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T1 signal intensity ratio of the pancreas as an imaging biomarker for the staging of chronic pancreatitis

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Abstract

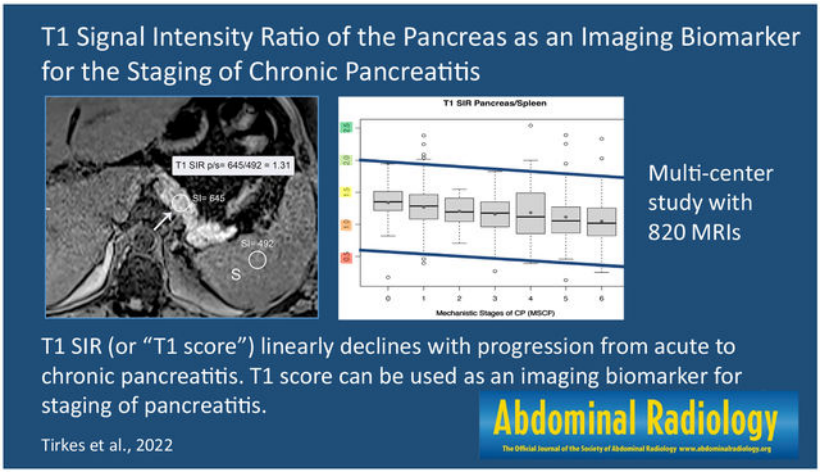
Purpose—Our purpose was to validate the T1 SIR (T1 score) as an imaging biomarker for the staging of CP in a large, multi-institutional, prospective study.

Methods—The prospective study population included 820 participants enrolled in the PROCEED study from nine clinical centers between June 2017 and December 2021. A radiologist at each institution used a standardized method to measure the T1 signal intensity of the pancreas and the reference organs (spleen, paraspinal muscle, liver), which was used to derive respective T1 scores. Participants were stratified according to the seven mechanistic stages of chronic pancreatitis (MSCP 0–6) based on their clinical history, MRCP, and CT findings.

Results—The mean pancreas-to-spleen T1 score was 1.30 in participants with chronic abdominal pain, 1.22 in those with acute or recurrent acute pancreatitis, and 1.03 in definite CP. After adjusting for covariates, we observed a linear, progressive decline in the pancreas-to-spleen T1 score with increasing MSCP from 0 to 6. The mean pancreas-to-spleen T1 scores were 1.34 (MSCP 0), 1.27 (MSCP 1), 1.21 (MSCP 2), 1.16 (MSCP 3), 1.18 (MSCP 4), 1.12 (MSCP 5), and 1.05 (MSCP 6) ($p < 0.0001$). The pancreas-to-liver and pancreas-to-muscle T1 scores showed less linear trends and wider confidence intervals.

Conclusion—The T1 score calculated by SIR of the pancreas-to-spleen shows a negative linear correlation with the progression of chronic pancreatitis. It holds promise as a practical imaging biomarker in evaluating disease severity in clinical research and practice.

Graphical abstract



Keywords

T1 score; Mechanistic Stages of Chronic Pancreatitis; MRI

Introduction

Chronic pancreatitis (CP) is a chronic inflammatory condition of the pancreas with clinical manifestations including abdominal pain, acute pancreatitis (AP), exocrine and/or endocrine pancreatic dysfunction (diabetes mellitus), and increased risk of pancreatic cancer [1]. The histologic hallmarks of CP include the triad of fibrosis, loss of acinar and islet cells, and ductal changes [2]. Because histology is not easily or readily available in clinical practice, cross-sectional imaging studies, such as computerized tomography (CT) and magnetic resonance imaging (MRI) with or without magnetic resonance cholangiopancreatography (MRCP), are recommended as the first-line diagnostic modalities by the American College of Gastroenterology [3]. The American Pancreatic Association guidelines suggest extrapolating findings of the Cambridge classification [4] which was designed primarily to interpret ductal changes on endoscopic retrograde cholangiopancreatography (ERCP) [5]. However, pancreatic ducts comprise only a fraction of the parenchyma, and ductal imaging does not reflect the parenchymal fibrosis or loss of acinar tissue described in the histopathology triad. Therefore, in patients who lack pancreatic calcifications on CT or moderate-to-severe ductal abnormalities on MRCP, establishing a CP diagnosis can be elusive and delayed. In addition, Cambridge classification with MRCP has variable interpretation [6] and moderate interobserver agreement (weighted kappa of 0.68) among the experienced abdominal radiologists [7, 8]. Prior reports, expert panel reviews, consensus guidelines, and histopathologic correlation studies have suggested that parenchymal MRI findings can detect CP earlier and might be better suited for the staging and longitudinal evaluation of CP [9–12].

On MRI examinations, a normal pancreas demonstrates a higher T1 signal intensity than a normal muscle or a normal spleen or liver, a difference attributed to the presence of rich proteinaceous material in the acinar cells containing abundant rough endoplasmic reticulum

[13–15]. In conditions such as CP, proteinaceous material in the acini is reduced by chronic inflammation, and eventually, the acinar cells are replaced by fibrosis. Studies have reported that these changes prolong the T1 relaxation time and decrease in T1-weighted signal intensity ratio (SIR) [15–19]. The T1 SIR has also been correlated with exocrine pancreatic dysfunction [16, 20, 21] and fibrosis by histopathology [12, 22–24]. However, all of these studies were retrospective, performed at a single institution, and unable to assess the potential confounding effects of key variables.

In this multicenter, prospectively ascertained cohort study, we hypothesized that the T1 SIR of the pancreas could serve as an imaging biomarker for CP. MRI findings were captured systematically and T1 SIR correlated with different stages of CP [25]. The disease stages, which we defined according to a scale we named the “mechanistic stages of chronic pancreatitis” (MSCP), were determined by considering clinical history, ductal findings on MRCP, and calcifications on CT. The large sample size enabled us to control several confounding factors that otherwise could have weakened our ability to evaluate the relationship between the T1 SIR and stages of CP.

