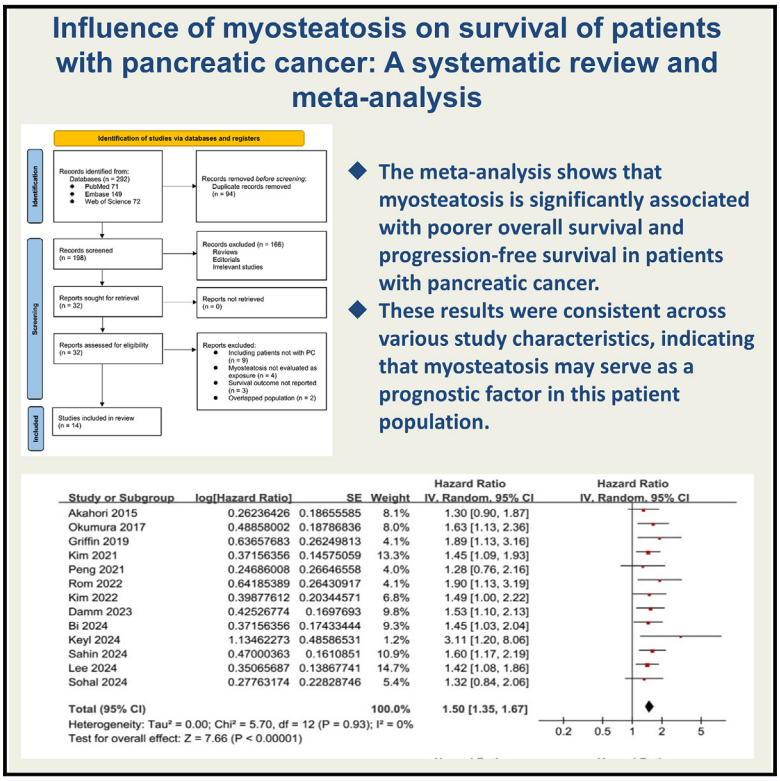
iScience

Article

# Influence of myosteatosis on survival of patients with pancreatic cancer: A systematic review and meta-analysis

## Graphical abstract




## Highlights

- Myosteatosis is associated with poorer overall survival in pancreatic cancer
- Myosteatosis correlates with worse progression-free survival in pancreatic cancer
- Subgroup analysis shows consistent results across different study characteristics
- Myosteatosis may serve as a prognostic factor in pancreatic cancer survival outcomes

## Authors

Xin Zhang, Licheng Wei, Jiangguo Li, Yuexia Deng, Wei Xu, Dongkui Chen, Xing Li

## Correspondence

875595327@qq.com

## In brief

Health sciences; Medicine; Medical specialty; Internal medicine; Oncology

Zhang et al., 2024, iScience *27*, 111343
December 20, 2024 
https://doi.org/10.1016/j.isci.2024.111343

CellPress

iScience

CellPress
OPEN ACCESS

Article

# Influence of myosteatosis on survival of patients with pancreatic cancer: A systematic review and meta-analysis

Xin Zhang,[1,3] Licheng Wei,[1,3] Jiangguo Li,[1] Yuexia Deng,[1] Wei Xu,[1] Dongkui Chen,[1] and Xing Li[2,4,*]

[1]Department of Gastroenterology, The Fourth Hospital of Changsha, Changsha City, Hunan Province 410006, P.R. China

[2]Department of Critical Care Medicine, Changsha Hospital of Traditional Chinese Medicine (Changsha No. 8 Hospital), Changsha City, Hunan Province 410100, P.R. China

[3]These authors contributed equally

[4]Lead contact

*Correspondence: 875595327@qq.com

https://doi.org/10.1016/j.isci.2024.111343

## SUMMARY

The present meta-analysis aims to evaluate the impact of myosteatosis on overall survival (OS) and progression-free survival (PFS) in patients with pancreatic cancer (PC). A comprehensive literature search was conducted in the Medline, Web of Science, and Embase databases. The hazard ratio (HR) and corresponding 95% confidence interval (CI) for the association between myosteatosis and survival outcomes were pooled using a random-effects model. A total of 14 studies were included. The pooled analysis demonstrated that myosteatosis was significantly associated to poorer OS (HR: 1.50, 95% CI: 1.35–1.67, $p < 0.001$; $I^2 = 0\%$). The subgroup analysis revealed consistent results across various study characteristics, including geographic regions, cancer stages, follow-up durations, and study quality. In addition, myosteatosis was associated to worse PFS (HR: 1.34, 95% CI: 1.15–1.57, $p < 0.001$; $I^2 = 34\%$). The present meta-analysis indicates that myosteatosis is associated to significantly worse OS and PFS in patients with PC.

## INTRODUCTION

Pancreatic cancer (PC) is one of the leading causes of cancer-related mortality worldwide, with a dismal 5-year survival rate of less than 10%.[1,2] The incidence of PC has been steadily rising in recent decades.[1,3] Early-stage PC is often asymptomatic, resulting in late diagnosis and limited therapeutic options.[4] Present diagnostic methods include imaging techniques, such as computed tomography (CT), magnetic resonance imaging, and endoscopic ultrasound, along with serum biomarkers, such as CA 19-9, etc.[5] The treatment typically involves surgical resection, chemotherapy, and radiation therapy. However, the prognosis remains poor, emphasizing the urgent need to identify risk factors that contribute to poor survival in PC patients.[6,7]

Myosteatosis, which is characterized by the infiltration of adipose tissue in the skeletal muscle, has emerged as a potential prognostic factor in various cancers.[8,9] Defined by decreased muscle density and increased intramuscular fat deposition, myosteatosis is detectable by CT scan, particularly at the third lumbar vertebra.[10,11] The mechanisms underlying myosteatosis include chronic inflammation, insulin resistance, and hormonal changes, which can contribute to muscle degradation and impaired metabolic function.[12] In cancer patients, myosteatosis has been associated to reduced physical function, increased treatment toxicity, and poorer overall survival (OS) and progression-free survival (PFS).[13] A previous study revealed that myosteatosis may adversely influence the survival outcomes in overall cancer patients.[14] However, this influence may vary according to the site of cancer.[14]

Despite the recognition of myosteatosis as a detrimental factor in several malignancies, such as lung cancer,[15] colorectal cancer,[16] gastric cancer,[17] and hepatocellular carcinoma,[18] its impact on the survival of PC patients remain underexplored. Although the majority of evidences suggest a correlation between myosteatosis and adverse outcomes in PC,[19–28] some studies have failed to identify such correlation.[29–32] In addition, previous studies that evaluated the association between myosteatosis and the survival of patients with PC are often limited by small sample sizes and heterogeneous methodologies. Thus, the present meta-analysis aimed to systematically evaluate the influence of myosteatosis on OS and PFS in PC patients, thereby providing a comprehensive synthesis of present research and identifying potential knowledge gaps.

## RESULTS

### Study inclusion

The study inclusion process is presented in Figure 1. Briefly, 292 potentially relevant articles were obtained after the comprehensive search of the three databases. Among these articles, 94 articles were excluded due to duplication. After the subsequent screening of titles and abstracts of the remaining articles, 166

