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Review Article

Prognostic value of PD-L1 expression in non-small cell lung cancer: a meta-analysis

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Abstract: Purpose: We conducted a meta-analysis to systematically assess the prognostic and clinicopathological value of programmed death ligand-1 (PD-L1) expression in non-small cell lung cancer (NSCLC). Methods: We searched PubMed, Embase and Web of Science to screen the literature for relevant studies up date to September 29, 2016. The associations of PD-L1 expression with clinicopathological parameters and overall survival (OS) were investigated using the meta-analysis for odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI). Results: A total of 11 trials with 3000 NSCLC patients were included in the meta-analysis. PD-L1 expression was found to be significantly associated with histology type (OR = 1.87, 95% CI: 1.12-3.12; *P* = 0.02), differentiation (OR = 1.95, 95% CI: 1.27-2.99; *P* = 0.002) and tumor stage (OR = 1.30, 95% CI: 1.04-1.63; *P* = 0.02), but not with gender (OR = 0.93, 95% CI: 0.64-1.34; *P* = 0.70), lymph node metastasis (OR = 1.47, 95% CI: 0.74-2.93; *P* = 0.28) and smoking status (OR = 1.17, 95% CI: 0.68-2.02; *P* = 0.56). The pooled results did not show a statistically significant relationship between PD-L1 expression and OS (HR = 0.967, 95% CI: 0.664-1.409, *P* = 0.863). However, a subgroup analysis showed PD-L1 overexpression was significantly associated with good prognosis in Western patients (HR = 0.635, 95% CI: 0.507-0.794, *P* < 0.001). There was no significant publication bias. Conclusion: Meta-analysis results indicated PD-L1 expression may not be a good predictive biomarker for NSCLC outcome.

Keywords: Meta-analysis, non-small cell lung cancer, programmed death ligand-1, clinicopathological parameters, prognosis, overall survival

Introduction

Lung cancer remains one of the most common diagnosed cancer and the most lethal cancer worldwide. Non-small cell lung cancer (NSCLC), mainly composed of adenocarcinoma (ADC) and squamous cell carcinoma (SCC), approximately accounts for 85% of lung cancers [1]. Despite significant advances in multidisciplinary cancer therapies, the overall 5-year survival rate still remains less than 15% [2]. Novel therapeutic strategies, including immunotherapy, are in progress to improve patients' poor prognosis.

Programmed death-1 (PD-1), a member of immunoglobulin superfamily, is a receptor expressed on the surface of activated T cells, regulatory T cells, B cells, natural killer cells, activated monocytes and dendritic cells [3]. Programmed death ligand-1 (PD-L1, also known as B7-H1), a member of the B7 superfamily, is a PD-1 ligand and expressed on antigen presenting cells, activated B- and T-cells and endothelial cells. The interaction of PD-1 and PD-L1 leads to apoptosis or inactivation of activated T-cells and furthermore, resulting in a negative regulation of immune activity [4, 5].

PD-L1 is also thought to be involved in the process of cancer cells to evade host immune surveillance [6]. During tumor progression, PD-1/PD-L1 interaction leads to T-cell apoptosis and cytokine secretion, which plays a crucial role in tumor-mediated immunosuppression and tumor evasion [3, 7]. Overexpression of PD-L1 has been evaluated in a number of human cancers, including lung, kidney, esophagus, pancreas, head and neck, colorectal, and skin (melanoma) [8-14].

Blocking PD-1/PD-L1 mediated co-inhibition of T-cells to promote immune eradication of tumor cells provides a promising therapeutic opportu-

nity. Monoclonal antibodies targeting PD-L1 or PD-1, are currently being studied in clinical trials, and remarkable response rates have been reported against NSCLC, non-Hodgkin lymphoma, malignant melanoma, triple-negative breast cancer, and renal cell carcinoma [15-19].

The association between PD-L1 expression and survival in lung cancer patients has been studied for several years. However, no consensus have been reached and conflicting results have been reported from different laboratories. Whether discrepancy in these results attributed to limited sample size or genuine heterogeneity is still confusing. Therefore, an up-to-date meta-analysis was carried out to evaluate the clinicopathological and prognostic significance of PD-L1 expression in NSCLC patients.

