

Prognostic value of PD-L1 expression in patients with pancreatic cancer

A PRISMA-compliant meta-analysis

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Abstract

Background: Programmed cell death ligand 1 (PD-L1) expression was reported to be associated with poor prognosis in various solid tumors. However, the prognosis value of PD-L1 in pancreatic cancer remained inconclusive. We performed a meta-analysis to assess the clinical value of PD-L1 as a novel prognostic biomarker of pancreatic cancer.

Methods: PubMed, Embase, and Web of Science were searched up to October 2018. The HRs and 95% CIs for overall survival (OS) and cancer-specific survival (CSS) according to the expressional status of PD-L1 were pooled. The combined odd ratios (ORs) and 95% CIs were utilized to assess the association between PD-L1 and clinicopathological characteristics.

Results: A total of 9 studies with 993 patients were included. Elevated PD-L1 expression was related with poor OS (HR = 1.63, 95% CI = 1.34–1.98, $P < .001$) and CSS (HR = 1.86, 95% CI = 1.34–2.57, $P < .001$). Furthermore, high PD-L1 expression was also demonstrated to be associated with positive N stage (OR = 1.81, 95% CI = 1.21–2.71, $P = .004$), advanced T stage (OR = 1.86, 95% CI = 1.08–3.19, $P = .025$), and low differentiation (OR = 2.24, 95% CI = 1.16–4.33, $P = .017$). However, PD-L1 has nonsignificant correlation with M stage, gender, or age.

Conclusion: This study suggests that PD-L1 is a potential prognostic biomarker and may be helpful to clinicians aiming to select the appropriate immunotherapy for pancreatic cancer.

Abbreviations: CSS = cancer-specific survival, IHC = immunohistochemistry, OR = odd ratio, OS = overall survival, PD-1 = programmed cell death 1, PD-L1 = programmed cell death ligand 1, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Keywords: clinical features, meta-analysis, pancreatic cancer, PD-L1, survival

1. Introduction

Pancreatic cancer is a highly lethal malignancy with 5-year survival rate as low as 6%.^[1] Pancreatic cancer is the seventh leading cause of cancer-related death both in men and women worldwide.^[2] Therapeutic strategies of pancreatic cancer include surgery, chemotherapy, radiotherapy, and palliative care. Although treatment techniques have been developed in recent

years, the prognosis of pancreatic cancer is not significantly improved. To date, a group of prognostic factors are identified for clinical management of pancreatic cancer.^[3–5] However, these markers are lack of accuracy to predict and are not widely adopted. Therefore, it is still important to find out novel and available prognostic biomarkers for patients with pancreatic cancer.

Programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway plays an important role in cancer immune editing.^[6,7] In the tumor microenvironment, cancer cells and infiltrating immune cells express PD-L1,^[8,9] which can combine with PD-1 on T cells and then suppress the proliferative and effector responses of T cells. Blockade of PD-L1 is a prevalent strategy of cancer immunotherapy,^[10,11] which is called immune checkpoint inhibitors.^[9] Previous studies reported the prognostic significance of PD-L1 expression in malignant solid tumors including breast cancer,^[12] gastric cancer,^[13] hepatocellular carcinoma,^[14] non-small cell lung cancer,^[15] and renal cell carcinoma.^[16] A number of studies also investigated the association of PD-L1 and prognosis of pancreatic cancer,^[17–21] with controversial results presented. For example, Nomi et al reported PD-L1 overexpression as a prognostic factor of poor overall survival (OS) ($P = .016$) in patients with pancreatic cancer receiving surgery.^[17] However, other studies showed nonsignificant prognostic value of PD-L1 in pancreatic cancer.^[20,22,23] In the present study, a meta-analysis was carried out to assess the correlation between PD-L1 expression and survival outcomes and clinicopathological characteristics in pancreatic cancer patients.

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2. Materials and methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.^[24] An ethical approval was not necessary since meta-analysis was based on secondary data.

