

Validation of the Semi-Quantitative MRI (SQ-MRI) Score as a Biomarker for Non-Calculic Chronic Pancreatitis in a Multicenter Cohort

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Research Article

Keywords: Chronic Pancreatitis, T1, MRI, Size, Enhancement

Posted Date: August 18th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10504233/v1>

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Additional Declarations: No competing interests reported.

TITLE

Validation of the Semi-Quantitative MRI (SQ-MRI) Score as a Biomarker for Non-Calcific Chronic Pancreatitis in a Multicenter Cohort.

ABSTRACT

Purpose

Validate the semiquantitative (SQ)-MRI score for chronic pancreatitis (CP) diagnosis in an independent, multicenter cohort.

Methods

We analyzed MRIs performed at baseline in 337 participants with acute (AP) or recurrent AP (RAP) and 67 with non-calcific chronic pancreatitis (NCCP) enrolled in the PROCEED study from 6/2017 to 3/2023. MRIs were performed at multiple clinical centers using site-specific clinical protocols and a variety of MRI vendors to evaluate the SQ-MRI score in a real-world setting. The SQ-MRI score was calculated using the T1 signal intensity ratio of the pancreas to the spleen (T1 score), arteriovenous enhancement ratio (AVR), and pancreatic body diameter (PBD). We adjusted for confounding by participant characteristics via propensity score weighting.

Results

Median AVR was higher in AP/RAP (1.18, IQR: 0.97-1.44) than in the NCCP group (1.03, IQR: 0.78-1.22, $p = 0.007$). Pancreatic body diameters were larger in AP/RAP than in the NCCP group - 7-14 mm (10% vs 25%), 14-20 mm (40% vs 54%), and >20 mm (50% vs 21%), respectively ($p < 0.01$). Median T1 score was higher in AP/RAP (1.18, IQR: 0.96-1.40) than in the NCCP group (1.04, IQR: 0.86-1.32, $p = 0.10$). Median SQ-MRI score in the AP/RAP group was significantly lower, 1.91 (IQR: 0.97, 2.95), than in the NCCP group, 2.74 (IQR: 2.04-4.03) ($p < 0.001$). The propensity score-adjusted AUC for SQ-MRI to distinguish AP/RAP from NCCP was 0.64, which was higher than for individual parameters.

Conclusion

We have validated the SQ-MRI score in a multicenter cohort using an independent, real-world MRI dataset.

ABBREVIATIONS

AP	Acute Pancreatitis
AVR	Arterial-to-Venous enhancement Ratio
CP	Chronic Pancreatitis
CPCRC	The Chronic Pancreatitis Clinical Research Consortium
EPD	Exocrine Pancreatic Dysfunction
MRI	Magnetic Resonance Imaging
MRCP	Magnetic Resonance Cholangiopancreatography
MINIMAP	Magnetic resonance imaging as a non-invasive method for the assessment of pancreatic fibrosis
PROCEED	Prospective evaluation of chronic pancreatitis for epidemiologic and translational studies
RAP	Recurrent Acute Pancreatitis
SQ-MRI	Semi-Quantitative MRI

KEYWORDS

Chronic Pancreatitis; T1; MRI; Size; Enhancement

INTRODUCTION

Chronic pancreatitis (CP) is a fibroinflammatory syndrome commonly associated with chronic pain, exocrine and endocrine pancreatic insufficiency, reduced quality of life, and shortened life expectancy [1]. The incidence and prevalence of CP are rising, and curative treatment remains unavailable [1]. Most patients present with acute pancreatitis (AP) or recurrent acute pancreatitis (RAP) before CP diagnosis, yet we currently lack tools to prevent disease progression or enable early CP diagnosis. The American College of Radiology and American College of Gastroenterology practice guidelines recommend computed tomography (CT) and magnetic resonance imaging (MRI), including magnetic resonance cholangiopancreatography (MRCP), as first-line modalities for CP [2, 3]. MRCP scoring is based on the Cambridge classification, developed for endoscopic retrograde cholangiopancreatography (ERCP) in the 1980s [4]. Over the years, several limitations of this ductal classification have been reported, largely because ductal imaging overlooks other histopathological features, such as parenchymal fibrosis and loss of acinar tissue [5, 6]. Changes evaluated by the Cambridge classification reflect periductal fibrosis, a complication of moderate-to-severe CP, not commonly seen in early stages of the disease. The pancreatic ductal system comprises only 4% of the pancreas, while acinar tissue accounts for over 80% of pancreatic volume [7-10]. Several retrospective studies have investigated parenchymal MRI features in CP and reported benefits over MRCP alone [11]. Expert panel reports and meta-analyses highlight the need for a robust imaging biomarker that integrates parenchymal and ductal features to improve the diagnostic performance of MRI and MRCP [9].

The National Cancer Institute and the National Institute for Diabetes and Digestive and Kidney Diseases established the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) in 2015 to address research gaps and foster multidisciplinary collaborations, including early diagnosis and management of CP [12]. The Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED) (NCT03099850) is a prospective cohort study of CP within the CPDPC in US adults [13]. The consortium is now known as the Chronic Pancreatitis Clinical Research Consortium (CPCRC). An ancillary study of the CPDPC, the Magnetic Resonance Imaging as a Non-Invasive Method for the Assessment of Pancreatic Fibrosis (MINIMAP) study [14], developed the semi-quantitative MRI (SQ-

MRI) score using scans collected with a standardized imaging protocol [15]. In the current study, data from the PROCEED study were used to validate the SQ-MRI score. PROCEED MRI/MRCPs were performed at clinical centers using site-specific clinical protocols, MRI vendors, and 1.5T or 3.0T magnet strengths to validate the SQ-MRI score for CP in a real-world setting.

