

Prognostic value of PD-L1 overexpression for pancreatic cancer: evidence from a meta-analysis

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Abstract: Programmed death-ligand 1 (PD-L1) is an immune checkpoint that is often activated in cancer and plays a pivotal role in the initiation and progression of cancer. However, the clinicopathologic significance and prognostic value of PD-L1 in pancreatic cancer (PC) remains controversial. In this study, we conducted a meta-analysis to retrospectively evaluate the relationship between PD-L1 and PC. PubMed and other databases were searched for the clinical studies published up to March 21, 2017, to be included in the meta-analysis. Hazard ratios and their 95% CIs were calculated. Risk ratios (RRs) were extracted to assess the correlations between the clinicopathologic parameters and PD-L1 expression. Ten studies including 1,058 patients were included in the meta-analysis. The pooled results indicated that positive PD-L1 expression was correlated with a poor overall survival outcome in PC patients (hazard ratio = 1.76, 95% CI: 1.43–2.17, $P < 0.00001$). Interestingly, high PD-L1 expression was correlated with poor pathologic differentiation (RR = 1.57, 95% CI: 1.25–1.98, $P = 0.0001$) and neural invasion (RR = 1.30, 95% CI: 1.03–1.64, $P = 0.03$). However, there were no significant correlations between PD-L1 expression and other clinicopathologic characteristics. In summary, our meta-analysis implied that PD-L1 could serve as a negative predictor for the overall survival of PC patients, and high expression of PD-L1 was correlated with poor differentiation and neural invasion, indicating that anti-PD-L1 treatments should be evaluated in PC patients, especially in those who exhibit these two characteristics.

Keywords: pancreatic cancer, programmed death-ligand 1, prognosis, clinicopathologic characteristics, meta-analysis, immune checkpoint

Introduction

Pancreatic cancer (PC) is a lethal malignancy with an overall 5-year relative survival rate of 5%.¹ In 2015, an estimated 90,100 new patients were diagnosed with PC in China, with an estimated 79,400 deaths occurring as a result of delayed diagnosis and treatment resistance.² At the time of clinical diagnosis, most cancers are either locally advanced or metastatic, and surgical resection is very difficult.³ In addition, PC is resistant to radiotherapy and chemotherapy.⁴ One of the reasons that the PC responds poorly to treatment is due to its ability to evade host immune surveillance.⁵ Emerging evidence has shown that the coinhibitory receptors, such as programmed death 1 (PD-1), play a critical role in cancer immunoediting.⁶

Programmed death-ligand 1 (PD-L1 or B7-H1), the major ligand for PD-1, plays a crucial role in PD-1-dependent immune suppression, which is mediated by an antigen-specific T-cell response.^{7,8} PD-L1 is expressed on various tumor cells, including PC cells, and immune cells, including activated CD4⁺ and CD8⁺ T cells, dendritic cells, macrophages, and regulatory T cells.^{9–12} PD-L1 is not highly expressed in normal tissues; however, PD-L1 is upregulated in many tumors to attenuate the antitumor

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immune response via downregulating antitumor T-cell activity or suppressing apoptosis.¹³

Accumulating studies related to tumoral PD-L1 have been performed on malignancies, such as esophageal, liver, colorectal, breast, lung, glioblastoma, and blood cancers.^{14–18} However, the prognostic role of PD-L1 is still debated. Overexpression of PD-L1 indicates a poor outcome in gastric cancer and non-small-cell lung cancer;^{19,20} in contrast, a better prognosis was observed in glioblastoma patients.¹⁸ The association between aberrant PD-L1 expression and PC survival has also been evaluated. Due to the relatively small sample sizes, it is necessary to evaluate the association between PD-L1 and the prognosis of PC patients using a meta-analysis of a large cohort of up-to-date reports. In this study, we aimed to conduct a meta-analysis to reveal the association between PC and the clinicopathologic significance and prognostic value of PD-L1.

Materials and methods

Literature search strategy

A literature search was performed up to March 21, 2017, for published articles using the electronic databases PubMed, Web of Science, Scopus, and the Cochrane Library. We also searched the Chinese databases of Wanfang Data, China National Knowledge Infrastructure (CNKI), and SinoMed. Searches were limited to human studies without language restriction. The following terms and their combinations were searched in the title/abstract field: “programmed cell death-ligand 1”, “PD-L1”, “CD274”, “B7-H1”, “pancreatic cancer”, and “pancreatic adenocarcinoma”. We also carried out manual searches of references cited in the retrieved articles and preceding reviews. In addition, we searched meeting abstracts and virtual presentations of the American Society of Clinical Oncology annual meetings and the European Society of Medical Oncology congresses from 2010 to 2017.

