MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2021; 27: e930545
DOI: 10.12659/MSM.930545

Received: 2020.12.17
Accepted: 2021.04.19
Available online: 2021.04.28
Published: 2021.08.16

Prognostic Significance of Microvascular Invasion in Pancreatic Ductal Adenocarcinoma: A Systematic Review and Meta-Analysis

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Financial support: The work was funded by grants from the Science and Technology Project of Zhejiang Medical and Health [2021KY1103], Key Discipline of Hepatobiliary and Pancreatic Surgery of Jiaxing City (2019-cx-01), the First Project of First Hospital of Jiaxing [2018-YA-34, 2020-YA-01], and the Qimingxing Project of First Hospital of Jiaxing [2019QMX008]

Background: The incidence, pathogenesis, and prognostic effect of microvascular invasion on pancreatic ductal adenocarcinoma (PDAC) remain controversial. This study aimed to summarize the incidence, pathogenesis, role in clinical management, recurrence, and prognostic significance of microvascular invasion in PDAC.

Material/Methods: A literature review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Systematic literature searches were conducted using PubMed and Google Scholar up to February 2021.

Results: Seventeen studies were included in the meta-analysis. The incidence of microvascular invasion was 49.0% (95% confidence interval [CI], 43.8-54.5%) among PDAC patients who underwent surgery. The weighted multivariate Cox proportional hazards model hazard ratio for disease-free survival of 8 studies was 1.78 (95% CI 1.53-2.08, P<0.001), and there was no statistically significant difference between the subgroups (P=0.477). The hazard ratio for overall survival of 14 studies was 1.49 (95% CI 1.27-1.74, P<0.001), and there was no statistically significant difference between the subgroups (P=0.676).

Conclusions: Microvascular invasion occurred in nearly half of PDAC patients after surgery and was closely related to disease-free and overall survival. Understanding the role of microvascular invasion in PDAC will help provide more personalized and effective preoperative or postoperative strategies to achieve better survival outcomes.

Keywords: Incidence • Microvessels • Pancreatic Neoplasms

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/930545

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Background

Pancreatic cancer (PC) remains a leading cause of cancer-related deaths, and 80-85% of patients develop unresectable locally advanced or distant metastases at the time of diagnosis [1]. Furthermore, even in ≥80% of patients who can undergo surgery, the long-term survival outcomes are unsatisfactory because of the high incidences of local tumor recurrence and distant metastasis [2], which often occur within 1 year [3,4]. Pancreatic ductal adenocarcinoma (PDAC) is the major histological subtype of pancreatic cancer, accounting for more than 85% of cases [5]. For PDAC patients undergoing surgery, microvascular invasion (MVI) is an observable pathological parameter; despite the controversy that exists [6-8], many studies still suggest that it may be a predictor of early recurrence and metastasis of PDAC [9-15].

MVI is a microtubule invasion state that can only be observed around the tumor under a microscope [9,16]. It is described in the literature as "microvascular invasion" or "microscopic lymphovascular invasion" (LVI) [10,17]. MVI mostly describes microvessel invasion [18], while LVI is used to indicate micro-lymph-tubule invasion [19]. However, in the literature reviewed, only a few studies distinguished the 2 terms [9,15]; in most cases, they refer to the same pathological characteristics [7,11,12,14,20-23], which leads to confusion. In addition, the incidence of MVI in PDAC varies considerably [7-12,14,15,20-24] and the literature rarely discusses the potential mechanism of MVI in the progression of PDAC, so the mechanism and clinical significance of MVI in poor PDAC outcomes remains incompletely understood. We therefore conducted a systematic review and meta-analysis of all observational studies to examine the incidence, definition, clinical significance, and potential mechanism of MVI in PDAC, to help guide more personalized and effective preoperative or postoperative strategies to achieve better survival outcomes in patients with PC.

Material and Methods

Search Strategy and Inclusion Criteria

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. We searched for all eligible studies in PubMed and Google Scholar in February 2021. In both databases, we used the uniform search strings: "pancreatic cancer, microvascular invasion" or "pancreatic cancer, lymphovascular invasion". The literature search and reference screening were conducted by Li HB and Pan WW. If the title was too ambiguous to allow exclusion, we reviewed the abstract and full texts and decided whether or not to include the study.

We included all observational studies that (a) reported the type of disease as "pancreatic cancer" or "pancreatic ductal adenocarcinoma," (b) reported the incidence of MVI or LVI, and (c) provided a relevant risk estimate in terms of the hazard ratio (HR) of disease-free survival (DFS) or overall survival (OS). We subsequently excluded papers that did not present full texts in English or Chinese and papers that reported the disease as "intraductal papillary carcinoma" or "pancreatic neuroendocrine tumors." Conference abstracts were ineligible for inclusion.

Data Extraction

Data extraction was performed independently by 2 authors (Xu L and Yin D), and disagreements were settled by consensus. For each study, we extracted descriptive information (author, year, country, study design, MVI or LVI cases, sample size, description of invasion, cancer type), and HR with 95% confidence interval (CI) of multivariate Cox regression analysis for DFS or OS.

Assessment of Study Quality and Risk of Bias

The Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to assess the quality of each study [26]. The risk of publication bias was assessed using funnel plots and Egger's test.