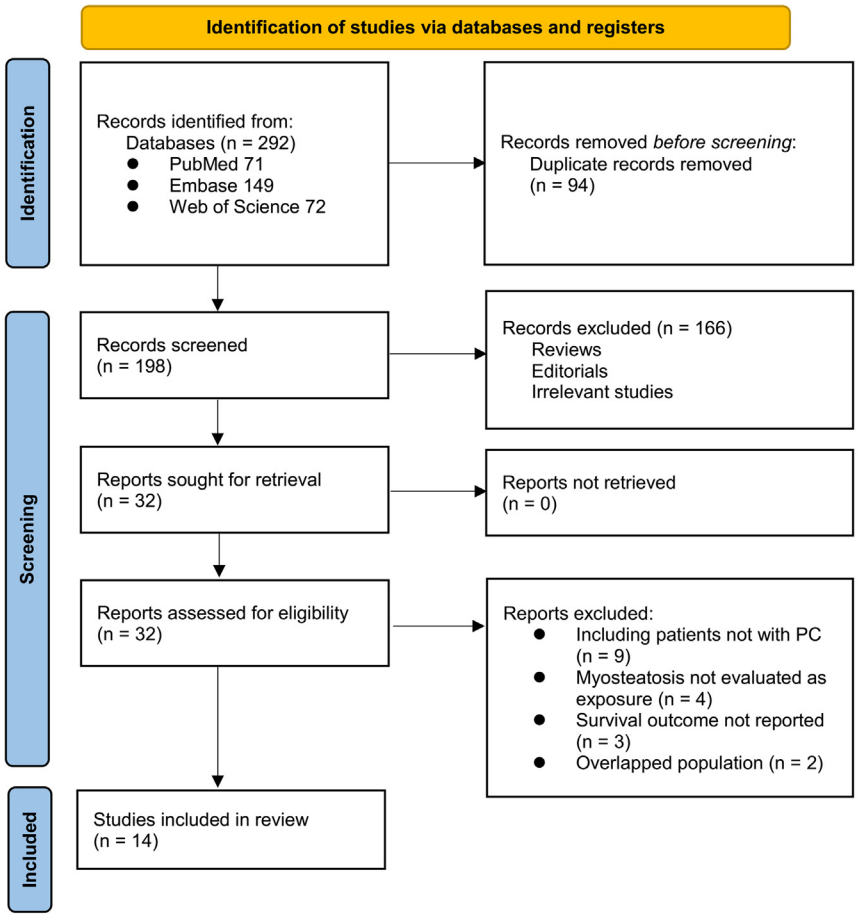



**Figure 1. The flowchart depicts the database search and study inclusion process**

articles were further excluded, which were mostly because these were not related to the aim of the meta-analysis. Then, the full texts of the remaining 32 articles were reviewed by two independent authors. Among these 32 articles, 18 articles were further excluded (the reasons are listed in Figure 1). Finally, 14 longitudinal follow-up studies were considered to be suitable for the subsequent quantitative analysis.[19–32]

## Overview of study characteristics

Tables 1 and 2 present the summarized characteristics of the included studies. Overall, 14 studies, which involved one prospective cohort study,[20] 12 retrospective cohort studies,[19,21–31] and one pose-hoc analysis of clinical study,[32] were included in the meta-analysis. These studies were published between 2015 and 2024 and performed in Japan, Ireland, Korea, China, Israel, the Netherlands, Germany, the United Kingdom, Turkey, and the United States. For the diagnosis, patients with localized or resectable PC were included in eight studies,[19,20,22,23,25,29,31,32] and patients with advanced or metastatic PC were included in three studies,[21,26–28] whereas two studies did not specify the cancer status of the patients.[24,30] A total of 3,693 patients with PC were included in these studies. The age of male patients varied within 61.20–68.00 years old, and the proportion of male patients ranged within 47.00%–65.30%. Furthermore, 13 studies included patients with pancreatic ductal adenocarcinoma (PADC),[20–32] whereas one study did not specify the histologic type of the cancer.[19] Surgical resection was the main treatment for patients in seven studies,[19,22,23,25,30–32] whereas neoadjuvant chemoradiotherapy,[20,29] chemotherapy,[21,26–28] or comprehensive treatments[24] were the main treatments for patients in the remaining studies. Myosteatosis was evaluated by CT imaging at the third lumbar vertebrae level, and the cut-offs for defining myosteatosis varied among the studies. The median follow-up duration was 11–46 months. The outcome of OS was reported in 13 studies,[19–30,32] and PFS was reported in seven studies.[19,22,23,25,28,30,31] Multivariate analysis was performed for 13 studies when the association between myosteatosis and survival of PC was evaluated,[19–28,30–32] whereas univariate analysis was performed for the remaining study.[29] The NOS scores of the included studies ranged within 6–9 stars, suggesting overall moderate-to-good study quality (Table 3).

### *Association between myosteatosis and OS*

The pooled results of 13 studies[19–30,32] with a randomized-effects model suggested that compared to PC patients without myosteatosis at enrollment, patients with myosteatosis were associated to poorer OS (HR: 1.50, 95% CI: 1.35–1.67, $p < 0.001$; $I^2 = 0\%$; Figure 2A). The further sensitivity analysis to assess the impact of consistently excluding an individual study revealed similar results (HR: 1.49–1.52; all, $p < 0.05$). In particular, the sensitivity analysis that excluded only one study with a univariate analysis[29] revealed similar results (HR: 1.52, 95% CI: 1.37–1.70, $p < 0.001$; $I^2 = 0\%$). The further subgroup analysis revealed similar results in studies from Asian and non-Asian countries (HR: 1.44 vs. 1.63, $p$ for subgroup difference = 0.25; Figure 2B), for patients with localized/resectable PC and advanced/metastatic PC (HR: 1.51 vs. 1.51, $p$ for subgroup difference = 1.00; Figure 2C), in studies with a follow-up duration of $\leq$24 or >24 months (HR: 1.48 vs. 1.54, $p$ for subgroup difference = 0.73; Figure 3A), and in studies with NOS scores of 6–7 and 8–9 (HR: 1.47 vs. 1.57, $p$ for subgroup difference = 0.56; Figure 3B).

### *Association between myosteatosis and OS*

The meta-analysis results for the seven multivariate studies[19,22,23,25,28,30,31] indicated that myosteatosis was associated to poorer PFS in patients with PC (HR: 1.34, 95% CI: 1.15–1.57, $p < 0.001$; $I^2 = 34\%$; Figure 4A). The further sensitivity analysis that excluded one study at a time did not significantly change these results (HR: 1.30–1.45; all, $p < 0.05$). The further subgroup analysis

**Table 1. Characteristics of the included patients in each study**

| Study | Country | Design | Diagnosis | Patient number | Mean age (years) | Male (%) | Histology | Tumor stage | Main treatment |
|---|---|---|---|---|---|---|---|---|---|
| Akahori et al.[29] 2015 | Japan | RC | Resectable or partial resectable pancreatic cancer | 83 | 65.20 | 55.40 | PDAC | NR | Neoadjuvant chemoradiotherapy |
| Okumura et al.[19] 2017 | Japan | RC | Localized pancreatic cancer | 301 | 68.00 | 55.80 | NR | IA–IIB | Surgical resection |
| Griffin et al.[20] 2019 | Ireland | PC | Resectable or partial resectable pancreatic cancer | 78 | 64.20 | 47.00 | PDAC | NR | Neoadjuvant chemotherapy |
| Kim et al.[21] 2021 | Korea | RC | Metastatic pancreatic cancer | 330 | 63.40 | 64.10 | PDAC | IV | Chemotherapy |
| Peng et al.[30] 2021 | China | RC | Pancreatic cancer | 116 | 66.20 | 58.60 | PDAC | I–IV | Surgical resection |
| Rom et al.[23] 2022 | Israel | RC | Resectable pancreatic cancer | 111 | 67.00 | 53.00 | PDAC | I–IV | Surgical resection |
| Aziz et al.[31] 2022 | The Netherlands | RC | Resectable pancreatic cancer | 415 | 66.00 | 53.30 | PDAC | NR | Surgical resection |
| Kim et al.[22] 2022 | Korea | RC | Resectable pancreatic cancer | 347 | 63.60 | 58.20 | PDAC | I–III | Surgical resection |
| Damm et al.[24] 2023 | Germany and UK | RC | Pancreatic cancer | 354 | 68.00 | 60.00 | PDAC | I–IV | Comprehensive treatments |
| Bi et al.[25] 2024 | China | RC | Resectable pancreatic cancer | 215 | 61.30 | 61.90 | PDAC | I–III | Surgical resection |
| Keyl et al.[26] 2024 | Germany | RC | Advanced pancreatic cancer | 601 | 66.00 | 55.60 | PDAC | I–IV | Chemotherapy |
| Sahin et al.[28] 2024 | Turkey | RC | Advanced pancreatic cancer | 196 | 62.00 | 65.30 | PDAC | NR | Chemotherapy |
| Lee et al.[27] 2024 | Korea | RC | Metastatic pancreatic cancer | 456 | 61.20 | 59.60 | PDAC | IV | Palliative chemotherapy |
| Sohal et al.[32] 2024 | USA | Post-hoc analysis | Resectable pancreatic cancer | 90 | 63.20 | 56.70 | PDAC | NR | Surgical resection |

Notes: RC, retrospective cohort; PDAC, pancreatic ductal adenocarcinoma; NR, not reported.

suggested similar results in studies from Asian and non-Asian countries (HR: 1.42 vs. 1.30, $p$ for subgroup difference = 0.62; Figure 4B), for patients with localized/resectable PC and advanced/metastatic PC (HR: 1.37 vs. 1.48, $p$ for subgroup difference = 0.67; Figure 4C), in studies with a follow-up duration of $\leq$24 or >24 months (HR: 1.39 vs. 1.34, $p$ for subgroup difference = 0.82; Figure 5A), and in studies with NOS scores of 6–7 and 8–9 (HR: 1.48 vs. 1.32, $p$ for subgroup difference = 0.53; Figure 5B).

