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Laboratory prognostic factors correspondence to independent postoperative histo-pathological prognostic factors in pancreatic ductal adenocarcinoma

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ABSTRACT

Background: Investigating the various prognostic factors affecting pancreatic cancer prognosis is of great value in their management during clinical practice. This study aimed to identify all these prognostic factors used in the systematic review in a correlation analysis to conduct their influence on pancreatic cancer patients. *Material and Methods*: Systematic review search was conducted in PubMed, EMBASE, and EBSCO through July 2020. The meta-analysis was applied in 32 study articles and reported their hazard ratios (HRs), 95% confidence intervals (CIs), and their effects on the prognosis of the pancreatic cancer patients. *Results*: Thirty-two studies with 7778 patients were included in the study. The pooled analysis indicated bad prognosis in lymph node metastasis (HR= 1.61; 95% CI; 1.01-2.22), lymph node ratio (HR= 2.63; 95% CI; 1.23-6.50), lymphatic invasion (HR= 1.29; 95% CI; 0.89-1.69), lymphovascular invasion (HR= 2.08; 95% CI; 0.38-3.79), vascular invasion (HR= 1.55; 95% CI; 1.04-2.25), duodenal invasion (HR= 1.17; 95% CI; 0.95-1.38), NLR (HR= 1.11; 95% CI; 1.03-1.19), PLR (HR= 1.04; 95% CI; 0.95-1.13), neutrophil count (HR= 2.94; 95% CI; 0.18-5.70) and good prognosis with high LMR (HR= 0.83; 95% CI; 0.74-0.93) while the marginal invasion (HR= 1.00; 95% CI; 0.24-1.75). *Conclusion*: The results of the meta-analysis showed that the following prognostic factors; lymph node metastasis, lymph node ratio, lymphovascular invasion, lymphatic invasion, vascular invasion, duodenal invasion, NLR, PLR, neutrophil count and lymphocyte count are of worse prognosis. However, high LMR referred to a good prognosis in pancreatic cancer patients. We recommend physicians and health care providers to deem the aforesaid results while assessing the prognosis among pancreatic adenocarcinoma patients.

Keywords: Pancreatic Ductal Adenocarcinoma, lymph node metastasis, pancreatic Malignancy, Histo-pathology, Prognostic factors, management.

1. INTRODUCTION

Pancreatic adenocarcinoma is a deadly condition that has a poor prognosis and is becoming more common. It still remains a major public health issue and is the fourth leading cause of cancer-related death worldwide (Siegel et al., 2013). Pancreatic cancer (PanCA) is ranked as the 14th most common cancer, and the 7th highest cause of cancer mortality in the world (McGuigan et al., 2018). PanCA is the fourth leading cause of cancer-related deaths in the United States, with 43,090 deaths expected in 2017 (Siegel et al., 2017). Similar mortality rates for PanCA can be found in other developed nations, with pancreatic cancer being the fifth and fourth leading causes of cancer-related deaths in men and women, respectively, according to global statistics for developed countries (Jemal, 2012; Ferlay et al., 2015). The incidence rates vary significantly between countries. The highest age-standardized incidence is seen in Europe and North America, and the lowest in Africa and South-Central Asia (Ilic & Ilic, 2016). There is a general trend of higher incidence rates in developed countries compared to developing countries, which was supported by Wong et al., (2016), who demonstrated that in countries with higher human development index, there are increased incidences of pancreatic cancer in both men and women.

Pancreatic cancer is typically a disease of the elderly. It is extremely rare for patients to be diagnosed before the age of 30 and 90% of newly diagnosed patients are aged over 55 years of age, with the majority in their seventh and eighth decade of life (Midha et al., 2016; Wood et al., 2006). Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with a median age of diagnosis around 71 years (Ilic & Ilic, 2016). Nearly 60%-70% of pancreatic adenocarcinomas arise in the head of the pancreas, with the remainder being found in the body (15%) and tail (15%). At the time of diagnosis, most pancreatic adenocarcinomas have already spread beyond the pancreas, and nodal metastases are not uncommon (Luchini et al., 2016). Although ductal cells have long been believed to be the source of PDAC, new evidence suggests that acinar cells may also play a role. Acinar cells Trans-differentiate to ductal cells in response to pancreatic injury or mutation (acinar-ductal metaplasia, ADM). Ductal cells transform into lesions known as pancreatic intraepithelial neoplasia (PanINs) that eventually progress to PDAC (Wong et al., 2016).

Pancreatic cancer progresses from precursor lesions, including pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasm (MCN), and intra-ductal papillary mucinous neoplasm (IPMN) to advanced PDAC. PanINs are the most common precursor lesions in smaller pancreatic ducts (found in 30% of samples) and are graded from stage I to III (low, intermediate, and high grade, respectively) based on the extent of atypia (Brosens et al., 2015). Pancreatic cancer is difficult to diagnose, and the vast majority of cases are diagnosed late, with either locally advanced or metastatic disease. PanCA is often diagnosed at an advanced stage due to the general absence of symptoms until the later stages of the disease (Siegel et al., 2017; Kamisawa et al., 2016). Patients may present with a variety of symptoms by the time they are diagnosed, including unexplained weight loss, recent diabetes onset, jaundice, fatigue, and loss of appetite, as well as back and abdominal pain (Ryan et al., 2014).

One study highlighted that many people who were ultimately diagnosed with pancreatic cancer were falsely reassured by the intermittent nature of their symptoms over the preceding months (Keane et al., 2014). The comparative in frequency of pancreatic cancer moreover means that numerous primary care physicians will first realize a case every one few years on usual. Diagnosis of PanCA is generally done using various imaging modalities, including computer tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) (McIntyre et al., 2015) with biopsy. When the diagnosis of pancreatic malignancy has been established, staging can comprise CT or MRI of the chest, abdomen, and pelvis with IV contrast. EUS is also very important not only for tissue acquisition for diagnosis but for staging as well (Vareedayah et al., 2018). Approximately 1 in 4 patients with CT-demonstrated localized pancreatic cancer are found to have metastatic disease at laparoscopy (Garcea et al., 2012; Karmazanovsky et al., 2005). So, staging diagnostic laparoscopy is recommended in most patients prior to surgical exploration (Couch et al., 2007; Mayo et al., 2009).

It is critical to identify poor prognostic factors that can predict tumour recurrence and patient prognosis in order to select appropriate treatment protocols. As a result, in addition to well-known prognostic factors like clinical and pathological stage, performance status, and surgical margin, it's critical to identify new biological or pathological indicators related to survival (Boggi et al., 2009). If the tumour is localised to the pancreas and has spread to lymph nodes or distant organs, these are the primary surgical or pathological factors that influence prognosis (Siegel et al., 2013). The TNM staging system is used, as well as tumour size, peripancreatic extension, and vascular involvement. Traditionally, TNM staging, especially in the presence of metastasis (advanced stage), has been found to be an important prognostic factor in patients with pancreatic cancer for survival (Zhang et al., 2012).

In prognostic sub-classification of pancreatic adenocarcinomas after pancreas to duodenectomy, lymph node ratio (LNR) may be more helpful than nodal (N) status. Recent studies have suggested that LNR may also be an important prognostic factor in pancreatic cancer (Berger et al., 2004; Pawlik et al., 2007). Riediger et al., 2009, in 204 resected patients, reported that LNR was the

strongest predictor of survival, and they concluded that the routine estimation of the LNR might be supportive not only for the separate guess of prognosis but also for the suggestion of adjuvant treatment. In the TNM staging system, the quantity of resected lymph nodes may be very significant. The analysis of Surveillance, Epidemiology, and End Results and MGH (Massachusetts General Hospital) in 10254 and 827 resected patients, respectively, showed that higher LNR (> 0.2) was associated with worse survival by univariate analysis, and in addition, the hazard ratio (HR) raised proportionally when more lymph nodes were examined in multivariate analysis, the study concluded that LNR was strongly associated with survival, and thus, LNR provided a stronger and more accurate predictor of survival (Valsangkar et al., 2013).

Blood vessel invasion (BVI) has previously been studied in pancreatic cancer patients and found to be a significant prognostic factor for survival (Andrén-Sandberg, 2012). In a study performed by Chatterjee et al., (2011), BVI was found to be associated with the overall survival (OS) and lymph node status in patients who were treated with neoadjuvant treatment. The median OS was healthier in cases devoid of BVI likened with cases with BVI (34 mo vs. 22 mo), and the author concluded that BVI was a significantly poor prognostic indicator (Chatterjee et al. 2011). Platelet, lymphocyte, and neutrophil counts, mean platelet volume, and the ratios of various hematologic cells have been shown to be valuable prognostic factors in various malignancies (Donskov & von der Maase, 2006; Sierko & Wojtukiewicz, 2004). Schwarz et al., (2001), demonstrated that pre-operative platelet count predicts survival after resection of pancreatic adenocarcinoma. However, in a study comprising 205 patients performed by Dominguez et al., (2008), there was no confirmation to sustenance pre-operative platelet count as whichever an contrary or encouraging prognostic influence in pancreatic ductal adenocarcinoma.

The prognostic value of pre-treatment platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) in patients with pancreatic cancer has also been evaluated (Stotz et al., 2013, Aliustaoglu et al., 2010). Song et al., (2009), defined pre-operative PLR as an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Surgical margin status is thought to affect the survival of patients after surgical resection of pancreatic cancer (Shibata et al., 2005). Portal vein and/or superior mesenteric vein resections appear to decrease survival compared to cases in which vein resections are not performed (Schnelldorfer et al., 2008). Vein resections increase survival. Vein resections do not necessarily indicate a negative possibility of long-term survival after surgical resection of pancreatic cancer, as previous studies have shown (Liberati et al., 2009). Generally, prognosis associated with pancreatic cancer has not improved over the last 20 years so, investigations on predictive factors in pancreatic cancer are needed because these factors should have predictive value in relation to longer survival after surgery than after palliative treatment.

Aim

To pool all these prognostic factors that were used in the literature review, in a correlation analysis between each other looking for specific trends that may facilitate better prioritization of some prognostic factors in the future clinical practice and clinical trials.

Objectives

1. To list the pre-operative and post-operative disease-free survival (DFS) predictive factors if found and overall survival id DFS is not available and to report the possible domains for each factor. (i.e., (1) Staging radiological assessment local vascular invasion, duodenal invasion and lymph nodes (2) Acute-phase inflammatory markers: platelet count, PLR, NLR and MLR (3) Histopathology assessment: duodenal invasion, vascular invasion, margin involvement, and lymph node metastasis,
2. To use multivariate vs.univariate analysis for correlation assessment and contrast used prognostic predictors to each other, and
3. To change the current local practice at our center in assessing the prognostic indicators in borderline resectable pancreatic adenocarcinoma.

2. MATERIALS AND METHODS

Study design

Systematic review and meta-analysis

Search duration: Searches run on 1– 31 July 2020.

Search strategy

We performed this meta-analysis according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement (Mourad et al., 2016). The systematic review was identified by two reviewers through conducting a structured literature

search of electronic databases using Medical Subject Headings (MeSH terms) and keywords related to "pancreatic cancer or carcinoma or adenocarcinoma", "prognostic factors," and "pre-operative or post-operative," which were combined through the Boolean operator "AND" and "OR. The Electronic searches were carried out in PubMed, EMBASE, and EBSCO in July 2020.

