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High prevalence of pancreatic steatosis in pancreatic cancer patients: A meta-analysis and systematic review

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ABSTRACT

Objective: In the last decade there has been increasing interest in defining pancreatic steatosis (PS) and establishing its association with pancreatic ductal adenocarcinoma (PDAC). However, no consensus guidelines have yet been published on the management of PS. In this systematic review and meta-analysis performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we investigated the association between PS and PDAC.
Design: Medical literature between 2007 and 2023 was reviewed for eligible trials investigating the prevalence of PS in patients with PDAC. Eligible studies reporting on PS, assessed via imaging or histology, were included. The primary objective was to determine the association between PDAC and PS by comparing the prevalence of PS in individuals with- and without PDAC. Secondary, an evaluation was conducted to establish whether the method of assessment correlated with the association of PDAC and PS, and the prevalence of PDAC in individuals with PS. Measures of effect size were determined using odds ratios (ORs) and corresponding 95 % confidence intervals (95 % CI).
Results: The systematic review identified a total of 23 studies, of which seventeen studies examined PS prevalence among PDAC patients and were included in the meta-analysis. Overall, the pooled prevalence of PS in patients with PDAC was 53.6 % (95 % CI 40.9–66.2). No significant difference in PS prevalence was observed across various diagnostic methods or geographical regions. Overall, the pooled OR for PS in patients with PDAC compared to controls was 3.23 (95 % CI 1.86–5.60).
Conclusions: PDAC patients have a high prevalence of PS, and they are significantly more likely to have PS compared to controls. These findings emphasize the need to prioritize a standardized approach to the

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diagnosis, follow-up, and treatment of PS, with future studies focusing on identifying patients who would benefit from PDAC surveillance programs.
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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal cancers due to delayed symptom onset and high chemotherapy resistance. Unfortunately, the majority of patients (up to 80 %) present with locally advanced or metastasized disease upon diagnosis [1]. Enhancing the survival rates of PDAC necessitates a strategic emphasis on early detection methods that facilitate timely and curative interventions. Identifying individuals at high risk of developing PDAC and including these in PDAC surveillance programs is a proposed strategy for earlier detection [2]. For this strategy to be effective, robust risk factors for developing PDAC are needed to aid in the selection of individuals for surveillance. This will enable accurate identification and selection of individuals who should undergo surveillance. In the preceding decade, increased focus has been directed towards elucidating the role of pancreatic steatosis (PS) in the pathophysiology underlying PDAC and as a risk factor for PDAC [3].

Pancreatic steatosis, or other terms, such as fatty pancreas, pancreatic lipomatosis, and NAFPD (nonalcoholic fatty pancreatic disease), have been used interchangeably to denote the accumulation of fat in the pancreas. Nonalcoholic fatty pancreatic disease specifically refers to fat accumulation in patients without risk factors that would explain the fat infiltration, such as alcohol abuse or genetic mutations. Inflammation resulting from the accumulation of adipocytes has been termed nonalcoholic steato-pancreatitis (NASP). Fig. 1 provides a summary of the multifactorial etiology of PS [4–6].

Prior research on pancreas resection specimens has established an association between PS, obesity, and precancerous PanIN lesions [3,4]. Furthermore, pancreatic carcinogenesis may be promoted by PS due to chronic inflammatory changes that occur secondary to fat infiltration [7]. The rising prevalence of obesity and overweight in developed nations, consequently contributing to PS, therefore presents a significant concern in pancreatology [8]. Even though the etiology of PDAC and PS is multifactorial, the question remains whether PS can be considered an early feature or risk factor of PDAC.

The absence of established guidelines on how to diagnose and manage PS and the importance of identifying early predictors of PDAC motivated this review and meta-analysis. In this study, we aimed to summarize and elucidate the impact of PS as a risk factor for PDAC.

2. Methods

2.1. search strategy and protocol

A systematic review and meta-analysis of the literature was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines from 2020 [9]. Databases reviewed included PUBMED, MEDLINE and Cochrane Central Register of Controlled Trials. The following search terms were used: pancreatic steatosis (or pancreatic lipomatosis, fatty pancreas, fatty infiltration, NAFPD, or NASP) and pancreatic cancer (or pancreatic ductal adenocarcinoma or PDAC). All studies published between January 2007 and August 2023 that evaluated PS in PDAC patients by imaging methods (MRI, CT, EUS) or histology were considered eligible. Only peer-reviewed full-text articles written in English were included. References of relevant articles were reviewed to identify additional studies that may have been missed during the systematic search.

The primary search was conducted by four independent reviewers using the web application Rayyan [10]. Title and abstracts were screened and assessed on eligibility. After the first selection, all potentially relevant screened articles were evaluated in detail by reviewing the full article. Systematic reviews, meta-analyses, case reports, editorials, conference reports, book sections, and duplicated articles were excluded.

2.2. Data extraction

The following data was extracted by four independent investigators (DT, CS, TH, CV): country of origin, year and design of the study, modality used to assess PS (histology/MRI/CT/EUS), number of patients with PDAC and PS from the study (when available), number of controls with PS (when available) and main findings of the studies (Table 1). Consensus was achieved by discussions in case of disagreements.

2.3. Objective

The primary objective of the meta-analysis was to determine the association between PDAC and PS by comparing the prevalence of PS in patients with- and without PDAC.

