

# 10-Year Survivorship, Metastatic Risk, and Clinicopathologic Characteristics of Early-Onset Pancreatic Cancer: A Meta-Analysis and Meta-Regression

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## Research Article

**Keywords:** Early-onset pancreatic cancer, meta analysis, survival outcome, metastasis, risk factors

**Posted Date:** October 14th, 2026

**DOI:** <https://doi.org/10.21203/rs.3.rs-11100651/v1>

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**Additional Declarations:** No competing interests reported.

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# Abstract

## Purpose

Pancreatic cancer (PC) remains a global burden with low overall survival yet a distinct group referred to as early-onset (EOPC) remains poorly observed. This review aims to investigate survival outcomes, metastatic risk, and clinicopathologic features of EOPC compared with non-early-onset PC using meta analysis, meta regression, and individual patient data (IPD) reconstruction.

## Methods

Literature search was conducted on January 9, 2026, in PubMed, Scopus, and ScienceDirect. Random-effects meta-analysis conducted using risk ratios or mean differences. IPD was reconstructed under Guyot's protocol.

## Results

22 articles comprising 364,319 patients were analyzed. EOPC observed in 6.1% of total PC patients. EOPC had a 25% lower hazard of death than non-EOPC (HR = 0.75,  $p < 0.001$ ). EOPC was higher in males (RR 1.09,  $p = 0.004$ ), with smoking history (RR 1.22,  $p < 0.001$ ), but lower diabetes mellitus (RR 0.34,  $p = 0.001$ ). EOPC were likely to be presented with pain (RR 1.39,  $p = 0.017$ ), higher metastasis risk (RR = 1.11,  $p = 0.02$ ), higher T3/T4 stage (RR 1.06,  $p = 0.002$ ), and higher III/IV stage (RR 1.08,  $p = 0.008$ ). Using meta regression, metastasis of EOPC was associated with smoking status ( $\beta = 3.06$ ,  $p < 0.001$ , residual  $I^2 = 11\%$ ), but neither with each study country's SDI, tumor location, proportion of obesity, patient's mean age, nor proportion of alcohol intake.

## Conclusions

EOPC was distinct to non-EOPC with 25% lower hazard of death. Early detection should target younger patients with risk factors such as active smoking to avoid advanced stages of disease.

### 1. Background

Over the past 25 years, the global incidence of pancreatic cancer (PC) has risen by 63%, establishing it as one of the most rapidly growing malignancies worldwide, which is also one of the most lethal types of cancer (Lippi and Mattiuzzi 2020). As of 2022, PC ranks as the sixth leading cause of cancer-related death worldwide, and by 2040, it was projected to be the second most common cancer-related mortality worldwide (Leiphakpam et al. 2025; Lippi and Mattiuzzi 2020; Siegel et al. 2024). The 5-year relative survival of PC was only 13.3% reflecting the disease's limited treatment responsiveness (Diniz da Conceição et al. 2025).

PC is a gastrointestinal neoplasm developed from several risk factors, such as hereditary genes, smoking, obesity, chronic pancreatitis, and diabetes (Capasso et al. 2018; Halfdanarson et al. 2014; Haugvik et al. 2015; Midha et al. 2016). The stepwise acquisition of these comorbidities underlies the prolonged latency characteristics of PC, with two-thirds of cases presenting after 65 years (Hayman et al. 2015; Sehgal et al. 2014) and the median age of diagnosis at 71 years of age (Park et al. 2021). However, a distinct subset, approximately 5 to 10% of patients, have been diagnosed at an age less than 50 years, a presentation referred to as early-onset pancreatic cancer (EOPC) (Li et al. 2025).

EOPC may harbor a unique clinicopathologic profile that differs substantially from conventional late-onset PC, which a projection study indicates that in 2040, the EOPC incidence and mortality are predicted to be increased by 10.6% (Diniz da Conceição et al. 2025). Previous global burden disease (GBD) data suggest that EOPC was diagnosed at a more advanced stage, especially in low SDI countries (Li et al. 2025), and appears to be associated with the proportion of male patients, greater smoking history, and paradoxically improved overall survival compared to late-onset PC (Fang et al. 2025). Despite these observations, the current understanding of survival outcomes, clinical characteristics, and risk factors associated with EOPC remains unclear with no dedicated meta-analysis existing to date.

Herein, we aimed to comprehensively review current available data and perform a thorough meta-analysis to investigate the survival outcomes, metastatic risk, and clinicopathologic features of EOPC compared with non-early onset PC.

## **2. Materials and Methods**

### **2.1 Study design**

This study is a systematic review, meta-analysis, and meta regression followed the reporting guideline of the PRISMA 2020 guideline (Page et al. 2021), with the protocol available in PROSPERO under identifier CRD420261391350. This study also conducted an IPD reconstruction under Guyot's protocol (Guyot et al. 2012).

### **2.2 Eligibility criteria**

Studies were included if designated as an original observational study that (1) analyzed adult patient (> 18 years old) with confirmed pancreatic cancer through either histopathology, imaging, or clinical-based based on the European Society of Medical Oncology (Conroy et al. 2023), (2) assessing early onset pancreatic cancer with cut off age of at least less than 50 years with the comparator of other group of age. Otherwise, studies were excluded if (1) designed as non-observational (case report, letter to editor, conference abstracts, correspondence), (2) published in languages other than English, (3) not published as a full paper, or (4) no outcome of interest reported in the article.

