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SURVIVAL OUTCOMES OF VASCULAR AND LYMPHOVASCULAR INVASION AMONG PANCREATIC ADENOCARCINOMA PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract:
Study aim: *This systematic review aims to quantitatively assess vascular and lymphovascular invasion as prognostic factors for pancreatic adenocarcinoma.* ***Methods:*** *We carried out this systematic review meta-analysis in accordance with the PRISMA guidelines. We searched PubMed and EMBASE using EBSCO. We used Rayyan (Intelligent Systematic Reviews) website for duplication removal and study screening, and we used Review Manager 5.4 software to conduct a random-effect model meta-analysis pooling hazard ratios extracted from the included studies.* ***Results:*** *The study included 17 studies. The total number of participants from all studies was 5256 patients diagnosed with pancreatic cancer. The random-effects model analysis found that the pooled HR for vascular invasion is 1.37 (95% CI: 1.14, 1.6), where the test for the overall effect is significant ($p<0.001$). We found that the pooled HR for lymphovascular invasion is 1.44 (95% CI: 1.06, 1.83), where the test for the overall effect is significant ($p<0.001$). Analyses show significant inter-study heterogeneity for both investigations ($I^2 > 50\%$).* ***Conclusion:*** *Our meta-analysis showed that both vascular invasion and lymphovascular invasion have poor prognosis and lower survival outcomes among patients with pancreatic cancer.*

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BACKGROUND:

The term "pancreatic cancer" refers to an adenocarcinoma that develops in the exocrine part of the gland's ductal epithelium. The most frequent pancreatic tumour, accounting for 85% of all Trypsin Carboxypeptidase Chymotrypsin Amylase Lipase, Bile Salts neoplasms, is ductal adenocarcinoma. About the origins of pancreatic cancer, nothing is known. Smoking, obesity, family history, chronic pancreatitis, diabetes mellitus, and pancreatic cysts are the risk factors that are most often mentioned [1]. Between the ages of 60 and 80, pancreatic cancer incidence peaks. Patients under 50 years old are uncommon and make up between 5 and 10 percent of all cases [2].

Early identification of pancreatic cancer is challenging since the disease's symptoms often manifest late in the course of the illness. Because they directly constrict the common bile duct, most tumours at the head of the pancreas eventually result in obstructive jaundice. Such individuals can have pale-colored faeces, darkened urine, and yellowing of the skin and eyes. Another symptom that may indicate substantial nerve invasion by the tumour is back discomfort that radiates from the abdomen [3]. Dramatic weight loss is common and often occurs in conjunction with a very severe case of wasting disease or cachexia [4].

According to the TNM classification, clinical staging is done and divides patients into three stages: resectable, locally progressed, and metastatic illness [5]. For resectability prediction, CT is around 70–85 percent accurate [6,7]. When metastases, such as for ambiguous lesions on CT, are suspected, positron emission tomography may be beneficial [8]. Although it is not done often, laparoscopy may detect peritoneal metastases and is sometimes used to treat pancreatic body and tail cancers. The most suitable first therapy is determined by staging. In contrast to locally advanced pancreatic cancer, which has a median survival time of 8-14 months, and metastatic pancreatic cancer, which has a median survival time of 4-6 months, resectable pancreatic cancer has a median survival duration of 17–23 months with adjuvant chemotherapy [9]. Although theoretically treatable, borderline resectable pancreatic cancer has a significant chance of margin-positive resection unless preoperative (neoadjuvant) treatment is used [10]. This subtype of pancreatic cancer is distinguished by low vascular involvement.

The TNM staging approach is presently used as the primary tool for determining patient prognosis, although it is very nondiscriminatory for patients having resection for pancreatic cancer since it only takes into account the T, N, and M stages. A prognosis model may be created to more accurately predict a patient's survival by integrating additional prognostic indicators.

