Comprehensive, long-term evaluation of pancreatic exocrine insufficiency after pancreatoduodenectomy

Powell-Brett, Sarah; Halle-Smith, James M; Hall, Lewis A; Hodson, James; Phillips, Mary E; Roberts, Keith J

DOI:
10.1016/j.pan.2023.11.016

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Powell-Brett, S, Halle-Smith, JM, Hall, LA, Hodson, J, Phillips, ME & Roberts, KJ 2024, 'Comprehensive, long-term evaluation of pancreatic exocrine insufficiency after pancreatoduodenectomy', *Pancreatology*, vol. 24, no. 2, pp. 298-305. https://doi.org/10.1016/j.pan.2023.11.016

Pancreatology 24 (2024) 298–305

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Comprehensive, long-term evaluation of pancreatic exocrine insufficiency after pancreatoduodenectomy

Sarah Powell-Brett [a, b, *], James M. Halle-Smith [a, b], Lewis A. Hall [a, b], James Hodson [c], Mary E. Phillips [d], Keith J. Roberts [a, b]

[a] Department of Hepatobiliary, Pancreatic and Transplant Surgery, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[b] School of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
[c] Research Development and Innovation, Institute of Translational Medicine, University Hospitals Birmingham NHS Foundation Trust, UK
[d] University of Surrey, School of Biosciences and Medicine, UK

ARTICLE INFO

Article history:
Received 29 September 2023
Received in revised form
21 November 2023
Accepted 22 November 2023
Available online 12 December 2023

Keywords:
Pancreatic function
Exocrine pancreatic insufficiency
^{13}C breath test

ABSTRACT

Aims: Treatment of pancreatic exocrine insufficiency (PEI) following pancreatoduodenectomy (PD) improves quality of life, clinical outcomes, and survival. However, diagnosing PEI following PD is challenging owing to the difficulties with current tests and often non-specific symptoms. This work aims to quantify the true rate of long-term PEI in patients following a PD.

Methods: Patients underwent a PEI screen approximately one to two years following PD for oncologic indication, including the ^{13}C Mixed triglyceride breath test (^{13}CMTGT), faecal elastase 1 (FE-1) and the PEI Questionnaire (PEI-Q). Four reviewers with expertise in PEI reviewed the results blinded to other decisions to classify PEI status; disagreements were resolved on consensus.

Results: 26 patients were recruited. Of those with valid test results, these were indicative of PEI based on pre-specified thresholds for 60 % (15/25) for the ^{13}CMTGT, 82 % (18/22) for FE-1, and 88 % (22/25) for the PEI-Q. After discussion between reviewers, the consensus PEI prevalence was 81 % (95 % CI: 61–93 %; 21/26), with 50 % (N = 13) classified as having severe, 23 % (N = 6) moderate, and 8 % (N = 2) mild PEI.

Discussion: Since no ideal test exists for PEI, this collation of diagnostic modalities and blinded expert review was designed to ascertain the true rate of long-term PEI following PD. This required our cohort to survive a year, travel to hospital, and undergo a period of starvation and PERT hold, and therefore there is likely to be recruitment bias towards fitter, younger patients with less aggressive pathology. Despite this, over 80 % were deemed to have PEI, with over 90 % of these being considered moderate or severe.

1. Introduction

The prevalence of pancreatic exocrine insufficiency (PEI) following pancreaticoduodenectomy (PD) is difficult to define, due to heterogeneity of the current literature. A 2016 systematic review and meta-analysis based mainly on faecal elastase 1 (FE-1) reported a PEI prevalence of 74 %, whilst a later review, expanded to include studies that use symptom assessment alone returned a lower prevalence of 43 %, and a more recent cohort study using the ^{13}C-mixed triglyceride breath test (^{13}CMTGT) at six-weeks post PD reported a prevalence of 68 % [1–3]. The variability in the reported prevalence is likely a result of studies being limited by small sample sizes, variable (often short) follow-up intervals, and heterogenous modalities of diagnosis. Despite good evidence that treatment with PERT improves post-operative outcomes, access to adjuvant treatment, quality of life and even survival, PEI is often underdiagnosed and undertreated; part of the reason for this is the unsatisfactory nature of current diagnostic tests [4–6].

In the non-operated patient with pancreatic cancer, it is recognised that PEI is progressive. However, there is currently limited evidence for the operated patient, due to a paucity of studies with longer-term follow-up. Here, we present a multi-modal assessment of PEI in patients up to two years post PD. The aim of this study is to clarify the long-term prevalence of PEI following PD for oncologic indications. Given that current diagnostic tests, including the ^{13}CMTGT, are limited in their accuracy, this study used a battery of

* Corresponding author. Department of Hepatobiliary, Pancreatic and Transplant surgery. 3rd floor, Nuffield House, University Hospital Birmingham. Mendelsohn way, Edgbaston, Birmingham, B15 2GW, UK.
E-mail address: Sarah.powell-brett1@nhs.net (S. Powell-Brett).

https://doi.org/10.1016/j.pan.2023.11.016

three tests, which underwent blinded review by experts, to provide consensus for each patient's PEI status.

2. Methods

2.1. Study design

The cohort used in the present study was a subgroup of the patients recruited as part of the larger DETECTION trial (The DEvelopmenT of a mEtabolomiC Test to dIagnOse and quantify paNcreatic exocrine insufficiency - NCT05980221), which was a prospectively registered study investigating PEI diagnosis. This part of the DETECTION trial recruited patients undergoing PD for malignant indication between September 2018 and December 2020. The present study approached these patients between September 2020 and December 2021, approximately one to two years post-operatively, with a view to estimating the prevalence of PEI. The exclusion criteria were: age under 18 years, pregnancy, medications that may affect gastric emptying, active infection, currently receiving chemotherapy, too frail to complete the assessments, or undergoing any other upper gastrointestinal operations (other than PD). All patients recruited provided written, informed consent, and the DETECTION trial was approved prospectively by the Health Research Authority through the West Midlands - Black Country Research Ethics Committee (19/WM/0358).

