

The chronic pancreatitis (CP) Type Cambridge 2 as a cause of unclear upper abdominal pain: a radiologically underestimated diagnosis

Die chronische Pankreatitis (CP) Typ Cambridge 2 als Ursache unklarer Oberbauchschmerzen: eine radiologisch unterschätzte Diagnose

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ABSTRACT

Objective The time interval from symptom onset to the diagnosis of chronic pancreatitis (CP) remains disproportionately long today due to nonspecific symptoms and the absence of a definitive laboratory marker. Nevertheless, mortality is increased by 3.6 times compared to the general population. Additionally, the risk of developing pancreatic carcinoma is 16 times higher in the presence of CP. According to the current S3 guideline, the morphological staging of CP should be based on the Cambridge Classification for CT/MRCP. Most radiologists morphologically associate CP with Cambridge

Stage 4, which is characterized by classic calcifications. The subtle morphologies of earlier Cambridge Stages are often unrecognized, leading to delayed diagnosis. The aim of this study was to diagnose CP at Cambridge Stage 2 as the cause of unexplained upper abdominal discomfort.

Materials and Methods A retrospective analysis was conducted on 266 patients with unexplained upper abdominal pain who underwent outpatient MRI with MRCP between January 1, 2021, and October 1, 2023. The criteria for Cambridge Stage 2 were evaluated: pancreatic duct in the corpus measuring between 2 and 4 mm, pancreatic hypertrophy, cystic changes < 10 mm, irregularities in the duct, or > 3 pathological side branches. Patients with known tumors or other leading diagnoses, which explained the discomfort, were excluded.

Results 25 patients (15 female, 10 male) met the criteria for CP Stage 2 (9%). Ductal dilation between 2 and 4 mm was visible in 21 cases. Pancreatic hypertrophy was observed in six cases. Cystic changes < 10 mm were identified in three cases. Irregularities in the duct ("wavy duct") were diagnosed in 19 patients. Dilation of > 3 side branches was recognized in 17 cases. Lipase levels were additionally determined, with 13 patients showing pathologically elevated levels (> 60 U/l).

Conclusions CP at Cambridge Stage 2 is an important and underestimated diagnosis in patients with unexplained upper abdominal pain in the outpatient setting. Radiologists should pay attention not only to common signs like calcifications, large cysts, or duct strictures but also to subtle changes such as duct irregularities ("wavy duct configuration") and pathologically dilated side branches, which could lead to a significantly earlier diagnosis of CP. Lipase determination may be an additional indication of chronic pancreatitis in this context.

Key Points

- Early-stage Cambridge 2 CP is an important and underestimated diagnosis in patients with unexplained upper abdominal pain in the outpatient setting.
- Radiologists should pay attention to subtle signs of early CP.
- Additional information about lipase levels can be helpful in the diagnostic process.

Citation Format

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ZUSAMMENFASSUNG

Ziel Der Zeitraum von Symptombeginn bis zur Diagnose „chronische Pankreatitis“ (CP) ist heute meist unverhältnismäßig lang, was an unspezifischen Symptomen und dem Fehlen eines eindeutigen Laborparameters liegt. Die Sterblichkeit gegenüber der Normalbevölkerung ist um das 3,6-fache erhöht. Zudem ist das Risiko, an einem Pankreaskarzinom zu erkranken, bei Vorliegen einer CP 16-fach erhöht.

Die morphologische Stadieneinteilung der CP sollte gemäß der aktuellen S3-Leitlinie anhand der Cambridge-Klassifikation für CT/MRCP erfolgen.

Morphologisch verstehen viele Radiologen unter einer CP noch immer das Cambridge-Stadium 4 mit den klassischen Verkalkungen. Die subtilen Morphologien früherer Cambridge-Stadien sind oft unbekannt, sodass die Erkrankung oft zu spät diagnostiziert wird.

Ziel dieser Studie war der Nachweis morphologischer Kriterien einer CP im Cambridge-Stadium 2 als mögliche Ursache unklarer Oberbauchbeschwerden.

