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How Are Imaging Findings Associated with Exocrine Insufficiency in Idiopathic Chronic Pancreatitis?

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Abstract

Aim The aim is to study the association between imaging findings in chronic pancreatitis and fecal elastase 1 (FE1) in patients with idiopathic chronic pancreatitis (ICP).

Methods In this retrospective study on a prospectively maintained database of patients with ICP, a radiologist blinded to clinical and laboratory findings reviewed CT and/or MRI. Findings were documented according to recommendations of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, October 2018. Low FE1 ($<$100 µg elastase/g) was considered diagnostic of pancreatic exocrine insufficiency (PEI). Association between imaging findings and FE1 was studied.

Results In total, 70 patients (M: F = 37:33) with ICP with mean age of 24.2 (SD 6.5) years, range 10 to 37 years and mean disease duration of 5.6 (SD 4.6) years, range 0 to 20 years were included. Mean FE level was 82.5 (SD 120.1), range 5 to 501 µg elastase/g. Mean main pancreatic duct (MPD) caliber was 7 (SD 4) mm, range 3 to 21 mm and mean pancreatic parenchymal thickness (PPT) was 13.7 (SD 5.5) mm, range 5 to 27 mm. There was a significant association between FE1 and MPD size, PPT, type of pancreatic calcification; presence of intraductal stones, side branch dilatation on magnetic resonance cholangiopancreatography and extent of pancreatic involvement (p $<$0.05). In total, 79%, 86%, and 78% with moderate to severe MPD dilatation, pancreatic atrophy, and side branch dilatation had low FE1, respectively. But nearly half of those with no or mild structural abnormality on imaging had low FE1.

Conclusion Significant association between FE1 and specific imaging findings demonstrates its potential as a marker of exocrine insufficiency and disease severity in chronic pancreatitis. But imaging and FE1 are complementary rather than supplementary.

Keywords
- chronic pancreatitis
- CT
- fecal elastase 1
- MRI
- pancreatic exocrine insufficiency

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Introduction

Chronic pancreatitis (CP) is a multifactorial, ongoing inflammatory condition of pancreas of varying intensity which causes persistent pain, ultimately resulting in exocrine and endocrine insufficiency, reduced quality of life, and shorter life expectancy.[1–4] Identifying pancreatic exocrine insufficiency (PEI) is indispensable for managing patients with CP.[5–7] It is essential to detect PEI in early stages because it is associated with malnutrition, endocrine dysfunction, and also has a high risk for osteoporosis and cardiovascular diseases among patients with CP.[8–10]

CT and MR cholangiopancreatography are frequently used as cross-sectional imaging studies for evaluating CP,[11]yet no universal reporting standards have been established. Findings such as calcifications, parenchymal T1 signal changes, focal or diffuse gland atrophy, or irregular contour of the gland, which are routinely reported in these imaging modalities have not been incorporated into standardized diagnostic criteria. Apart from ductal features described in the Cambridge classification, there is a lack of consensus on quantification of disease severity in CP.[12] Thus, the value of imaging findings and its association with the disease severity and the tests of PEI are less well understood. The Adult Chronic Pancreatitis Working Group belonging to the consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer (CPDPC) developed a list of features and their definitions for reporting on imaging studies in patients with CP. This was aimed to standardize diagnosis and assessment of disease severity for clinical trials.[12]

There are direct and indirect tests for diagnosing PEI. Direct function tests like secretin, secretin-cholecystokinin have good accuracy rates in diagnosing pancreatic insufficiency, however, they are expensive, invasive, cumbersome, and time consuming. On the other hand, pancreatic fecal elastase-1 (FE-1) test is a widely available test, less expensive, non-invasive, and easier to perform. Most importantly, it does not require interruption of patient treatments with oral pancreatic enzyme supplements as the immunoassay is directed toward detecting only human form of FE-1.[11,13,14]

In this retrospective study of patients with idiopathic CP, our aim was to study the the association between the imaging findings as described and graded by CPDPC and FE1 test. Secondly, to know if there is a need for systemic change in how we report CP, we audited the free text radiology reports to identify how many of the findings associated with FE1 were routinely mentioned in the radiology reports.

