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Prognostic significance of PD-L1 expression in pancreatic cancer: evidence from an updated meta-analysis

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Recent studies revealed that programmed cell death ligand 1 (PD-L1) expression was associated with unfavorable prognosis in various solid tumors, but its clinical relevance for pancreatic cancer has not yet been well established. This meta-analysis summarizes the potential prognostic value of PD-L1 in pancreatic cancer. A quantitative meta-analysis was performed by a systematic search of databases including PubMed, EMBASE, Web of Science, Cochrane library, Scopus and Ovid for eligible studies on the prognostic significance of PD-L1 in pancreatic cancer patients. Pooled hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated to evaluate the strength of the link between PD-L1 expression and clinical prognosis of patients. Seventeen eligible studies with 2669 patients were included in our study. A significant association was observed between PD-L1 abundance and poor overall survival (OS) of patients with pancreatic cancers, with a pooled hazard ratio (HR) of 1.902, 95% CI: 1.657-2.184. Sensitivity analysis confirmed the reliability of our results. Subgroup analysis shows that differences in regions and detection methods of PD-L1 did not change the overall predictive value of PD-L1 for poor prognosis in pancreatic cancer patients. This meta-analysis indicated that the expression of PD-L1 is associated with a worse OS in pancreatic cancer patients. Additionally, PD-L1 may act as a potential parameter for predicting poor prognosis and thus providing a promising target for anticancer therapy in pancreatic cancer.

Key words: PD-L1, pancreatic cancer, prognosis, meta-analysis.

Introduction

Pancreatic cancer is one of the malignant tumors of the digestive system characterized by a dismal prognosis and limited potential for oncologic treatment, having the fourth place in cancer related mortality. One of the major histological types of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC or PDA), which is often diagnosed at an advanced stage due to the difficulty of early detection and resistance to chemotherapy and radiotherapy [1]. In addition, undifferentiated carcinomas with osteoclast-like giant cells of the pancreas (UCOGCP) are a rare variant of PDAC, which represents about 0.4%

of pancreatic carcinomas in resection specimens [2]. The overall 5-year survival rate of PDAC is 26% in resectable patients and the rate drops to 2% if the tumor was unresectable [3]. This poses a great threat to human health and survival. The reasons underlying such a poor prognosis have been postulated to relate to the advanced stage at the time of diagnosis, and resistance to standard chemotherapies as well as its ability to evade the host immune surveillance [4, 5].

PD-L1 (B7-H1) expressing on the cell membrane of several types of cells, including tumor cells, is a member of the B7 family, and it binds the PD-1 receptor to induce T cell apoptosis within various kinds of cancer tissues [6-9]. Studies show that PD-1 and its ligand (PD-L1) checkpoint pathway play a critical role in tumour immune escape and cancer immunoediting [9, 10]. Recently, increasing numbers of studies have investigated the prognostic significance of PD-L1 expression in pancreatic cancer patients [11-15], but the results are controversial. A previous meta-analysis performed in 2017 **which** included 10 articles implied that PD-L1 expression was correlated with a poor overall survival outcome in PC patients (hazard ratio = 1.76, 95% CI: 1.43-2.17, $p < 0.00001$) and PD-L1 could serve as a negative predictor for the overall survival of pancreatic cancer patients [16]. Another meta-analysis carried out in 2018 which included 9 studies with 993 patients showed that elevated PD-L1 expression was related to relative poor overall survival (OS) (HR = 1.63, 95% CI: 1.34-1.98, $p < 0.001$) and CSS (HR = 1.86, 95% CI: 1.34-2.57, $p < 0.001$), indicating that PD-L1 is a potential prognostic biomarker and may be helpful for clinicians to select the appropriate immunotherapy for pancreatic cancer patients [17]. However, other studies showed non-significant prognostic value of PD-L1 in pancreatic cancer patients [15, 18, 19]. Hence, there is still insufficient evidence to implicate PD-L1 with poor prognosis in pancreatic cancer patients. Furthermore, several pertinent larger cohort studies have been published in recent years and some studies included in previous meta-analysis have been retracted by the authors. Therefore, we performed an updated meta-analysis of published studies to evaluate the prognostic value of PD-L1 expression in pancreatic cancer patients.

Material and methods

Search strategy

A systematic literature search of PubMed, EMBASE, Web of Science, Cochrane library, Scopus and Ovid was conducted. The literature was restricted to publications in English language. The following search terms were used: "PD-L1", "programmed cell death ligand 1", "B7-H1", "CD274", "pancreatic neoplasm", "pancreatic cancer", "pancreatic adenocarcinoma", "prognosis". The literature search stopped on February 10th, 2023. In addition, a recursive search of the reference articles of included studies was conducted manually to identify possible relevant articles. Studies were included or excluded based on the consensus between two authors (Chenchen Liu and Yingjie Shi) and when necessary with the assistance of Qian Wu. All selections were performed in duplicate. All analyses were performed based on previous published studies, thus no ethical approval or patient consent was needed.

Selection criteria

Two investigators (Chenchen and Lijuan Fan) independently assessed all the eligible studies and then extracted the data. We included studies that met the following inclusion criteria: (1) studies focusing on pancreatic cancer; (2) the histologic target was pancreatic tissues; (3) the association between PD-L1 expression, prognosis, and clinicopathologic features was investigated; (4) the expression of PD-L1 was categorized into high (and/or positive) and low (and/or negative) groups; (5) statistically acceptable methods of data collection and analysis; (6) hazard ratios (HRs) for survival rates and their 95% confidence intervals as well as those with enough information for calculating these data by using Tierney's method; (7) full manuscript publication in English language. Studies were excluded by the following exclusion criteria: (1) duplicates, reviews, conference abstracts, or letters; (2) studies about PC cell lines, animal studies, and other types of cancer; (3) studies not about PD-L1; and (4) incomplete data.