### **2.3 Outcome of interest**

The outcomes of interest were (1) survival outcomes (overall, progression-free, and recurrence-free survival), (2) metastasis proportion, and (3) patient's characteristics including age, BMI, sex, presenting

symptoms, AJCC staging, tumor grading, and tumor location, (4) risk factors of pancreatic cancer including history of smoking, history of alcohol consumption, diabetes mellitus status. All outcomes must be reported on both EOPC group and nEOPC group.

## 2.4 Search strategy

A comprehensive literature search incorporating keywords of “Pancreatic cancer”, “Metastasis”, “Survival outcome”, and “Risk factors”. Full search string was available at Online Resource 1. Data search was conducted on January 9, 2026, in three databases: PubMed, Scopus, and ScienceDirect with filters applied including English language, research type document, and full article availability. Year of publication was not restricted to include all available data. Two independent authors screened studies in the Rayyan.ai tool with any discrepancies were resolved by the third author. The data from the included studies were retrieved in a Microsoft Excel format, including study characteristics, patient information, and outcomes.

## 2.5 Study quality assessment

Risk of bias was assessed across studies using Cochrane’s risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E) tool (Higgins et al. 2024) by two independent authors with any disagreement resolved with third author. The tool consisted of seven domains, with each study categorized as “Low risk”, “Some concerns”, or “High risk”. Overall quality was concluded by the highest risk of bias of at least one domain.

## 2.6 Statistical analysis

Analysis was conducted in R (version 4.3.2) with packages including *meta*, *survival*, *metafor*, and *ggplot2*. We used a random effect, the restricted maximum likelihood (REML) estimator meta-analysis using risk ratios (RR) to assess categorical variables, and mean differences for continuous variables, while the generic inverse variance of hazard ratios (HR) for survival outcomes. The p-value of less than 0.05 was considered significant. Heterogeneity of analysis was assessed using  $I^2$ . Sensitivity analysis using leave-one-out was also conducted to assess the robustness of the analysis. Meta regression analysis performed to evaluate metastatic risk utilizing the study country’s 2023 Socio-demographic Index (SDI) (Global Burden of Disease Collaborative Network 2025), proportion of smoking, tumor location, proportion of obesity, patient’s mean age, and proportion of alcohol intake history. The Survival data from included articles were obtained to estimate individual patient data (IPD) according to Guyot’s protocol (Guyot et al. 2012).

## 3. Results

### 3.1 General findings

22 studies with a total of 364,319 patients were included; among them, 6.1% were EOPC. The complete selection flow is provided in Online Resource 2. The included studies were published no earlier than 2015. Every study used a cutoff for EOPC at 50 years of age, except for some studies published before 2018. There were six studies included published in the United States, eight in Europe, and seven in Asia-Pacific. The complete study characteristics are presented in Table 1. Four studies had a high risk of publication bias

in domains 1 and 5, which was present due to uncontrolled confounding factors and high number of missing population (Online Resource 3) (Eguchi et al. 2016; Ntala et al. 2018; Ohmoto et al. 2015; Rashad et al. 2024). Other domains were generally low-to-moderate across studies.

Table 1  
Characteristics of the included studies

| Study ID                 | Country                              | Database                                                             | EOPC Definition | Metastatic patients | Number of Patients |        |        |
|--------------------------|--------------------------------------|----------------------------------------------------------------------|-----------------|---------------------|--------------------|--------|--------|
|                          |                                      |                                                                      |                 |                     | EOPC               | nEOPC  | Total  |
| Jayakrishnan et al. 2025 | USA                                  | Cleveland Clinic Foundation                                          | < 50 years      | Excluded            | 24                 | 20     | 44     |
| Tschaidse et al. 2025    | Germany                              | StuDoQ National pancreas registry                                    | < 50 years      | Included            | 110                | 1,502  | 1,612  |
| Mendis et al. 2024       | Australia, New Zealand and Singapore | Multicenter PURPLE Registry                                          | ≤ 50 years      | Included            | 112                | 1,571  | 1,683  |
| Rashad et al. 2024       | Egypt                                | Shefaa Al Orman Cancer Center                                        | ≤ 50 years      | Included            | 84                 | 328    | 412    |
| Remond et al. 2024       | France                               | Institut Gustave Roussy                                              | ≤ 50 years      | Included            | 123                | 765    | 888    |
| Castet et al. 2023       | Spain                                | Vall d'Hebron Institute of Oncology                                  | ≤ 50 years      | Included            | 139                | 197    | 336    |
| Ren et al. 2023          | USA                                  | SEER Database, NCI USA                                               | < 50 years      | Included            | 2,916              | 39,468 | 42,384 |
| Whitley et al. 2023      | Czech                                | National database                                                    | ≤ 50 years      | Included            | 1,324              | 17,564 | 18,888 |
| Zironda et al. 2023      | USA                                  | Mayo Clinic Rochester                                                | ≤ 50 years      | Excluded            | 65                 | 1,068  | 1,133  |
| Kim et al. 2022          | South Korea                          | National KOTUS-BP database                                           | < 50 years      | Excluded            | 379                | 2,091  | 2,470  |
| Takeda et al. 2022       | Japan                                | Cancer Institute Hospital of Japanese Foundation for Cancer Research | ≤ 50 years      | Included            | 127                | 1,519  | 1,646  |
| Raffenne et al. 2021     | France                               | Multinational multicenter                                            | ≤ 55 years      | Included            | 106                | 149    | 255    |