Materials and Methods

Setting and Patients

This is an institutional review board (IRB min no. = 14,019) approved retrospective study conducted by Departments of Radiology and Gastrointestinal Sciences of a tertiary care teaching hospital. Patients were identified from a prospectively maintained database of patients with idiopathic CP. Consecutive adult patients diagnosed with idiopathic CP between 2014 to 2020 and who underwent FE1 test, and either CT or MRI studies at our center were included in the study. Other known etiologies of CP, children (<18 years), those without FE 1 test, those with images from elsewhere, or poor-quality CT/MRI images due to artifacts were excluded from the study. ►**Fig. 1** shows the flowchart of patients included in the study.

Imaging

Contrast-enhanced CT scans of the abdomen and pelvis were performed in one of the following multi-detector CT scanners using standard scan parameters: Siemens SOMATOM sensation CT Scanner, Erlangen, Germany; Philips Brilliance 16-Slice CT Scanner, Best, The Netherlands; Discovery 750HD, GE Healthcare, Milwaukee, WI. One liter of water was given as neutral oral contrast. Following intravenous injection of 80 to 120 mL of non-ionic iodinated contrast agent using a power injector, images were obtained in late arterial (40-second delay) and venous phases (65–70-second delay). While arterial phase images were obtained from the dome of diaphragm to the adrenal glands, entire abdomen and pelvis from dome of diaphragm to symphysis pubis was imaged in venous phase. Axial images of 2 to 3 mm slice thickness and coronal images of 3 to 5 mm slice thickness were available for review.

All MRI studies were performed in one of the following two MRI scanners: Intera 22 Achieva 3.0 T. (Philips Healthcare, Best, Netherlands) and Magnetom Avanto fit,1.5 T (Siemens Healthcare Erlangen, Germany).

MRI protocol included T2-weighted axial images of the upper abdomen, magnetic resonance cholangiopancreatography (MRCP), and axial DWI obtained using respiratory-triggered, single shot echoplanar imaging with *b*-values of 50 and 800 s/mm^2. Apparent diffusion coefficient maps were automatically generated. T1-weighted images were not routinely done at our center. For the purpose of this study, only T2-weighted axial MRI and MRCP images were reviewed.

Image Interpretation

An experienced abdominal radiologist blinded to clinical and laboratory findings reviewed CT and/or MRI. Findings were interpreted and documented according to recommendations of the Consortium for the Study of CPDPC October 2018.[12] ►**Figs. 2** and **3** show few examples of imaging features in CP. ►**Fig. 4** illustrates the method of measuring pancreatic parenchymal thickness (PT) in the mid body level. Measurements such as main pancreatic duct (MPD) diameter (►**Fig. 4**), pancreatic PT (►**Fig. 4**), largest size of intraductal stones (►**Fig. 3**) were measured on PACS. Findings such as pancreatic duct contour (►**Figs. 3** and **5**), presence or absence of stricture (►**Fig. 5**), location and the number of the calculus (►**Figs. 2** and **3**), presence or absence of side branches (►**Fig. 5**) were documented as described by Tirkes et al in their article.[12,15,16] An independent investigator reviewed free text radiology reports and documented findings mentioned in the report.

Fecal Elastase 1 Test

PEI was diagnosed using FE1 test. FE1 estimation was done using Pancreatic Elastase ELISA kit from BioServ Diagnostics