### Publication bias evaluation

Upon visual inspection, the funnel plots for the meta-analysis of the relationship of myosteatosis with OS and PFS appeared symmetrical, indicating a low likelihood of publication bias (Figures 6A and 6B). In addition, the Egger's regression test results supported this conclusion, suggesting low risk of publication bias (for the outcome of OS, $p$ = 0.79; for the outcome of PFS, $p$ = 0.44).

## DISCUSSION

The present meta-analysis investigated the influence of myosteatosis on survival outcomes in patients with PC. The present pooled results obtained from 14 studies, which involved 3,693 PC patients, revealed that myosteatosis is significantly associated to poorer OS and PFS. Specifically, patients with myosteatosis had a 50% higher risk of mortality, and a 34% higher risk of disease progression, when compared to patients without myosteatosis. These findings underscore the prognostic significance of myosteatosis in PC and highlights the need to consider this condition in clinical assessments and treatment planning.

The association between myosteatosis and adverse survival outcomes can be attributed to several underlying mechanisms. Myosteatosis reflects the increase in intramuscular adipose tissue, which is often accompanied by chronic inflammation,[33] oxidative stress,[34] and metabolic dysfunction.[35] These conditions can promote tumor progression and resistance to therapy. Furthermore, myosteatosis is linked to insulin resistance and hormonal imbalances, such as altered levels of adipokines and cytokines,[36,37] which may create a tumor-promoting environment. In addition, muscle degradation associated to myosteatosis can lead to decreased physical function, reduced tolerance to cancer treatments, and overall frailty, contributing to poorer survival outcomes.[38] Finally, a recent study suggested the

**Table 2. Details for the diagnosis of myosteatosis and reported survival outcomes in each included study**

| Study | Methods for myosteatosis measurement | Definition of myosteatosis | Number of patients with myosteatosis | Median follow-up duration (months) | Outcomes reported | Variables adjusted |
|---|---|---|---|---|---|---|
| Akahori et al.[29] 2015 | CT, L3 | Lowest quartile of the total group HU | 20 | 37.90 | OS | None |
| Okumura et al.[19] 2017 | CT, L3 | ROC-curve-analysis-derived cut-off, 35.1 HU in men, 30.7 HU in women | 144 | 30.00 | OS and PFS | Age, gender, BMI, TLC, CRP, albumin, CA199, sarcopenia (SMI), tumor size, stage, and postoperative outcomes |
| Griffin et al.[20] 2019 | CT, L3 | <33 HU in patients with BMI $\geq$25 kg/m$^2$ and <41 HU in patients with BMI <25 kg/m$^2$ | 40 | 24.00 | OS | Age, gender, BMI, CRP, albumin, CA199, sarcopenia, and Glasgow prognostic score |
| Kim et al.[21] 2021 | CT, L3 | <33 HU in overweight patients and <41 HU in non-overweight patients | 85 | 20.00 | OS | Age, gender, ECOG PS, BMI, CA199, and sarcopenia (SMI) |
| Peng et al.[30] 2021 | CT, L3 | <33 HU in patients with BMI $\geq$25 kg/m$^2$ and <41 HU in patients with BMI <25 kg/m$^2$ | 46 | 23.70 | OS and PFS | Age, gender, BMI, sarcopenia, diabetes, tumor stage, grade, and R1 resection |
| Rom et al.[23] 2022 | CT, L3 | Lowest quartile of the total group HU (men: 44.4 HU, women: 34.8 HU) | 25 | 46.00 | OS and PFS | Age, gender, BMI, CA199, tumor size, location, stage, surgical outcomes, and sarcopenia (SMI) |
| Aziz et al.[31] 2022 | CT, L3 | Previous literatures defined cut-offs: men 35.5 HU, women 32.5 HU | 177 | 30.00 | PFS | Age, gender, BMI, SII, CRP, CA199, albumin, tumor stage, differentiation, location, and sarcopenia |
| Kim et al.[22] 2022 | CT, L3 | Contal and O'Quigley method derived cut-off (age, gender, and BMI specified) | 190 | 31.80 | OS and PFS | Age, gender, tumor stage, differentiation, R1 resection, CA199, adjuvant treatment, and sarcopenia |
| Damm et al.[24] 2023 | CT, L3 | Cut-offs adjusted for age, gender and BMI (men: 25.2 HU, women: 16.6 HU) | 61 | 11.20 | OS | Age, gender, BMI, CCI, tumor stage, curative resection, and sarcopenia |
| Bi et al.[25] 2024 | CT, L3 | <33 HU in patients with BMI $\geq$25 kg/m$^2$ and <41 HU in patients with BMI <25 kg/m$^2$ | 104 | 40.00 | OS and PFS | Age, gender, DM, tumor size, location, stage, CA199, sarcopenia, and surgical outcome |
| Keyl et al.[26] 2024 | CT, L3 | Median | 300 | 30.00 | OS | Age, gender, and tumor stage |
| Sahin et al.[28] 2024 | CT, L3 | <33 HU in patients with BMI $\geq$25 kg/m$^2$ and <41 HU in patients with BMI <25 kg/m$^2$ | NR | 11.20 | OS and PFS | Age, gender, BMI, ECOG PS, tumor stage, albumin, and sarcopenia |
| Lee et al.[27] 2024 | CT, L3 | Median (44.4 HU) | 228 | 11.70 | OS | Age, gender, CCI, ECOG PS, CA199, and sarcopenia (SMI) |
| Sohal et al.[32] 2024 | CT, L3 | Median | 45 | 24.00 | OS | Age, gender, race, BMI, ECOG PS, contrast use, and sarcopenia |

Notes: CT, computed tomography; L3, the third lumbar vertebrae; HU, Hounsfield unit; OS, overall survival; ROC, receiver operating characteristic; PFS, progression-free survival; BMI, body mass index; TLC, total lymphocyte count; CRP, C-reactive protein; CA199, carbohydrate antigen 199; SMI, skeletal muscle index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; SII, systemic immune-inflammation index; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; NR, not reported.

potential association between myosteatosis and increased risk of toxicity in patients with PC on chemotherapy,[39] which may be an important underlying reason for the poor prognosis in these patients.

The present sensitivity analysis revealed the robustness of the primary findings, consistently showing the significant association between myosteatosis and poor OS, even when individual studies were excluded one at a time. This indicates that the results were not driven by any single study and reinforces the robustness of the present conclusions. Furthermore, the subgroup analysis revealed that the adverse impact of myosteatosis on survival was consistent across different geographic regions, cancer stages, follow-up durations, and study quality scores. These consistent findings across various subgroups suggest that myosteatosis is a universal risk factor for poor survival in PC patients, regardless of the demographic or clinical characteristics.

The clinical implications of these present findings are significant. Recognizing myosteatosis as a prognostic factor in

**Table 3. Study quality evaluation using the Newcastle-Ottawa scale**

| Study | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Outcome not present at baseline | Control for age and gender | Control for other confounding factors | Assessment of outcome | Enough long follow-up duration | Adequacy of follow-up of cohorts | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Akahori et al.[29] 2015 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 |
| Okumura et al.[19] 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 8 |
| Griffin et al.[20] 2019 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 8 |
| Kim et al.[21] 2021 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Peng et al.[30] 2021 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Rom et al.[23] 2022 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Aziz et al.[31] 2022 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 8 |
| Kim et al.[22] 2022 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 8 |
| Damm et al.[24] 2023 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Bi et al.[25] 2024 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Keyl et al.[26] 2024 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Sahin et al.[28] 2024 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Lee et al.[27] 2024 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Sohal et al.[32] 2024 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |

PC patients can enhance risk stratification and personalize treatment approaches. Integrating the routine assessment of myosteatosis using CT scans in clinical practice can help identify high-risk patients who may benefit from more intensive monitoring and tailored interventions. Furthermore, interventions aimed in reducing intramuscular fat deposition, such as exercise and nutritional programs, can potentially improve survival outcomes. Given the complex interplay between muscle quality and cancer prognosis, multidisciplinary management that involves oncologists, nutritionists, and physiotherapists is essential. A recent feasibility clinical trial indicated that integrating dietary assessment and muscle analysis in a multimodal prehabilitation program is achievable for patients with early-stage surgical lung cancer.[40] However, further investigations through adequately powered randomized controlled trials are needed to better understand the functional and clinical outcomes for these patients after intervention. In addition, future research should focus on elucidating the precise biological mechanisms that link myosteatosis to poor survival in PC. Longitudinal studies with standardized criteria for defining and measuring myosteatosis are needed to validate the present findings and establish causality. Investigating the impact of interventions that target muscle quality on survival outcomes can provide valuable insights into potential therapeutic strategies. Furthermore, exploring the role of myosteatosis in combination with other prognostic factors, such as cachexia and sarcopenia, can offer a more comprehensive understanding of muscle-related prognostic markers in PC.