2.2. PEI assessments

All patients were given an information pack and pre-test instructions at the time of recruitment, and asked to attend for a single study day, at which three markers of PEI were assessed. The information pack included the Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) [7], the mean symptom score of which was used for analysis. Patients were also asked to provide a stool sample on attendance, which was used to test FE-1 levels. The final marker was the ^{13}CMTGT. Patients were asked to refrain from ingesting foods rich in ^{13}Carbon (corn products, cane sugar, pineapple, kiwi, broccoli, or sweetcorn) for 48 h preceding the start of this test, and were asked to fast (except for small volumes of water) and refrain from smoking for the 12 h preceding the test. Patients on PERT were asked not to take this on the day before the study day, with the final dose being at the evening meal on the preceding day (i.e. approximately 36 h before the ^{13}CMTGT assessment). Breath samples were collected by blowing through a straw into an inverted exetainer (Exetainer®; Labco Limited, High Wycombe, UK) and immediately capping. Patients attended 30 min before the test start time, to allow their heart rate and temperature to settle. Baseline breath samples were then taken, and a standardised, high-fat test meal incorporating 250 mg of ^{13}C-mixed triglyceride (weighed on a five-figure balance) was ingested over a maximum of 5 min at 8am. Repeat samples were then taken over a total period of 6 h. Patients remained sedentary and fasted for the duration of the test. The $^{13}CO_2$ content of the breath samples was determined by gas chromatography isotope ratio mass spectrometry (GC-IRMS). Enrichment of $^{13}CO_2$ in the post-test meal samples was calculated by subtracting the abundance of $^{13}CO_2$ in the baseline sample from that of each post-test meal sample. The percentage dose of ^{13}C recovered (PDR) for each sample was calculated using the below equation (with VCO_2 predicted using the formula by Shreeve et al.) [8].

$$PDR\ h^{-1} = \frac{VCO_2\left(mmol.h^{-1}\right)\ x\ Breath\ CO_2\ enrichment\ (ppm\ 13C\ excess) x\ 100}{Tracer\ dose\ (mmol)\ x\ Tracer\ enrichment\ \left(atom\ \%\ excess\ x\ 10^4\right)}$$

The cumulative PDR over 6 h (^{13}CMTGT-cPDR) was then calculated by adding individual PDR values averaged over the time interval.

2.3. PEI diagnosis

The results of the PEI-Q, FE-1 and ^{13}CMTGT-cPDR assessments were then sent to four reviewers, to determine the PEI status of each patient. The reviewers each had expertise and experience in PEI, but from different backgrounds, namely: 1) a consultant hepato-pancreato-biliary surgeon with a specialist interest in PEI; 2) an expert dietician, who led the UK consensus guidelines for PEI management; 3) a senior hepato-pancreato-biliary registrar currently undertaking a PhD in PEI diagnostics; and 4) a junior doctor with a BSc in PEI diagnostics. Reviewers were asked to determine whether the assessments were indicative of PEI, and to quantify the severity of PEI on a four-point scale (none, mild, moderate, or severe) for each patient, blinded to the decisions of the other reviewers. Reviewers were provided with suggested diagnostic criteria for each assessment for reference, but were free to deviate from these. Specifically, a ^{13}CMTGT-cPDR of $\leq$29 % was considered diagnostic for PEI [9,10]; FE-1 of <100, 100–200 and > 200 μg/g were classified as severe PEI, mild-moderate PEI and normal, respectively [11]; and PEI-Q mean symptom scores of <0.60, 0.60–1.39, 1.40–1.79, and ≥1.80 were classified as normal, mild PEI, moderate PEI and severe PEI, respectively [7].

The PEI status for each patient was then compared across reviewers, to assess inter-reviewer consistency. For patients where there were disagreements, reviewers were then provided additional information; namely patient's PERT dosing, responsiveness to the PERT hold for the study day, and post-operative CT reports; and discussed the patient until a consensus on the PEI status was reached. The consensus PEI severity grade was calculated by taking the mean across the four reviewers (coded as 0 = normal, 1 = mild, 2 = moderate and 3 = severe PEI), which was rounded to the nearest integer.

2.4. Data collection

In addition to the PEI assessments, data were collected for a range of demographic and operative factors. Pre-operative CT scans were assessed to measure the pancreatic duct width. Patient co-morbidities were collected via a questionnaire on the study day,

from which the Charlson Comorbidity Index was calculated [12]. Patients' weights were also collected both at the pre-operative assessment and the study day, from which the body mass index (BMI) was calculated.

2.5. Statistical methods

Inter-rater consistency of PEI severity grading was quantified using an intra-class correlation coefficient (ICC), with a two-way random-effects model of absolute agreement. In addition, the percentage agreement was calculated by comparing the severity grades made by each pair of reviewers for each patient. Comparisons between the consensus PEI diagnosis and non-PEI groups were performed using Mann-Whitney U tests for ordinal or continuous variables, or Fisher's exact tests for nominal variables. Correlations between PEI assessments were assessed using Spearman's correlation coefficients (rho).

All analyses were performed using IBM SPSS 24 (IBM Corp. Armonk, NY), with $p < 0.05$ deemed to be indicative of statistical significance throughout. Continuous variables are summarised as *median (interquartile range; IQR)*, and prevalences/ICCs are reported alongside 95 % confidence intervals (95 % CIs). Missing data were handled using pairwise deletion, with cases only being excluded from analyses of the affected factor.