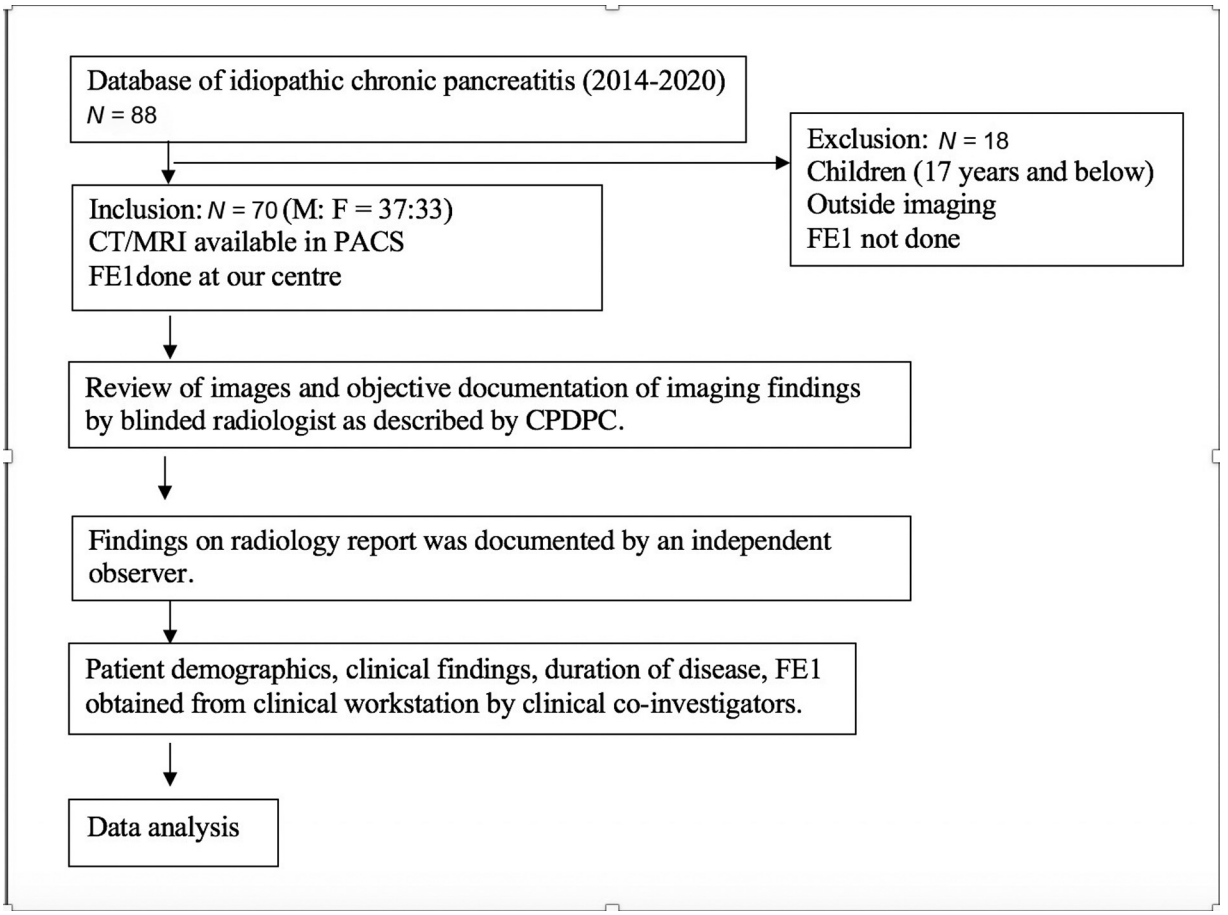

Fig. 1 Flowchart of patients included in the study.

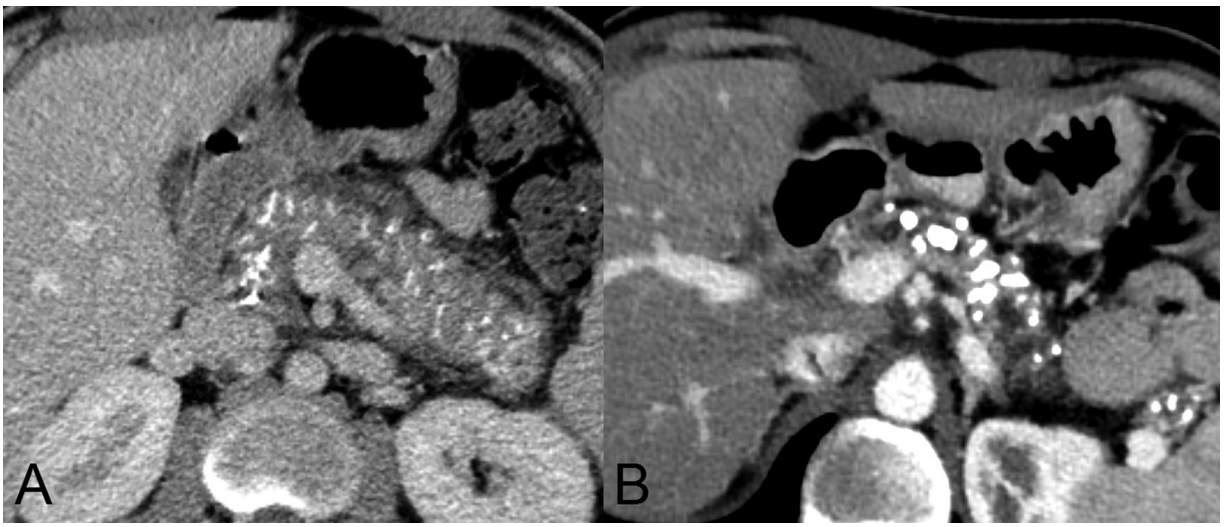

Fig. 2 CT images showing examples of types of pancreatic parenchymal calcifications. (**A**) Diffuse fine punctate calcification. (**B**) Coarse calcification.