## Limitations of the study

The present study had several strengths and limitations. The main strength of the present study was the comprehensive literature search conducted, which retrieved 14 up-to-date studies, according to the aim of the meta-analysis. Nine of these studies were published within the recent 3 years. Merely studies with longitudinal follow-ups were considered, allowing these to derive the sequential relationship between myosteatosis and the poor survival of these patients. Finally, a multivariate analysis was performed for all included studies, except for one study,[29] and the sensitivity analysis that excluded this study revealed similar results, minimizing the influence of potential confounding factors on the results of the meta-analysis. Nonetheless, limitations exist. The heterogeneity in the definition and

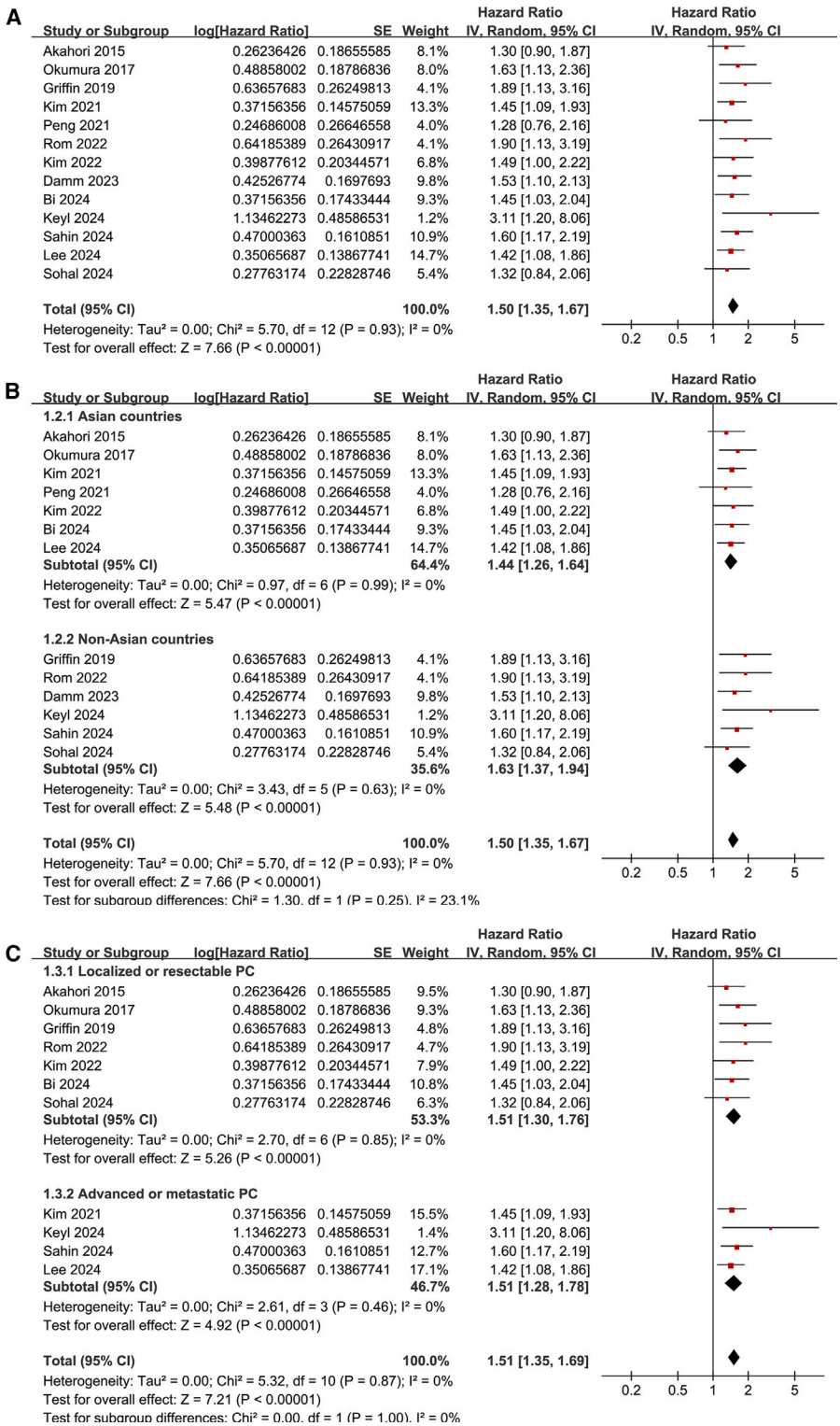



**Figure 2. Forest plots for the meta-analysis of the association between myosteatosis and the overall survival of patients with pancreatic cancer**

(A) Overall meta-analysis.

(B) Subgroup analysis according to study country.

(C) Subgroup analysis according to the status of cancer. Data are represented as HR and 95% CI.

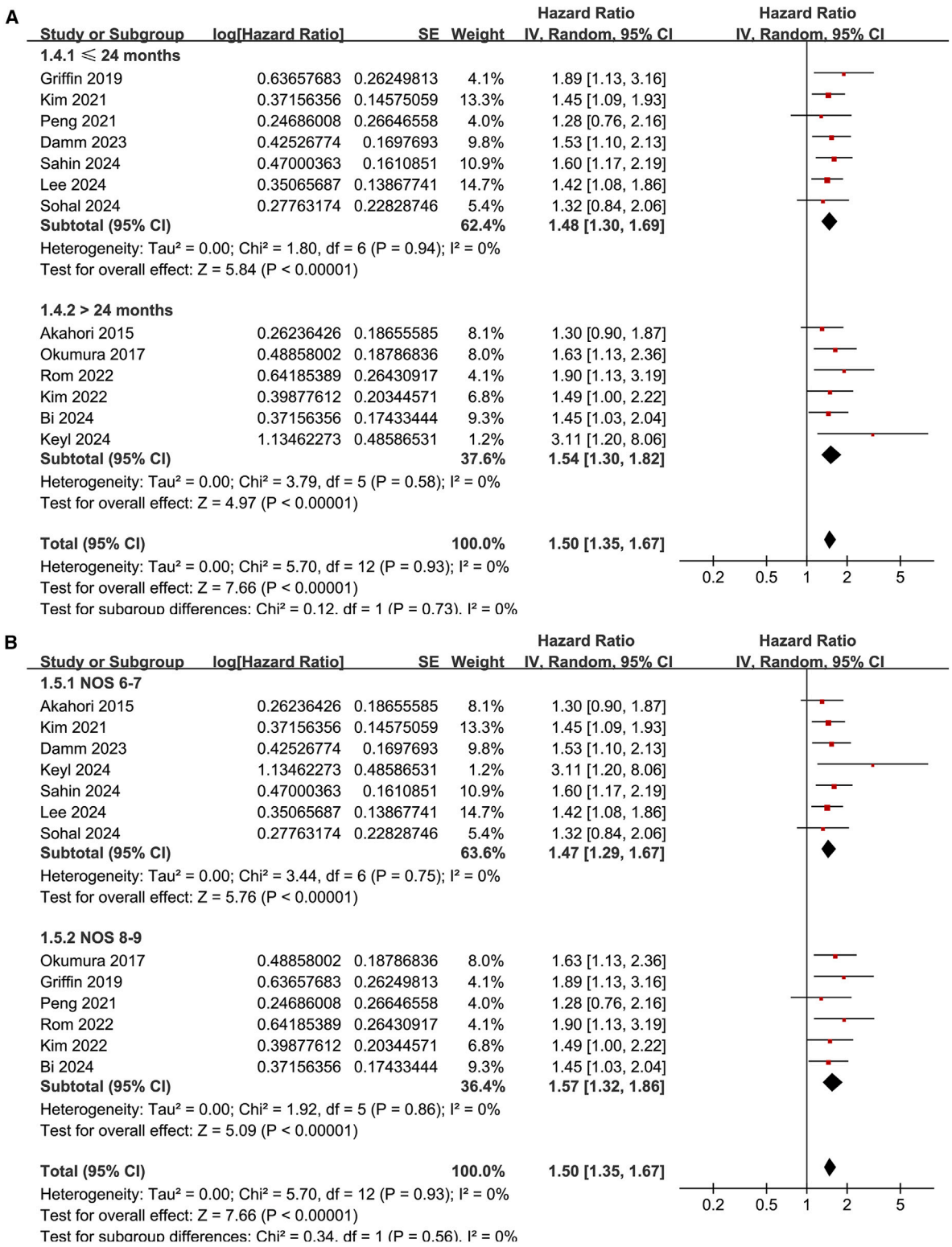



**Figure 3. Forest plots for the subgroup analysis of the association between myosteatosis and the overall survival of patients with pancreatic cancer**

(A) Subgroup analysis according to follow-up duration.