Statistical Analyses

Fixed- or random-effects models were used to pool the study-specific risk estimates and calculated an overall effect estimate with associated 95% CI [27]. The I^2 and Q tests were used to assess study heterogeneity. A multivariate Cox proportional hazards model was used to identify the factors which were independently associated with DFS and OS. $P<0.05$ was considered statistically significant. Statistical analyses were performed using R (version 4.0.2, www.r-project.org).

Results

Literature Search

An electronic database search and survey of other sources identified 277 articles. By removing duplicate studies and studies with unmatched inclusion criteria, 32 full-text papers reported the incidence of MVI or LVI. After excluding the studies that did not report the relationship between MVI or LVI and prognosis, 17 articles were finally included in the systematic review and meta-analysis.

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Table 1. Characteristics of included studies.

Study	Year	Country	Total cases	Description of invasion	Type of prognosis
Takahashi et al [20]	2020	USA	130	LVI	OS
Panaro et al [10]	2019	France	79	MVI	DFS, OS
Jing et al [11]	2019	China	161	MVI	DFS, OS
Tsuchiya et al [15]	2019	Japan	61	MVI	DFS
Groot et al [21]	2019	USA	957	LVI	DFS
Yamada et al [9]	2018	Japan	352	MVI	OS
Fang et al [22]	2018	China	496	MVI	OS
Kim et al [24]	2018	Korea	70	LVI	OS
Delpero et al [29]	2017	France	129	LVI	OS
Epstein et al [17]	2017	USA	2481	LVI	OS
Okumura et al [12]	2017	Japan	301	MVI	DFS, OS
Liu et al [23]	2016	China	532	MVI	DFS, OS
Wang et al [14]	2013	China	57	MVI	DFS
Crippa et al [8]	2012	Italy	502	MVI	OS
Chatterjee et al [30]	2012	USA	212	LVI	DFS, OS
Hong et al [28]	2012	USA	209	MVI	OS
Pawlik et al [7]	2007	USA	698	MVI	OS

CI – confidence interval; DFS – disease-free survival; HR – Hazard ratio; LVI – lymphovascular invasion; MVI – microvascular invasion; OS – overall survival.

Characteristics of Included Studies and Quality Assessment

The characteristics of the 17 studies with a total of 7427 patients are summarized in **Table 1** [7-12,14,15,17,20-24,28-30]. All articles were retrospective and observational studies, 4 of which were from China, 6 were from the USA, 3 were from Japan, and the others were from Italy, South Korea, and France. Six studies reported MVI as LVI. The risk of publication bias was assessed using funnel plots (**Figure 1**), and reports on the incidence of MVI were biased (**Figure 1A**).

Incidences of MVI in PC

We identified 17 reports of retrospective studies that described the incidence of MVI in PDAC cases (**Figure 2**) [7-12,14,15,17,20-24,28-30]. Thesestudies evaluated 7427 cases of PDAC, including 4029 cases with MVI. The I^2 value was 96.2%, and a random-effects model was selected. The pooled incidence of MVI was 49.0% (95% CI, 43.8-54.5%) among PDAC patients who underwent surgery. Although the group defined as "LVI" seemed to have a higher incidence than the MVI group, there was no statistically significant difference between them (P=0.201).

Relationship Between MVI and PDAC Prognosis

Eight studies reported on DFS [10-12,14,15,21,23,30], with a weighted multivariate Cox proportional hazards model HR for DFS of 1.78 (95% CI, 1.53-2.08; P<0.001) and no statistically significant difference between the subgroups (P=0.477). The I^2 value was 26% and a fixed-effects model was selected (**Figure 3A**). Fourteen studies reported on OS [7-12,17,20,22-24,28-30], with an HR for OS of 1.49 (95% CI, 1.27-1.74; P<0.001) and no statistically significant difference between the subgroups (P=0.676). The I2 value was 68.3% and a random-effects model was selected (**Figure 3B**). Since the OS reported by Epstein et al only included HR [17], its 95% CI was calculated according to the algorithm provided by Altman et al [31].

Sensitivity Analysis

Sensitivity analyses were further performed to determine the robustness of the results described above. For the incidences of MVI in PC and the relationship between MVI and PDAC prognosis, the results were not altered by deletion of any single study (**Supplementary Figure 1**).