Material und Methoden Retrospektive Auswertung von 266 Patienten mit unklaren Oberbauchschmerzen, die zwischen dem 01.01.2021 und dem 01.10.2023 im ambulanten Setting mittels MRT mit MRCP untersucht wurden. Evaluiert wurden die Kriterien des Cambridge-Stadiums 2: Pankreasgang im Corpus zwischen 2 und 4 mm, Pankreashypertrophie, heterogene Parenchymstruktur, zystische Veränderungen

< 10 mm, Gangunregelmäßigkeiten beziehungsweise mehr als 3 pathologische Seitengänge. Ausgeschlossen wurden Patienten mit bekanntem Tumorleiden und anderer bekannter Diagnose als Erklärung für die Beschwerden.

Ergebnisse 25 Patienten (15 weiblich, 10 männlich) erfüllten die Kriterien eines CP-Stadiums 2 (9%). Eine Erweiterung des Ductus pancreaticus zwischen 2 und 4 mm war dabei in 21 Fällen erkennbar. Eine Pankreas-Hypertrophie bestand in sechs Fällen. Zystische Veränderungen < 10 mm waren in drei Fällen erkennbar. Gangunregelmäßigkeiten („welliger Gang“) wurden bei 19 Patienten diagnostiziert. Eine Erweiterung von mehr als drei Nebengängen wurde in 17 Fällen erkannt. Zusätzlich wurden die Lipasewerte bestimmt. Hierbei zeigten 13 Patienten pathologisch erhöhte Werte (> 60 U/l).

Schlussfolgerungen Die CP im Stadium Cambridge 2 ist eine relevante und unterschätzte Diagnose bei Patienten mit unklaren Oberbauchschmerzen im ambulanten Setting. Radiologen sollten neben den geläufigen Zeichen wie Verkalkungen, großen Zysten oder Gangstrikturen besonders auf subtile Veränderungen wie Gangunregelmäßigkeiten („wellige Gangkonfiguration“) und pathologisch erweiterte Nebengänge achten, was zu einer deutlich früheren Diagnose einer CP führen könnte. Die Bestimmung der Lipase kann in diesem Zusammenhang ein weiterer Hinweis auf eine chronische Pankreatitis sein.

Kernaussagen

- Die CP im Frühstadium Typ Cambridge 2 ist eine wichtige Diagnose bei Patienten mit unklaren Oberbauchschmerzen im ambulanten Setting.
- Radiologen sollten auf die subtilen Zeichen einer frühen CP achten.
- Die zusätzliche Kenntnis über die Lipase kann bei der Diagnosefindung hilfreich sein.

Introduction

Chronic pancreatitis (CP) is a complex and progressive disease of the exocrine pancreas characterized by persistent inflammation and irreversible changes in the pancreatic tissue. In 2017, the incidence in Germany was 23 per 100,000 population, with an increasing trend. In the same year, 24 per 100,000 population were hospitalized due to CP [1, 2]. The diagnosis of CP and our understanding of the pathophysiology have benefited in recent decades from advances in radiology, in particular magnetic resonance imaging with magnetic resonance cholangiopancreatography (MRI/MRCP).

The pathophysiology of CP is extremely complex and involves multiple factors, which makes diagnosis and treatment a major challenge [1, 2, 3]. Radiology plays a critical role in providing non-invasive methods for visual assessment of pancreatic morphology. MRI in particular has become established as a highly effective imaging method that provides detailed information about the pancreatic tissue, the pancreatic ducts, and possible structural abnormalities.

Many radiologists are familiar with the criteria for advanced CP, such as calcifications, severe pancreatic duct dilations or duct stones, or post-inflammatory pseudocysts. However, the signs of early-stage CP are much less well known.

In 2021, as part of the publication of a new, first-ever complete S3 guideline on acute, chronic, and autoimmune pancreatitis, uniform recommendations were established in the German-speaking region with regard to radiological imaging [4, 5]. In addition, recommendations from the European guideline on chronic pancreatitis show a comprehensive approach to the diagnosis and treatment of this disease [6, 7, 8].

These guidelines are based on the Cambridge classification, developed by the Cambridge Pancreatitis Study Group, which has gained in importance in recent years and provides a systematic method for classifying the morphology of chronic pancreatitis based on imaging findings. This classification allows a more precise characterization of the disease and can help to develop individualized treatment strategies for patients [4, 9]. In each case, the classification uses stage-adjusted morphologies adapted to the imaging technique in question. Specifically, these include:

► **Table 1** Standardized sequence protocol for contrast-enhanced MRI/MRCP at 1.5 Tesla field strength.