| Study ID               | Country        | Database                                                             | EOPC Definition | Metastatic patients | Number of Patients |         |         |
|------------------------|----------------|----------------------------------------------------------------------|-----------------|---------------------|--------------------|---------|---------|
|                        |                |                                                                      |                 |                     | EOPC               | nEOPC   | Total   |
| Saadat et al. 2021     | USA            | the National Cancer Database                                         | < 50 years      | Included            | 15,710             | 232,924 | 248,634 |
| Bunduc et al. 2018     | Romania        | Fundeni Clinical Institute, Bucharest                                | ≤ 45 years      | Included            | 24                 | 120     | 144     |
| Ntala et al. 2018      | United Kingdom | the Royal London Hospital                                            | ≤ 50 years      | Included            | 35                 | 334     | 369     |
| Jiang et al. 2017      | China          | Chinese Academy of Medical Sciences and Peking Union Medical College | ≤ 45 years      | Included            | 156                | 1,633   | 1,789   |
| Kang et al. 2017       | South Korea    | Seoul National University College of Medicine                        | < 45 years      | Included            | 34                 | 665     | 699     |
| Eguchi et al. 2016     | Japan          | the Japan Pancreas Society's National Registry                       | < 40 years      | Included            | 526                | 35,619  | 36,145  |
| Fadiel et al. 2016     | USA            | Vanderbilt University Medical Center                                 | < 50 years      | Included            | 118                | 1,289   | 1,407   |
| McWilliams et al. 2016 | USA            | Multicenter PanC4 Study                                              | < 45 years      | Included            | 226                | 1,954   | 2,180   |
| Ohmoto et al. 2015     | Japan          | the National Cancer Center Hospital                                  | ≤ 40 years      | Included            | 17                 | 891     | 908     |
| Piciucchi et al. 2015  | Italy          | Sant'Andrea Hospital, University of Rome                             | ≤ 50 years      | Included            | 25                 | 268     | 293     |

## 3.2 Survival Outcomes

Thirteen studies were reconstructed with included patients of 57,432 (54,868 nEOPC and 2,564 EOPC) (Castet et al. 2023; Eguchi et al. 2016; Jiang et al. 2017; Kang et al. 2017; Kim et al. 2023; Mendis et al. 2024; Ntala et al. 2018; Piciucchi et al. 2015; Rashad et al. 2024; Rémond et al. 2024; Ren et al. 2023; Takeda et al. 2022; Zironda et al. 2024). The EOPC group had significantly higher overall survival compared to nEOPC, with a significant value [HR = 0.75, 95%CI: 0.72–0.79;  $p < 0.001$ ; Fig. 1]. Using generic inverse variance meta-analysis, three and four studies were included in the progression-free survival (PFS) and recurrence-free survival (RFS) analysis, respectively. PFS was comparable between EOPC and nEOPC [HR = 0.84, 95%CI (0.70–1.02);  $p = 0.079$ ; Fig. 2a]. RFS for resectable patients was also comparable between both groups [HR = 0.88, 95%CI (0.75–1.02);  $p = 0.096$ ; Fig. 2b].

### 3.3 Clinical features

From meta-analysis, EOPC patients were significantly younger at baseline, (MD – 25.06 years, 95% CI (– 27.13 to – 23.00),  $p < 0.001$ ,  $I^2 = 99\%$ ) higher male proportion, (RR 1.09, 95%CI (1.03 to 1.16),  $p = 0.004$ ,  $I^2 = 88\%$ ), and more commonly associated with pain at presentation compared to nEOPC (RR 1.39, 95%CI (1.06 to 1.83),  $p = 0.017$ ,  $I^2 = 79\%$ ).

Regarding baseline risk factors, EOPC patients had significantly higher smoking history (RR 1.22, 95%CI (1.12 to 1.32),  $p < 0.001$ ,  $I^2 = 0\%$ ) but lower diabetes mellitus history (RR 0.34, 95%CI (0.18 to 0.66),  $p = 0.001$ ,  $I^2 = 89\%$ ). Other risk factors such as familial history of cancer, history of chronic pancreatitis, alcohol intake, BMI, and obesity status were comparable in EOPC and nEOPC.

EOPC was diagnosed at a more advanced tumor stage. EOPC had a higher T3/T4 stage compared to the control (RR 1.06, 95%CI (1.02 to 1.10),  $p = 0.002$ ,  $I^2 = 57\%$ ), higher metastasis (RR = 1.11, 95%CI (1.01–1.22);  $p = 0.02$ ,  $I^2 = 68\%$ ), and higher tumor stage III/IV (RR 1.08, 95%CI (1.02 to 1.15),  $p = 0.008$ ,  $I^2 = 77\%$ ), with all analyses showing robust results in leave-one-out sensitivity analysis. All analyses were summarized in Table 2 and Online Resource 4.