Data extraction and quality assessment

The two investigators (Yingjie Shi and Chenchen Liu) extracted the data independently and any discrepancies in interpretation were resolved by consensus of all authors. Relevant articles were reviewed in full to ensure suitability according to the predefined inclusion and exclusion criteria. The following characteristics of research articles were collected: first author's name, country, publication year, cancer type, clinical stage of tumor, sample size, methods of detecting PD-L1, survival analysis, HRs of elevated PD-L1 for OS as well as their 95% CIs.

We utilized two methods to obtain the HRs in our article. In method 1, we obtained the HRs directly from the article. In method 2, we extracted the HRs from Kaplan-Meier curves and then we reconstructed the HR estimate by extracting some survival rates at specified times from the survival curves using the Engauge Digitizer software, and next we calculate these data by Tierney's method [20-22].

We assessed the quality of all studies included under the criteria of Newcastle-Ottawa, which con-

tain four parts including selection (4 points), comparability (2 points), and outcome (3 points) with a score range of 0-9. The NOS assigns a maximum of 4 questions for selection, 2 questions for comparability, and 3 questions for exposure/outcome, with a maximum 1 point for each question. Points were scored only when the data were explicitly stated. Therefore, a higher score indicates better quality, with 9 points being the highest quality. The final decision and interpretation were based on the consensus of two authors (Chenchen Liu and Xuan Sun) and when necessary with the assistance of Yingjie Shi. All selections were performed in duplicate. Points of all eligible studies scored presented in Table I, with a higher score indicating a better methodological quality.

Statistical analysis

Our meta-analysis was performed using the Stata 12.0 software. The heterogeneity between studies included was determined by the chi square-based Q test and an I^2 statistics. A p-value less than 0.05 for the Q test and I^2 value above 50% were considered to be significantly heterogeneous, by which condition the random effects model was adopted. If the I^2 value was below 50%, the fixed effects model was applied. Publication bias was assessed using a funnel plot and Egger's test. To test the robustness of the main results, we utilized one-way sensitivity analysis to evaluate the stability of the meta-analysis by sequentially excluding one study each time. A p-value less than 0.05 was considered statistically significant.

Results

The baseline characteristics of the included studies are summarized in Table I.

The initial search identified 178 citations, the titles and abstracts were then carefully reviewed. After excluding duplicates, 58 irrelevant studies and duplicates were then excluded, and 120 citations were considered of potential value. Then, we further browsed the title, abstract, and full text of the literature; 79 citations were excluded based on the context. The full text of these 41 articles was further assessed for eligibility and retrieved for detailed evaluation. After further evaluation, 25 of them were subsequently excluded from the meta-analysis for not meeting the predefined criteria or insufficient data and outcomes. One additional article was obtained by a manual search of different sources. Eventually, 17 articles published from April 2007 to May 2022 comprising 2669 pancreatic cancer patients were included in our meta-analysis [11, 12, 14, 15, 18, 19, 23-33]. (Figure 1 shows the study flow diagram). These studies included a total of 646 cases of PD-L1 (+) patients and 2023 PD-L1 (–) controls. Among all the studies included, eight studies were performed on pancreatic cancer (PC) patients, eight on pancreatic ductal adenocarcinoma (PDAC or PDA) patients and one on UCOGCP patients. Of the 17 studies, five studies were conducted in Japan [11, 15, 18, 27, 30], seven in China [12, 19, 23, 24, 31-33], one in France [25], one in the UK [26], two in the USA [14, 28], and one in the Czech Republic [29] (Table I). Fifteen studies used the immunohistochemical (IHC) method to detect the PD-L1 expression, Quantitative reverse transcription-polymerase chain reaction (RT-PCR) was used in one study to detect the PD-L1 expression, and gene set enrichment analysis was used in one study (Table I).

Association between PD-L1 and patient survival in pancreatic cancer

There was no significant heterogeneity among the studies ($I^2 = 38.6\%$, $p = 0.053$), and we used the fixed-effects model to calculate the pooled HR (Fig. 2). Fourteen studies reported the overall survival (OS), one study reported both the OS and recurrence free survival (RFS), one study reported both the OS and progression-free survival (PFS), and one study report disease-specific survival (DSS) as well as PFS in our meta-analysis. Finally, we choose OS as the main parameter in our meta-analysis since OS remains the gold-standard efficacy endpoint for the development of new treatments in oncology. A significant association was observed between PD-L1 and OS in pancreatic cancer patients (HR 1.902, 95% CI: 1.657-2.184) (Fig. 2). When omitting the UCOGCP, the HR was 1.949, 95% CI: 1.608-2.362. The results revealed that patients with high PD-L1 expression were more likely to have significant shorter OS. We further divided patients into different groups under the criteria of different regions and methods of detecting PD-L1 and the survival outcomes. Due to geographic differences in PC prevalence, subgroup analysis according to studies conducted in Western and Asian countries were performed. In subgroup analysis of Asian countries, twelve studies with a total of 394 cases and 1330 controls were included. Meta-analysis of these studies showed that the pooled HR 1.946, 95% CI: 1.645-2.302, I^2 46.3%) (Fig. 3A). In subgroup analysis of Western country studies, four studies with a total of 252 cases and 693 controls were included, the pooled HR 1.814, 95% CI: 1.423-2.313, I^2 25.5% (Fig. 3B). In subgroup analysis based on items of methods of detecting PD-L1, the pooled HRs for IHC was 1.821, 95% CI: 1.568-2.114 (Fig. 3C), the HR was 1.863, 95% CI: 1.514-2.293 in conventional PC patients omitting the UCOGCP. Among all the studies included, 16 studies provided OS as the main outcome, while the study by Yue Zhang utilized the DSS and PFS