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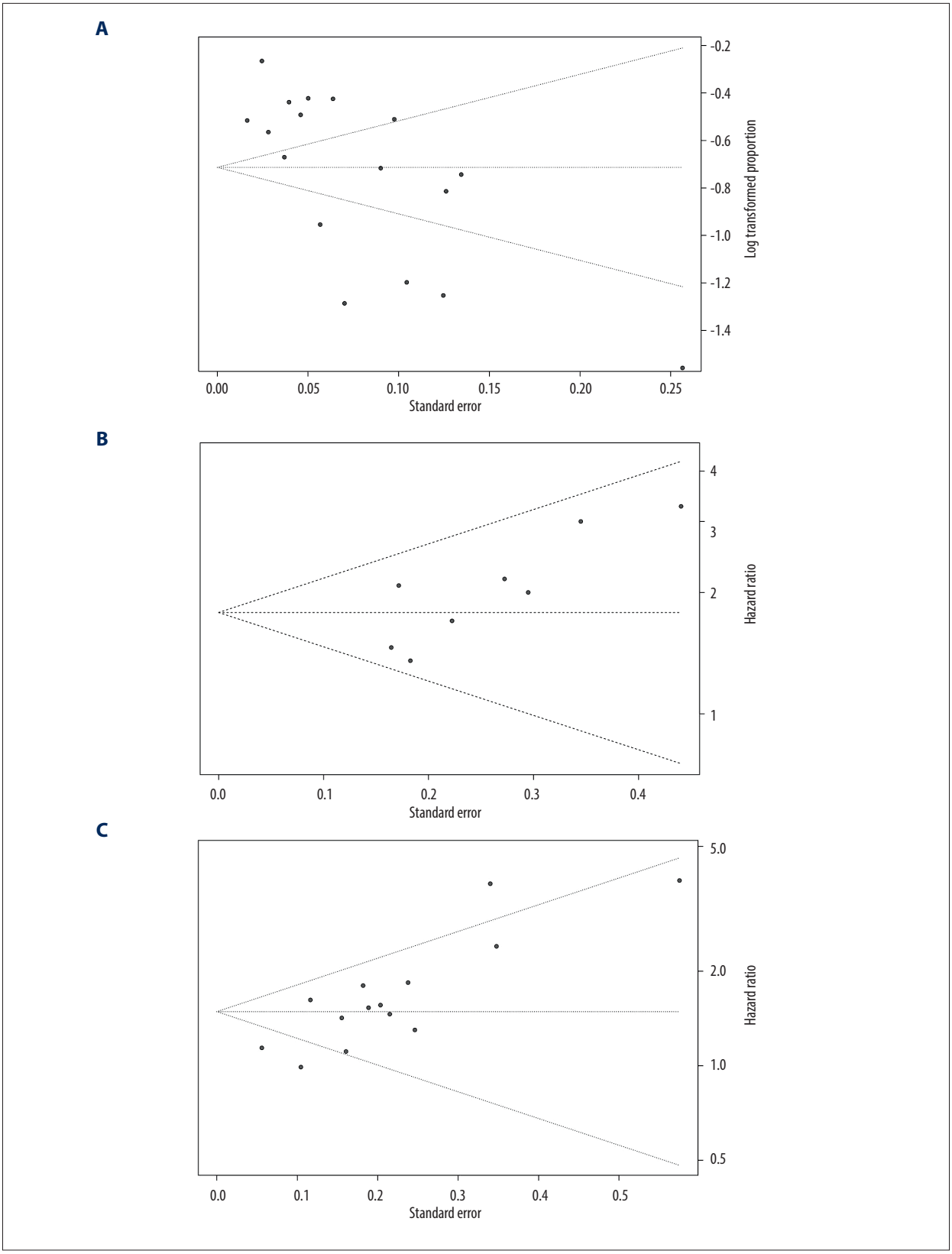

Figure 1. Funnel plots of microvascular invasion incidence (**A**), disease-free survival (**B**), and overall survival (**C**).

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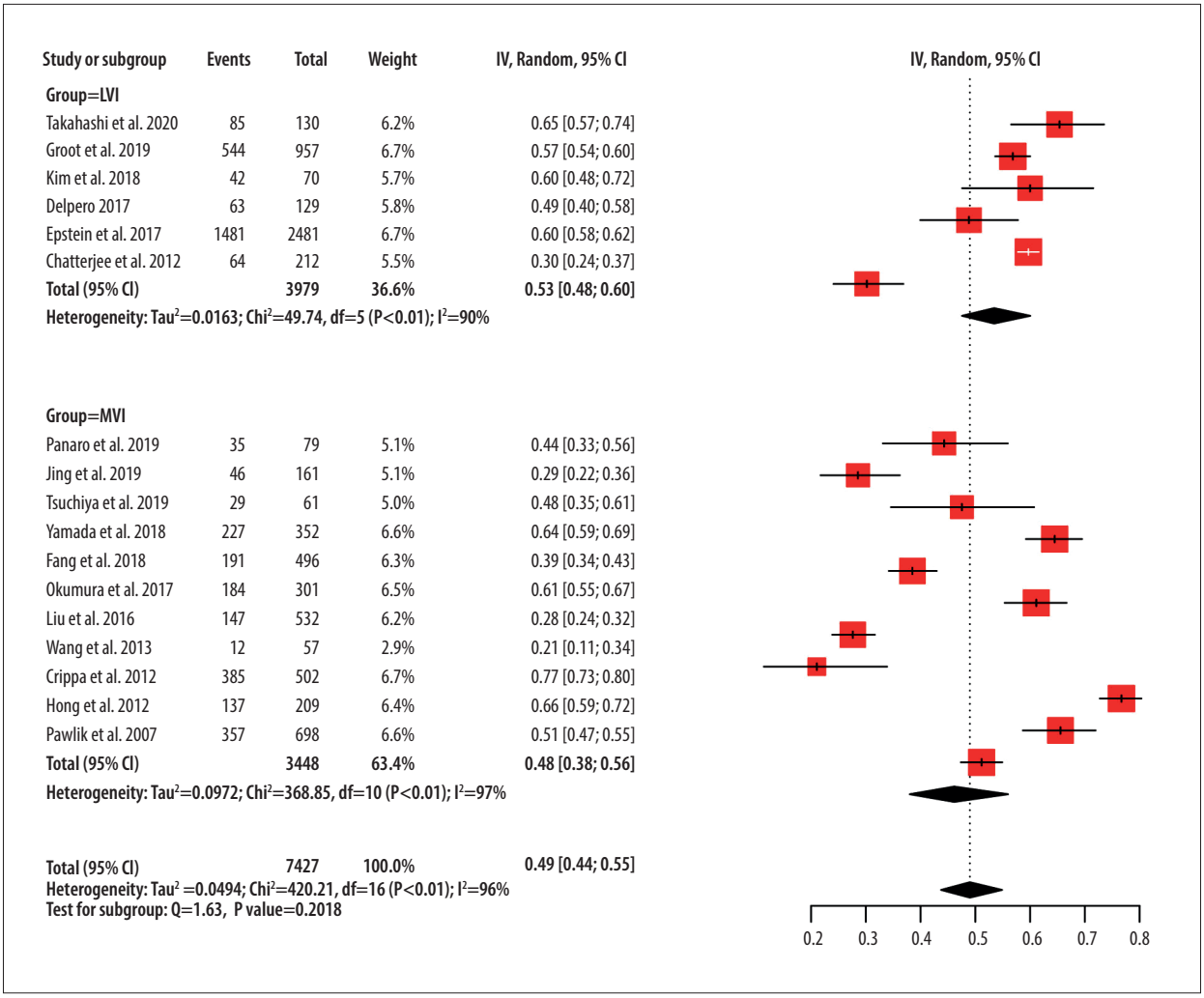