3. Results

3.1. Cohort characteristics

A total of N = 114 patients underwent PD for an oncologic indication between September 2018 and December 2020, and were assessed for study eligibility. Of these, N = 57 were excluded due to having died, being on palliative chemotherapy, or being unsuitable to approach due to being too frail or unwell; N = 4 were not contactable. The remaining N = 53 were deemed eligible for approach, with N = 26 declining after having read and discussed the information leaflet, mostly due to travel logistics, or the need for repeated blood samples. The remaining N = 27 consented to involvement in the study (Fig. 1). Of these, one patient did not attend the study day, as they had developed metastatic disease and commenced chemotherapy after consenting, hence were no longer eligible for inclusion, leaving N = 26. These patients had a median age at the time of surgery of 69 years (IQR: 62–73), with histologies of pancreatic ductal adenocarcinoma (PDAC; 69 %), ampullary cancer (15 %), cholangiocarcinoma (8 %), intraductal papillary mucinous neoplasm (4 %) and pancreatic neuroendocrine tumour (pNET) (4 %). Most patients underwent pylorus preserving PD (rather than classical PD; 77 %); the study day was a median of 15 months (IQR: 12–21; range: 8–27) post-resection. All patients were being treated with PERT, although this was paused for the study day, to allow for the PEI assessments to be performed. Further details of the cohort are reported in Table 1.

3.2. PEI prevalence

All N = 26 patients completed the ^{13}CMTGT-cPDR; however, one patient was unable to refrain from smoking for the duration, hence their ^{13}CMTGT-cPDR was excluded from analysis, leaving N = 25. FE-1 levels were reported for N = 22 patients, with two samples not being processed due to problems with laboratory services related to the COVID-19 pandemic, one patient being unable to produce a sample, and one sample being too liquid to assay. The PEI-Q was completed by N = 25; the remaining patient did not return their questionnaire during the study day. All patients had data recorded for at least two of the three PEI assessments, with N = 6 having two and N = 20 having three assessments for analysis.

After evaluating the PEI assessments, the four reviewers gave concordant PEI statuses for 92 % (24/26) of patients. Of the two patients where consensus was not achieved, the first was classified as not having PEI by three reviewers, with the remaining reviewer diagnosing mild PEI. This patient had a ^{13}CMTGT-cPDR of 42.0 %, and a FE-1 of 238 μg/g; PEI-Q data were not available. Further review

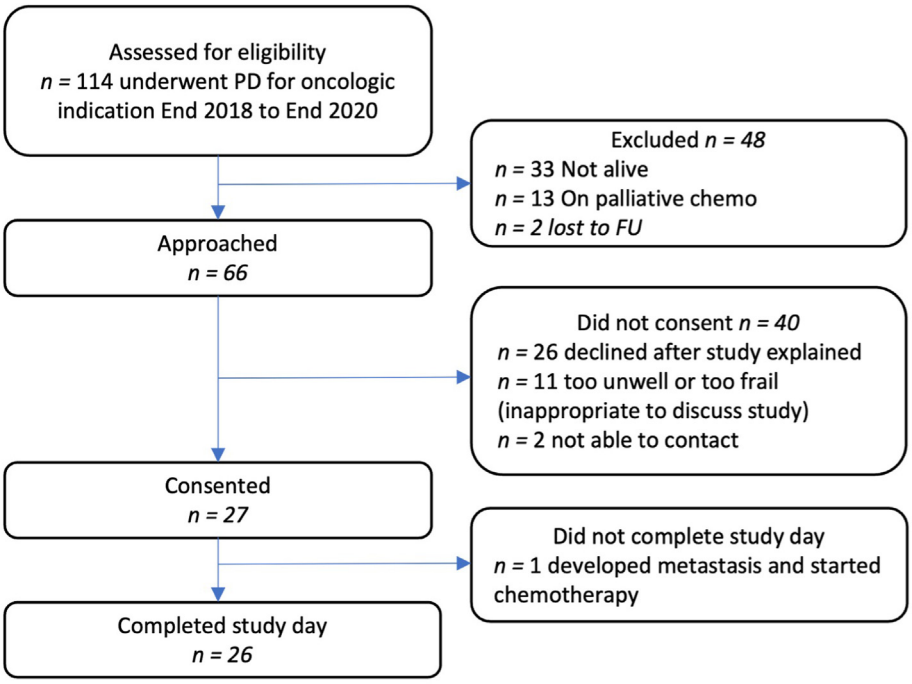

Fig. 1. Study inclusion flowchart
Abbreviations: PD = pancreatoduodenectomy.

Table 1
Cohort characteristics.