In PubMed search the two reviewers applied the Medical Subject Headings (MeSH terms): (("Pre-operative Period" [Mesh] OR "Laboratories" [Mesh] AND "Carcinoma, Pancreatic Ductal" [Mesh] AND "Prognosis" [Mesh]). ((("Preoperative Period"[Mesh] AND "Laboratories"[Mesh]) OR "Radiology"[Mesh]) OR "Blood Platelets"[Mesh]) OR "Neoplasm Invasiveness"[Mesh] AND "Carcinoma, Pancreatic Ductal"[Mesh] AND "Prognosis"[Mesh]). For Embase and EBSCO searching, "Emtree" and "Subject terms" as a search strategy were applied respectively using the following keywords: (Preoperative) AND (laboratory) OR (Radiological) OR (Vascular invasion) OR (Duodenal invasion) OR (lymph nodes) OR (Platelet count) OR (Platelet) OR (PLR) OR (Platelet-lymphocyte ratio) OR (platelet to lymphocyte ratio) OR (neutrophil-lymphocyte ratio) OR (neutrophil to lymphocyte ratio) OR (NLR) OR (monocyte to lymphocyte ratio) OR (monocyte-lymphocyte ratio) OR (Marginal involvement) AND (prognostic) AND (Independent) AND (postoperative) AND (post-operative) AND (Histopathology) OR (Histopathological) OR Histo-pathological) AND (ductal adenocarcinoma) OR (PDAC) AND (pancreatic).

Inclusion and exclusion criteria

Two authors independently screened the titles and abstracts for eligibility. Then a full-text screening was attained according to the following inclusion and exclusion criteria.

Inclusion criteria

We included studies followed these criteria:

Studies in which patients were diagnosed with pancreatic adenocarcinoma and deemed by any method of diagnosis by the author

Studies analyzing the correlation of pre-operative and post-operative prognostic factors for Disease-free survival (DFS) when present or overall survival if DFS is not available including hazard ratios (HRs) with 95% confidence intervals

Exclusion criteria

Studies were excluded if they have the following criteria:

Meta-analyses and systematic reviews

Randomized-control trials

Studies that have no full-text access

Studies that are not in the English language.

Studies were excluded in case the pancreatic adenocarcinoma is self-reported.

Data extraction, Synthesis, and Quality Assessment

The primary eligibility form used for data extraction included the title of the publication, ID number, and general population. The initially identified articles were imported to Rayyan QCRI, the systematic review web app citation manager (Stang, 2010), and duplicates were removed.

In the systematic review full-screening phase, the two authors reviewed each study article and recorded the title of the article, study ID number, the authors, time period, study design, population type, patient characteristics (mean and median age, age-range, and sex), prognostic factors which included (vascular invasion, duodenal invasion, lymph vascular invasion, lymph node metastasis, marginal involvement lymph node ratio, and acute-phase inflammatory markers: NLR, PLR, LMR, Neutrophil count, and Lymphocyte count) and also indicated the post- and pre-operative differences as well as univariate and multivariate analyses.

All studies were assessed for the risk of bias using the Newcastle-Ottawa Scale (Der Simonian & Laird, 1986) for coding cohort studies. It is classified into three classes (Selection, Comparability, and outcome), and furthermore, it is categorized into eight questions, nine stars for a total. Each element is evaluated for one star except for the "Comparability" domain, which was evaluated for two stars. The systematic review that met the inclusion criteria was finally exposed to a critical appraisal. The sum total of the disagreements have been selected and settled to an assent.

Statistical analysis

We used STATA version 16 (Stata Corporation, College Station, TX, USA) for the meta-analysis. HRs with their correlated 95% confidence interval (CI) were directly educed from each study full-text and used for comparing multivariate and univariate analyses. Pooled HRs and their related 95% CIs were calculated using a random-effects model (DerSimonian-Laird method)

(Higgins & Thompson, 2002). The heterogeneity among studies was estimated by the Cochran's Q test, and the Higgins I^2 statistic ($p < 0.10$ or $I^2 > 50\%$ was considered significant (Begg & Mazumdar, 1994). Publication bias was assessed visually by Begg's funnel plots (Yamada et al., 2018).

3. RESULTS

Search results

The identification and screening processes for this meta-analysis are illustrated in Fig 1. A total of 1213 studies were obtained from the initial literature search using the following databases PubMed, EMBASE, and EBSCO. Of all, 48 duplicates were removed using Rayyan QCRI, 1097 studies were excluded based on the title and abstract screening, and eventually, 66 full-text articles were reviewed and excluded to consider supplemental eligibility. Finally, 32 competent studies were included in the meta-analysis.

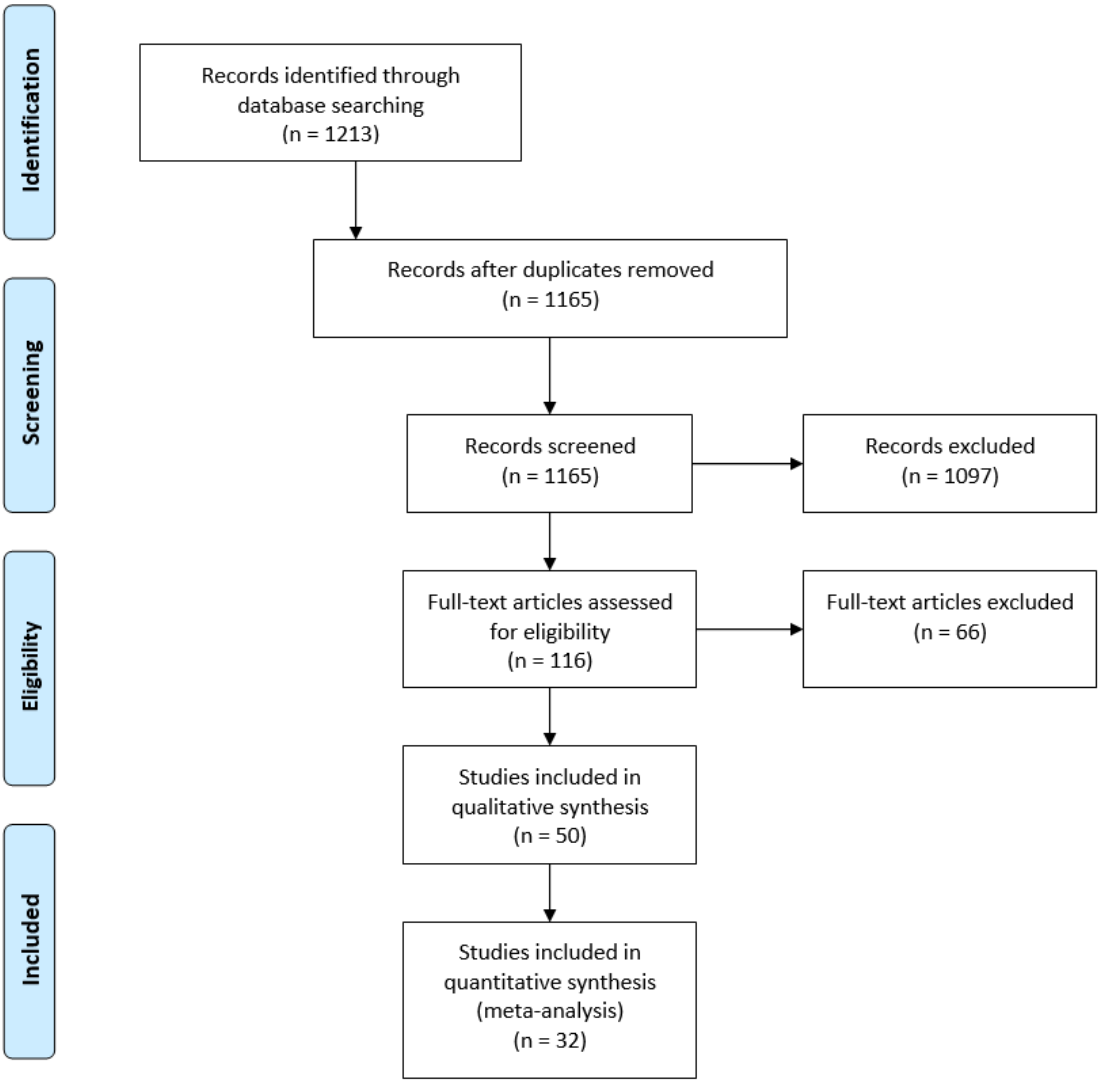

Figure 1 PRISMA flow diagram for study selection and data acquisition.

Study characteristics

The 32 eligible studies included a total of 7779 patients. The main characteristics of the patients are presented in Table 1. The study population size ranged from 42 to 1183 patients. HR with their associated 95% Confidence intervals were conducted in 13 studies using univariate analysis, 8 studies using Multivariate analysis and 11 studies counting on both univariate and multivariate analyses. Among the included studies there were 18 studies from the Asian countries; Japan (n = 11) (Shirai et al., 2017; Yamada et al., 2015; Okabayashi et al., 2018; Kato et al., 2019; An et al., 2012; Morita et al., 2015; Maréchal et al., 2010; Cloyd et al., 2010; Drouillard et al., 2008; Szkander et al., 2013; Asariet al., 2013) China (n = 6)(Ben et al., 2010; Xu et al., 2017; Kondo et al., 2010; Yamaki et al., 2017; Li et al., 2014; Zhang et al., 2012) and South Korea (n = 1) (Hu et al., 2016), 10 studies were from the European

countries; United Kingdom (n= 4) (Alhasan et al., 2016; Bhatti et al., 2008; Smith et al., 2009; Stotz et al., 2012), Belgium (n = 1) (Nejati et al., 2007) and Austria (n = 3) (Xue et al., 2012; Xie et al., 2012), 4 studies were conducted in the United States of America (n = 4) (Chawla et al., 2018; Dal Molin et al., 2017; Park et al., 2016; Szkandera et al., 2014) and 2 studies were a cooperation between the USA and Italy (n = 2) (Marchegiani et al., 2017; Oguro et al., 2018) (table 2).