(BioServ Analytics and Medical Devices Ltd., Rostock, Germany). The assay is a solid phase enzyme immunoassay based on double sandwich technique, which uses two polyclonal antibodies that recognize different epitopes on human pancreatic elastase sequences.[6,7,17–20] The test was conducted as per kit manufacturer's instructions. A single spot sample of stool was used for the test. A cut-off value of <100 µg elastase/g for FE1 was interpreted as indicator of severe PEI.[21,22]

Data Collection

Patient demographics, age at presentation, duration of disease, symptoms, complications, and treatment history were

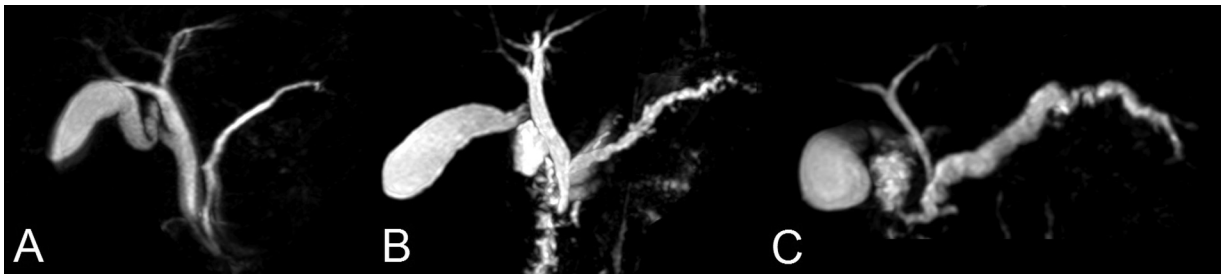

Fig. 3 MRCP images showing examples of main pancreatic duct (MPD) dilatation and contour. (**A**) Diffuse smooth dilatation of MPD. (**B**) Moderately dilated irregular MPD. (**C**) Severely dilated irregular beaded MPD. MRCP, magnetic resonance cholangiopancreatography.