Materials and methods

Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED) is an ongoing, longitudinal cohort study of CP in adult participants in the US (NCT# 03099850) [26]. It is one of the four major studies conducted by the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, established by the National Cancer Institute and the National Institute of Diabetes and Digestive and Kidney Diseases [27, 28]. A detailed methodology of the PROCEED study was published previously [26]. The study was approved by the Institutional Review Board of all nine participating centers: Indiana University in Indianapolis, IN, University of Pittsburgh Medical Center in Pittsburgh, PA, The Ohio State University Wexner Medical Center in Columbus, OH, Mayo Clinic in Rochester, MN, Stanford University in Stanford, CA, Cedars-Sinai Medical Center in Los Angeles, CA, The Permanente Medical Group in San Francisco, CA, University of Florida in Gainesville, FL, and Baylor University in Houston, TX and the Data Coordinating Center in The University of Texas MD Anderson Cancer Center in Houston, TX. All the participants provided informed consent before any study procedures were performed.

Study cohort

The PROCEED cohort consists of subgroups purposefully selected based on the mechanistic definition [25] to represent our current understanding of the different stages of CP. The full details of the study can be found in the methodology publication [26]. Briefly, the PROCEED subgroups are as follows:

- Healthy volunteers: no abdominal symptoms and no personal or family history of pancreatic disease (*Green I*). Participants were not required to have an MRI.
- Chronic abdominal pain of suspected pancreatic origin and normal-appearing pancreas on both CT scan and MRI and/or MRCP (*Green II*)

- Indeterminate CP: chronic abdominal pain with no history of AP and presence of Cambridge stage 1 or 2 on CT scan and/or MRI/MRCP (*Yellow I*)
- One episode of AP and Cambridge stage 0, 1, or 2 on MRCP and/or CT scan (*Yellow II*)
- Recurrent AP and Cambridge stage 0, 1, or 2 on CT scan and/or MRCP (*Yellow III*)
- Definite CP: Cambridge stage 3 or 4 or presence of calcifications on CT scan and/or MRI/MRCP or histologic evidence of CP (*Red*)

All the participants in the Green II and Yellow subgroups were required to have a contrast-enhanced CT scan and an MRI/MRCP within 2 years before or 6 months after enrollment in the study. If not needed for clinical purposes, the MRI/MRCP study was performed for research purposes. A contrast-enhanced CT scan was performed on 92% (754/820) of the participants.

There were 1163 consecutive participants in the Green II through Red groups of the PROCEED study from June 2017 to December 2021. The study protocol did not require all participants to have an MRI/MRCP [26]. We found 833 qualifying MRIs prior to, or as part of their baseline assessment. A total of 820 participants were included in the analysis following excluding 13 of them for reasons listed in Fig. 1. The demographics of the three major PROCEED groups used in this study are listed in Table 1.

Before the statistical analysis, we classified participants a priori from the various PROCEED groups according to the MSCP based on their clinical history (i.e., abdominal pain suspected of pancreatic origin, AP or RAP), the Cambridge grade on MRCP, and the presence of parenchymal and/or ductal calcifications on the CT scan as seen on Table 2. The demographics of participants stratified according to the MSCP are listed in Table 3.

Imaging protocol

The standard imaging protocol is listed in Table 4. The MR image used for this analysis was an unenhanced T1-weighted gradient echo sequence with fat suppression. MRI/MRCP examinations were performed in 1.5 or 3T and was not selective to any specific manufacturer. Imaging performed at institutions not participating in the PROCEED study was considered acceptable if the examination had the required MR sequence.

Image analysis

Imaging data collection was performed independently by ten radiologists (TT, AKD, ZKS, STC, CAF, JRG, NK, SKV, AW, and KM) enlisted as co-investigators at nine clinical centers. The protocol for recording imaging data was developed before the initiation of this study, and a training module was completed [10, 26]. All the MR examinations were required to have an unenhanced T1-weighted gradient echo image with fat suppression to measure the T1 signal intensity. The region-of-interest measurement was obtained at a homogenous region of the pancreatic body/tail, avoiding volume averaging from the retroperitoneal fat, edema, vessels, and dilated pancreatic duct. We used the spleen, paraspinal muscle, and liver [29] as reference organs. Three T1 SIRs were calculated

by dividing the SI of the pancreas by those of the three reference organs: T1 SIR = $T1_{pancreas}/T1\ signal_{reference}$.

Statistical analysis

Three co-authors (LL, SL, and YY) performed the statistical analysis at the Data Coordinating Center of the CPDPC. The baseline characteristics of the study population are according to the PROCEED subgroups and the MSCP. For the continuous variables, the median, 25th and 75th quantiles and a Kruskal–Wallis test results are presented; for the categorical variables, the count, the proportion, and Fisher's exact test results are presented. The association between the T1 SIR and the MSCP was examined with one-way analysis of variance, and its statistical significance was determined with an F-test. The distribution of the T1 SIR by each MSCP was visualized with comparative boxplots. To assess whether the MSCP had an association with the T1 SIR that was independent of patient characteristics, we performed a linear regression analysis of the T1 SIR on the MSCP, adjusting for demographics (age, gender, race, body mass index), behavioral covariates (tobacco use and drinking), and clinical covariates (diabetes and exocrine pancreatic dysfunction). We used 0.05 as the threshold of statistical significance.