(B) Subgroup analysis according to the Newcastle-Ottawa scale (NOS) score. Data are represented as HR and 95% CI.

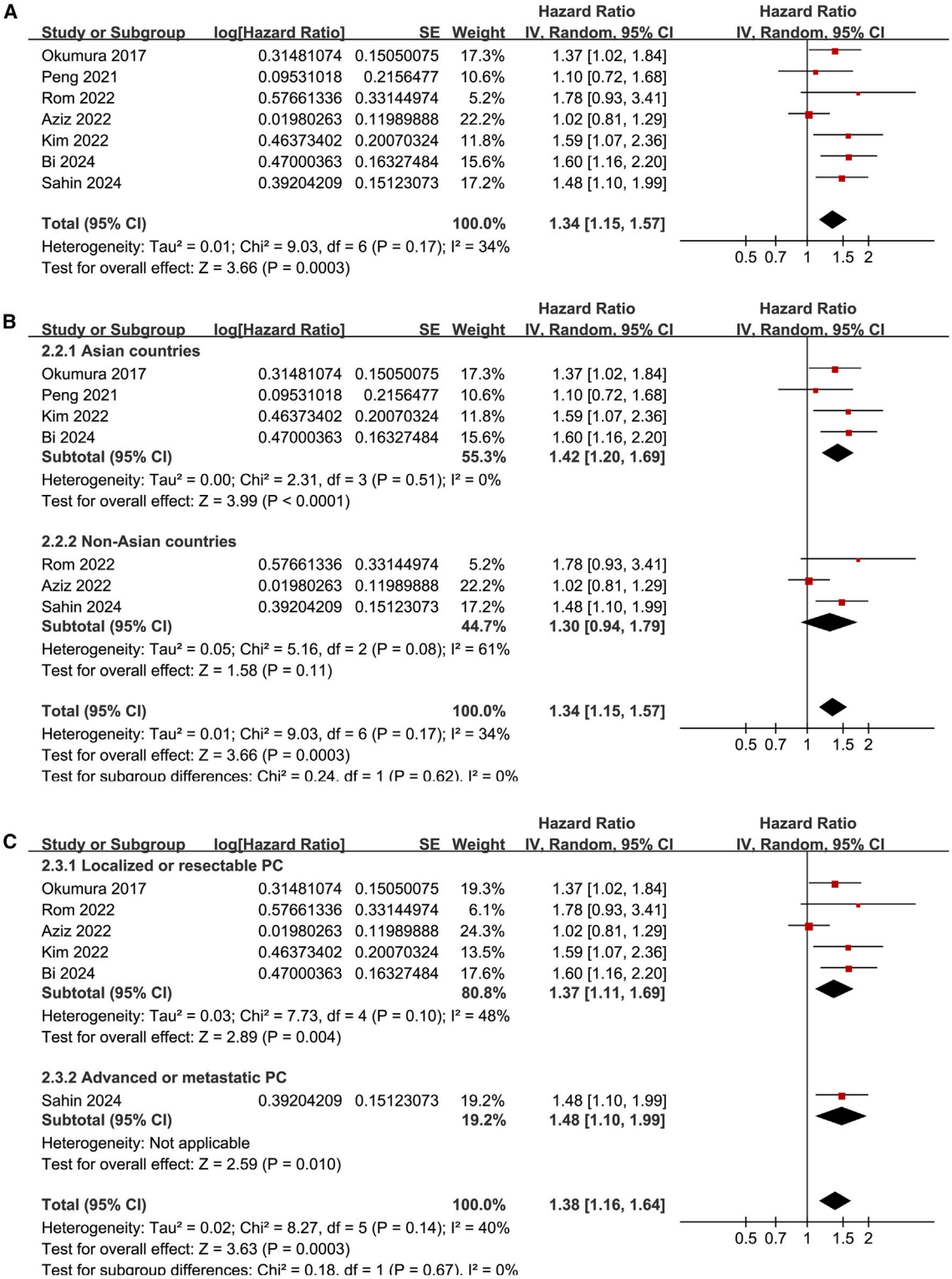



**Figure 4. Forest plots for the meta-analysis of the association between myosteatosis and the progression-free survival of patients with pancreatic cancer**

(A) Overall meta-analysis.

(B) Subgroup analysis according to study country.

(C) Subgroup analysis according to the status of cancer. Data are represented as HR and 95% CI.

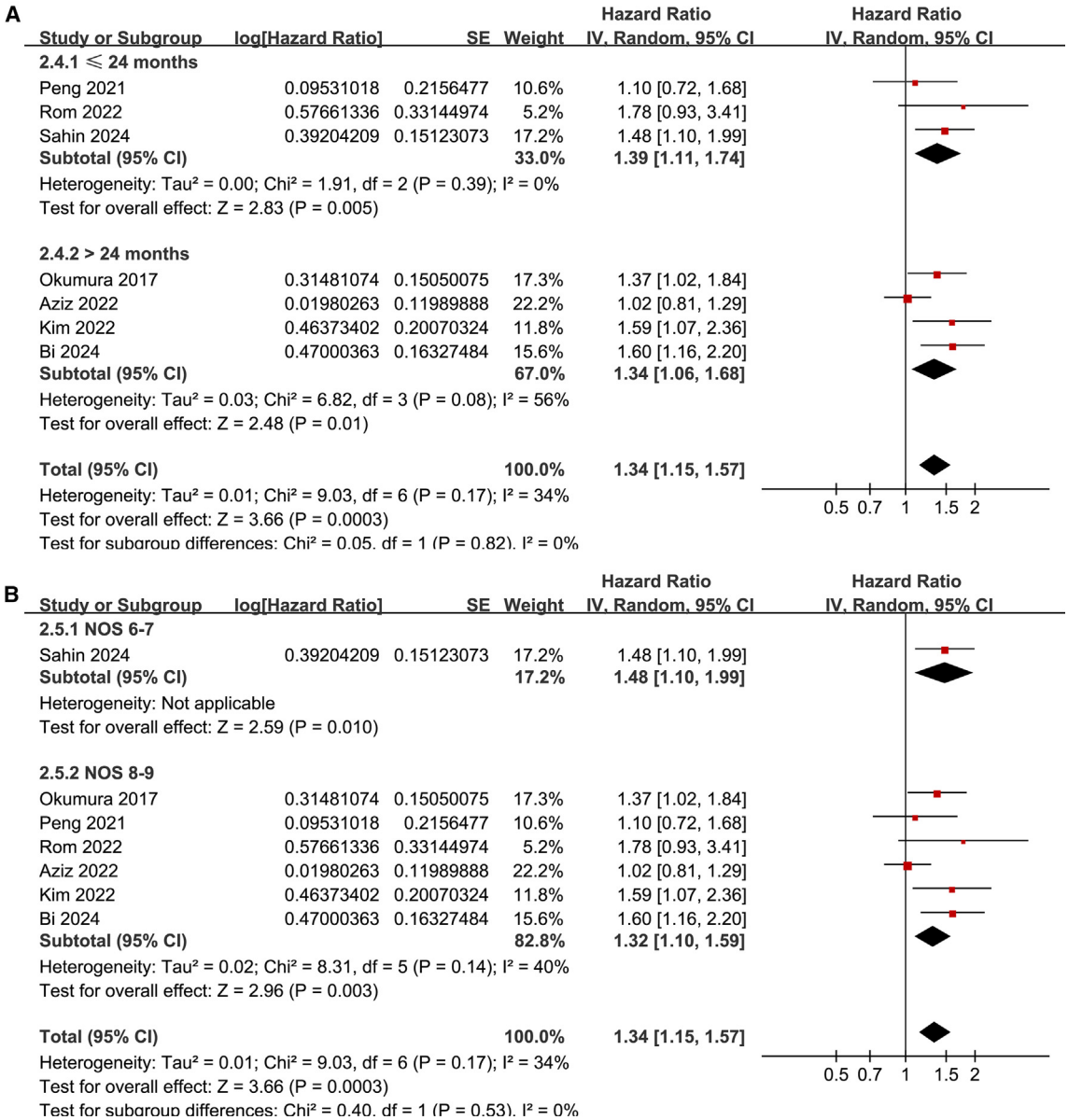



**Figure 5. Forest plots for the subgroup analysis of the association between myosteatosis and the progression-free survival of patients with PC**

(A) Subgroup analysis according to follow-up duration.

(B) Subgroup analysis according to the Newcastle-Ottawa scale (NOS) score. Data are represented as HR and 95% CI.

measurement of myosteatosis across studies might have influenced the pooled estimates. Although a random-effects model was used to account for this variability, standardization in assessing myosteatosis would improve the comparability in future research. In addition, the observational nature of the included studies limited the ability to establish causality between myosteatosis and survival outcomes. Furthermore, residual confounding factors, such as variations in treatment protocols and patient comorbidities, may have impacted the observed associations. Finally, 13 of the included studies had a retrospective design, which may be associated to recall and selection biases. These findings should be validated through large-scale prospective studies.