	Whole Cohort		Consensus PEI Diagnosis		
	N	Statistic	No (N = 5)	Yes (N = 21)	p-Value
At Time of Surgery					
Age at Surgery (Years)	26	69 (62, 73)	58 (54, 73)	69 (66, 73)	0.313
Sex (% Male)	26	18 (69 %)	4 (80 %)	14 (67 %)	1.000
Histology	26				**0.029**
PDAC		18 (69 %)	1 (20 %)	17 (81 %)	
Ampullary		4 (15 %)	2 (40 %)	2 (10 %)	
Cholangiocarcinoma		2 (8 %)	1 (20 %)	1 (5 %)	
Others		2 (8 %)	1 (20 %)	1 (5 %)	
Pancreatic Duct Width*					
Width (mm)	25	5 (2, 7)	2 (1, 3)	6 (3, 8)	**0.026**
Dilated (>3 mm)	26	16 (62 %)	1 (20 %)	15 (71 %)	0.055
Type of Surgery	26				0.298
Classical PD		6 (23 %)	0 (0 %)	6 (29 %)	
Pylorus preserving PD		20 (77 %)	5 (100 %)	15 (71 %)	
On Study Day					
Days from Surgery to Study Day	26	452 (375, 650)	579 (542, 650)	422 (375, 586)	0.536
Charlson Comorbidity Index	26	3 (2, 3)	1 (1, 3)	3 (2, 3)	0.318
Smoker	26				1.000
Non-		22 (85 %)	5 (100 %)	17 (81 %)	
Ex-		2 (8 %)	0 (0 %)	2 (10 %)	
Current		2 (8 %)	0 (0 %)	2 (10 %)	
Adjuvant Chemotherapy	26	22 (85 %)	4 (80 %)	18 (86 %)	1.000
Weight (kg)					
Pre-operative	26	77.2 (69.5, 83.4)	83.4 (81.7, 104.1)	75.1 (69.4, 78.0)	**0.010**
Study Day	26	66.4 (59.0, 82.3)	90.0 (82.0, 102.0)	63.5 (58.0, 70.0)	**0.004**
*Change***	26	−6.4 (−10.7, −4.0)	−1.4 (−2.4, 8.9)	−8.1 (−11.6, −6.0)	**0.002**
BMI (kg/m^2)					
Pre-operative	26	25.9 (23.9, 28.9)	30.3 (30.0, 33.6)	25.5 (23.6, 26.7)	**0.005**
Study Day	26	23.2 (20.8, 27.1)	29.8 (29.1, 33.7)	22.6 (20.0, 23.8)	**0.001**
*Change***	26	−2.2 (−3.6, −1.3)	−0.5 (−0.8, 2.9)	−2.6 (−4.0, −1.9)	**0.004**

Data are reported as median (interquartile range), with p-values from Mann-Whitney U tests, or as N (%), with p-values from Fisher's exact tests. Bold p-values are significant at $p < 0.05$. *On the pre-operative CT scan. **The change from the pre-operative assessment to the study day. Abbreviations: BMI = body mass index, PD = pancreaticoduodenectomy, PDAC = pancreatic ductal adenocarcinoma, PEI = pancreatic exocrine insufficiency.

found that they were receiving low dose PERT and had no definitive symptoms of PEI after a PERT hold for the study day; hence, they were classified as not having PEI after discussion. The second patient was classified as not having PEI by two reviewers, with the other two reviewers diagnosing mild and moderate PEI, respectively. This patient had a ^{13}CMTGT-cPDR of 38.2 %, which was not indicative of PEI using the pre-specified thresholds, but had a PEI-Q of 1.82, indicating severe PEI; FE-1 data were not available. Further review found that the patient developed significant symptoms and clinical steathorrhoea after a PERT hold for the study day; hence, was diagnosed with PEI after discussion. Consequently, the prevalence of PEI in this cohort was 81 % (95 % CI: 61–93 %; 21/26).

Reviewers additionally quantified the severity of PEI on a four-point scale. High levels of consistency were observed, with an ICC of 0.90 (95 % CI: 0.82–0.95), and 76 % (118/156) pairs of assessments having concordant PEI severities. Where there were discrepancies, these were generally differences of one severity grade, most commonly between moderate vs. severe PEI (Table 2). Averaging the grades across reviewers to produce a consensus grade for each patient found that 50 % (N = 13) of the cohort were classified as having severe PEI, with 23 % (N = 6) moderate, and 8 % (N = 2) mild.

Table 2
Consistency of PEI grading.

Reviewer 1	Reviewer 2			
	None	Mild	Moderate	Severe
None	28			
Mild	5	**6**		
Moderate	2	6	**20**	
Severe	0	1	24	**64**

Results are based on comparisons of each pair of reviewers, hence N = 156 (i.e. N = 26 patients times N = 6 permutations of four reviewers). Where there were discrepancies between reviewers, the direction of the difference was standardised, such that "Reviewer 1" was deemed to assign the higher PEI severity grade than "Reviewer 2". Bold values indicate cases where the pair of reviewers gave consistent grades. Abbreviations: PEI = pancreatic exocrine insufficiency.

3.3. Cohort characteristics by consensus PEI status

Patients with a consensus PEI diagnosis had significantly greater pancreatic duct width on pre-operative CT, with a median of 6 mm (IQR: 3–8) compared to 2 mm (IQR: 1–3) in those without PEI ($p = 0.026$, Table 1). PEI was also significantly more common in patients with PDAC, compared to other histologies (94 % [17/18] vs. 50 % [4/8], $p = 0.029$). Patients with PEI had significantly lower BMI at the pre-operative assessment (median: 25.5 vs. 30.3 kg/m^2, $p = 0.005$), which was followed by a significant greater reduction in BMI between the pre-operative assessment and the study day (median reduction: 2.6 vs. 0.5 kg/m^2, $p = 0.004$).

3.4. Comparisons between PEI assessments

The distributions of each of PEI assessment for the cohort as a whole, as well by PEI status are reported in Table 3, and Figs. 2 and 3. For FE-1, the pre-specified threshold of ≤200 μg/g yielded a PEI rate of 82 % (18/22). This threshold was consistent with the consensus diagnosis for all but one patient, who was deemed not to have PEI, despite an FE-1 of 200 μg/g. The highest observed FE-1 in a patient with PEI was 143 μg/g; hence, a threshold within the range 143–200 μg/g (e.g. 170 μg/g) would result in concordance with the consensus diagnosis of PEI for all patients in this cohort.

Table 3
PEI assessments.

