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Fatty Pancreas as a Marker of Tumor Dissemination in Pancreatic Cancer: A Systematic Review and Meta-analysis

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Abstract

Pancreatic steatosis is common in pancreatic cancer, but previous syntheses addressed mainly prevalence and cancer risk rather than tumor behavior after diagnosis. We evaluated whether fatty pancreas is associated with greater dissemination in adults with established pancreatic cancer. Five databases were searched through June 19, 2026 under a registered protocol (PROSPERO CRD420261445124). Observational studies classifying fatty pancreas by imaging or histology were eligible. Lymph node metastasis was the primary outcome and overall survival the secondary outcome. Estimates were pooled with random-effects models; risk of bias was assessed with Quality In Prognosis Studies and certainty with GRADE. Six studies (416 patients) were included. Fatty pancreas was associated with a modest excess of nodal positivity (four studies, 275 patients; risk ratio 1.27, 95% CI 1.03–1.57; I^2 = 3%), but significance was lost when any of three studies was omitted. No statistically significant association with overall survival was identified (three studies, 268 patients; hazard ratio 1.23, 95% CI 0.64–2.38; I^2 = 77%). Certainty was very low for both outcomes, and these hypothesis-generating findings do not support a current clinical role.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal solid tumors and is projected to be among the leading causes of cancer death worldwide [1]. It is usually detected late, disseminates early through lymphatic and haematogenous routes, and recurs in most patients even after margin-negative resection. Lymph node involvement is a proximal, reproducible and clinically consequential marker of that spread, with direct implications for staging, resectability assessment and treatment planning. Anatomical staging and carbohydrate antigen 19 – 9 (CA19-9) capture much, but not all, of the biological variability that drives dissemination, which sustains interest in complementary tissue-level markers of post-diagnosis tumor behaviour.

Fatty pancreas, also termed pancreatic steatosis, intrapancreatic fat deposition (IPFD) or non-alcoholic fatty pancreas disease, denotes fat accumulation within the pancreatic parenchyma, either as intralobular and interlobular adipocyte infiltration or as intracellular lipid. It can be classified by computed tomography (CT) attenuation, by magnetic resonance imaging (MRI) including proton-density fat fraction, by endoscopic ultrasound (EUS) or transabdominal ultrasound echogenicity, or by histology [2, 3]. Unlike body mass index or generalized adiposity, fatty pancreas is an organ-level phenotype that reflects the metabolic and cellular milieu immediately surrounding the tumor and is measurable on routine staging imaging or on surgical pathology [4].

The existing evidence base is essentially one of prevalence and risk. A systematic review and meta-analysis reported a pooled prevalence of pancreatic steatosis of 53.6% (95% CI 40.9–66.2) among patients with PDAC and a pooled odds ratio of 3.23 (95% CI 1.86–5.60) for the presence of PDAC in individuals with steatosis [5]. Consistent with an early role in the disease course, pancreatic steatosis on CT has been described up to three years before clinical diagnosis [6], histological fatty infiltration is enriched in resected PDAC specimens [7], and IPFD relates differently to distinct carcinoma types [8]. The risk of developing pancreatic cancer and the behaviour of cancer already established are, however, non-equivalent constructs, and the latter has not been addressed by formal synthesis.

There is biological plausibility for a relationship between intrapancreatic fat and tumor behaviour. An adipocyte-rich intrapancreatic microenvironment may favour tumor progression through adipocytokine signalling, chronic low-grade inflammation, lipotoxicity and altered fatty-acid metabolism [2, 3]. Histopathological work links pancreatic fatty infiltration with acinar-to-ductal metaplasia and pancreatic intraepithelial neoplasia [9], and mechanistic reviews position non-alcoholic fatty pancreas disease as a pre-neoplastic niche [10]. In murine models, high IPFD accelerated PDAC growth, liver metastasis and intraperitoneal dissemination, with upregulation of fatty acid-binding protein 5 (FABP5) and of RAC1-dependent migration [11]. This experimental evidence is contextual only and does not establish causality in patients.

We therefore conducted a systematic review and meta-analysis to evaluate whether fatty pancreas is associated with greater tumor dissemination in adults with established pancreatic cancer, taking lymph node metastasis as the primary outcome and overall survival as the secondary outcome, with additional clinicopathological outcomes summarized narratively. Associative rather than causal language is used throughout.

Methods

Protocol and reporting

This systematic review and meta-analysis was registered in PROSPERO (CRD420261445124) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12] and, for observational evidence, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations [13]. Outcomes that could not be pooled were summarized

following the Synthesis Without Meta-analysis (SWiM) reporting guideline [14]. The completed PRISMA 2020 and MOOSE checklists are provided in Online Resource 1, Tables S5 and S6.

Search strategy

We searched MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection and the Cochrane Library from inception to June 19, 2026, combining controlled vocabulary with free-text terms for pancreatic cancer and for fatty pancreas, pancreatic steatosis and intrapancreatic fat deposition. Outcome terms were not required in MEDLINE/PubMed, Embase, Scopus or Web of Science; preliminary testing showed that requiring prognosis, survival, metastasis or lymph-node terminology reduced retrieval sensitivity and risked omitting eligible studies, so a broad disease–exposure strategy was used to maximize sensitivity. In the Cochrane Library, a broad disease–exposure set and a supplementary outcome-focused set were both run. Reference lists of included studies and relevant reviews were hand-searched; no language restriction was applied. Complete database-specific strategies with exact syntax and the records retrieved per database are given in Online Resource 1, Table S1.

