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Pancreatic exocrine insufficiency after pancreatic resection: a systematic review

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Abstract

Introduction Pancreatic exocrine insufficiency (PEI) is a condition defined by a reduction in pancreatic exocrine activity that impairs normal digestion. Despite established guidelines recommendations, precise diagnosis of PEI after pancreatic resection are infrequently achieved. This review aims to provide a comprehensive overview of the methodology and accuracy of diagnostic tools available for evaluating PEI after pancreatic resection.

Methods A review of PEI diagnostic tests was conducted using a combined text and MeSH search strategy to identify relevant articles focused on post-pancreatectomy PEI diagnosis.

Results The literature search yielded 4,874 records, and 30 studies were included in the analysis, with a total of 2,305 patients. The reported frequency of PEI across the included studies varied widely, though more than two-thirds of included papers reported an incidence of PEI above 65% in patients who underwent pancreatoduodenectomy or distal pancreatectomy. The faecal elastase-1 (FE-1) test was the most frequently used test for diagnosing post-pancreatectomy PEI. Six studies compared the diagnostic accuracy of FE-1 with faecal fat tests or 13 C breath tests, finding no significant differences. Five studies reported on micronutrient deficiencies.

Conclusion The FE-1 test is the most commonly used diagnostic tool for post-pancreatectomy PEI; however, well-designed studies comparing the diagnostic accuracy of various tests for PEI are lacking. Additionally, few studies report on micronutrient deficiencies, variations in anthropometric data or PEI-related patient-reported outcomes. Future studies should aim to establish a gold standard for diagnosis and severity assessment of post-pancreatectomy PEI and provide guidance for tailored pancreatic enzyme replacement therapy.

Keywords Pancreatectomy, Pancreatoduodenectomy, Distal pancreatectomy, Pancreatic enzyme, Pancreatic insufficiency, Pancreatic replacement therapy, PERT

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Introduction

Pancreatic exocrine insufficiency (PEI) is a condition defined as a reduction of pancreatic exocrine activity in the intestine at a level that prevents normal digestion [1]. It is characterised by gastrointestinal symptoms such as diarrhoea, steatorrhea (fatty stools), and deficiencies in essential fats and fat-soluble vitamins (A, D, E, and K) [2]. Reports suggest prevalence rates of 70–90% after pancreatoduodenectomy (PD) and 20–50% after distal pancreatectomy (DP). However, estimating the true prevalence of PEI is difficult due to the limitations of diagnostic tests and to the challenges in distinguishing it from other causes of post pancreatectomy diarrhoea or malnutrition [3].

According to clinical guidelines [1, 3–13], the diagnosis of PEI relies on a combination of symptom assessment and laboratory tests. Laboratory tests are categorized into direct pancreatic secretion tests and indirect pancreatic function tests, aiming to provide a more objective assessment of pancreatic exocrine function. Imaging techniques, like magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT), are used to identify structural causes of PEI.

Test based on direct measurements of pancreatic secretions are the most accurate but are invasive and time-consuming. These involve stimulating the pancreas, collecting pancreatic juices, and analysing them for bicarbonate concentration and digestive enzymes [14]. These tests are more commonly used for diagnosing early-stage chronic pancreatitis rather than post-pancreatectomy PEI. The most widely used indirect test is the faecal elastase-1 (FE-1) test, which is non-invasive and relatively inexpensive [15–17]. It measures the levels of elastase-1 in stool, which correlates with pancreatic enzyme production. Despite its utility, the FE-1 test has limitations, such as being less accurate with mild PEI and requiring formed or semi-formed stool for accurate results [18]. Other indirect tests include measuring serum pancreatic enzyme levels in stool or urine sample, such as chymotrypsin, which is unreliable if there is ongoing pancreatic inflammation [3]. Breath tests can diagnose PEI by measuring diminished fat digestion in the intestine. These tests involve ingesting triglycerides labelled with non-radioactive 13–14 C, which are broken down by pancreatic enzymes. The resulting $13CO_2$ or $14CO_2$ is measured in exhaled breath [4, 19]. These tests have the advantage of directly measuring pancreatic enzyme-specific digestion but require several hours of breath collection. Finally, steatorrhea can be precisely assessed by the determination of faecal fat. However, the diagnostic test involves a burdensome process of ingesting a diet with known fat content over five days, whose compliance can influence the accuracy of the test, and collecting stool samples for fat measurement over the last three days [20].