Inclusion and exclusion criteria

Qualified studies meeting the following eligibility criteria were included: 1) the histologic target was PC; 2) the association between PD-L1 expression, prognosis, and clinicopathologic features was investigated; 3) the expression of PD-L1 was categorized into high (positive) and low (negative) groups; and 4) relevant information could be acquired from the full-text study. Exclusion criteria included 1) duplicates, ongoing studies, letters, and reviews; 2) studies about PC cell lines, animal experiments, and other types of cancer; 3) studies not about PD-L1; and 4) incomplete data.

Data extraction and outcomes interest

Data from the included studies were acquired and summarized independently by two reviewers (Yongxun Zhuan-Sun and Fengting Huang). Disagreement was resolved by a discussion among the authors. The following information was extracted from the included studies: first author’s name, year of publication, sample size, and survival time.

The primary outcome measure was the relationship between PD-L1 expression and overall survival. The secondary outcomes were the associations between PD-L1 expression and clinicopathologic characteristics.

Quality assessment and statistical analysis

The quality of trials was evaluated by the Newcastle–Ottawa scale,²¹ which consists of three factors: patient selection, comparability, and assessment of outcome. A score of 0–9 (allocated as stars) was allocated to each study; those that achieved six or more stars were considered to be high quality.

All the meta-analyses were performed by Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). We addressed time-to-event outcomes by pooling hazard ratios (HRs) from Cox proportional hazards models. If the article supplied the HR with a 95% CI, we used the data. If the study did not supply the HR with a 95% CI, we calculated the HR and 95% CI according to Kaplan–Meier survival curves using Engauge Digitizer version 4.1 (Engauge Digitizer Software). The data were used following the method proposed by Tierney et al.²² The generic inverse-variance method was performed to summarize the data. Pooled dichotomous data from other secondary outcomes were presented as risk ratios (RRs). Statistical heterogeneity between studies was assessed using chi-square tests with $P < 0.10$ as significance, and heterogeneity was quantified using the I^2 statistic. The random-effects model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was used.

Results

Characteristics of included studies

A total of 10 studies including 1,058 PC patients were used in the final analysis. The initially included studies comprised seven from Asia and three from Europe. All of these studies were cohort studies. Eight articles were published in English and two were in Chinese. PD-L1 expression was examined by immunohistochemistry in eight studies, while the other two studies used quantitative reverse transcription polymerase chain reaction. Based on multivariate analysis, four studies^{23–26} provided HRs with 95% CIs, while another five

studies^{27–31} provided survival curves with which to calculate HRs with 95% CIs. However, the remaining one study³² provided neither survival curves nor HRs with 95% CIs and only provided the correlation between clinicopathologic characteristics and PD-L1 expression. Therefore, it was excluded from the overall survival analysis. The characteristics of the included studies are shown in Table 1.

Effect of PD-L1 expression on the overall survival of PC patients

Nine studies were included. A fixed-effects model was applied in the meta-analysis for the HR, since the heterogeneity analysis showed that there was no significant heterogeneity among the studies ($I^2=0\%$, $P=0.54$). A significant difference was indicated by the pooled HR of 1.76 (95% CI: 1.43–2.17, $P<0.00001$) between high and low PD-L1 expression groups (Figure 1).

Correlation between PD-L1 expression and clinicopathologic characteristics

The clinicopathologic characteristics analyzed included tumor status, pathologic stage (TNM stage), metastatic status,

differentiation, lymph node metastasis, vascular invasion, and neural invasion. Interestingly, high-level PD-L1 expression was correlated with poor differentiation (RR: 1.57, 95% CI: 1.25–1.98, $P=0.0001$) and neural invasion (RR: 1.30, 95% CI: 1.03–1.64, $P=0.03$), whereas other clinicopathologic characteristics were not significantly correlated with PD-L1 expression. The combined RRs for tumor status, pathologic (TNM) stage, metastatic status, lymph node metastasis, and vascular invasion were 1.04 (RR for higher tumor status, 95% CI: 0.85–1.27, $P=0.74$), 1.22 (RR for higher pathologic stage, 95% CI: 0.20–7.64, $P=0.83$), 1.40 (RR for M1, 95% CI: 0.88–2.23, $P=0.16$), 1.09 (RR for lymph node metastasis, 95% CI: 0.97–1.23, $P=0.14$), and 0.96 (RR for vascular invasion, 95% CI: 0.73–1.26, $P=0.76$), respectively (Table 2).