	Whole Cohort		Consensus PEI Diagnosis	
	N	Statistic	No	Yes
FE-1 (μg/g)	22	92 (21, 143)	238 (225, 500)	62 (15, 98)
<100 (Severe PEI)		13 (59 %)	0 (0 %)	13 (76 %)
100–200 (Mild-Moderate PEI)		5 (23 %)	1 (20 %)	4 (24 %)
>200 (Normal)		4 (18 %)	4 (80 %)	0 (0 %)
^{13}CMTGT-cPDR (%)	25	27.8 (25.7, 31.1)	47.6 (42.0, 56.3)	27.4 (22.3, 29.1)
≤29 % (PEI)		15 (60 %)	0 (0 %)	15 (75 %)
>29 % (Normal)		10 (40 %)	5 (100 %)	5 (25 %)
PEI-Q	25	1.55 (1.13, 1.82)	0.55 (0.28, 0.97)	1.68 (1.49, 1.84)
<0.60 (Normal)		3 (12 %)	2 (50 %)	1 (5 %)
0.60-1.39 (Mild PEI)		6 (24 %)	2 (50 %)	4 (19 %)
1.40-1.79 (Moderate PEI)		8 (32 %)	0 (0 %)	8 (38 %)
≥1.80 (Severe PEI)		8 (32 %)	0 (0 %)	8 (38 %)

Average values are reported as median (interquartile range). Each assessment is also divided into categories based on the pre-specified diagnostic thresholds, with the proportion of patients in each category reported. Abbreviations: ^{13}CMTGT-cPDR = ^{13}C mixed triglyceride breath test-cumulative percentage dose recovered, FE-1 = faecal elastase 1, PEI = pancreatic exocrine insufficiency, PEI-Q = pancreatic exocrine insufficiency questionnaire mean symptom score.

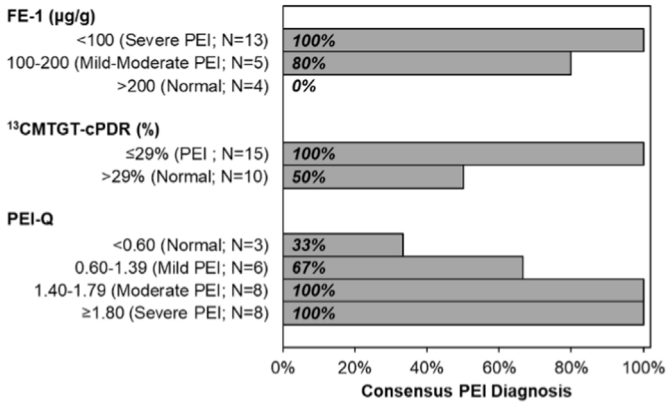

Fig. 2. PEI rates by PEI assessment diagnostic criteria
Abbreviations: ^{13}CMTGT-cPDR = ^{13}C mixed triglyceride breath test-cumulative percentage dose recovered, FE-1 = faecal elastase 1, PEI = pancreatic exocrine insufficiency, PEI-Q = pancreatic exocrine insufficiency questionnaire mean symptom score.

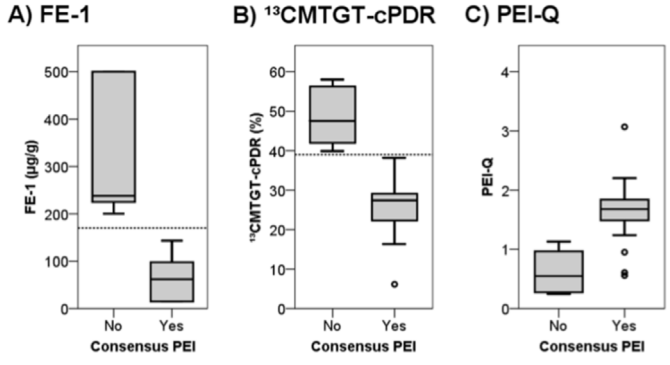

Fig. 3. Association between PEI assessments and consensus PEI diagnosis
Points indicate outliers as defined by Tukey's Fences method, namely cases that were above the upper quartile or below the lower quartile by > 1.5 times the interquartile range. Broken lines are plotted at the thresholds that perfectly divide the consensus PEI diagnosis and non-PEI groups in this cohort, namely FE-1 = 170 μg/g and ^{13}CMTGT-cPDR = 39 %; this was not possible for PEI-Q. Abbreviations: ^{13}CMTGT-cPDR = ^{13}C mixed triglyceride breath test-cumulative percentage dose recovered, FE-1 = faecal elastase 1, PEI = pancreatic exocrine insufficiency, PEI-Q = pancreatic exocrine insufficiency questionnaire mean symptom score.

For ^{13}CMTGT-cPDR, the pre-specified threshold of ≤29 % yielded a PEI rate of only 60 % (15/25). Whilst all N = 15 patients below this threshold had a consensus diagnosis of PEI, 50 % (5/10) of those with "normal" ^{13}CMTGT-cPDR also had a consensus diagnosis of PEI. All of those with a "normal" ^{13}CMTGT-cPDR that were diagnosed with PEI after panel review had FE-1 levels <200 μg/g (except for one patient, where FE-1 was unavailable), which was the main rationale for the consensus PEI diagnosis. However, in four of these patients, the ^{13}CMTGT-cPDR were only marginally above the pre-specified threshold (values of 29.3 %, 29.4 %, 29.5 % and 31.1 %, respectively), with the final patient having a ^{13}CMTGT-cPDR of 38.2 %. As such, a small increase of the ^{13}CMTGT-cPDR threshold to ≤32 % would yield agreement with the consensus PEI diagnosis of 96 % (24/25), whilst a threshold of ≤39 % would result in 100 % agreement in this cohort (since the lowest ^{13}CMTGT-cPDR in the non-PEI group was 39.9 %).