In clinical practice, despite established guidelines, precise diagnosis of pancreatic insufficiency after pancreatic resection are infrequently achieved. Consequently, pancreatic enzyme replacement therapy (PERT) is often initiated at a standard dosage, regardless of individual patient characteristics, confirmation of PEI diagnosis, or severity. The present review aims to provide a comprehensive overview of the methodology and accuracy of diagnostic tools available for evaluating PEI in patients undergoing different types of pancreatic resection.

Methods

Search strategy

The search was undertaken according to the PRISMA guidelines [1]. Two researchers systematically searched Medline, EMBASE and the Cochrane Library for reports published before the 8th of February 2024, not limited to the English language, using a combined text and MeSH search strategy. The search terms for the literature review contained the terms "pancreatic exocrine insufficiency, "PEI" and "surgery". A snapshot on clinical guidelines published over the last 10 years on diagnostic tools for PEI was prepared using the search strategy. The search was further broadened by extensive cross-checking of all the references in the articles retrieved to identify eventual additional non-indexed literature.

Study selection

Studies included in the review met the following criteria: (a) patients older than 18 years old; (b) patients who underwent any type of pancreatic surgery; (c) experimental or observational (prospective and retrospective) studies regarding the diagnosis of PEI.

Exclusion criteria were: experimental studies on animal models, case series, case reports, reviews, editorials and comments were excluded. When duplicate reports from the same study were identified, only the most recent publication or the one with the longest follow-up period was included. The full text of each article was assessed if it was not excluded in the initial review. If the perioperative outcomes were not reported or were impossible to extract from each of the two groups, the studies were excluded.

Data collection

Four researchers (MDM, AHR, AS and GS) assessed titles and abstracts of selected studies to determine their eligibility in Rayyan web app for systematic reviews (https://www.rayyan.ai/). Full articles were selected for further assessment. Inconsistencies were resolved through discussion until a consensus was reached. The extracted data included: country of study, design, number of participants included, age, sex; method of diagnosis; type of surgery; use of perioperative chemotherapy; use

of pancreatic enzyme replacement therapy; methods of the diagnostic test used; reference level reported, months of follow-up. Disagreements over data extraction were resolved by consensus between the authors.

Evaluation of studies and statistical analysis

Two researchers (AS and MDM) independently evaluated included studies for quality assessment according to the Newcastle-Ottawa Scale (NOS) [21]: scores ≥ 7–9, between 4 and 6 and < 4 were considered low, intermediate, and high risk, respectively. The data were described as proportions and median along with a corresponding minimum-maximum range.

Results

The literature search yielded 4,874 records, and after excluding duplicates and conducting title screening, 4,696 records were excluded due to study characteristics and methodology. The full-text articles of 78 papers were assessed for eligibility. Exclusion reasons included methodological issues and lack of data on primary outcomes. Ultimately, 30 studies were included in the analysis [22–51] with a total of 2305 patients (Fig. 1).

No randomised clinical trial (RCT) was found; 12 papers were based on prospective registries [25, 27, 29, 31–33, 35, 42–44, 46, 48], and 18 on retrospective studies (Table 1) [22–24, 26, 28, 30, 34, 36–41, 45, 47, 49–51]. Only six papers [24, 25, 27, 37, 38, 43] compared the accuracy of two different diagnostic tools for post-pancreatectomy PEI evaluation, and all of them used FE-1 as the reference standard for the comparison. None of the included studies employed matching statistical analysis techniques. The mean age of the participants ranged from 50 to 69 years. The mean follow-up ranged from 1 month to 10 years.

Only one of the included studies was considered at low risk of bias [27], two were at high risk of bias [29, 44], and the remaining 27 [22–26, 28, 30–43, 45–51] at intermediate risk (Supplementary Table 1).

None of the included papers used a test based on a direct measurement of pancreatic secretions as a reference standard for the diagnosis of PEI, preferring indirect measurements instead. Table 2 provide detailed information on sample collection and reference values used in included papers. Stool tests, specifically FE-1 measured in a stool sample, were used in 19 out of 30 included papers [22, 24, 25, 27, 31–33, 35–39, 42, 43, 45, 46, 48–50]. Data were consistent in defining normal values as FE-1 > 200 mg/g. Two papers [34, 41] measured faecal chymotrypsin, collected either from a stool sample or over a 72-hour period; in both cases, normal values were considered to be faecal chymotrypsin > 6 U/g. Three papers [24, 25, 27] measured faecal fat: patients needed to follow specific dietary requirements, stool samples were collected over a 72-hour period, and a coefficient of fat absorption (CFA) > 93% or a faecal fat excretion (FFE) < 6–7 g/day were taken as indicative of normal pancreatic exocrine function. Breath tests were used in eleven included papers [23, 26, 28–30, 37, 38, 40, 43, 44, 51], with different cut-off values depending on the substrate administered. Finally, one paper measured the N-benzoyl-L-tyrosyl-p-aminobenzoic acid (BT-PABA) recovered in a urine sample, diagnosing PEI as urinary BT-PABA < 70% of the administered dose.