Table 1 Summary of included studies, year, type, country, no. of participants, age range, age mean ±SD, male no. and percentage, and NOS score

Author	Year	Study type	Country	No. Participants	Age range	Age (Mean±SD)	Age (Median)	Males (n)	Males (%)	NOS
Yamada M	2007-2015	Retrospective study	Japan	352	38-88			211	59.9	9
Alhasan SF	2016	Retrospective study	UK	93			65.3	53	56.9	7
Shirai Y	2017	Retrospective review	Japan	107	61-74		68	62	57.9	8
Okabayashi T	2018	Retrospective review	Japan	240	34-91		72	108	45	8
Ben QW	2010	Unknown type	China	94	31-79	60	59	55	58.5	9
Dal Molin M	2017	Prospective study	USA	925		66.37±10.76		488	52.8	9
Chawla A	2017	Retrospective study	USA	217	29-88.8		69.3	110	50.6	8
Xu J	2017	Unknown type	China	265	16-84	58.4±13.4		131	49.4	9
Kato Y	2019	Retrospective study	Japan	369	34-84		66	227	61.5	9
Marchegiani G	2017	Prospective study	Italy&USA	324	32-91		64	199	49.4	7
Oguro S	2013	Retrospective review	Italy&USA	1183	28-93		66	559	51.2	9
An W	2012	Retrospective review	Japan	393				234	59.5	9
Kondo N	2010	Retrospective study	China	190	31-79	60.5		111	58.4	8
Morita K	2002-2015	Retrospective study	Japan	109	43-78		70	56	51	9
Maréchal R	2010	Retrospective study	Japan	60	36-83	67.8 ± 1.3	70	29	48.3	9
Cloyd J.M	2009-2012	Retrospective study	Japan	83	41-84	66.0 ± 7.6		51	61.4	8
Park I	2008-2014	Prospective study	USA	127		64.6 ± 8.9		68	53.5	8
Hu S.-P.	2006-2016	Retrospective study	South Korea	88	34-83		65	59	67	9
Li H	2008-2014	Retrospective study	China	282		58.7 ±13.5	72.9	117	41.1	8
Yamaki S	2001-2007	Prospective study	China	258	21-75	59	58.64	146	56.5	9
Drouillard A	1998-2008	Prospective study	Japan	42	50-83	65		26	61.9	8
Nejati R	1999-2007	Prospective study	Belgium	65	42-85		62	42	65	9
Szkandera J	2004-2010	Retrospective study	USA	163	42-84		63.5	83	50.9	9
Xue P	2006-2012	Retrospective study	Austria	474		64.6±10.4		256	54	8
Szkandera J	2001-2012	Retrospective study	Japan	252						9
Stotz M	2004-2010	Retrospective study	Austria	474		64.5±10.4		256	54	9
Xie H	1999-2007	Retrospective study	Austria	110	35-93		65	51	46.4	8
Zhang Y	2012	Retrospective study	China	117	35-93		65	68	58.1	8
Bhatti I	1998-2008	Prospective study	UK	84	70-79		63.7	50	59.5	8
Smith RA	1997-2006	Prospective study	UK	84	51-79		65	48	57.1	8
Asari S	2000-2013	Retrospective study	Japan	221	60-73		68	129	58.4	9
Stotz M	2004-2012	Retrospective study	UK	110	61-73		67	65	59	9

Table 2 Summary of included studies results: analysis, pre-/post-operative, prognostic factor, and HR (95% CI)

Author, year (s)	No. of Participants	Analysis	Pre-/Postoperative	Prognostic Factor	HR (95% CI)
Yamada M, 2007-2015	352	Multivariate	Postoperative	Vascular invasion	1.84 (1.15-2.92)
	352	Multivariate	Post-operative	Lymphatic	1.13 (0.58-2.2)

				invasion	
	352	Multivariate	Post-operative	Lymph node metastasis	2.95 (1.59-5.48)
Alhasan SF, 2016	93	Univariate	Postoperative	Vascular invasion	1.49 (0.84-2.65)
	93	Univariate	Post-operative	Margin positivity	1.32 (0.83-2.1)
	93	Univariate	Post-operative	Lymphatic invasion	1.33 (0.85-2.09)
Shirai Y, 2017	107	Univariate	Postoperative	PLR	1.575 (1.014-2.493)
	107	Univariate	Post-operative	NLR	1.414 (0.868-2.276)
	107	Univariate	Pre-operative	Margin positivity	1.419 (0.875-2.455)
Okabayashi T, 2018	240	Univariate	Preoperative	Vascular invasion	1.54 (1.3-1.82)
	240	Univariate	Post-operative	PLR	1.14 (0.84-1.59)
	240	Univariate	Post-operative	NLR	1.6 (1.17-2.17)
	240	Univariate	Pre-operative	Lymphatic invasion	1.44 (1.21-1.71)
Ben QW, 2010	94	Univariate	Postoperative	Vascular invasion	2.579 (1.585-4.197)
Dal Molin M, 2017	925	Multivariate	Postoperative	Vascular invasion	1.07 (0.86-1.25)
	925	Multivariate	Post-operative	Invasion of duodenum	1.33 (1.08-1.57)
Chawla A, 2017	217	Univariate	Postoperative	Vascular invasion	1.095 (0.754-1.59)
	217	Univariate	Post-operative	PLR	1 (0.999-1.001)
	217	Multivariate	Post-operative	PLR	0.998 (0.997-1)
	217	Univariate	Post-operative	NLR	0.993 (0.97-1.016)
	217	Multivariate	Post-operative	NLR	1.012 (0.982-1.043)
	217	Univariate	Post-operative	Margin positivity	1.553 (1.162-2.075)
	217	Multivariate	Post-operative	Margin positivity	1.223 (0.884-1.693)
	217	Univariate	Post-operative	Lymphovascular invasion	1.773 (1.336-2.353)
	217	Multivariate	Post-operative	Lymphovascular invasion	1.344 (0.958-1.885)
	217	Univariate	Post-operative	Lymph node ratio	5.076 (2.461-10.467)
	217	Multivariate	Post-operative	Lymph node ratio	5.949 (2.394-14.785)
Xu J, 2017	265	Multivariate	Postoperative	Vascular invasion	2.05 (1.52-2.764)
	265	Multivariate	Post-operative	PLR	1.099 (1.007-1.11)
	265	Multivariate	Post-operative	NLR	1.063 (1.031-

					1.097)
Kato Y, 2019	369	Multivariate	Pre-operative	Lymph node metastasis	1.55 (1.16-2.06)
	369	Multivariate	Pre-operative	Invasion of duodenum	0.97 (0.71-1.32)
Marchegiani G, 2017	324	Univariate	Postoperative	Vascular invasion	0.79 (0.57-1.09)
	1183	Univariate	Post-operative	Vascular invasion	0.79 (0.57-1.09)
	324	Univariate	Post-operative	Lymphovascular invasion	1.16 (0.91-1.48)
	1183	Univariate	Post-operative	Lymphovascular invasion	1.16 (0.91-1.48)
Oguro S, 2013	393	Univariate	Postoperative	Vascular invasion	2.35 (1.744-3.167)
	393	Multivariate	Post-operative	Vascular invasion	1.522 (1.099-2.108)
	393	Univariate	Post-operative	Margin positivity	1.89 (1.464-2.44)
	393	Univariate	Post-operative	Lymphatic invasion	2.181 (1.635-2.909)
An W, 2012	190	Univariate	Postoperative	Vascular invasion	1.26 (0.91-1.74)
Kondo N, 2010	109	Multivariate	Postoperative	Lymph node metastasis	1.2 (0.85-1.72)
Morita K, 2002-2015	60	Multivariate	Postoperative	Lymphovascular invasion	2.257 (1.141-4.464)
	60	Multivariate	Post-operative	Lymphovascular invasion	5.065 (2.084-12.308)
	60	Multivariate	Post-operative	Lymph node metastasis	2.187 (1.084-4.414)
	60	Multivariate	Post-operative	Lymph node metastasis	2.349 (1.185-4.654)
Maréchal R, 2010	45	Univariate	Postoperative	Lymph node ratio	1.81 (0.89-3.64)
	45	Multivariate	Post-operative	Lymph node ratio	1.46 (0.69-3.06)
	45	Univariate	Post-operative	Lymph node metastasis	1.59 (0.71-3.57)
Cloyd J.M, 2009-2012	127	Univariate	Postoperative	Margin positivity	1.57 (0.57-4.3)
	127	Univariate	Post-operative	Lymphovascular invasion	2.04 (1.31-3.19)
	127	Univariate	Post-operative	Lymph node ratio	4.34 (2.36-7.96)
	127	Univariate	Post-operative	Lymph node metastasis	1.98 (1.26-3.1)
Park I, 2008-2014	88	Multivariate	Preoperative	Neutrophil count	2.94 (1.27-6.79)
Hu S.-P., 2006-2016	282	Univariate	Pre-operative	Vascular invasion	1.589 (1.176-2.147)
	282	Univariate	Pre-operative	Lymph node metastasis	1.638 (1.231-2.181)
	282	Univariate	Pre-operative	Invasion of duodenum	1.715 (1.301-2.262)

Li H, 2008-2014	258	Univariate	Postoperative	PLR	1.156 (0.762-1.753)
	258	Univariate	Post-operative	NLR	1.765 (1.164-2.676)
	258	Multivariate	Post-operative	NLR	1.198 (1.033-1.389)
	258	Univariate	Post-operative	LMR	0.501 (0.328-0.762)
	258	Multivariate	Post-operative	LMR	0.846 (0.734-0.97)
Yamaki S, 2001-2007	42	Univariate	Postoperative	Vascular invasion	1.15 (0.57-2.5)
	42	Univariate	Post-operative	Lymphatic invasion	1.23 (0.6-2.65)
Drouillard A, 1998-2008	65	Univariate	Postoperative	Vascular invasion	1.21 (0.66-2.19)
	65	Univariate	Post-operative	Lymphatic invasion	1.62 (1.04-2.72)
	65	Univariate	Post-operative	Lymph node metastasis	3 (1.61-5.63)
	65	Multivariate	Post-operative	Lymph node metastasis	3.43 (1.8-6.6)
Nejati R, 1999-2007	163	Univariate	Postoperative	Margin positivity	1.27 (0.69-2.32)
	163	Univariate	Post-operative	Lymph node metastasis	1.63 (1.05-2.51)
	163	Multivariate	Post-operative	Lymph node metastasis	1.89 (1.22-2.94)
Szkandera J, 2004-2010	474	Univariate	Postoperative	PLR	1.18 (0.89-1.58)
	474	Multivariate	Post-operative	PLR	0.93 (0.66-1.31)
	474	Univariate	Post-operative	NLR	1.78 (1.46-2.17)
	474	Multivariate	Post-operative	NLR	1.47 (1.15-1.89)
Xue P, 2006-2012	252	Univariate	Postoperative	PLR	10.6 (9.6-11.6)
	252	Univariate	Post-operative	NLR	6 (2.8-9.2)
Szkandera J, 2001-2012	474	Univariate	Postoperative	NLR	1.53 (1.25-1.86)
	474	Multivariate	Post-operative	NLR	1.24 (1.01-1.51)
Stotz M, 2004-2010	110	Univariate	Postoperative	PLR	1.071 (0.822-1.396)
	110	Univariate	Post-operative	NLR	2.193 (1.664-2.889)
	110	Multivariate	Post-operative	NLR	1.611 (1.024-2.534)
	110	Univariate	Post-operative	Margin positivity	1.884 (1.11-3.199)
	110	Multivariate	Post-operative	Margin positivity	1.699 (0.951-3.035)
Xie H, 1999-2007	117	Univariate	Postoperative	Margin positivity	1.3 (0.9-2.1)
	117	Univariate	Post-operative	Lymphovascular	1.4 (0.9-2)

				invasion	
Zhang Y, 2012	84	Multivariate	Postoperative	Margin positivity	0.381 (0.207-0.701)
	84	Multivariate	Post-operative	Lymphovascular invasion	0.817 (0.453-1.473)
	84	Multivariate	Post-operative	Lymph node metastasis	0.448 (0.239-0.841)
Bhatti I, 1998-2008	84	Univariate	Preoperative	PLR	0.978 (0.899-1.075)
	84	Univariate	Pre-operative	NLR	1.784 (1.085-2.934)
	84	Univariate	Pre-operative	Neutrophil count	1.011 (0.811-1.261)
	84	Univariate	Pre-operative	Lymphocyte count	1.56 (1.019-2.39)
Smith RA, 1997-2006	110	Univariate	Preoperative	PLR	1.004 (1.002-1.006)
	110	Multivariate	Pre-operative	PLR	1.004 (1.002-1.006)
	110	Univariate	Pre-operative	NLR	1.047 (0.985-1.113)
	110	Univariate	Pre-operative	Neutrophil count	1.038 (0.956-1.127)
	110	Univariate	Pre-operative	Lymphocyte count	0.677 (0.511-0.897)
Asari S, 2000-2013	37	Multivariate	Preoperative	PLR	3.05 (1.169-7.468)
	184	Multivariate	Pre-operative	NLR	1.911 (1.281-2.832)
	37	Multivariate	Pre-operative	NLR	2.98 (1.251-6.92)
Stotz M, 2004-2012	474	Univariate	Postoperative	LMR	0.7 (0.57-0.85)
	474	Multivariate	Post-operative	LMR	0.81 (0.66-0.99)

Meta-analysis

Lymph node metastasis as an independent prognostic factor

Eleven studies with a total of 1656 patients were involved in a comparison between multivariate and univariate analysis expressing lymph node metastasis as a prognostic factor in pancreatic adenocarcinoma (figure 2). Our meta-analysis found that lymph node metastasis that the pooled hazard ratio for the multivariate analysis was (HR= 1.56; 95% CI: 0.93-2.19) and the pooled hazard ratio for the univariate analysis is worse (HR=1.72; 95% CI: 1.37-2.07) and they both indicate poor prognosis.