Finally, for PEI-Q, the pre-specified threshold score of ≥0.6 resulted in a PEI rate of 88 % (22/25). This threshold was inconsistent with the consensus PEI diagnosis in N = 3 patients, with one patient having a consensus diagnosis of PEI despite a score of 0.56, and two patients being in the non-PEI group despite scores of 0.80 and 1.13, respectively. Unlike the other two assessments, it was not possible to define a diagnostic threshold for PEI-Q that would be concordant with the consensus diagnosis of PEI in all cases.

Comparisons between the assessments found strong correlations between ^{13}CMTGT-cPDR and both FE-1 (rho: 0.68) and PEI-Q (rho: −0.64); however, FE-1 and PEI-Q were only moderately correlated (rho: −0.36, Fig. 4).

4. Discussion

The aim of this study was to determine the prevalence of PEI in the years following PD for oncologic indication. The key finding is that the long-term (median: 15 months post-resection) prevalence of PEI after oncologic PD is over 80 %. Diagnoses of PEI were generally consistent across the four reviewers. Of the three PEI assessments used, the ^{13}CMTGT-cPDR and FE-1 tests showed strong correlation, both with each other, and with the consensus PEI status; however, the PEI-Q showed poorer performance in both regards. Additional findings are that long-term PEI was associated with significantly larger pre-operative pancreatic duct width, and significantly lower pre-operative BMI. Concerningly, PEI was also associated with considerable weight loss in the post-operative period, despite all patients being treated with PERT, suggesting that there is a degree of undertreatment for PEI.

The prevalence of PEI following resection is challenging to ascertain and is likely underestimated. Due to the relative rarity of

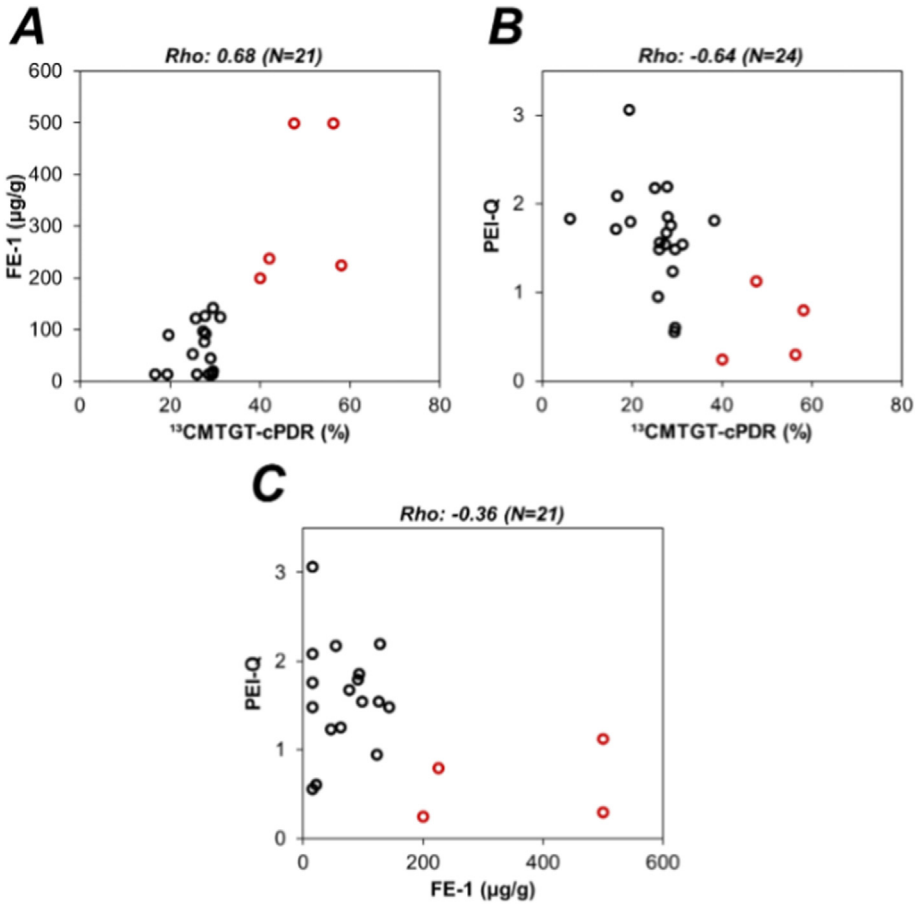

Fig. 4. Associations between PEI assessments
Only those patients with data available for both assessments are included in each analysis, with the total N reported above each plot. Abbreviations: ^{13}CMTGT-cPDR = ^{13}C mixed triglyceride breath test-cumulative percentage dose recovered, FE-1 = faecal elastase 1, PEI = pancreatic exocrine insufficiency, PEI-Q = pancreatic exocrine insufficiency questionnaire mean symptom score, Rho = Spearman's correlation coefficient.

pancreatic cancer, and the high rates of recurrence and metastatic disease, it is difficult to recruit the large sample sizes that would be required to precisely estimate the long-term prevalence of PEI. As such, two major systematic reviews have been performed, to pool the results of all relevant studies in the literature; however, these returned quite different findings. The first is Tseng et al. (2016), which included 9 studies, the majority of which used FE-1 as a diagnostic test; this pooled studies assessing PEI at least six months after PD, and reported a median prevalence of PEI of 74 %, which is consistent with the prevalence observed in the present study [1]. Only one of the studies included in the Tseng et al. review evaluated longer-term PEI (Halloran et al.), reporting a prevalence of 83 % at one year, based on the FE-1 [13]. The second systematic review was a more recent investigation by Moore et al. (2021), which added an additional 28 studies to the review by Tseng et al., and reported a median PEI prevalence following PD of only 43 % [2]. However, most of the included studies diagnosed PEI based on symptomatic assessment alone, with only four using a diagnostic test, none of which had a median follow up of longer than 7 months. Both systematic reviews had considerable limitations, mainly regarding the heterogeneity of the patient cohorts, timing of the PEI assessments, and the diagnostic tests used, which may have reduced the precision and generalizability of the estimates of the PEI prevalence.