Materials and methods

We performed this meta-analysis according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses [20].

Search strategy

A comprehensive literature search was performed using the electronic databases of PubMed, Embase, and Web of Science. The last search was conducted on September 29, 2016. The key terms employed for literature retrieval included "PD-L1", "programmed death ligand-1", "B7-H1", or "B7 homolog 1"; "NSCLC"; and "prognosis". All references cited in relevant articles were screened to identify additional published work.

Inclusion and exclusion criteria

Eligible studies had to meet the following inclusion criteria: (1) the cancer was histologically diagnosed as NSCLC; (2) evaluated the association of PD-L1 expression with prognosis and pathological features; (3) clearly provided direct data of hazard ratio (HR) for overall survival (OS) and 95% confidence interval (CI); (4) PD-L1 expression was divided into high (positive) and low (negative) categories. To avoid duplicate data, only the most complete and recent of two related studies were included. Studies were excluded if they met any of the following criteria: (1) duplicate reports, ongoing studies, letters, conference papers and reviews; (2) studies about lung cancer cell lines, animal models and other types of cancer; (3) papers not in English.

Data extraction

To find all eligible research, two investigators (Ke Ma and Yuan Hu) independently searched the databases according to the above criteria. The following information was extracted from the eligible studies: first author surname, publication year, sample source, sample size, histology type, tumor node metastasis (TNM) stage, PD-L1 detection method, cut-off values for the positive rates of PD-L1 expression and expression-related survival. **Table 1** shows the included studies' specific clinical characteristics. Disagreements were resolved by discussion and consensus.

Qualitative assessment

Two authors (Wenxia Niu and Yangwei Fan) independently assessed the quality of all studies on the basis of a 9-score system of the Newcastle-Ottawa Scale (NOS) [21]. Discrepancies in the score were resolved through discussion between the authors. Each study included in the meta-analysis was judged on three broad perspectives: (I) the selection of the groups of study (four items, one score each); (II) the comparability (one item, up to two scores); (III) the ascertainment of either the exposure or outcome of interest (three items, one score each). Studies labeled with six or more scores were considered to be of high quality.

Statistical analysis

Stata/SE 12.0 for Windows (Stata Corporation, College Station, TX, USA) and Review Manager 5.2 (Cochrane Collaboration, London, UK) were used to perform the statistical analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) was used to analyze the connection between PD-L1 expression and clinical characteristics. HR with 95% CI was used to evaluate the relationship between PD-L1 expression and NSCLC prognosis. All HRs of these studies could be directly extracted from the full-text. An HR that was greater than 1 reflected shorter OS for PD-L1-positive patients. Cochrane's Q test (Chi-squared test; Chi^2) and I^2 metric were used to evaluate the statistical heterogeneity of the pooled HR with 95% CI [22]. If $I^2 < 50\%$ or $P \geq$

Table 1. Main characteristics and results of the eligible studies

Author	Publication year	Sample source	Sample size	Histology type	TNM stage	Method	Cut-off values	PD-L1 expression		Outcome	HR	95% CI	NOS scores
								Positive	Negative				
Velcheti et al [26*]	2014	Greece	340	NSCLC	I-IV	QIF	AQUA scores	75	265	OS	0.61	0.39-0.95	7
Velcheti et al [26#]	2014	USA	155	NSCLC	I-IV	QIF	AQUA scores	56	99	OS	0.63	0.40-0.98	7
Azuma et al [27]	2014	Japan	164	NSCLC	I-III	IHC	H-score > 30	82	82	OS	1.602	1.078-2.380	8
Mao et al [28]	2014	China	128	NSCLC	I-III	IHC	Media H-score	96	32	OS	1.90	1.09-3.30	8
Lin et al [29]	2015	China	56	ADC	NM	IHC	Mean H-score	30	26	OS	0.26	0.11-0.62	7
Tang et al [30]	2015	China	170	NSCLC	IIIB-IV	IHC	NM	112	58	OS	1.901	0.953-3.790	7
Cooper et al [31]	2015	Australia	678	NSCLC	I-III	IHC	Percentage 50%	50	628	OS	0.65	0.45-0.85	8
Yang et al [32]	2015	Taiwan	105	SCC	I	IHC	Percentage 5%	59	46	OS	0.282	0.139-0.572	9
Inoue et al [33]	2016	Japan	654	NSCLC	I-III	FISH	NM	201	453	OS	1.23	0.86-1.76	8
Shimoji et al [34]	2016	Japan	165	ADC	I	IHC	H-score > 5	37	128	OS	2.388	1.005-5.507	6
Song et al [35]	2016	China	385	ADC	I-III	IHC	Percentage 5%	186	199	OS	1.79	1.30-2.46	7