Lymph node ratio as an independent prognostic factor

Three studies were analyzed considering "lymph node ratio" as a prognostic factor, including 389 patients in total, and the following was concluded; the multivariate analyses and the univariate analyses they both showed poor prognosis and their pooled hazard ratio (HR= 2.63; 95% CI; 1.23-6.50), (HR= 3.22; 95% CI; 1.08-5.37) respectively (figure 3).

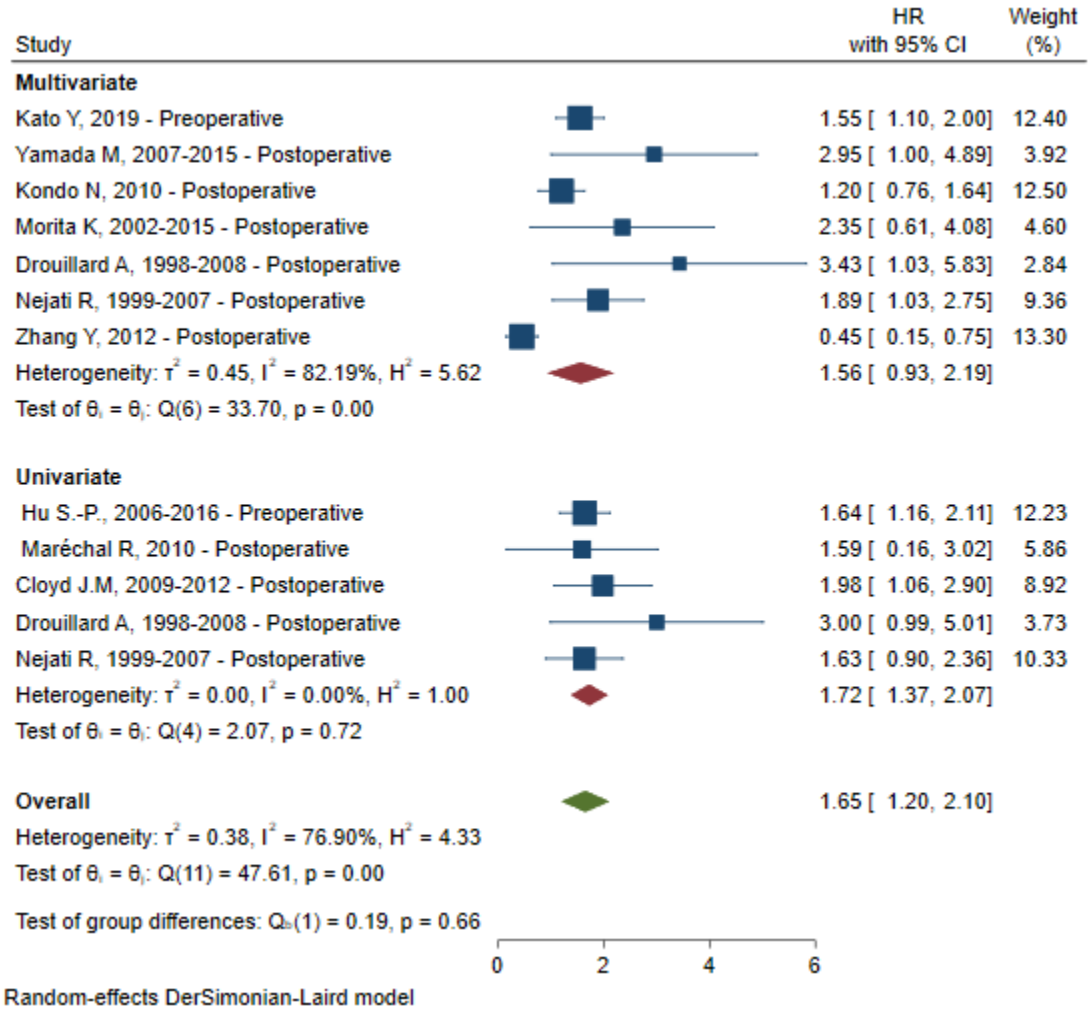

Figure 2 Forest plot for survival outcomes of (lymph node metastasis) among pancreatic adenocarcinoma patients.

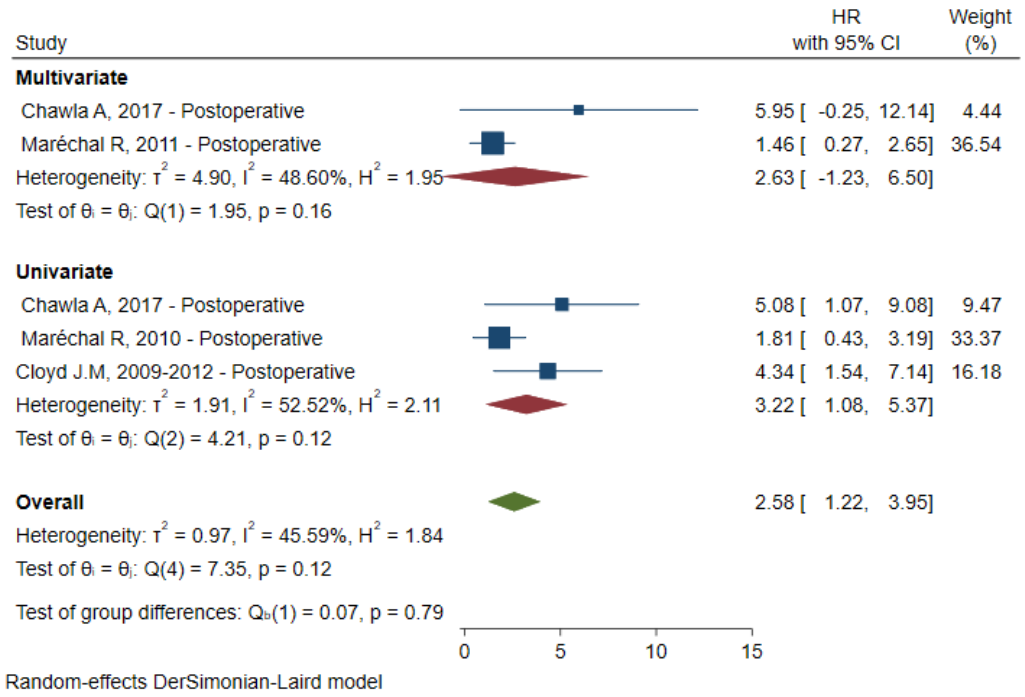

Figure 3 Forest plot for survival outcomes of (lymph node ratio) among pancreatic adenocarcinoma patients.

Lymphatic invasion

The pooled results included seven studies with a total of 1402 patients and showed that the univariate analysis (HR= 1.54; 95% CI; 1.26-1.83) regarding "lymphatic invasion" as a prognostic factor indicates bad prognosis as the multivariate analysis (HR= 1.29; 95% CI; 0.89-1.69) also indicate the same (figure 4).

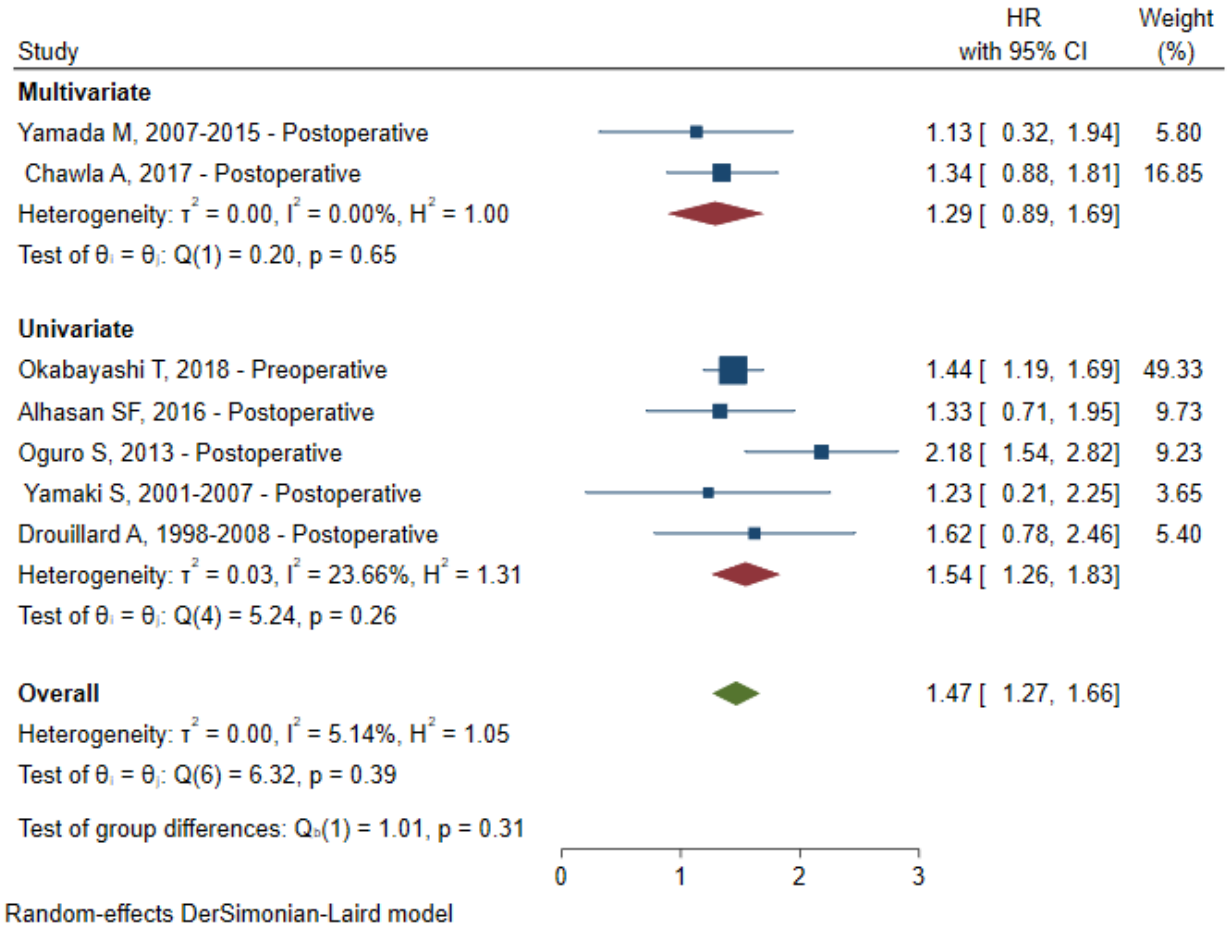

Figure 4 Forest plot for survival outcomes of (lymphatic invasion) among pancreatic adenocarcinoma patients.