In contrast to tumours found in the head of the pancreas, pancreatic cancers found in the body or tail of the organ are often discovered at a later stage. The predictive significance of tumour site for individuals having resection, however, is debatable [11]. One of the main tumour extension patterns and a key component in predicting survival is lymphatic dissemination [12-14]. The degree of glandular differentiation in a tumour has been observed to strongly correlate with postoperative survival [13, 15]. Reproducibility may be limited in grading systems since they are so heavily based on subjective judgement. A poorer prognosis has been documented for tumours with perineural invasion [16] and peripancreatic fat infiltration [17]. Patients with resected pancreatic cancer had longer survival times while receiving postoperative adjuvant treatment [18-21]. Further research is required to determine the significance of novel prognostic indicators as the activated stroma-index [22], histological necrosis [23], and molecular markers [24].

Study aim

This systematic review aims to quantitatively assess vascular and lymphovascular invasion as prognostic factors for pancreatic adenocarcinoma.

METHODOLOGY:

Study design

We carried out this systematic review meta-analysis in accordance with the PRISMA declaration [25], which specifies the preferred reporting items for systematic reviews and meta-analyses.

Search duration

We conducted the search strategy on June 10 – 25, 2022.

Search strategy

Through the use of Medical Subject Headings (MeSH terms), keywords related to "pancreatic cancer or carcinoma or adenocarcinoma," "prognostic factors," and "pre-operative or post-operative" that were merged using the Boolean operators "AND" and "OR," the systematic review was identified. In June 2022, electronic searches were conducted in PubMed and EMBASE using EBSCO.

The Medical Subject Headings (MeSH) terms were used by the two reviewers in their PubMed search to find the following articles: (("Preoperative Period"[Mesh] OR "Laboratories"[Mesh] AND "Carcinoma, Pancreatic Ductal"[Mesh] AND "Prognosis"[Mesh]) ((("Preoperative Period"[Mesh] OR "Neoplasm Invasive".

The following keywords were entered into the search engines Embase and EBSCO using the "Emtree" and "Subject terms" strategies, respectively: (Preoperative) AND (Laboratory) OR (Vascular invasion) OR (lymphovascular invasion) AND (prognostic) AND (Independent) AND (Postoperative) AND (Post-operative) AND (Histopathology) OR (Histopathological) OR Histo-pathological) AND (ductal adeno (pancreatic).

Inclusion and exclusion criteria

The eligibility of the titles and abstracts was checked separately by two authors. The following inclusion and exclusion criteria were used to reach a full-text screening.

Inclusion criteria

We included studies that met the following criteria:

- Studies in which the author used any method to diagnose individuals who had been given a pancreatic cancer diagnosis.
- Studies that examine the overall survival or disease free survival reporting the hazard ratios (HRs) with 95 percent confidence intervals.

Exclusion criteria:

We excluded studies that had no full-text access, studies that were not available in English language, and studies with self-reported diagnosis of pancreatic cancer.

Data extraction, Synthesis and Quality Assessment

We used the Rayyan (Intelligent Systematic Reviews) website for managing the imported records and for duplicate removal [26].

After study selection was done, a Microsoft Excel sheet was used for data extraction that covered items on study design, duration, patient characteristics, prognostic factor and findings.

The Newcastle-Ottawa Scale [27] for classifying cohort studies was used to evaluate the risk of bias in all studies. It is divided into three categories (Selection, Comparability, and outcome), eight question ratings, and a total of nine star categories. With the exception of the "Comparability" domain, which was assessed for two stars, each element is rated for one star.

Statistical analysis

HRs with their correlated 95% confidence interval (CI) were directly educed from each study full-text. We used Review Managed 5.4 software to perform the quantitative data synthesis. Forest plots were generated and inter-study heterogeneity was examined using the Higgin's I-square test where a p value <0.1 or I^2 > 50% was considered statistically significant.

RESULTS:

Search results

Figure 1 shows the identification and screening procedures for this meta-analysis. Using the following databases: PubMed, EMBASE, and EBSCO, the first literature search yielded a total of 701 studies. Using Rayyan QCRI, 322 duplicates were eliminated from the total, 348 studies were excluded based on their titles and abstracts, and 30 full-text publications were ultimately evaluated and 13 of them were excluded. Finally, the meta-analysis comprised 17 reliable research.