2.1. Search strategy

Electronic databases of PubMed, Embase, and Web of Science were searched. Different combinations of the following keywords were used: “PD-L1”, “programmed cell death ligand 1”, “B7-H1”, “CD274”, “pancreatic neoplasm”, “pancreatic cancer”, “prognosis”, “prognostic,” and “outcome”. The last search was up to October 2018. References of the retrieved studies were also manually searched for possible inclusions.

2.2. Selection criteria

Inclusion criteria were as follows:

- (1) immunohistochemistry (IHC) was used to measure PD-L1 expression in pancreatic tissues;
- (2) studies focus on pancreatic cancer;
- (3) studies evaluating the relationship between PD-L1 and survival outcomes and/or clinical features. If survival outcomes were not directly provided, enough information was given to compute the HR and 95% CI by using Tierney's method^[25];
- (4) English articles.

Studies were excluded by the following exclusion criteria:

- (1) reviews, conference abstracts, or letters;
- (2) using other method than IHC to detect PD-L1;
- (3) overlapping studies.

Cancer-specific survival (CSS) was defined as the period from the time of surgery to patient death of pancreatic cancer. OS was defined as the period from the time of surgery to patient death of any cause.

2.3. Data extraction and quality assessment

Two investigators independently reviewed eligible articles and extracted information as follows: name of first author, publication year, country, number of cases, age, tumor stage, treatment, detection method, pathologic data, and survival outcomes. Disagreements between the two authors were resolved through discussion. Quality assessment of included studies was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS) checklist.^[26] The maximum score of NOS is 9 points and studies with a score ≥ 6 are considered high-quality studies.

2.4. Statistical analysis

The HRs and 95% CIs for OS and CSS according to the expressional status of PD-L1 were pooled. Moreover, the combined odd ratios (ORs) and 95% CIs were utilized to assess the association between PD-L1 and clinicopathological characteristics. Statistical heterogeneity among studies was assessed using Cochran's Q test and Higgins I^2 statistic. A P value $< .1$ or an $I^2 > 50\%$ indicated significant heterogeneity among studies; in this case, a random-effects model was used. Otherwise, a fixed-effects model was selected. Publication bias was measured using Begg's funnel plots. Statistical analyses were performed with

Stata 12.0 software (Stata Corporation, College Station, TX). A P -value $< .05$ was considered statistically significant.

3. Results

3.1. Study characteristics

A total of 230 studies were identified through database searching. After duplicates were removed, 154 studies were screened by title and abstract and 139 records were further excluded. The remaining 15 studies were examined by reading full-texts. Eight studies were removed with reasons and 7 studies were eligible (Fig. 1). Moreover, the updated search found another 2 eligible studies. At last, 9 studies^[17–23,27,28] were included in meta-analysis. The detailed information of the included studies was shown in Table 1. Five studies were from China,^[18,19,23,27,28] three were from Japan,^[17,21,22] and one was from United States.^[20] The total sample size was 993, ranging from 36 to 373. Eight studies^[17,19–23,27,28] investigated the prognostic role of PD-L1 for OS and 3 studies^[18,22,27] explored the association between PD-L1 and CSS. They were published between 2007 and 2018. All studies were with a NOS score ≥ 6 .

3.2. Prognostic value of PD-L1 for OS and CSS

Eight studies with a total of 912 patients were included to explore the association between PD-L1 expression and OS. A fixed-effects model was used due to nonsignificant heterogeneity ($I^2=0$, $P=.678$; Fig. 2). The pooled HR was 1.63, with 95% CI=1.34–1.98, $P<.001$. The impact of PD-L1 on prognosis of CSS was shown in 3 studies.^[18,22,27] The combined results were: HR=1.86, 95% CI=1.34–2.57, $P<.001$, with nonsignificant heterogeneity ($I^2=0$, $P=.878$; Fig. 3).