Subgroup analysis

Subsequently, we carried out a subgroup analysis according to the methods detecting the expression of PD-L1. As shown in Figure 2, a statistical significance of the pooled HR was observed in both the subgroup analyzed by polymerase chain reaction (HR: 2.24, 95% CI: 1.53–3.28, $P<0.0001$) and the subgroup analyzed by immunohistochemistry (HR: 1.59,

Table 1 Characteristics of included studies

Study	Region	Cancer type	Method	Cutoff	No of patients		Outcome	Quality score
					PD-L1 high	PD-L1 low		
Birnbaum et al, ²³ 2016	France	PC	qRT-PCR	Mean PD-L1 mRNA expression in normal pancreatic samples	87	366	OS and pathologic features	★★★★★★
Chen et al, ²⁷ 2014	China	PC	IHC	Cases with >10% cells clearly stained were considered to be positive	24	39	OS and pathologic features	★★★★
Chu et al, ³² 2011	China	PC	IHC	Staining score of ≥ 4 was considered to be positive ^a	37	6	Pathologic features	★★★★
Diana et al, ²⁴ 2016	UK	PDAC	IHC	Median score value ^b	41	104	OS and pathologic features	★★★★
Liu et al, ²⁸ 2016	China	PC	IHC	Cases with >10% PD-L1-positive tumor cells were considered to be positive	26	20	OS	★★★
Loos et al, ²⁹ 2008	Germany	PDAC	qRT-PCR	Median PD-L1 mRNA expression level	20	20	OS and pathologic features	★★★
Nomi et al, ³⁰ 2007	Japan	PC	IHC	Specimens with $\geq 10\%$ PD-L1-positive tumor cells were classified as positive	20	31	OS and pathologic features	★★★
Wang et al, ³¹ 2010	China	PC	IHC	Specimens with >5% cells of the total tumor area stained positive were considered to be positive	40	41	OS and pathologic features	★★★
Wang et al, ²⁶ 2017	China	PC	IHC	Staining score of ≥ 6 was considered to be high expression ^a	27	67	OS and pathologic features	★★★★★★
Yamaki et al, ²⁵ 2017	Japan	PDAC	IHC	The threshold value for judging positive PID staining of PD-L1 was set to 3.0	26	16	OS and pathologic features	★★★★★

Notes: ^aPD-L1 staining scores were obtained by multiplying the staining intensities (0, negative; 1, weak; 2, medium; 3, strong) and the percentage of positive tumor (0, <5%; 1, 5%–25%; 2, 26%–50%; 3, 51%–75%; 4, >75%); ^bScoring was based on the proportion of PD-L1-positive tumor cells: 1, absent cells, 2, <25% cell density, 3, 25%–50% cell density, 4, >50% cell density.

Abbreviations: IHC, immunohistochemistry; OS, overall survival; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