Figure 2. Forest plots of microvascular invasion incidence. CI – confidence interval; LVI – lymphovascular invasion; MVI – microvascular invasion.

Discussion

Although many studies have explored the role of MVI in PC [7-12,14,15,20-24], the incidence, definition, and prognosis of MVI are not uniform, and few studies have attempted to explore the mechanism of MVI in PC. This study found that the incidence of MVI in PC was 49.0% (95% CI, 43.8-54.5%) and that MVI was an independent risk factor affecting early recurrence (DFS HR=1.78; 95% CI, 1.53-2.08; P<0.001) and overall prognosis (OS HR=1.49; 95% CI, 1.27-1.74; P<0.001). In addition, by consulting the literature, we tried to summarize an acceptable definition and potential mechanism.

Definition of MVI

The definition of MVI in PDAC was not uniform (**Table 2**). Most studies described microvascular invasion of PDAC as MVI (11/17) [7-12,14,15,22,23,28], and the rest as LVI (6/17) [17,20,21,24,29,30]. In the studies that clearly explained the definition of microvascular or lymphatic invasion, 4 defined MVI as originating from blood vessels [9,10,14,32], 1 defined LVI as originating from lymphatic vessels [32], and 1 did not distinguish between them [17]. Although other studies specifically used the terms MVI or LVI, all of these studies' research objectives were regarding MVI according to the articles' descriptions [7,8,11,12,15,20-24,28,29]. In addition, from the data in **Figure 3**, we found that although different studies have different definitions of MVI, there was no significant difference between the 2 groups (MVI vs LVI) in either DFS or OS. Distinguishing between LVI or MVI requires immunohistochemical analyses with a combination of lymphatic markers (D2-40 and anti-podoplanin) and endothelial markers (ERG, CD31, CD34, and factor VIII) for accurate differentiation, which could be difficult to perform in a large sample or in routine clinical work [6,9,17,32]. It is difficult to distinguish between lymphatic and blood vessels in clinical work. This study proposes

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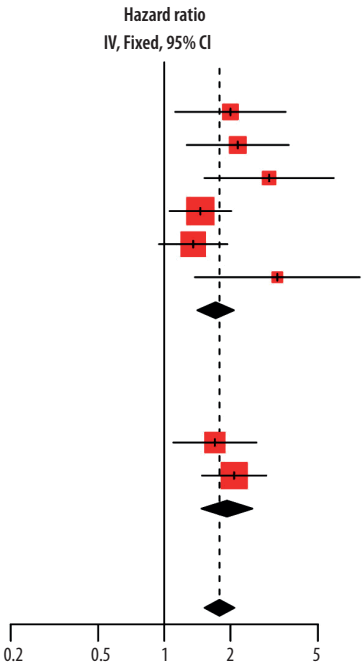
A

Study or subgroup	TE	SE	Weight	Hazard ratio IV, Fixed, 95% CI
Group=MVI				
Panaro et al. 2019	0.69	0.2949	7.2%	2.00 [1.12; 3.57]
Jing et al. 2019	0.77	0.2724	8.4%	2.16 [1.27; 3.68]
Tsuchiya et al. 2019	1.10	0.3450	5.3%	3.00 [1.53; 5.90]
Okumura et al. 2017	0.38	0.1645	23.2%	1.46 [1.06; 2.02]
Liu et al. 2016	0.30	0.1827	18.8%	1.35 [0.95; 1.94]
Wang et al. 2013	1.18	0.4405	3.2%	3.27 [1.38; 7.75]
Total (95% CI)			**66.1%**	**1.71 [1.42; 2.07]**
Heterogeneity: Tau²=0.0424; Chi²=8.39, df=5 (P=0.014); I²=40%				
Group=LVI				
Groot et al. 2019	0.53	0.2224	12.7%	1.70 [1.10; 2.63]
Chatterjee et al. 2012	0.73	0.1716	21.3%	2.08 [1.49; 2.91]
Total (95% CI)			**33.9%**	**1.93 [1.48; 2.52]**
Heterogeneity: Tau²=0.0181; Chi²=9.42, df=7 (P=0.22); I²=26%				
Total (95% CI)			**100.0%**	**1.78 [1.53; 2.08]**
Heterogeneity: Tau² =0.0181; Chi²=9.42, df=78 (P=0.22); I²=26%				
Test for subgroup: Q=1.51, P value=0.477				