Table 2  
Results of the meta-analysis

| Outcome                                                                                                                                                                                                                                                                                                     | k  | Data | Effect | 95%CI           | P value             | I <sup>2</sup> | Sensitivity |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|--------|-----------------|---------------------|----------------|-------------|
| <b>Clinical Characteristics</b>                                                                                                                                                                                                                                                                             |    |      |        |                 |                     |                |             |
| Age                                                                                                                                                                                                                                                                                                         | 15 | MD   | -25.06 | -27.13 – -23.00 | <b>&lt; 0.0001*</b> | 99%            | Robust      |
| Male gender                                                                                                                                                                                                                                                                                                 | 21 | RR   | 1.09   | 1.03–1.16       | <b>0.004*</b>       | 88%            | Robust      |
| BMI                                                                                                                                                                                                                                                                                                         | 8  | MD   | 0.22   | -0.10–0.54      | 0.185               | 0%             | Robust      |
| Obesity                                                                                                                                                                                                                                                                                                     | 5  | RR   | 1      | 0.68–1.46       | 0.980               | 72%            | Not robust  |
| Alcohol history                                                                                                                                                                                                                                                                                             | 10 | RR   | 1.17   | 0.82–1.68       | 0.379               | 75%            | Robust      |
| Chronic pancreatitis history                                                                                                                                                                                                                                                                                | 5  | RR   | 1.04   | 0.68–1.58       | 0.872               | 0%             | Robust      |
| Diabetes melitus history                                                                                                                                                                                                                                                                                    | 8  | RR   | 0.34   | 0.18–0.66       | <b>0.001*</b>       | 89%            | Robust      |
| Smoking history                                                                                                                                                                                                                                                                                             | 11 | RR   | 1.22   | 1.12–1.32       | <b>&lt; 0.0001*</b> | 0%             | Robust      |
| Family history of any cancer                                                                                                                                                                                                                                                                                | 5  | RR   | 0.98   | 0.87–1.09       | 0.655               | 0%             | Robust      |
| Family history of pancreatic cancer                                                                                                                                                                                                                                                                         | 9  | RR   | 0.94   | 0.74–1.19       | 0.595               | 18%            | Robust      |
| <b>Presenting Symptoms</b>                                                                                                                                                                                                                                                                                  |    |      |        |                 |                     |                |             |
| Jaundice                                                                                                                                                                                                                                                                                                    | 6  | RR   | 0.81   | 0.58–1.15       | 0.242               | 68%            | Robust      |
| New onset diabetes mellitus                                                                                                                                                                                                                                                                                 | 2  | RR   | 0.37   | 0.12–1.14       | 0.083               | 0%             | Robust      |
| Pain                                                                                                                                                                                                                                                                                                        | 5  | RR   | 1.39   | 1.06–1.83       | <b>0.017*</b>       | 79%            | Robust      |
| Weight loss                                                                                                                                                                                                                                                                                                 | 5  | RR   | 0.78   | 0.54–1.12       | 0.173               | 60%            | Not robust  |
| <b>Pathological characteristics</b>                                                                                                                                                                                                                                                                         |    |      |        |                 |                     |                |             |
| <b>TNM staging</b>                                                                                                                                                                                                                                                                                          |    |      |        |                 |                     |                |             |
| Abbreviations: CI: Confidence Interval, HR: Hazard Ratio, I <sup>2</sup> : I-squared (index of heterogeneity, indicating the percentage of total variation across studies due to true heterogeneity rather than sampling error/chance), k: number of included studies, MD: Mean difference, RR: Risk ratio. |    |      |        |                 |                     |                |             |

| Outcome                                                                                                                                                                                                                                                                                            | k         | Data | Effect | 95%CI      | P value       | $I^2$ | Sensitivity |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|------|--------|------------|---------------|-------|-------------|
| <b>Clinical Characteristics</b>                                                                                                                                                                                                                                                                    |           |      |        |            |               |       |             |
| T1/T2                                                                                                                                                                                                                                                                                              | Reference |      |        |            |               |       |             |
| T3/T4                                                                                                                                                                                                                                                                                              | 6         | RR   | 1.06   | 1.02–1.1   | <b>0.002*</b> | 57%   | Robust      |
| N+                                                                                                                                                                                                                                                                                                 | 6         | RR   | 1.05   | 0.99–1.12  | 0.133         | 45%   | Not robust  |
| M+                                                                                                                                                                                                                                                                                                 | 9         | RR   | 1.11   | 1.01–1.21  | <b>0.025*</b> | 68%   | Robust      |
| Stage I/II                                                                                                                                                                                                                                                                                         | Reference |      |        |            |               |       |             |
| Stage III/IV                                                                                                                                                                                                                                                                                       | 10        | RR   | 1.08   | 1.02–1.15  | <b>0.008*</b> | 77%   | Robust      |
| <b>NCCN Stage</b>                                                                                                                                                                                                                                                                                  |           |      |        |            |               |       |             |
| Resectable/Borderline                                                                                                                                                                                                                                                                              | Reference |      |        |            |               |       |             |
| Locally advanced/metastasis                                                                                                                                                                                                                                                                        | 6         | RR   | 1.05   | 0.93–1.2   | 0.418         | 77%   | Robust      |
| <b>Tumor location</b>                                                                                                                                                                                                                                                                              |           |      |        |            |               |       |             |
| Head location                                                                                                                                                                                                                                                                                      | Reference |      |        |            |               |       |             |
| Body/Tail location                                                                                                                                                                                                                                                                                 | 14        | RR   | 1      | 0.9–1.1    | 0.957         | 47%   | Robust      |
| <b>Tumor differentiation</b>                                                                                                                                                                                                                                                                       |           |      |        |            |               |       |             |
| Well differentiation                                                                                                                                                                                                                                                                               | 7         | RR   | 0.94   | 0.78–1.14  | 0.551         | 34%   | Robust      |
| Moderate differentiation                                                                                                                                                                                                                                                                           | 7         | RR   | 1      | 0.96–1.04  | 0.927         | 22%   | Robust      |
| Poor differentiation                                                                                                                                                                                                                                                                               | 7         | RR   | 1.02   | 0.85–1.23  | 0.799         | 51%   | Robust      |
| <b>Other pathological outcomes</b>                                                                                                                                                                                                                                                                 |           |      |        |            |               |       |             |
| Tumor size                                                                                                                                                                                                                                                                                         | 6         | MD   | 1.11   | -1.11–3.32 | 0.327         | 85%   | Not robust  |
| Lymphovascular involvement                                                                                                                                                                                                                                                                         | 4         | RR   | 0.98   | 0.71–1.35  | 0.896         | 69%   | Robust      |
| Perineural involvement                                                                                                                                                                                                                                                                             | 4         | RR   | 0.98   | 0.71–1.35  | 0.896         | 69%   | Robust      |
| Abbreviations: CI: Confidence Interval, HR: Hazard Ratio, $I^2$ : I-squared (index of heterogeneity, indicating the percentage of total variation across studies due to true heterogeneity rather than sampling error/chance), k: number of included studies, MD: Mean difference, RR: Risk ratio. |           |      |        |            |               |       |             |