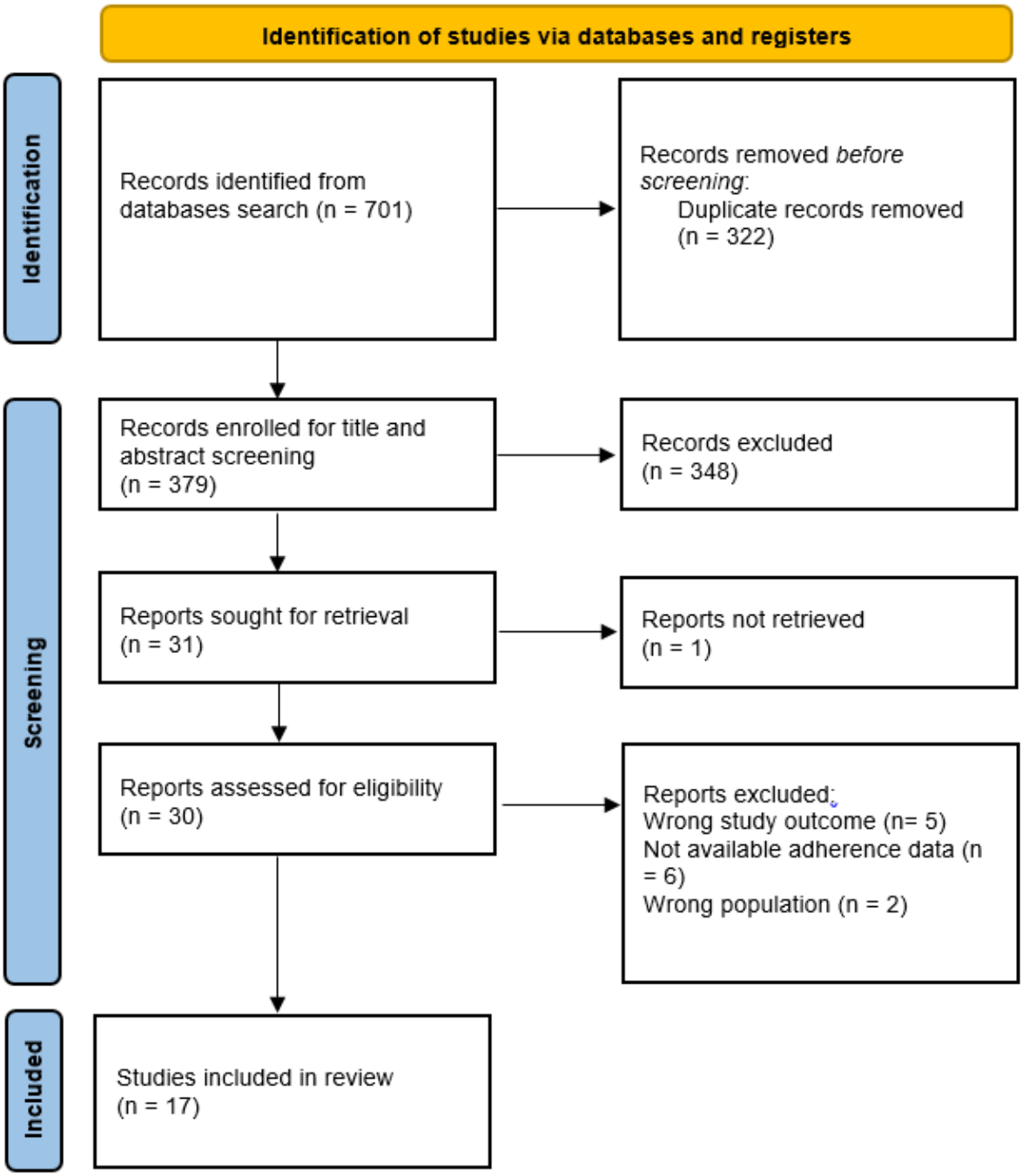

Figure 1: PRISMA flow chart summarising the search process.