Vascular invasion

Twelve studies with total patients 4665 were reviewed and analyzed to conclude that there is an articulated sign of poor prognosis in the two subgroups as the univariate analyses (HR= 1.33; 95% CI; 1.04-1.62) and the multivariate analyses (HR= 1.55; 95% CI; 1.04-2.05) (figure 5).

Duodenal invasion

Multivariate and univariate analyses in these four studies were pursued on 1636 patients, and the results were (HR= 1.17; 95% CI; 0.95-1.38) and (HR= 1.72; 95% CI; 1.23-2.20) respectively, and they both show bad outcome (figure 6).

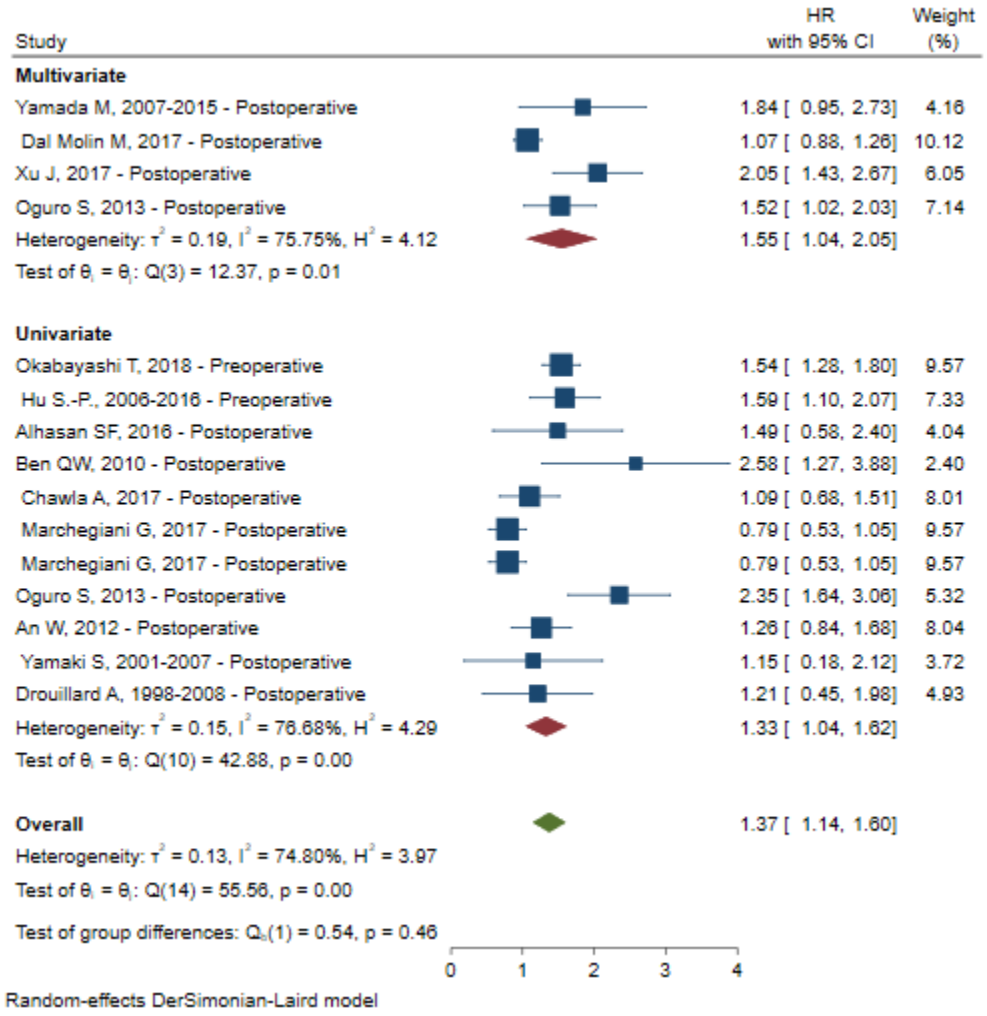

Figure 5 Forest plot for survival outcomes of (Vascular invasion) among pancreatic adenocarcinoma patients.

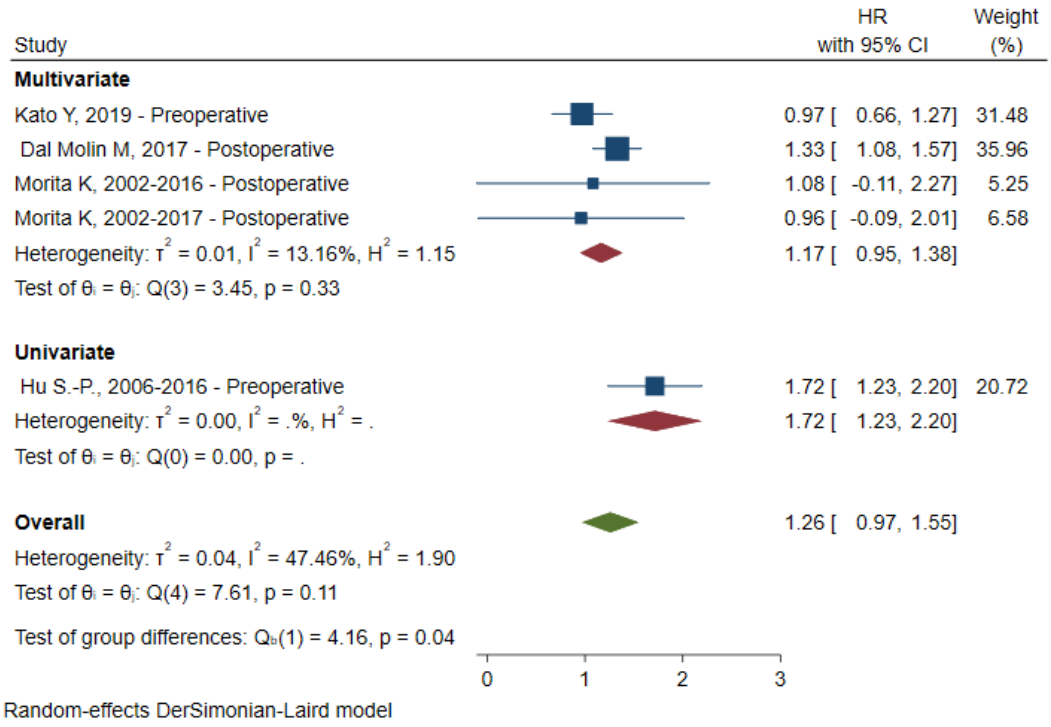

Figure 6 Forest plot for survival outcomes of (duodenal invasion) among pancreatic adenocarcinoma patients.

Lymphovascular invasion

Six studies with total of 2112 patients were resolved. "Lymphovascular invasion" as an independent prognostic factor was taken in account, and the following outcomes were found; multivariate analysis (HR= 2.08; 95% CI; 0.38-3.79), univariate analysis (HR= 1.36; 95% CI; 1.10-1.63), with an indication of poor prognosis in both subgroups (figure 7).

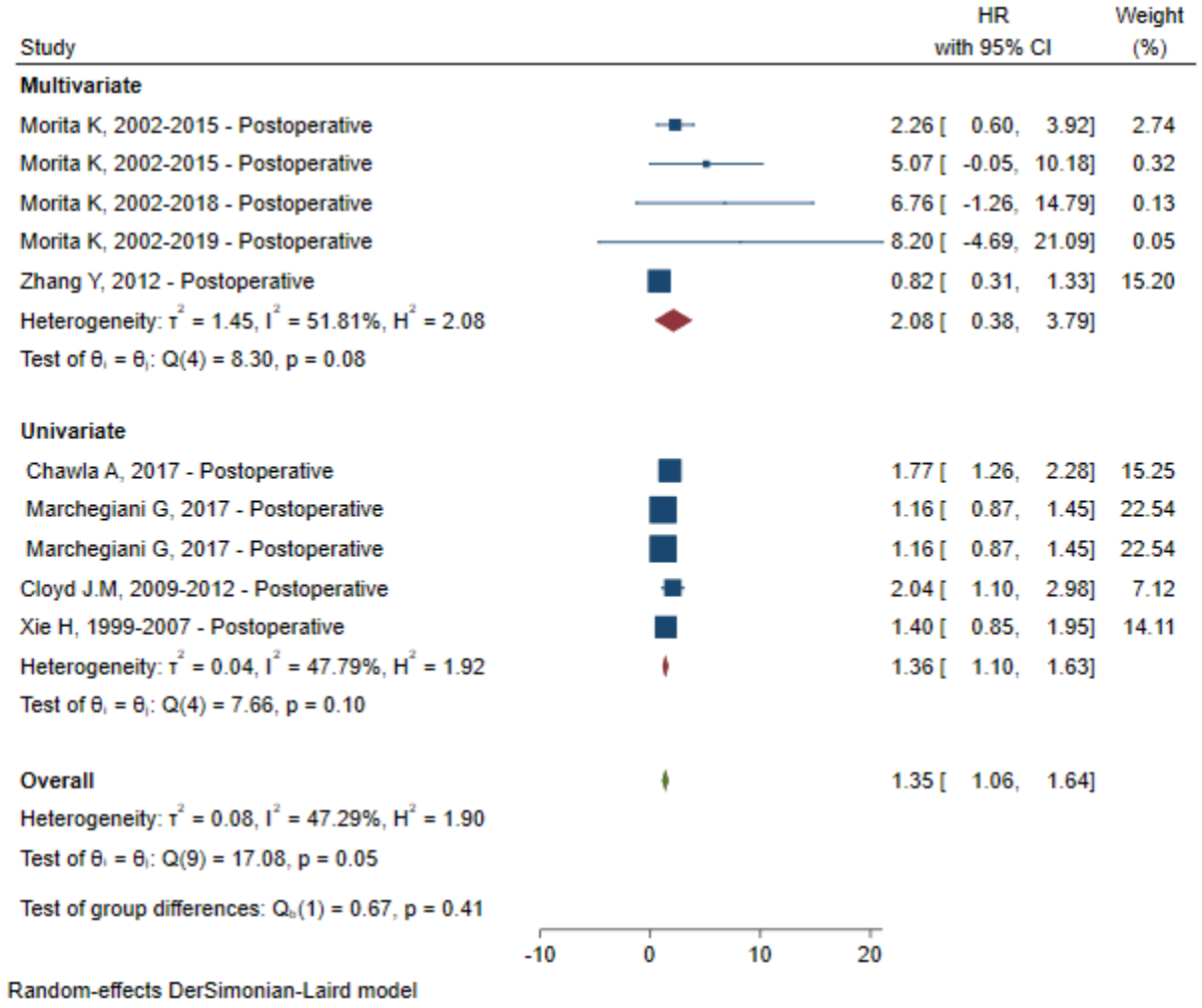

Figure 7 Forest plot for survival outcomes of (lymphovascular invasion) among pancreatic adenocarcinoma patients.

