various imaging examinations were recorded. In this paper we present analyses of the diagnostic imaging data collected upon inclusion, applying a cross-sectional design. We included all patients who had a complete imaging workup, including CT, US, and EUS. Patients were excluded if image quality/visualization was insufficient in any of the three examinations.

Diagnostic standards

The reference standard was a modified version of the Mayo score [7] based on EUS, clinical presentation, and exocrine and endocrine function status (▶**Table. 1**). To avoid the diagnostic standard being impacted by the tested modalities, CT and US were not included in the score. The EUS imaging features that were used were parenchymal calcifications, ductal stones, dilated or irregular main pancreatic duct contour, dilated side ducts, pseudocysts, and honeycomb-patterned lobulation. Four points were given if parenchymal calcifications or ductal stones were present, and 3 points were given if any of the other features were present. Patients with Mayo score ≥ 4 were categorized as CP, and patients with scores < 4 were categorized as non-CP. EUS is the recommended modality for diagnosing early CP. However, our reference standard did not include an evaluation of early CP.

EUS imaging

EUS examinations were performed by an experienced operator (R.F.H.) using a linear EG-3870 UTK or radial EG-3670 URK scope (Pentax Medical, Pentax Europe, Hamburg, Germany), with frequencies 7.5–12 MHz. We used a Hitachi Ascendus scanner (Hitachi Medical Systems Europe, Zug, Switzerland). Patients were offered intravenous conscious sedation as per local guidelines (Midazolam and Pethidine or Fentanyl). The examination was performed by scanning the pancreatic body and tail from the gastric ventricle, and then scanning the pancreatic head under slow retraction from the second part of the duodenum. The findings were registered according to definitions from the Rosemont classification [16] (▶**Table 1**). In addition to being part of the reference standard, findings from EUS were included in the single feature agreement analyses to allow for the comparison of CT versus US versus EUS. Scoring of EUS was performed immediately after examinations, and the operator was blinded to the patients' medical history, other imaging, and test results.

US imaging and scoring

Transabdominal US examinations were performed by a gastroenterologist (T.E.) with > 10 years of experience in pancreatic ultrasound and imaging. Examinations and scoring were performed with blinding to the patients' medical history, other imaging, and test results. Scoring was performed immediately after examinations. US was carried out using a GE Logic E9 scanner (GE Healthcare, Chicago, IL, USA) with a 1–5 MHz curvilinear probe, and when possible,

▶ **Table 1** Diagnostic scoring systems for chronic pancreatitis

The modified Mayo score		
The CP diagnosis requires ≥ 4 points		
4 points	Pancreatic calcifications on EUS or typical histologic findings	
3 points	Moderate or marked morphologic changes on EUS *	
2 points	Reduced exocrine pancreatic function †	
2 points	History of acute pancreatitis or upper abdominal pain	
1 point	Diabetes mellitus, glycated hemoglobin ≥ 48 mmol/mol.	
The modified Cambridge classification for CT		
Cambridge grade	CT features	
0 - Normal	None	
1 - Equivocal	Cannot be delimited on CT with current methods	
2 - Mild	2 or more of the following changes: – Pancreatic duct between 2 and 4 mm in the body of the pancreas ‡ – Heterogeneous parenchymal structure – Small cystic changes (< 10 mm) – Duct irregularities (1-2 mm variation) – 3 or more pathological side ducts (Excluded criteria: slight enlargement of the pancreas)	
3 - Moderate	All changes specified in 2 plus pathological main duct (> 4 mm)	
4 - Marked	One of the changes specified in 2 and 3 plus one or more of the following: – Cystic structures (≥ 10 mm) – Parenchymal calcifications – Intraductal filling defects (chalk stones) – Duct obstruction (strictures) – Severe duct irregularities (> 2 mm variation)	
The Rosemont classification for US		
Parenchymal features		
Hyperechoic foci with shadowing		Major A
Lobularity		
A: without honeycombing		Minor
B: with honeycombing		Major B
Hyperechoic foci without shadowing		Minor
Cysts		Minor
Stranding		Minor
Ductal features		
MPD calculi		Major A
Irregular MPD contour		Minor
Dilated side branches		Minor
MPD dilatation		Minor
Hyperechoic MPD margin		Minor
1 - Consistent with CP	A. 1 major A feature + ≥ 3 minor features B. 1 major A feature + 1 major B feature C. C. 2 major A features	
2 - Suggestive of CP	A. 1 major A feature + < 3 minor features B. 1 major B feature + ≥ 3 minor features C. C. ≥ 5 minor features (any)	
3 - Indeterminate for CP	A. 3 to 4 minor features, no major features B. B. Major B feature alone or with < 3 minor features	
4 - Normal	≤ 2 minor features, no major features	