A more recent, significant, robust study by Hartman et al. (2023) used ^{13}CMTGT to evaluate PEI in 78 patients six weeks after head of pancreas resection. This study found the prevalence of PEI to be 64.1 % for the cohort as a whole, increasing to 78.6 % when considering PDAC alone [3]. However, since the assessment was performed at six weeks, the findings may not be generalizable to the longer term, as previous work by Lim et al. suggests that more than 45 % of those that develop PEI do so at more than 90 days following resection [14]. Therefore, a longer follow up period is essential to fully realise the prevalence of PEI. We believe that, by using a multi-modal diagnostic model at a median of 15 months, we have overcome some of the limitations of the previous studies in the literature, and estimate the long-term prevalence of PEI after PD for oncologic indication to be 81 % (95 % CI: 61–93 %).

Oncologic PD causes PEI both directly, by removal of pancreatic tissue, and indirectly, by altering the delicately balanced physiology of pancreatic secretion. For correct function, pancreatic enzymes need concomitant secretion of bicarbonate to neutralise stomach acid, require activation by enterokinase (present in the duodenal brush border), and need to be delivered to the small bowel at the same time as chyme from the stomach. The result of resection and reconstruction leads to enzymes being delivered to the wrong place, often at the wrong time and in a lower volume. Even prior to resection, an obstructing head of pancreas lesion can cause pancreatic atrophy, further lessening the capacity of the remnant pancreas to maintain adequate enzymatic secretion. The results of this study suggest that PEI persists for years after resection; hence, that the gastrointestinal tract is unlikely to recover its digestive ability over time, unlike after bowel resection, where adaptation of

the remaining bowel has been observed [15]. This has implications for clinical practice, as studies of PERT prescribing show a disconnect between the incidence of PEI and population levels of treatment. The 2018 UK national audit RICOCHET found PERT to be prescribed in less than 75 % of patients with resectable pancreatic cancer, and less than 50 % with unresectable pancreatic cancer [6]. Sadly, despite national campaigns to increase awareness and implementation of National Institute for Health and Care Excellence (NICE) guidance, audits using the OpenSAFELY research platform still found rates of PERT prescribing in unresectable pancreatic cancer to be under 50 % [6,16]. This problem is not limited to the UK, with American, Australian and European population-based studies all showing PERT prescribing levels of under 50 % [17–19]. The risk of undertreatment with PERT may potentially become more common further from the time of surgery, where patients will tend to be reviewed less frequently by specialist pancreatic teams, instead being followed-up by oncologists in local hospitals. Such undertreatment would prevent patients from accessing the beneficial effects of PERT, including improved symptom control, improved quality of life, and minimised risk of malnutrition; PERT has also been shown to prolong survival in patients with PDAC [20]. Whilst specialist pancreatic centres should endeavour to commence all patients on PERT post-operatively, subsequent follow-up of patients will likely fall to managing teams in the local hospital. As such, given the high prevalence of PEI in the present study, clinicians responsible for the long-term follow-up of these patients must be equally vigilant in assessing for PEI, and monitoring PERT prescribing and compliance, to optimise patient outcomes. It is important to note that there may be other contributing factors to malnutrition and gastrointestinal symptoms following pancreatic head resection, such as small intestinal bacterial overgrowth (SIBO) and bile salt malabsorption. In patients refractory to appropriate PERT dosing, these should be considered and investigated appropriately.

Historically, it has been difficult to measure PEI after pancreatic resection. Whilst direct testing of pancreatic secretion is possible, this is not able to identify instances of PEI where secretory capacity is maintained, but where physiological and anatomical changes prevent the enzymes from reaching the small bowel, either in sufficient quantity or at the correct time. As such, accurate diagnosis of PEI following PD requires an indirect test. The 72-h faecal fat test (the gold standard of indirect testing) is time-consuming and unpleasant, and not available in most settings; it also does not differentiate the steatorrhea of PEI from other forms of fat malabsorption. FE-1 alone can underestimate PEI, and has been shown to lack sensitivity for mild or moderate PEI after pancreatic resection [21]. The ^{13}CMTGT is still far from ideal, as it requires a 6 h attendance, strict in-test control measures, and is not currently used in the UK outside of a research setting. However, it is non-invasive, accurate, and our unit has been using it to good effect within the pancreatic research team [22]. In the absence of other appropriate tests, by using the ^{13}CMTGT breath test in this study (supported by FE-1 and PEI-Q and assessed by a panel of experts), we believe that we have given the most practical and accurate assessment of PEI in long-term survivors after PD currently possible.

5. Limitations

The primary limitation of this study was the small sample size, particularly for the subgroup of patients in the non-PEI group. As such, the estimate of the rate of PEI was subject to a wide confidence interval, and comparisons of patient characteristics between the consensus PEI and non-PEI groups will have had low statistical power and, hence, and inflated false-negative rate. Secondly, data were not available for all three PEI assessments for all patients, meaning that reviewers had to determine the PEI status using only two of the three assessments for N = 6 patients, which may have impacted their final decision. Thirdly, the PEI assessments included were not exhaustive, and other markers, such as fat-soluble vitamin levels and more granular longitudinal assessments of weight stability, may have increased the reliability of PEI diagnosis. Fourthly, there was considerable variability in the timing of the assessments, ranging from 8 to 27 months post-resection. As such, if the prevalence of PEI varied across this period, the resulting rate may not be generalizable in practice. Whilst there was no evidence that this was the case, with no significant association detected between the timing of the assessment and consensus PEI rate, this analysis was limited by the aforementioned low statistical power. Finally, due to the exclusion criteria applied, the results are only generalizable to the study population, namely those that were alive, non-frail, and not on chemotherapy approximately 1–2 years post-resection, which likely represents a cohort that are younger and fitter with less aggressive pathology which, again, may lead to an underestimate in PEI prevalence. In light of these limitations, further work in this area would be warranted, with particular focus on increasing the range of PEI assessments used, and recruiting a larger and more generalizable cohort of patients. Depending on the availability of funding, we plan to perform such a study in the future.