2.4. Definitions

In this review, the term PS will be employed to encompass all the various terminologies from the literature [11]. PS can be assessed by different types of modalities, either by imaging or histology. CT and MRI are the most commonly applied methods to assess PS and quantify the amount of pancreatic fat [4]. Pathological changes of PS are correlated with the attenuation of the pancreas on CT images without contrast. PS on CT is defined as a pancreas-to-spleen (P/S) attenuation ratio <0.7 or <0.8 [12–14]. In MRI, pancreatic fat content can be quantified by measuring the proton-density fat fraction [15]. On histology, PS was defined as >5 % fatty infiltration in the pancreas [12,16]. By EUS, PS is defined as a hyperechoic pancreatic pattern compared to the spleen or kidney and, therefore, operator-dependent [4].

2.5. Statistical analysis

First, data on the prevalence of PS in patients with PDAC was retrieved from each of the included studies. PS prevalence was defined as the proportion of PDAC patients with PS and 95 % confidence intervals (CIs) were calculated using the Aggresti-Coull method. For the meta-analysis, a random-effects model with maximum likelihood estimates was used. Secondly, a risk estimate of the association between PS and PDAC was retrieved, preferring fully adjusted odds ratios (ORs). When missing, unadjusted OR and 95 % confidence intervals based on numbers of exposed (with PS) and unexposed cases (without PS) and controls were calculated. For

the meta-analysis of relative risk, we used random-effects models with a generic inverse variance method. Heterogeneity among studies was assessed using the Cochran Q test. The percentage of total variation across studies due to heterogeneity was evaluated by the I2 measure. Heterogeneity was explored by the subgroup analysis and a meta-regression analysis. Forest plots and drapery plots were produced to show estimates and p-value curves for individual studies and meta-analysis estimates, respectively. The probability of publication bias was assessed using funnel plots with the test of Begg, which assesses if there is a significant correlation between the ranks of the effect estimates and the ranks of their variances. Statistical analyses were performed using the R package metaprop and metagen. Statistical analyses were performed using the "meta" package within R version 4.0.3 (R Core Team, a language and environment for statistical computing, Vienna, Austria, 2020, https://www.R-project.org/). Two-sided p-values were used. To establish the quality assessment of included articles, the Ottawa quality assessment tool was used [5].

3. Results

3.1. Study selection criteria and study quality

From the search strategy, we obtained 2317 articles, of which 133 were considered relevant based on title/abstract and selected for extensive assessment performed by four investigators independently after the primary screening. Fifteen articles were added by reviewing the reference list of relevant articles. Of these 148 articles, 23 studies focusing on PS in PDAC patients were included in the systematic review, as shown in the PRISMA flow diagram (Supplementary Material Fig. 1), and 17 articles were included in the meta-analysis. Based on the Ottawa quality assessment, eighteen articles were of good quality, five were of fair quality, and none were of poor quality (Supplementary Material Table 1).

3.2. Prevalence of pancreatic steatosis in patients with PDAC

The prevalence of PS in PDAC was described in seventeen studies, including 998 patients with PDAC (Supplementary Material Table 1). Sample sizes varied from 10 to 165 patients. Eleven studies were conducted in Japan, four in the USA, one in Indonesia and one in Israel. PS was assessed by CT in seven studies, EUS in six studies and histology of resected pancreatic tissue in four studies. Heterogeneity of the prevalence of PS in PDAC patients was found across studies (I^2 = 98 %, Q = 948.8 with 16 degrees of freedom, p < 0.0001) varying from 18.7 % (95 % CI 11.3–29.1) to 100 % (95 % CI 90.4–100) (Fig. 2). Overall, the pooled prevalence of PS was 53.6 % (95 % CI 40.9–66.2). The heterogeneity was further exposed in the drapery plot (Fig. 3a), showing very little overlap of the 95 % confidence intervals around the prevalence reported in the different studies. Examination of the funnel plot revealed no evidence of publication bias (p = 0.25 by Begg's test) (Fig. 3b).

In the subgroup analyses, we observed no difference according to study country (p = 0.50) or method of assessment of PS (p = 0.71), but there was overall a strong and significant heterogeneity across studies within each of the subgroup considered (I^2 ranging from 87 % to 98 %) (Table 2, Supplementary Material Figs. 2–3).

3.3. Pancreatic steatosis in patients with - and without PDAC

Risk estimates for the association between PS and PDAC were available in fourteen studies (Table 3, Fig. 4). This included nine studies from Japan, three from the USA, one from Indonesia and one from Israel. PS was assessed by CT in six studies, EUS in five studies, histology examination of resection specimens in two studies and MRI in one study. Most of the studies (12 out of 14) used non-malignant pancreatic diseases or non-pancreatic diseases as control. However, one study used healthy controls [6], while another study used both healthy controls and patients with other GI pathology as controls [17]. Overall, the pooled OR for PS in PDAC patients, as compared to controls, was 3.23 (95 % CI 1.86–5.60). Examination of the funnel plot revealed evidence of publication bias (p = 0.03 by Begg's test) (Fig. 5b). Again, significant heterogeneity regarding the magnitude of association between PS and PDAC was demonstrated (I2 = 85 %, Q = 84.3 with 13 degrees of freedom, p < 0.0001) varying from 0.69 (95 % CI 0.28–1.70) to 164.7 (95 % CI 9.70–2797) (Fig. 5a).