Reported incidence of PEI according to the surgical procedure performed and the test used

The reported frequency of PEI from included papers presented a very wide range, between 26 and 100% of patients submitted to pancreatic resection. Only two papers reported an incidence below 30% [26, 34]; eight reported and incidence between 30 and 60% [26, 29, 30, 37, 40, 41, 49, 51], while in the remaining it was above 60%.

The frequency of PEI was then assessed according to the type of pancreatic resection performed and the test used for the diagnosis of PEI. Eighteen [22–24, 28, 30–32, 36–39, 41, 43–47, 50] papers assessed patients who underwent PD, only one assessed patients who underwent DP [49], and the remaining eleven [25, 27, 29, 33–35, 38, 40, 42, 48, 51] evaluated patients who underwent both PD and DP.

As shown in Table 3, the reported incidence of PEI from papers evaluating outcomes of PD ranged from 47 to 100%. The paper describing the frequency of PEI in patients who underwent DP reported an incidence of only 59%. Papers assessing the incidence of PEI in both PD and DP reported an incidence ranging from 26 to 100%.

Papers reporting on PEI after PD described an incidence ranging from 47 to 100% when using FE-1 [22, 24, 31, 32, 36, 37, 39, 43, 45, 46, 50] and 47–82% when using the 13 C breath test [23, 29, 30, 37, 38, 43, 44]. Other tests described a wider range of PEI frequency, between 36 and 86% [24, 41, 47]. Papers reporting on the frequency of PEI after pancreatic resection, without specifying the type of resection, described an incidence of PEI between 65 and 100% using FE-1 [25–27, 33, 35, 42, 48] and 54–69% using the 13 C breath test [26, 28, 40, 51]. As above, other tests included in the analysis reported a wider range of frequency, ranging from 26 to 100% [25, 27, 34].

Comparative studies, micronutrient deficiency, weight lost and time to recover weight

A total of six comparative papers were included in the analysis [24–27, 37, 43]. As shown in Table 4 Three of these compared FE-1 with faecal fat tests [24, 25, 27]