Mayo score [7] was modified not to incorporate findings from CT and US, and it was used as the reference standard for the CP diagnosis. We used the modified Cambridge classification [15] to score results from CT imaging and the Rosemont classification [16] for US. CP = chronic pancreatitis; CT = computed tomography; EUS = endoscopic ultrasonography; MPD = main pancreatic duct; US = transabdominal ultrasonography. * Moderate or marked morphologic changes on EUS were defined as the presence of one or more of the following features: irregular or dilated main pancreatic duct contour, dilated side ducts, pseudocysts and honeycomb-patterned lobulation. † Reduced exocrine pancreatic function by endoscopic short test or fecal elastase 1 level. Cut-offs: fecal elastase 1 < 200 µg/g and endoscopic short test, peak value of bicarbonate concentration < 80 mmol/L. ‡ The typical definition of duct dilatation in the body of the pancreas uses a cut-off ≥ 3 mm. Patients scored positive if the duct diameter was ≥ 3 mm and ≤ 4 mm.

a 9 MHz linear probe. Patients were examined after overnight fasting to optimize visualization. US was performed with patients in a supine or right lateral position, and the probe were placed in transverse and oblique positions in the lateral/posterior left subcostal region. Standardized abdominal US settings were applied: Frequency 4.0 MHz (curvilinear probe) and 9.0 MHz (linear probe), dynamic range 34, and frame rate 15–22 frames per second. US examinations were completed in B-mode and supplemented with color Doppler to evaluate, *e. g.*, twinkling artifacts around edged calcifications. Scanning depth varied depending on the patient anatomy. US visualization of the pancreatic head, body, and tail was graded from 1 to 4 (1 = good, 2 = adequate, 3 = poor, and 4 = not visible), and patients were excluded if the visualization was 3 or higher in all segments.

The Rosemont classification (▶ **Table 1**) originally developed for EUS was used to score ductal and parenchymal features on US [16, 19]. The Rosemont categories for US are: 1 = consistent with CP, 2 = suggestive of CP, 3 = indeterminate for CP, and 4 = normal. In the Rosemont classification, the cut-off for the CP diagnosis is ≤ 2. We also counted the number of positive single criteria from the Rosemont classification (unweighted US score), using a cut-off ≥ 2 according to a previous publication [19]. ▶ **Fig. 1** shows a US image in a patient with CP.

CT imaging and scoring

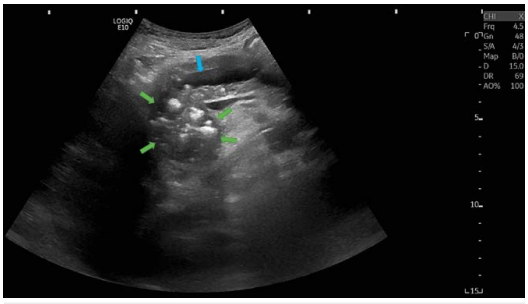
CT scans were performed using standard abdominal or pancreatic CT protocols on clinical hospital scanners. Intravenous contrast was administered in 97 % (71/73) of the CT scans. Abdominal protocols included scanning in the portal venous phase, and pancreatic protocols included scans pre-contrast and in the late arterial and portal venous phase. Scans were stored and re-evaluated for the purpose of this study. Image quality was evaluated by two observers (T.E., gastroenterologist, and I.K.N., medical doctor), and patients were excluded if the quality was deemed insufficient. CT imaging was scored by I.K.N., who was blinded to the patients' medical history, other imaging, and test results. Parenchymal and ductal features were assessed and scored using the modified Cambridge classification (▶ **Table 1**) [15], following predefined reading standards. The classification categorizes patients into five groups (0 = normal, 1 = equivocal, 2 = mild, 3 = moderate, and 4 = marked). We also applied an unweighted CT score, where the score was equal to the number of positive single criteria from the Cambridge classification. The cut-off was ≥ 2 according to a previous publication [20]. ▶ **Figure 2** shows a CT image in a patient with CP.