Table I. Characteristics of studies included in the meta-analysis

Author	Year	Country	Total number	Cancer type	Tumor stage	Age median (range)	Treatment	PD-L1 positive	PD-L1 negative	Detection method	Survival analysis	NOS	HR	LL	UL
Nomi *et al.* [11]	2007	Japan	51	PC	I-IV	63 (46-73)	Surgery	20	31	IHC	OS	8	2.08	0.97	4.46
Wang *et al.* [12]	2010	China	81	PC	I-III	55 (34-76)	Surgery	40	41	IHC	OS	7	1.93	0.97	3.84
Hutcheson *et al.* [14]	2016	USA	158	PDA	NA	65 (27-89)	Surgery	100	58	IHC	OS	7	1.619	0.981	2.671
Imai *et al.* [18]	2017	Japan	36	PDA	I-IV	68 (51-89)	Surgery	11	25	IHC	OS, RFS	7	1.81	0.5	6.5
Wang *et al.* [19]	2017	China	94	PC	I-IV	62 (31-78)	Surgery	27	67	IHC	OS	8	1.2	0.64	2.26
Yamaki *et al.* [15]	2017	Japan	42	PDAC	I-IV	65 (50-83)	Surgery	26	16	IHC	OS	7	2.07	0.97	4.41
Liang *et al.* [23]	2018	China	373	PDAC	I-IV	61 (29-82)	Surgery	12	361	IHC	OS, PFS	8	4.8	2.29	10.06
Wang *et al.* [24]	2018	China	95	PC	I-IV	55 (18-76)	Surgery	48	47	IHC	OS	7	2.08	1.02	4.23
Birnbaum *et al.* [25]	2016	France	453	PC	I-III	NA	Surgery	87	366	qRT-PCR	OS	7	2.22	1.48	3.33
Diana *et al.* [26]	2016	UK	145	PDAC	I-III	NA	Surgery	41	104	IHC	OS	6	1.166	0.706	1.93
Tsukamoto *et al.* [27]	2019	Japan	235	PDAC	I-IV	NA	Surgery	33	202	IHC	OS	7	2.31	1.56	3.4
Danilova *et al.* [28]	2019	USA	152	PC	I-III	66 (60-70.5)	Surgery	11	141	IHC	OS	7	2.55	1.15	5.64
Hrudka *et al.* [29]	2020	Czech Republic	37	UCO-GCP	I-IV	69.9 (53-79)	Needle biopsies	13	24	IHC	OS	7	2.51	1.06	5.95
Iwatate *et al.* [30]	2020	Japan	107	PDAC	I-III	70 (50-87)	Surgery	36	71	IHC	OS	7	1.97	1.094	3.547
Li *et al.* [31]	2021	China	169	PC	I-IV	NA	Tissues samples	20	149	Gene set enrichment analysis	OS	6	3.673	1.622	8.118
Zhu *et al.* [32]	2022	China	177	PC	I-III	NA	Surgery	67	110	IHC	OS	7	2.47	1.55	3.95
Zhang *et al.* [33]	2022	China	264	PDAC	I-IV	61 (25-83)	Surgery	54	210	IHC	DSS, PFS	7	1.131	0.781	1.636

IHC – immunohistochemistry; OS – overall survival; PC – pancreatic cancer; PDAC or PDA – pancreatic ductal adenocarcinoma; PD-L1 – programmed death-ligand 1; UCOGCP – undifferentiated carcinomas with osteoclast-like giant cells of the pancreas; PFS – progression-free survival; DSS – disease-specific survival; qRT-PCR – quantitative reverse transcription polymerase chain reaction; NA – not available