Eligibility criteria

We included observational studies (cohort, case-control and cross-sectional) of adults with established pancreatic cancer, prioritizing histologically confirmed PDAC, that classified fatty pancreas by imaging or histology and reported at least one measure of tumor dissemination, aggressiveness or survival by fatty-pancreas status. Broader pancreatic cancer cohorts were included when invasive ductal adenocarcinoma data were separable. We excluded pancreatic neuroendocrine neoplasms, acinar cell carcinoma, solid pseudopapillary neoplasms and non-invasive cystic or intraductal papillary mucinous neoplasms without invasive carcinoma, unless separable invasive PDAC data were available. Studies addressing only the prevalence of, or the risk of developing, pancreatic cancer were not eligible for quantitative synthesis; such studies, together with prior reviews, consensus statements and animal or in vitro work, were used only as background. Conference abstracts and registry or protocol records without extractable results were excluded.

Study selection and data extraction

Searches were run in the native database interfaces. Records were exported, deduplicated, and screened using a structured electronic review workflow. Titles and abstracts were screened and full texts then assessed against the eligibility criteria; selection and extraction were performed independently and in duplicate by two reviewers, with disagreements resolved by discussion or a third reviewer. We extracted study identifiers and design, country and setting, cancer population and method of confirmation, total cohort size and the analytic sample contributing to each estimate, baseline demographic and metabolic characteristics, the modality, threshold and anatomical region used to classify fatty pancreas, the outcomes reported, effect estimates with measures of precision, covariates used for adjustment, follow-up, and notes on incomplete or inconsistent reporting. Where an outcome was reported both crude and adjusted, both were recorded, and reconstructed estimates were identified explicitly.

Exposure and outcome definitions

The exposure was fatty pancreas, pancreatic steatosis or IPFD, classified by CT attenuation (including pancreas-to-spleen ratios), by MRI, by EUS or ultrasound echogenicity, or by histological pancreatic fat fraction or adipocyte quantification. The comparator was absent fatty pancreas or a lower pancreatic-fat category according to each study definition. Thresholds were study-specific and were not standardized retrospectively; each definition, threshold and measurement region is reported in Table 2 and in Online Resource 1, Table S7. CT, MRI, EUS and histology quantify different constructs, and low statistical heterogeneity was not interpreted as evidence of clinical equivalence between them.

Because pancreatic fat measured within tumor tissue or at the invasive front is liable to misclassification, we recorded whether pancreatic fat was measured in non-tumoral parenchyma or in an anatomically unspecified region to evaluate potential exposure misclassification. Nodal ascertainment was similarly heterogeneous: pathological nodal status in resected cohorts is not interchangeable with clinical or endosonographic nodal staging in predominantly unresectable disease. Both were treated as measures of nodal dissemination in the primary analysis, and the difference was examined in a subgroup analysis.

Lymph node metastasis or nodal positivity was evaluated as the primary outcome because it represents a direct measure of tumor dissemination and was sufficiently comparable across studies for quantitative synthesis. Overall survival or all-cause mortality was evaluated as the secondary outcome, with adjusted hazard ratios (HRs) preferentially extracted. Exploratory outcomes, summarized

narratively because definitions and reporting were not sufficiently comparable for pooling, were advanced clinical stage, distant metastasis, tumor size, T stage, tumor location, histological grade, lymphatic, vascular and perineural invasion, CA19-9, resection margin status, recurrence and recurrence-free or progression-free survival, and postoperative outcomes including clinically relevant pancreatic fistula. Every outcome evaluated in the review is reported, either as a pooled estimate or narratively, in Online Resource 1, Table S8.

Risk-of-bias assessment

Risk of bias was assessed with the Quality In Prognosis Studies (QUIPS) tool [15], chosen because fatty pancreas was evaluated as a prognostic, tissue-level exposure rather than a therapeutic intervention. All six QUIPS domains were assessed: study participation, attrition, prognostic-factor measurement, outcome measurement, confounding, and statistical analysis and reporting. Confounders considered during judgement were age, sex, adiposity, diabetes and metabolic comorbidity, chronic pancreatitis, tumor site and size, stage and resectability, CA19-9, nodal and margin status, histological grade, lymphovascular and perineural invasion, and treatment received. Each domain was judged as low, moderate or high risk of bias; overall judgements reflected the likely impact of domain-level limitations on the association between fatty pancreas and the outcome and were not derived from a numerical score. Domain-level judgements are given in Online Resource 1, Table S3, and Supplementary Figs. S1a, S1b.

Statistical analysis

Analyses were oriented as fatty pancreas versus no fatty pancreas. For the primary dichotomous outcome we pooled risk ratios (RRs) with 95% confidence intervals (CI), because nodal events are common and the RR is more interpretable than the odds ratio. A 0.5 continuity correction was applied to all cells of any two-by-two table containing a zero cell. For overall survival we pooled the natural logarithm of the HR and its standard error (SE) by inverse-variance weighting, with HR > 1 indicating higher mortality with fatty pancreas. Random-effects models were used for all syntheses; between-study variance (τ^2) was estimated by restricted maximum likelihood (REML) and CIs were Wald-type. Heterogeneity was quantified with Cochran Q, τ^2 and I^2; I^2 was derived from the REML estimate of τ^2 relative to the typical within-study variance, as implemented in the software, and therefore differs slightly from the value obtained from Cochran Q alone. Analyses were performed in Review Manager (RevMan) version 11.3.1 [16].

Normal-approximation prediction intervals were calculated as the pooled effect plus or minus 1.96 times the square root of the sum of τ^2 and the squared standard error of the pooled effect. They were reported as exploratory descriptors and interpreted cautiously because only three or four studies contributed to each synthesis.

One survival estimate was not reported with a CI or SE and was reconstructed from the reported HR (1.031) and its two-sided P value (0.923) using the standard relationships between log(HR), the standard normal quantile and the SE [17], giving HR 1.03 (95% CI 0.56–1.91). Because both inputs were rounded, the derivation was repeated across a half-unit in the last reported digit of each input; the resulting variation did not materially affect the assigned weight. The full derivation and rounding check are given in Online Resource 1. The estimate is labelled as reconstructed throughout and was examined in a sensitivity analysis.