MATERIALS AND METHODS

This study included participants enrolled from 10 clinical centers in the PROCEED study [13]. The study was approved by the by the single Institutional Review Board and conducted at 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 participants provided written informed consent before study procedures. Detailed data were collected at enrollment using case report forms completed by study participants, clinical research coordinators, and enrolling physicians. The detailed methodology of the PROCEED study has been published [13].

Study Population

Participants for this study were identified from the PROCEED study, which enrolled 605 in the AP/RAP group and 674 in the definite CP group, from 06/27/2017 to 03/29/2023. AP was defined by the Revised Atlanta Classification [16]; RAP by documented evidence of 2 or more episodes of AP; and CP by Cambridge 3 or 4 changes, pancreatic or ductal calcifications on CT scan and/or MRI/MRCP [17]. **Figure 1** presents the selection criteria used to derive the final study population. The final study population included 337 participants with AP/RAP and 67 with non-calcific CP (NCCP) who had baseline MRIs and all three parameters available to derive the SQ-MRI score [13]. Cases lacking the necessary MRI data were excluded from the analysis.

MR Imaging

Imaging was performed on 1.5T or 3.0T MRI scanners from multiple manufacturers, in accordance with site-specific imaging protocols. Participants whose MRIs were performed at imaging sites outside the participating centers were also considered eligible for inclusion if the examination included the required sequences for calculating the SQ-MRI score. The data points required to calculate the SQ-MRI score are obtained from T1-weighted gradient-echo images acquired during the unenhanced phase and the post-contrast arterial and venous phases.

Image Analysis

MRI/MRCP data collection points and the tutorial were defined in accordance with the CP reporting standards at the inception of the PROCEED study [13, 17]. Data were manually collected by a site radiologist blinded to the clinical information at each participating center and entered into structured case report forms [17]. All site radiologists completed the training materials before participating in the study. The region of interest was at least 1 cm² and placed over a homogeneous region of the pancreas, avoiding areas with findings of ongoing acute pancreatitis, such as edema or fluid collection, the pancreatic duct, retroperitoneal fat, and vessels.

The T1 score is the T1-weighted (T1W) signal-intensity ratio of the pancreas to the spleen, measured on unenhanced T1W gradient-echo images.

$$T1\ Score = \frac{T1\ W\ signal\ of\ unenhanced\ pancreas}{T1W\ signal\ of\ unenhanced\ spleen}$$

The arterial-to-venous enhancement ratio (AVR) is the ratio of relative contrast enhancement between the arterial and venous phases. It is calculated from the parenchymal T1W signal intensity during the unenhanced, arterial, and venous phases:

$$AVR = \frac{T1W\ signal\ arterial - T1W\ signal\ unenhanced}{T1W\ signal\ venous - T1W\ signal\ unenhanced}$$

The diameter of the pancreatic body (PBD) was measured at the left lateral margin of the vertebral body, with a caliper set perpendicular to the main pancreatic duct (cross-section of the parenchyma) [18].

Statistical Analysis

For baseline characteristics, the median with interquartile range (IQR) and frequency with proportion (%) were used to summarize continuous and categorical variables, respectively. Baseline characteristics were compared using the Kruskal-Wallis test for continuous variables and either the Chi-square test or Fisher's Exact test for categorical variables. All statistical tests used a 5% significance level.

For analysis in this study, we had to account for differences between the designs of the MINIMAP and PROCEED studies. The MINIMAP study measured pancreatic diameter in millimeters, whereas the PROCEED study categorized PBDs into three groups: 7-14 mm, 15-20 mm, and >20 mm. We re-estimated the SQ-MRI score using a logistic regression of NCCP (vs. AP/RAP) with T1 score, AVR, and categorized PBD as covariates. We used widely adopted min-max normalization to linearly transform the logistic regression's linear predictor into the range 0 to 5 for easier interpretation. Min-max normalization is robust to extreme outliers, with 0 and 5 anchored at the 1st and 99th percentiles of the PROCEED data, respectively.

The PROCEED SQ-MRI score was calculated using the following formula:

$$SQMRI = 5.678 - 0.731 \times I_{>20mm}(PBD) + 1.695 \times I_{7-14mm}(PBD) - 1.536 \times AVR - 1.495 \times T1\ score$$

where the categorized PBD is defined as:

$$I_{>20mm} = \begin{cases} 1, & \text{If } PBD = "> 20mm" \\ 0, & \text{Otherwise} \end{cases}, \quad I_{7-14mm} = \begin{cases} 1, & \text{If } PBD = "7 - 14mm" \\ 0, & \text{Otherwise} \end{cases}$$

We compared SQ-MRI and other MRI parameters between the AP/RAP and NCCP groups using boxplots and an ROC curve. We also used propensity score weighting to reduce potential confounding by baseline characteristics, including age, sex, race, body mass index (BMI), alcohol use, tobacco use, pancreatitis etiology, diabetes status, and exocrine pancreatic dysfunction status. The propensity scores were estimated using the covariate-balancing propensity score (CBPS) algorithm [19], with inverse probability weighting to balance covariate distributions between groups. The propensity score adjustment removes confounding from the selected participant characteristics; it is interpreted as the ROC curve we would observe in all subgroups of AP/RAP and NCCP that share identical baseline characteristics. An AUC greater than 0.5 in this adjusted analysis indicates that the association between SQ-MRI and the AP/RAP and NCCP groups is not attributable to confounding.