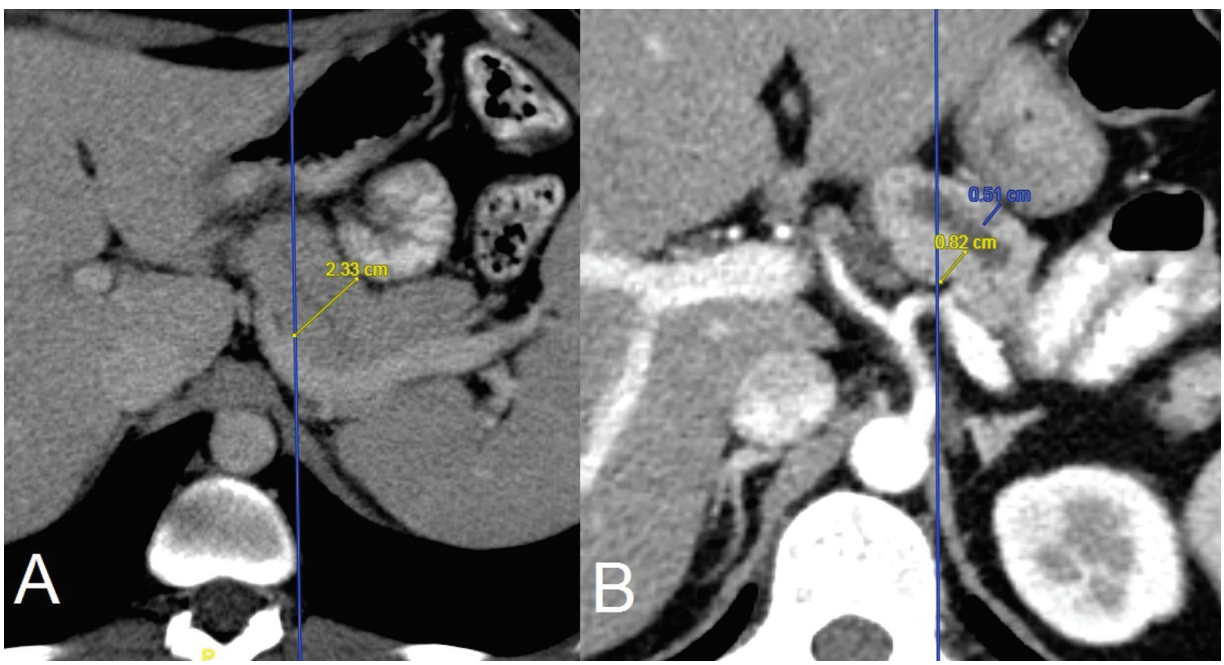

Fig. 4 Technique of measuring parenchymal thickness in the mid body of pancreas. (**A**) Parenchymal thickness is measured in an axial CT section, perpendicular to the pancreatic parenchyma, at the lateral margin of adjacent vertebral body. (**B**) In patients with dilated main pancreatic duct, duct diameter is excluded from the measurement.

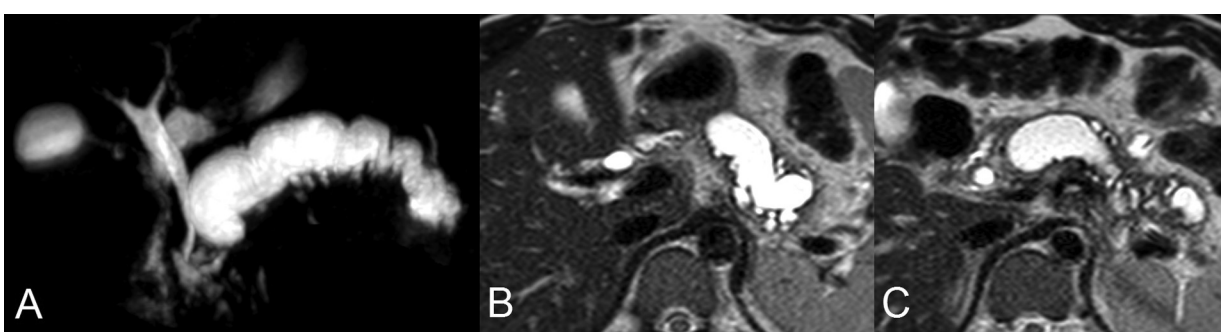

Fig. 5 (**A**) MRCP and (**B**, **C**) T2-weighted axial MR images of a patient with main pancreatic duct stenosis at the head of pancreas. Note the severe dilatation of MPD distal to the level of stenosis. MRCP, magnetic resonance cholangiopancreatography.

obtained from the clinical workstation and electronic medical records by an independent investigator blinded to imaging findings.

Statistical Analysis

For continuous data of the descriptive statistics mean (SD) was reported, and for non-normally distributed data, median (interquartile range) was reported. The categorical data was presented as number of patients and percentage. Association between imaging features and FE 1 test were tabulated and compared using one of the following tests: independent sample *t*-test, non-parametric Mann-Whitney U test, Pearsons Chi-square test or Spearman's correlation coefficient. $p < 0.05$ were considered statistically significant. The

Table 1 Association between demographic and clinical findings and fecal elastase 1 (FE-1).

	$N = 70$	FE1 <100 ($n = 50$)	FE1 >100 ($n = 20$)	p-Value
Age	24.2 ± 6.5 y	24.6 ± 6.8 y	23 ± 5.4 y	0.353
Sex	M:F = 37:33	M:F = 26:24	M:F = 7:17	0.153
BMI	21.1 ± 3.5	20.5 ± 3.4	22 ± 3.5	0.098
Age of onset of symptoms	18.5 ± 7 y	18.3 ± 7.3 y	19 ± 6.4 y	0.735
Duration of disease	5.6 ± 4.6 y	6.3 ± 5.3 y	4 ± 3 y	**0.027**
Duration of pain	64 ± 56.6	69 ± 62 mo	49.8 ± 32 mo	0.185
Duration of diabetes	31.2 ± 37.3 mo	40.7 ± 37.9 mo	1 ± 0.5 mo	**0.002**
Duration of steatorrhea	18.1 ± 21.6 mo	19.63 ± 22.6 mo	6 ± 0 mo	0.588
HB g/L	12.9 ± 2.1	12.6 ± 2.1	13.5 ± 1.9	0.106
Albumin g/dL	4.6 ± 0.48	4.58 ± 0.49	4.79 ± 0.42	0.087
Blood sugar mg/dL	120.5 ± 54.6	125.7 ± 61.8	107.62 ± 28.6	0.320
Fecal elastase1 µg/g	82.5 ± 120.11	17.42 ± 17.7	245.20 ± 112.12	

proportion of free text reports containing imaging findings significantly associated with FE1 test was presented as number and percentage. Statistical analysis was done using SPSS v.22 software (SPSS Inc., Chicago, Illinois, United States).