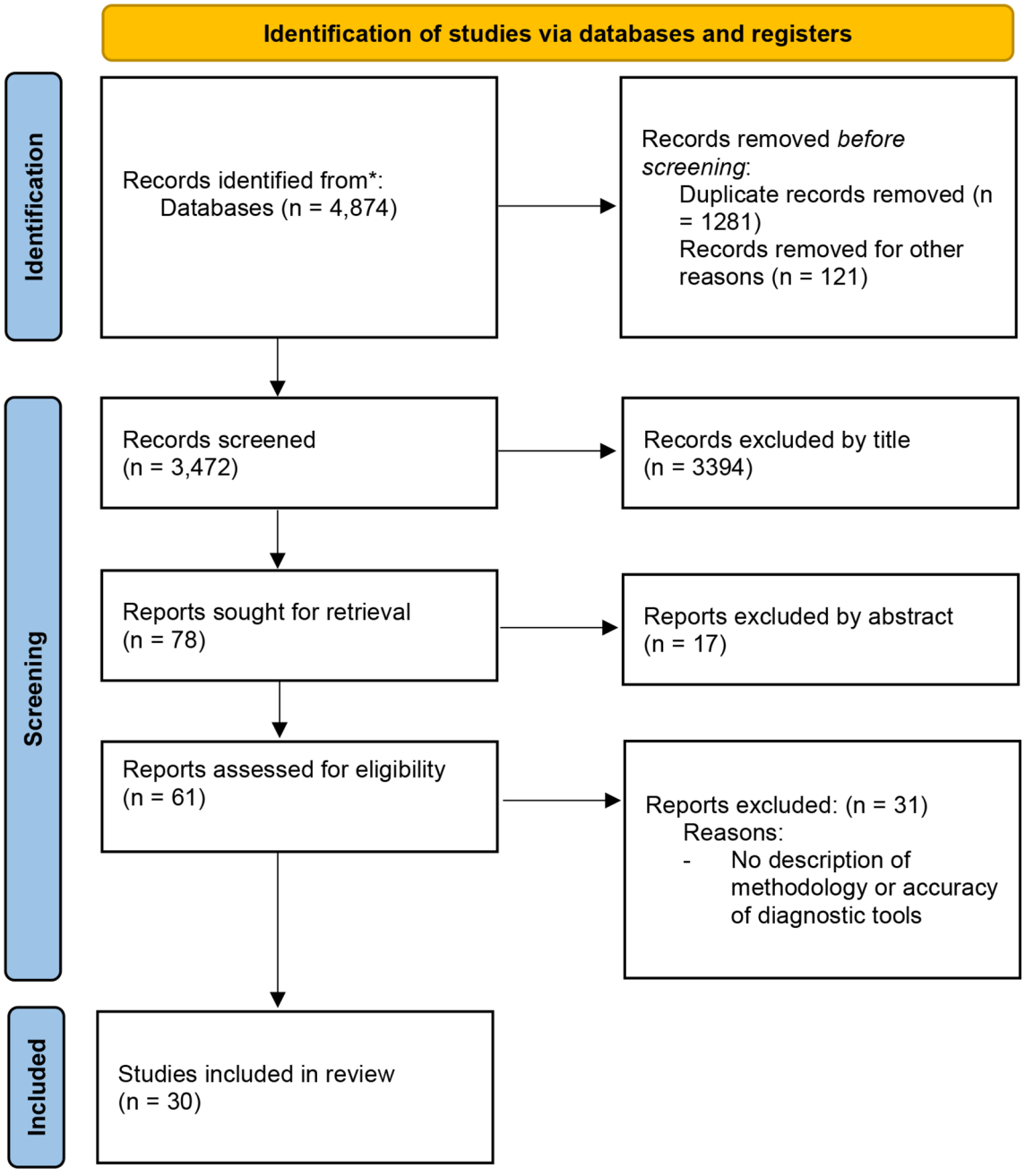

Figure. 1 Flow chart of included studies

while the other three compared FE-1 with 13 C breath tests [26, 37, 43]. Reported sensitivity, specificity and diagnostic accuracy of tests are detailed in Table 4. Only one paper [26] specifically aimed to evaluate the diagnostic accuracy of the two tests. They suggested that findings from the 13 C breath correlated with the FE-1 test, however, the former showed higher incidence and accuracy in the diagnosis of PEI; therefore, it could be more useful in the assessment of pancreatic exocrine function after pancreatic resection.

Five papers [23, 24, 31, 37, 42] reported on micronutrient deficiencies. In two cases [31, 37] the studies measured levels of vitamins A, D, E, and K, and in one case [31] levels of iron, copper, zinc, serum retinol, alpha-tocopherol, and vitamin C were also assessed. Although many of the included papers mentioned weight measurement, changes in body weight, time to recover weight, and other anthropometric measurements were not used as clinical outcomes in any of the studies.