Sequence protocol	Slice thickness [mm]	Echo time TE [ms]	Repetition time TR [ms]	Flip angle [°]
T2 haste coronal	5.0	91	1300	152
T2 haste transversal	5.0	91	1300	180
T1 in-phase transversal	5.0	4.78	120	70
T1 opposed-phase transversal	5.0	2.37	120	70
MRCP thick slice coronal	5.0	750	4500	180
ep2w diff transversal	5.0	65	6800	90
Apparent Diffusion Coefficient transversal	5.0	65	6800	90
3D MRCP	1.0	702	4801	140
MRCP MIP coronal	72	702	4801	140
T1 vibe fs transversal	3.5	1.46	3.67	15
T1 vibe fs coronal	1.6	2.39	6.76	10

- Endoscopic retrograde cholangiopancreatichography (ERCP),
- Transabdominal ultrasound,
- Endoscopic ultrasound (EUS), and
- Computed tomography (CT), or MRCP [10].

Stage 0 means there are no signs of CP. Stage 1 is currently not detectable on CT or MRI. The earliest possible stage that can be diagnosed by CT or MRCP is stage 2. Stages 3 and 4 describe the late stages of CP.

The aim of this study was to evaluate the morphological criteria for early-stage CP (Cambridge 2) as a possible cause of upper abdominal discomfort.

Materials and Methods

Study Design and Cohort Selection

This retrospective study has been reviewed and approved by the Ethics Committee of the University of Regensburg. All procedures performed in this study complied with the ethical standards of our institution and with the Declaration of Helsinki of 1964 and its subsequent amendments. Patients gave their consent to the subsequent use of their imaging and clinical data prior to the study. Consent was also obtained for the publication of identifying information and images. The study included all patients who presented with unclear abdominal pain over a period of at least six weeks, without any other diagnosis. All patients underwent a diagnostic MRI/MRCP of the upper abdomen with an extensive sequence protocol (► **Table 1**).

Image Acquisition, Sequence Protocols and Parameters

All patients underwent MRI with MRCP performed on a 1.5 Tesla field strength MRI device (Siemens Aera, Siemens AG Healthcare, Erlangen, Germany). The examination was performed both without contrast and with application of a gadolinium contrast agent, using a standardized sequence protocol (► **Table 1**).

► **Table 2** Cambridge classification evaluation criteria for CT and MRI.

Cambridge 0	None
Cambridge 1	Cannot be detected on CT/MRI using current methods
Cambridge 2	Two or more of the following changes: <ul style="list-style-type: none"> ▪ Pancreatic duct between 2 and 4 mm in the pancreatic body ▪ Mild pancreatic enlargement ▪ Heterogeneous parenchymal structure ▪ Small cystic changes (< 10 mm) ▪ Duct irregularities Pathological secondary ducts > 3
Cambridge 3	All changes listed under 2, plus one pathological main duct (> 4 mm)
Cambridge 4	One of the changes listed under 2 and 3, plus one or more of the following: <ul style="list-style-type: none"> ▪ Cystic structures > 10 mm ▪ Parenchymal calcifications ▪ Intraductal filling defects (calcifications) ▪ Duct obstruction/narrowing Severe duct irregularities

Cambridge Classification System

The morphological evaluation was based on the Cambridge classification (► **Table 2**) for MRI/MRCP. The consensus-based findings were established by two radiologists with special expertise in pancreatic diagnostics, with 28 and 10 years of experience respectively. The following criteria were analyzed for early-stage Cambridge 2:

- Pancreatic duct in the corpus between 2 and 4 mm
- Pancreatic hypertrophy
- Cystic changes < 10 mm
- Duct irregularities
- More than three pathological lateral ducts
- Heterogeneous pancreatic tissue

Tissue and parenchyma analysis and assessment of lateral ducts were performed in a standardized manner according to Tirkes et al. [11]. The thickness was measured in the pancreatic corpus perpendicular to the longitudinal axis. T1w and T2w images were used for the measurement. The cut-off for the hypertrophy is 21 mm. There is no standard cut-off for the side branches, they are considered dilated if detectable in the T2w images. The cut-off for the main duct is 3 mm in the pancreatic head and 2 mm in the pancreatic body. In addition, in all patients who met the criteria for CP Cambridge 2, lipase levels were determined within two weeks of the imaging examination. Serum lipase was assessed as pathological from a value >60 U/L.