Marginal invasion

Nine studies with a total of 1425 patients were collectively analyzed regarding "Marginal involvement" as a prognostic factor, and the following results were detected; the multivariate analyses (HR= 1.00; 95% CI; 0.24-1.75), the univariate analyses (HR= 1.54; 95% CI; 1.31-1.77) and inclusively there's a reference of poor prognosis in the aggregate results (figure 8).

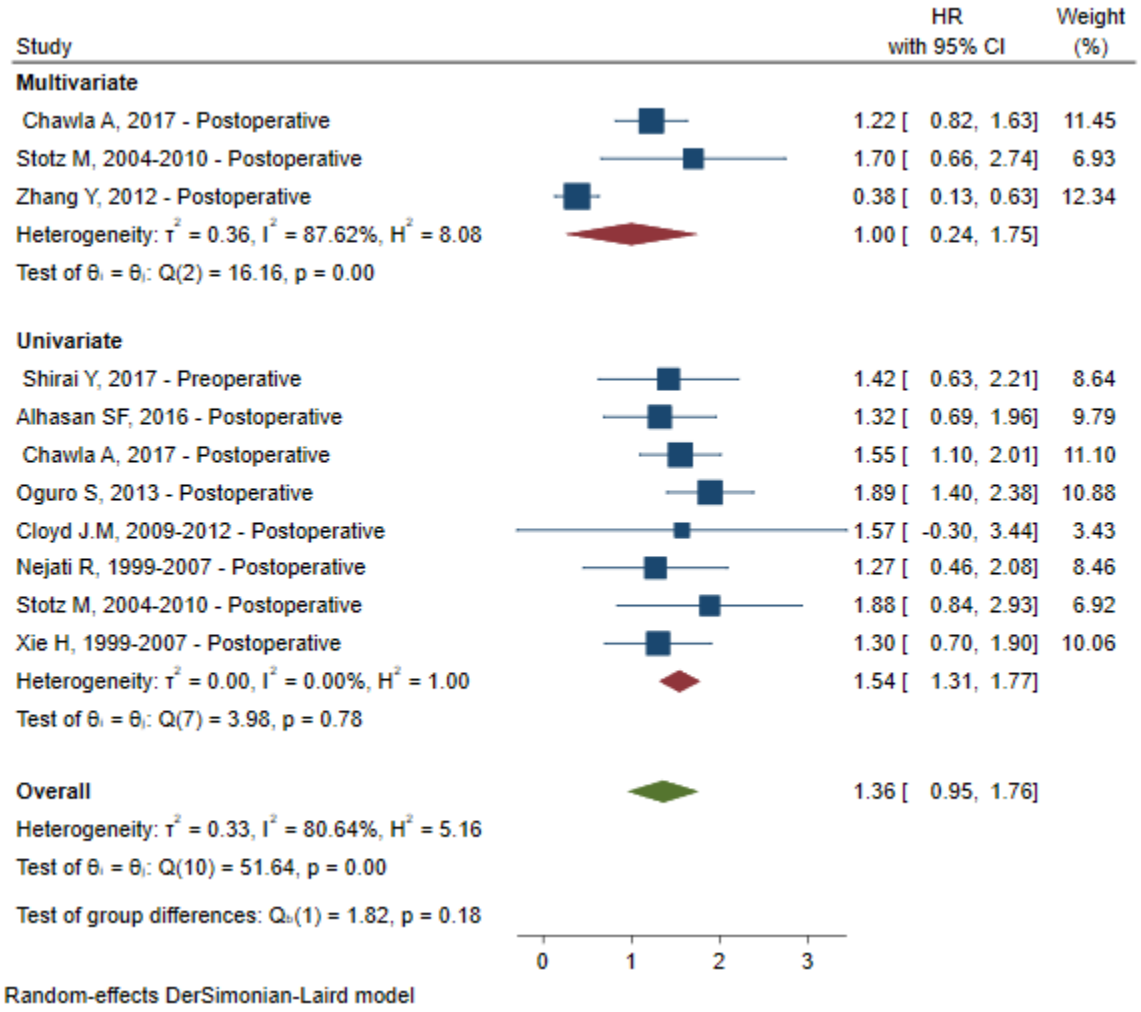

Figure 8 Forest plot for survival outcomes of (marginal invasion) among pancreatic adenocarcinoma patients.

Neutrophil to lymphocyte ratio (NLR)

As for NLR as an independent prognostic factor, ten studies were run on 2465 patients comparing two subgroups; univariate analyses (HR= 1.39; 95% CI; 1.21-1.56), multivariate analyses (HR= 1.11; 95% CI; 1.03-1.19) and they show bad outcomes in both subgroups (figure 9).

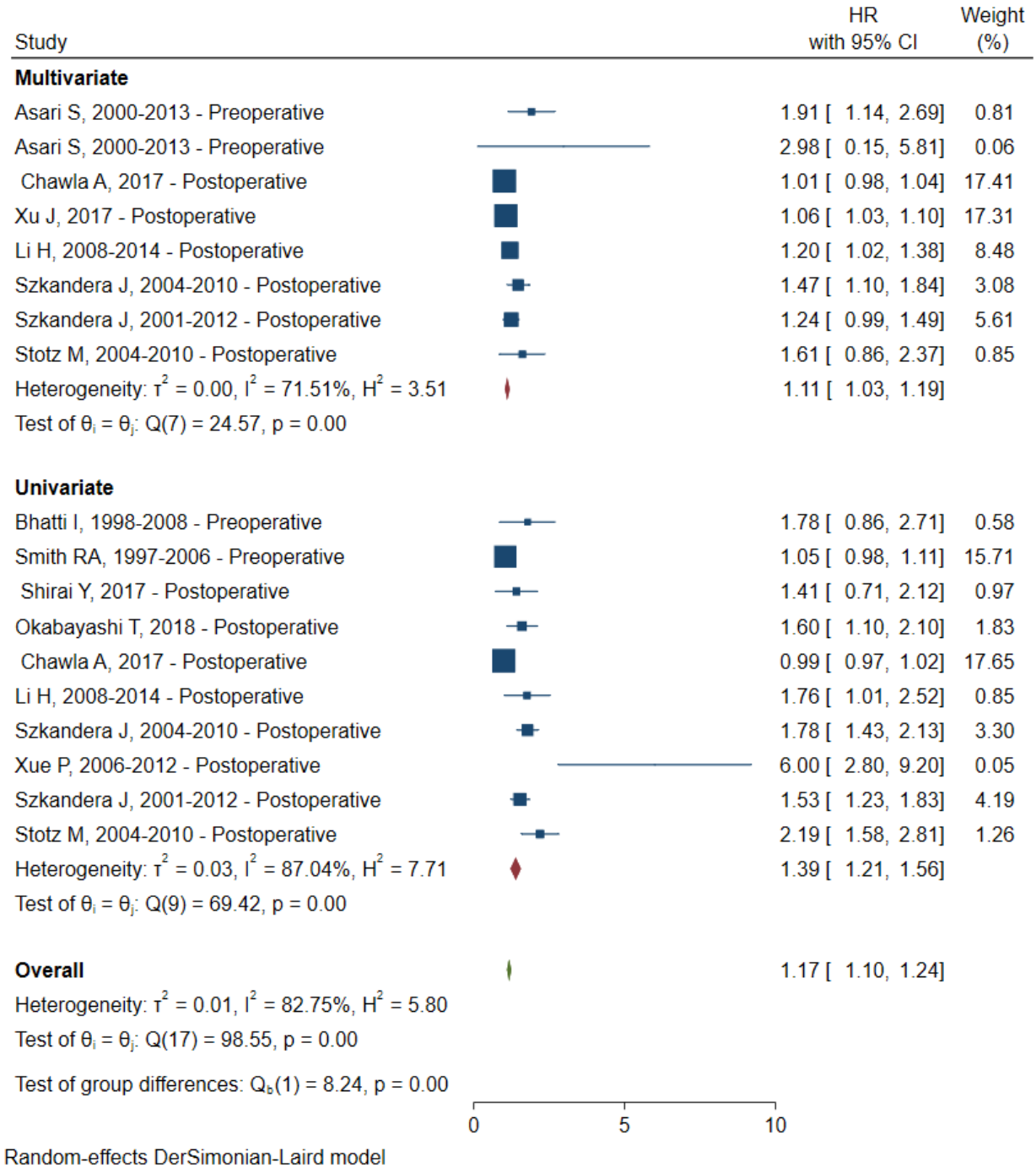

Figure 9 Forest plot for survival outcomes of (NLR) among pancreatic adenocarcinoma patients.

Lymphocyte to Monocyte ratio (LMR)

LMR was included in 3 studies with a total of 842 patients. The analysis held a comparison between two subgroups that showed good prognosis in both; the univariate analyses (HR= 0.62; 95% CI; 0.43-0.81), the multivariate analyses (HR= 0.83; 95% CI; 0.74-0.93) (figure 10).

Platelet to Lymphocyte ratio (PLR)

Eleven studies involved 2168 patients and showed that; the univariate analyses (HR= 1.87; 95% CI; 1.47-2.27), the multivariate analyses (HR= 1.04; 95% CI; 0.95-1.13) and they indicated worse prognosis in both subsets (figure 11).

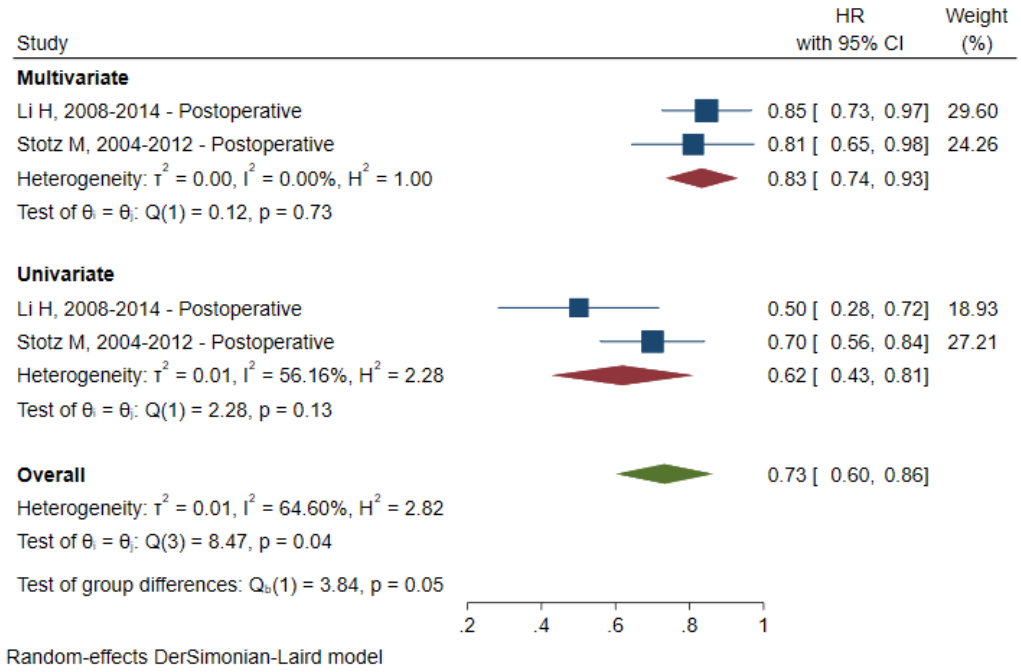

Figure 10 Forest plot for survival outcomes of (LMR) among pancreatic adenocarcinoma patients.