Table 1 Characteristics of included papers

Study	Country	RCT	Prospective or retrospective	Comparative study	Sample size	Test used
Alfieri 2020 [22]	Italy	No	Retrospective	No	32	13 C breath test
Benini 2019 [2]	Italy	No	Retrospective	Yes	34	FE-1 test / Faecal fat
Cho 2022 [24]	Korea	No	Retrospective	No	202	FE-1 test
Falconi 2008	Italy	No	Retrospective	No	135	Faecal chymotrypsin test
Halloran 2011 [25]	UK	No	Prospective	Yes	40	FE-1 test / Faecal fat
Hartman 2020 [26]	Belgium	No	Retrospective	No	29	13 C breath test
Hartman 2023 [27]	Belgium	No	Prospective	No	254	13 C breath test
Hirono 2015 [28]	Japan	No	Retrospective	No	189	13 C breath test
Kanwat 2023 [29]	India	No	Retrospective	No	64	FE-1 test
Kroon 2022 [30]	Netherlands	No	Prospective	No	23	FE-1 test
Kumar 2021 [31]	India	No	Prospective	No	30	FE-1 test
Lemaire 2000 [32]	France	No	Prospective	Yes	19	FE-1 test / Faecal fat
Maignan 2018 [33]	France	No	Prospective	No	91	FE-1 test
Matsumoto 2006 [34]	USA	No	Retrospective	No	82	FE-1 test
Muniz 2014 [35]	Brazil	No	Retrospective	Yes	15	FE-1 test / 13 C breath test
Nakamura 2009 [36]	Japan	No	Retrospective	Yes	95	FE-1 test / 13 C breath test
Nakamura 2011 [37]	Japan	No	Retrospective	No	52	13 C breath test
Nordback 2007 [38]	Finland	No	Retrospective	No	26	FE-1 test
Okano 2016 [39]	Japan	No	Retrospective	No	227	13 C breath test
Ong 2000 [40]	Singapore	No	Retrospective	No	11	Faecal chymotrypsin test
Percy 2022 [41]	Australia	No	Prospective	No	98	FE-1 test
Powell-Brett 2024 [42]	UK	No	Prospective	Yes	26	FE-1 test / 13 C breath test
Roeyen 2017 [43]	Belgium	No	Prospective	No	78	13 C breath test
Saluja 2019 [44]	India	No	Prospective	No	102	FE-1 test
Sato 1998 [45]	Japan	No	Retrospective	No	44	BT-PABA test
Sikkens 2014 [46]	Netherlands	No	Prospective	No	29	FE-1 test
Speicher 2010 [47]	USA	No	Retrospective	No	83	FE-1 test
Stern 2023 [48]	Germany	No	Prospective	No	77	FE-1 test
Tran 2008 [49]	Netherlands	No	Retrospective	No	74	FE-1 test
Yuasa 2012 [50]	Japan	No	Retrospective	No	110	13 C breath test

RCT: Randomised clinical trial; FE-1: Faecal elastase 1; 13 C: 13 C-labelled mixed triglyceride breath test; BT-PABA: N-benzoyl-L-tyrosyl-p-aminobenzoic acid

Snapshot on current guidelines recommendations

A total of seven clinical guidelines or consensus documents were found regarding recommendations for diagnostic tools for PEI [1, 4, 8–13]. Only one [12] focused specifically on patients who underwent pancreatic resection, while the other four provided general recommendations for patients with possible PEI. A summary of the guidelines' recommendations, including the grade of evidence when available, is reported in Table 5. Overall, the FE-1 test was consistently recommended by the included guidelines as recommended test. It was suggested that stool samples should be adjusted for water content when possible, and additional markers of malnutrition and measurements of micronutrients should be considered to support unclear diagnosis of PEI.

Discussion

PEI is a frequent complication after pancreatic surgery. Despite the wide heterogeneity and low quality of the included papers, more than two-thirds of them reported an incidence above 65% in patients who underwent PD or DP. The FE-1 test was the most frequently used test for the diagnosis of post-pancreatectomy PEI, as consistently recommended by the most recent clinical guidelines [1, 4, 8–13]. Very few studies compared the diagnostic accuracy of tests for post-pancreatectomy PEI. Additionally, very few studies reported on micronutrient deficiencies, variation in anthropometric data or time to recover weight. Whether PEI is a valid surrogate outcome for malnutrition and nutritional deficiency after pancreatic surgery remains to be determined and whether available diagnostic tests can capture the entire spectrum of this issue is still to be determined.

Patients after pancreatic resections frequently present malnutrition with significant weight loss and struggle to recover from that. Currently available investigations mainly focus on PEI defined by diagnostic tools such as of CFA, FFE, FE-1 elastase test or the 13 C breath test. Direct measurement of excreted pancreatic enzymes is rarely used, due to its invasive nature, complexity of and impracticality following PD. Similarly, the measurement of CFA or FFE, that require a specific dietary regimen

Table 2 Description of test used as reference standard for diagnosis of PEI from included papers