Characters of the included studies

The study included 17 studies [28-44], of which five studies were conducted in Japan [37-39, 42, 43], four in China [29, 30, 40, 41], three in the USA [31-33], two in the UK [28, 44], one in Belgium [34], and one in USA & Italy [36]. The total number of participants from all studies was 5256 patients diagnosed with pancreatic cancer. Age of patients ranged from 16 to 93 years. Female ratios ranged from 35% [34] to 58.9% [35].

Table 1: Characters of included studies (n=17).

ID	Author (Last, F)	Study design	Country	Participants number	Age range/ mean±SD/ median, y	Females (%)	NOS
28	Alhasan et al., 2016	Retrospective study	UK	93	65.3	43.1	7
29	An et al., 2012	Retrospective review	China	190	31-79	41.6	9
30	Ben et al., 2010	Correlation study	China	94	31-79	41.5	9
31	Chawla et al., 2018	Retrospective study	USA	217	29-88.8	49.4	8
32	Cloyd et al., 2018	Retrospective study	USA	127	64.6 ± 8.9	46.5	8
33	Dal Molin et al., 2017	Prospective study	USA	1128	66.37±10.7	47.2	8
34	Drouillard et al., 2016	Prospective study	Belgium	65	42-85	35	8
35	Hu et al., 2020	Retrospective study	China	282	58.7 ±13.5	58.9	8
36	Marchegiani et al., 2017	Prospective study	USA & Italy	324	32-91	50.6	7
				1183	28-93	48.8	
37	Morita et al., 2018	Retrospective study	Japan	60	36-83	51.7	9
38	Oguro et al., 2013	Retrospective study	Japan	393	66	40.5	9
39	Okabayashi et al., 2018	Retrospective study	Japan	240	34-91	55	8
40	Xie et al., 2012	Retrospective study	China	117	35-93	41.9	8
41	Xu et al., 2017	Retrospective study	China	265	16-84	50.6	7
42	Yamada et al., 2018	Retrospective study	Japan	352	38-88	40.1	8
43	Yamaki et al., 2017	Prospective study	Japan	42	50-83	38.1	9
44	Zhang et al., 2012	Retrospective study	UK	84	70.4-79.5	40.5	8

Vascular invasion as a prognostic factor for pancreatic cancer

A total of 14 analyses involving 4544 patients from 13 studies were included in the quantitative estimation of pooled HR for vascular invasion as a prognostic factor to pancreatic cancer. The random-effects model analysis found that the pooled HR for vascular invasion is 1.43 (95% CI: 1.19, 1.67), where the test for the overall effect is significant ($p<0.001$) (figure 2). HRs ranged from 0.8 in the study of Marchegiani and colleagues [36] to 2.6 in the study of Ben et al. [30]. Figure 3 shows the corresponding funnel plots for assessing publication bias.

Lymphovascular invasion as a prognostic factor for pancreatic cancer

Nine analyses from six studies including 2112 patients were used for quantitative data synthesis for lymphovascular invasion as a prognostic indicator for pancreatic cancer. We found that the pooled HR for lymphovascular invasion

is 1.44 (95% CI: 1.06, 1.83), where the test for the overall effect is significant (p<0.001) (figure 4). Figure 5 shows the corresponding funnel plots for assessing publication bias.

Publication bias and inter-study heterogeneity

Figures 3 and 5 show funnel plots for detection of publication bias. By visual inspection of the funnel plots, they reveal asymmetry that might denote existing publication bias. Analyses show significant inter-study heterogeneity for both investigations (I^2 > 50%).