3.3. Correlation of PD-L1 expression with clinicopathological characteristics

As shown in Figure 4 and Table 2, the association of PD-L1 and 6 clinicopathological characteristics was investigated through meta-analysis. The pooled data demonstrated that high PD-L1 expression was associated with positive N stage (OR=1.81, 95% CI=1.21–2.71, $P=.004$; fixed effect), advanced T stage (OR=1.86, 95% CI=1.08–3.19, $P=.025$; fixed effect), and low differentiation (OR=2.24, 95% CI=1.16–4.33, $P=.017$; fixed effect). However, PD-L1 has nonsignificant correlation with gender (OR=1.76, 95% CI=0.92–3.35, $P=.086$; random effect), M stage (OR=1.64, 95% CI=0.84–3.19, $P=.149$; fixed effect), or age (OR=0.62, 95% CI=0.37–1.04, $P=.071$; fixed effect).

3.4. Publication bias

Begg's funnel plots were used for publication bias evaluation. The results were Begg's $P=.902$ for OS and Begg's $P=1$ for CSS (Fig. 5). The data suggested that there was nonsignificant publication bias in this meta-analysis.

4. Discussion

The prognostic value of PD-L1 in pancreatic cancer remained inconsistent according to previous studies. By pooling data of 9 relevant studies including 993 patients, this meta-analysis showed that elevated PD-L1 expression was related with poor OS (HR=1.63, 95% CI=1.34–1.98, $P<.001$) and CSS (HR=