Subgroup analysis did not reveal any difference according to country (p = 0.52), but higher OR was observed in studies using EUS for the assessment of PS (pooled OR = 6.26, 95 % CI 1.23–31.8) compared to studies using CT (pooled OR = 3.31, 95 % CI 1.93–5.68),

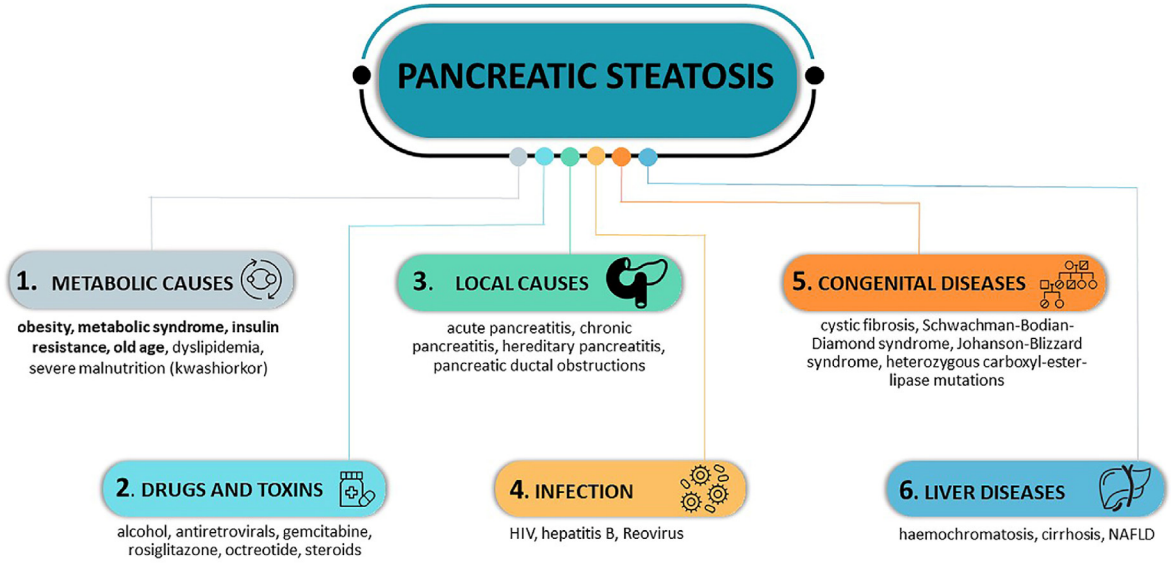

Fig. 1. Infographic showing risk factors involved in pancreatic steatosis [8–10]
Most frequent risk factors involved in PS.

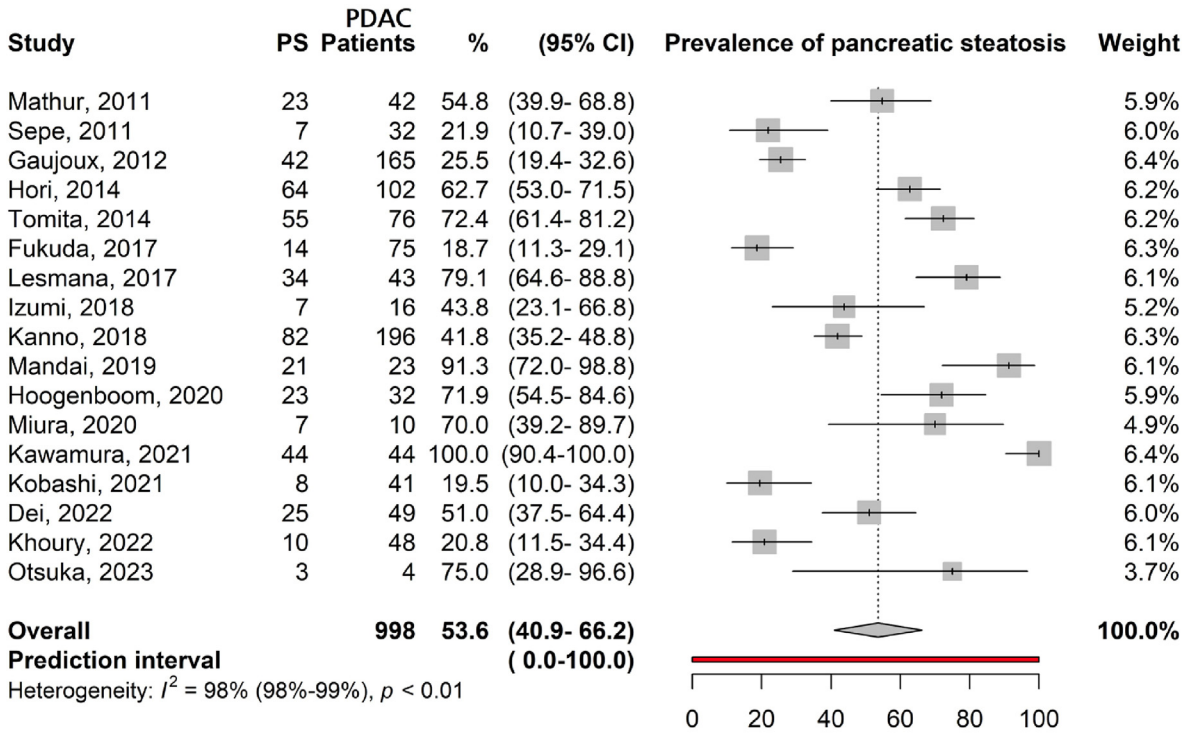

Fig. 2. Forrest plot presenting the PS prevalence in PDAC population.

histology (pooled OR = 1.76, 95 % CI 1.22–2.54) or MRI (pooled OR = 1.19, 95 % CI 1.06–1.33) (Supplementary Material Figs. 4–5). Heterogeneity of ORs was present for most of the subgroups considered (Table 4).

4. Discussion

Since pancreatic cancer is such a dismal disease, identifying and attending to risk factors is one way to prevent the development of a hitherto-incurable disease. Pancreatic steatosis is such a risk factor.