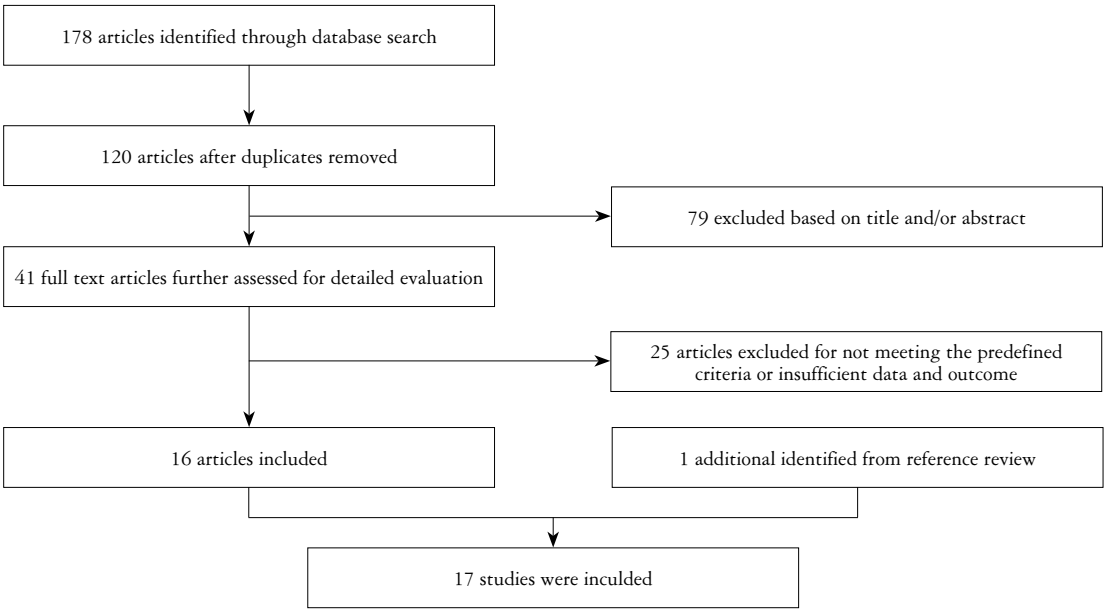
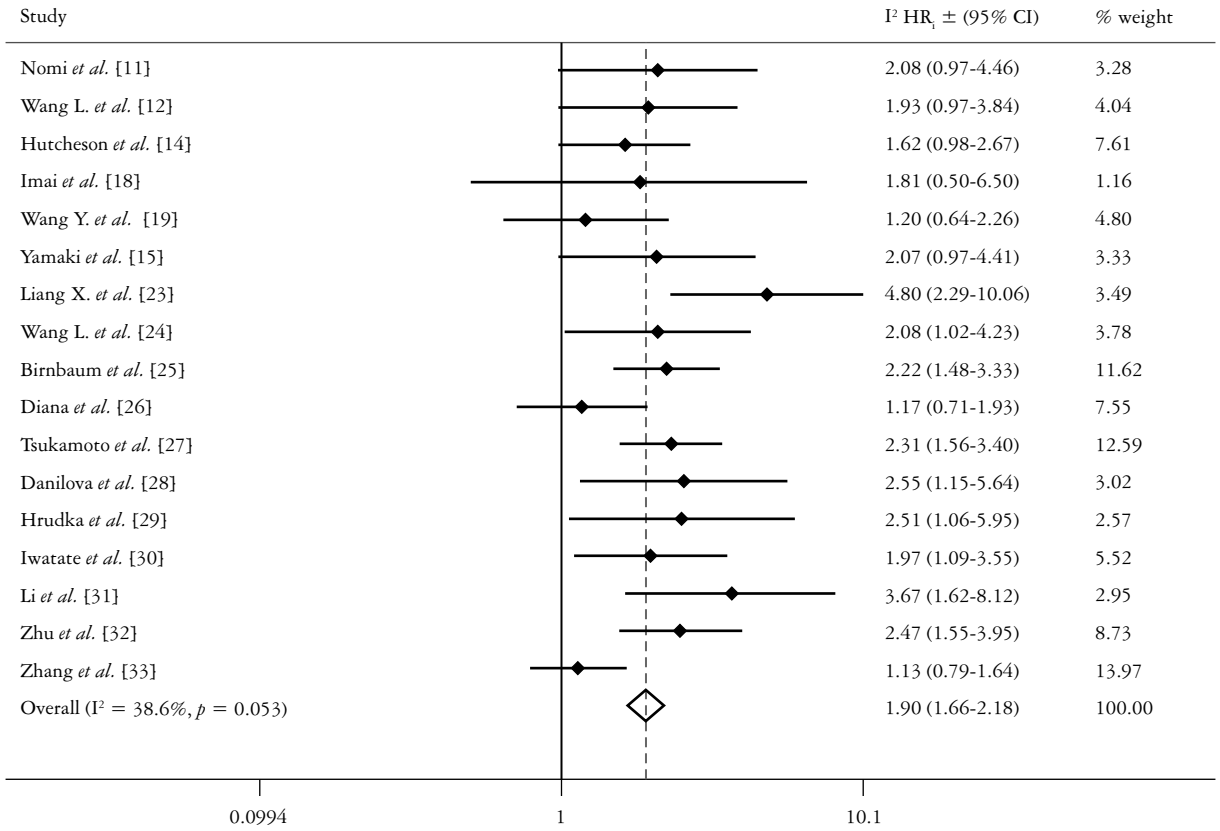