B

Study or subgroup	TE	SE	Weight	Hazard ratio IV, Random, 95% CI
Group=LVI				
Takahashi et al. 2020	0.88	0.3477	3.8%	2.40 [1.21; 4.75]
Kim et al. 2018	1.36	0.5752	1.7%	3.89 [1.26; 12.01]
Delpero 2017	0.26	0.5462	5.8%	1.30 [0.80; 2.11]
Epstein et al. 2017	0.13	0.0559	12.1%	1.14 [1.02; 1.27]
Chatterjee et al. 2012	0.59	0.1818	7.7%	7.7 [1.12; 2.57]
Total (95% CI)			**31.1%**	**1.61 [1.13; 2.28]**
Heterogeneity: Tau²=0.0960; Chi²=13.97, df=4 (P<0.001); I²=71%				
Group=MVI				
Panaro et al. 2019	1.34	0.3399	3.9%	3.80 [1.10; 2.63]
Jing et al. 2019	0.48	0.1163	10.1%	1.08 [1.49; 2.91]
Yamada et al. 2018	0.61	0.2377	6.0%	1.84 [1.15; 2.93]
Fang et al. 2018	0.35	0.1553	8.7%	1.42 [1.05; 1.93]
Okumura et al. 2017	0.43	0.1886	7.5%	1.53 [1.06; 2.21]
Liu et al. 2016	0.44	0.2034	7.0%	1.56 [1.05; 2.32]
Crippa et al. 2012	0.10	0.1606	8.5%	1.11 [0.81; 1.52]
Hongetal.2012	0.38	0.2150	6.7%	1.46 [0.96; 2.23]
Pawlik et al. 2007	-0.1	0.1045	1.5%	0.99 [0.81; 1.21]
Total (95% CI)			**68.9%**	**1.47 [1.21; 1.80]**
Heterogeneity: Tau²=0.05852; Chi²=24.88, df=8 (P<0.01); I²=68%				
Total (95% CI)			**100.0%**	**1.49 [1.27; 1.74]**
Heterogeneity: Tau²=0.0505; Chi²=40.97, df=13 (P<0.01); I²=68%				
Test for subgroup: Q=0.17, P value=0.676				

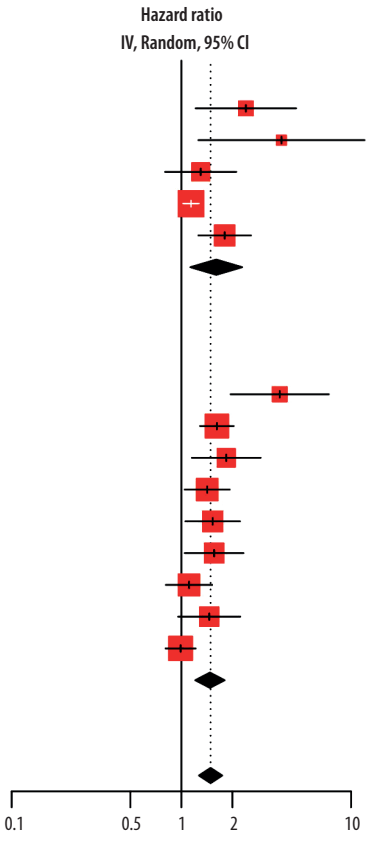


Figure 3. Forest plots of disease-free survival (**A**) and overall survival (**B**) for MVI. CI – confidence interval; LVI – lymphovascular invasion; MVI – microvascular invasion; SE – standard error of treatment estimate; TE – estimate of treatment effect, log hazard ratio.

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Table 2. Definition of MVI in PDAC in different studies.

Study	Description	Origin	Definition methodology	Definition
Yamada et al [9]	Microscopic venous invasion	Blood	Elastica-Masson staining	1
Wang et al [14]	Microvascular invasion	Blood	Immunohistochemical, CD34 as a marker of vascular endothelial cell	1
Panaro et al [10]	Microvascular invasion	Blood	NA	1
Naito et al [32]	Lymphovascular invasion and microvessel invasion	Lymph and blood	D2-40 for LVI, Elastica-van Giesson for MVI	2
Epstein et al [17]	Lymphovascular invasion	Blood or lymph	Hematoxylin and eosin, vascular or lymphatic vessels were not distinguished	3
Chatterjee et al [30]	Lymphovascular invasion	Blood or lymph	Hematoxylin and eosin, lymphovascular was distinguished by micro-muscular vessels invaded (MVI) or not (LVI)	4

1. A cluster of intravascular cancer cells surrounded by an elastic layer; 2. Tumor cell invasion into lymph ducts comprised of D2-40 positive endothelial cells was categorized as LVI. Tumor cell invasion findings in veins with elastic fiber measuring more than half the diameter on Elastica-van Giesson staining or Victoria blue hematoxylin and eosin staining were categorized as MVI; 3. Spreading of cancer cells into microscopic vascular or lymphatic vessels; 4. Tumor invasion into lymphovascular spaces lined by endothelium without muscle layer (LVI) and tumor invasion into micro-muscular vessels (MVI). LVI – lymphovascular invasion; MVI – microvascular invasion.

defining MVI as a cluster of tumor cells surrounded by microvessels lined by epithelium in the peritumoral domain or tumor microenvironment, and there is no need to distinguish its histological origin (ie, blood vessels or lymphatic vessels), as this does not affect prognostic evaluation.