## Conclusions

In conclusion, the present meta-analysis provides pilot evidence that myosteatosis is associated to significantly poorer survival in patients with PC. These findings highlight the importance of considering myosteatosis in the prognostic assessment and management of PC patients. As the burden of pancreatic cancer

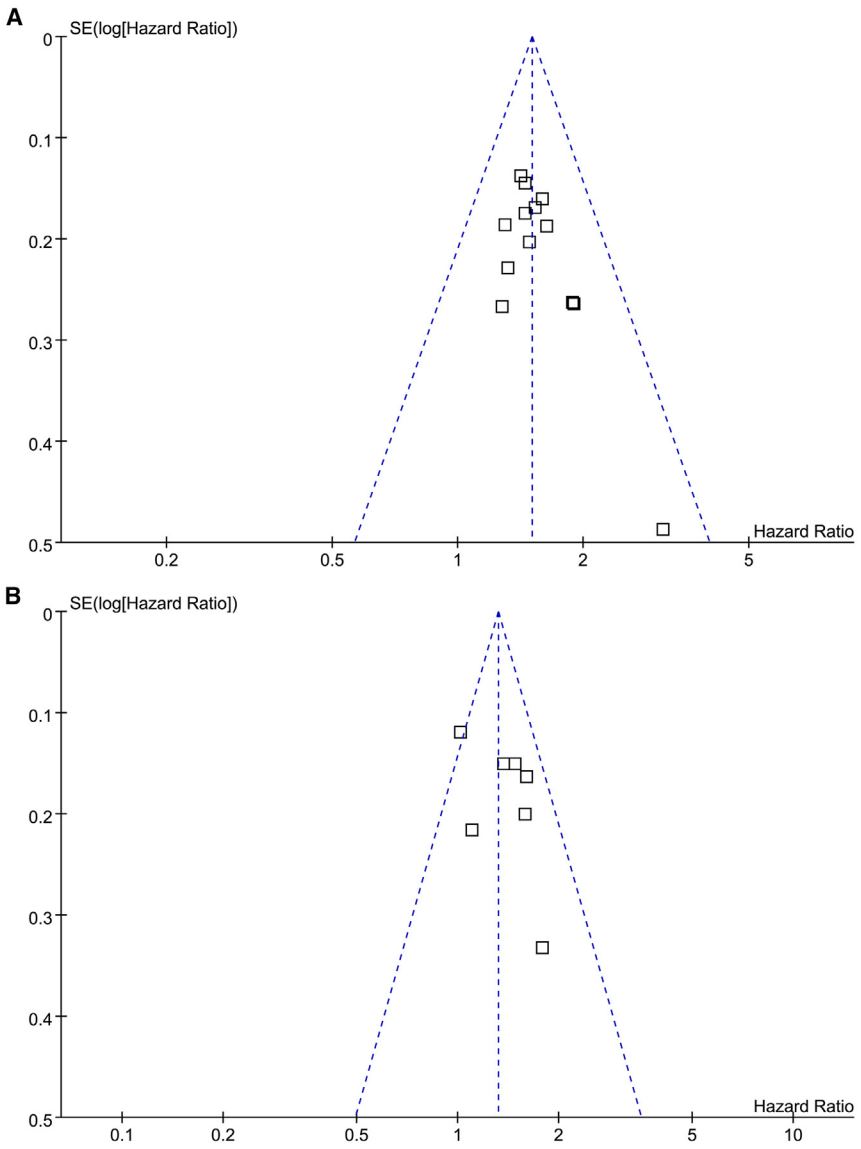



**Figure 6. Funnel plots for the meta-analysis of the association between myosteatosis and the survival outcomes of patients with PC**

(A) Funnel plots for the association between myosteatosis and overall survival.

(B) Funnel plots for the association between myosteatosis and progression-free survival.

continues to rise, integrating myosteatosis assessments in clinical practice may be important in enhancing patient outcomes and guiding therapeutic strategies.

## RESOURCE AVAILABILITY

### Lead contact

Further information and requests for resources can be directed to and would be fulfilled by the lead contact, Xing Li (875595327@qq.com).

### Materials availability

The present study is a meta-analysis and did not use or generate any reagents.

### Data and code availability

The data used for the present meta-analysis were obtained from published studies, and no new data or codes were used. All data are described in the ''key resources table'' section. Any additional information required to reanalyze the data reported in the study is available from the lead contact upon request.

## ACKNOWLEDGMENTS

The study was funded by the following funding sources:

(1) Natural Science Foundation of Changsha City, Grant number: Kq 2208467.

(2) Natural Science Foundation of Changsha City, Grant number: Kq 2208489.

(3) Natural Science Foundation of Changsha City Health Commission, Grant number: KJ-A2023012.

(4) Scientific Research Foundation of Administration of Traditional Chinese Medicine of Hunan Province, Grant number: A2024048.

(5) Natural Science Foundation of Hunan Province, Grant number: 2024JJ9525.

We would like to thank Medjaden Inc. for the scientific editing of the manuscript.

## AUTHOR CONTRIBUTIONS

X.Z., funding acquisition, investigation, methodology, and writing—original draft; L.W., investigation, project administration, supervision, validation, visualization, and writing—review and editing; J.L. and Y.D., data curation, software, and writing—review and editing; W.X. and D.C., formal analysis, resources, and writing—review and editing; X.L., conceptualization, funding acquisition, methodology, project administration, supervision, visualization, and writing—review and editing.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
- METHOD DETAILS
  - Literature search
  - Inclusion and exclusion criteria
  - Study quality evaluation and data extraction
- QUANTIFICATION AND STATISTICAL ANALYSIS

## SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.111343.

Received: August 12, 2024
Revised: August 28, 2024
Accepted: November 5, 2024
Published: November 7, 2024