Note: H-score = SI (staining intensity) ×PP (percentage of positive cells). SI was determined as 0, negative; 1, weak; 2, moderate and 3, strong. PP was defined as 0, negative; 1-100 or 1%-100% positive cells. *Greek cohort; #Yale cohort. Abbreviations: NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; IHC, immunohistochemistry; QIF, quantitative fluorescence; AQUA, automated quantitative analysis; FISH, fluorescence *in situ* hybridization; OS, overall survival; HR, hazard ratio; CI, confidence interval; NOS, Newcastle-Ottawa Quality Assessment Scale; NM, not mentioned.

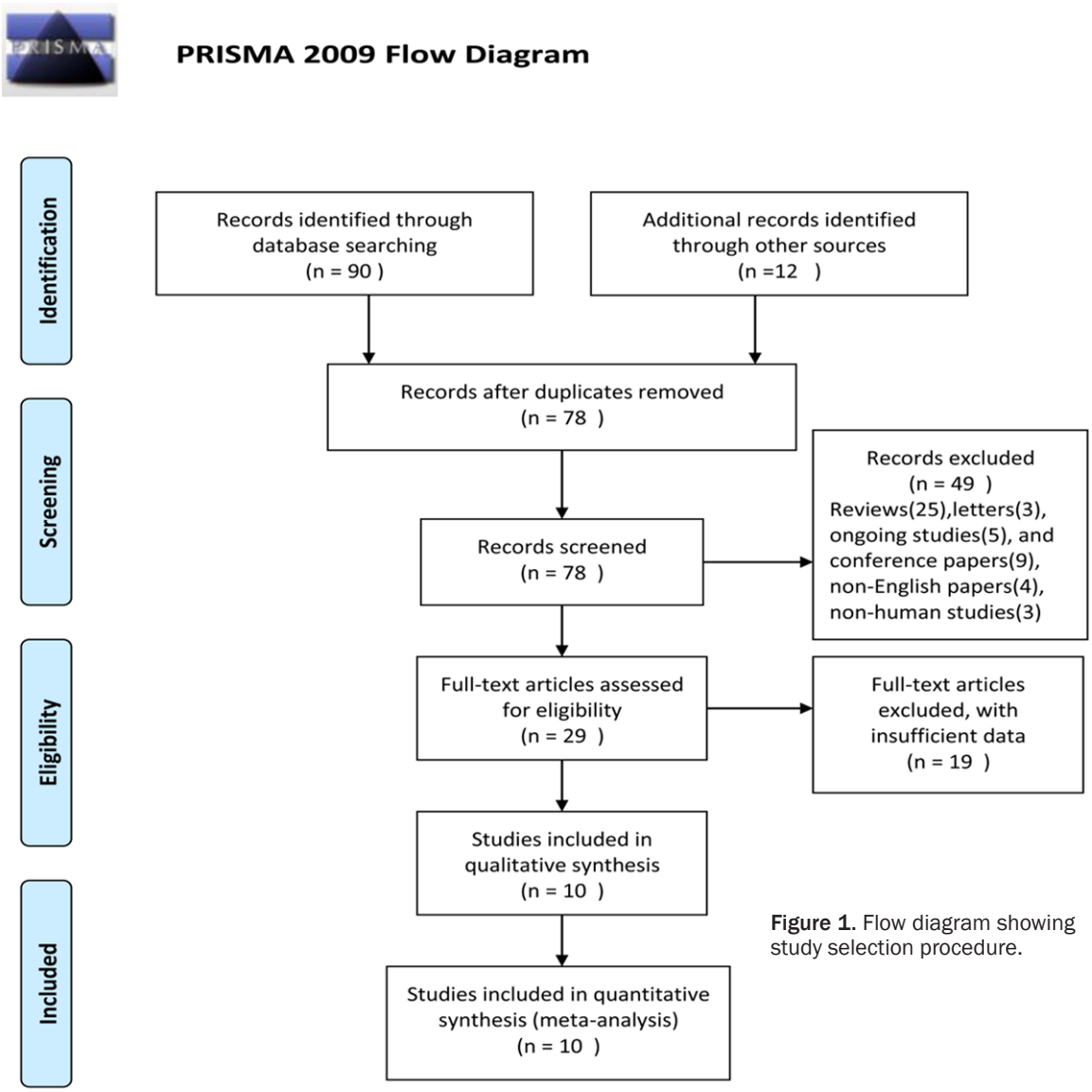

Figure 1. Flow diagram showing study selection procedure.

0.10 in a Q test, a fixed-effect model (the Mantele-Haenszel method) was applied in the following meta-analysis. Otherwise, a random-effect model was appropriate for the analysis [23]. Publication bias was evaluated using objective Begg's or Egger's tests [24, 25]. All *p* values were based on two-sided test and P was considered statistically significant if it was less than 0.05.

Results

Search results

A total of 102 records on the association of PD-L1 expression with NSCLC were identified via initial database searching. Upon further reviewing the full text, 12 additional articles from reference