Test used	Dietary and test requirements	Sample collected	Reference values	Papers reporting reference values
Type of indirect measurement: stool samples				
FE-1 test ($n=19$)	Rarely specified, some mention to a low-fat diet 1–3 days before the test [23, 25, 32]	Stool sample of about 100 mg [48, 49]	Normal value > 200 mg/g Mildly impaired 100–200 mg/g Severely impaired < 100 mg/g	19 [23–25, 29–35, 37, 38, 41, 42, 44, 46–49]
Faecal chymotrypsin test ($n=2$)	NS	Stool sample of about 100 mg [40] or Stool samples collected over a 72-hour period [51]	Normal value > 6 U/g Possible PEI if 3–6 U/g PEI if < 3 U/g	2 [40, 51]
Faecal fat test ($n=3$)	Low-fat diet 3 days before the test with (50 to 100 g of fat per day) [23, 25]	Stool samples collected over a 72-hour period [23, 25, 32]	Normal value CFA > 93% Normal value FFE between 2–7 g/day	3 [23, 25, 32]
Type of indirect measurement: breath tests				
13 C breath test ($n=11$)	200 mg of the 13 C-labeled triglyceride mixed to a test meal [28, 35–37, 39]	Breath sample	PEI if Percentage of cumulative recovery of $13CO^2$ at 7 h < 5% [28, 35–37, 39, 50]	5 [28, 35–37, 39, 50]
	250 mg 13 C-labeled triglyceride mixed to a test meal [22, 26, 27, 42, 43]		PEI if percentage of cumulative recovery of $13CO^2$ at 4 h < 15% [22]	1 [22]
			PEI if percentage of cumulative recovery of $13CO^2$ at 6 h < 23% [26, 27]	2 [26, 27]
Type of indirect measurement: urinary samples				
BT-PABA test [45] ($n=1$)	Aadministration of 500 mg of BT-PABA after an overnight fast	Urine sample collected over a 6-hour period	Impaired function if BT-PABA < 70%	1 [45]

NS: Not specified; FE-1: Faecal elastase 1; 13 C: 13 C-labelled mixed triglyceride breath test; BT-PABA: N-benzoyl-L-tyrosyl-p-aminobenzoic acid; PEI: Pancreatic exocrine insufficiency; CFA: coefficient of fat absorption; FFE: faecal fat excretion

Table 3 Reported incidence of PEI according to the to the test used and the surgical procedure performed

Test used	Surgical procedure performed	*N*	Reported incidence of PEI
FE-1 test [23–25, 29–36, 38, 41, 42, 44, 46–49]		19	47–100%
	PD [23, 24, 29–31, 34, 35, 38, 42, 44, 49]	11	47–100%
	DP [47]	1	59%
	PD and DP [25, 32, 33, 36, 41, 46, 48]	7	65–100%
13 C breath test [22, 26–28, 35–37, 39, 42, 43, 50]		11	47–82%
	PD [22, 27, 28, 35, 37, 42, 49]	7	47–82%
	PD and DP [26, 36, 39, 50]	4	54–69%
Other tests [23, 25, 32, 40, 45, 51]		6	26–100%
	PD [23, 40, 45]	3	36–86%
	PD and DP [25, 32, 51]	3	26–100%

FE-1: Faecal elastase 1; 13 C: 13 C-labelled mixed triglyceride breath test. PD: pancreatoduodenectomy; DP: distal pancreatectomy

over a period or three days, whose compliance can alter test results and is rarely used in the clinical practice. As shown by the present review the FE-1 elastase or the 13 C breath test were used in 26 out of 30 included papers with a wide range of reported incidence after both PD and DP. However, reliable data on their sensitivity, specificity, and diagnostic accuracy remain sparse. When evaluated, stool-based tests such as CFA and FFE but also more subjective clinical signs like steatorrhea, were used as reference standards for diagnostic accuracy [25–27]. Therefore, the present analysis highlights not only the absence of precise data on definition and incidence of PEI after pancreatic resection but also lack of data on diagnostic accuracy of available test and of an agreement on a reference standard for its diagnosis. Other relevant issues to be considered when addressing this issue are also local availability, reproducibility and cost-effectiveness of available diagnostic tools in the real practice. These aspects remain only partially addressed in the current literature.

Also, whether PEI correctly reflect patients' malnutrition status and serves as an adequate surrogate outcome for patient-reported outcomes following pancreatic resection remain controversial. The influence on the changes of anthropometric data after pancreatic