Results

Study population

Baseline participant characteristics based on the three PROCEED subgroups are shown in Table 1. Compared to participants with chronic abdominal pain, AP/RAP, participants with definite CP were older (49, 46, and 53 years, respectively), had lower BMI (25, 27, and 24, respectively), were more likely to use tobacco (18%: 17/94, 16%: 57/348, and 36%: 136/378, respectively) and drink very heavily (12%: 11/94, 15%: 53/348, and 25%: 93/378 respectively). Men represented 50% (190/378) of the participants with definite CP, 48% (168/348) of the AP/RAP, and 33% (31/94) of those with chronic abdominal pain. Participants with definite CP were more likely to have alcohol etiology (39%: 147/378) than those with AP/RAP (17%: 58/344), more likely to have diabetes (37%: 135/363) than those with AP/RAP (21%: 70/326) and with chronic abdominal pain (16%: 12/77) and more likely to have confirmed exocrine pancreatic dysfunction (37%: 141/378) than those with AP/RAP (12%: 41/348) and those with chronic abdominal pain (11%: 10/94). The median time between enrollment in the PROCEED study and the qualifying MRI/MRCP examination was less than 96 days. No adverse events were reported specifically for the T1-weighted image acquisition. Calcifications were noted on CT studies in 69% (262/378) of participants with definite CP.

T1 score of pancreas-to-spleen

On univariate analysis, the pancreas-to-spleen T1 SIR decreased significantly ($p < 0.001$) from those with chronic abdominal pain to the AP/RAP and definite CP groups (Table 1). Similarly, a progressive decrease in the T1 score was associated with increasing MSCP ($p < 0.0001$) in both the unadjusted and adjusted covariate models (Table 5). Mean T1 score of the pancreas-to-spleen were 1.34 in MSCP 0, 1.27 in MSCP 1, 1.21 in MSCP 2, 1.16 in MSCP 3, 1.18 in MSCP 4, 1.12 in MSCP 5, and 1.05 in MSCP 6 ($p < 0.0001$) (Fig. 2a).

T1 score of pancreas-to-muscle and pancreas-to-liver

Results for the T1 score of the pancreas-to-liver and pancreas-to-muscle in the MSCP with or without adjustment for covariates are shown in Table 5, and box-and-whisker plots are shown in Fig. 2b and c. Although there was a general trend towards a decline in T1 score with increasing MSCP, the trends were not as linear and had wider confidence intervals than those of the pancreas-to-spleen T1 score.

Receiver operating curve (ROC) analysis

ROC analysis comparing the AP/RAP group with the definite CP group showed an area under the curve (AUC) of 0.660 (95% CI 0.604–0.715). The results were nearly identical when participants from the chronic abdominal pain group were combined with the AP/RAP group and compared with the definite CP group (AUC: 0.657, 95% CI 0.603–0.712).

Discussion

In this large multicenter study, including prospectively enrolled participants, 820 MRI scans were systematically evaluated to demonstrate that the T1 SIR (T1 score) correlates with different stages of CP. In stark contrast to the design of prior studies, our results have high validity and generalizability attributed to the study's large sample size and independent of confounding factors. These observations have important implications. We propose that the T1 score can serve as an imaging biomarker for the staging of CP severity. In clinical practice, the T1 score can serve as a severity metric for the mechanistic stage of chronic pancreatitis. It may also be considered as a potential outcome measure in clinical trials to assess response to drug therapies or nonsurgical interventions.

Premise

In current practice, CT, MRI with MRCP, endoscopic ultra-sound, and endoscopic pancreatic function tests are used to establish a diagnosis of CP [4]. The MRCP literature adopted the Cambridge classification to grade CP, from ERCP-based studies older than four decades [5]. Findings on the accompanying MRI of the parenchyma have yet to be incorporated into a reporting system. Our study is the first prospective, multicenter study with a large population that aims to fill this gap. The unenhanced T1-weighted gradient echo image used in this study is performed in almost all abdominal MR examinations. Our results show that the T1 score, as a quantitative metric, correlates with the CP stage as determined by either the three PROCEED groups, or a more granular seven-group subclassification (MSCP). Thus, our study validates the potential of the T1 score as a practical imaging biomarker.

The rationale for using the T1 signal of the parenchyma

The cardinal histopathologic features of CP are the triad of fibrosis, loss of acinar tissue (atrophy), and duct changes (distortion and dilatation) [2]. Ductal findings seen on MRCP primarily capture periductal fibrosis and do not reflect the loss of acinar cells or fibrosis in the rest of the parenchyma. Because the pancreatic duct comprises only 4% of the entire pancreas, [30, 31] using ductal imaging alone might delay and render the diagnosis of non-calcific CP elusive. Changes in the MRI parenchymal signal may provide a complete

evaluation of CP [9–11] since acinar cells comprise 85% of the pancreas [32]. Many prior studies and consensus guidelines have noted the potential benefit of parenchymal imaging [9–11].