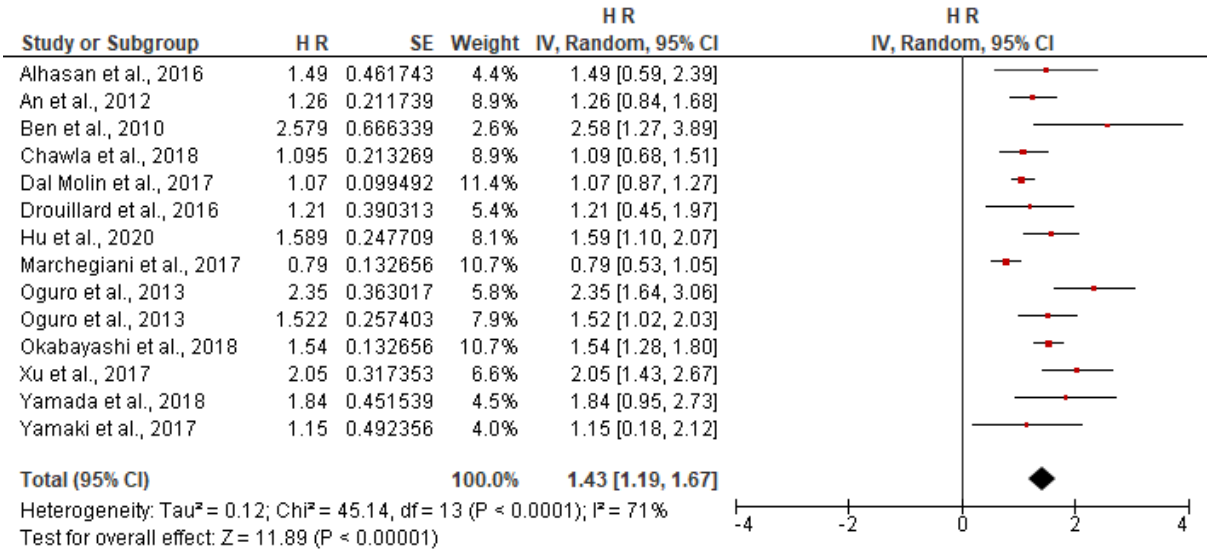

Figure 2: Forest plot of the HR of pancreatic cancer vascular invasion on prognosis.

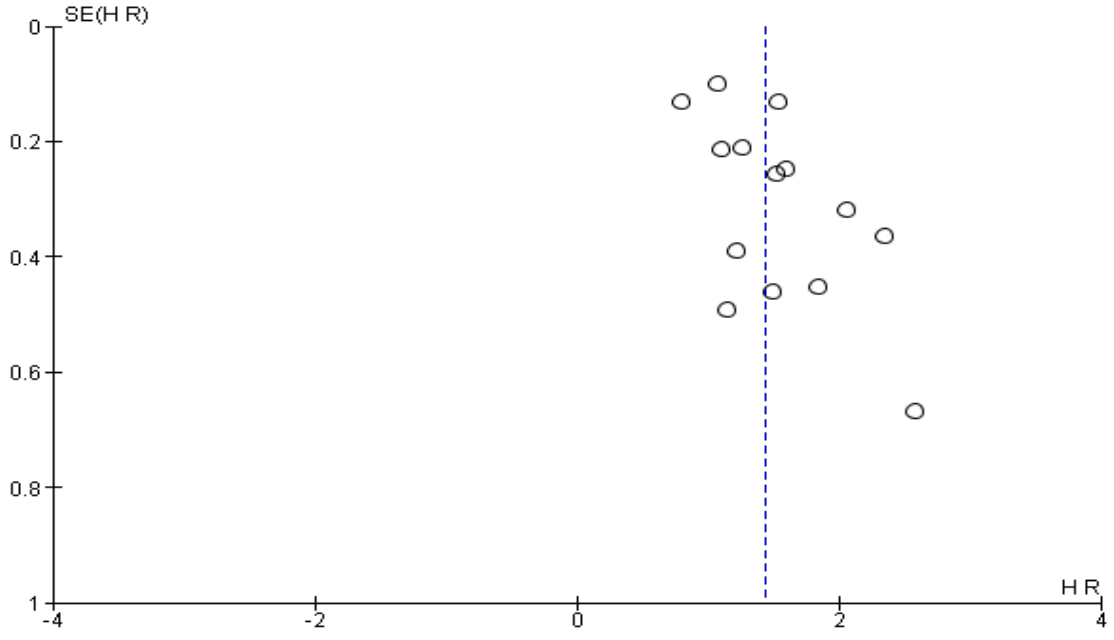

Figure 3: Funnel plot of the vascular invasion data.