Within the MRI sequences, abnormal diffusion featuring an elevated signal in the high-b image or a drop in signal in the ADC map was also evaluated.

Statistical Analysis

Descriptive statistics were calculated for the analysis and reported as minimum, maximum, median, mean, and standard deviation values. To investigate the correlation between the lipase value and the other binary variables, the Spearman correlation coefficient was used to analyze the relationship between quantitative and binary data. Descriptive statistical analysis was performed using SPSS version 29.0.0.

Results

Basic Characteristics of the Patient Cohort

The basic characteristics of the patients are summarized in ► **Table 3**. A total of 266 patients (157 women) were enrolled in the study. The median age was 61 years. Twenty-five patients met the criteria of CP Cambridge 2. Of these, 15 (60%) were female.

Total Diagnoses Based on MRI/MRCP

In 161 patients (60.5%), no conclusive diagnosis could be made; the MRI was found to be unremarkable. In all other cases, based on the MRI, a diagnosis was reached which was able to potentially explain the cause of the upper abdominal pain (overview in ► **Table 4**).

Criteria for CP Cambridge 2

Twenty-five patients met the criteria for early-stage Cambridge 2 pancreatitis (cf. ► **Table 5**).

In 21 cases, enlargement of the pancreatic duct between 2 and 4 mm was observed. Duct irregularities (“uneven surface”) were diagnosed in 19 patients. Enlargement of more than three secondary ducts was detected in 17 cases. Pancreatic hypertrophy was found in six cases. Cystic changes <10 mm were detectable in three cases. A heterogeneous structure was described in eight cases. The various morphologies are shown in ► **Fig. 1** and ► **Fig. 2**. The correlation coefficients of the variables are shown in the Spearman correlation matrix (► **Fig. 3**).

► **Table 3** Basic characteristics of the overall cohort and of the patients who met the criteria for CP Cambridge 2.

	Total cohort n = 266	CP Cambridge 2 n = 25
Age in years		
Min.	16	19
Mean (SD)	58.98 (13.01)	55.68 (14.7)
Median	61	61
Max.	87	80
Sex, n (%)		
Female	157 (59)	15 (60)
Male	109 (41)	10 (40)

► **Table 4** Overview of diagnoses for the entire cohort. After cholecystolithiasis, stage 2 CP, accounting for 9%, is the second highest among all diagnoses that could be assumed to explain the cause of the unclear upper abdominal discomfort.

Diagnosis	Frequency (%) among the total cohort n = 266
Cholecystolithiasis	37 (14)
Cholangitis	9 (3.3)
Acute cholecystitis	1 (0.3)
Gallbladder polyps	3 (1.1)
Acute pancreatitis	6 (2)
Pancreatic carcinoma	2 (0.7)
Groove pancreatitis	1 (0.3)
Chronic pancreatitis (Cambridge 2)	25 (9)
Chronic pancreatitis (Cambridge 4)	3 (1.1)
Mesenteric panniculitis	2 (0.7)
Newly infused kidney cysts	1 (0.3)
Gastric wall thickening	1 (0.3)
Gastric hernia	1 (0.3)
Umbilical hernia	1 (0.3)
Duodenal diverticulum	2 (0.7)
Stenosis at exit of celiac trunk	4 (1.5)
Suspicion of splenic echinococcal cyst	1 (0.3)
Large liver hemangiomas	2 (0.7)

Serum Lipase

In addition, lipase levels were determined. In this study, 13 patients showed pathologically elevated levels >60 U/L. The mean value was 142.86 (SD = 236.79; minimum = 21; maximum = 1,162) (► **Table 5**).

To investigate the correlation between the lipase value and the other binary variables, the Spearman correlation coefficient

was used to analyze the relationship between quantitative and binary data.