Results

Demographic Data

Of the 70 patients included for final analysis, 37 were males and 33 were females. Their mean age was 24.2 years with a range of 18 to 37 years; mean BMI of these patients was 21.1 kg/m^2. The mean disease duration was 5.6 years. While all patients had contrast-enhanced CT, only 32 patients had MRI/MRCP. Nearly all patients (98.6%) had complaints of pain; 25.7% of the patients had diabetes and 41.1% had steatorrhea. The mean FE 1 level was 82.5 ± 120 µg elastase/g with a range of 5 to 501 µg elastase/g. A total of 50 patients (71.4%) had low FE 1 level and the rest had normal FE 1 level.

There was no association between patient's age, gender, BMI, and age of onset of disease and the FE 1 levels. Those with low FE 1 had a significantly longer overall duration of disease ($p = 0.027$) and longer duration of diabetes ($p = 0.002$) than those with normal FE 1. ►**Table 1** summarizes the demographic data.

Association between the Imaging Findings and FE 1

►**Table 2** compares the imaging features among those with low and normal FE 1.

1. *Calcification:* There was significant association between the location, number, and the type of pancreatic calcification and the FE 1, $p < 0.05$. Significantly higher proportion of patients with low FE1 had both parenchymal and intraductal calcification (62 vs. 15%); had greater number of pancreatic calcifications (56 vs. 5%) and coarse type of calcifications (38 vs. 10%).
2. *Parenchymal thickness and distribution of disease:* There was more severe pancreatic parenchymal atrophy among those with low FE1. The mean PT of patients with low FE1 was significantly lower (12.4 ± 5.3 mm) than those with normal FE1 (17.1 ± 4.9 mm), $p = 0.001$. Also, 74% of those low FE1 had moderate to severe parenchymal atrophy (PT ≤13 mm), while only 30% of those with normal FE1 had this degree of atrophy, $p = 0.005$. There were also significant differences in the distribution of disease with greater number of those with low FE1 showing diffuse involvement of pancreas, $p = 0.005$.
3. *Pancreatic duct findings:* There was a significant association between the diameter of MPD and FE1, $p < 0.001$. Those with low FE1 had a significantly wider MPD diameter with a mean of 8.2 ± 4.2 mm compared with 4.2 ± 1.7 mm among those with normal FE1. Though 78% of patients with low FE1 had moderate to severe MPD dilatation, such degree of MPD dilatation was also seen among 50% of those with normal FE1. There was no association between FE1 and the morphology of MPD, i.e., MPD irregularity or stricture. There was a strong association between FE1 and the presence of intraductal calculus, $p < 0.001$. The majority (90%) of those with normal FE1 had no intraductal stones. Around 64% of the patients with low FE1 had intraductal stones and they were more common in the head and neck region of pancreas. But there was no association between FE1 and the size of intraductal stones. The majority (85.7%) of patients with low FE1 had dilatation of greater than three side branches of pancreatic duct. There was no association between FE1 and pancreatic duct anomalies.
4. *Complications:* Complications such as pseudocysts ($n = 6$), CBD stricture ($n = 4$), portal vein thrombosis ($n = 6$), and pancreatic cancer ($n = 1$) were seen in our cohort. However, no association could be established between these complications and FE1.