## REFERENCES

1. Klein, A.P. (2021). Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat. Rev. Gastroenterol. Hepatol. *18*, 493–502. https://doi.org/10.1038/s41575-021-00457-x.
2. Siegel, R.L., Giaquinto, A.N., and Jemal, A. (2024). Cancer statistics, 2024. CA. Cancer J. Clin. *74*, 12–49. https://doi.org/10.3322/caac.21820.
3. Hu, J.X., Zhao, C.F., Chen, W.B., Liu, Q.C., Li, Q.W., Lin, Y.Y., and Gao, F. (2021). Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J. Gastroenterol. *27*, 4298–4321. https://doi.org/10.3748/wjg.v27.i27.4298.
4. Yang, J., Xu, R., Wang, C., Qiu, J., Ren, B., and You, L. (2021). Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review. Cancer Commun. *41*, 1257–1274. https://doi.org/10.1002/cac2.12204.
5. Tonini, V., and Zanni, M. (2022). Early diagnosis of pancreatic cancer: What strategies to avoid a foretold catastrophe. World J. Gastroenterol. *28*, 4235–4248. https://doi.org/10.3748/wjg.v28.i31.4235.
6. Halbrook, C.J., Lyssiotis, C.A., Pasca di Magliano, M., and Maitra, A. (2023). Pancreatic cancer: Advances and challenges. Cell *186*, 1729–1754. https://doi.org/10.1016/j.cell.2023.02.014.
7. Milella, M., Bassi, C., Boggi, U., Brunetti, O., Cavaliere, A., Crippa, S., De Vita, F., Falconi, M., Frassineti, G.L., Giommoni, E., et al. (2022). Evolving pancreatic cancer treatment: From diagnosis to healthcare management. Crit. Rev. Oncol. Hematol. *169*, 103571. https://doi.org/10.1016/j.critrevonc.2021.103571.
8. Dondero, K., Friedman, B., Rekant, J., Landers-Ramos, R., and Addison, O. (2024). The effects of myosteatosis on skeletal muscle function in older adults. Physiol. Rep. *12*, e16042. https://doi.org/10.14814/phy2.16042.
9. Miljkovic, I., and Zmuda, J.M. (2010). Epidemiology of myosteatosis. Curr. Opin. Clin. Nutr. Metab. Care *13*, 260–264. https://doi.org/10.1097/MCO.0b013e328337d826.
10. Miljkovic, I., Vella, C.A., and Allison, M. (2021). Computed Tomography-Derived Myosteatosis and Metabolic Disorders. Diabetes Metab. J. *45*, 482–491. https://doi.org/10.4093/dmj.2020.0277.
11. Lortie, J., Gage, G., Rush, B., Heymsfield, S.B., Szczykutowicz, T.P., and Kuchnia, A.J. (2022). The effect of computed tomography parameters on sarcopenia and myosteatosis assessment: a scoping review. J. Cachexia Sarcopenia Muscle *13*, 2807–2819. https://doi.org/10.1002/jcsm.13068.
12. Correa-de-Araujo, R., Addison, O., Miljkovic, I., Goodpaster, B.H., Bergman, B.C., Clark, R.V., Elena, J.W., Esser, K.A., Ferrucci, L., Harris-Love, M.O., et al. (2020). Myosteatosis in the Context of Skeletal Muscle Function Deficit: An Interdisciplinary Workshop at the National Institute on Aging. Front. Physiol. *11*, 963. https://doi.org/10.3389/fphys.2020.00963.
13. Scopel Poltronieri, T., de Paula, N.S., and Chaves, G.V. (2022). Skeletal muscle radiodensity and cancer outcomes: A scoping review of the literature. Nutr. Clin. Pract. *37*, 1117–1141. https://doi.org/10.1002/ncp.10794.
14. Aleixo, G.F.P., Shachar, S.S., Nyrop, K.A., Muss, H.B., Malpica, L., and Williams, G.R. (2020). Myosteatosis and prognosis in cancer: Systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. *145*, 102839. https://doi.org/10.1016/j.critrevonc.2019.102839.
15. Feng, S., Mu, H., Hou, R., Liu, Y., Zou, J., Zhao, Z., and Zhu, Y. (2022). Prognostic value of myosteatosis in patients with lung cancer: a systematic review and meta-analysis. Int. J. Clin. Oncol. *27*, 1127–1138. https://doi.org/10.1007/s10147-022-02181-1.
16. Lee, C.M., and Kang, J. (2020). Prognostic impact of myosteatosis in patients with colorectal cancer: a systematic review and meta-analysis. J. Cachexia Sarcopenia Muscle *11*, 1270–1282. https://doi.org/10.1002/jcsm.12575.
17. Fang, T., Gong, Y., and Wang, Y. (2023). Prognostic values of myosteatosis for overall survival in patients with gastric cancers: A meta-analysis with trial sequential analysis. Nutrition *105*, 111866. https://doi.org/10.1016/j.nut.2022.111866.
18. Kamiliou, A., Lekakis, V., Xynos, G., and Cholongitas, E. (2024). Prevalence of and Impact on the Outcome of Myosteatosis in Patients with Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Cancers *16*, 952. https://doi.org/10.3390/cancers16050952.
19. Okumura, S., Kaido, T., Hamaguchi, Y., Kobayashi, A., Shirai, H., Yao, S., Yagi, S., Kamo, N., Hatano, E., Okajima, H., et al. (2017). Visceral Adiposity and Sarcopenic Visceral Obesity are Associated with Poor Prognosis After Resection of Pancreatic Cancer. Ann. Surg Oncol. *24*, 3732–3740. https://doi.org/10.1245/s10434-017-6077-y.
20. Griffin, O.M., Duggan, S.N., Ryan, R., McDermott, R., Geoghegan, J., and Conlon, K.C. (2019). Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. Pancreatology *19*, 850–857. https://doi.org/10.1016/j.pan.2019.07.039.
21. Kim, I.H., Choi, M.H., Lee, I.S., Hong, T.H., and Lee, M.A. (2021). Clinical significance of skeletal muscle density and sarcopenia in patients with pancreatic cancer undergoing first-line chemotherapy: a retrospective observational study. BMC Cancer *21*, 77. https://doi.org/10.1186/s12885-020-07753-w.
22. Kim, D.W., Ahn, H., Kim, K.W., Lee, S.S., Kim, H.J., Ko, Y., Park, T., and Lee, J. (2022). Prognostic Value of Sarcopenia and Myosteatosis in Patients with Resectable Pancreatic Ductal Adenocarcinoma. Korean J. Radiol. *23*, 1055–1066. https://doi.org/10.3348/kjr.2022.0277.
23. Rom, H., Tamir, S., Van Vugt, J.L.A., Berger, Y., Perl, G., Morgenstern, S., Tovar, A., Brenner, B., Benchimol, D., Kashtan, H., and Sadot, E. (2022).

Sarcopenia as a Predictor of Survival in Patients with Pancreatic Adenocarcinoma After Pancreatectomy. Ann. Surg Oncol. *29*, 1553–1563. https://doi.org/10.1245/s10434-021-10995-y.

24. Damm, M., Efremov, L., Jalal, M., Nadeem, N., Dober, J., Michl, P., Wohlgemuth, W.A., Wadsley, J., Hopper, A.D., Krug, S., and Rosendahl, J. (2023). Body composition parameters predict survival in pancreatic cancer-A retrospective multicenter analysis. United European Gastroenterol. J. *11*, 998–1009. https://doi.org/10.1002/ueg2.12489.
25. Bi, S., Jiang, Y., Guan, G., Sun, X., Wang, X., Zhang, L., and Jing, X. (2024). Prognostic Value of Myosteatosis and Creatinine-to-Cystatin C Ratio in Patients with Pancreatic Cancer Who Underwent Radical Surgery. Ann. Surg Oncol. *31*, 2913–2924. https://doi.org/10.1245/s10434-024-14969-8.
26. Keyl, J., Bucher, A., Jungmann, F., Hosch, R., Ziller, A., Armbruster, R., Malkomes, P., Reissig, T.M., Koitka, S., Tzianopoulos, I., et al. (2024). Prognostic value of deep learning-derived body composition in advanced pancreatic cancer-a retrospective multicenter study. ESMO Open *9*, 102219. https://doi.org/10.1016/j.esmoop.2023.102219.
27. Lee, M.W., Jeon, S.K., Paik, W.H., Yoon, J.H., Joo, I., Lee, J.M., and Lee, S.H. (2024). Prognostic value of initial and longitudinal changes in body composition in metastatic pancreatic cancer. J. Cachexia Sarcopenia Muscle *15*, 735–745. https://doi.org/10.1002/jcsm.13437.
28. Sahin, T.K., Ozbay, Y., Altunbulak, A.Y., Altunbulak, H.I., Onur, M.R., Ceylan, F., Guven, D.C., Yalcin, S., and Dizdar, O. (2024). Albumin-myosteatosis gauge as a prognostic factor in patients with advanced pancreatic cancer undergoing first-line chemotherapy. Int. J. Clin. Oncol. *29*, 822–831. https://doi.org/10.1007/s10147-024-02512-4.
29. Akahori, T., Sho, M., Kinoshita, S., Nagai, M., Nishiwada, S., Tanaka, T., Tamamoto, T., Ohbayashi, C., Hasegawa, M., Kichikawa, K., and Nakajima, Y. (2015). Prognostic Significance of Muscle Attenuation in Pancreatic Cancer Patients Treated with Neoadjuvant Chemoradiotherapy. World J. Surg. *39*, 2975–2982. https://doi.org/10.1007/s00268-015-3205-3.
30. Peng, Y.C., Wu, C.H., Tien, Y.W., Lu, T.P., Wang, Y.H., and Chen, B.B. (2021). Preoperative sarcopenia is associated with poor overall survival in pancreatic cancer patients following pancreaticoduodenectomy. Eur. Radiol. *31*, 2472–2481. https://doi.org/10.1007/s00330-020-07294-7.
31. Aziz, M.H., van Dongen, J.C., Saida, L., Suker, M., van Vugt, J.L.A., van Putten, Y., Sideras, K., Groen, J.V., Mieog, J.S.D., Lucassen, C.J., et al. (2022). High Systemic Immune Inflammation Index Is Associated With Low Skeletal Muscle Quantity in Resectable Pancreatic Ductal Adenocarcinoma. Front. Oncol. *12*, 827755. https://doi.org/10.3389/fonc.2022.827755.
32. Sohal, D.P.S., Boutin, R.D., Lenchik, L., Kim, J., Beg, M.S., Wang-Gillam, A., Wade, J.L., 3rd, Guthrie, K.A., Chiorean, E.G., Ahmad, S.A., et al. (2024). Body composition measurements and clinical outcomes in patients with resectable pancreatic adenocarcinoma - analysis from SWOG S1505. J. Gastrointest. Surg. *28*, 232–235. https://doi.org/10.1016/j.gassur.2023.12.022.
33. Persson, H.L., Sioutas, A., Kentson, M., Jacobson, P., Lundberg, P., Dahlqvist Leinhard, O., and Forsgren, M.F. (2022). Skeletal Myosteatosis is Associated with Systemic Inflammation and a Loss of Muscle Bioenergetics in Stable COPD. J. Inflamm. Res. *15*, 4367–4384. https://doi.org/10.2147/JIR.S366204.
34. Axelrod, C.L., Dantas, W.S., and Kirwan, J.P. (2023). Sarcopenic obesity: emerging mechanisms and therapeutic potential. Metabolism *146*, 155639. https://doi.org/10.1016/j.metabol.2023.155639.
35. Lee, M., and Park, S. (2023). Myosteatosis: a potential missing link between hypertension and metabolic disorder in the Asian population. Hypertens. Res. *46*, 1603–1605. https://doi.org/10.1038/s41440-023-01270-6.
36. Zoico, E., Corzato, F., Bambace, C., Rossi, A.P., Micciolo, R., Cinti, S., Harris, T.B., and Zamboni, M. (2013). Myosteatosis and myofibrosis: relationship with aging, inflammation and insulin resistance. Arch. Gerontol. Geriatr. *57*, 411–416. https://doi.org/10.1016/j.archger.2013.06.001.
37. Tabara, Y., Okada, Y., Ochi, M., Ohyagi, Y., and Igase, M. (2023). Associations between adiponectin and leptin levels and skeletal muscle mass and myosteatosis in older adults: The Shimanami Health Promoting Program study. Geriatr. Gerontol. Int. *23*, 444–449. https://doi.org/10.1111/ggi.14582.
38. Shaver, A.L., Noyes, K., Platek, M.E., Singh, A.K., Erickson, K., Wendel, E., Wilding, G., Ochs-Balcom, H.M., and Ray, A. (2022). Cross-sectional analysis of myosteatosis and physical function in pretreatment head and neck cancer patients. Support. Care Cancer *30*, 3401–3408. https://doi.org/10.1007/s00520-022-06808-x.
39. Hong, S., Kim, K.W., Park, H.J., Ko, Y., Yoo, C., Park, S.Y., Khang, S., Jeong, H., and Lee, J. (2022). Impact of Baseline Muscle Mass and Myosteatosis on the Development of Early Toxicity During First-Line Chemotherapy in Patients With Initially Metastatic Pancreatic Cancer. Front. Oncol. *12*, 878472. https://doi.org/10.3389/fonc.2022.878472.
40. Lawson, C., Ferreira, V., Carli, F., and Chevalier, S. (2021). Effects of multimodal prehabilitation on muscle size, myosteatosis, and dietary intake of surgical patients with lung cancer - a randomized feasibility study. Appl Physiol Nutr Metab *46*, 1407–1416. https://doi.org/10.1139/apnm-2021-0249.
41. Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ *372*, n71. https://doi.org/10.1136/bmj.n71.
42. Page, M.J., Moher, D., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., et al. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ *372*, n160. https://doi.org/10.1136/bmj.n160.
43. Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., and Welch, V. (2021). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (The Cochrane Collaboration). www.training.cochrane.org/handbook.
44. Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., and Tugwell, P. (2010). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
45. Higgins, J.P.T., and Thompson, S.G. (2002). Quantifying heterogeneity in a meta-analysis. Stat. Med. *21*, 1539–1558. https://doi.org/10.1002/sim.1186.
46. Egger, M., Davey Smith, G., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ *315*, 629–634.