Spearman correlation coefficients between the lipase values (“Lipase U/L [up to 60]”) and imaging:

- Mild hypertrophy: 0.637
- Heterogeneous structure: 0.559
- Duct irregularities (uneven surface): 0.167
- Cyst < 10 mm: 0.068
- Duct between 2 and 4 mm in the corpus: -0.041
- 3 pathological secondary ducts: -0.131

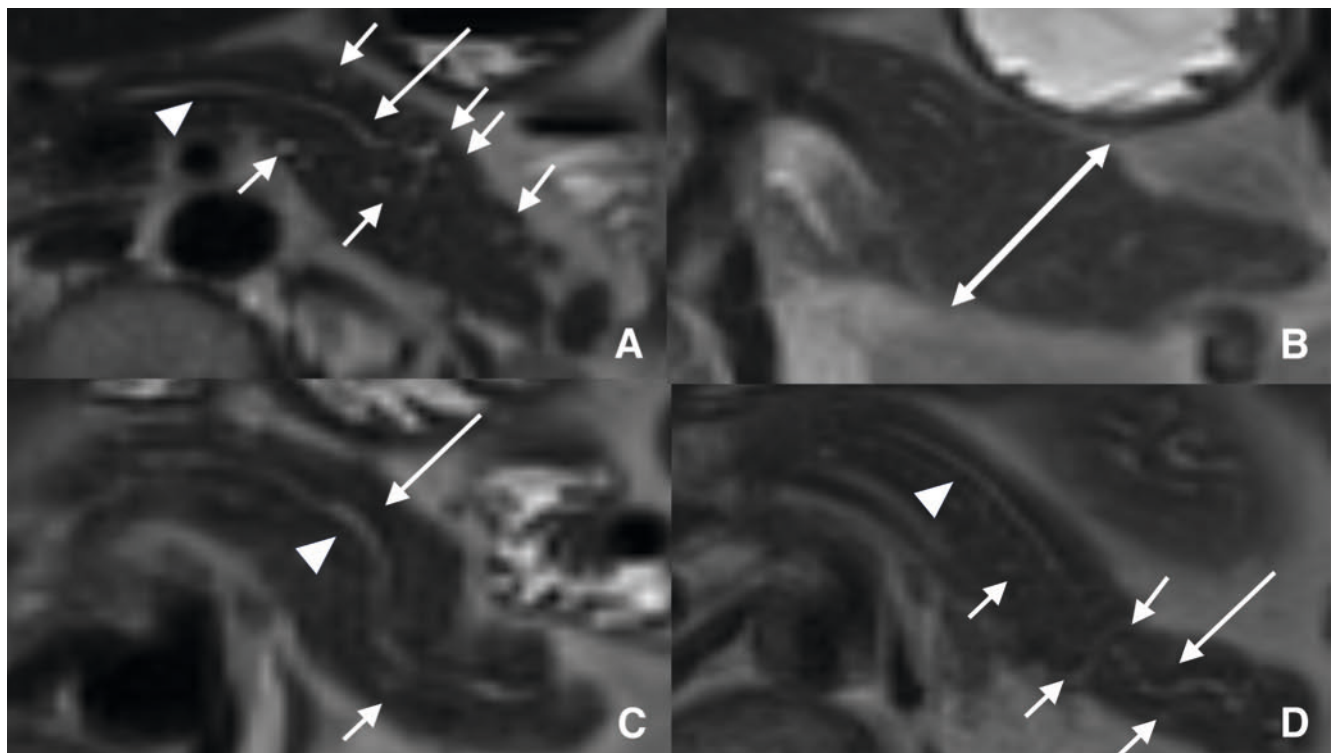
The Spearman correlation coefficients show the strength and direction of the relationship between the lipase value and the respective variables. A positive correlation (as in “mild hypertrophy” and “heterogeneous structure”) suggests that higher lipase levels tend to be associated with the presence of these features. Negative values (as in “> 3 pathological secondary ducts”) indicate a tendency for higher lipase levels to occur less frequently in patients with this feature. Values close to zero (as in “duct between 2 and 4 mm in the corpus”) indicate a weak relationship or no relationship.