RESULTS

Table 1 presents the participants' demographic data, behavioral risk factors, and clinical findings. There were no differences in age, sex, race, BMI, or drinking status between the AP/RAP and NCCP groups ($p > 0.05$). Alcohol was the etiology in 17% of the AP/RAP group and 31% of the NCCP group ($p = 0.01$). The AP/RAP group had a higher proportion of 'never smokers' (13% vs 9%, $p = 0.002$), and the NCCP group had twice as many with EPD (40% vs 18%, $p = 0.003$).

Univariate Analysis of MRI Parameters in the AP/RAP and NCCP Cohorts.

Table 2 and **Figure 2** present results for the three individual parameters and the SQ-MRI score in the AP/RAP and NCCP groups. AVR was higher in the AP/RAP group (median: 1.18, IQR: 0.97–1.44) than in the NCCP group (median: 1.03, IQR: 0.78–1.22, $p = 0.007$). PBDs were larger in the AP/RAP group than in the NCCP group: 7-14 mm (10% vs 25%), 14-20 mm (40% vs 54%), and >20 mm (50% vs 21%), respectively ($p < 0.01$). Although the AP/RAP group had a higher median T1 score (1.18, IQR: 0.96–1.40) than the NCCP group (1.04, IQR: 0.86–1.32), this difference was not statistically significant ($p = 0.10$). The SQ-MRI score in the AP/RAP group was significantly lower (median: 1.91, IQR: 0.97–2.95) than in the NCCP group (median: 2.74, IQR: 2.04–4.03, $p < 0.001$).

ROC analysis

Figure 3 compares the ROC curves for the three individual parameters and the SQ-MRI score, with and without propensity score weighting. Figure 3(a) shows that the propensity score-adjusted AUCs for T1 score and AVR are 0.54 and 0.59, respectively. Because the ROC curve and AUC are designed for continuous biomarkers, the AUC for PBD does not have its usual interpretation and is included in Figure 3 mainly for reference. The propensity score-adjusted AUC for the SQ-MRI score was 0.64, higher than those of T1 and AVR.

For the use of SQ-MRI as a diagnostic test, the relevant diagnostic performance is shown in Figure 3(b) and **Table 3**, which present results without propensity score adjustment. The AUCs for T1 score, AVR, and SQ-

MRI were 0.56, 0.60, and 0.67, respectively. These are slightly higher than the propensity score-adjusted results. Since the AUC quantifies the difference in image scores between AP/RAP and NCCP, and this difference diminishes only slightly after removing confounders, this result suggests that only a small fraction of the imaging parameters' diagnostic performance was attributable to confounders.

PPV and NPV

Overall, an AUC of 0.66 for SQ-MRI indicates moderate diagnostic performance. However, the ROC curve in **Figure 3(b)** also suggests that the diagnostic test threshold for SQ-MRI can be adjusted to generate Rule-out and Rule-in tests tailored to different clinical contexts, as proposed in our previously published CP-PRoBE guidelines for biomarker development in CP [20]. **Table 3** shows the trade-off between increasing sensitivity and increasing specificity at various thresholds. **Table 4** shows, for selected thresholds and the anticipated prevalence of NCCP in the population to which the diagnostic test is applied, how the Positive Predictive Value (PPV) and Negative Predictive Value (NPV) would change.

DISCUSSION

In our biomarker discovery publication from the MINIMAP study, we reported that the SQ-MRI score demonstrates high diagnostic performance for CP [15]. In the current analysis, we validated our results in an independent population, which is the next step in biomarker development. The prospective, multicenter PROCEED study extends these findings to a clinically relevant population of patients with AP or RAP who are at elevated risk of progression. Longitudinal follow-up of the PROCEED cohort is ongoing at the time of this publication, and future analysis will also provide an opportunity to evaluate the performance of SQ-MRI in predicting progression from AP or RAP to CP.

While a CT scan is sufficient to diagnose moderate-to-severe CP when calcifications are present, establishing an early diagnosis remains elusive [21-24]. As recommended by the American College of Radiology, MRI of the abdomen, with or without IV contrast, combined with MRCP, offers an advantage over CT for earlier CP diagnosis because of its higher sensitivity for detecting parenchymal and ductal changes [3]. Prior studies have

reported that parenchymal features on MRI could differentiate suspected CP from controls, even when the Cambridge score is normal [17, 25]. In the current analysis, we excluded patients with parenchymal and/or ductal calcifications to focus on early CP detection.

We conducted a cross-sectional study of patients with AP/RAP and definite CP to model differentiation between suspected and definite CP. The decision to develop a multi-parametric scoring system (rather than a single imaging parameter) was based on multiple parameters that reflect the diverse pathophysiological features of CP and demonstrated higher performance in the discovery study [15]. The two most common histologic features of CP are loss of acinar tissue (atrophy) and replacement by fibrosis [5]. Fibrosis may surround the lobules (perilobular or interlobular fibrosis) or extend into the lobules of acinar tissue (intralobular fibrosis) [26]. Chronic inflammatory infiltration may be present in earlier stages, but this feature is highly variable and disappears late in CP.