## 3.4 Metastatic risk

For metastasis risk, nine studies were analyzed (Castet et al. 2023; Eguchi et al. 2016; Jiang et al. 2017; Kang et al. 2017; Mendis et al. 2024; Ntala et al. 2018; Rémond et al. 2024; Ren et al. 2023; Takeda et al. 2022). Metastasis was significantly higher in EOPC group [RR = 1.11, 95%CI (1.01–1.22);  $p = 0.02$ ]. Meta regression assessing metastasis risk with each study country's SDI, proportion of smoking, tumor location, proportion of obesity, patient's mean age, and proportion of alcohol intake history was conducted. We found that there was a positive correlation in which higher smoking history tended to be found with higher metastasis risk at diagnosis in EOPC ( $\beta = 3.06$ ,  $p < 0.001$ , residual  $I^2 = 11\%$ ) (Fig. 3). The other evaluated risks were found to be not correlated with metastasis based on meta-regression.

## 4. Discussion

Understanding the comprehensive burden, characteristics, and prognosis of PC and its subtype was among the priorities worldwide, as PC was identified as the most rapidly growing malignancy with low overall survival. In our study, we demonstrated that the survival outcomes of those with EOPC was 25% better than nEOPC, and it was identified as more common in male patients, with pain at presentation, with smoking history, presented with a more advanced stage, and at higher risk of metastasis.

The most important consideration of our study was perhaps that from our reconstructed 10-year data, those with EOPC demonstrated higher survival. A large-scale characterization study demonstrated that younger PC is associated with a distinct molecular and immune landscape compared to late-onset PC (Ogobuiro et al. 2023). Notably, current evidence indicates that younger onset PC has a higher prevalence of BRCA2 and PALB2 mutations and lower rates of oncogenic KRAS alterations (Ogobuiro et al. 2023). In this population, KRAS-wild type tumors are enriched with NRG1 and MET fusion (Ogobuiro et al. 2023). This molecular subset may, at least in part, explain the superior overall survival advantage, which seems to be confined to patients with KRAS-wild type rather than reflecting age-related benefit (Ulanja et al. 2022). These findings are also consistent with additional observations showing that mutations CDKN2A, FOXC2, and SMAD4 are significantly more common in EOPC, and KRAS mutations are comparatively less frequent (Luo et al. 2025). Taken together, this suggests that those with EOPC may be driven by fundamentally divergent oncogenic pathways that generate different therapeutic vulnerabilities (Luo et al. 2025; Ogobuiro et al. 2023; Ulanja et al. 2022).

From a target therapy standpoint, the higher overall survival may also be due to the favorable therapeutic responsiveness of EOPC, as ESCAT tier I-IIIa variants were more frequent in EOPC than in nEOPC (Castet et al. 2023; Varghese et al. 2021). Somatic profiling at major centers has also identified a subset of RAS wild-type EOPC harboring clinically actionable fusions and mutations, such as NTRK fusions, NRG1 fusions, and IDH1 mutations, which may contribute to higher survival when matched to targeted therapies (Castet et al. 2023; Varghese et al. 2021).

Although the definition of EOPC, specifically whether it constitutes a distinct biological subtype, remains a matter of debate, the survival advantage in EOPC may also serve as inadvertent proof-of-concept for an

early detection paradigm, regardless of differences in tumor biology. The 2030 ESMO guideline explicitly states that the opportunity to detect PC when potentially curable is contingent upon early diagnosis and identification of high-risk patients before symptoms even arise (Conroy et al. 2023). Blackford et al., in 2024, have demonstrated that surveillance of genetically high-risk individuals yielded a higher proportion of stage I cancer (31% vs 10%), greater five-year survival outcomes (50% vs 9% ), and reduced cancer-related death (43% vs 86%) (Blackford et al. 2024). The NCCN clinical guidelines for pancreatic adenocarcinoma (PDAC) now also mandate universal germline testing for all patients alongside somatic molecular profiling; a recommendation that may be relevant for EOPC, given its established enrichment for targetable genomic variants (Ko 2024). Taken together, our data should not be interpreted as a causal relationship, but rather as hypothesis-generating, suggesting that a structured, guideline-directed strategy and precision-matched therapy in younger patients with PC may amplify the survival advantage we empirically observed within this cohort.