Statistical analysis

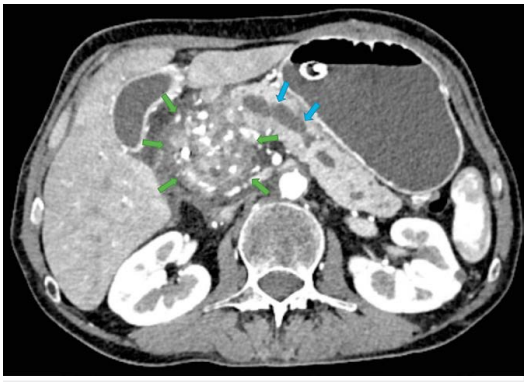
Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM, Armonk, NY, USA). Data are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR). Normality distributions were tested using Q-Q plots and Shapiro-Wilk's test. When comparing groups, we used independent samples t-test and Mann-Whitney U test for parametric and non-parametric continuous data, respectively. Pearson's χ^2-test was used for binary and categorical data. We applied Fisher's Exact Probability test if the minimum expected cell count was < 5 in any cells when comparing frequencies between groups. Results on diagnostic accuracy are presented as area under the receiver operating characteristic curves (AUROCs), sensitivity, and specificity with 95 % confidence intervals. Differences in AUROCs were evaluated using a paired-sample AUROCs comparison in SPSS. Cohen's kappa (κ) was used to evaluate the agreement for binary variables, and weighted kappa was used for ordinal variables. The level of agreement was defined as follows: poor (κ < 0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80), and very good (κ = 0.81–1). A value of $p < 0.05$ was considered statistically significant.

Ethics

The study was conducted according to the Helsinki Declarations and approved by the Regional Committees for Medical and Health Research Ethics, Western Norway (REK-Vest, registration numbers 2011/590 and 2019/1037). All patients received written and oral information about the study and signed an informed consent form before inclusion in the database and prior to any study related examinations. This paper adheres to the Standards for Reporting of Diagnostic Accuracy (STARD) [21].



▶ **Fig. 1** US image illustrating a large inflammatory mass (green arrows) with calcifications, and an irregular and dilated main pancreatic duct (blue arrow) in a patient with chronic pancreatitis. Fig. 2 shows a CT image of the same patient.



▶ **Fig. 2** CT image illustrating a large inflammatory mass (green arrows) with calcifications, and an irregular and dilated main pancreatic duct (blue arrows) in a patient with chronic pancreatitis. Fig. 1 shows a US image of the same patient.

Results

Participants

From the database cohort comprised of 141 patients, 84 patients had completed both CT, EUS and US, and were considered eligible for the study. We excluded nine patients due to insufficient visualization on US and two patients due to poor CT image quality. In total, 73 patients were included in the analyses. 53 patients (73 %) had a Mayo score ≥ 4, fulfilling the diagnostic criteria of CP. The remaining 20 patients (27 %) were categorized as non-CP (▶ **Fig. 3**). Non-CP patients were diagnosed with other conditions explaining the symptoms, including recurring acute pancreatitis, bile stone disease, and functional dyspepsia. The CP group had a significantly lower body mass index and fecal elastase levels than the non-CP group, but there were no significant differences in age, gender, or glycated hemoglobin (▶ **Table 2**). Pancreatic CT protocols were used in 47 % (34/73) and abdominal CT protocols in 53 % (39/73). The use of CT protocols (abdominal *vs.* pancreatic) was not significantly different between CP and non-CP patients ($p = 0.223$).