This meta-analysis highlights a substantial prevalence of PS among the investigated PDAC cohort, standing at 53.6 % (95 % CI: 40.9–66.2). PDAC patients have a more than threefold higher risk of PS than the control population. These findings emphasize the crucial role of identifying PS promptly, as it may either represent a reversible risk factor or an early indicator of PDAC.

Recently, a comparable meta-analysis was published, reporting an even higher OR of 6.1 (95 % CI 2.6–14.4) for PS in PDAC [18]. However, our study included six additional relevant studies that were not incorporated into the aforementioned meta-analysis, enhancing the comprehensiveness and power of our study [12,14,19–22]. Furthermore, additional subgroup analyses were conducted in our study, based on the diagnostic modality for identifying PS and the geographical region of the studies. Notably, PS was more frequently detected on EUS in PDAC patients than controls (pooled OR = 6.26, 95 % CI 1.23–31.8). One potential reason behind the elevated incidence of PS detected could be attributed to

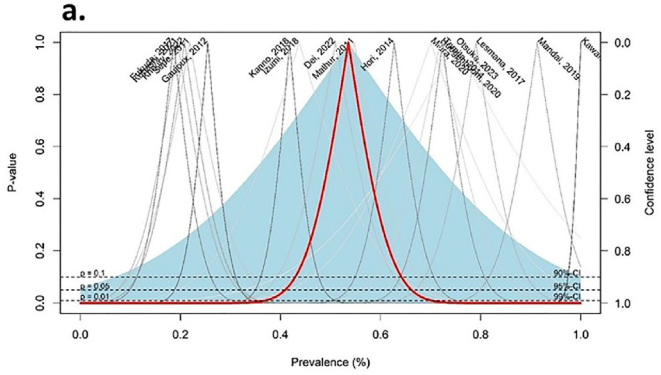

Fig. 3a. Drapery plot.

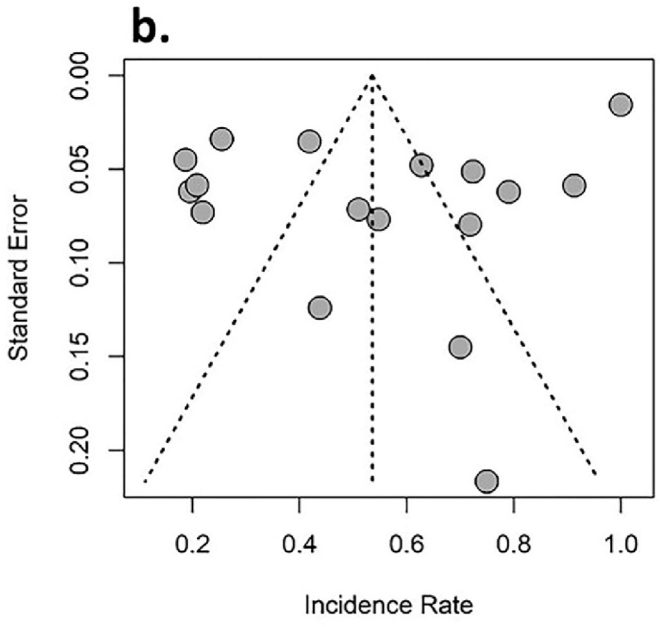

Fig. 3b. Funnel plot for PS prevalence.