sources were included. Of these, 24 references were excluded because of duplication, and another 49 references (25 reviews, 3 letters, 5 ongoing studies, and 9 conference papers, 4 non-English papers, 3 non-human studies) were excluded after the titles and abstracts were read. Then we access the full-text of the remaining articles and 19 studies without sufficient survival data were further excluded. Eventually, 10 articles reporting 11 studies were included in our meta-analysis and were subjected to further statistical evaluation [26-35] (**Figure 1**).

Table 2. Correlation between PD-L1 expression and the clinicopathological characteristics

Clinicopathological characteristics	No. of studies	Heterogeneity		OR	95% CI	*P*-value
		P-value	I^2 (%)			
Gender	10	0.001	67	0.93	0.64-1.34	0.70
Histology type	**5**	**0.008**	**71**	**1.87**	**1.12-3.12**	**0.02**
Differentiation	**4**	**0.29**	**20**	**1.95**	**1.27-2.99**	**0.002**
Tumor stage	**6**	**0.16**	**37**	**1.30**	**1.04-1.63**	**0.02**
Lymph node metastasis	3	0.07	62	1.47	0.74-2.93	0.28
Smoking status	7	< 0.0001	79	1.17	0.68-2.02	0.56

Notes: Bold values indicate PD-L1 expression was significantly associated with histology type, differentiation and tumor stage. Abbreviations: OR, odds ratio; CI, confidence interval.