The T1 score, calculated from the pancreas-to-spleen T1W signal intensity ratio, showed a negative linear correlation with CP progression [27] and exocrine pancreatic dysfunction [28]. In the MINIMAP study, peak enhancement in the pancreatic arterial phase was lower than in the venous phase, consistent with the current validation study using the PROCEED dataset [15]. Progressive enhancement in CP presumably reflects sustained contrast uptake by fibrotic tissue, distinguishing it from active inflammation or necrosis [29]. In prior imaging studies, we observed changes in the arteriovenous enhancement ratio with AP and CP, indicating disturbances in pancreatic hemodynamic regulation [30, 31]. Our results on hemodynamic changes in CP are consistent with a prior study by Zhang et al., which examined differences in enhancement curves between the control and pancreatitis groups. In the control group, the greatest enhancement after injection occurred during the arterial phase and was significantly higher than in the early venous phase ($p < 0.01$) and the late venous phase ($p < 0.001$). The pancreatitis group, however, had significantly lower arterial-phase intensity than the control group's early venous-phase ($p < 0.05$) and arterial-phase ($p < 0.01$) [32].

The PROCEED study did not systematically collect histopathologic data; however, radiologic-pathologic correlation of CP has been reported in other studies. A recent study by Metri et al. correlated MRI

parenchymal features with histopathology in 56 patients scheduled to undergo total pancreatectomy with islet autotransplantation (TPIAT) [33]. The T1 score was significantly associated with pancreatic fibrosis ($p = 0.004$). Venous-phase enhancement intensity could differentiate among indeterminate CP, RAP, and definite CP groups. Definite CP showed a progressive enhancement curve, with signal intensity steadily rising from the pre-contrast phase to the venous phase. Indeterminate CP showed a plateau enhancement pattern, with an initial increase from the pre-contrast to the arterial phase, followed by a slight decline through the venous and delayed phases. RAP demonstrated a washout enhancement curve, with signal intensity rising from the pre-contrast to the venous phase, followed by a subsequent decrease [33]. A study by Tirkes et al. compared histopathologic correlations of MRI features with the Cambridge classification in 60 CP patients who underwent surgical resection after MRI/MRCP. Correlations between fibrosis score and T1 score, and between fibrosis score and AVR, were $\rho = -0.54$ ($P = 0.0001$) and $\rho = -0.39$ ($P = 0.003$), respectively. The correlation between the Cambridge grade and the fibrosis score was the weakest, with $\rho = 0.26$ ($p = 0.07$). A T1 score ≤ 1.20 provided a sensitivity of 74% and a specificity of 50% (AUC: 0.74), while an AVR ≤ 1.10 provided a sensitivity of 75% and a specificity of 55% (AUC: 0.68) to detect a fibrosis score ≥ 6 [34].

Diminished pancreatic size (and volume) due to loss of acinar cells is a common finding in CP [5, 35]. Both the body and tail diameters equally reflected tissue loss in the biomarker discovery study [15]. This observation was reported by several investigators, including Schrader et al., who used CT to measure pancreatic volume and found a significant reduction in CP patients compared with controls [36]. In another notable study by Faghih et al., progressive volume loss was observed in patients with RAP and indeterminate/definite CP who eventually underwent total pancreatectomy with islet cell autotransplantation [37].

Prior studies suggested that parenchymal measurements for grading CP changes might be more reliable than interpreting MRCP images to assess the Cambridge grade [6, 38]. Regarding the reproducibility of the SQ-MRI scoring components, we reported high interobserver agreement of 0.88 for the T1 score and AVR, and 0.73 for pancreatic diameter. Conversely, in the same MRI study that also included MRCP, the weighted kappa for the Cambridge score was only 0.54 [39]. Lower-than-desired interobserver agreement with the ductal criteria may reflect challenges in obtaining high-quality MRCPs, which can lead to suboptimal agreement even

among experienced abdominal radiologists [10]. Another study by Wang et al. measured pancreatic diameter on MRI in participants without pancreatic disease and reported a near-perfect correlation coefficient (over 0.95) [35].

The pancreas is a relatively small but highly productive exocrine gland with a daily secretory output of up to 2 liters of fluid containing protein-rich digestive enzymes and bicarbonate [40, 41]. Higher T1-weighted signal in the normal pancreas is a well-known MRI feature, attributed to the rich proteinaceous content of acinar cell cytoplasm. A higher number of hydrogen atoms in a molecule shortens the T1 relaxation time and increases the T1-weighted signal [42]. Although the normal pancreas has higher T1-weighted signal intensity than the spleen (or paraspinal muscle and liver), this property is progressively lost as CP develops [43, 44]. In previous work, we showed that the T1 score is negatively correlated with CP progression and may serve as a single imaging biomarker to evaluate disease severity in clinical practice [27]. The mean T1 score was 1.30 in participants with no evidence of CP, 1.22 in AP/RAP, and 1.03 in those with definite CP; a T1 score of less than 1.20 was considered the threshold for abnormal. An inverse correlation between T1 signal intensity in CP and pancreatic fibrosis has been supported by a few histopathologic correlation studies [34, 43, 45, 46]. In addition, some studies have reported lower T1 scores with EPD, as determined by endoscopic pancreatic function tests [25, 28, 47].