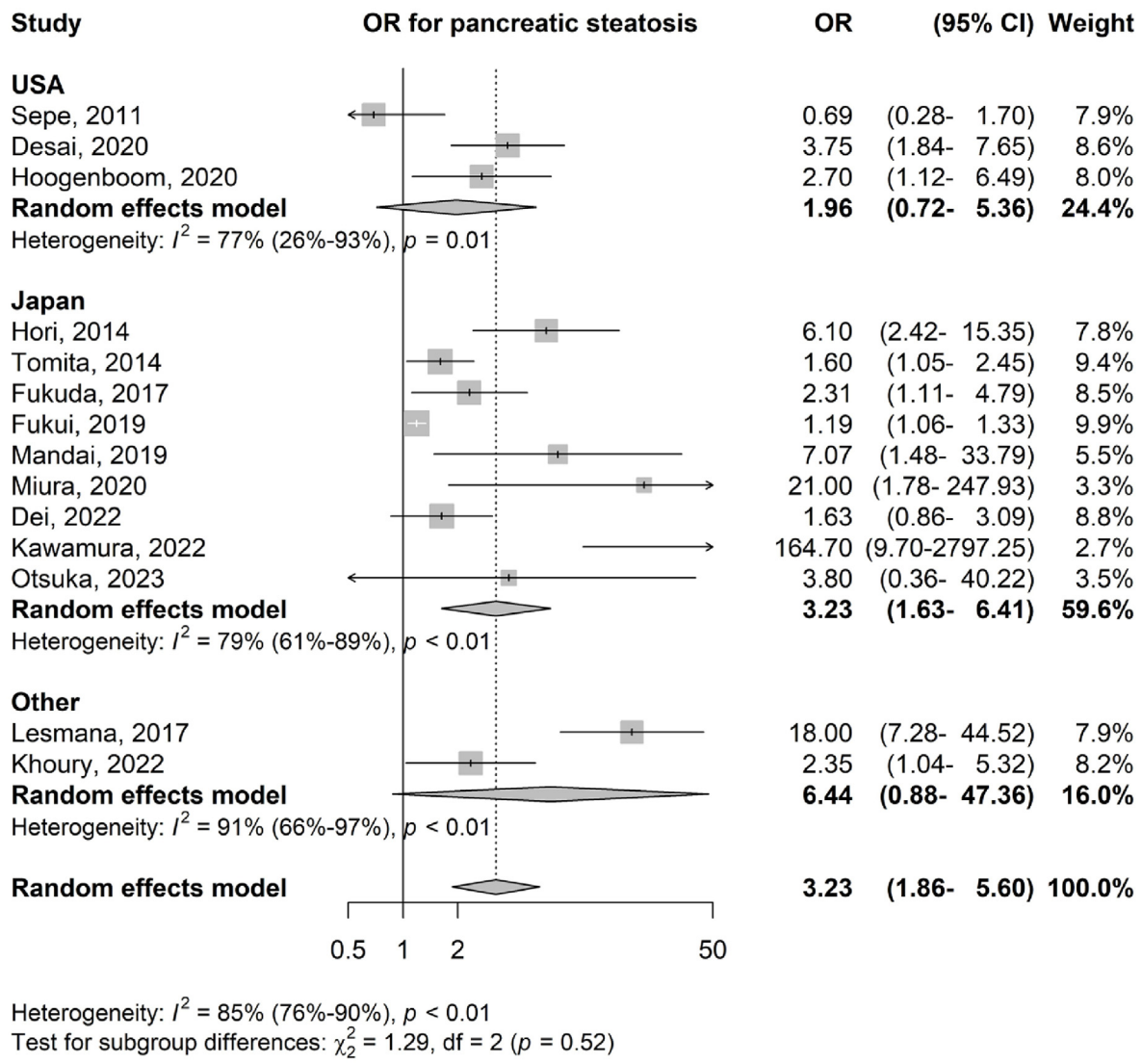

Fig. 4. Forrest plot representing Odds Ratio of PS amongst PDAC patients within the studies from the meta-analysis; OR: odds ratio; CI: confidence interval.

the absence of pancreatic fat quantification or grading systems in EUS. The evaluation of "excessive" pancreatic fat is operator-dependent and therefore inherently subjective.

Previous studies conducted in individuals without PDAC have indicated varying prevalence rates of PS, ranging from 16 % to 35 % in Asia, while notably higher rates of 45 %–51 % have been reported in the United States [4,23–25]. However, our subgroup analysis demonstrated no statistically significant variance in the prevalence of PS among the various countries where the original studies were conducted, for both PDAC patients and the control group.

The pathogenesis of PS and its connection with PDAC is multifactorial, with both conditions being linked to factors such as obesity, diabetes mellitus, and advanced age [26–28]. Chronic inflammation resulting from fatty infiltration is believed to play a pivotal role in PDAC development, as shown by Tomita et al. [6]. In an animal model studied by Takahashi, various factors, including increased oxidative stress, metabolic syndrome, dysregulated adipocytokines, heightened N-nitrosobis and non-esterified fatty acids levels, were identified as significant contributors to PDAC onset [29]. Furthermore, the presence of PS in PDAC has been associated with prognosis, due to increased cancer dissemination, such as lymphatic metastasis, and heightened cancer lethality [30].

Clinical consequences of a reported high prevalence of PS among PDAC patients include treatment of metabolic syndrome manifestations such as hypertension, abdominal obesity, impaired glucose levels and dyslipidemia [31,32]. Preliminary studies found that interventions like weight loss, metformin or troglitazone administration in an animal study could diminish fatty infiltration and potentially mitigate the risk of PDAC [33–35]. Additionally, bariatric surgery may be an alternative approach to reducing pancreatic fat levels, as indicated by previous research findings [36,37]. Future research should point out the efficacy of targeting underlying conditions to mitigate the risk of PDAC.

Given the elevated prevalence of PS in PDAC patients, an important clinical consideration arises regarding whether individuals with incidentally discovered PS should undergo annual screening for PDAC. Presently, population-based screening for PDAC in asymptomatic adults is not advocated due to the incidence of PDAC and the absence of evidence indicating that treatment of screen-detected PDAC enhances survival rates [38]. Nonetheless, the identification and risk stratification of individuals at high risk for PDAC should persist, as mounting evidence indicates that surveillance of such high-risk groups results in the detection of PDAC at earlier stages, consequently enhancing survival rates [39–42].

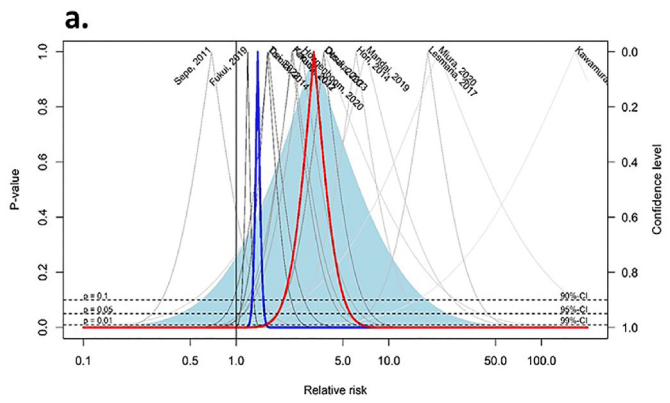

Fig. 5a. Drapery plot on odds ratio.