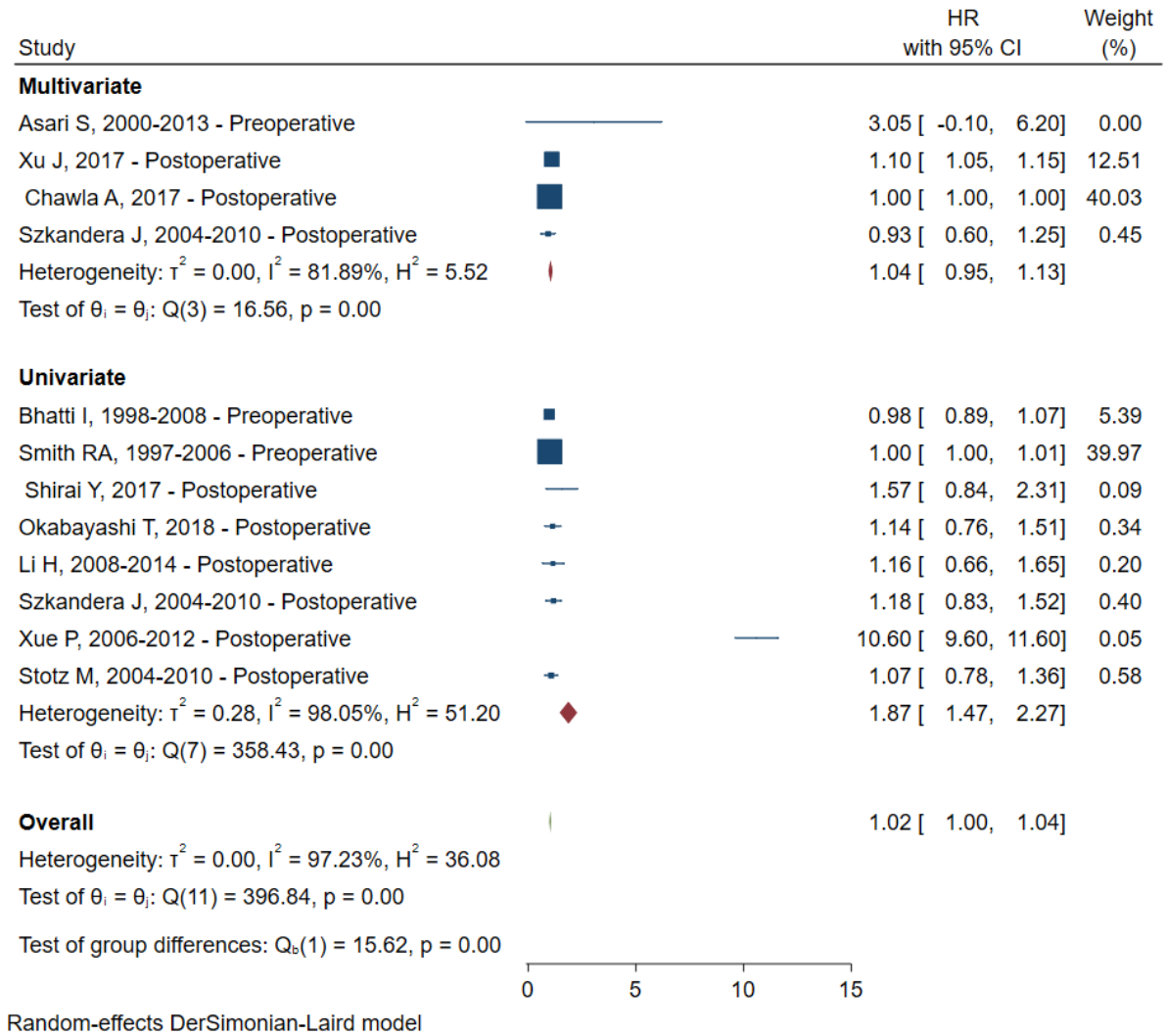

Figure 11 Forest plot for survival outcomes of (PLR) among pancreatic adenocarcinoma patients.

Lymphocyte count

Pre-operative lymphocyte count was discussed and analyzed in two studies with a total of 194 patients, and the univariate analyses (HR= 1.05; 95% CI; 0.20-1.91) was concluded with a sign of poor prognosis (figure 12).

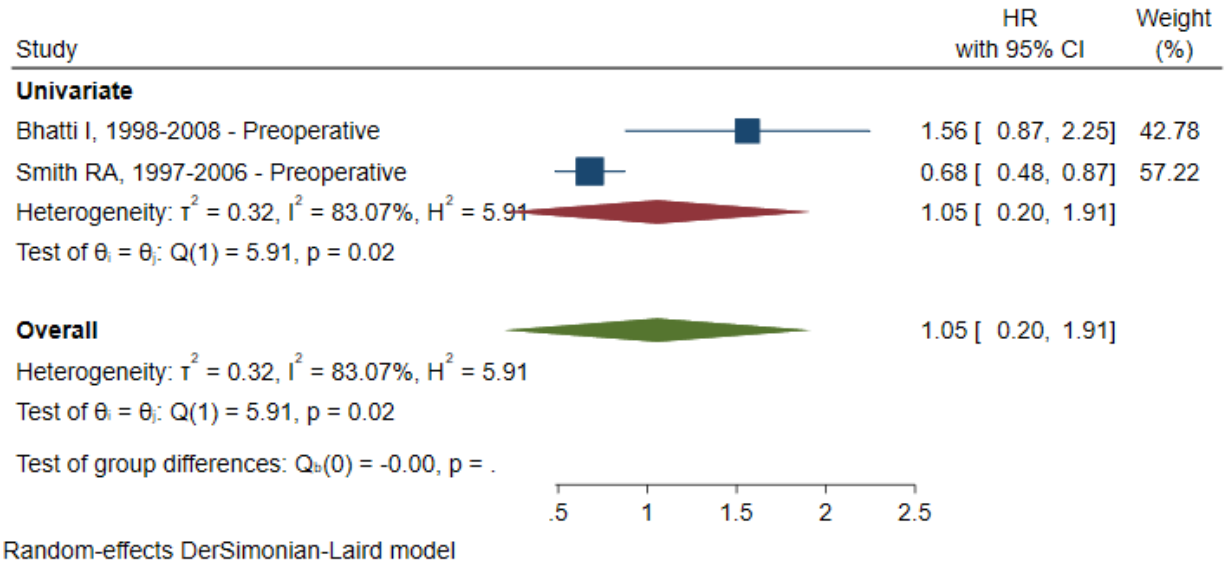

Figure 12 Forest plot for survival outcomes of (lymphocyte count) among pancreatic adenocarcinoma patients.

Neutrophil count

Three studies with a total of 282 patients in which pre-operative neutrophil count was included, and we concluded the following; the univariate analyses (HR= 1.03; 95% CI; 0.96-1.12), multivariate analyses (HR= 2.94; 95% CI; 0.18-5.70) and they both show bad prognosis (figure 13).

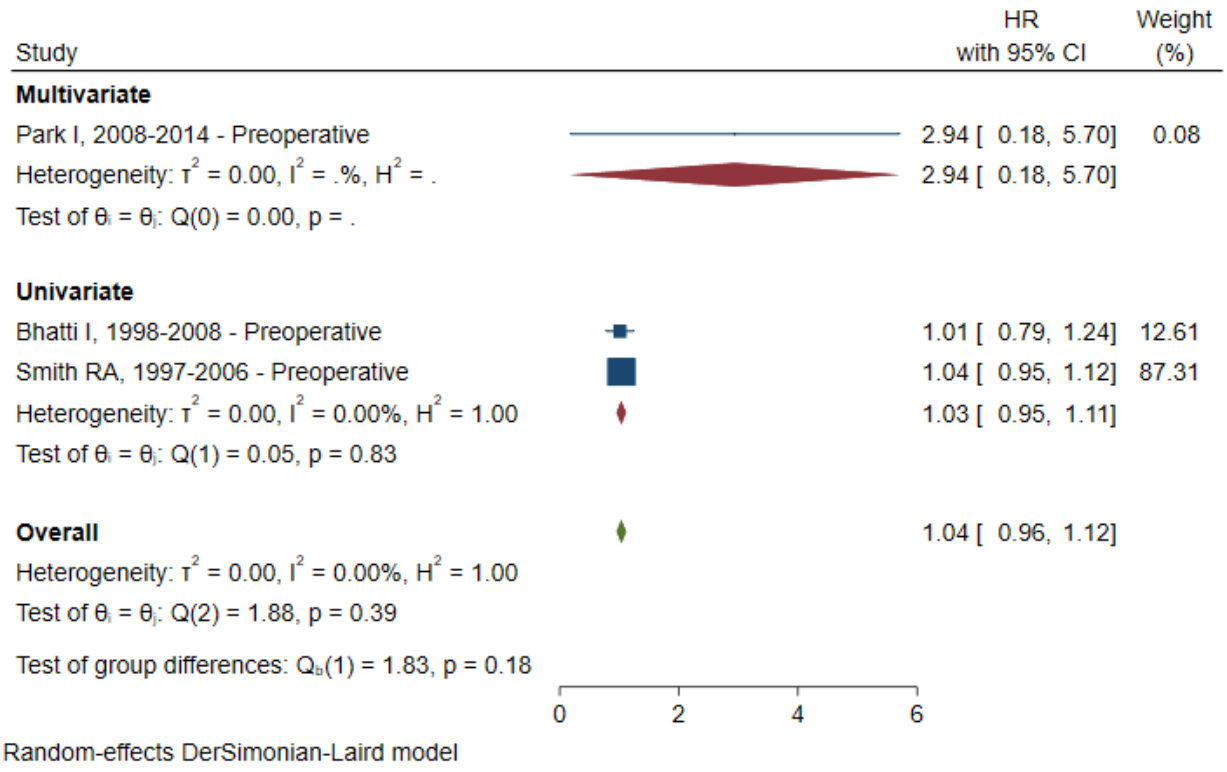

Figure 13 Forest plot for survival outcomes of (neutrophil count) among pancreatic adenocarcinoma patients.

Publication bias

The publication bias of the included studies was evaluated by funnel plots. Visual publication bias was established, as shown in Figure 14. This indicated that the asymmetry of the funnel plots might have arisen through heterogeneity. The funnel plots showed an asymmetrical distribution for some prognostic parameters among the studies, revealing that publication bias might exist.