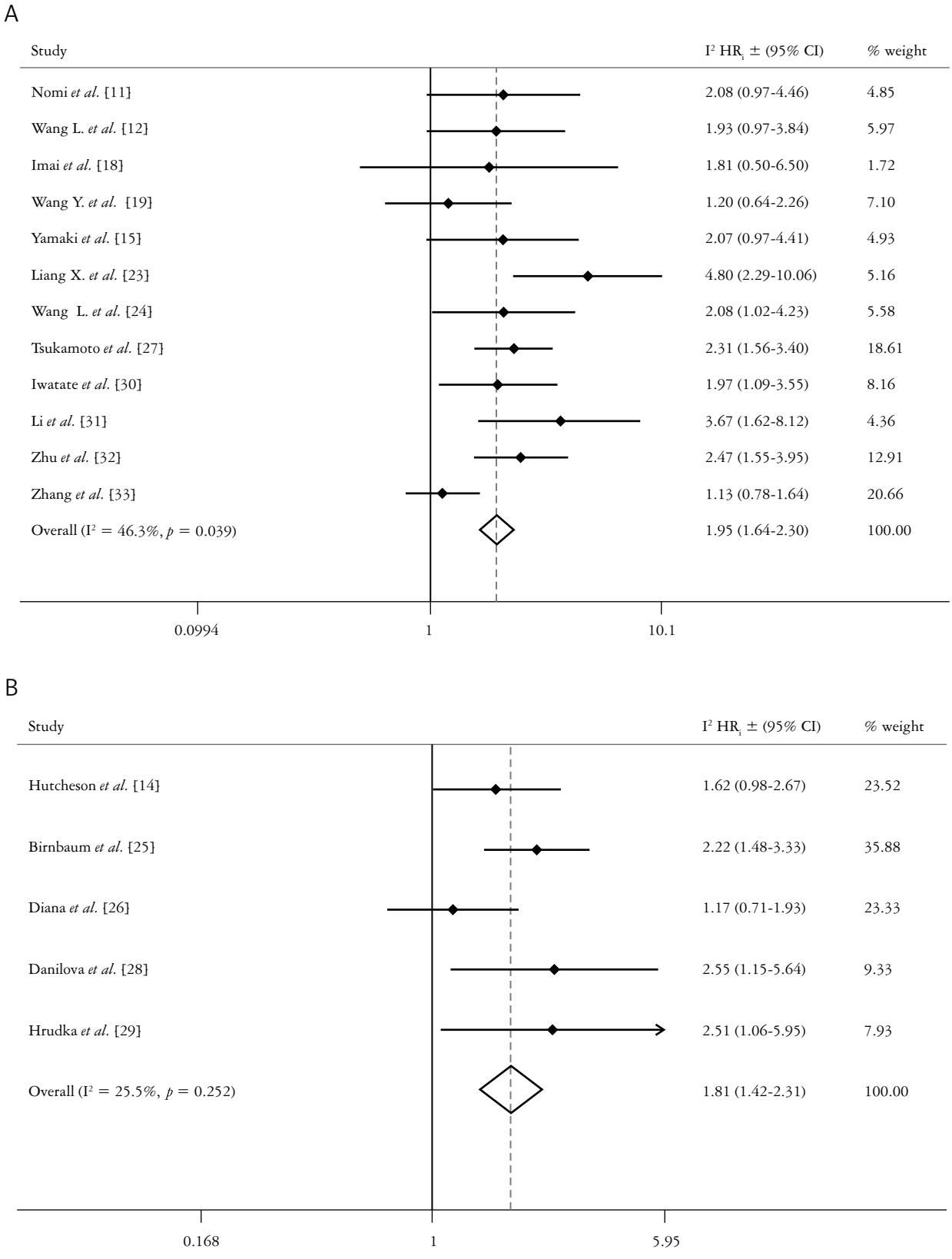