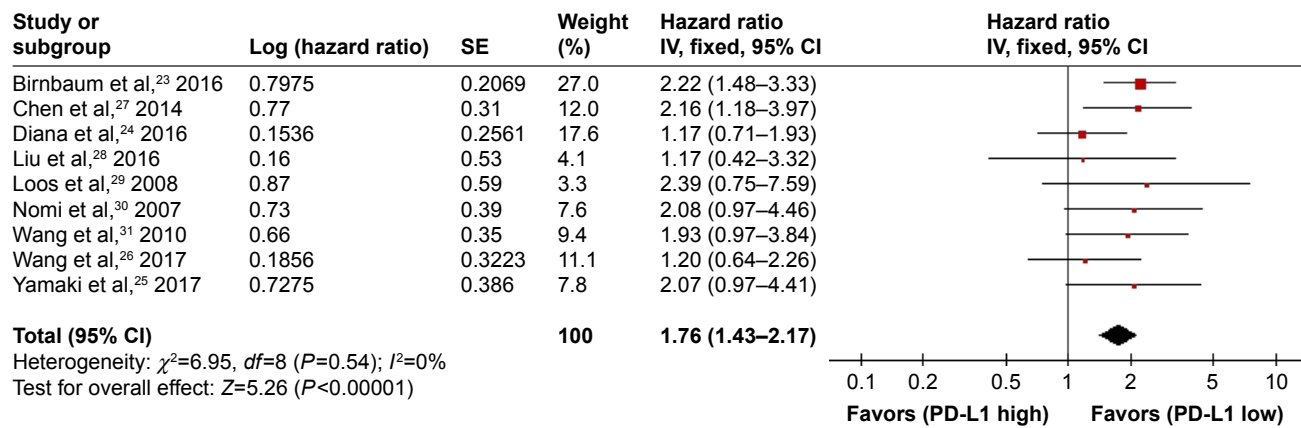


Figure 1 Forest plot and meta-analysis of the overall survival of the PD-L1 high expression group compared with the low expression group. **Note:** High PD-L1 expression was correlated with poorer overall survival in PC patients (HR: 1.76, 95% CI: 1.43–2.17, $P<0.00001$). **Abbreviations:** *df*, degrees of freedom; HR, hazard ratio; IV, generic inverse variance method; PC, pancreatic cancer; PD-L1, programmed death-ligand 1; SE, standard error.

95% CI: 1.23–2.04, $P=0.0003$) between high and low PD-L1 expression groups. The heterogeneity analysis detected no significant heterogeneity ($I^2=0\%$, $P=0.54$).

Publication bias

Figure 3 shows a funnel plot of the studies included in this meta-analysis, which illustrates the overall survival. There was no obvious publication bias.

Discussion

To date, the association between PD-L1 and PC patients remains inconclusive.^{24,30,33} Using meta-analysis, we examined data from a total of 1,058 patients from 10 independent studies.^{23–32} We assessed the clinicopathologic significance and prognostic value of PD-L1 in PC patients. Intriguingly, the pooled results of our analysis showed that positive PD-L1 expression was highly correlated with a poorer overall survival in PC patients. Moreover, high-level PD-L1 expression was correlated with poor differentiation and neural invasion, which is in accordance with a study on lung adenocarcinoma.³⁴

However, the analysis found no significant correlations between PD-L1 expression and other clinicopathologic characteristics, including tumor status, pathologic (TNM) stage, metastatic status, lymph node metastasis, and vascular invasion.

Two previous meta-analyses evaluated the relationship of PD-L1 expression and survival in solid tumors and digestive system cancers, both of which included PC patients with a limited number of studies and participants.^{35,36} Our result was comparable to that of Dai et al who analyzed the survival in PC patients.³⁶ In addition, our data provided more reliable evidence with more participants and a lower publication bias. Moreover, we analyzed the correlations between PD-L1 expression and other clinicopathologic characteristics, which were not included in the two aforementioned meta-analyses.

Smoking contributes to tumor development and progression in various types of cancer, including lung cancer, oral squamous cell carcinoma, and PC.^{37–39} Smoking cessation is one of the most effective strategies to reduce the risk of tumorigenicity. Interestingly, PD-L1 positivity is associated with smoking history in lung cancer and oral squamous cell

Table 2 Meta-analysis: correlation between PD-L1 overexpression and clinicopathologic characteristics

Outcomes of interest	No of studies	No of patients		RR	95% CI of RR	P-value	Study heterogeneity			
		PD-L1 high	PD-L1 low				χ^2	<i>df</i>	I^2 (%)	P-value
Tumor status	6	188	410	1.04	0.85–1.27	0.74	16.1	5	69	0.007
Pathologic stage ^a	3	97	78	1.22	0.20–7.64	0.83	25.3	2	92	<0.00001
Metastatic status	4	97	152	1.40	0.88–2.23	0.16	0.27	3	0	0.97
Differentiation	6	218	406	1.57	1.25–1.98	0.0001	7.41	5	33	0.19
Lymph node metastasis	7	224	414	1.09	0.97–1.23	0.14	8.52	6	30	0.20
Vascular invasion	3	105	176	0.96	0.73–1.26	0.76	1.35	2	0	0.51
Nervous invasion	4	145	217	1.30	1.03–1.64	0.03	3.79	3	21	0.29

Notes: ^aPathologic stage = TNM stage. RR was calculated for TNM stage III–IV. **Abbreviations:** *df*, degrees of freedom; PD-L1, programmed death-ligand 1; RR, risk ratio.