Diffusion Weighting

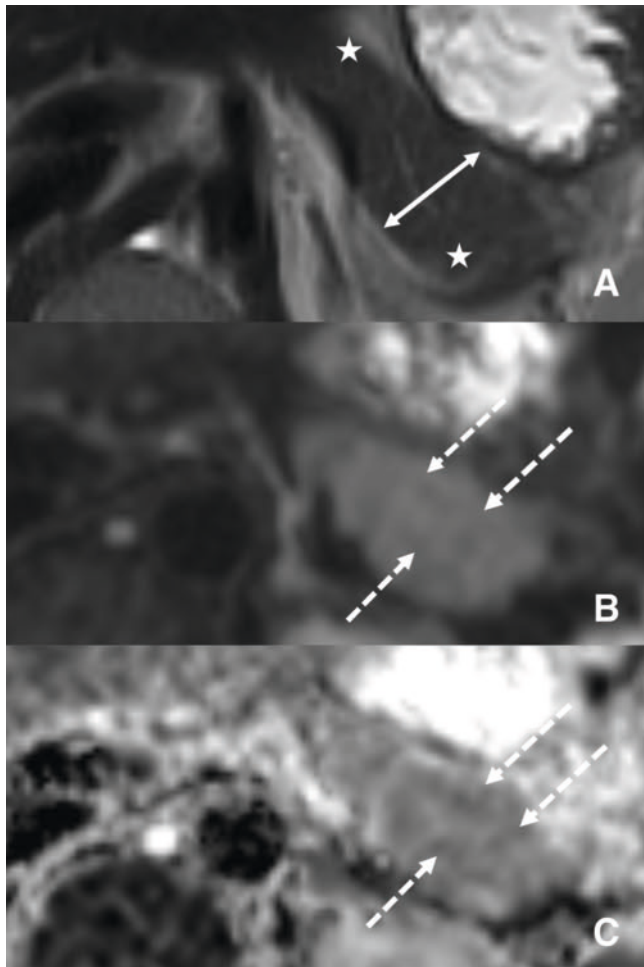
In seven patients who met the criteria for Cambridge 2 CP, diffusion restriction was also detected in the high-b image, with a corresponding drop in signal on the ADC map (cf. ▶ Table 5; ▶ Fig. 2).

▶ **Table 5** Diagnostic criteria for early-stage CP (Cambridge 2). Discrete duct dilations were the most common feature, detected in 93 % of cases. Duct irregularities (“uneven surface”) and lateral duct dilations were also common findings, detected in 76 % and 68 % of cases respectively.

Diagnostic criteria	Frequency (%) among the CP cohort n = 25
Cambridge 2 criteria	
Pancreatic duct dilation 2–4 mm	21 (93)
Pancreatic hypertrophy	6 (24)
Cystic changes < 10 mm	3 (12)
Duct irregularities (“uneven surface”)	19 (76)
Enlargement > 3 secondary ducts	17 (68)
Heterogeneous structure	8 (32)
Laboratory tests	
Lipase > 60 U/L	13 (52)
MRI	
DWI	7 (28)



▶ **Fig. 1** Presentation of the typical and most common morphological criteria for Cambridge 2 early-stage CP in four different patients (A–D). The three most common criteria are presented in figures A, C, and D: duct enlargement between 2 and 4 mm (arrowhead), duct irregularities/uneven surface (long arrow), and lateral duct dilations (short arrows). Figure B shows hypertrophy in the pancreatic tail (double arrow).



► **Fig. 2** Patient showing criteria for Cambridge 2 early-stage CP. Figure **A** shows recognizable hypertrophy in the pancreatic tail (double arrow). At the same time, the pancreatic tail stands out compared to the pancreatic corpus as having a slightly elevated T2w signal, indicating heterogeneity (stars). In figures **B** (b-image) and **C** (ADC map), slightly restricted diffusion is also detectable in the conspicuous area (dashed arrows).

Discussion

CP is an important diagnosis in everyday clinical practice, with an increasing incidence in recent years [1, 10, 12, 13]. Nevertheless, the diagnosis is often underestimated in clinical practice, especially in the outpatient setting. Although the current German S3 guideline from 2021 sets out criteria for diagnosing the different stages of CP in various diagnostic procedures such as ultrasound, endoscopy, and cross-sectional imaging procedures [4, 5, 14], many radiologists still only associate diagnosis of this disease with the most advanced stage, Cambridge 4, and its typical changes such as irregular duct configuration, duct stones, large cysts, or coarse-shaped parenchymal calcifications.