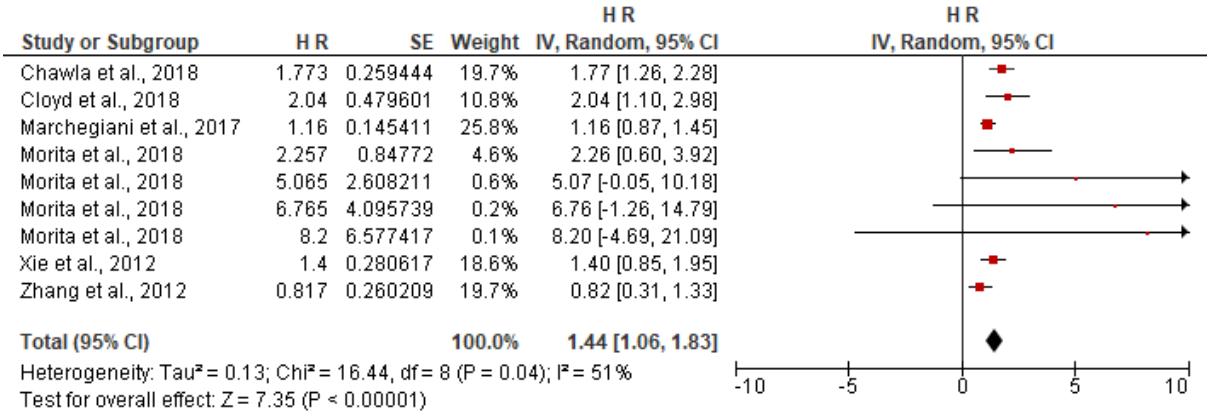

Figure 4: Forest plot of the HR of pancreatic cancer lymphovascular invasion on prognosis.