Visualization

On US, the entire pancreas was visualized in 62 % of the included patients. The pancreatic tail was sufficiently visualized (scores 1 or 2) in 65 %, the body in 97 %, and the head in 89 %.

Diagnostic performance indices

Diagnostic performance indices for CT and US were calculated using the modified Mayo score as the reference standard: CT (Cambridge classification, cut-off ≥ 2) yielded a sensitivity of 68 % and a specificity of 75 %, and US (Rosemont classification, cut-off ≤ 2) yielded a sensitivity of 64 % and a specificity of 85 % (▶ **Table 3**).

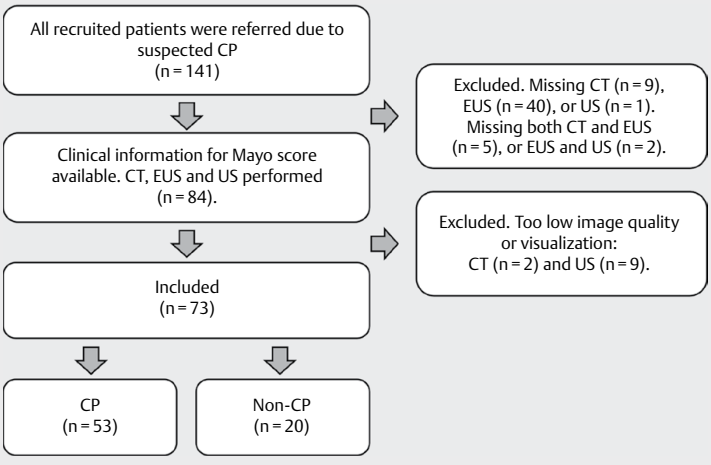
For CT, the areas under the receiver operating characteristic curves (AUROCs) were lower when using the Cambridge classification (0.75, 95 % CI 0.63–0.87) compared to when using the unweighted CT score (0.80, 95 % CI 0.70–0.90), $p = 0.05$. The AUROCs for US were 0.81 (95 % CI 0.71–0.91) for the Rosemont classification and 0.84 (95 % CI 0.74–0.94) for the unweighted US score, $p = 0.188$. Any differences in AUROCs between CT and US were non-significant ($p > 0.05$). ROC curves are presented in ▶ **Fig. 4**.

Agreement analyses

We found moderate agreement (κ = 0.45) for the CP diagnosis between CT and US when using the modified Cambridge and the Rosemont classifications, and fair agreement (κ = 0.37) when using the unweighted scores. We found moderate agreement (weighted κ = 0.43) between the categories from the modified Cambridge classification and the inverted Rosemont classification. The most frequent feature was calcifications, which were present in 51 % of CP patients on CT, 64 % on US and 59 % on EUS. We found good agreement for calcifications between CT and US (κ = 0.75) and between CT and EUS (κ = 0.69), and very good agreement between US and EUS (κ = 0.84). All agreement analyses are presented in ▶ **Table 4**. Frequencies of CP-related imaging features on CT and US are presented in ▶ **Table 5** and ▶ **Table 6**, respectively.

Discussion

In this head-to-head study, we aimed to compare the diagnostic accuracy of CT and US in patients with suspected CP. The reference standard was a modified Mayo score based on findings from EUS, clinical presentation and results from exocrine and endocrine pancreatic function tests. Our results showed that CT and US yielded comparable moderate diagnostic accuracies for diagnosing CP and a moderate agreement between the imaging scoring systems: CT had a sensitivity of 68 % and specificity of 75 %, and US had a sensitivity of 64 % and a specificity of 85 %. The agreement for calcifica-



▶ **Fig. 3** Flowchart showing patient enrollment. CP = chronic pancreatitis; CT = computed tomography; EUS = endoscopic ultrasound; US = ultrasound.