In our study, the observed clinicopathologic outcomes were not incidental, but may reflect a deeply mechanistically grounded portrait of EOPC. First, the EPIC study demonstrated that the longer a woman breastfeeds and the longer the patient receives postmenopausal hormone therapy, the lower the risk of PC, potentially reflecting the protective role of estrogen that can induce an anti-proliferative signal, modulate inflammatory pathways, and improve metabolic homeostasis (Naudin et al. 2020; Ren et al. 2023). In parallel, the androgenic receptor hypothesis also provides a complementary explanation, in which, in an experimental PC model, azaserine-induced preneoplastic lesions were significantly predominant in male rats, which establishing a tumor-promoting role for androgenic signaling in the pancreatic microenvironment (Roebuck and Longnecker 1977). Second, the predominant pain at presentation in EOPC may be multifactorial. While the perineural invasion (PNI) is well-established as an etiology of cancer-related pain and PC was known to cause PNI, it remains on limited evidences whether these processes were more prevalent in EOPC (Swords et al. 2015). Alternatively, this observation may reflect bias in symptom-driven detection, as younger patients are less likely to undergo incidental or surveillance-based diagnosis and therefore more frequently present pain-related symptoms (Swords et al. 2015).

In this study, we found similar results with the previous systematic review, that despite the higher rate of metastasis, patients with EOPC had statistically comparable RFS with nEOPC (Renaldi and William 2024). The explanation of this result lies in the differential therapeutic intensity received by this cohort. Patients with EOPC receive more treatment than nEOPC (39% vs 19%), which may have mitigated the adverse prognostic outcomes of more advanced disease at presentation, thereby contributing to comparable RFS outcomes (Renaldi and William 2024; Saadat et al. 2021). In essence, higher metastatic burden and equivalent disease progression may exist because the aggressiveness of EOPC is being counterbalanced by the aggressiveness of therapeutic response.

The meta-regression findings of smoking and metastatic risk may be expected and linked to the nature of tobacco and pancreatic carcinogenesis. Cigarette smoke significantly upregulates MUC4 mucin expression in PC via  $\alpha 7$  nicotinic acetylcholine receptor stimulation, and subsequently activates the JAK2/STAT3 and MEK/ERK1/2 downstream – which pathway that increased the invasion and metastatic colonization in PC (Momi et al. 2013). At the transcriptional level, nicotine and nitrosamine NNK elicit a pro-metastatic

response in PC through osteopontin production via  $\alpha 7$  nAChR-dependent mechanisms, that critical in inducing systemic metastatic response in PC (Momi et al. 2012). These findings suggest that smoking not only the driver of EOPC, but as an active ongoing determinant of systemic metastasis.

This review represents a comprehensive report of EOPC and the first reconstructed 10-year data of survival outcomes of EOPC. However, several limitations should be noted. First, a cautious interpretation should also be made in survival observation. Those with nEOPC were inherently constituted by older individuals. In this context, older patients with PC may be disproportionately burdened by comorbid disease, which elevates the all-cause mortality irrespective of the presence of PC. Since we can only reconstruct overall survival, any excess of non-cancer-related mortality in the older cohort would inflate the survival benefit of EOPC. Second, the definition of EOPC in our analysis ranged from 40 to 50 years. This definition heterogeneity may induce a non-trivial source of variability between studies in our study. Third, although meta-regression found a significant association between smoking and metastatic risk, the ecological nature of meta-regression should be acknowledged. Other potentially relevant covariates may not have been captured, as meta-regression is limited to its sensitivity to detect complex associations.

The survival paradox that we observed, where EOPC demonstrated a 25% overall survival advantage despite more advanced stage and higher metastatic risk, highlights the value of age-sensitive early detection targeting younger patients with risk factors, including active smoking and germline susceptibility variants. In the future, the enrichment of actionable genomic alterations of EOPC, including BRCA1/2, PALB2, and NRG1, underscores the relevance of systematic molecular profiling and a precision-guided treatment approach.

## 5. Conclusions

EOPC occurred in approximately 6.1% of all PC cases, which presented with a significantly higher male proportion, more common pain at presentation, and a higher smoking proportion at baseline compared with nEOPC. EOPC were presented with a significantly more advanced stage and a higher risk of metastasis. At the same time, EOPC had higher overall survival with consistent findings throughout the 10-year observation time.

## Declarations

## Ethics approval

This study is a systematic review and meta-analysis of previously published, de-identified aggregate data. Ethics approval and informed consent were therefore not required, and no new studies involving human participants or animals were performed by any of the authors.

## Consent to participate

Not applicable. No individual participants were recruited by the authors for this study.

## Consent to publish

Not applicable. This manuscript does not contain any confidential data, individual patient records, institutional records, or photographs of participants.

## Competing interests

The authors declare that they have no known competing financial interests, personal relationships, or institutional affiliations that could have appeared to influence the work reported in this paper. No author holds any relationship with industrial or commercial entities relevant to the subject matter of this manuscript.

## Funding

This research was self-funded by the authors. It received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. No funder had any role in the study design, the collection, analysis, or interpretation of data, the writing of the manuscript, or the decision to submit it for publication.

## Author Contribution

Conceptualization, EMK, AJS; Methodology, EMK; Formal Analysis, EMK; Investigation, CDT, NRS, JAH; Data Curation, JAH; Writing – Original Draft, EMK, JAH; Writing – Review & Editing, CS, AJS; Visualization, JAH; Supervision, CS, AJS.

## Acknowledgements

The authors did not receive assistance from any individual or institution outside the listed authorship in the conception, conduct, analysis, or reporting of this study. This research was self-funded by the authors and received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Data availability

All data supporting the conclusions of this article are included within the article and its supplementary file.