6. Conclusion

To summarise, the current evidence shows that PEI is a significant problem after PD, especially for malignancy, but the prevalence in the longer term has previously been poorly investigated, with systematic reviews being limited by studies having short follow-up, heterogenous methods of diagnosis, and broad inclusion criteria for types of pancreatic resection. This study uses a multimodal approach to PEI diagnosis, and shows a PEI prevalence of over 80 % at a median of 15 months post-pancreatic head resection. The high and sustained prevalence of PEI suggests that patients should remain on PERT lifelong, and all healthcare professionals involved in the longer-term care of this cohort need to remain vigilant to ensure correct PERT prescribing and compliance.

Author contributions

SPB designed the study, collected, and analysed the data, prepared the manuscript, and approved the final version. LH collected and interpreted the data, prepared the manuscript, and approved the final version. JHS assisted in preparation of the manuscript. KR conceived the idea for the study, prepared the manuscript and approved the final version. JH performed statistical analysis and prepared the manuscript. MP interpreted data and edited the manuscript. No authors have any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

Decleration of competing ineterest

No authors have any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

Acknowledgments

Funding for part of this work was received by PCUK.

References

[1] Tseng DS, et al. Pancreatic exocrine insufficiency in patients with pancreatic or periampullary cancer: a systematic review. Pancreas 2016;45(3):325–30.
[2] Moore JV, et al. Exocrine pancreatic insufficiency after pancreatectomy for malignancy: systematic review and optimal management recommendations. J Gastrointest Surg 2021.
[3] Hartman V, et al. Prevalence of pancreatic exocrine insufficiency after pancreatic surgery measured by (13)C mixed triglyceride breath test: a prospective cohort study. Pancreatology 2023.
[4] Powell-Brett S, de Liguori Carino N, Roberts K. Understanding pancreatic exocrine insufficiency and replacement therapy in pancreatic cancer. Eur J Surg Oncol; 2020.
[5] Roberts KJ, et al. Pancreas exocrine replacement therapy is associated with increased survival following pancreatoduodenectomy for periampullary malignancy. Hpb 2017;19(10):859–67.
[6] Pancreatic enzyme replacement therapy in patients with pancreatic cancer: a national prospective study. Pancreatology 2021.
[7] Johnson CD, et al. Psychometric evaluation of a patient-reported outcome measure in pancreatic exocrine insufficiency (PEI). Pancreatology 2019;19(1):182–90.
[8] Shreeve WW, Cerasi E, Luft R. Metabolism of [2-14C] pyruvate in normal, acromegalic and hgh-treated human subjects. Acta Endocrinol 1970;65(1):155–69.
[9] Dominguez-Munoz JE, et al. Development and diagnostic accuracy of a breath test for pancreatic exocrine insufficiency in chronic pancreatitis. Pancreas 2016;45(2):241–7.
[10] Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol 2013;19(42).
[11] Leodolter A, et al. Comparison of two tubeless function tests in the assessment of mild-to-moderate exocrine pancreatic insufficiency. Eur J Gastroenterol Hepatol 2000;12(12):1335–8.
[12] Charlson ME, et al. Charlson comorbidity index: a critical review of clinimetric properties. Psychother Psychosom 2022;91(1):8–35.
[13] Halloran CM, et al. Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. Pancreatology 2011;11(6):535–45.
[14] Lim PW, et al. Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. HPB (Oxford) 2016;18(4):360–6.
[15] Warner BW. The pathogenesis of resection-associated intestinal adaptation. Cell Mol Gastroenterol Hepatol 2016;2(4):429–38.
[16] Lemanska A, et al. A national audit of pancreatic enzyme prescribing in pancreatic cancer from 2015 to 2023 in england using OpenSAFELY-TPP. Semin Oncol Nurs 2023;39(3):151439.
[17] Landers A, Muircroft W, Brown H. Pancreatic enzyme replacement therapy (PERT) for malabsorption in patients with metastatic pancreatic cancer. BMJ Support Palliat Care 2016;6(1):75–9.
[18] Sikkens EC, et al. The daily practice of pancreatic enzyme replacement therapy after pancreatic surgery: a northern European survey: enzyme replacement after surgery. J Gastrointest Surg 2012;16(8):1487–92.
[19] Elliott IA, et al. Population-level incidence and predictors of surgically induced diabetes and exocrine insufficiency after partial pancreatic resection. Perm J 2017;21:16–95.
[20] Roberts KJ, Bannister CA, Schrem H. Enzyme replacement improves survival among patients with pancreatic cancer: results of a population based study. Pancreatology 2019;19(1):114–21.
[21] Lan X, et al. Challenges in diagnosis and treatment of pancreatic exocrine insufficiency among patients with pancreatic ductal adenocarcinoma. Cancers 2023;15(4).
[22] Powell-Brett S, et al. A systematic review and meta-analysis of the accuracy and methodology of the (13)C mixed triglyceride breath test for the evaluation of pancreatic function. Pancreatology 2023;23(3):283–93.