▶ **Table 2** Patient characteristics and imaging scoring results in a multimodal imaging study on chronic pancreatitis

	Non-CP (n = 20)	CP (n = 53)	Missing (n)	p
Females, n (%)	10 (50)	33 (62)	0	ns
Age, mean (SD)	54 (13)	54 (13)	0	ns
Fecal elastase 1 (µg/g), median (IQR)	433 (270–500)	159 (39–500)	6	0.001
PEI frequency, n (%)	2 (10)	27 (57)	6	<0.001
BMI (kg/m^2), median (IQR)	24.3 (19.9–27.5)	21.2 (18.4–24.1)	8	0.040
Underweight frequency, n (%)	0	12 (25)	8	0.022
HbA1c (mmol/mol), median (IQR)	5,5 (5,2–5,9)	5,7 (5,4–6,5)	3	ns
Diabetes frequency, n (%)	2 (11)	12 (23)	3	ns
Smokers frequency, n (%)	3 (17)	26 (51)	4	0.011
Alcohol consumption, frequencies, n (%)				
Current non-drinkers	8 (47)	27 (55)	7	ns
Current regular drinkers, ≥ 7 std. drinks per week	1 (6)	4 (8)	7	ns
CT Cambridge classification, n (%)			0	0.005
0 – normal	9 (45)	8 (15)		
1 – equivocal	6 (30)	9 (17)		
2 – mild	1 (5)	1 (2)		
3 – moderate	0	0		
4 – marked	4 (20)	35 (66)		
US Rosemont classification, n (%)			0	<0.001
1 – consistent with CP	1 (5)	22 (42)		
2 – suggestive of CP	2 (10)	12 (23)		
3 – indeterminate for CP	0	6 (11)		
4 – normal	17 (85)	13 (25)		
Unweighted CT score, median (IQR)	0 (0–2)	3 (1–5)	0	<0.001
Unweighted US score, median (IQR)	0 (0–1)	3 (1–5)	0	<0.001

Pancreatic exocrine insufficiency was defined as fecal elastase 1 < 200 µg/g, underweight as BMI ≤ 18.5 kg/m^2 and diabetes as HbA1c ≥ 48 mmol/mol. Overall *p*-values from χ^2-test are given for the Cambridge classifications (0–4) and the Rosemont classifications (1–4). BMI = body mass index; CP = chronic pancreatitis; CT = computed tomography; HbA1c = glycated hemoglobin; IQR = interquartile range; PEI = pancreatic exocrine insufficiency; SD = standard deviation; US = ultrasound.

tions was very good between US and EUS, and agreements between modalities for duct dilatations ranged from poor to moderate.

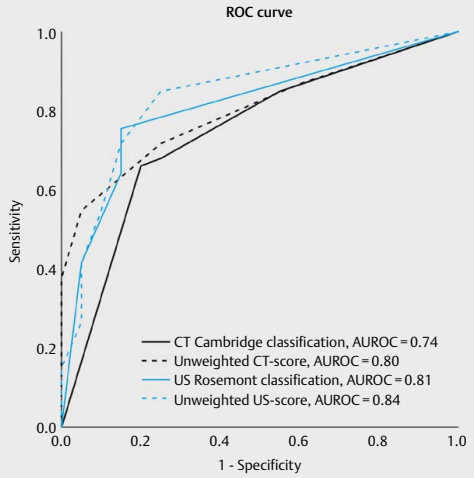
Previous studies on the diagnostic accuracy of CT and/or US in CP have shown divergent results, with sensitivities ranging from 58–100 % for CT and 38–100 % for US, and specificities ranging from 59–100 % for CT and 34–100 % for US [19, 20, 22–25]. The most recent study [19] reported good diagnostic accuracy of modern transabdominal US in CP, with a sensitivity of 81 % and a specificity of 97 % for the Rosemont classification, and a sensitivity of 69 % and a specificity of 97 % for the unweighted US score. The US scoring tools were identical, but the reference standard also included results from CT. An EUS-based reference standard has the potential to detect more cases of early CP. Because patients with early CP typically do not present with irreversible morphologic changes, increasing imaging sensitivity is associated with decreasing specificity [5], possibly explaining why we now present lower diagnostic performance indices for US.