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## Figures

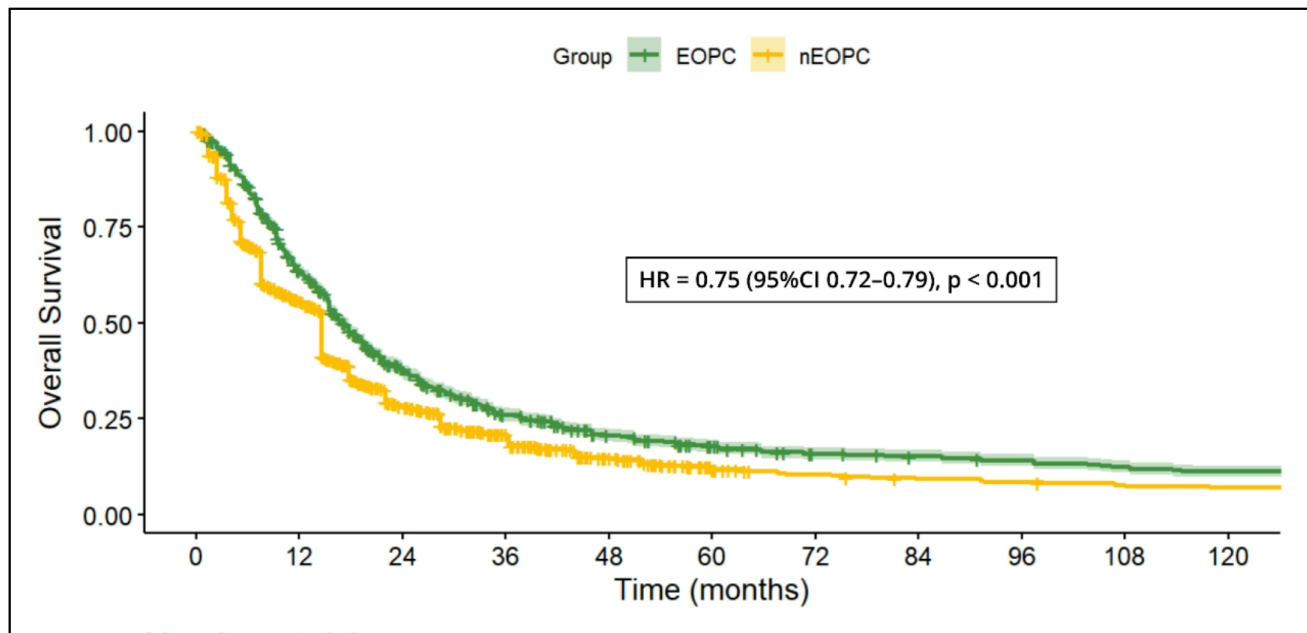


**Figure 1**

Kaplan-Meier overall survival graph of EOPC and nEOPC throughout the 10-year observation time