## STAR★METHODS

### KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---|---|---|
| Deposited data | | |
| PubMed | https://pubmed.ncbi.nlm.nih.gov/ | N/A |
| EMBASE | https://www.embase.com/ | N/A |
| Web of Science | https://www.webofscience.com/wos/author/search | N/A |
| Software and algorithms | | |
| Stata software Version 12.0 | Downloaded STATA software | https://www.stata.com/products/ |
| Review Manager 5.4 | The Cochrane Collaboration | https://revman.cochrane.org/info |

### EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The study did not use experimental models typical in the life sciences.

### METHOD DETAILS

The investigators adhered to the guidelines outlined in PRISMA 2020,[41,42] and the Cochrane Handbook for Systematic Reviews and Meta-analyses[43] throughout the present meta-analysis, which comprised the study design, data collection, statistical analysis, and interpretation of results. The protocol of the meta-analysis was registered at the International Prospective Register of Systematic Reviews (Registration code: CRD42024563270).

#### Literature search

In order to identify studies relevant to the aim of the meta-analysis, the Medline, Web of Science, and Embase databases were searched using the following comprehensive search terms: (1) "myosteatosis" OR "muscle density" OR "muscle attenuation" OR "intramuscular adipose tissue content" OR "intramuscular adipose tissue infiltration" OR "intramuscular adipose tissue deposition" OR "intramuscular fat content" OR "intramuscular fat infiltration" OR "intramuscular fat deposition"; (2) "pancreatic" OR "pancreas"; (3) "neoplasms" OR "carcinoma" OR "cancer" OR "tumor" OR "malignancy" OR "adenoma" OR "adenocarcinoma". Merely studies published as full-length articles in the English language in peer-reviewed journals were included. The full search strategies for each database used in the meta-analysis are provided in Table S1. In addition, the references of relevant original and review articles were manually examined for potential pertinent studies. Literature published from the inception of the database until May 26, 2024 were reviewed.

#### Inclusion and exclusion criteria

The inclusion criteria were designated according to the PCIOS principle for potential studies, as follows:

P (patients): patients with confirmed diagnosis of PC, with no limitations on tumor stage or main treatment; I (exposure): patients with myosteatosis at baseline, and the methods and cut-off values for defining myosteatosis were consistent with the criteria used in the original studies; C (comparison): patients without myosteatosis at baseline;

O (outcome): survival outcomes, including OS and/or PFS, which were compared between patients with and without myosteatosis at baseline (In general, OS was defined as the time from enrollment to the date of death from any cause, and PFS was defined as the interval between the enrollment and first recurrence/progression of PC.); S (study design): observational studies with longitudinal follow-up, such as cohort studies, nested case-control studies, and post-hoc analysis of clinical trials (Reviews, editorials, meta-analyses, preclinical studies, cross-sectional studies, studies that included other cancer patients rather than PC, studies that did not evaluate myosteatosis, and studies that did not report the survival outcomes were excluded. If studies with overlapping populations were retrieved, the one with the largest sample size was included in the meta-analysis.).

#### Study quality evaluation and data extraction

The literature search, study identification, study quality assessment, and data collection were independently carried out by two authors. In the screening process for the present meta-analysis, the titles and abstracts of the retrieved articles were independently reviewed by two authors based on the predefined inclusion and exclusion criteria. Then, the full-text articles of potentially relevant studies were assessed by the same authors, with any disagreements resolved through discussion or consultation with a third author.

EndNote (version X4) was used to organize the references, track inclusion/exclusion decisions, and remove duplicates. In order to minimize bias, the screening was performed with blinding, where feasible. The authors involved in the screening process were blinded to the identities of the other reviewers' decisions to reduce potential bias. However, since some disagreements required discussion and consensus, full blinding was not always maintained throughout the process. Duplicates were initially removed using the automated deduplication function of EndNote, followed by manual checks, in order to ensure that each study was reviewed only once. In order to evaluate the quality of the included studies, the Newcastle-Ottawa scale (NOS)[44] was utilized, which assesses three aspects, namely, the selection of the population, control of confounders, and outcome measurement and analysis. The NOS scores ranged within 1–9, with 9 indicating superior quality. The following data were extracted from each study for the subsequent analysis: study information (author, year, country and design), patient and cancer characteristics (diagnosis, sample size, age, gender, histology, tumor stage, and main treatment), methods for evaluating myosteatosis, number of patients with myosteatosis, follow-up duration, survival outcomes reported, and variables adjusted when reporting the association between myosteatosis and the survival outcomes of patients with PC.

## QUANTIFICATION AND STATISTICAL ANALYSIS

The relationship between myosteatosis and the survival outcomes of patients with PC was summarized using hazard ratio (HR) and the corresponding 95% confidence interval (CI), and compared between subjects with and without myosteatosis at enrollment. The HRs and its standard errors were computed based on the 95% CIs or *p*-values, followed by logarithmic transformation for variance stabilization. Heterogeneity among studies was evaluated using the Cochrane Q test and $I^2$ statistics,[45] where $I^2 > 50\%$ indicated significant statistical heterogeneity. The findings were combined using the random-effects model that accounted for the potential influence of heterogeneity.[43] A sensitivity analysis that involved the exclusion of one study at a time was conducted to assess the robustness of the results. Predefined subgroup analysis was carried out to determine how the study characteristics influenced the outcome, such as the study country, cancer stage (localized/resectable vs. advanced/metastatic PC), follow-up duration, and study quality score. The median values of continuous variables were used as cut-offs in defining the subgroups. Publication bias in the meta-analysis was assessed by constructing funnel plots, along with visual inspection, for plot symmetry.[46] In addition, Egger's regression test was performed.[46] The statistical analysis was conducted using RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and the Stata software (version 12.0; Stata Corporation, College Station, TX, USA).