Incidences of MVI

The reported incidence of MVI varied widely (**Figure 2**). The primary reason is that different research centers have different definitions of MVI, as mentioned earlier. Given the critical role of MVI in prognostic evaluation, it is necessary for the pathologist to carefully check whether there is MVI when examining a sample, based on the above definition.

The Potential Mechanism for MVI in PDAC

Cancer metastasis involves a sequence of physical translocation steps from the primary tumor to distant organs [33]. During this process, MVI and the subsequent peripheral blood circulation of cancer cells and/or lymphatic metastasis are necessary and important routes of metastasis [9]. MVI even appears earlier than peripheral circulating tumor cells [33]; therefore, MVI is an essential early event in cancer metastasis.

Epithelial-to-mesenchymal transition (EMT) is a critical biological process by which cancer cells lose their polarized organization, degrade the surrounding extracellular matrix, and acquire migratory and invasive capabilities [34]. Multiple studies have directly confirmed that EMT is the biological basis of MVI in liver cancer [35-37]. Even though EMT is an important step in PDAC metastasis [38-41], the direct relationship between EMT and MVI in PDAC has rarely been reported in the literature. Stress-inducible phosphoprotein-1 (STIP1) is positively correlated with MVI in PDAC [11] and induces EMT in gastric and lung cancers [42,43], and it may be the potential key link between EMT and MVI in PDAC.

In addition to EMT (**Figure 4A(a)**), alterations in the endothelial permeability of the microvascular endothelial monolayer may also be a potential mechanism of MVI (**Figure 4A(b)**). Increased permeability of the microvascular endothelium, which acts as a metastatic barrier, facilitates invasion of tumor cells to the microvasculature, leading to MVI [44,45]. This phenomenon was confirmed in liver cancer [46]. The circular RNA IARS (circ-IARS), located within exosomes, promotes MVI in PDAC by increasing microvascular endothelial monolayer permeability via the downregulation of miR-122 [47].

The Potential Relationship Between MVI and PDAC Metastasis

The precise mechanism underlying MVI in PDAC is controversial and complicated. Based on the existing literature, local recurrence may be attributed to residual MVI [15,18], while distant metastasis may be based on the following 3 routes (**Figure 4B**) [48-53]. First, cancer cells may directly enter the portal vein through the microvasculature originating from blood vessels and subsequently develop liver metastases (**Figure 4B(1)**) [52,53]. Second, perilesional lymphangiogenesis and luminal invasion may provide lymphatic structural support for MVI [54].

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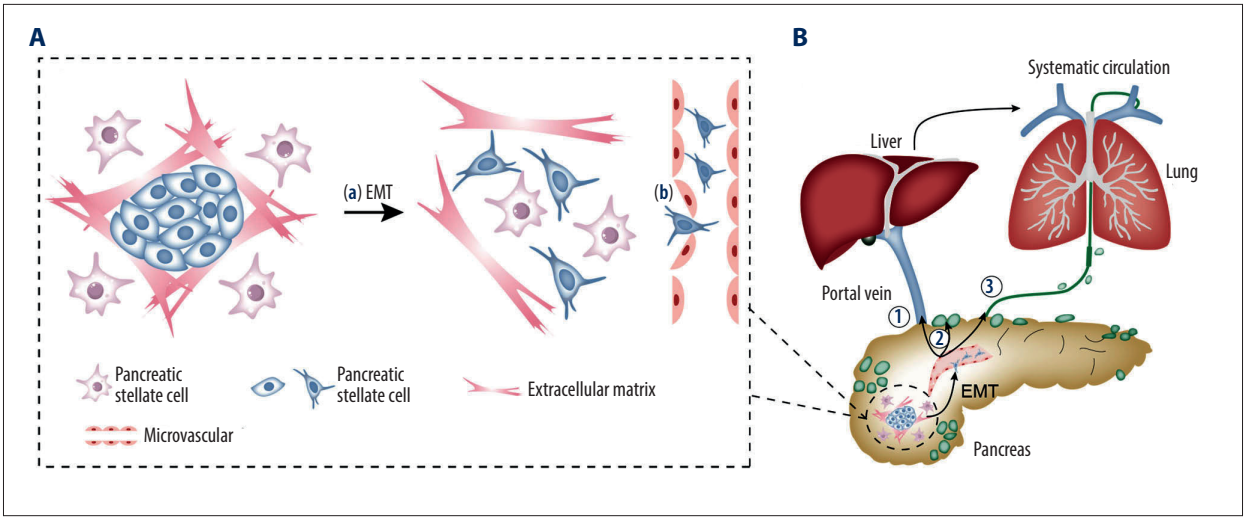

Figure 4. The mechanism of MVI in pancreatic cancer and the relationship between MVI and metastasis. (**A**) The mechanism of MVI in pancreatic cancer. (**a**) Tumor cells gain mobility and invasion capabilities through EMT. (**b**) Increased permeability of the microvascular endothelium facilitates tumor cells to invade into the microvasculature. (**B**) The relationship between MVI and metastasis. (**1**) Angiogenesis, leading to blood transfer and/or liver transfer through the portal vein. (**2**) Lymphangiogenesis, leading to metastasis to the draining lymph nodes. (**3**) Lymphangiogenesis, leading to metastasis to the lymphatic duct. EMT – epithelial-to-mesenchymal transition; MVI – microvascular invasion.