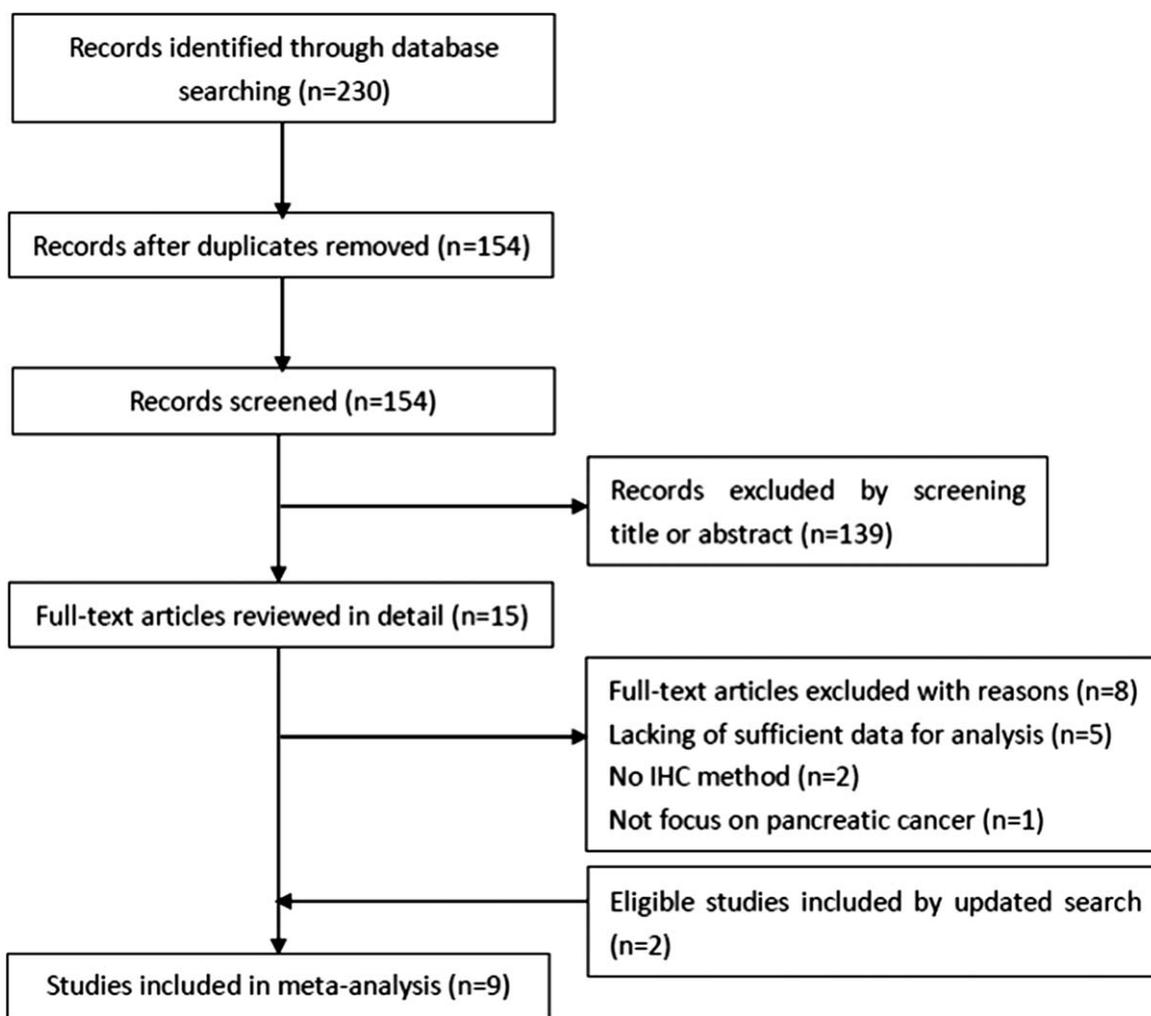


Figure 1. Flow diagram of literature search and study selection.

1.86, 95% CI=1.34–2.57, $P < .001$). Furthermore, high PD-L1 expression was also demonstrated to be associated with positive N stage (OR=1.81, 95% CI=1.21–2.71, $P = .004$), advanced T stage (OR=1.86, 95% CI=1.08–3.19, $P = .025$), and low differentiation (OR=2.24, 95% CI=1.16–4.33, $P = .017$). This meta-analysis suggested that PD-L1 overexpression was a potential biomarker for survival prediction of patients with pancreatic cancer. Those patients with high PD-L1 expression

might be suffering from more aggressive disease because of poor differentiation and advanced stage.

PD-L1, as known as B7-H1, which was first cloned in 1999,^[29] is the ligand of PD-1. PD-L1 is expressed on various cell types, including cancer cells, muscle, mesenchymal stem cells, B cells, T cells, dendritic cells, and placenta.^[30,31] PD-1 is a T-cell immune checkpoint involved in dampening autoimmunity during T-cell activation. In a variety of cancer types, the combination of PD-1

Table 1
Characteristics of included studies.

Study	Year	Country	No. of patients	TNM stage	Age Median (range)	Detection method	Treatment	PD-L1 expression		Survival analysis	NOS score
								Positive	Negative		
Nomi	2007	Japan	51	I–IV	63 (46–73)	IHC	Surgery	20	31	OS	8
Wang	2010	China	81	I–III	55 (34–76)	IHC	Surgery	40	41	CSS	7
Chen	2014	China	63	NA	NA	IHC	Surgery	24	39	OS	6
Hutcheson	2016	USA	158	NA	65 (27–89)	IHC	Surgery	100	58	OS	7
Imai	2017	Japan	36	I–IV	68 (51–89)	IHC	Surgery	11	25	OS, CSS	7
Wang	2017	China	94	I–IV	62 (31–78)	IHC	Surgery	27	67	OS	8
Yamaki	2017	Japan	42	I–IV	65 (50–83)	IHC	Surgery	26	16	OS	7
Liang	2018	China	373	I–IV	61 (29–82)	IHC	Surgery	12	361	OS, CSS	8
Wang	2018	China	95	I–IV	55 (18–76)	IHC	Surgery	48	47	OS	7

CSS=cancer-specific survival, IHC=immunohistochemical staining, NA=not available, NOS=Newcastle–Ottawa Scale, OS=overall survival, PD-L1=programmed cell death ligand 1.