Epidemiologic studies estimate a 10% risk of progression to CP after a single episode of AP and ~33% among patients with RAP [48]. Using the sensitivity, specificity, and a selected SQ-MRI threshold, the PPV and NPV can be derived from the known or anticipated prevalence of CP in a population. Following CP-PRoBE guidelines [20], an SQ-MRI threshold can be selected based on the clinical consequences of false positives (incorrectly diagnosing an AP/RAP patient as CP) and false negatives (incorrectly diagnosing a CP patient as AP/RAP). In the current cross-sectional analysis, the prevalence of noncalcific CP was 17% (67/404), which falls within the range (10-33%) for the proportion of patients with AP/RAP expected to progress to CP over time in typical clinical settings [48]. Applying an SQ-MRI threshold of ≥ 3.5 , with a sensitivity of 37% and a high specificity of 86%, to our study population yields a PPV and NPV of 35% and 87%, respectively (**Table**

4). This suggests that, in a high-risk group (AP/RAP), this threshold doubles the likelihood that a positive test truly reflects underlying CP (increasing pre-test probability from 17% to a post-test probability of 35%). Similarly, the likelihood that an SQ-MRI score < 3,5 reflects underlying CP is low, given the high NPV (86%). Although a threshold of >3.5 will miss the diagnosis of underlying CP in many patients, in the absence of established tools to predict progression, the moderate discriminatory performance of SQ-MRI in differentiating CP from AP/RAP is clinically meaningful. In a subset of patients with a higher prevalence of or risk of progression to CP than our current study population (e.g., RAP only, alcohol etiology), the PPV will be greater (53% when CP prevalence is 30%). Future longitudinal analyses can evaluate the ability of the SQ-MRI score to predict progression to CP in such patients.

Our study has limitations. The MINIMAP study measured diameter in millimeters, whereas the PROCEED study used size measurement criteria from the consensus statement for reporting CP features [17]. Therefore, we slightly modified the SQ-MRI formula for pancreatic tail diameter to 3 categories (7-14 mm, 15-20 mm, and >20 mm) for the current analysis [15]. Potential artifacts occur in conventional MR imaging, where tissue contrast depends on multiple factors, including acquisition parameters, receiver coil geometry, sensitivity, and signal amplifier gains. Variation in MRI signal intensity is commonly observed when selecting a gradient-echo pulse sequence and adjusting acquisition parameters (e.g., flip angle, echo time, repetition time, and inversion time). Unfortunately, these limitations are inherent to all MRI evaluations and are difficult to avoid.

In conclusion, this study validates the SQ-MRI score in a large, independent, well-phenotyped multicenter cohort, using diverse imaging protocols across multiple hardware vendors and magnet strengths. Future studies should evaluate the performance of SQ-MRI in predicting progression from AP and RAP to CP in longitudinal analyses. Ultimately, developing a robust imaging biomarker that integrates parenchymal and ductal features is expected to improve the diagnostic performance of MRI and MRCP for cross-sectional and longitudinal evaluation in patients with pancreatitis.

FIGURES

Figure 1. Consort diagram showing selection of AP/RAP and CP groups for this study from the PROCEED cohort.