The pancreas is a highly productive exocrine gland of the digestive system. Each day, it secretes approximately 1–2 L of proteinaceous fluid that contains digestive enzymes and bicarbonate [33, 34]. Due to the abundance of proteinaceous material in the acinar cells, the normal pancreas shows a higher T1 SI than other solid organs in the upper abdomen [15, 22] as seen in an MSCP 0 participant in Fig. 3. Several publications have reported a correlation of the T1 SIR with the diagnosis and staging of CP using the pancreas-to-spleen, pancreas-to-paraspinal muscle, and pancreas-to-liver, all of which have been reported as useful methods for evaluation of CP [15, 19, 22, 29, 35]. Some studies have reported a correlation of the T1 SIR specifically with pancreatic exocrine dysfunction as measured by the endoscopic pancreatic function tests [16, 19]. In these studies, the decision to correlate the T1 SIR with the ductal features or exocrine function rather than histopathology reflects the challenges associated with acquiring pancreatic tissue from humans (e.g., the procedural complications of core biopsies) and interpreting the results (e.g., the absence of a universally accepted histological grading system for CP) [2]. Four recent publications have correlated the MRI parenchymal features (T1 SIR, T1 relaxation time, arterial-to-delayed venous enhancement ratio, diffusion-weighted imaging, and MR elastography) with surgical specimens [12, 22–24]. These studies reported a significant correlation of MRI parenchymal findings with the degree of fibrosis. In a recent study of 60 patients who had pancreatic resections and a preoperative MRI, the pancreas-to-spleen T1 SIR, pancreas-to-muscle T1 SIR, arterial-to-venous enhancement ratio of the parenchyma, and Cambridge grades were correlated with the fibrosis score [12]. The pancreas-to-spleen T1 SIR showed the highest correlation with fibrosis ($r = -0.54$, $p = 0.0001$), followed by the arterial-to-venous enhancement ratio ($r = -0.39$), Cambridge classification ($r = 0.26$), and pancreas-to-muscle T1 SIR ($r = 0.19$). The strongest inter-observer agreement was also with the pancreas-to-spleen T1 SIR (weighted kappa of 0.78), which was higher than what was previously reported for the Cambridge classification [7]. Histopathologic correlation studies agree that the T1 SIR as a quantitative metric can detect acinar cell replacement by the chronic fibroinflammatory process and decreased production of proteinaceous material.

Prior interobserver agreement studies have suggested that parenchymal features may yield a less subjective evaluation of CP. A multicenter study reported that the interobserver variability of the Cambridge classification given by experienced abdominal radiologists was moderate (weighted kappa of 0.68). Another multicenter study agreed that interobserver agreement was better for quantitative measures of the pancreas than for subjective imaging findings [8]. All things considered, we conclude that the T1 score is a practical and noninvasive imaging method for assessing CP staging and should improve the care of CP patients.

Implications for using the T1 score

A T1 score may positively impact patient care if used in clinical practice to detect parenchymal changes of non-calcific CP before moderate-to-severe ductal changes become

visible with MRCP. The T1 score of the pancreas-to-spleen progressively declines from ~ 1.3 to ~ 1.0 as the CP progresses. In other words, the normal pancreas has a 30% higher T1 signal intensity than the spleen, but this signal decreases with the progression of CP. Figure 4 shows decreased T1 SIR in an MSCP 5 participant. We saw this decline whether we used the three PROCEED groups or the more granular MSCP categorization. Prior studies have reported that the T1 SIR has the potential to detect CP earlier than ductal imaging [16, 35]. This is presumably because T1 SIR correlates with exocrine pancreatic dysfunction which can occur before the periductal fibrosis becomes visible by MRCP. A recent longitudinal study confirmed that parenchymal findings to be a better imaging biomarker than ductal changes for follow-up of CP patients since the damage to the ductal anatomy might not be reversible with therapy [9]. In clinical practice, temporal changes in the T1 score may also facilitate the assessment of disease progression. In clinical trials, they may facilitate the evaluation of response to a drug or nonsurgical intervention. Longitudinal studies such as the PROCEED are currently underway to investigate this potential. Although our analysis shows that the T1 score is a valuable quantitative metric for staging the disease, the performance characteristics of the T1 score (AUC of 0.66) do not support using it as the standalone diagnostic test for CP.

Limitations and caveats

Severe fatty replacement, heavy calcification, edema, or iron deposition of the primary (pancreas) or reference organ (spleen, paraspinal muscle, or liver) can alter the T1 signal. Clinical scenarios that can alter T1 signal are cystic fibrosis (due to severe fatty infiltration of the pancreas), hemochromatosis or hemosiderosis (iron deposition in the pancreas, spleen, or liver), acute pancreatitis (edema in the parenchyma) and segmental cholestasis in the liver [36]. It would be helpful to review the MR fat detection sequences (e.g., DIXON series) to make sure that the region-of-interest measurement is obtained from a segment of the pancreas where fatty infiltration is not present. Measurements should be made within the homogenous region of the parenchyma and avoid the edge of the organ where edge artifact can alter the T1 signal. Ideally, measurements should be performed in the head, body and tail of the pancreas and use the average of the entire pancreas or individual segments to calculate the signal intensity ratio.

Conclusion

In this multicenter prospective study, we have confirmed that the T1 score declines linearly with the progression of CP and can be used as an imaging biomarker for CP staging. For clinical practice, we suggest using the T1 score of the pancreas-to-spleen as a metric for the mechanistic staging of chronic pancreatitis. The T1 score also has the potential to be used in clinical trials to assess response to drug therapies or nonsurgical interventions, and longitudinal studies such as the PROCEED study are underway to confirm this potential.

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LL). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Abbreviations

CP	Chronic pancreatitis
CT	Computerized tomography
MRI	Magnetic resonance imaging
MRCP	Magnetic resonance cholangiopancreatography
SIR	Signal intensity ratio
MSCP	Mechanistic stages of chronic pancreatitis
CPDPC	The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer
PROCEED	Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies

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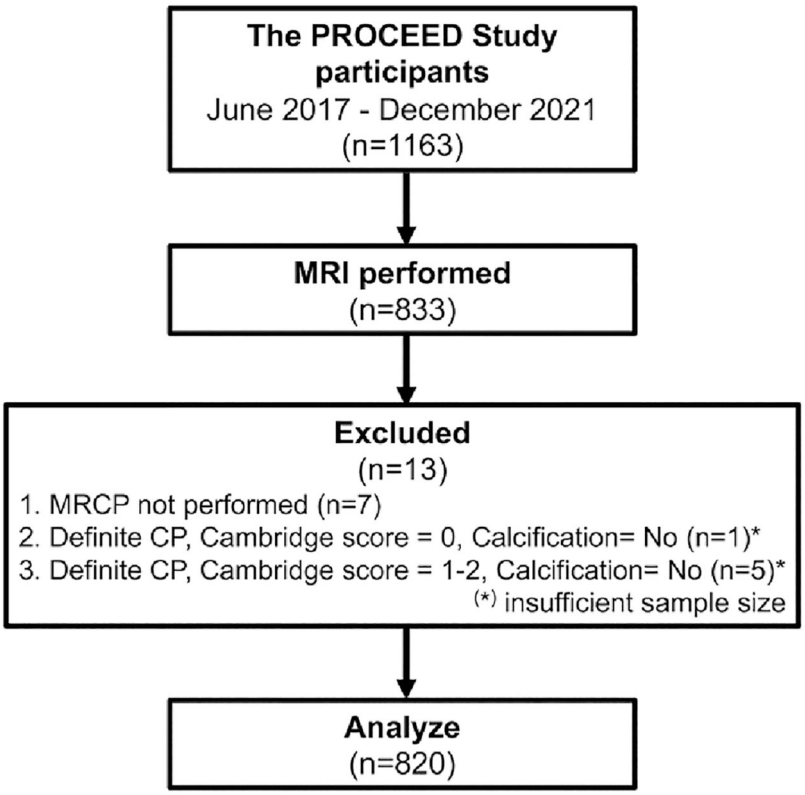

Fig. 1.
Participant enrollment flowchart

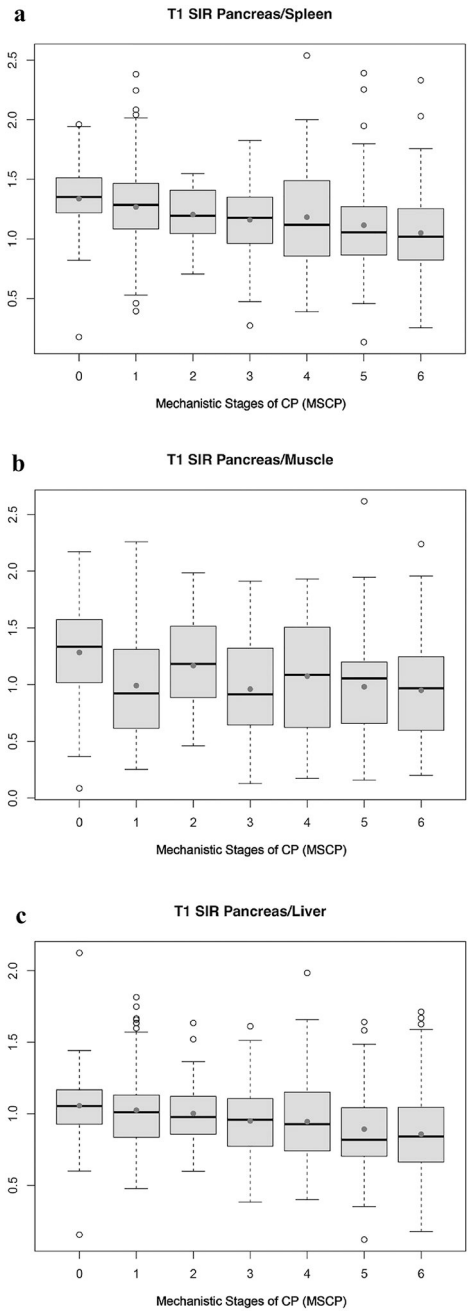

Fig. 2.

Distribution of the T1 SIR by the MSCP; **a** T1 SIR pancreas-to-spleen, **b** T1 SIR pancreas-to-muscle, and **c** pancreas-to-liver by the MSCP. The boxplots show the minimum, the 25th, 50th (median), 75th quantiles, and the maximum. The gray dots represent the mean SIR, and the empty dots represent outliers

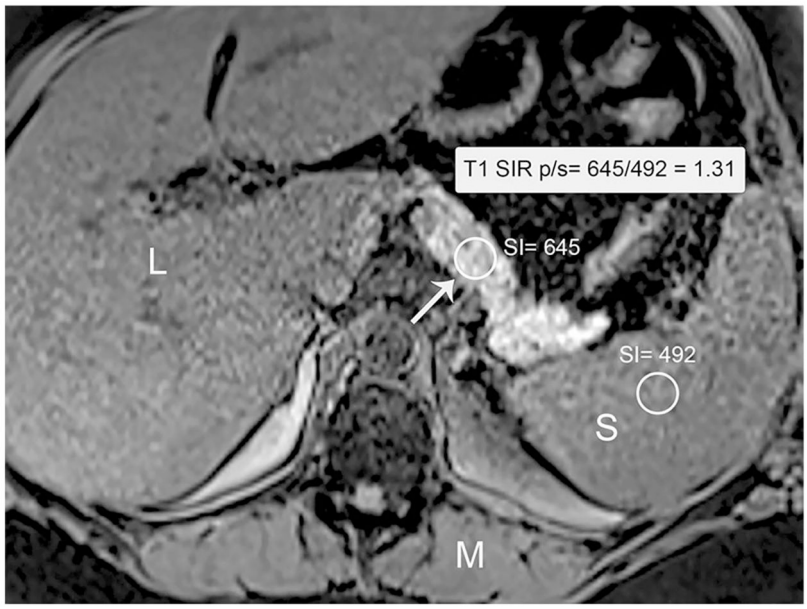

Fig. 3.