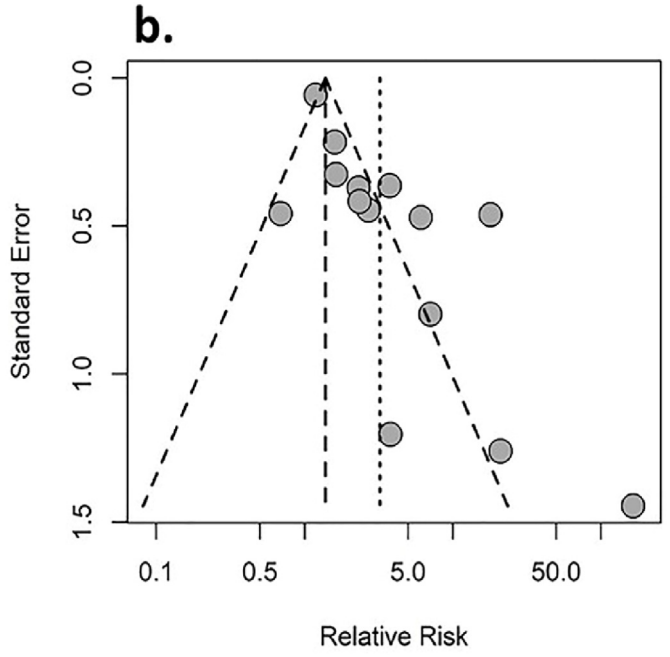

Fig. 5b. Funnel plot on odds ratio.

Future studies should endeavor to validate the potential utility of pancreatic steatosis as a novel risk indicator for PDAC within surveillance programs for high-risk individuals. By investigating the correlation between pancreatic steatosis and PDAC within this specific context, the role of this imaging finding as a predictive marker can be further elucidated. Additionally, forthcoming studies may clarify the optimal imaging modality for surveillance purposes.

Potential imaging techniques include CT, MRI, EUS and abdominal ultrasound. Despite the ease of access to abdominal ultrasound, its specificity and sensitivity for detecting pancreatic steatosis are low, and visualization of the entire gland is often impractical, rendering the procedure highly operator-dependent. Consequently, abdominal ultrasonography is not considered suitable for pancreatic steatosis detection [43,44].

In the included studies by Sepe et al. and Mandai et al., PS was evaluated using EUS, albeit lacking objective quantification [19,45]. Kawamura employed various regions of interest (ROIs) in the pancreas, spleen, and left kidney to calculate pancreatic fat infiltration [17]. Furthermore, strain histograms and strain ratios offer more dynamic information regarding pancreatic parenchyma compared to assessments of the spleen, gastrointestinal wall, and left kidney [46]. Despite EUS and its complementary modules can provide crucial insights into pancreatic parenchymal characteristics, the procedural invasiveness, requirement for sedation, operator dependency, and limited accessibility collectively diminish the utility of EUS as a screening tool for PS.

CT without contrast can be used to measure the HU of the spleen and pancreas, and then calculate the pancreas-to-spleen attenuation ratio (P/S ratio). Despite the fact that CT leads to ionizing radiation exposure, there are multiple advantages of this procedure, including high accessibility and reproducibility [47]. As demonstrated in our meta-analysis, CT evaluation emerged as the predominant method for assessing PS, making it the most commonly utilized diagnostic tool. However, for MRI, several techniques have been devised to evaluate pancreatic fat content, including proton density fat fraction (PDFF), elastography (MRE), and spectroscopy (MRS) [15,46,48]. PS on MR is characterized by hyperintense parenchyma in T1-weighted and T2-weighted sequences compared to liver [28]. Interestingly, a recent study has unveiled a novel approach to the assessment of PS utilizing advanced artificial intelligence techniques. Specifically, this study demonstrated the feasibility of quantifying PS through CT and MRI employing a convolutional neural network (CNN) algorithm [49].

Future research endeavors should place emphasis on advancing noninvasive imaging methodologies and leveraging the capabilities of artificial intelligence (AI)-based algorithms for the detection of PS. This necessitates the establishment of standardized imaging protocols alongside unequivocal grading definitions for PS.

Obesity remains an independent risk factor in PDAC, doubling its relative risk [30]. Several studies link NASP to pancreatic cancer, though not enough evidence is available [28]. Iyengar et al. demonstrated that tumorigenesis in breast cancer cells is stimulated by adipocyte-dependent inflammation [50]. These results were extended in pancreatology when Tomita et al. demonstrated that inflammation from fatty infiltration is a predisposing factor for PDAC [6]. The hypothesis for PS as a risk factor for PDAC is multifactorial, including increased oxidative stress, metabolic syndrome, adipocytokines dysregulation, increased N-nitrosobis and non-esterified fatty acids, as demonstrated in an animal model by Takahashi [29]. Mathur et al. showed that patients with PS present a worse prognosis in PDAC due to increased dissemination (lymphatic metastasis) and lethality of cancer [30]. Both Dei et al. and Noda et al. have associated higher rates of postoperative pancreatic fistula with fatty pancreas [22,51]. Therefore, measuring PS prior to surgery should become mandatory, being considered a potential postoperative predictive factor, its presence being linked to negative outcome due to increased risk of fistula [32]. PS can be taken into consideration as a risk factor for premalignant pancreatic lesions such as PanIN lesions and IPMN [47].

Multiple factors can interfere with pancreatic exocrine insufficiency, such as lipotoxicity, negative paracrine effect and cellular apoptosis due to fatty replacement [28,32]. Tahtaci et al. have demonstrated decreased levels of faecal elastase in patients with PS compared with the non-steatosis control group [52].

The robustness of this meta-analysis lies in its comprehensive scope, representing the most extensive study so far regarding PS in PDAC patients. However, our study faces certain limitations that warrant consideration. Primarily, a notable challenge arises from the high degree of heterogeneity observed across the studies included in our meta-analysis. Despite efforts to account for variables, such as the analysis of different imaging modalities and geographical sites of the study populations, the underlying factors contributing to this heterogeneity remain elusive. This suggests true heterogeneity among the population effect sizes, as estimated by the individual studies although the differences between studies

Table 1
Studies focused on pancreatic steatosis and PDAC [4,6,12,14,17,19–23,30,45,48,51,53–61].