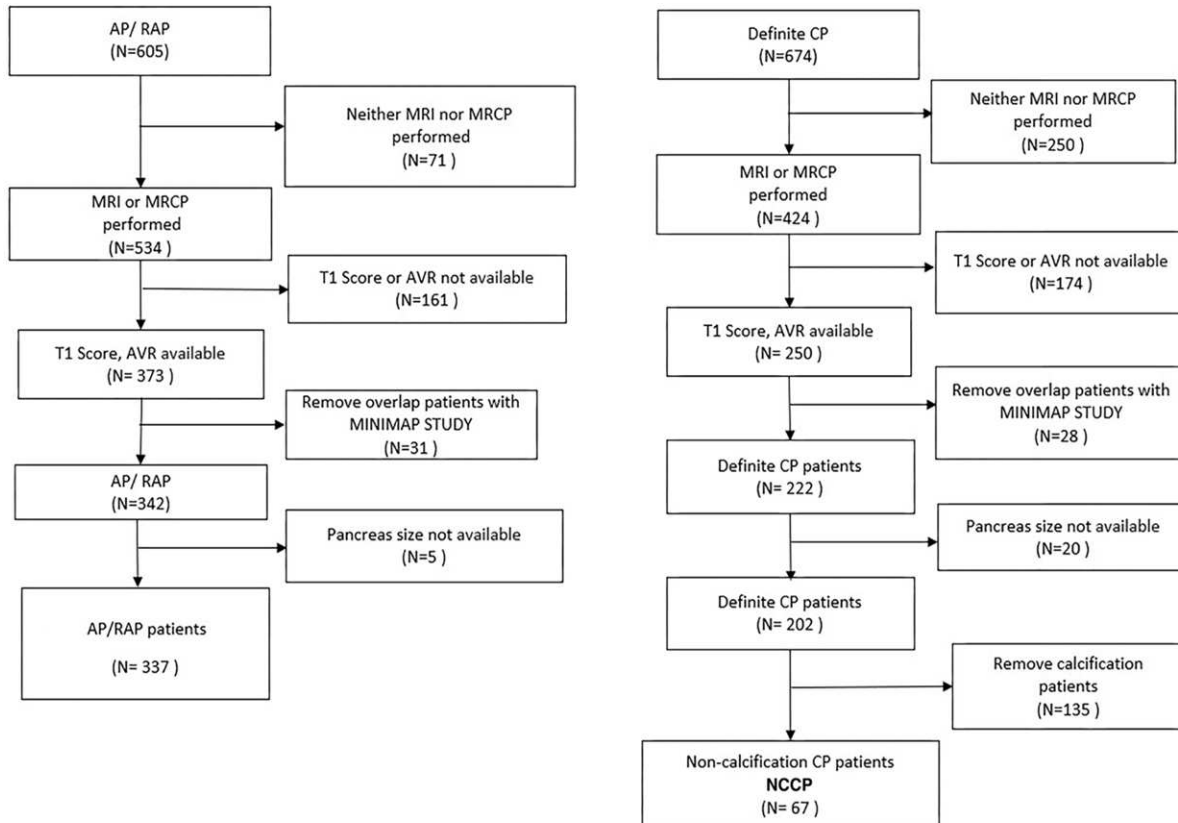


Figure 2. Univariate comparison of T1 score, AVR, and SQ-MRI score between the AP/RAP and NCCP groups. The upper and lower ends of the box plots represent the 25th and 75th quartiles of the data. The bar represents the median, while the box represents the interquartile range (IQR). The whiskers extend from the box to the minimum and maximum data values. Less than 1% of the SQ-MRI scores may be less than 0.0 or greater than 5.0 because the min-max normalization anchors 0 and 5 at the 1st and 99th percentiles of the PROCEED data.

Fig. 2-a. The T1 score tended to be higher in the AP/RAP (median: 1.18, IQR: 0.96-1.40) than in the NCCP (median: 1.04, IQR: 0.86-1.32), but the difference was not statistically significant ($p = 0.10$).

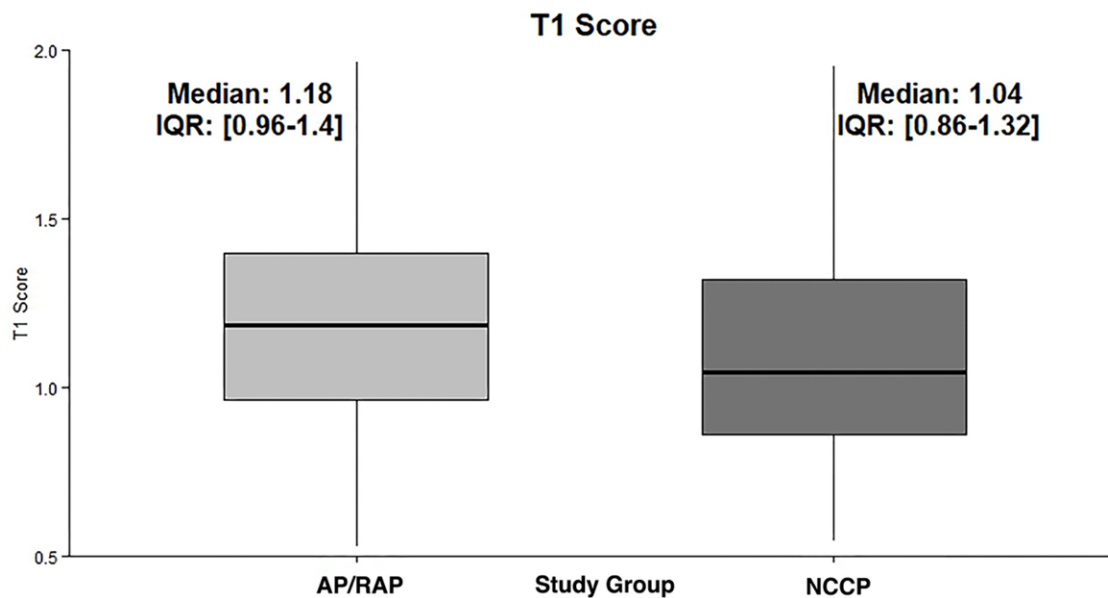


Fig. 2-b. The AVR was significantly higher in the AP/RAP (median: 1.18, IQR: 0.97-1.44) than in the NCCP (median: 1.03, IQR: 0.78-1.22; $p = 0.007$).

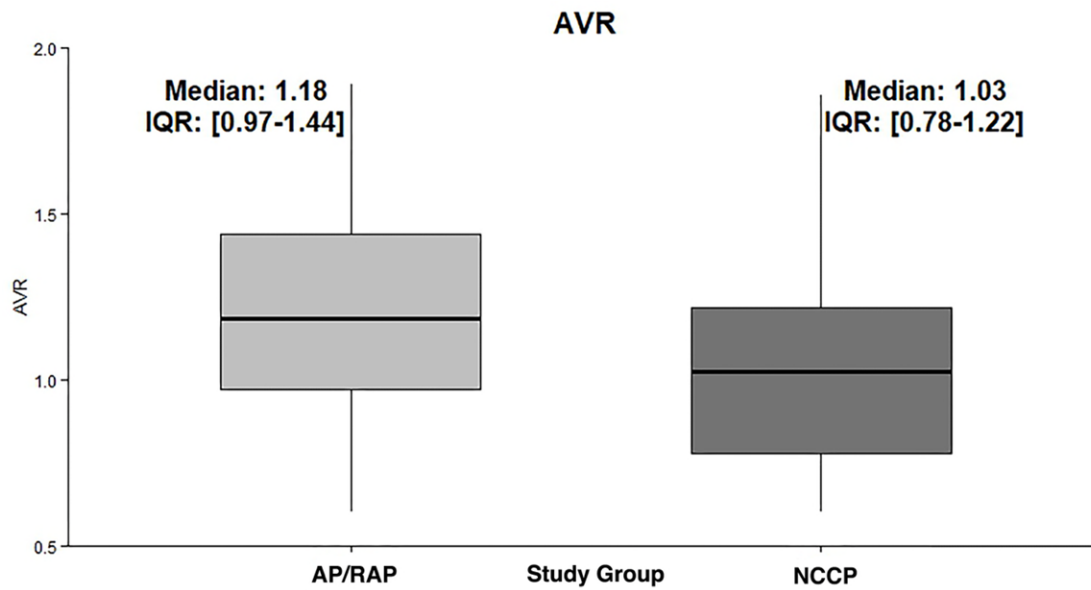


Fig. 2-c. The SQ-MRI score in the AP/RAP cohort was significantly lower (median: 1.91, IQR: 0.97-2.95) than in the NCCP cohort (median: 2.74, IQR: 2.04-4.03; $p < 0.001$).