T1 signal intensity of the pancreas in an MSCP 0 participant. This is an unenhanced axial T1-weighted gradient echo image with fat suppression in a 49-year-old woman with a history of abdominal pain of suspected CP origin but a normal MRCP and CT. T1 signal intensity of the pancreas (arrow) is higher than that of the spleen (S), paraspinal muscle (M), and liver (L). Circles represent region-of-interest measurements

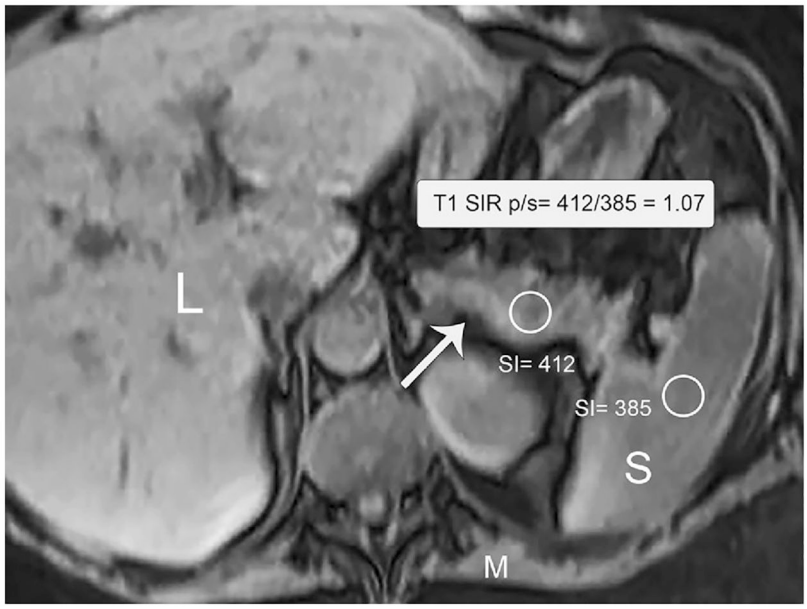

Fig. 4.

T1 signal intensity of the pancreas in an MSCP 5 participant. This is an unenhanced axial T1-weighted gradient echo image in a 46-year-old woman with a history of CP (Cambridge grade 3). The T1-weighted signal intensity of the pancreas (arrow) compared to that of the spleen (S), liver (L), and paraspinal muscle (M) is lower than the case in Fig. 3

Table 1

Characteristics of the participants in the analysis, summarized by the three PROCEED groups

	Chronic abdominal pain suspected of pancreatic origin (Green II, Yellow I)	Acute or recurrent acute pancreatitis (Yellow II, III)	Definite CP (Red)	*p* value
N	94	348	378	
Age at enrollment	49 (39, 59)	46 (36, 57)	53 (43, 62)	< 0.001
Gender (male)	31 (33)	168 (48)	190 (50)	0.010
Race				0.975
Black	4 (4)	18 (5)	18 (4)	
White	76 (84)	285 (82)	309 (81)	
Other	10 (11)	41 (11)	50 (13)	
Body mass index (kg/m^2)	25.4 (22.2, 29.1)[4]	27.3 (23.9, 31.6)[4]	24.4 (21.4, 28.5)[2]	< 0.001
Tobacco use (cigarette smoking, cigar, tobacco chewing)				< 0.001
Never	54 (59.34)[3]	178 (53.29)[14]	114 (30.65)[6]	
Past	20 (21.98)	99 (29.64)	122 (32.80)	
Current	17 (18.68)	57 (17.07)	136 (36.56)	
Cigarette smoking (Pack-years)	18.5 (4.5, 40.0)[3]	9.2 (2.4, 21.8)[22]	19.0 (8.0, 33.0)[18]	< 0.001
Drinking status				0.798
Never	13 (14)[3]	51 (15)[14]	49 (13)[6]	
Past	58 (63)	197 (58)	235 (63)	
Current	20 (21)	86 (25)	88 (23)	
Drinking category				0.004
Abstainer	13 (15)[12]	51 (17)[49]	49 (14)[37]	
Light drinker	28 (34)	70 (23)	55 (16)	
Moderate drinker	16 (19)	60 (20)	66 (19)	
Heavy drinker	14 (17)	65 (21)	78 (22)	
Very heavy drinker	11 (13)	53 (17)	93 (27)	
Etiology				< 0.001[a]
Alcohol	NA	58 (17)[4]	147 (39)	
Idiopathic		194 (64)	143 (41)	
All other		92 (30)	88 (25)	

	Chronic abdominal pain suspected of pancreatic origin (Green II, Yellow I)	Acute or recurrent acute pancreatitis (Yellow II, III)	Definite CP (Red)	*p* value
Diabetes present	12 (16)[17]	70 (21)[22]	135 (37)[15]	< 0.001
Exocrine pancreatic dysfunction				< 0.001
Yes	10 (11)	41 (12)	141 (37)	
No	47 (58)[13]	168 (48)	100 (26)	
Not tested	24 (30)	139 (40)	137 (36)	
Calcification present	0 (0)	0 (0)	262 (69)	N/A
Days between enrollment and MRI/MRCP[b]	− 10.5 (− 90.0, 18.0)	− 18.5 (− 132.5, 6.5)	− 95.5 (− 324.0, − 9.0)	< 0.001
T1 score: pancreas-to-spleen	1.30 (1.14, 1.45)[10]	1.22 (1.00, 1.43)[37]	1.03 (0.83, 1.27)[53]	< 0.001
T1 score: pancreas-to-muscle	1.29 (0.94, 1.55)[10]	0.91 (0.61, 1.31)[36]	0.98 (0.61, 1.25)[53]	< 0.001
T1 score: pancreas-to-liver	1.03 (0.89, 1.16)[10]	0.99 (0.82, 1.13)[37]	0.84 (0.69, 1.05)[52]	< 0.001

Medians (25th, 75th quantiles) are reported for continuous variables. Counts (column percentages) are reported for categorical variables

Superscripts indicate the missing value counts and are excluded from the percentage calculation

p values are based on a comparison of the three groups

[a]Comparing chronic abdominal pain, AP/RAP with definite CP

[b]Negative (positive) numbers indicate that the image scan was before (after) enrollment