Table 4 Comparative studies on incidence of PEI after pancreatic resection

Study	Prospective or retrospective	Sample size	Surgical procedures	Indication for surgical procedure	Test used	Reported PEI incidence	Reported Sensitivity -Specificity	Significant differences
Benini 2019 [23]	Retrospective	34	PD 100% DP 0%	Malignant lesions, NET, benign lesions, other	FE-1 test Faecal fat	84% 77%	NA	NA
Halloran 2011 [25]	Prospective	40	PD 93% DP 7%	Malignant lesions	FE-1 test Faecal fat	83% 55%	Sens. 91% Specif. 35% Accuracy 70% for FE-1 (CFA > 93% as reference standard)	NA
Lemaire 2000 [32]	Prospective	19	PD 89% DP 0%	Malignant lesion (pancreatic cancer excluded), benign lesions	FE-1 test Faecal fat	100% 94%	Sens. 91% Specif. 35% for FE-1 (FFE > 6 g as reference standard)	NA
Muniz 2014 [35]	Retrospective	15	PD 100% DP 0%	NA	FE-1 test 13 C breath test	47% 47%	NA	NA
Nakamura 2009 [36]	Retrospective	95	PD 54% DP 14%	Malignant lesions, NET, benign lesions, other	FE-1 test 13 C breath test	62% 88%	Sens. 90% Specif. 52% Accuracy 62% for FE-1 Sens. 69% Specif. 93% Accuracy 88% for 13 C breath test (steatorrhea as reference standard)	NA
Powell-Brett 2024 [42]	Prospective	26	PD 100% DP 0%	Malignant lesions, NET, benign lesions	FE-1 test 13 C breath test	88% 60%	NA	NA

FE-1: Faecal elastase 1; 13 C: 13 C-labelled mixed triglyceride breath test; PD: pancreatoduodenectomy; DP: distal pancreatectomy; NET: Neuroendocrine tumours; CFA: coefficient of fat absorption; FFE: faecal fat excretion; NA: Not available

surgery of specific micronutrient deficiencies remains an unexplored issue. Similarly, time to recover weight after surgery, which is a relevant clinical indicator as it is frequently related to patient functional recovery is seldom assessed. Tools such as the PEI Questionnaire (PEI-Q), developed by Johnson et al. [52], designed to assess patient reported symptoms and impact on health-related quality of life are rarely included in papers assessing post-pancreatectomy PEI. The present review confirmed the lack of solid data on these aspect in included papers.

As a measure to limit the malnutrition clinical guidelines recommend the universal utilisation of pancreatic enzyme replacement from the early the post-pancreatectomy recovery period [1, 3–6, 12, 53]. However, their utilization is not always able to completely resolve patients' symptoms. While malnutrition may seem relatively less clinically relevant compared to post-operative mortality or major complications, it can still influence the time to start and the type of adjuvant chemotherapy protocol. Additionally, the patient-perceived quality of life, especially in subjects whose life expectancy frequently does not exceed 24–36 months, should not be underestimated. What is still missing from the current available literature is a post-pancreatectomy personalised nutrition assessment according to patient- or procedure-related risk factors, including post-operative complications.

A reliable diagnostic test for PEI, both pre- and post-pancreatectomy, would be invaluable for achieving accurate diagnosis and personalized supplementation therapy. With a precise diagnostic tool, clinicians could identify true PEI cases, quantify severity, and prescribe tailored PERT. This is particularly relevant, as current data indicate that approximately 30% of patients may not require PERT. Reducing unnecessary PERT prescriptions would not only prevent potential side effects for patients without confirmed PEI but also lower costs for healthcare systems [54, 55]. In light of recent international shortages of PERT, optimizing prescriptions becomes even more critical [56]. A robust, widely accessible PEI test could thus enhance patient management and resource efficiency, ensuring PERT supplies are directed to those with verified needs and potentially reducing the impact of supply constraints on patient care. Several limitations should be considered in the context of the present review.

Table 5 Snapshot on current guidelines recommendations on recommendations for diagnostic test for pancreatic exocrine insufficiency