Subgroup analyses compared imaging-defined with histology-defined fatty pancreas, CT-defined estimates alone, pathological with clinical or endosonographic nodal ascertainment, resected with non-resected cohorts, and adjusted with unadjusted estimates; differences were tested with a chi-squared test on one degree of freedom. Sensitivity analyses comprised a fixed-effect model, leave-one-out analysis and exclusion of the reconstructed survival estimate. Funnel plots and Egger's test were not performed because fewer than 10 studies contributed to any outcome.

Certainty of evidence

Certainty for each pooled outcome was rated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach across risk of bias, inconsistency, indirectness, imprecision and publication bias [18]. Observational prognostic evidence started at low certainty and could be rated down further; no criterion for rating up was met. Absolute effects for the nodal outcome were obtained by applying the pooled RR and its 95% CI limits to the assumed risk derived from the pooled comparator arms. Certainty judgements are summarized in Online Resource 1, Table S4.

Use of AI-assisted translation tools

The Google Gemini web application and the DeepL Translator web application, accessed in July 2026, were used solely to assist and cross-check the translation of one Chinese-language article during full-text screening and data verification. The specific Gemini model identifier was not displayed in the user interface. These tools did not make eligibility decisions, independently extract data, assess risk of bias,

perform statistical analyses, grade the certainty of evidence, or determine the scientific interpretation. All AI-assisted translations were checked against the original article by the authors, who take full responsibility for the accuracy and integrity of the review.

Results

Study selection

The searches identified 1,227 records (MEDLINE/PubMed, 209; Embase, 416; Scopus, 265; Web of Science Core Collection, 334; Cochrane Library, 3). After 675 duplicates were removed, 552 records were screened by title and abstract and 527 were excluded. Twenty-five full-text reports were assessed for eligibility, and nineteen were excluded for the reasons summarized in Fig. 1 and detailed in Online Resource 1, Table S2. Six studies met the inclusion criteria and entered the qualitative synthesis; four contributed to the primary nodal meta-analysis and three to the secondary survival meta-analysis. The selection process is shown in Fig. 1 [19].

Study characteristics

The six included studies comprised 416 patients and were retrospective cohort or case-control analyses conducted at single centers in China [20], Japan [21], Taiwan [22], Mexico [23] and the United States [24, 25]. Four studies restricted enrolment to histologically confirmed PDAC and three of these included only resected patients [20, 21, 24, 25]; one enrolled newly diagnosed pancreatic cancer, of which 82 of 101 cases (81.2%) were pathologically confirmed and 53 of 101 (52.5%) were stage IV [22]; and one enrolled ductal adenocarcinoma confirmed by EUS-guided fine-needle aspiration in a predominantly unresectable population, in which only 2 of 30 patients underwent resection [23]. Study and population characteristics are given in Table 1.

Fatty pancreas was classified heterogeneously. Two studies used non-contrast CT attenuation, one applying a pancreas-to-spleen ratio below 0.7 [20] and one using pancreatic attenuation in Hounsfield units with perirenal visceral fat [24]; one used CT or chemical-shift MRI with the measurement area placed away from the tumor [22]; one used EUS echogenicity relative to the renal cortex, graded I–III, in tumor-free parenchyma [23]; and two used histology, one applying a receiver operating characteristic (ROC)-derived study threshold for the histological pancreatic fat fraction of 11.3% in non-tumoral parenchyma [21] and one counting pancreatic fat cells at the pancreatic neck margin [25]. Fatty pancreas was present in 43 of 116 [20], 38 of 87 [21], 30 of 101 [22], 12 of 30 [23] and 23 of 42 [24] patients; the remaining study compared 20 node-positive with 20 matched node-negative patients using a continuous fat-cell count and provided no dichotomous exposure contrast [25]. Definitions, measurement regions, outcome ascertainment and the contribution of each study to each analysis are set out in Table 2 and in Online Resource 1, Table S7.

Four studies contributed to the nodal meta-analysis (275 patients) [20, 21, 23, 24] and three to the survival meta-analysis (268 patients) [20, 21, 22]. For survival the analytic sample was smaller than the enrolled cohort in one study, in which 80 of 116 patients had follow-up data [20]; the other two contributed their full cohorts of 87 [21] and 101 [22] patients. One study contributed to the qualitative synthesis only [25]. No cohort overlap was identified; the two reports by Mathur et al. originated from different institutions and patient series [24, 25].

Table 1
Study and population characteristics of the six included studies

Study	Country	Design and setting	Population and confirmation	Total, N	Fatty pancreas, n/N (%)	Age, years	Female, n (%)	BMI, kg/m²	Diabetes, n (%)
Dong et al. 2025	China	Retrospective cohort, single-center, 2013–2022	Histologically confirmed PDAC, radical resection	116	43/116 (37.1)	60 (54–65)	31 (26.7)	NR; BMI ≥ 25 kg/m² in 30/96	NR
Fukuda et al. 2025	Japan	Retrospective cohort, single-center, 2000–2022	Pathologically confirmed conventional PDAC, potentially curative pancreatectomy	87	38/87 (43.7)	72 (47–85)	42 (48.3)	22.1 (15.0–29.9)	NR
Chan et al. 2024	Taiwan	Retrospective imaging cohort, single-center, 2022	Newly diagnosed pancreatic cancer; 82/101 (81.2%) pathologically confirmed; 53/101 (52.5%) stage IV	101	30/101 (29.7)	66 (56.5–74)	50 (49.5)	22.6 (20.6–25.7)	30 (29.7)
Tróchez-Mejía et al. 2019	Mexico	Retrospective cohort, single-center, 2018–2019	Ductal adenocarcinoma confirmed by EUS-guided fine-needle aspiration; predominantly unresectable (2/30 resected)	30	12/30 (40.0)	62 (42–86)	17 (56.7)	> 25 in 11/30 (36.6)	10 (33.3)
Mathur et al. 2011	United States	Retrospective cohort, single-center	Resected pancreatic adenocarcinoma (pancreatoduodenectomy)	42	23/42 (54.8)	66 (mean)	19 (45.2)	27–28 across groups	21%–39% across groups
Mathur et al. 2009	United States	Matched case-control, single-center	Resected pancreatic adenocarcinoma; 20 node-positive vs 20 matched node-negative	40	Not applicable	59–63 (means)	14 (35.0)	24.5–25.6 across groups	10%–20% across groups