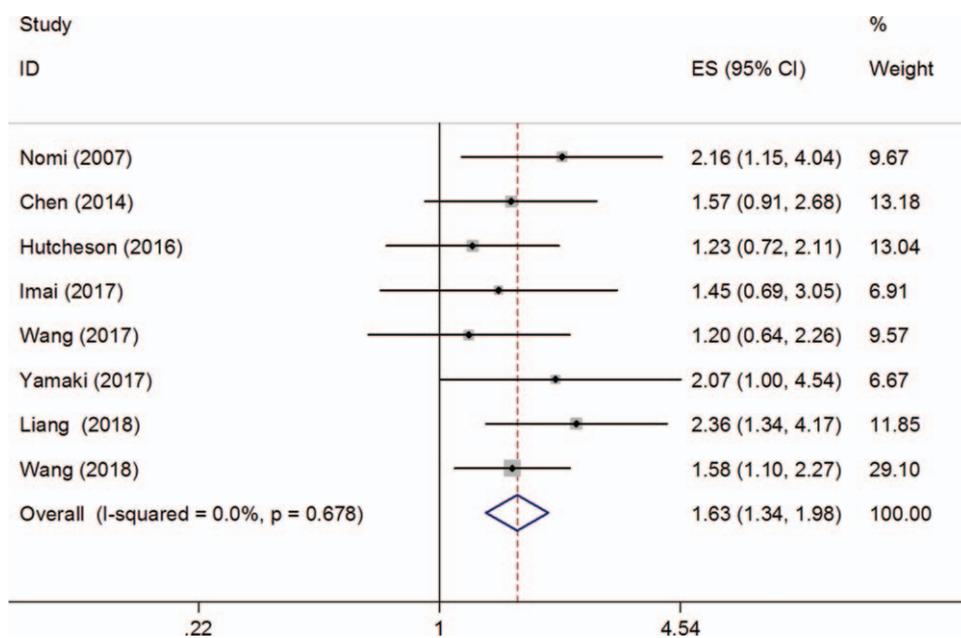


Figure 2. Forest plot describing the association between PD-L1 expression and OS of patients with pancreatic cancer. OS=overall survival, PD-L1=programmed cell death ligand 1.

and PD-L1 generates an immunosuppressive tumor microenvironment and protect cancer cells from T cell cytotoxicity.^[32,33] Binding of PD-L1 to PD-1 facilitates immune escape of tumor cells and results in poor prognosis.^[34] PD-L1 overexpression was observed in multiple solid tumors and hematologic malignancies and was associated with clinical outcomes.^[35–38]

A large number of meta-analyses also investigated the prognostic value of PD-L1 in various types of cancer.^[13,39–44] A recent meta-analysis including 61 studies showed that PD-L1 overexpression was correlated with worse OS in patients with various solid tumors, although the correlations differed according to tumor types.^[43] Wang’s work^[12] suggested PD-L1

overexpression in breast cancer associated with multiple clinicopathological parameters that indicated poor outcomes.^[12] In addition, Dai et al showed that the expression of PD-L1 is associated with worse OS in digestive system cancers, especially in gastric cancer and pancreatic cancer.^[45] However, we noticed that this study on digestive system cancers only included 3 studies of pancreatic cancer and the correlation between PD-L1 and clinicopathological features was not investigated. In our meta-analysis, we included 9 most recent studies and investigated the association between PD-L1 expression and survival outcomes as well as clinical factors in pancreatic cancer. A recent meta-analysis conducted by Zhuan-Sun et al^[46] showed that elevated