Fig. 1. Flow chart of the study search and selection.



OS – overall survival

Fig. 2. Forest plot for the correlation between PD-L1 expression and poor prognosis OS of pancreatic cancer patients

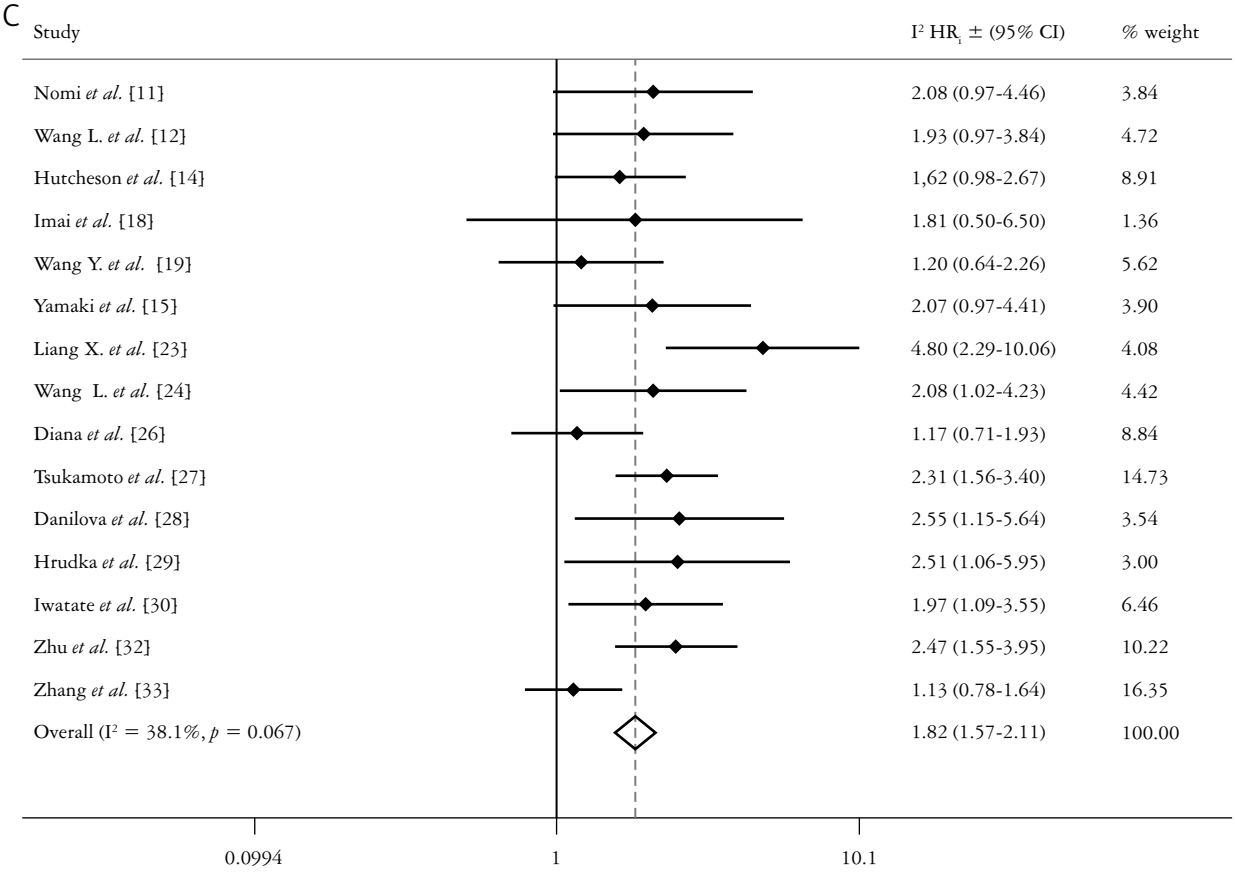


A: Asian countries B: Western counties C: detection method of PD-L1 (IHC) D: survival outcome : OS

OS – overall survival; IHC – immunohistochemical

Fig. 3. Forest plot of subgroup analysis showed the correlation of PD-L1 expression with poor prognosis in pancreatic cancer patients

C


Study
I² HR$_i$ ± (95% CI)
% weight
Nomi et al. [11] 2.08 (0.97-4.46) 3.84
Wang L. et al. [12] 1.93 (0.97-3.84) 4.72
Hutcheson et al. [14] 1,62 (0.98-2.67) 8.91
Imai et al. [18] 1.81 (0.50-6.50) 1.36
Wang Y. et al. [19] 1.20 (0.64-2.26) 5.62
Yamaki et al. [15] 2.07 (0.97-4.41) 3.90
Liang X. et al. [23] 4.80 (2.29-10.06) 4.08
Wang L. et al. [24] 2.08 (1.02-4.23) 4.42
Diana et al. [26] 1.17 (0.71-1.93) 8.84
Tsukamoto et al. [27] 2.31 (1.56-3.40) 14.73
Danilova et al. [28] 2.55 (1.15-5.64) 3.54
Hrudka et al. [29] 2.51 (1.06-5.95) 3.00
Iwatate et al. [30] 1.97 (1.09-3.55) 6.46
Zhu et al. [32] 2.47 (1.55-3.95) 10.22
Zhang et al. [33] 1.13 (0.78-1.64) 16.35
Overall (I² = 38.1%, p = 0.067) 1.82 (1.57-2.11) 100.00
0.0994
1
10.1