Table 2 Association between imaging findings and fecal elastase 1 (FE 1)

Imaging findings	$N = 70$ (%)	FE1 <100 ($n = 50$)*	FE1 >100 ($n = 20$)*	*p*-Value
Calcification				
Location of calcification				
No calcification	18 (25.7)	10 (20)	8 (40)	0.001
Parenchymal	18 (25.7)	9 (18)	9 (45)	
Both parenchymal and intraductal	34 (48.5)	31 (62)	3 (15)	
Number of calcifications				
None	18 (25.7)	9 (18)	9 (45)	0.001
Few punctate (<7)	2 (2.9)	1 (2)	1 (5)	
7–49 punctate	21 (30.0)	12 (24)	9 (45)	
Innumerable	29 (41.4)	28 (56)	1 (5)	
Type of calcification				
None	18 (25.7)	9(18)	9 (45)	0.025
Coarse	21 (30.0)	19 (38)	2 (10)	
Fine specks	12 (17.1)	7 (14)	5 (25)	
Mixed	19 (27.1)	15 (30)	4 (20)	
Parenchymal thickness and distribution of disease				
Pancreatic parenchymal thickness (mm)	13.7 ± 5.5	12.4 ± 5.3	17.1 ± 4.9	0.001
Parenchymal thickness (mm)				
≥21 mm	11 (15.7)	6 (12)	5 (25)	0.005
14–20 mm	16 (22.9)	7 (14)	9 (45)	
7–13 mm	36 (51.4)	30 (60)	6 (30)	
< 7 mm	7 (10.0)	7 (14)	0	
Distribution of findings				
Normal	2 (2.9)	2 (4)	0	0.005
< 30%	1 (1.4)	0	1 (5)	
30–70%	6 (8.6)	1 (2)	5 (25)	
> 70%	61 (87.1)	47 (94)	14 (70)	
Pancreatic duct				
MPD (mm)	7.1 ± 4.1	8.2 ± 4.2	4.2 ± 1.7	0.000
MPD caliber				
Normal	13 (18.6)	8 (16)	5 (25)	0.007
Mild (<3.5 mm)	8 (11.4)	3 (6)	5 (25)	
Moderate (3.5– 7 mm)	26 (37.1)	17 (34)	9 (45)	
Severe (>7 mm)	23 (32.9)	22 (44)	1 (5)	
MPD contour				
Smooth	7 (10)	3 (6)	4 (20)	0.300
Mildly irregular	12 (17.1)	8 (16)	4 (20)	
Very irregular	40 (57.1)	31 (62)	9 (45)	
MPD stricture	9 (12.9)	7 (14)	2 (10)	
Tail/body	4	4	0	0.495
Head/neck	5	3	2	0.746
Intraductal calculus				
Yes	34 (48.6)	32 (64)	2 (10)	0.000

(*Continued*)

Table 2 (*Continued*)

Imaging findings	*N* = 70 (%)	FE1 <100 (*n* = 50)*	FE1 >100 (*n* = 20)*	*p*-Value
No	36 (51.4)	18 (36)	18 (90)	
Intraductal calculus size (mm)	16.1 ± 8.35	16.4 ± 8.5	11 ± 4.2	0.383
Intraductal calculus site				
Tail/body	9 (12.8)	5 (10)	0	0.004
Head/neck	25 (35.7)	23 (46)	2 (10)	
Diffuse	8 (11.4)	8 (16)	0	
Side branch dilatation on MRI				
Not dilated	6 (8.6)	2 (9.5)	4 (36.4)	0.055
< 3 side branches	3 (4.3)	1 (48)	2 (18.2)	
> 3 side branches	23 (32.9)	18 (85.7)	5 (45.5)	
PD anomaly				
Absent	65 (92.9)	48 (96)	17 (85)	0.137
Present	5 (7.1)	2 (4)	3 (15)	

*Results are in N (%).

Proportion of Free Text Reports Which Mention Findings Associated with FE1

►**Table 3** summarizes the proportion of free text radiology reports which mention findings that were associated with FE1. While the majority of free text reports mentioned presence of parenchymal calcification (84.2%), parenchymal atrophy (72.5%), MPD caliber (81.2%), and the presence of intraductal calculi (81.2%), only fewer reports (30% or less) mentioned grade for parenchymal atrophy, PT, and the distribution of disease. None of the reports mentioned the presence or absence of pancreatic duct stenosis (►**Fig. 5**).

Discussion

In this study of 70 patients with idiopathic CP, we could demonstrate strong association between imaging findings and FE1. Those with low FE1 more commonly had both parenchymal and intraductal calcification, more numbers of calcific foci, coarse parenchymal calcification, more severe MPD dilatation, moderate to severe parenchymal atrophy, greater than three side branches dilatation, and diffuse pancreatic involvement, $p < 0.05$. Our results thus demonstrate promising role of imaging findings seen on routine CT/MRI in predicting PEI.