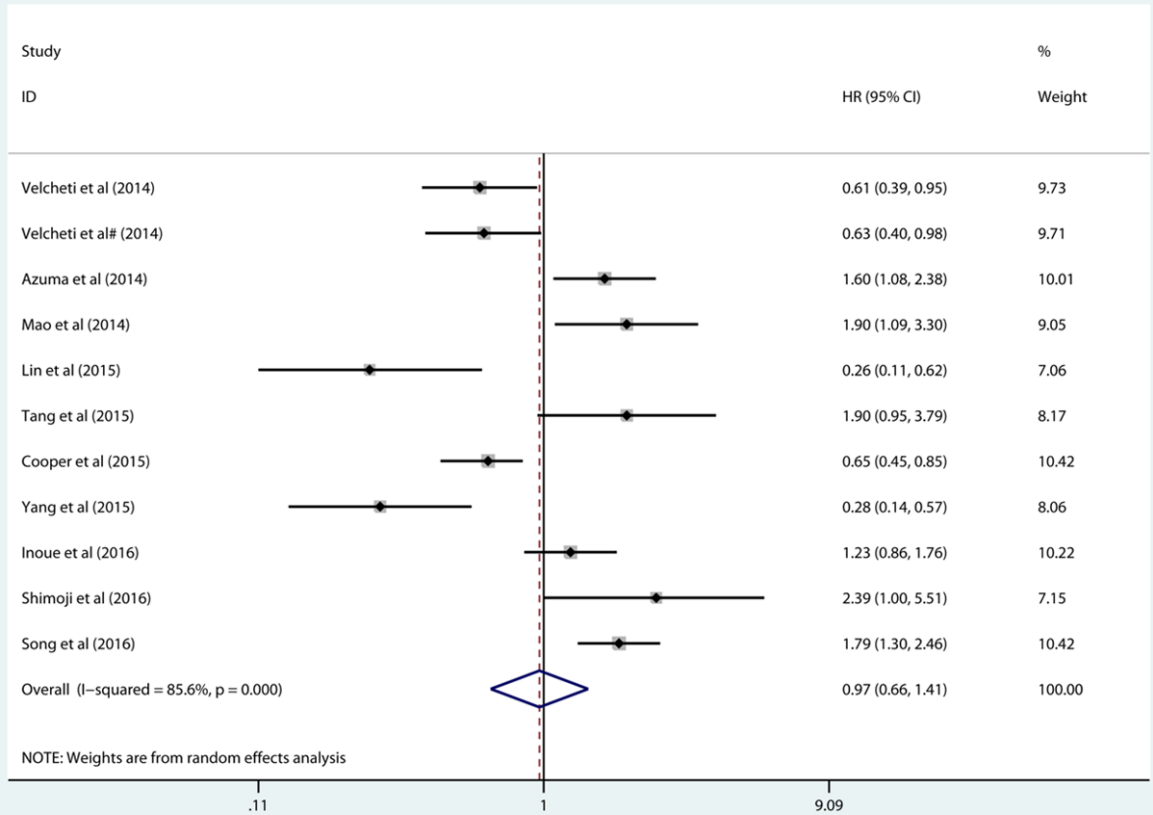

Figure 2. Forest plot showing HR from random-effects model for the association between PD-L1 expression and OS. Note: The squares and horizontal lines represent HR and 95% CI. The diamonds represent the pooled HR and 95% CI. The solid vertical line is at the null value. Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval.

Characteristics of studies

All detailed features of the 11 eligible studies are listed in **Table 1**. The publication years of the eligible studies are concentrated in 2014 to 2016. All the studies were designed retrospectively respectively conducted in China (5), Japan (3), USA (1), Greece (1) and Austialia (1). The number of patients ranged from 56 to 678 (mean sample size, 273 patients). Three studies analyzed just adenocarcinoma cancer (ADC), one analyzed squamous cell cancer (SCC), and the other studies focused on the whole NSCLC. PD-L1 expression was detected by immunohistochemistry (IHC) in 8 studies, quantitative immunofluorescence (QIF) in two studies, and fluorescence *in situ* hybridization (FISH) in one. The cutoff value for PD-L1 expres-

Table 3. Summary of subgroup analysis in studies that reported OS stratified by PD-L1 status

Subgroup	No. of studies	Heterogeneity		HR for OS	95% CI	*P*-value
		P-value	I^2 (%)			
Overall	11	< 0.001	85.6	0.967	0.664-1.409	0.863
Regions						
Asian	8	0.974	82.9	1.162	0.745-1.813	0.508
Westerner	**3**	**< 0.001**	**0.0**	**0.635**	**0.507-0.794**	**< 0.001**
Sample size						
More than 300	4	< 0.001	88.4	0.975	0.579-1.641	0.923
Less than 300	7	< 0.001	86.2	0.955	0.520-1.754	0.881
Histology types						
Not all ADC	8	< 0.001	83.4	0.923	0.622-1.371	0.691
All ADC	3	< 0.001	89.0	1.070	0.335-3.412	0.910
Methods						
Other than IHC	3	0.019	74.8	0.792	0.491-1.277	0.338
IHC	8	< 0.001	87.7	1.049	0.630-1.747	0.855
Antibody source and type						
Rabbit polyclonal	5	< 0.001	85.8	0.810	0.441-1.487	0.496
Mouse monoclonal	2	0.001	90.8	1.084	0.379-3.098	0.880
NM	4	< 0.001	84.1	1.150	0.606-2.183	0.669