D

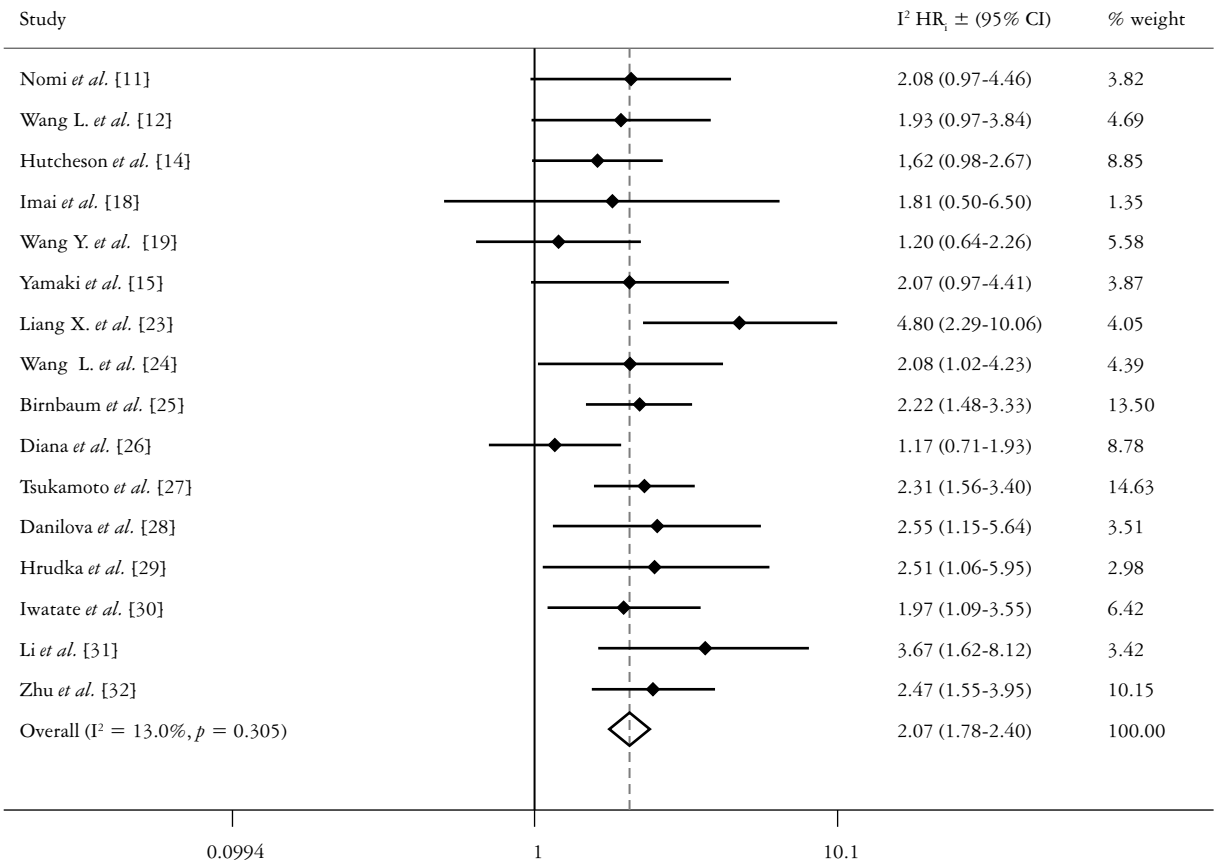

Study
I² HR$_i$ ± (95% CI)
% weight
Nomi et al. [11] 2.08 (0.97-4.46) 3.82
Wang L. et al. [12] 1.93 (0.97-3.84) 4.69
Hutcheson et al. [14] 1,62 (0.98-2.67) 8.85
Imai et al. [18] 1.81 (0.50-6.50) 1.35
Wang Y. et al. [19] 1.20 (0.64-2.26) 5.58
Yamaki et al. [15] 2.07 (0.97-4.41) 3.87
Liang X. et al. [23] 4.80 (2.29-10.06) 4.05
Wang L. et al. [24] 2.08 (1.02-4.23) 4.39
Birnbaum et al. [25] 2.22 (1.48-3.33) 13.50
Diana et al. [26] 1.17 (0.71-1.93) 8.78
Tsukamoto et al. [27] 2.31 (1.56-3.40) 14.63
Danilova et al. [28] 2.55 (1.15-5.64) 3.51
Hrudka et al. [29] 2.51 (1.06-5.95) 2.98
Iwatate et al. [30] 1.97 (1.09-3.55) 6.42
Li et al. [31] 3.67 (1.62-8.12) 3.42
Zhu et al. [32] 2.47 (1.55-3.95) 10.15
Overall (I² = 13.0%, p = 0.305) 2.07 (1.78-2.40) 100.00
0.0994
1
10.1

Fig. 3. Cont.

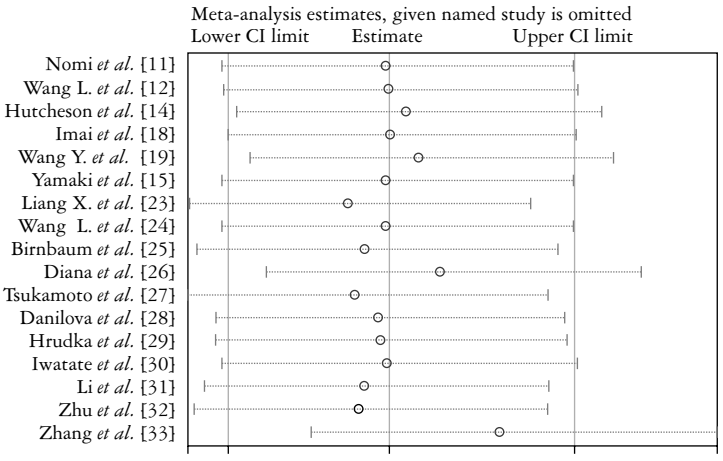


Fig. 4. Sensitivity analysis of the included studies for the association between PD-L1 expression and overall survival

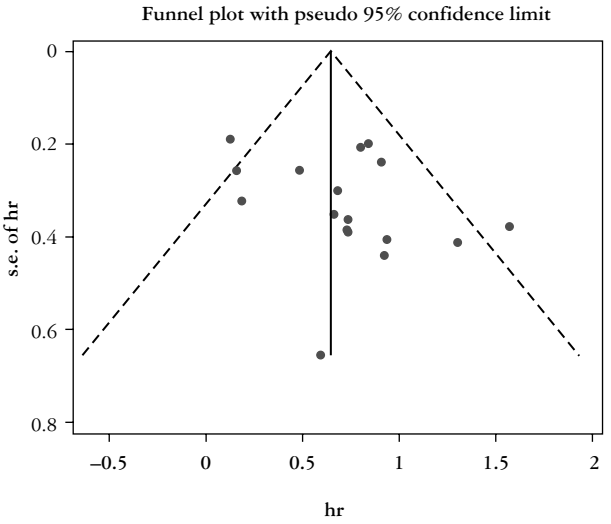


Fig. 5. Funnel plot analysis

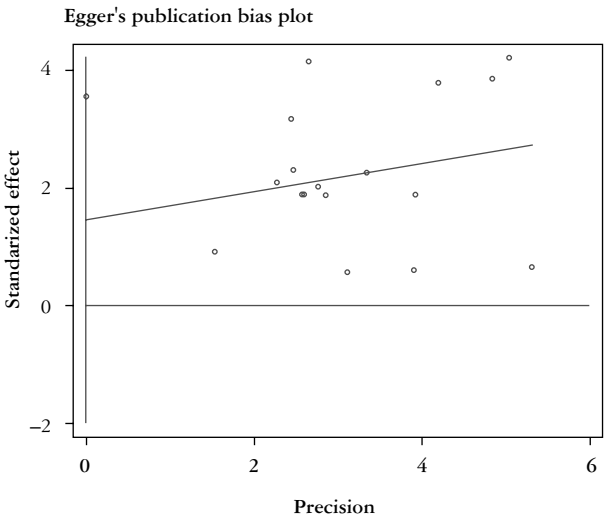


Fig. 6. Egger's test of potential publication bias

as the main parameter, when we omit this study the pooled HR of the rest was 2.070, 95% CI: 1.783-2.402, I^2 13.0%) (Fig. 3D). No significant heterogeneity was observed in all the subgroup analysis. Collectively, this meta-analysis showed that PD-L1 was an independent prognostic factor for pancreatic cancers.