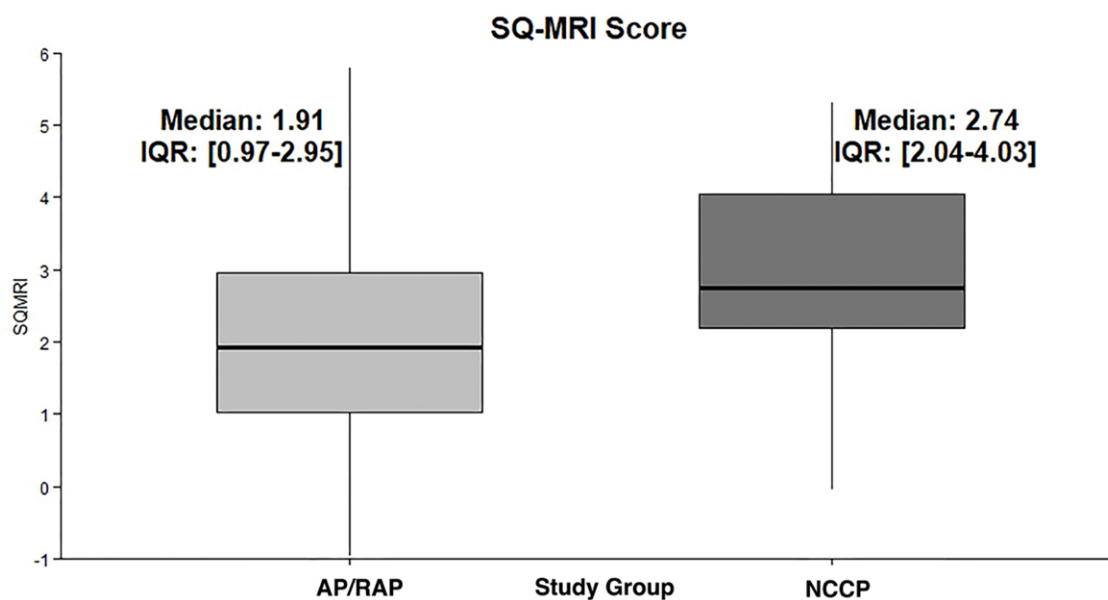
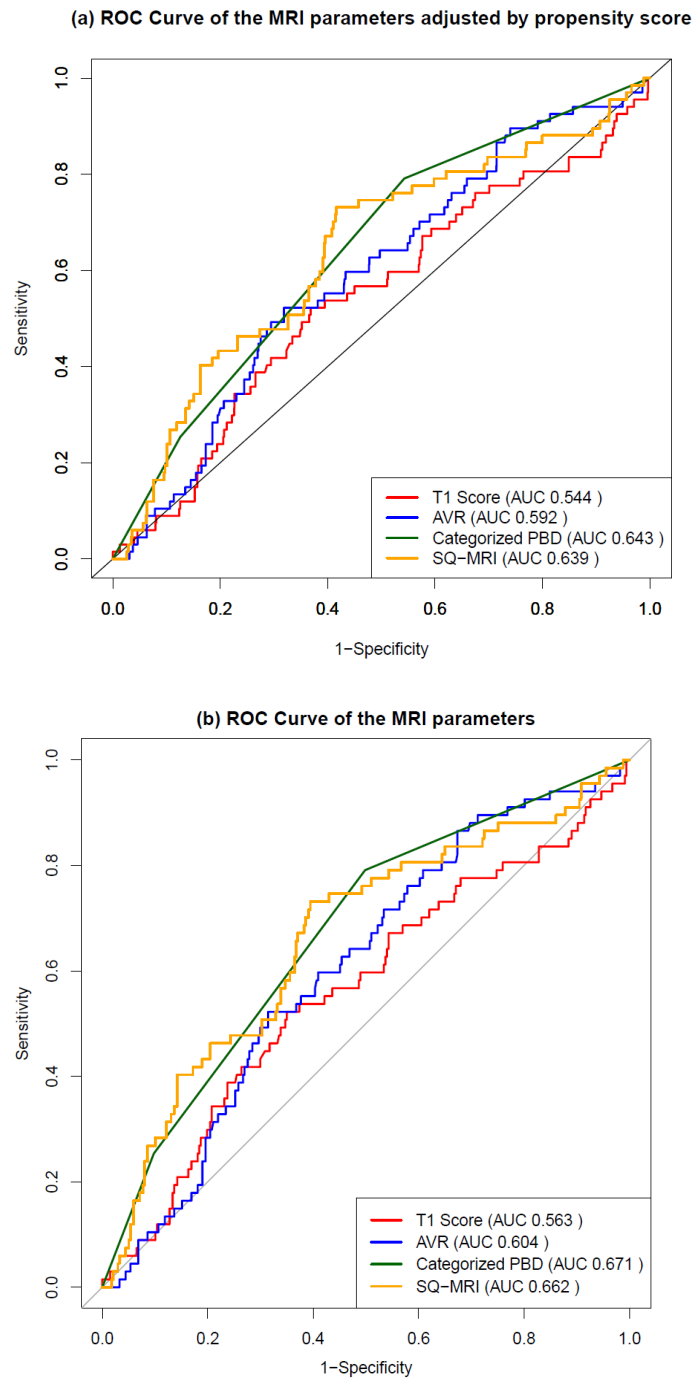


Figure 3. ROC curves for SQ-MRI and its three parameter components. In the sensitivity and specificity calculations, NCCP is treated as the “positive case,” and AP/RAP is treated as the “negative control.” Plots (a) and (b) display ROC curves with and without propensity score weighting, respectively.