Age is reported as median (interquartile range) by Dong et al. and Chan et al., as median (range) by Fukuda et al., and as mean (range) by Tróchez-Mejía et al. BMI was reported dichotomously by Dong et al., with data missing for 20 patients. Mathur et al. 2009 analyzed the exposure as a continuous pancreatic fat-cell count in groups defined by nodal status, so no dichotomous fatty-pancreas contrast was available. N denotes the total enrolled cohort and n the number in a group or analytic subset. BMI, body mass index; EUS, endoscopic ultrasound; NR, not reported; PDAC, pancreatic ductal adenocarcinoma

Table 2
Fatty-pancreas assessment, outcome ascertainment, and contribution of each study to the synthesis

Study	Modality and definition of fatty pancreas	Region in which fat was measured	Nodal ascertainment	Survival estimate	Contribution to synthesis
Dong et al. 2025	Non-contrast CT; pancreas-to-spleen mean attenuation ratio < 0.7, from 1 cm² regions of interest at head, body and tail, measured three times each	Whole gland; avoidance of the tumor not specified	Pathological N stage (N1–2 vs N0), AJCC 8th edition	Cox model; HR 1.031, P = 0.923; unadjusted; standard error reconstructed	Nodal (n = 116); survival (n = 80 with follow-up); exploratory outcomes
Fukuda et al. 2025	Histology; histological pancreatic fat fraction ≥ 11.3% (ROC-derived study threshold), image analysis, blinded assessment	Non-tumoral parenchyma proximal to the tumor; fat at the invasive front quantified separately and found to be scarce (median 0.0%)	Pathological lymph-node positivity (N1 vs N0)	Multivariable Cox; HR 2.32 (95% CI 1.38–3.91), adjusted for CA19-9, T stage, nodal status, lymphatic invasion and adjuvant chemotherapy	Nodal (n = 87); survival (n = 87); recurrence-free survival; exploratory outcomes
Chan et al. 2024	Non-contrast CT pancreas-to-spleen attenuation (pancreas below spleen), or chemical-shift in-phase and out-of-phase MRI	Measurement area placed away from the tumor and from cysts	Not reported	Univariable Cox; HR 0.78 (95% CI 0.47–1.28), P = 0.324; unadjusted	Survival (n = 101); exploratory outcomes
Tróchez-Mejía et al. 2019	EUS; increased parenchymal echogenicity relative to the renal cortex, graded I–III (mild 8, moderate 3, severe 1)	Tumor-free pancreatic remnant (non-tumoral)	Clinical and endosonographic N category; the binary contrast was derived from the reported N distribution	Not reported	Nodal (n = 30); exploratory outcomes
Mathur et al. 2011	Preoperative CT pancreatic body attenuation below 30 Hounsfield units, scored by two blinded investigators, together with perirenal visceral fat	Pancreatic body and tail	Pathological lymphatic metastasis	No difference in mean survival by steatosis status (16 ± 15 vs 18 ± 11 months, P = 0.7); shorter survival among node-positive patients with perirenal fat ≥ 10 mm	Nodal (n = 42); narrative survival
Mathur et al. 2009	Histology; pancreatic fat-cell count per five high-power fields, reviewed blind in duplicate	Pancreatic neck margin (non-tumoral)	Groups defined a priori by pathological nodal status	Mean survival compared by nodal status	Qualitative synthesis only

N denotes the total enrolled cohort and n the analytic sample contributing to each estimate. AJCC, American Joint Committee on Cancer; CA19-9, carbohydrate antigen 19 – 9; CI, confidence interval; CT, computed tomography; EUS, endoscopic ultrasound; HR, hazard ratio; MRI, magnetic resonance imaging; ROC, receiver operating characteristic

Risk of bias

Risk-of-bias concerns were common: retrospective single-center design, heterogeneous definitions and modalities for classifying fatty pancreas, inconsistent adjustment for metabolic and oncological confounders, small samples, and incomplete reporting of adjusted estimates. Prognostic-factor measurement was most robust in the histology-based study that quantified fat in non-tumoral parenchyma using a ROC-derived study threshold with blinded assessment [21]. Outcome measurement was more reliable for pathological nodal status than for clinical nodal staging, recurrence or survival. Attrition was judged high in the study in which follow-up was available for 69% of the cohort and the group sizes reported for the survival analysis were not reconcilable with those of the main cohort [20]. Confounding was judged high risk in four studies because adiposity, diabetes, stage and treatment were inconsistently handled. Overall, four studies were rated at high and two at moderate risk of bias (Online Resource 1, Table S3; Supplementary Figs. S1a, S1b).