Lankisch et al[21] in their study of 79 patients with CP showed no significant association between pancreatic calcification and severe exocrine insufficiency. In our study, though significantly higher number of patients with low FE1 had innumerable and coarse type of calcifications, the absence of calcifications did not rule out severe PEI. Around 55% patients with low FE1 had no parenchymal and ductal calcifications. Similarly, around 50% of patients with normal FE1 also showed severe MPD dilatation and parenchymal atrophy. Thus, these results suggest that imaging and FE1 test are more likely to be complimentary tests rather than supplementary.

Studies[11,14,23,24] have shown that pancreatic volume is decreased in patients with exocrine/endocrine insufficiency and that CP can be diagnosed based on atrophy, parenchymal heterogeneity, calcifications, duct irregularities, and/ or duct dilatation. While most free text radiology reports of our study cohort had mentioned pancreatic calcification, duct dilatation, intraductal calcification, and parenchymal atrophy, reports infrequently mentioned pancreatic PT or the degree of pancreatic parenchymal atrophy and the distribution of disease. Most patients who have a combination of pancreatic exocrine and endocrine insufficiency, the body of pancreas is the first to reduce in anteroposterior dimension compared with the rest of pancreas. Thus, it is useful to mention pancreatic PT at mid body of pancreas in radiology reports. At the same time we need to be aware about age-related variations in the thickness of pancreas. For example, pancreatic PT of 14 mm may be normal among elderly, but the same may be atrophic for young patients.[25,26] As per study done by Sato et al,[25] 15.76 mm was considered as the mean normal PT in the pancreatic body taken in anteroposterior dimension between 20 and 39 years of age, 14.90 mm among patients aged 40 to 59 years, 13.96 mm for 60 to 79-year-old patients, and 12.36 mm for patients above 80 years. Heuck et al[26] also had similar findings with 19.1 mm being normal pancreatic body thickness for 20 to 30 years, 18.2 mm for 31 to 40 years, 17.8 mm for 41 to 50 years,15.8 mm for 41 to 50 years, and 14.4 mm for 71 to 80 years.

Bilgin et al[27] in their recent study compared MRI and MRCP findings of pancreas in patients with diabetes mellitus with or without PEI, which was determined by low fecal elastase levels. Their study showed that majority (79%) of patients with combined diabetes and PEI had more than three abnormal side branches. Our results were similar with 78% of the patients with low FE1 having greater than three dilated side branches of pancreatic duct.

Table 3 Proportion of free text reports which mention imaging findings which were significantly associated with pancreatic exocrine insufficiency

Item	*N*	Proportion of free text reports with finding
Parenchymal calcification	59	84.2%
Parenchymal atrophy	51	72.5%
Grade of parenchymal atrophy	22	30.4%
Pancreatic parenchymal thickness	2	2.9%
MPD caliber	57	81.2%
Intraductal stones	57	81.2%
Distribution of disease	20	28.5%
PD stenosis	0	0%

Our study was limited by the use of a less than an optimal diagnostic test for PEI such as FE1 since FE1 has a low sensitivity for mild to moderate exocrine pancreatic insufficiency. But the study was aimed at identifying severe PEI and the range of FE1 was chosen appropriately. Secondly, a structured proforma to assess imaging findings during a re-reading session may have influenced the radiologist's focus in identifying certain features such as pancreatic duct stenosis. Thirdly, only half the number of patients had MRI and the studies only had MRCP and T2-weighted images. Thus, evaluation did not completely conform to recommendations of CPDPC. Fourthly, our study is prone to clinical selection bias since some patients who may have been treated by other departments such as endocrinology and diabetology and those with potentially milder disease may not have had imaging and thus may not have entered the study. Lastly, there are several genetic causes for hypoplastic pancreas and low FE1. Since this is a retrospective study and genetic testing is not being routinely done, this may have added to clinical selection bias. Thus, larger multicentric studies may be needed to confirm findings of this study.

In conclusion, through this preliminary study, we have shown significant association between multiple imaging findings on CT/MRI and FE1 demonstrating its potential as a marker of exocrine insufficiency in patients with idiopathic CP. But imaging and FE1 tests are complementary rather than supplementary. We have also demonstrated the need for incorporating standard definitions and checklists for routine radiology reporting of CP.

Ethics Approval and Consent to Participate
IRB approval was taken, IRB Min. 14019.
Being a retrospective study, consent was waived.

Conflict of Interest
None declared.

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