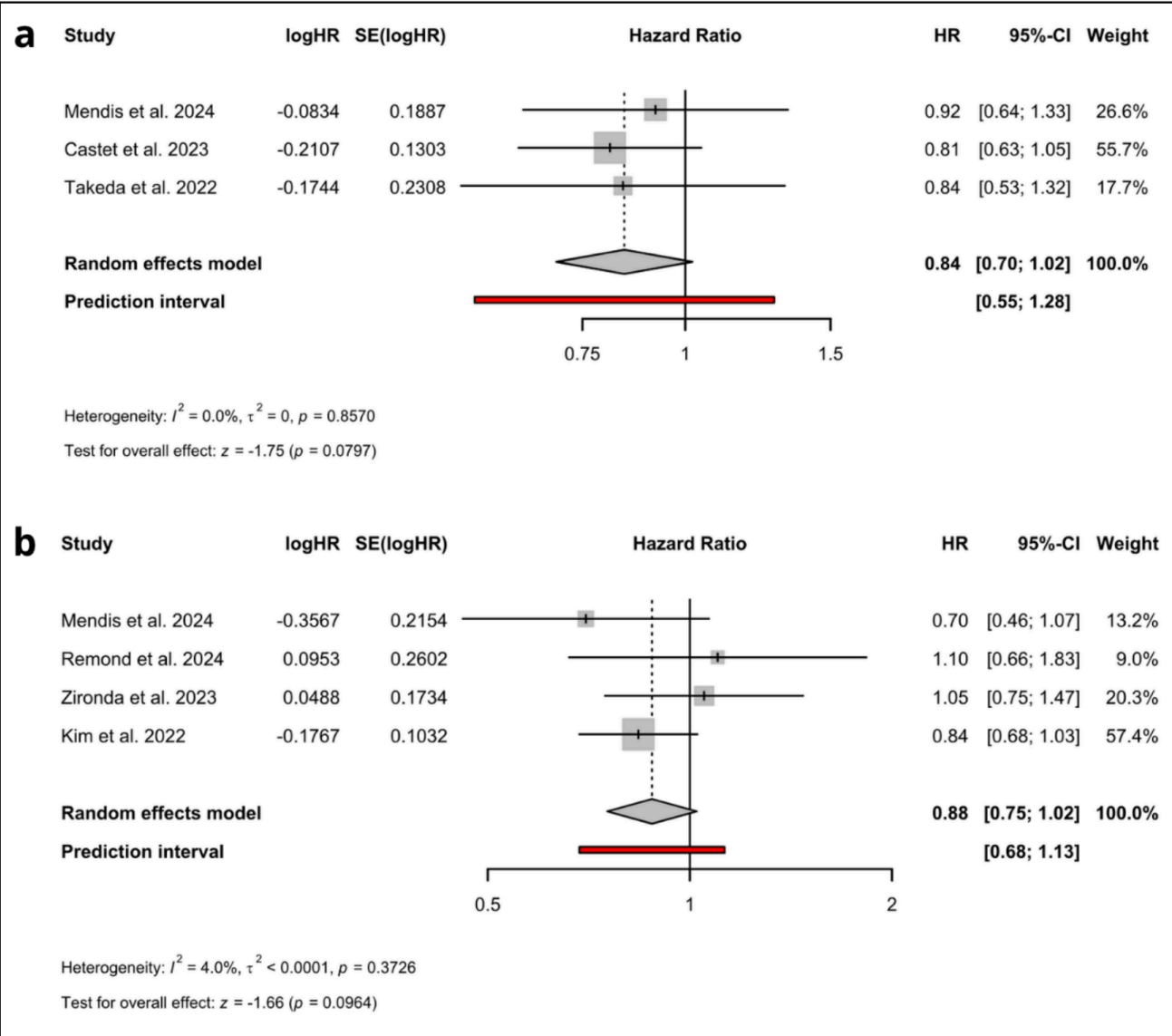


**Figure 2**

Generic inverse variance meta-analysis of a progression-free survival and b recurrence-free survival

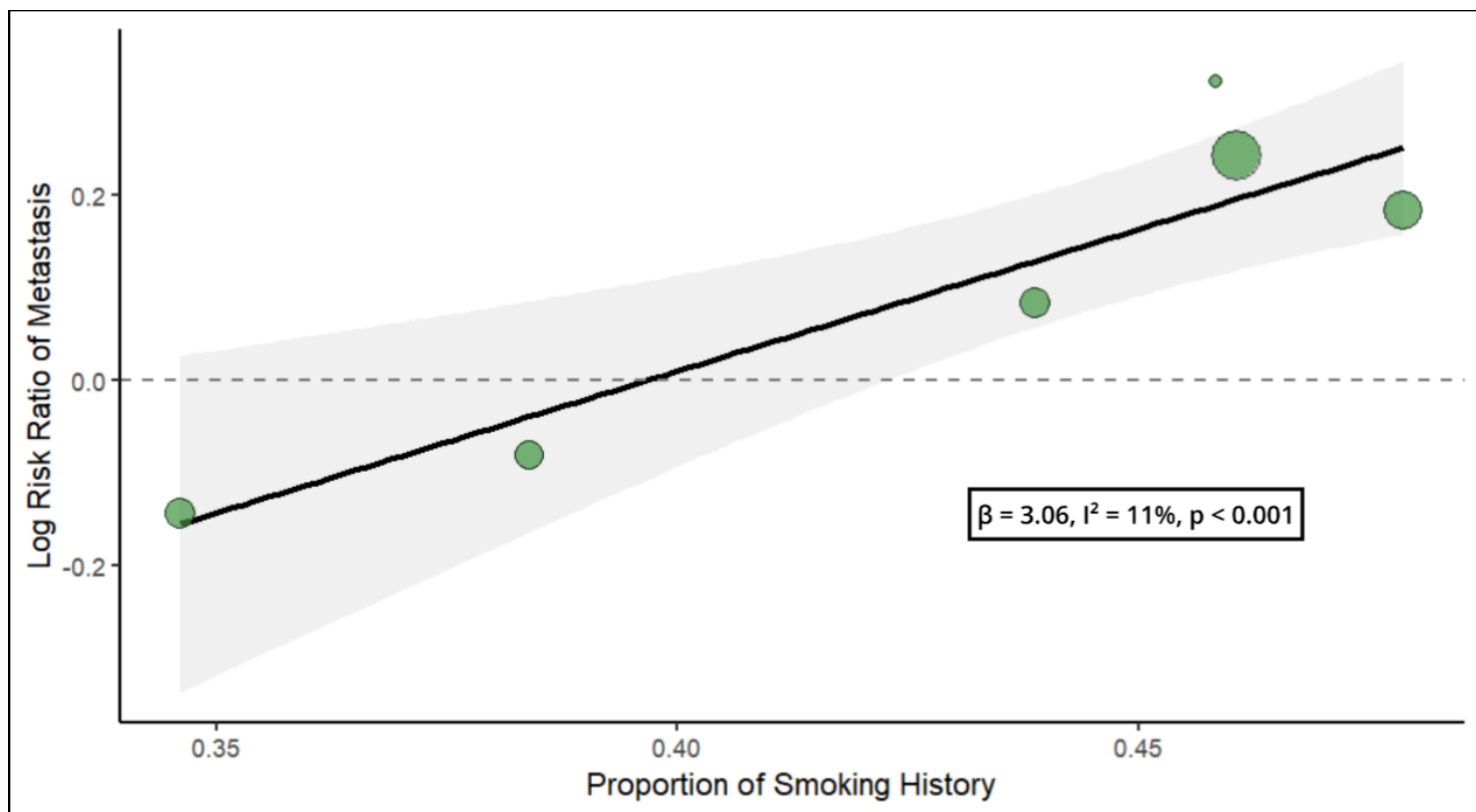


**Figure 3**

Meta-regression evaluating metastasis risk against the proportion of smokers

## Supplementary Files

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