Lymph node metastasis

Four studies contributed 275 patients, with 68 of 116 nodal events in the fatty-pancreas group and 76 of 159 in the comparator group [20, 21, 23, 24]. Under a random-effects model, fatty pancreas was associated with a modestly higher risk of nodal positivity (pooled RR 1.27,

95% CI 1.03–1.57; Z = 2.21, P = 0.03). Statistical heterogeneity was negligible ($\tau^2 = 0.00$; Q = 3.31, df = 3, P = 0.35; $I^2 = 3\%$) and the normal-approximation prediction interval was 1.01–1.59 (Fig. 2). Three of four point estimates were above 1 (RR 1.19, 95% CI 0.81–1.73 [21]; RR 1.46, 95% CI 1.04–2.06 [23]; RR 1.65, 95% CI 0.91–2.99 [24]), whereas one was close to and slightly below the null (RR 0.93, 95% CI 0.59–1.47) [20].

The pooled estimate was not robust. A fixed-effect model gave an essentially identical result (RR 1.27, 95% CI 1.03–1.56, P = 0.02), but in leave-one-out analysis statistical significance was retained only when the single null study was omitted (RR 1.37, 95% CI 1.09–1.74, P = 0.007; $I^2 = 0\%$) [20]. Omission of any of the other three studies abolished significance: RR 1.30 (95% CI 0.94–1.79, P = 0.11; $I^2 = 36\%$) without the histology-based study [21], RR 1.22 (95% CI 0.95–1.55, P = 0.12; $I^2 = 16\%$) without the CT-based resected cohort [24], and RR 1.17 (95% CI 0.90–1.52, P = 0.24; $I^2 = 0\%$) without the EUS-based cohort [23]. The last study carried the largest weight (36.3%) and was the only one contributing clinical rather than pathological nodal staging.

Subgroup analyses were concordant with this pattern. Restricting the synthesis to the three studies with pathological nodal ascertainment in resected cohorts yielded RR 1.17 (95% CI 0.90–1.52, P = 0.24; $I^2 = 0\%$; 245 patients). Imaging-defined fatty pancreas gave RR 1.30 (95% CI 0.94–1.79; $I^2 = 36\%$; three studies, 188 patients), the single histology-defined estimate was RR 1.19 (95% CI 0.81–1.73; 87 patients), and the two CT-only cohorts gave RR 1.20 (95% CI 0.69–2.10; $I^2 = 56\%$). Tests for subgroup differences were not significant (pathological versus clinical nodal ascertainment, $\chi^2 = 1.04$, df = 1, P = 0.31; imaging versus histology, $\chi^2 = 0.13$, df = 1, P = 0.72), but with one to three studies per subgroup these tests had very low power and should not be read as evidence of equivalence. Full sensitivity and subgroup results are tabulated in Online Resource 1, Table S9.

Overall survival

Three studies contributed 268 patients [20, 21, 22]. No statistically significant association between fatty pancreas and overall survival was identified (pooled HR 1.23, 95% CI 0.64–2.38; Z = 0.63, P = 0.53); heterogeneity was substantial ($\tau^2 = 0.26$; Q = 9.19, df = 2, P = 0.01; $I^2 = 77\%$) and the normal-approximation prediction interval was wide (0.37–4.07) (Fig. 3). The contributing estimates pointed in opposite directions: HR 0.78 (95% CI 0.47–1.28) from an unadjusted Cox model [22], HR 1.03 (95% CI 0.56–1.91) reconstructed from a rounded HR and P value [20], and HR 2.32 (95% CI 1.38–3.91) from a multivariable model adjusted for CA19-9, T stage, nodal status, lymphatic invasion and adjuvant chemotherapy [21].

Sensitivity analyses did not resolve the uncertainty. The fixed-effect model remained non-significant (HR 1.24, 95% CI 0.91–1.69), as did exclusion of the reconstructed estimate (HR 1.34, 95% CI 0.46–3.91; $I^2 = 89\%$). Leave-one-out estimates ranged from HR 0.87 to 1.57, and the pooled direction depended on inclusion of the single adjusted, histology-based study. Because only one adjusted estimate was available, adjusted and unadjusted estimates were combined in the primary analysis, limiting interpretation (Online Resource 1, Table S9).

Exploratory outcomes

No exploratory outcome could be pooled, and the narrative pattern was mixed rather than uniformly concordant with the nodal result. The EUS-based cohort reported more advanced TNM stage (P = 0.034), greater nodal dissemination (P = 0.01), more frequent distant metastasis (10/12 vs 5/18, P = 0.004) and universal assignment to first-line palliative chemotherapy (P = 0.007) among patients with steatosis, but no association with tumor size or resectability [23]. The histology-based resected cohort reported worse recurrence-free survival with fatty pancreas (adjusted HR 2.33, 95% CI 1.42–3.81, P = 0.0008) and non-significant trends toward vascular invasion and clinically relevant pancreatic fistula, but no difference in T stage, lymphatic or perineural invasion, differentiation or CA19-9 [21]. In contrast, the CT-based resected cohort found no association with T stage, nodal stage, lymphovascular or perineural invasion, or CA19-9 [20], and the imaging cohort of newly diagnosed pancreatic cancer found no association with stage or survival, identifying chronic pancreatitis as the factor most strongly associated with steatosis (P = 0.009) [22]. The matched case-control study found more pancreatic fat cells and less fibrosis in node-positive than node-negative disease (P < 0.02 for both) with shorter mean survival (18.9 vs 30.8 months, P < 0.04), but by design compared groups defined by nodal status rather than by steatosis [25]. The remaining resected cohort reported more frequent nodal positivity with fatty pancreas (70% vs 42%, P < 0.002), whereas mean survival did not differ by steatosis status (16 ± 15 vs 18 ± 11 months, P = 0.7) [24]. Every outcome evaluated in the review, including those not reported by any included study, is listed with its source, direction and reason for not pooling in Online Resource 1, Table S8.