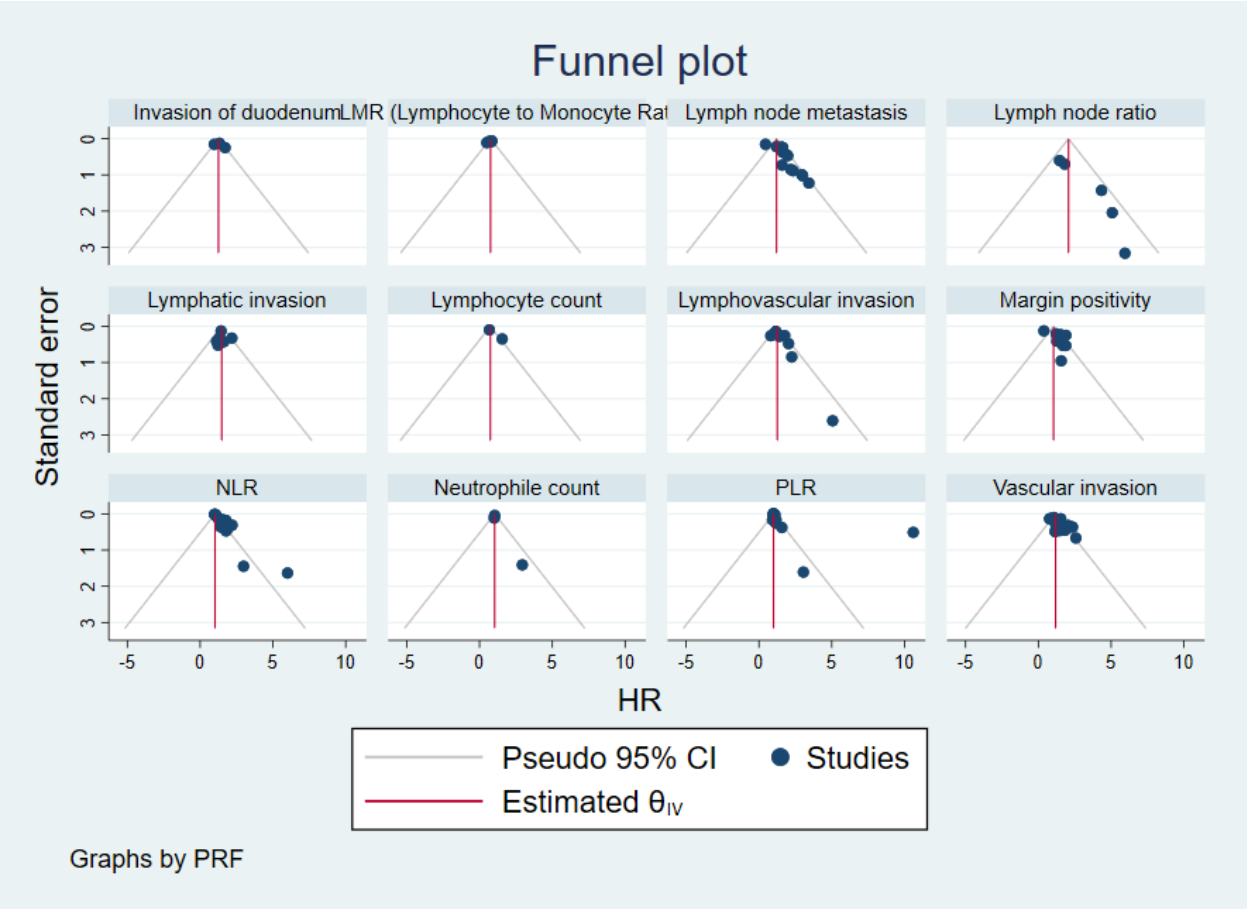

Figure 14 Funnel plots of the included studies of each prognostic factor.

4. DISCUSSION

Pancreatic cancer remains one of the leading causes of cancer-related mortality; with pancreatic ductal adenocarcinoma (PDAC) being the main histological type of resected specimens (Kanda et al., 2011). PDAC is one of the slow-growing tumors and is associated with poor prognosis. This meta-analysis aimed to pool all the prognostic factors with their associate pre-operative and post-operative characteristics and to compare between the univariate and multivariate analyses. After the search process, 32 studies with 7779 patients were included in the quantitative data synthesis. It showed that each prognostic factor portends a worse prognosis in any case of which the hazard ratios and their associated 95% CIs were deliberated from multivariate or univariate analyses in patients who underwent various types of surgery (pancreatoduodenectomy, distal resection, and total pancreatectomy) either preoperatively or postoperatively.

We found that the majority of the screened prognostic factors are of poor prognosis to pancreatic cancer patients according to the multivariate analyses as follow; lymph node metastasis (HR= 1.61; 95% CI; 1.01-2.22), lymph node ratio (HR= 2.63; 95% CI; 1.23-6.50), lymphatic invasion (HR= 1.29; 95% CI; 0.89-1.69), Lymphovascular invasion (HR= 2.08; 95% CI; 0.38-3.79), vascular invasion (HR= 1.55; 95% CI; 1.04-2.25), duodenal invasion (HR= 1.17; 95% CI; 0.95-1.38), NLR (HR= 1.11; 95% CI; 1.03-1.19), PLR (HR= 1.04; 95% CI; 0.95-1.13), neutrophil count (HR= 2.94; 95% CI; 0.18-5.70). On the other hand high LMR as a prognostic factor showed a good prognosis in patients with PC (HR= 0.83; 95% CI; 0.74-0.93) and the marginal invasion was a poor indicator with (HR= 1.00; 95% CI; 0.24-1.75).

Lymph node (LN) metastasis has been reported in 35%-60% of patients with pancreatic cancer, it is considered to be an important prognostic factor, and the prognosis of patients with LN metastasis was significantly poorer than that of patients without LN metastasis (John et al., 2013). This is consistent with our meta-analysis findings as to the pooled HR in multivariate analyses

(HR= 1.61; 95% CI; 1.01-2.22). Lymph node ratio (LNR) is the ratio of the number of positive nodes to the total number of nodes evaluated (Elshaer et al., 2017). Zhou et al., (2017) conducted a systematic review of 19 studies, and they found that the lymph node ratio was significantly associated with poor overall survival in 17 out of total articles. Our meta-analysis revealed similar outcomes as the HR in the multivariate analyses (HR= 2.63; 95% CI; 1.23-6.50).

A meta-analysis which was conducted by Chen et al., (2010) has reported that poor prognosis is related to the fact that many patients present with advanced disease at the time of surgery, as reflected by the high incidence of lymph node metastasis (43%) and lymphatic invasion (52%). Another study supported that the absence of lymphovascular invasion was associated with improved survival (Geer et al., 1993). As in the prior reports, we also recorded "lymphovascular invasion" as a robust prognostic factor in pancreatic cancer patients, HR in multivariate analyses (HR= 2.08; 95% CI; 0.38-3.79). Vascular invasion is regarded to be a strong predictor for prognosis. It is the most significant indicator of poor prognosis after local resection in pancreatic cancer patients (Berardi et al., 2013). A systematic review by Berardi et al. held a comparison between the effect of the absence and presence of vascular invasion in pancreatic cancer patients and found that; the median survival in tumors with vascular invasion is 11.9 months and 20.6 months in its absence. It also supported that vascular invasion is accountable for metastatic recurrence of the disease and consequently related to a greater influence on survival (Tanaka et al., 2007). Our meta-synthesis supported the previous findings with significant pooled HR in the multivariate analyses (HR= 1.55; 95% CI; 1.04-2.25).

A study reported that among pancreatic cancer patients, 35.7% of patients were suffering from duodenal infiltration (Lee et al., 1994), and 2.6% of the patients have gastrointestinal bleeding as an initial manifestation (Mouaqit et al., 2013). The other studies revealed the seriousness of the conditions in two points; (a) in many cases, not even biopsy can differentiate with certitude that the duodenal invasion is caused by a pancreatic tumor or vice versa (Chang et al., 2016), (b) many authors supported that duodenal invasion significantly decrease the survival rate in pancreatic neoplasms (S.I et al., 2010). We also found that duodenal invasion as a prognostic factor in pancreatic cancer patients indicates poor prognosis (HR= 1.17; 95% CI; 0.95-1.38).

The accurate mechanisms that explain the relationship between high NLR and PLR values and poor prognosis in pancreatic cancer patients are obscure. Systemic inflammation has a conclusive role in the development of neoplasms at different stages, including starting, promotion, malignant transformation, infiltration, and metastasis (Oh et al., 2018). A meta-analysis by Pollard et al., (2004) concluded that high NLR and PLR are valuable indicators of bad prognosis in patients with pancreatic cancer. These variables can be of a good benefit in identifying high-risk patients and for marking individual treatment strategies. Our meta-analysis also supported that both NLR and PLR are of poor prognosis (HR= 1.11; 95% CI; 1.03-1.19), (HR= 1.04; 95% CI; 0.95-1.13) respectively.

Tumor-associated macrophages (TAMs) are involved in enhancing tumor invasion and angiogenesis; besides, they have immunosuppressive effects on the anti-tumor response of lymphocytes by outputting the growth factors and cytokine (Zikos et al., 2011). On the other hand, CD4+ and CD8+ T lymphocytes have a significant turn in anti-tumor immunity reaction as they induct cytotoxic cell death and prohibit tumor cell multiplication and migration (Rosenberg, 2001; Hu et al., 2018). Thus a meta-analysis by Hu et al., (2018) included ten studies with 2557 patients and indicated the prognostic value of the LMR in pancreatic cancer patients. Low LMR was associated with worse OS (HR: 0.60, 95% CI: 0.50–0.71, $p < 0.001$)(Li et al., 2017). Another narrative review implied that a high LMR is correlated with convenient survival in patients with pancreatic cancer. It also the LMR can be a commonly obtainable prognostic factor of pancreatic cancer in clinical practice (Xiao et al., 2016). Our results came out as a supporter of the previous meta-analyses with a good prognosis of LMR (HR= 0.83; 95% CI; 0.74-0.93).

A retrospective study included 288 pancreatic cancer patients found that neutrophil and lymphocyte counts could be valuable prognostic factors in pancreatic cancer survival, particularly lymphocyte count. Patients who have an aberration in these two blood conductors should be given more concern (Tunners et al., 2019). Our meta-analysis also put the neutrophil count (HR= 2.94; 95% CI; 0.18-5.70) and lymphocyte count (HR= 1.05; 95% CI; 0.20-1.91) in account as important prognostic factors. A retrospective study reported that patients who have R1 resection (marginal invasion are with median OS of 15 months in comparison with 22 months in those who had R0 resection (no marginal invasion) (Tunners et al., 2019). Our meta-analysis found that marginal invasion has no significant effect on the pancreatic cancer prognosis (HR= 1.00; 95% CI; 0.24-1.75).

Limitations

Strength of this review: Since there have been no similar reviews covering twelve highly relevant prognostic factors, strictly following PRISMA guidelines. Using the NOS adds to the strength of this review. The limitations include the fact that different methodologies, analytical models, and cut-off values have been used in the included studies, and we did not include a comparison between the subgroups, overall survival, and disease-free survival. However, the presence of an overall low statistical heterogeneity among each subgroup is an additional strength of the review.

5. CONCLUSION

Our study found that lymph node metastasis, lymph node ratio, lymphovascular invasion, lymphatic invasion, vascular invasion, duodenal invasion, NLR, PLR, neutrophil count, and lymphocyte count are all significant biomarkers of worse prognosis; however, high LMR as an independent prognostic factor indicates good prognosis in pancreatic cancer patients. We recommend health care providers to consider the aforementioned outcomes while assessing the prognosis among pancreatic adenocarcinoma patients.

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Authors' contributions

Dr. Ahmed Tabaan Alenezi, setting the study design, research objectives, data collection plan, data entry and conducted the statistical analysis, write the results, write up and revising of the manuscript. The author read and approved the final manuscript.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Data and materials availability

All data associated with this study are present in the paper.

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