Based on the structure, cancer cells enter the microlymphatic vessels around the lesion and drain into the adjacent lymph nodes (**Figure 4B(2)**), which is supported by evidence that the rate of lymph node metastasis and the incidence of MVI are positively correlated [17]. Third, cancer cells enter the lymphatic ducts through the microlymphatic vessels and subsequently enter the venous system, which leads to liver, lung, and bone metastasis [55] (**Figure 4B(3)**). However, these 3 routes are interrelated [55]. Lymphatic and hematogenous metastases are positively related in PDAC [9], and patients with lymph node metastasis have higher rates of liver and lung metastasis than those without [56]. Lymphatic metastasis may occur before hematogenous metastasis due to the lack of the tight interendothelial junctions typically seen in blood vessels but not in lymphatic capillaries [48,51].

Clinical Significance of MVI

MVI often indicates a higher rate of positive margins [9,30,57]. For patients at high risk of MVI in the preoperative evaluation, the distance from the tumor to the resection margin should be appropriately increased. For pathologically confirmed MVI cases after surgery, surgical specimen margins should be examined more carefully.

The histopathological presence of MVI in PDAC specimens can predict the risk of early recurrence [15,21], and patients with MVI had higher rates of locoregional recurrence, liver metastasis, and lung metastasis [9]. As such, MVI is an independent risk factor for DFS and OS (**Figure 3**). Neoadjuvant chemotherapy may be useful for reducing the MVI rate in cases of both resectable [28] and borderline resectable PDAC [29,32]. As PC patients cannot benefit from expanded surgery [58], patients with MVI should receive more aggressive postoperative adjuvant chemotherapy [59].

Preoperatively predicting the risk of MVI in liver cancer helps guide surgical decision-making and postoperative management based on radiographic and clinical parameters [60-64]. However, there are only a few similar studies involving PDAC cases. Yamada et al reported that MVI was significantly predicted by serum carbohydrate antigen 19-9, maximum standard uptake value from fluorodeoxyglucose positron emission tomography, and tumor size from preoperative computed tomography [9]. Andreasi et al also reported that plasma vasostatin-1 concentrations could be used to preoperatively predict the presence of MVI [65]. Other studies have revealed that MVI is positively correlated with STIP-1 and CD34 levels in PDAC [11,14]. Further research may help develop a model to predict the risk of MVI based on non-invasive parameters, similar to models for liver cancer, which will require studies to assess the relationships between MVI, radiographic parameters, and clinical parameters in PDAC cases.

In the era of precision medicine, accurate prognostication helps guide the selection of appropriate and effective treatment strategies [66]. Thus, many studies have aimed to develop prognostic models to predict outcomes in PDAC [67-69]. However, it is unfortunate that these studies have failed to consider the prognostic relevance of MVI. As MVI is an independent risk

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factor affecting postoperative recurrence and overall survival, it will be of clinical significance to develop a postoperative recurrence prediction model or prognosis model incorporating MVI to more precisely assess the prognosis.

Conclusions

MVI occurred in nearly half of PDAC patients after surgery and is closely related to DFS and OS. Understanding the role of MVI in PDAC helps provide more personalized and effective preoperative or postoperative strategies to achieve better survival outcomes. There are many important items that need to be resolved in the future. First, although previous literature analysis indicates that it may not be necessary to distinguish between microlymphatic or microvascular invasion, this inference still needs to be verified by strictly designed experiments. Second, robust prediction models for preoperative MVI status and postoperative prognosis are urgently needed. Finally, the details of molecules, pathways, and biological processes involved in MVI, along with the regulation of MVI and its role in PDAC metastases, remain to be completely elucidated.