Certainty of evidence

Fatty pancreas may be associated with a higher risk of lymph node metastasis, but certainty of evidence is very low (four studies, 275 patients). Applied to an assumed risk of 478 nodal events per 1,000 patients without fatty pancreas, the pooled RR corresponds to 607 per 1,000 (492 to 750). The evidence is very uncertain about the association with overall survival (three studies, 268 patients). All evidence came from observational studies and was rated down for risk of bias and imprecision, and the survival evidence was rated down further for inconsistency. Statistical heterogeneity was low for the nodal outcome, although important clinical and measurement heterogeneity

remained. Publication bias was not formally assessed because fewer than 10 studies contributed to either outcome, and is therefore reported as not assessed rather than as undetected; not assessed does not imply absence of bias (Online Resource 1, Table S4).

Discussion

In this systematic review and meta-analysis of adults with established pancreatic cancer, fatty pancreas was associated with a modestly higher risk of lymph node metastasis, whereas its association with overall survival was non-significant, heterogeneous and imprecise. Certainty was very low for both outcomes. The central observation is therefore nodal rather than survival-related, and that signal is statistically fragile.

The pooled nodal association was modest, the lower confidence bound lay close to unity, and statistical significance was lost in three of four leave-one-out analyses; restriction to pathological nodal ascertainment attenuated the estimate further. The significant pooled result therefore depended disproportionately on a single small study that used endosonographic rather than pathological nodal staging in a predominantly unresectable population [23]. Low statistical heterogeneity (I^2 = 3%) should not be mistaken for clinical or methodological homogeneity: CT attenuation, chemical-shift MRI, EUS echogenicity and histological fat fraction quantify different physical quantities at different thresholds, and clinical and pathological nodal staging are not interchangeable constructs. Statistical significance here should not be equated with clinical utility.

The survival findings are weaker still and must not be read as evidence of no effect. Only three studies contributed and individual estimates pointed in opposite directions; the direction of the pooled estimate was determined by whether the single adjusted, histology-based study was included [21]. Combining adjusted and unadjusted estimates is methodologically undesirable, and we did so only because one adjusted estimate was available. Overall survival is also a distal composite endpoint shaped by stage, resectability, systemic therapy, surgical outcome, follow-up duration and metabolic comorbidity, so inconsistent adjustment may have attenuated, amplified or obscured any underlying association.

These results extend rather than duplicate the existing literature. Previous synthesis established that pancreatic steatosis is common in PDAC and is associated with having the disease [5], and imaging and histological studies suggest it may precede clinical diagnosis [6, 7] and relate differently to distinct carcinoma types [8]. The present review addresses the complementary post-diagnosis question and, to our knowledge, provides the first quantitative synthesis of nodal dissemination and survival by fatty-pancreas status in patients who already have pancreatic cancer. Framing fatty pancreas as a candidate marker of post-diagnosis tumor behaviour, rather than only as a risk-associated phenotype, is the conceptual contribution of this work; the supporting evidence is, however, of very low certainty.

A nodal association would be biologically plausible. An adipocyte-rich intrapancreatic microenvironment may support tumor progression through adipocytokine signalling, chronic inflammation, lipotoxicity and altered fatty-acid metabolism [2, 3]. Human histopathological data link fatty infiltration with acinar-to-ductal metaplasia and pancreatic intraepithelial neoplasia [9, 10], whereas murine work implicates FABP5 upregulation and RAC1-dependent migration under conditions of high IPFD [11]. The preclinical data offer candidate pathways for translational study but cannot be used to infer causality in patients. Only the histology-based study explicitly separated fat in non-tumoral parenchyma from fat at the invasive front, where lipid droplets were scarce, which supports measurement of pancreatic fat away from the tumor [21].

Reverse causation is a substantive alternative explanation that the present design cannot exclude. Neoplastic obstruction of the pancreatic duct may induce acinar cell loss with fibrosis and lobular atrophy upstream of the lesion [26], and focal fatty replacement of the parenchyma adjacent to a pancreatic ductal neoplasm has been documented histologically [27]. Pancreatic fat measured after diagnosis could therefore be partly a consequence or correlate of tumor burden, duct obstruction and cancer-associated metabolic change rather than an antecedent host characteristic. Because all included studies measured pancreatic fat at or after diagnosis, the temporal ordering required to distinguish whether pancreatic fat precedes, accompanies or partly results from the tumor is absent.

Residual confounding is a further limitation. The pooled nodal estimate was derived primarily from unadjusted event counts, and only one pooled survival estimate was adjusted. Age, sex, adiposity, diabetes, chronic pancreatitis, tumor location and size, stage, CA19-9, histological grade, margin status, lymphovascular and perineural invasion and treatment received are all plausible confounders, and none was handled consistently across studies. Fatty pancreas cannot be described as an independent prognostic factor on the basis of these data.

Generalizability is limited. Three of the four studies contributing nodal data enrolled resected patients [20, 21, 24], a selected, fitter and less advanced population in whom nodal status is determined pathologically; the remaining nodal study used endosonographic staging in a predominantly unresectable cohort [23], and the largest survival cohort was mostly stage IV [22]. All studies were small and single-center,

drawn from different geographical and metabolic contexts in East Asia, Latin America and North America. These findings cannot be generalized automatically to all populations with pancreatic cancer.

The strengths of this review are a focused post-diagnosis question, a broad search without language restriction, consistent orientation of effect estimates, an explicit distinction between total cohort size and analytic sample size, transparent labelling and sensitivity testing of a reconstructed estimate, a contribution matrix linking each study to each analysis, and complete reporting of every outcome evaluated. Its limitations are the small number of small, retrospective and heterogeneous studies, the mixture of imaging and histological exposure definitions and of clinical and pathological ascertainment, incomplete and in one instance internally inconsistent reporting, the absence of individual participant data, and the impossibility of assessing small-study effects with fewer than 10 studies per outcome.