Issa et al. [22] published a systematic review on the diagnostic performance of different imaging modalities in CP. They presented pooled sensitivity and specificity data for CT, US, EUS, MRI, and endoscopic retrograde pancreatography, plus a head-to-head analysis of subjects who had undergone both CT and US. Their analyses showed that CT had a sensitivity of 75 % and a specificity of 91 %, and US had a sensitivity of 67 % and a specificity of 98 %. Their head-to-head analyses were particularly similar to our results. The majority of the studies on CT and/or US were published between 1977 and 1999 [22]. This complicates the comparison to our data for two reasons. First, CT and US technologies have evolved considerably during this period [22, 26], and second, with EUS facilitating the diagnosis of early CP [2], the diagnostic standards and disease severity among newly diagnosed patients have changed. All studies

▶ **Table 3** Diagnostic performance indices for diagnosing chronic pancreatitis

	AUROC	Cut-off	Sensitivity (%)	Specificity (%)
CT Cambridge	0.75 (0.63–0.87)	≥ 2	68 (54–80)	75 (51–91)
CT Unweighted	0.80 (0.70–0.90)	≥ 2	72 (58–83)	75 (51–91)
US Rosemont	0.81 (0.71–0.91)	≤ 2	64 (50–77)	85 (62–97)
US Unweighted	0.84 (0.74–0.94)	≥ 2	72 (58–83)	85 (62–97)

The table shows areas under the receiver operating characteristic curves (AUROCs) and diagnostic performance indices with 95 % confidence intervals. AUROC for the Cambridge classification was significantly lower than AUROC for the unweighted CT score ($p = 0.050$). CT = computed tomography; US = ultrasound.



▶ **Fig. 4** ROC curve with areas under the ROC curves (AUROCs) for CT and US in diagnosing chronic pancreatitis. AUROC for the Cambridge classification was lower than AUROC for the unweighted CT score (p = 0.050). Other differences in AUROCs were non-significant (Cambridge vs. Rosemont: p = 0.377, Cambridge vs. unweighted US-score: p = 0.173, Rosemont vs. unweighted US-score: p = 0.188, Rosemont vs. unweighted CT-score: p = 0.886, unweighted US-score vs. unweighted CT-score: p = 0.519). CP = chronic pancreatitis; CT = computed tomography; US = ultrasound.

in the review recruited patients with suspected CP or suspected pancreatic disease, but the reference standard was only similar to ours in one of them [23]. There were also differences in scoring methods used for CT and US, and in some publications, the scoring methods were not available.

In the agreement analyses, we found that US and EUS had higher agreement on duct dilatations compared to CT and EUS, indicating that US may be better than CT in detecting ductal changes. However, the difference may also be explained by the slight difference in the definitions of duct dilatations between the Cambridge and Rosemont classifications. Calcifications are not as apparent on US as on CT, but our results confirm the ability of US to detecting calcifications: US has good and very good agreement with CT and EUS, respectively.

Though good results have been achieved with Rosemont for transabdominal US previously [19, 27], the score is complex, and a simpler US scoring tool, as recently proposed by Pagliari et al. [28], is warranted. The Cambridge classification for CT has several weaknesses, including its somewhat complex structure and large focus on ductal changes and other subtle changes. Given the current scoring systems, neither CT nor US has sufficient diagnostic accuracy to recommend one over the other.