The early stages of CP are often overlooked, or tend to be unfamiliar; as a result, these cases of chronic pancreatitis are not diagnosed and remain hidden, i. e., patients have chronic pain without a diagnosis. Accordingly, the duration from the initial symptoms to the final diagnosis can often be very long. To our knowledge, no

studies have been performed to date that systematically investigate the presence of early-stage CP in an outpatient setting.

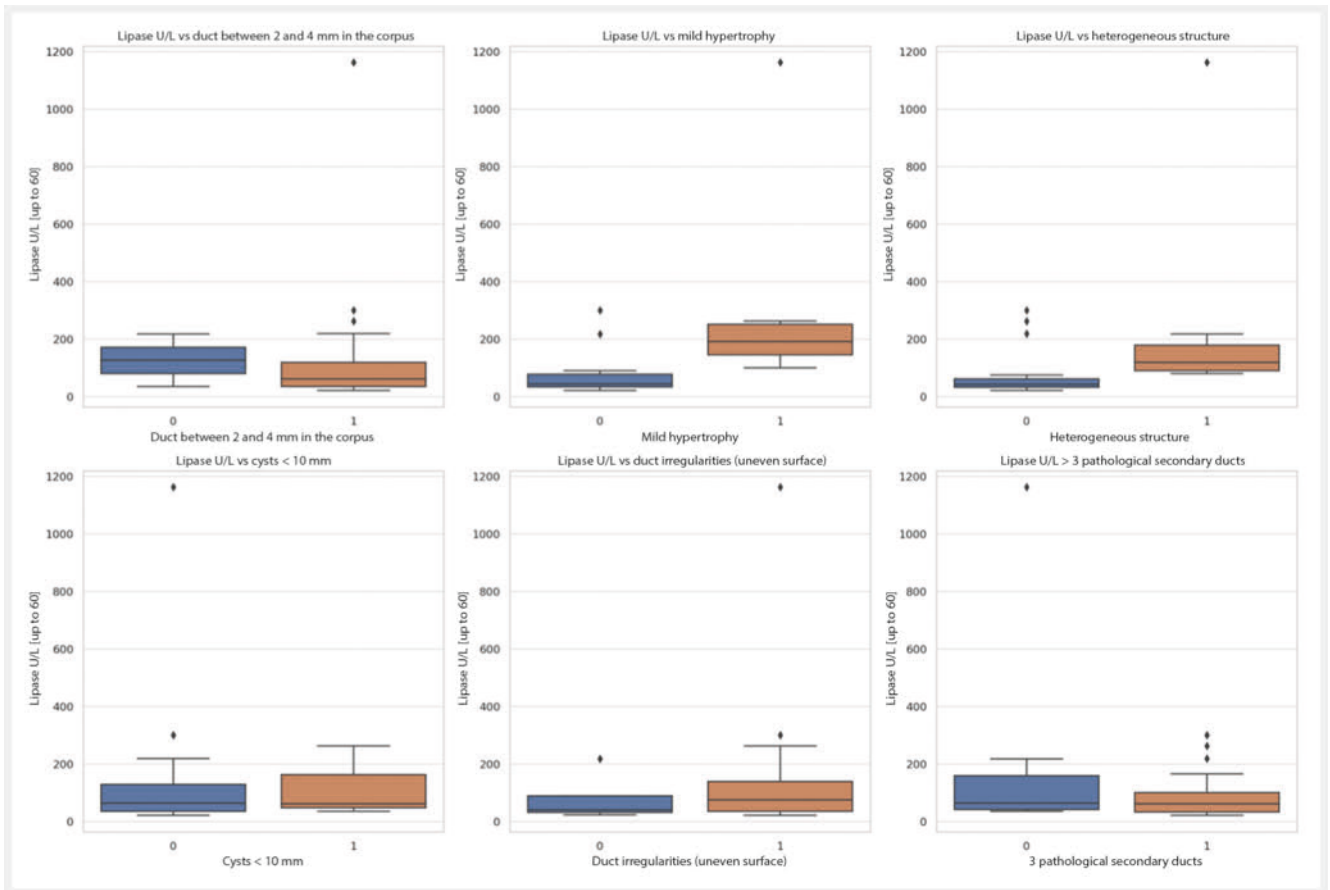
The aim of this study was to diagnose early-stage CP based on the morphological criteria of the Cambridge classification in an outpatient setting in patients who had presented with unclear upper abdominal pain for at least six weeks.