The clinical implication is one of hypothesis generation, not practice change. Fatty pancreas is a tissue-level phenotype already visible on routine staging imaging and on surgical pathology, an attractive potential adjunct to established markers; on the present evidence, however, it is not a validated prognostic biomarker and should not influence staging, treatment selection or follow-up intensity. Although pancreatic fat is a potentially modifiable metabolic phenotype, whether it can be modified in established pancreatic cancer, and whether doing so would alter outcome, is unknown. Future work should standardize measurement of pancreatic fat across CT, MRI proton-density fat fraction, EUS and histology, separating non-tumoral parenchymal fat from tumor-adjacent and intratumoral adiposity; report the region and threshold used; record harmonized metabolic covariates and adjusted estimates; analyse resectable, locally advanced and metastatic disease separately; and, where possible, capture pancreatic fat before diagnosis to address reverse causation.

Conclusion

In adults with established pancreatic cancer, fatty pancreas was associated with a modest excess of lymph node metastasis, but the association was statistically fragile, and the association with overall survival remained uncertain. Certainty of evidence was very low for both outcomes. Prospective validation with standardized definitions of pancreatic fat is required before any clinical role can be considered; fatty pancreas has no current role in staging, treatment selection or follow-up planning.

Abbreviations

CA19-9
carbohydrate antigen 19 – 9
CI
confidence interval
CT
computed tomography
EUS
endoscopic ultrasound
FABP5
fatty acid-binding protein 5
GRADE
Grading of Recommendations Assessment,Development and Evaluation
HR
hazard ratio
IPFD
intrapancreatic fat deposition
MOOSE
Meta-analysis Of Observational Studies in Epidemiology
MRI
magnetic resonance imaging
PDAC
pancreatic ductal adenocarcinoma
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUIPS
Quality In Prognosis Studies
REML

restricted maximum likelihood
ROC
receiver operating characteristic
RR
risk ratio
SE
standard error
SWiM
Synthesis Without Meta-analysis

Statements and Declarations

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Author Contributions Study conception and design and supervision of the review: FJN-S, AC-N and JSC-V. Literature search, study screening, data extraction and verification of extracted information: OEV-G, AR-N, ALV-G and ANI-G. Formal analysis, statistical verification and validation of all pooled estimates and sensitivity analyses: JSC-V, FJN-S and AC-N. Drafting and substantial revision of the manuscript: JSC-V, FJN-S and AC-N. All authors interpreted the findings, critically revised the manuscript for important intellectual content, read and approved the final manuscript, and agree to be accountable for all aspects of the work.

Data Availability All data analyzed in this systematic review were extracted from published studies cited in the article. The study-level extraction dataset and analytic decisions are available from the corresponding author on reasonable request.

Ethics Approval Ethics approval was not required because this systematic review and meta-analysis used previously published aggregate data and did not involve access to individual-level identifiable participant data.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