Several factors influence the choice of imaging modality in the diagnostic workup of CP. CT and US are widely available and at relatively low costs. However, their other strengths and limitations differ. CT image quality was sufficient in 82 of the 84 patients we evaluated, and because CT performs well in visualizing the whole pancreas, it has an advantage in ruling out differential diagnoses and can function as a baseline examination [6, 12]. Due to ionizing radiation and risk associated with intravenous contrast agents, repeated use and use of CT in young patients or patients with impaired kidney function should be limited. US does not have such limitations and can easily be repeated if needed for frequent follow-up. Furthermore, bedside US enables the clinician to get immediate answers. Intestinal gas and obesity may, however, hinder adequate visualization on US. Importantly, the whole pancreas was only visualized in 62 % of our patients, indicating that US should not be the sole modality if pancreatic cancer is suspected. Ruling out concomitant cancer in a pancreas structurally altered by CP is difficult [1, 2], and even though EUS may be the best modality to detect malignancies [1], a combination of different imaging modalities may be recommended, particularly when indicated based on clinical suspicion or known risk factors [2]. The full potential for advanced US in diagnosing CP is still unclear, but contrast-enhanced US reportedly improves the diagnostic accuracy when characterizing focal pancreatic lesions [1, 29], and US elastography may also prove beneficial [30].

Our findings provide a reminder of the differences in strengths and limitations connected to each modality, pinpointing the importance of a multimodal and individually adapted approach. Further exploration of strengths and limitations of CT and US is warranted, and combined with the development and validation of updated scoring systems, this may provide better diagnostics for patients with CP.

Limitations

The conclusions regarding diagnostic accuracy are highly dependent on the scoring systems used to evaluate diagnosis and imaging, and the results are limited by the strengths and weaknesses in these mainly expert opinion-based systems. None of the systems are properly validated, and inaccuracies in any one of the three scoring systems will have implications for results and further inter-

▶ **Table 4** Agreement analyses on diagnosis and imaging parameters in patients with chronic pancreatitis

				Agreement		
				%	κ	
CP diagnosis	CT Cambridge classification	vs.	US Rosemont classification	77	0.51	Moderate
	CT Cambridge classification	vs.	Unweighted CT score	97	0.94	Very good
	US Rosemont classification	vs.	Unweighted US score	81	0.62	Good
	Unweighted CT score	vs.	Unweighted US score	75	0.50	Moderate
Calcifications	CT	vs.	US	84	0.67	Good
	CT	vs.	EUS	84	0.66	Good
	US	vs.	EUS	92	0.84	Very good
Pseudocysts	CT	vs.	US	81	0.35	Fair
	CT	vs.	EUS	74	0.36	Fair
	US	vs.	EUS	72	0.32	Fair
Duct dilatations	CT	vs.	US	64	0.30	Fair
	CT	vs.	EUS	63	0.28	Fair
	US	vs.	EUS	75	0.48	Moderate
				Weighted agreement		
Scores	CT Cambridge classification	vs.	US Rosemont classification		0.43	Moderate

Agreement between scoring systems and modalities for diagnosis and three key features. Results are presented as percent agreement (%) and Cohen's kappa (κ). Calcifications include both parenchymal and ductal calcifications. CP = chronic pancreatitis; CT = computed tomography; EUS = endoscopic ultrasound; US = transabdominal ultrasound.

▶ **Table 5** CP-related imaging features on CT in a cohort of patients with suspected chronic pancreatitis

	Total	Non-CP	CP	Missing	*p*
MPD dilatation 2–4 mm, pancreatic body	26 (37)	6 (32)	20 (39)	2	ns
Heterogeneous parenchymal structure	38 (52)	5 (25)	33 (62)	0	0.004
Small cystic changes	5 (7)	2 (10)	3 (6)	0	ns
Duct irregularities	12 (17)	1 (5)	11 (21)	2	ns
Side ducts	0	-	-	0	-
MPD > 4 mm	15 (21)	0	15 (29)	1	0.007
Large cystic structures	14 (19)	2 (10)	12 (23)	0	ns
Parenchymal calcifications	28 (38)	2 (10)	26 (49)	0	0.003
Intraductal filling defects	19 (26)	0	19 (36)	0	0.001
Duct obstructions	16 (22)	0	16 (31)	1	0.004
Severe duct irregularities	13 (18)	0	13 (25)	1	0.014
All calcifications	29 (40)	2 (10)	27 (51)	0	0.001

The frequencies of positive single features from CT examinations are presented as number of cases (%). Missing data are expressed as number of cases. Definitions according to the modified Cambridge classification for CT. CP = chronic pancreatitis; CT = computed tomography; MPD = main pancreatic duct.