	STUDY CHARACTERISTICS	STUDY DESIGN	ASSESSMENT OF PS	IS PS A RISK FACTOR FOR PDAC?	MAIN FINDINGS	Patients with PDAC and PS	Patients with PDAC	Controls with PS	Controls without PS
1	*Mathur, 2011, USA*	retrospective	CT	NA	Increased pancreatic steatosis is associated with lymphatic metastasis in PDAC.	23	42	NA	NA
2	*Sepe, P. 2011, USA*	prospective	EUS	NO	No association was proved between PS and PDAC.	7	32	57	198
3	*Gaujoux, 2012, USA*	retrospective	PATHOLOGY	NA	Body weight and fat distribution are not correlated with histologic changes or survival in patients with PDAC.	42	165	NA	NA
4	*Hori, 2014, Japan*	retrospective	CT	YES	Fat infiltration in the pancreatic parenchyma is associated with PDAC, after adjustment for BMI, diabetes and other confounding factors.	64	102	30	85
5	*Tomita, 2014, Japan*	retrospective	PATHOLOGY	YES	Pancreatic inflammation due to fatty infiltration is a predisposing factor to PDAC.	55	76	43	98
6	*Hori, 2016, Japan*	retrospective	CT	NA	Pancreatic fatty infiltration can easily and more accessible be calculated by CT than by histopathology.	NA	37	NA	NA
7	*Fukuda, 2017, Japan*	retrospective	CT, PATHOLOGY	YES	Pancreatic CT index (pancreas to spleen ratio in Hounsfield units) over 0.7 can be used as predictor for PDAC.	14	75	14	43
8	*Lesmana, 2017, Indonesia*	retrospective	EUS	YES	PS is more frequently encountered in patients with PDAC.	34	43	19	119
9	*Kanno, 2018, Japan*	retrospective	CT	NA	Fat infiltration might be a specific marker in early PDAC.	82	196	NA	NA
10	*Schawkat, 2018, Switzerland*	retrospective	MRI, PATHOLOGY	NA	PDAC presents high magnetization transfer ratio compared with pancreatic parenchyma, thus higher fat content.	NA	20	NA	NA
11	*Izumi, 2019, Japan*	retrospective	EUS	NA	In situ pancreatic carcinoma often is seen alongside PS and chronic pancreatitis.	7	16	NA	NA
12	*Fukui, 2019, Japan*	retrospective	MRI AND CT, PATOLOGY	NA	Prevalence of PS on pathology, CT and MRI is higher is patients with PDAC than controls. MRI is a superior to CT in assessing PS.	NS	24	NS	31
13	*Mandai, 2019, Japan*	retrospective	EUS, US	YES	Hyperechoic pancreas is a risk factor for PDAC in IPMN patients.	21	23	60	92
14	*Noda, 2019, Japan*	retrospective	PATHOLOGY, MRI	YES (pathology), NO (MRI)	Histopathological changes of PS are more frequent in PDAC than non PDAC patients.	20	31	NA	NA
15	*Hoogenboom, 2020, USA*	retrospective	CT	YES	Pancreatic steatosis was present in 71.9% of cases compared to 45.3% of controls.	23	32	53	117
16	*Miura, 2020, Japan*	retrospective	PATHOLOGY	YES	Focal pancreatic parenchymal fat is seen more frequently in PDAC patients compared to patients presenting benign lesions.	7	10	1	10
17	*Desai, 2020, USA*	retrospective	CT	YES	Fatty infiltration of the pancreas is a risk factor for PDAC.	NS	68	NS	235
18	*Janssens, 2021, USA*	retrospective	CT	N/A	Pancreatic mean HU is significantly lower in prediagnostic PDAC patients as compared to controls	NA	46	NA	NA
19	*Kawamura, 2021, Japan*	retrospective	EUS	YES	PDAC can be determined by ectopic pancreatic fat infiltration.	44	44	23	66

20	*Kobashi, 2021, Japan*	retrospective	CT	NO	Even though the "K-sign" can be considered a predictor for PDAC, the study cannot associate PS as risk factor for PDAC.	8	41	NA	NA
21	*Khoury T, 2022*	retrospective	EUS	YES	PS is an important risk factor for PDAC, with an OR of 2.53 (95% CI: 1.23-5.57, p=0.01)	10	48	NA	NA
22	*Dei, 2022, Japan*	retrospective	CT	YES	Pancreatic steatosis is associated with higher risks of post-operative pancreatic fistula.	25	49	67	179
23	*Otsuka, 2023*	retrospective	CT	YES	Autophagy destruction is promoted by fat infiltration in the pancreatic parenchima, thus rendering PS as risk factor for PDAC.	3	4	15	34

CT: computerized tomography; EUS: endosonography; OR: odds ratio; MRI: magnetic resonance imaging; PDAC: pancreatic ductal adenocarcinoma; PS: pancreatic steatosis; NA: not available

Studies that were included in the prevalence analysis

Studies that were not included in the prevalence analysis due to lack of data from the control groups

Table 2
Stratified analysis of PS according to country of origin and method of diagnosis.