Table 2

Definition of the MSCP

MSCP	PROCEED cohort	Cambridge grade by MRCP	Calcification by CT	Sample size (n)
0	Chronic abdominal pain or indeterminate CP	0	−	56
1	Acute or recurrent AP	0	−	179
2	Chronic abdominal pain or indeterminate CP	1 or 2	−	38
3	Acute or recurrent AP	1 or 2	−	169
4	Definite CP	0, 1, or 2	+	49
5	Definite CP	3 or 4	−	116
6	Definite CP	3 or 4	+	213

Table 3

Participant characteristics corresponding to the MSCP

	MSCP 0 *n* = 56	MSCP 1 *n* = 179	MSCP 2 *n* = 38	MSCP 3 *n* = 169	MSCP 4 *n* = 49	MSCP 5 *n* = 116	MSCP 6 *n* = 213	ALL *n* = 820	*p* value
Age at enrollment	46.5 (34.5, 56.5)	42.0 (33.0, 55.0)	55.5 (48.0, 64.0)	50.0 (40.0, 59.0)	58.0 (46.0, 64.0)	49.5 (43.0, 61.0)	53.0 (43.0, 62.0)	50.0 (40.0, 60.0)	< 0.001
Gender (male)	17 (30)	84 (47)	14 (37)	84 (50)	26 (53)	57 (49)	107 (50)	389 (47)	0.1211
Race									0.7264
Black	2 (4)	8 (5)	2 (6)	10 (6)	0 (0)	6 (5)	12 (6)	40 (5)	
Other	7 (13)	27 (15)	3 (8)	14 (8)	8 (16)	14 (12)	28 (13)	101 (12)	
White	45 (83)	141 (80)	31 (86)	144 (86)	41 (84)	96 (83)	172 (81)	670 (83)	
Body mass index (kg/m2)	24.6 (22.0, 28.1)[2]	27.3 (23.9, 32.2)[3]	25.6 (22.7, 30.3)[2]	27.2 (23.9, 31.0)[1]	26.0 (22.2, 28.3)[1]	25.8 (22.2, 30.1)	23.2 (20.7, 26.8)[1]	25.7 (22.3, 29.7)[10]	< 0.001
Tobacco use (Cigarette smoking, cigar, tobacco chewing)									< 0.001
Never	35 (64)[1]	93 (56)[12]	19 (53)[2]	85 (51)[2]	20 (43)[3]	40 (35)[2]	54 (25)[1]	346 (43)[23]	
Past	13 (24)	51 (31)	7 (19)	48 (29)	15 (33)	41 (36)	66 (31)	241 (30)	
Current	7 (13)	23 (14)	10 (28)	34 (20)	11 (24)	33 (29)	92 (43)	210 (26)	
Cigarette smoking (pack-years)	7.4 (1.5, 15.4)[1]	8.0 (2.1, 20.0)[17]	37.0 (24.0, 42.5)[2]	19.0 (8.0, 39.8)[5]	19.0 (8.0, 39.8)[4]	14.0 (8.0, 29.0)[7]	19.5 (7.8, 34.5)[7]	15.5 (5.5, 30.0)[43]	< 0.001
Drinking status									0.942
Never	10 (18)[1]	27 (16)[12]	3 (8)[2]	24 (14)[2]	7 (15)[3]	13 (11)[2]	29 (14)[1]	113 (14)[23]	
Past	33 (60)	100 (60)	25 (69)	97 (58)	28 (61)	77 (68)	130 (61)	490 (61)	
Current	12 (22)	40 (24)	8 (22)	46 (28)	11 (24)	24 (21)	53 (25)	194 (24)	
Drinking category									0.0242
Abstainers	10 (20)[6]	27 (18)[27]	3 (9)[6]	24 (16)[22]	7 (16)[4]	13 (13)[12]	29 (15)[21]	113 (16)[98]	
Light drinkers	17 (34)	40 (26)	11 (34)	30 (20)	6 (13)	14 (13)	35 (18)	153 (21)	
Moderate drinkers	8 (16)	31 (20)	8 (25)	29 (20)	10 (22)	25 (24)	31 (16)	142 (20)	
Heavy drinkers	9 (18)	33 (22)	5 (16)	32 (22)	11 (24)	31 (30)	36 (19)	157 (22)	
Very heavy drinkers	6 (12)	21 (14)	5 (16)	32 (22)	11 (24)	21 (20)	61 (32)	157 (22)	
Etiology									< 0.001
Alcohol	NA	28 (16)	NA	30 (18)[4]	14 (29)	36 (31)	97 (46)	205 (28)[4]	
All others combined		41 (23)		51 (31)	11 (22)	34 (29)	43 (20)	180 (25)	
Idiopathic		110 (61)		84 (51)	24 (49)	46 (40)	73 (34)	337 (47)	

	MSCP 0 *n* = 56	MSCP 1 *n* = 179	MSCP 2 *n* = 38	MSCP 3 *n* = 169	MSCP 4 *n* = 49	MSCP 5 *n* = 116	MSCP 6 *n* = 213	ALL *n* = 820	*p* value
Diabetes present	3 (6)[5]	36 (21)[8]	9 (35)[12]	34 (22)[14]	15 (33)[3]	32 (29)[4]	88 (43)[8]	217 (28)[54]	< 0.001
Exocrine pancreatic dysfunction									< 0.001
No	36 (84)[13]	92 (51)	11 (29)	76 (45)	19 (39)	43 (37)	38 (18)	315 (39)	
Not tested	1 (2)	73 (41)	23 (61)	66 (39)	17 (35)	41 (35)	79 (37)	300 (37)	
Yes	6 (14)	14 (8)	4 (11)	27 (16)	13 (27)	32 (28)	96 (45)	192 (24)	
Calcification present	0 (0)	0 (0)	0 (0)	0 (0)	49 (100)	0 (0)	213 (100)	262 (32)	NA
Days from enrollment to MRI/MRCP[a]	− 15.5 (− 88.0, 18.5)	− 7.0 (− 112.0, 10.0)	− 9.5 (− 99.0, 9.0)	− 27.0 (− 163.0, 2.0)	− 115.0 (− 455.0, − 38.0)	− 57.0 (− 185.5, 0.0)	− 109.0 (− 377.0, − 19.0)	54.0 (− 197.0, 0.0)	< 0.001