TABLES

Table 1. Baseline characteristics of participants in the AP/RAP and NCCP groups.

Population characteristics	AP/RAP N = 337	NCCP N = 67	<i>p</i> value*
Age (years)	47.0 (38.0, 57.0)	49.0 (42.0, 59.0)	0.18
Male sex: n (%)	179 (53%)	37 (55%)	0.75
Race: n (%)			
White	285 (85%)	58 (87%)	0.81
Black	13 (4%)	3 (4%)	
Other, multiple	39 (12%)	6 (9%)	
BMI (kg/m ²)	27.4 (23.8, 31.6)	25.8 (22.4, 30.1)	0.07
Smoking status: n (%)			
Never	171 (52%) ¹¹	23 (35%) ²	0.002
Past	100 (31%)	19 (29%)	
Current	55 (17%)	23 (35%)	
Drinking status: n (%)			
Never	42 (13%) ¹¹	6 (9%) ²	0.69
Past	198 (61%)	42 (65%)	
Current	86 (26%)	17(26%)	
Etiology: n (%)			
Alcohol	58 (17%)	21 (31%)	0.01 [†]
All others combined	82 (24%)	18 (27%)	
Idiopathic	197 (58%)	28 (42%)	
Diabetes mellitus: n (%)	68 (22%)	17 (27%)	0.41
EPD status: n (%)	32 (18%)	14 (40%)	0.003 [†]

Categorical variables are presented as counts (percentages). Continuous variables are summarized by median

(25th, 75th quantiles). (*) Wilcoxon test for continuous variables and Fisher's exact test for categorical

variables was used. (†) This comparison is between the AP/RAP and NCCP groups. EPD: Exocrine pancreatic

dysfunction, BMI: Body mass index. Superscript values indicate numbers with missing data.

Table 2. Univariate comparison of imaging parameters between the AP/RAP and NCCP groups. Continuous imaging parameters are presented as medians (interquartile range).

		AP/RAP	NCCP	<i>p</i> value
		N = 337	N = 67	
MRI	AVR	1.18 (0.97, 1.44)	1.03 (0.78, 1.22)	0.007
	T1 score	1.18 (0.96, 1.40)	1.04 (0.86, 1.32)	0.103
	SQ-MRI score	1.91 (0.97, 2.95)	2.74 (2.04, 4.03)	<0.001
	PBD (pancreas body diameter)			
	7-14 mm	33 (10%)	17 (25%)	<0.001
	15-20 mm	135 (40%)	36 (54%)	
	>20 mm	169 (50%)	14 (21%)	

Table 3. The sensitivity and specificity of the SQ-MRI-based diagnostic test for NCCP vs. AP/RAP. The target population of this diagnostic test includes a mixture of AP/RAP and NCCP patients. This test generates a positive diagnosis of NCCP when the SQ-MRI is greater than or equal to the threshold, and an AP/RAP diagnosis otherwise. A larger threshold produces lower sensitivity but higher specificity. The sensitivity and specificity values in this table were extracted from the ROC curve in Figure 3b (without propensity score adjustment). Sensitivity does not reach 100%, and specificity does not reach 0 when the threshold is 0.0, because the min-max normalization anchors the 0 threshold at the 1st percentile of the PROCEED data rather than at the minimum; a similar phenomenon is observed when the threshold is 5.0.

SQ-MRI Threshold	Sensitivity (%)	Specificity (%)
0.0	97	5
0.5	91	11
1.0	87	26
1.5	81	40
2.0	75	53
2.5	60	64
3.0	46	76
3.5	37	86
4.0	27	91
4.5	12	94
5.0	3	97

Table 4. Example Positive Predictive Value (PPV) and Negative Predictive Value (NPV) calculations under various CP prevalences for selected thresholds of an SQ-MRI-based diagnostic test for NCCP. The target population of this diagnostic test includes a mixture of AP/RAP and noncalcific CP patients. The proportion of CP in this population is the prevalence. The sensitivity and specificity of this test are invariant with prevalence, whereas the PPV and NPV depend on it. Therefore, we present the PPV and NPV for hypothetical prevalences ranging from 0.10 to 0.50, as well as the CP prevalence of 0.17 observed in the current study. The first threshold corresponds to a rule-out test with high sensitivity and moderate specificity; the third corresponds to a rule-in test with high specificity and moderate sensitivity [20]; the second lies in between.

SQ-MRI Threshold	Sensitivity	Specificity	Prevalence	PPV	NPV
1.5	81	40	0.01	13	95
			0.17	22	91
			0.30	37	83
			0.50	57	67
2.5	60	64	0.10	15	93
			0.17	25	89
			0.30	41	79
			0.50	62	61
3.5	37	86	0.10	23	92
			0.17	35	87
			0.30	53	76
			0.50	72	58

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