▶ **Table 6** CP-related imaging features on transabdominal US in a cohort of patients with suspected chronic pancreatitis

	Total	Non-CP	CP	Missing	p-value
Hyperechoic foci with shadowing	36 (49)	3 (15)	33 (62)	0	<0.001
Lobularity (all)	2 (3)	0	2 (4)	0	ns
Hyperechoic foci without shadowing	13 (18)	2 (10)	11 (21)	0	ns
Cysts	10 (14)	1 (5)	9 (17)	0	ns
Stranding	19 (26)	1 (5)	18 (34)	0	0.015
MPD calculi	17 (23)	0	17 (32)	0	0.004
Irregular MPD contour	32 (44)	3 (15)	29 (55)	0	0.003
Dilated side branches	18 (25)	1 (5)	17 (32)	0	0.016
MPD dilatation	22 (30)	0	22 (42)	0	<0.001
Hyperechoic MPD margin	4 (5)	1 (5)	3 (6)	0	ns
Calcifications (all)	37 (51)	3 (15)	34 (64)	0	<0.001

The frequencies of positive single features from US examinations are presented as number of cases (%). Definitions according to the Rosemont classification. CP = chronic pancreatitis; MPD = main pancreatic duct; US = ultrasound.

pretation. We applied the most frequently used systems and included unweighted scores to offer an alternative to the weighted systems.

Because of the similarities between EUS and US with regards to technology and scoring systems, using EUS as part of the reference standard may have given US an advantage compared to CT. Histology from, *e. g.*, fine needle aspiration or fine needle biopsies would provide a better reference standard. However, due to the risk of complications related to such procedures, this could not be justified in our study population.

The study protocol was based on a consecutive intention-to-diagnose design, aiming to complete all the required imaging (CT, EUS, and US). Still, for various reasons, some patients failed to complete all imaging examinations. This may have created selection biases connected to individual patient characteristics or disease presentation. The results for US do not take into account the cases (n = 9) in which the pancreas could not be sufficiently visualized, and exclusion caused by bowel gas or obesity may also have caused a selection bias.

Due to the difference in experience levels between the observers scoring US and CT, CT examinations were interpreted by both observers. Analyses showed good interobserver agreement for scoring ($\kappa = 0.66$) and diagnosis ($\kappa = 0.67$) and no significant differences in AUROCs, indicating that this minimally effected the CT scoring results. Visualization assessments for EUS and US examinations were performed by single observers, while the quality of CT examinations were assessed by two observers. Both CT and US examinations were performed blinded to patient history and other examinations, but blinding for the general reason for referral (CT/US) plus patient appearance (US) was not feasible and may have produced blinding bias.

Operator experience level is relevant in pancreatic US, and diagnostic performance cannot be directly translated to a setting with an inexperienced operator. All imaging modalities require training to achieve a certain level of reliability. Particularly EUS has a long learning curve and can only be performed by skilled personnel [19].

Conclusion

In this head-to-head study, CT and US yielded similar, but only moderate diagnostic performance indices, not high enough to support that they should be used as single modalities. CT plays an important role in evaluating complications and differentiating CP from other diagnoses, and it is still the modality of choice in the initial diagnostic workup of CP. US does not have limitations related to ionizing radiation and CT contrast agents, and this study shows that US has comparable accuracy to that of CT given sufficient visualization. A combination of both CT and US may be beneficial in the primary workup for CP, and US seems particularly favorable for repeated examinations and follow-up in CP. The advantages and drawbacks of each modality are different, and the modality of choice should match the requirements in each patient's case.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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PAPER III

III

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