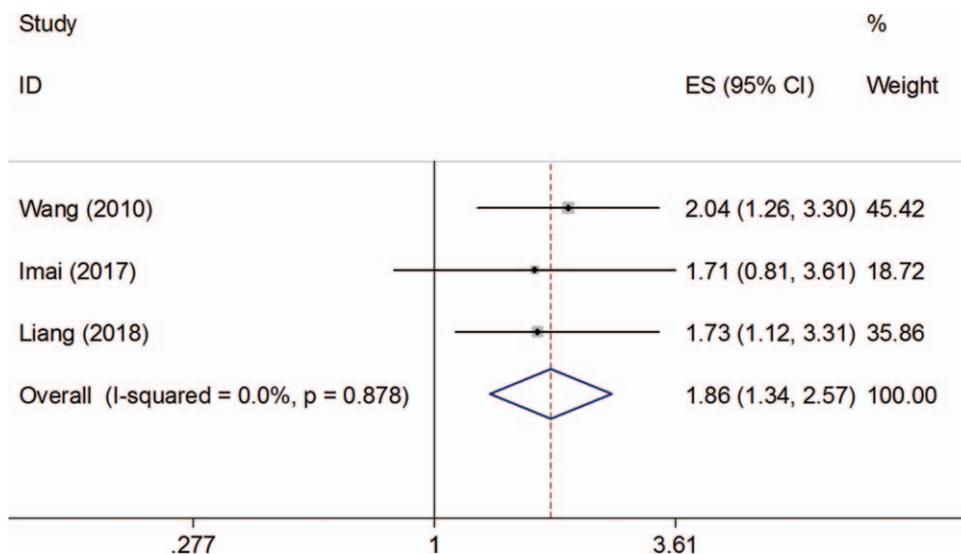


Figure 3. Forest plot describing the association between PD-L1 expression and CSS of patients with pancreatic cancer. CSS=cancer-specific survival, PD-L1=programmed cell death ligand 1.