Assessment of pancreatic morphology with regard to CP is based on the Cambridge classification [15], which is also included in the current guidelines. The earliest stage that can be diagnosed by cross-sectional imaging is stage 2. These criteria were met in 9% of patients. Thus, in this patient cohort, this diagnosis ranked second among all diagnoses that could be assumed to be correlated to the previously unclear upper abdominal pain, after the diagnosis of cholecystolithiasis. 52% of patients had concomitant elevated lipase levels > 60 U/L. Diffusion restriction in the high-b image with a correlated drop on the ADC map was found in 28% of patients.

The benefit of DWI imaging in detecting pancreatitis has already been demonstrated in other studies [16, 17, 18, 19]. Serum lipase is routinely measured as part of the diagnostic procedure for pancreatitis, and this test is therefore usually available in outpatient settings. In other studies, a comparable number of patients (approx. 50%) had elevated lipase levels with proven chronic pancreatitis [20, 21]. Higher lipase levels showed high coefficients for hypertrophy (0.627) and heterogeneous parenchyma (0.559).

The results suggest that DWI and lipase are more likely to show pathological values if an acute relapse occurred shortly before the examination. Therefore, in our opinion, the combination of morphological MRI criteria, diffusion imaging, and serum lipase is ideal for diagnosing early-stage CP.

This study evaluated all cases from a large outpatient center detected over a period of nearly three years by radiologists with particular expertise in pancreatic radiology. CP was diagnosed in the early stage in 9% of patients. Based on an assumption that some cases are clinically silent or may be masked by other pathologies, it is possible that the actual number of cases could be even higher, although such cases may be of questionable clinical relevance. The results of this study suggest that CP, even in the early stage, can be a possible cause of upper abdominal pain of unclear origin in many cases. In addition to acute complaints in the early stages, CP can often lead to complications and a high degree of suffering in the late stages. Knowledge of CP as a possible cause and familiarity with both the morphological criteria and the clinical and laboratory parameters are essential to enabling radiologists to make this diagnosis as early as possible. With the help of standardized findings, e. g., using the Cambridge classification and taking a precise medical history in advance, we believe that the diagnosis can be made even by radiologists without special knowledge of pancreatic imaging. This would allow CP to be diagnosed as early as possible based on imaging, leading to a significant improvement in patient care through rapid initiation of treatment. In the early stage, in addition to treating the symptoms, this essentially includes avoiding noxious agents and risk factors. The later CP is diagnosed, the more extensive and difficult the treatment becomes [22].



► **Fig. 3** The box plots show the relationship between elevated lipase levels and the different variables. The results show a strong positive correlation (Spearman: 0.637) for mild hypertrophy and a moderate positive correlation (Spearman: 0.559) for the heterogeneous structure. This could be caused by a recently resolved relapse in the context of CP.

Limitations

Although an extensive patient cohort was analyzed and 9% of patients met the criteria for CP, the number of cases is a limitation of this study, as is the retrospective study design. This made it impossible to perform further subgroup analyses, such as investigating gender-related differences.

Conclusion

In summary, it can be concluded that CP, even in its early stages, is a relevant diagnosis in patients with unclear upper abdominal pain in outpatient setting, for whom adequate treatment depends on being diagnosed as early as possible. In addition to the more commonly known signs of a late-stage CP, radiologists should also be familiar with and recognize the more subtle criteria of the early stages so as to reliably diagnose CP in the Cambridge 2 stage.

Besides the morphological criteria, additional knowledge of laboratory parameters and consideration of all MRI parameters, such as DWI, can provide indications of early-stage CP.

Abbreviations

MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
CP	chronic pancreatitis
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
CT	computed tomography

Conflict of Interest

The authors declare that they have no conflict of interest.

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