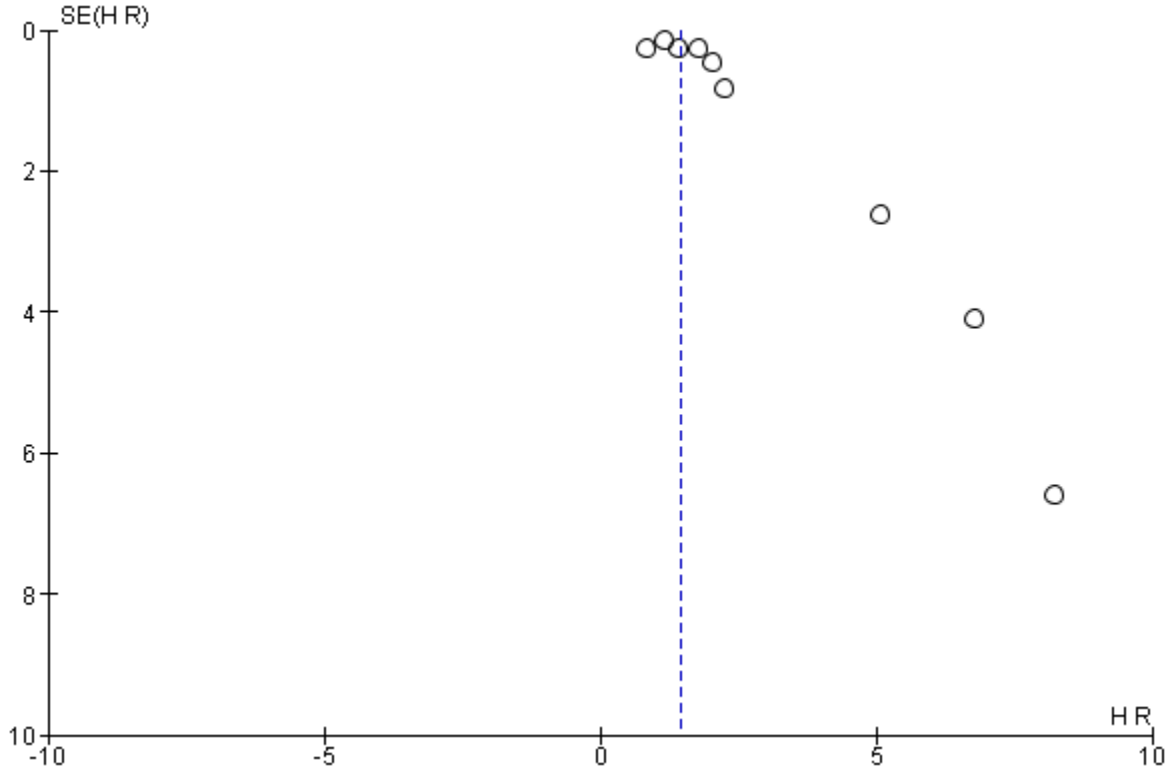

Figure 5: Funnel plot of the lymphovascular invasion data.

DISCUSSION:

The fourth highest cause of cancer-related fatalities in the US is pancreatic cancer as it continues to be one of oncology's biggest challenges. In high-income nations during the next ten years, pancreatic cancer is anticipated to rank second or third in terms of cancer-related fatalities [45, 46]. The most prevalent form, accounting for 85–90% of all pancreatic neoplasms, is pancreatic ductal adenocarcinoma (PDAC) and its variations. Age upon diagnosis is 70–71 years old on average [47, 48].

We conducted this systematic review and meta-analysis to quantitatively assess vascular and lymphovascular invasion as prognostic factors for pancreatic adenocarcinoma by estimating the pooled HR using current available literature. After search and study screening, we included 17 studies that fulfilled our study selection criteria.

According to the random-effects model analysis, the pooled HR for vascular invasion is 1.37 (95% CI: 1.14, 1.6), and the test for the overall effect is significant ($p < 0.001$). However, the data included in this analysis was significantly heterogonous. The total resection rate of pancreatic cancer is less than 20%, and the 5-year survival rate is less than 10% due to the disease's high degree of malignancy, ease of local vascular invasion, and other factors [49]. Nevertheless, several studies claimed that 17–32% of pancreatic cancer patients already had portal system invasion (invasion of the portal vein, superior mesenteric vein, and splenic vein) at the time of diagnosis [50]. Due to the closeness of the superior mesenteric vein (SMV) and portal vein (PV) to the pancreatic head and uncinate process, these veins are often invaded. In some individuals, potentially curative surgery combining pancreatic resection with en bloc resection of the PV-SMV venous axis is conceivable [51].

The effects of different vascular invasion types, classification (location, depth, and circumference), and anastomotic techniques of vascular reconstruction on prognosis are unclear, despite the fact that vascular invasion has been used as a prognostic factor in several studies that mainly focus on whether there is an association between vascular invasion and poor prognosis [50, 51].

For the quantitative data synthesis for lymphovascular invasion as a prognostic indicator for pancreatic cancer, nine analyses from six studies with 2112 patients were included. Our results show that that the pooled HR for lymphovascular invasion is 1.44 (95% CI: 1.06, 1.83), where the test for the overall effect is significant ($p<0.001$). In two studies, it was shown that pancreatic neuroendocrine tumours with lymphovascular invasion had worse survival rates. Lymphovascular infiltration may be the cause of local or distant metastases in lymph nodes or other organs including the lungs or liver [52, 53].

Surprisingly, despite the fact that pathologists commonly report lymphovascular invasion in clinical trials of resected PDA [54, 55], there are no research specifically examining the clinical importance of this pathologic finding. Outcome studies that concentrated on other prognostic variables have included lymphovascular invasion data as a supplementary variable; however, the power of these studies was insufficient to evaluate lymphovascular invasion data as a separate predictive feature in models that also included regional lymph node metastases [54]. Routine pathologic reporting still includes the lymphovascular invasion status, but there are no preceding studies to instruct doctors on how to evaluate this piece of information.

CONCLUSION:

Our meta-analysis showed that both vascular invasion and lymphovascular invasion have poor prognosis and lower survival outcomes among patients with pancreatic cancer.

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