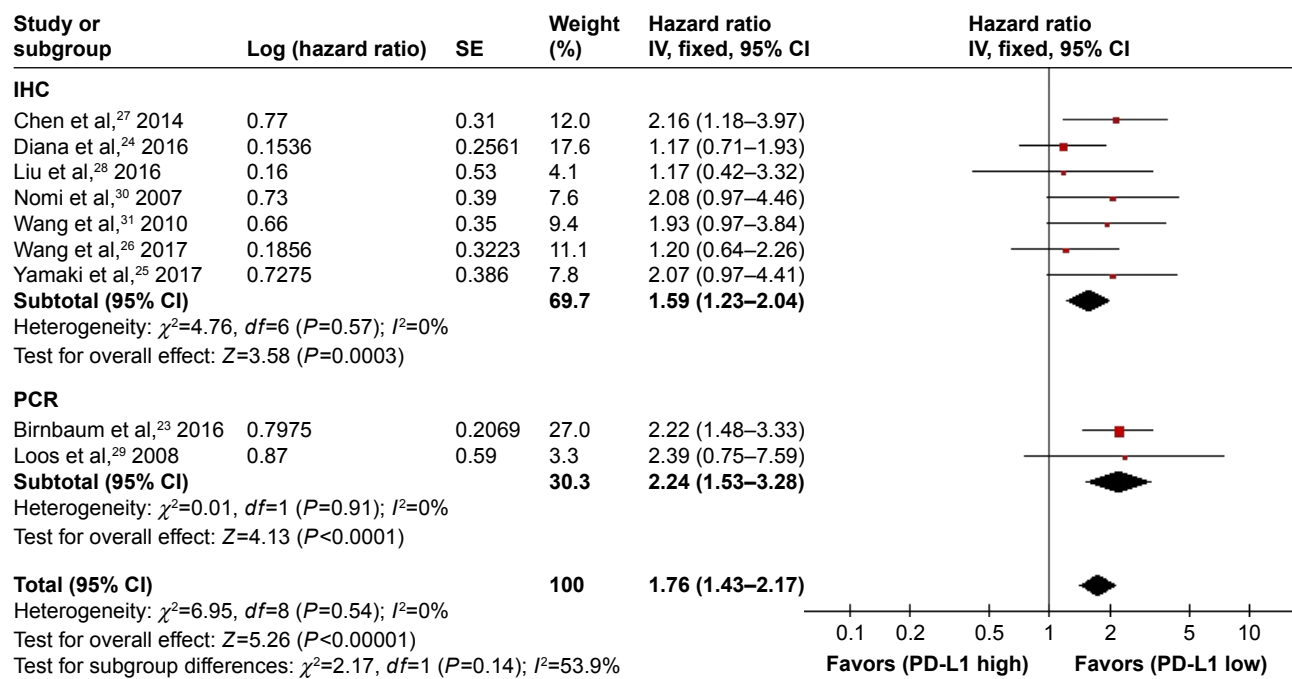


Figure 2 Subgroup analysis based on the methods used to detect PD-L1 expression.

Note: A statistical significance of the pooled HR was observed in both the subgroup with PCR method (HR: 2.24, 95% CI: 1.53–3.28, $P<0.0001$) and the subgroup with IHC method (HR: 1.59, 95% CI: 1.23–2.04, $P=0.0003$) between high and low PD-L1 expression groups.

Abbreviations: *df*, degrees of freedom; HR, hazard ratio; IHC, immunohistochemistry; IV, generic inverse variance method; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; SE, standard error.

carcinoma.^{34,40} High PD-L1 expression was a poor prognostic marker in the patients who were smokers, whereas this was not the case in those who never had a smoking habit among lung adenocarcinoma and oral squamous cell carcinoma patients.^{40,41} In addition, it was demonstrated that B7-H3, another member of the B7 family that is also known as an immune modulator, was associated with higher mortality in moderate/heavy smoking patients, but not in nonsmoking/light smoking patients in a study on lung adenocarcinoma.⁴²

It seemed that the impact of PD-L1 positivity on the survival in PC patients should be evaluated by stratification of smoking status. However, there were no data about the impact of PD-L1 positivity on the survival in PC patients stratified by smoking status in the studies included in this meta-analysis. Further studies are recommended to better interpret the impact of smoking on PD-L1 expression.