Clinical Guideline	Recommendations
American Gastroenterological Association (AGA) clinical practice update on the PEIdemiology, evaluation, and management of exocrine pancreatic insufficiency: expert review (2023) [4]	Faecal elastase test is the most appropriate initial test and must be performed on a semi-solid or solid stool specimen. A faecal elastase level < 100 mg/g of stool provides good evidence of PEI, while levels of 100–200 mg/g of stool are indeterminate for PEI.
Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines UK practical guidelines (2021) [1]	"Although the coefficient of fat absorption is regarded as the gold-standard diagnostic test for PEI, we recommend that the faecal pancreatic elastase (FE-1) test is a suitable first-line test for PEI (grade 1B)"
	"Stool samples for FEL-1 tests should undergo adjustment to standardised water content, when possible…" (grade 2B; 92% agreement)
	Positive markers of malnutrition, including clinical history, anthropometric measurements or serum micronutrient levels including magnesium, vitamin E and retinol-binding protein/vitamin A, can be used to support a diagnosis of PEI, if unclear. However, none of these markers should be considered in isolation when diagnosing PEI (grade 2 A; 97% agreement)
Chinese guidelines for the diagnosis and treatment of pancreatic exocrine insufficiency (2019) [8]	"The FE-1 test is currently the most commonly used indirect test; PEI is defined by an FE-1 level < 200 μg/g"
Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS) (2018) [9]	"Faecal elastase-1 is the most readily available clinical test for detection of PEI, but its sensitivity and specificity are not always reliable in patients who have undergone a pancreatic resection"
Russian consensus on exo- and endocrine pancreatic insufficiency after surgical treatment (2018) [10]	"In the context of current practice, costs and sensitivity of enzyme immunoassay for faecal elastase-1 would be optimal for evaluation of exocrine function, and fasting plasma glucose (FPG) concentration and glycosylated haemoglobin (HbA1c) are recommended for assessment of endocrine function"
Diagnosis and management of pancreatic exocrine insufficiency (2017) [11]	No recommendations issued
Evidence-based guidelines for the management of exocrine pancreatic insufficiency after pancreatic surgery (2016) [52]	No recommendations issued
Romanian guidelines on the diagnosis and treatment of exocrine pancreatic insufficiency (2015) [13]	The secretin direct test, although standard for quantification of enzyme secretion, is not appropriate for PEI and is rarely used in practice (A, 1b)
	Faecal elastase-1 measures pancreatic secretion and thus the probability of PEI (B, 3b)
	Quantification of the coefficient of fat absorption (CFA) and the 13 C-MTG breath test are useful for diagnosing PEI, but their availability in clinical practice is limited (C, 4)

There was a considerable degree of heterogeneity in the methods of included studies and baseline characteristics of the included patients. A possible selection bias in postoperative assessment should also be considered, as patients who do not survive a year, travel to the hospital, and undergo a period of starvation and hold pancreatic enzyme replacement therapy are likely to have been excluded from included studies. Therefore, there is likely to be a recruitment bias towards fitter, younger patients with less aggressive pathology. Additionally, there was a lack of relevant data on patient-reported outcomes, the diagnostic accuracy of PEI tests, and the reference standard diagnostic tools for post-pancreatectomy PEI. Improved diagnostic and treatment strategies for post-pancreatectomy malnutrition, including PEI and micronutrient deficiencies, as well as patient-reported outcomes related to PEI, need to be developed. Future research should aim to better capture the full spectrum of post-pancreatectomy malnutrition, aiming to identify a gold standard for the diagnosis of this clinical issue. Additionally, research should stratify potential risks for specific groups of patients and focus on time to weight and functional recovery after pancreatic surgery.

Conclusions

Post-pancreatectomy PEI presents a significant health challenge. The faecal elastase-1 (FE-1) test was the most used diagnostic tool. However, well-designed studies comparing the diagnostic accuracy of different tests for post-pancreatectomy PEI are lacking. Additionally, few studies reported on micronutrient deficiencies, variations in anthropometric data, weight recovery time, and PEI-related patient-reported outcomes. Future research should aim to establish a gold standard for diagnosis and severity assessment of post-pancreatectomy PEI, evaluate risks across patient groups and provide guidance for tailored pancreatic enzyme replacement therapy.

Abbreviations

BP-PABA	N-Benzoyl-L-Tyrosyl-P-Aminobenzoic acid
CT	Computed tomography
CFA	Coefficient Of fat absorption
DP	Distal pancreatectomy
FE-1	Faecal elastase-1
FFE	Faecal fat excretion

MRCP	Magnetic resonance cholangiopancreatography
NOS	Newcastle-ottawa scale
PD	Pancreatoduodenectomy
PEI	Pancreatic exocrine insufficiency
PEI-Q	PEI Questionnaire
PERT	Pancreatic enzyme replacement therapy
RCT	Randomised clinical trial

Supplementary Information

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Supplementary Material 1

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Marcello Di Martino: Conceptualization; data curation; formal analysis; investigation; methodology; software; validation; writing – original draft; writing – review &editing. Ángela la Hoz Rodriguez: Conceptualization; data curation; formal analysis; investigation; validation; writing – review & editing. Andrea Saibanti: data curation; formal analysis; investigation; software; validation; writing – original draft; writing – review &editing. Guillermo Salvador Camarmo: Data curation; software; visualization; writing – original. Nico Pagano: Data curation; visualization; writing – original draft. Elena Martín-Pérez: Conceptualization; investigation; methodology; supervision; validation; writing – review & editing. Matteo Donadon: Conceptualization; investigation; methodology; supervision; validation; writing – review & editing.

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Declarations

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