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Figures

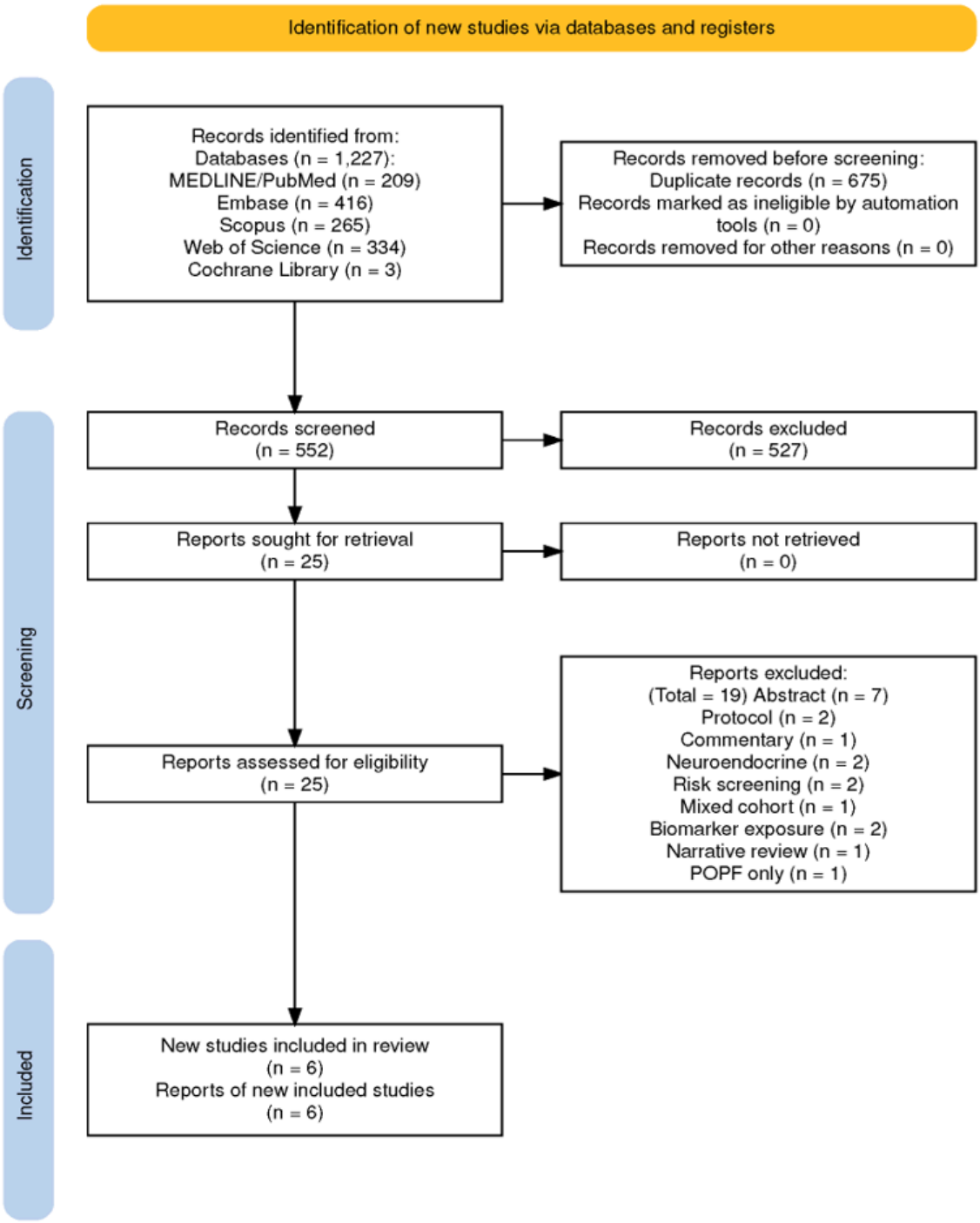


Figure 1

PRISMA [19]

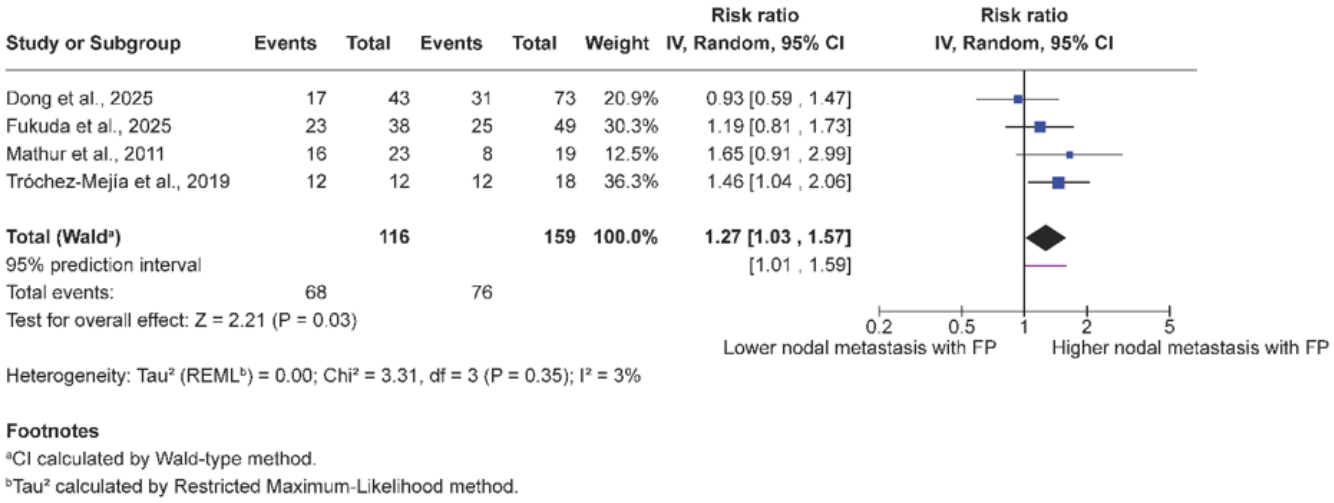


Figure 2

Nodal positivity [20, 21, 23, 24].

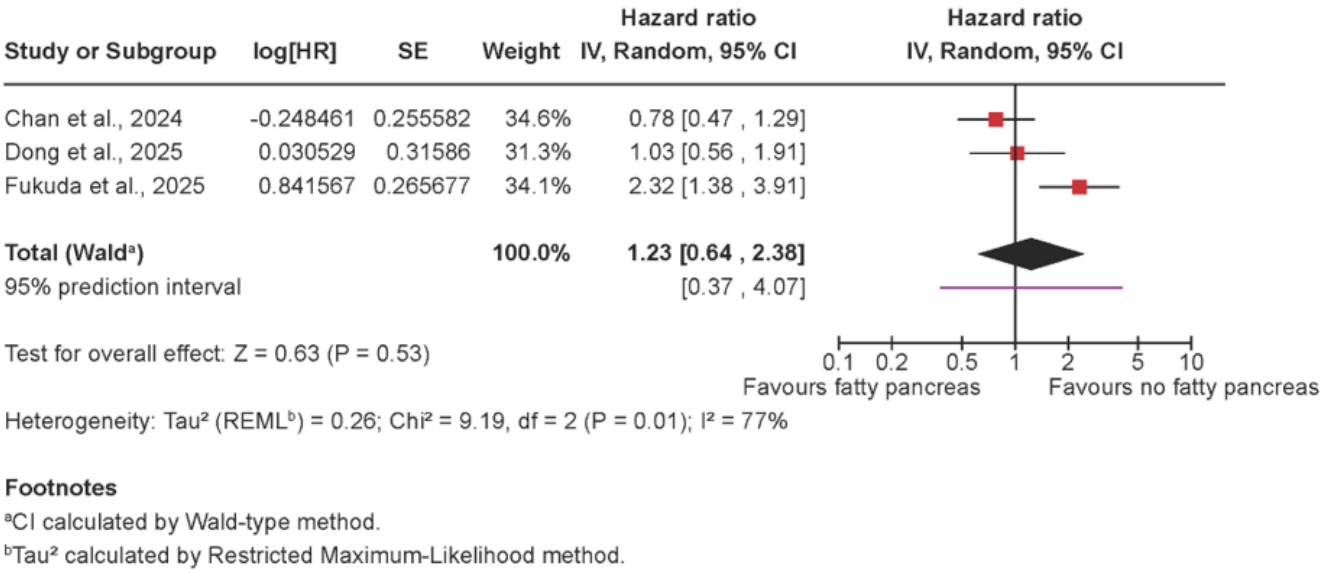


Figure 3

Overall survival [20–22].

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