The molecular mechanism of overexpressed PD-L1 in PC remains obscure. Upregulation of PD-L1 could be stimulated by cytokines produced by infiltrating immune cells, such as interferon- γ (IFN- γ), interleukin (IL)-4, IL-10, vascular endothelial growth factor, and growth cell stem factor, in some solid tumors.^{43–46} In addition, PD-L1 overexpression was observed in acute myeloid leukemia through IFN- γ or toll-like receptor stimulation in blast cells from patients via the mitogen-activated protein kinase kinase/extracellular signal-related kinase pathway and the myeloid primary differentiation response 88/tumor necrosis factor receptor-associated factor 6 pathway.⁴⁷ Moreover, constitutive oncogene pathway activation could also promote PD-L1 expression, for instance, in non-small-cell lung cancer, and specifically, the anaplastic lymphoma kinase/signal transducer and activator of transcription 3, phosphoinositide 3-kinase, and mitogen-activated protein kinase kinase/extracellular signal-related kinase/signal

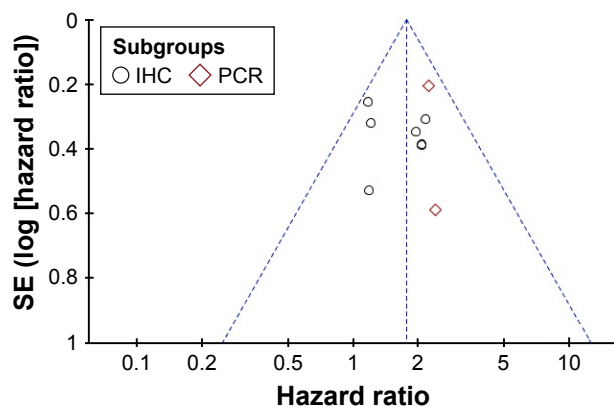


Figure 3 Funnel plot illustrating the meta-analysis of the overall survival.

Note: There was no obvious publication bias.

Abbreviations: IHC, immunohistochemistry; PCR, polymerase chain reaction; SE, standard error.

transducer and activator of transcription 1 pathways can activate PD-L1 expression.^{48,49} It was reported that the expression of PD-L1 in PC cells was induced via CD8⁺ T-cell IFN- γ secretion.^{50,51} Therefore, PD-L1 expression might be modulated via different pathways among different tumor types.^{43,44,49}

Due to conventional treatment resistance in PC, new immunotherapeutic strategies are urgently needed.^{52,53} Immunotherapy with immune checkpoint inhibition has shown promise as a therapeutic approach.⁵⁴ PD-L1, a critical immune checkpoint, is the primary PD-1 ligand, and it can decrease cytokine secretion and attenuate the biologic function of PD-1+ cells and tumor-infiltrating CD4⁺ and CD8⁺ T-cells.⁵⁵ These properties of PD-L1 may allow it to serve as a potentially promising target for cancer immunotherapy.⁵⁴ PD-L1 monoclonal antibodies exhibited an in vivo antitumor effect on murine PC by increasing CD8⁺ T-cell infiltration and triggering local immune function.⁵⁶ Furthermore, an effective outcome on murine PC was observed with the combined treatment of an anti-PD-L1 monoclonal antibody and gemcitabine. In addition, several clinical trials using an anti-PD-L1 monoclonal antibody, such as durvalumab and BMS-936559, were carried out and exhibited an appealing effect.⁵⁷

High-level PD-L1 expression was correlated with a poorer overall survival in PC patients in our meta-analysis, which suggested that an anti-PD-L1 monoclonal antibody may be a new, promising treatment strategy for PC patients. Additional clinical trials are needed to evaluate the efficacy and safety of anti-PD-L1 monoclonal antibodies in patients with PC. The positive correlations between high-level PD-L1 expression and poor differentiation and PC neural invasion may provide an additional indication for the application of anti-PD-L1 treatment strategies for PC patients with poorly differentiated PC and neural invasion.

Despite the promising result from this meta-analysis, there are several limitations that need to be further addressed. First, the number of studies in this meta-analysis was moderate with limited statistical power. Second, some studies were not included due to a lack of data about the association between PD-L1 expression and clinicopathologic characteristics.^{50,58} Moreover, studies included in this meta-analysis were mostly single-center retrospective studies and did not include multi-center prospective cohort studies.^{23,29,30} Finally, meta-analysis is a retrospective method that is subject to methodological limitations. Therefore, further studies are recommended to better interpret the available datasets.

Conclusion

Our meta-analysis implied that PD-L1 may act as a negative predictor for the overall survival of PC patients, and high

expression of PD-L1 was correlated with poor differentiation and neural invasion. However, further studies are recommended to better interpret the available datasets.

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Disclosure

The authors report no conflicts of interest in this work.

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