Medians (25th, 75th quantiles) are reported for continuous variables

Counts (column percentages) are reported for categorical variables

Superscripts indicate the missing value counts and are excluded from the percentage calculation

p values are based on comparing the three groups on each characteristic

[a]Negative (positive) numbers indicate that the image scan was before (after) enrollment

Table 4

Standard MRI imaging protocol of the PROCEED study

(1) Axial T1-weighted, 3-D, 2-point Dixon gradient echo sequence capable of generating water-only and fat-only images in addition to in-phase and op-phase images
(2) T2-weighted images: axial, with fat suppression
(3) T2-weighted images (turbo-spin-echo (TSE) or a variant of TSE): axial and coronal, without fat suppression
(4) MRCP images:
(a) 2D MRCP (thick slab), 40 mm thick, 8 para coronal projections to best show the pancreatic duct from different angles
(b) 3D MRCP (thin slab): 2–3 mm, respiratory synchronized 3-D TSE sequence. Create MIP from source images
(5) T1-weighted images: Axial T1-weighted 3-D gradient echo with fat suppression
(a) Unenhanced
(b) Arterial
(c) Venous
(d) 5-min delayed

Table 5

Mean T1 SIR values and differences in each MSCP groups, shown with and without adjustment for covariates using the regression model

T1 SIR	MSCP	Mean (Q1, median, Q3)	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)[a]
T1 score: pancreas-to-spleen	0	1.34 (1.22, 1.35, 1.51)	Reference	Reference
	1	1.27 (1.08, 1.29, 1.46)	− 0.07 (− 0.17, 0.03)	− 0.04 (− 0.15, 0.06)
	2	1.21 (1.04, 1.19, 1.44)	− 0.13 (− 0.27, 0.01)	− 0.08 (− 0.23, 0.07)
	3	1.16 (0.96, 1.18, 1.35)	− 0.17 (− 0.28, − 0.07)	− 0.15 (− 0.26, − 0.04)
	4	1.18 (0.86, 1.12, 1.49)	− 0.15 (− 0.29, − 0.01)	− 0.08 (− 0.22, 0.06)
	5	1.12 (0.86, 1.05, 1.27)	− 0.22 (− 0.33, − 0.10)	− 0.17 (− 0.29, − 0.05)
	6	1.05 (0.82, 1.02, 1.25)	− 0.28 (− 0.39, − 0.18)	− 0.23 (− 0.34, − 0.12)
	p value	0.0001	< 0.0001	< 0.0001
T1 score: pancreas-to-muscle	0	1.28 (1.02, 1.33, 1.57)	Reference	Reference
	1	0.99 (0.62, 0.92, 1.31)	− 0.290 (− 0.43, − 0.15)	− 0.26 (− 0.408, − 0.12)
	2	1.17 (0.85, 1.18, 1.54)	− 0.11 (− 0.31, 0.076)	− 0.12 (− 0.320, 0.08)
	3	0.96 (0.64, 0.92, 1.32)	− 0.321 (− 0.465, − 0.17)	− 0.30 (− 0.441, − 0.15)
	4	1.07 (0.62, 1.08, 1.50)	− 0.21 (− 0.39, − 0.02)	− 0.14 (− 0.334, 0.04)
	5	0.98 (0.65, 1.05, 1.20)	− 0.30 (− 0.45, − 0.14)	− 0.25 (− 0.403, − 0.09)
	6	0.95 (0.60, 0.97, 1.2)	− 0.33 (− 0.47, − 0.19)	− 0.30 (− 0.444, − 0.15)
	p value	0.0001	< 0.0001	0.0006
T1 score: pancreas-to-liver	0	1.06 (0.93, 1.05, 1.17)	Reference	Reference
	1	1.02 (0.84, 1.01, 1.13)	− 0.03 (− 0.11, 0.05)	− 0.04 (− 0.13, 0.05)
	2	1.00 (0.85, 0.98, 1.14)	− 0.05 (− 0.17, 0.06)	− 0.02 (− 0.14, 0.10)
	3	0.95 (0.78, 0.96, 1.11)	− 0.10 (− 0.19, − 0.02)	− 0.10 (− 0.19, − 0.01)
	4	0.95 (0.74, 0.93,1.15)	− 0.11 (− 0.22, 0.00)	− 0.07 (− 0.19, 0.04)
	5	0.89 (0.70, 0.82, 1.05)	− 0.16 (− 0.25, − 0.07)	− 0.14 (− 0.24, − 0.04)
	6	0.86 (0.67, 0.84, 1.04)	− 0.20 (− 0.28, − 0.11)	− 0.17 (− 0.26, − 0.07)
	p value	0.0001	< 0.0001	0.0004

Results are expressed as the unadjusted or adjusted mean difference in T1 score between each CP stage and the reference group (MSCP 0), along with 95% confidence intervals (CI)

The bottom row presents the *p* value from an overall F-test of any difference among the seven stages of CP

[a]Covariates adjusted for are age, gender, race, body mass index, tobacco use, pack-years, drinking status, drinking category, diabetes, and exocrine pancreatic dysfunction