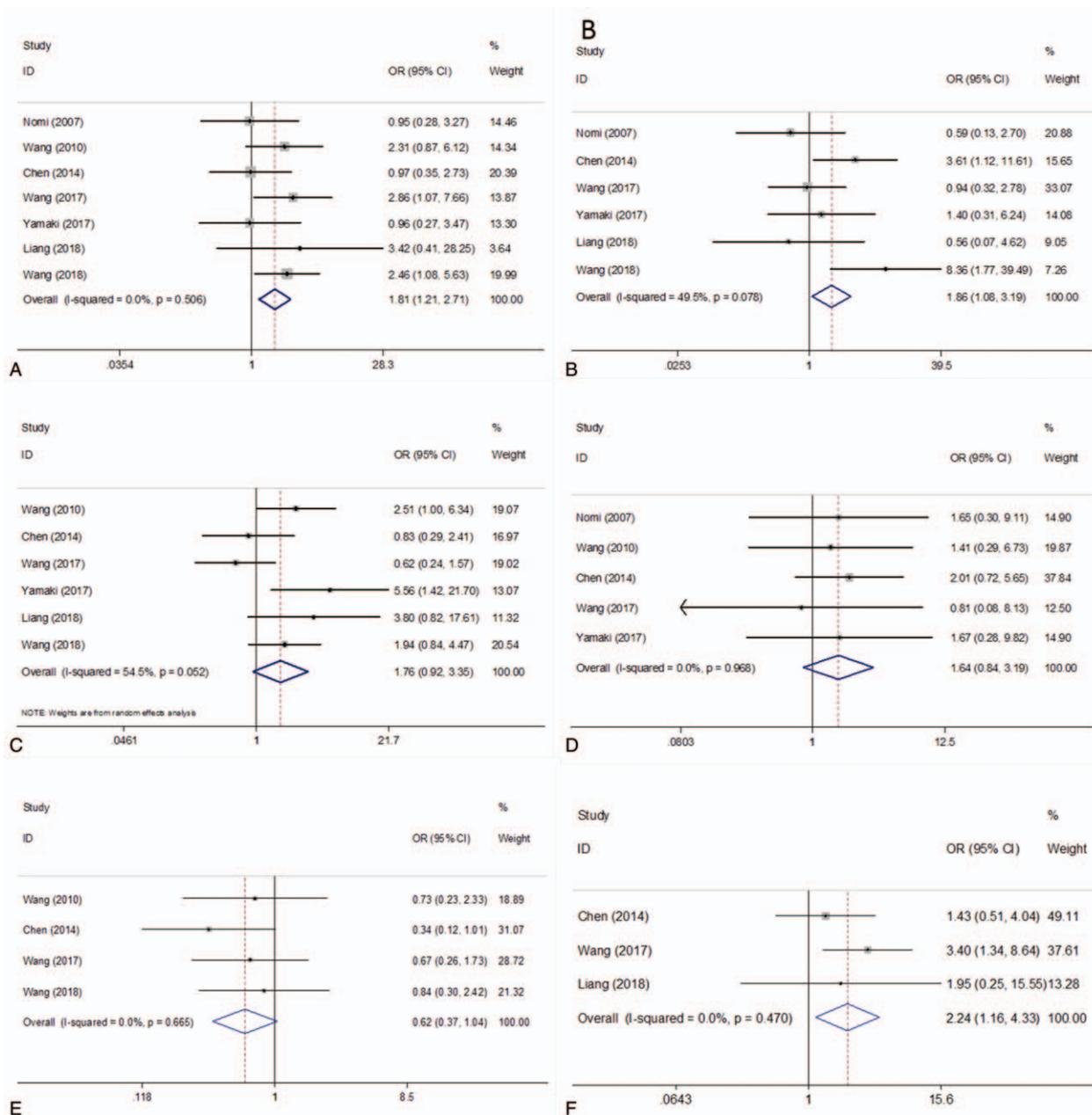


Figure 4. Forest plots for the association between PD-L1 expression and clinicopathological features. (A) N stage, (B) T stage, (C) gender, (D) M stage, (E) age, and (F) differentiation. PD-L1 = programmed cell death ligand 1.

Table 2
Relation between PD-L1 expression and clinicopathological features of pancreatic cancer.

Factors	No. of studies	OR (95% CI)	P	Heterogeneity		Effects model
				I ² (%)	P	
N stage (N1 vs. N0)	7	1.81 (1.21–2.71)	.004	0	.506	Fixed
T stage (T3–T4 vs. T1–T2)	6	1.86 (1.08–3.19)	.025	49.5	.078	Fixed
Gender (male vs. female)	6	1.76 (0.92–3.35)	.086	54.5	.052	Random
M stage (M1 vs. M0)	5	1.64 (0.84–3.19)	.149	0	.968	Fixed
Age (≥60 vs. <60)	4	0.62 (0.37–1.04)	.071	0	.665	Fixed
Differentiation (low vs. high/moderate)	3	2.24 (1.16–4.33)	.017	0	.470	Fixed

PD-L1 = programmed cell death ligand 1, OR = odd ratio.