Sensitivity analysis

Sensitivity analysis was performed to examine the effect of each single study on the overall meta-analysis results by omitting one study each time. The results showed that no study markedly influenced the significance of the summary HRs and the leave-one-out ORs ranged from 1.840 (95% CI: 1.598-2.117) to 2.069 (95% CI: 1.783-2.402), similar to the overall result, indicating that the pooled HR of OS was relatively reliable (Fig. 4).

Publication bias

Egger's p-value tests were used to assess the potential publication bias in this meta-analysis. The funnel plots were unsymmetrical (Fig. 5). Significant publication bias was observed across the studies, with a p-value of 0.160 for Egger's test (Fig. 6). Therefore, we assumed that the main results of our meta-analysis should be interpreted critically and carefully.

Discussion

Pancreatic cancer (PC) being a lethal disease with a dismal 5-year survival less than 10%, constitutes a major public health problem worldwide [1]. Given the poor prognosis of PC, it is of great importance to identify novel biomarkers, which could help to make a diagnosis at early stage and provide more precise and valuable information for better therapy. Currently, tumor immunotherapy is a relatively new strategy in cancer treatment, the aim of which is to block the immunosuppressive effect of tumoral cells. PD-L1, also known as B7-H1, was first cloned in 1999 [6]. The programmed cell death-1 protein receptor (PD-1) and its ligand (PD-L1) checkpoint pathway play an important role in tumour immune escape, thereby obstructing effective immune surveillance and thus promoting tumour growth [9, 10]. Several studies have reported a poor prognosis in pancreatic patients with increased expression of PD-L1. In a study conducted by Tessier-Cloutier *et al.* on patients with resected pancreatic tumors with high expression of PD-L1, the results showed that PD-L1 was associated with a poor disease specific survival (DFS) [34]. The study by Tsukamoto *et al*. revealed that PD-L1-high patients with PDAC had poorer prognoses than PD-L1-low patients [35]. Another study carried out by Yamaki *et al.* in a small group using immunostain-

ing with fluorescent phosphor-integrated dot (PID) nanoparticles showed similar results [15]. However, in another study it was demonstrated that pancreatic cancer patients with intense CD8+ TILS and PD-1+ TILs (tumor-infiltrating lymphocytes) infiltrate had a better prognosis [36]. A previous meta-analysis by Zhuan-Sun *et al.* which included 10 studies showed that PD-L1 may act as a negative predictor for the overall survival of PC patients with a pooled HR 1.76 (95% CI: 1.43-2.17), and in addition high expression of PD-L1 was correlated with poor differentiation and neural invasion [16]. Another meta-analysis which included 9 studies performed by Hu *et al.* demonstrated that high PD-L1 expression was associated with poor OS in patients with pancreatic cancer, and pooled HR was 1.63 (95% CI: 1.34-1.98) [17]. The prognostic significance of PD-L1 in pancreatic cancer remained inconsistent according to previous studies and the prognostic value of PD-L1 expression in pancreatic cancer was not well established. Hence, we carried out this meta-analysis to further clarify the prognostic value of PD-L1 expression in pancreatic cancers.

Our meta-analysis using a detailed search strategy which included 17 relevant studies with a total of 2669 patients, provided convincing evidence that PD-L1 expression is predictive of poor tumor survival, suggesting that PD-L1 may be used as a negative, unfavourable prognostic marker for pancreatic cancers. The combined results indicated that increased PD-L1expression was associated with a shorter OS in pancreatic cancer patients. A shorter overall survival time was observed in the patients of high PD-L1 expression compared with those of low PD-L1 expression. Subgroup analysis including region, an PD-L1 detection method showed that these factors did not alter the predictive value of PD-L1 for poor prognosis in pancreatic cancer patients and there was no evidence of statistically significant heterogeneity across the studies. Additionally, there was significant publication bias in our meta-analysis despite the fact that stable results were obtained in sensitivity analysis. There might be some explanations for this. First, the data collection may be incomplete because data from non-English language papers were not included. Second, most of the included studies reported positive results due to the fact that negative results are generally less likely to be published. Third, we only included studies with sufficient data to calculate the pooled HRs, omitting those with insufficient information for combined HRs. Thus, our results might overestimate the predictive significance of PD-L1 in prognosis of pancreatic cancer to some extent.

Nevertheless, we should note that there are several limitations in our study due to the discrete data across studies. First, not all the HRs are provided by the primary articles and we calculated some of them by reconstructing survival curves, which may cause bias, thus making the HR less accurate. Second, most of the patients included in the meta-analysis were from Asia countries, and thus our results may just represent patients from Asia. Third, the sample size was relatively small and we did not analyze the correlations between PD-L1 expression and clinicopathological characteristics of patients as the data were not complete.

In conclusion, our meta-analysis indicated that the expression of PD-L1 is associated with a worse OS in pancreatic cancer patients with a pooled HR of 1.902, 95% CI: 1.657-2.184. In addition, PD-L1 may act as a new parameter for predicting poor prognosis and a promising target for anticancer therapy in pancreatic cancer. However, considering the above limitations, larger, multi-center and higher-quality studies are recommended to further determine the prognostic value of PD-L1 expression in pancreatic cancer patients.

The authors declare no conflict of interest.

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