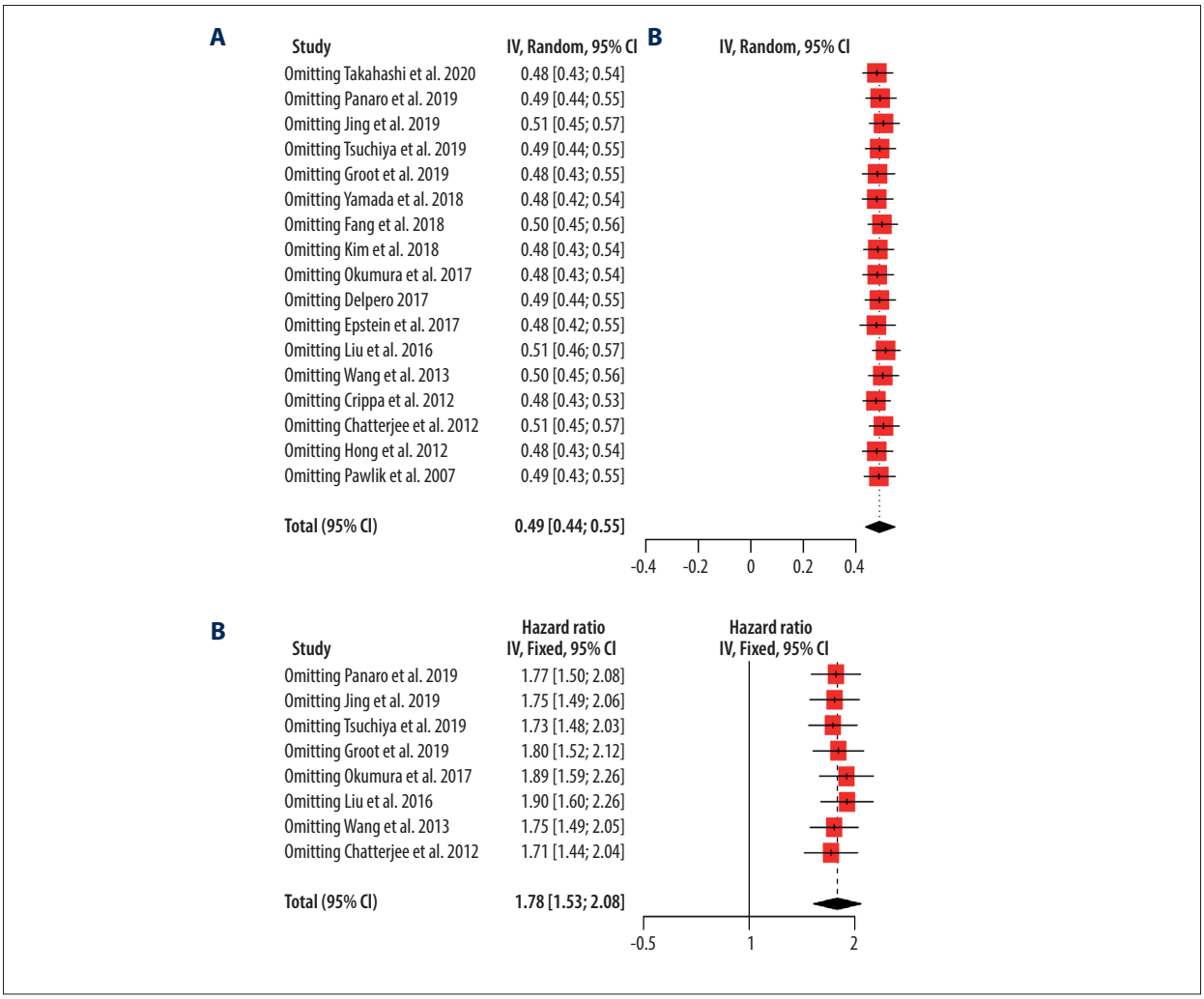
Availability of the Data

The data for statistical processing are available from the first author or corresponding author.

Conflicts of Interest

None.

Supplementary Data



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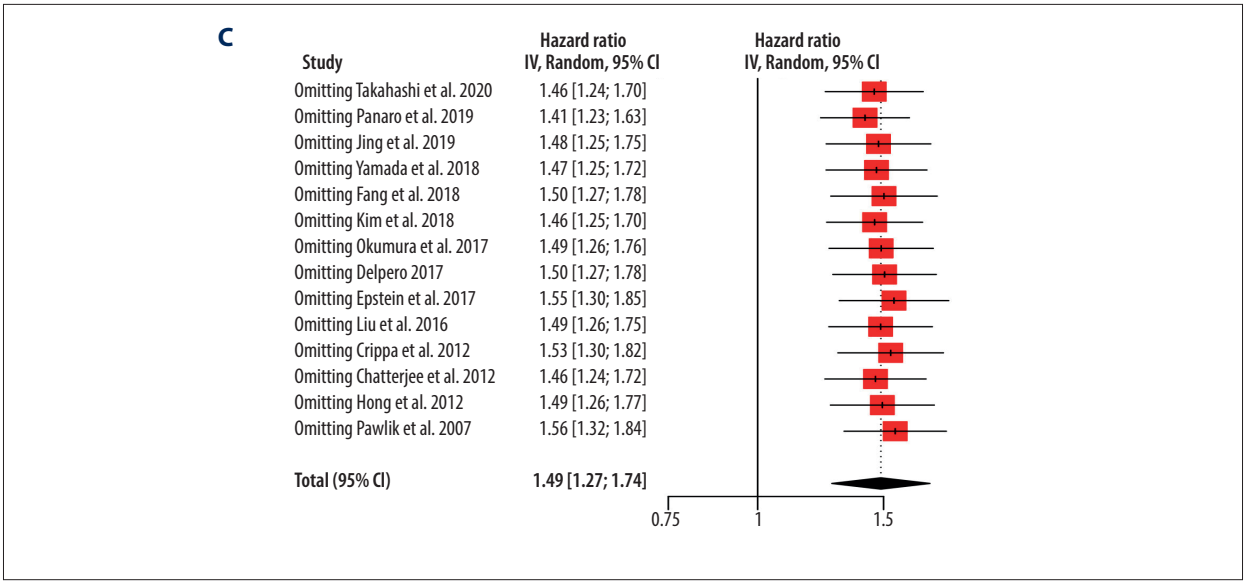

Supplementary Figure 1. Sensitivity for included studies. (**A**) Microvascular invasion incidence; (**B**) disease-free survival; (**C**) overall survival.

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