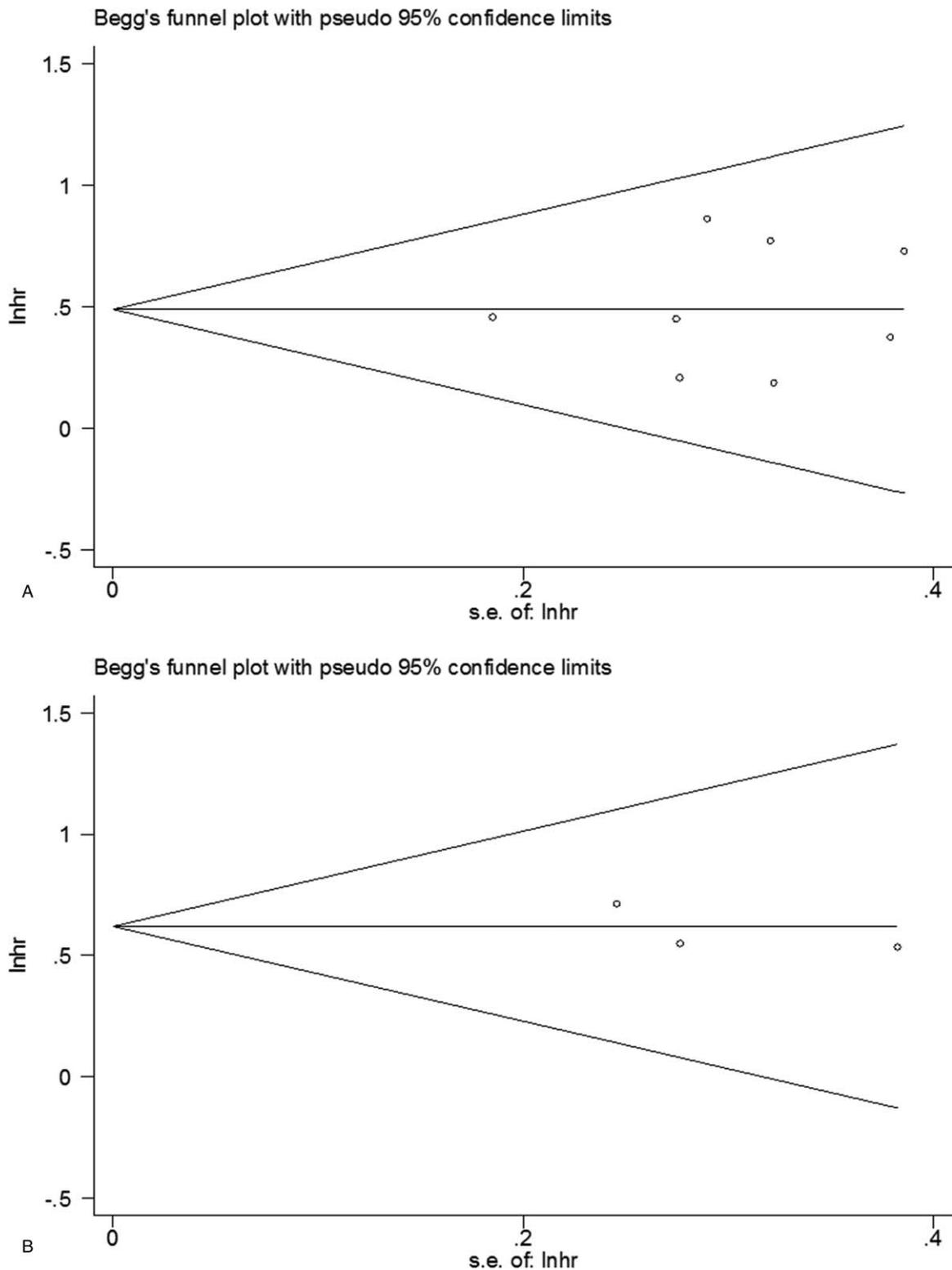


Figure 5. Publication bias test for (A) OS and (B) CSS. CSS=cancer-specific survival, OS=overall survival.

PD-L1 expression was associated with poor OS in pancreatic cancer. Zhuan-Sun's work was performed according to PRISMA guideline. Zhuan-Sun's study included eligible studies up to March 21, 2017 without language restriction. Compared with Zhuan-Sun's study, the present meta-analysis included eligible

studies up to October 2018 published in English using IHC method. Our study used more strict inclusion criteria and updated data; therefore, the results were more recent.

Several limitations should be noted when interpreting our results. First, the sample size was relatively small. Although 9

studies were included, only 993 patients were recruited. Second, most studies were performed in Asia, especially in China and Japan. Therefore, the results should be treated with caution in non-Asian patients. Third, to guarantee the homogeneity of the meta-analysis, only studies using IHC method were included. Therefore, the results may not be applicable for other types of specimens such as serum. Fourth, only 3 studies were included for CSS analysis, which may undermine the persuasiveness of the results.

In summary, this study demonstrated that high PD-L1 expression was associated with poor OS in patients with pancreatic cancer. Moreover, PD-L1 overexpression was correlated with positive N stage, advanced T stage, and poor tumor differentiation. The results suggest that PD-L1 may be helpful to clinicians aiming to select the appropriate immunotherapy for pancreatic cancer.

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