Subgroup	Studies (patients)	Pooled prevalence	Heterogeneity I^2, p-value	$\chi 2$ test for difference across subgroups
Overall	17 (998)	53.6 (40.9–66.2	98 %, p < 0.01	
Country				1.40 (df = 2, p = 0.50)
USA	4 (271)	42.8 (22.7–63.0)	92 %, p < 0.01	
Japan	11 (636)	58.2 (42.4–74.1)	98 %, p < 0.01	
Other[a]	2 (91)	49.9 (9.5–90.2)	98 %, p < 0.01	
Method				0.69 (df = 2, p = 0.71)
CT	7 (466)	51.4 (38.6–64.2)	87 %, p < 0.01	
EUS	6 (206)	60.1 (34.0–86.2)	98 %, p < 0.01	
Pathology	4 (326)	44.9 (20.6–69.2)	96 %, p < 0.01	

[a] Indonesia, Israel.

likely stem from the influence of multiple, but undetermined, characteristics that vary across these studies. However, this limitation highlights the gaps in research within this specific area of interest, as prospective studies in the field are exceedingly rare. There is an urgent need for randomized controlled trials on PS in PDAC patients to determine the most accurate diagnostic method and to develop a standardized approach, ensuring consistency and improving diagnostic outcomes in clinical practice. Moreover, while histological examination stands as the diagnostic standard for PS, its practical application is limited due to the invasive nature of the procedure and the inherent challenges associated with tissue acquisition. A notable drawback of our study is the reliance on imaging findings without histological validation in the majority of studies. This discrepancy introduces a significant constraint in the interpretation of our findings. Furthermore, it is essential to acknowledge that the retrospective nature of the studies included,

Table 3
Studies included for estimating the association between PS and PDAC measuring odds ratio.

Study	Method	Country	Year	PACA	-VE	+VE	CTRL	-VE	+VE	Adjustment	OR	95%Lower	95%Upper
Sepe, 2011	EUS	USA	2011	32	25	7	198	141	57	univariate	0.69	0.28	1.69
Hori, 2014	CT	Japan	2014	102	38	64	85	55	30	multivariate	6.1	2.4	15.2
Tomita, 2014	Pathology	Japan	2014	76	21	55	98	55	43	multivariate	1.6	1.05	2.46
Fukuda, 2017	Pathology	Japan	2017				43	29	14	multivariate	2.31	1.12	4.81
Lesmana, 2017	EUS	Indonesia	2017	43	9	34	119	100	19	multivariate	18	7.29	44.59
Fukui, 2019	MRI	Japan	2019	24			31			multivariate	1.19	1.06	1.33
Mandai, 2019	EUS	Japan	2019	23	2	21	92	32	60	multivariate	7.07	1.48	33.8
Desai, 2020	CT	USA	2020							multivariate	3.75	1.92	7.99
Hoogenboom, 2020	CT	USA	2020	32	9	23	117	64	53	multivariate	2.7	1.14	6.58
Miura, 2020	CT	Japan	2020	10	3	7	10	9	1	Univariate*	21	1.78	248.1
Dei, 2022	CT	Japan	2022	49	24	25	179	112	67	univariate	1.63	0.86	3.09
Kawamura, 2022	EUS	Japan	2022	44	0	44	66	33	23	Univariate*	164.7	9.7	2798
Khoury, 2022	EUS	Israel	2022	48	38	10	471	427	44	multivariate	2.35	1.04	5.33
Otsuka, 2023	CT	Japan	2023	4	1	3	34	19	15	univariate	3.8	0.36	40.33

Table 4
Stratified analysis on odds ratio of PS in PDAC comparing the country of origin and method of diagnosis.

Subgroup	Studies	Pooled Odds Ratio	Heterogeneity I^2, p-value	$\chi 2$ test for difference across subgroups
Overall	14	3.23 (1.86–5.60)	85 %, $p < 0.01$	
Country				1.29 ($df = 2$, $p = 0.52$)
USA	3	1.96 (0.72–5.36)	77 %, $p < 0.01$	
Japan	9	3.23 (1.63–6.41)	79 %, $p < 0.01$	
Other[a]	2	6.44 (0.88–47.4)	91 %, $p < 0.01$	
Method				20.1 ($df = 3$, $p < 0.01$)
CT	6	3.31 (1.93–5.68)	42 %, $p = 0.13$	
EUS	5	6.26 (1.23–31.8)	88 %, $p < 0.01$	
Pathology	2	1.76 (1.22–2.54)	0 %, $p = 0.39$	
MRI	1	1.19 (1.86–5.60)	–	

[a] Indonesia, Israel.

with the exception of one notable study [19], introduces a potential source of bias. Compared to the recent meta-analysis performed by Lipp et al., in the present study also subgroup analyses were performed on the method of assessment and country of origin [34]. Opting for pooled prevalence was optimal since there were no significant differences found in the subgroup analysis. We also noted the presence of publication bias indicating that larger or statistically significant effects (Odds ratios) were more likely to be published than smaller or non-statistically significant effects, eventually leading to an overestimation of the association. In summary, while our meta-analysis represents a comprehensive effort to elucidate the role of PS in PDAC, the identified limitations underscore the need for a cautious interpretation of our findings and highlight avenues for further research to address these constraints and enhance the validity of future studies in this domain.

5. Conclusions

Patients with PDAC have a notable prevalence of pancreatic steatosis (53.6 %). Furthermore, compared to controls, PDAC patients are significantly more likely to have PS (OR 3.23). These findings underscore the importance of prioritizing a standardized approach to the diagnosis, follow-up, and treatment of PS. Future studies should prioritize the identification of patients with PS who will benefit from PDAC surveillance programs.

Author contributions

Conceptualization, M.L., D.O, M.S. and S.H.; methodology, C.V., C.S., D.T., T.H.; formal analysis, P.M.; investigation and data collection, C.V., C.S., D.T., T.H.; writing—original draft preparation, C.V.; writing—review and editing, C.S., D.T., T.H., P.M. and S.H.; visualization, C.V and D.T.; supervision, P.M, M.L., D.O, and M.S.; project administration, C.V. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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