Notes: Bold values indicate PD-L1 overexpression was significantly associated with good prognosis in Western patients. Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval; ADC, adenocarcinoma; IHC, immunohistochemistry; NM, not mentioned.

sion depended on the method used. All the studies directly provided adjusted HR with 95% CI by multivariate Cox proportional models. The quality of the enrolled studies varied from 6 to 9 according to the 9-score system of the NOS, with a mean of 7.

Correlation between PD-L1 expression and clinicopathological characteristics

The relationship between PD-L1 expression and clinicopathologic parameters (reported in at least 3 studies) was presented in **Table 2**. Forest plots of studies evaluating the association between PD-L1 expression and clinical parameters were attached in Supplementary Figures 1 and 2. In NSCLC, PD-L1 expression was found to be significantly associated with histology type (OR = 1.87, 95% CI: 1.12-3.1[2]; *P* = 0.02), differentiation (OR = 1.95, 95% CI: 1.27-2.99; *P* = 0.002) and tumor stage (OR = 1.30, 95% CI: 1.04-1.63; *P* = 0.02), but not with gender (OR = 0.93, 95% CI: 0.64-1.34; *P* = 0.70), lymph node metastasis (OR = 1.47, 95% CI: 0.74-2.93; *P* = 0.28) and smoking status (OR = 1.17, 95% CI: 0.68-2.02; *P* = 0.56). Besides, we found a significant heterogeneity in terms of gender (I^2 = 67%), histology type (I^2 = 71%), lymph node metastasis (I^2 = 62%) and smoking status (I^2 = 79%).

Correlation between PD-L1 expression and OS

The pooled results of the 11 trials comprising 3,000 patients did not show a statistically significant relationship between PD-L1 expression and OS (HR = 0.967, 95% CI: 0.664-1.409, *P* = 0.863). However, there existed significant heterogeneity in the studies (I^2 = 85.6%, *P* < 0.001) (**Figure 2**). We removed each study sequentially but found the stable pooled HRs not significantly affected by each individual study (Supplementary Figure 3). Therefore, we conducted subgroup meta-analysis to explore whether the heterogeneity was due to different regions, sample size, histology types, detection methods, antibody source and type. As shown in **Table 3**, PD-L1 overexpression was significantly associated with good prognosis only in Western patients (HR = 0.635, 95% CI: 0.507-0.794, *P* < 0.001). Nevertheless, we couldn't find out any other statistical relationship between PD-L1 expression and NSCLC prognosis in the remaining subgroups.

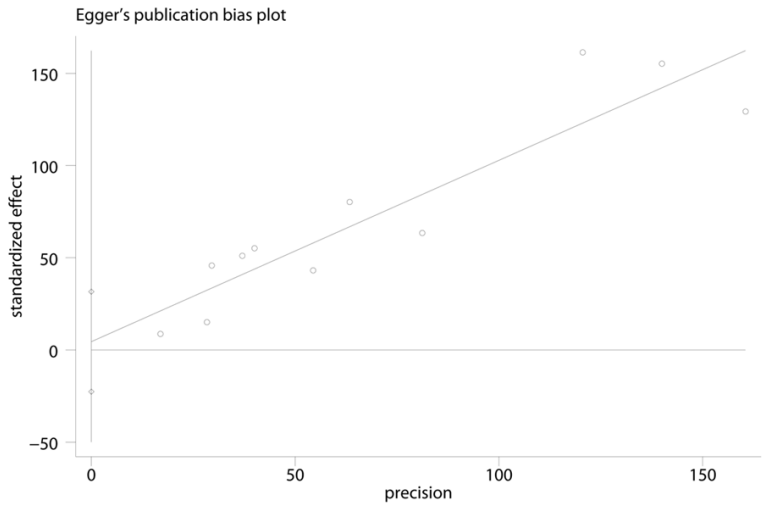

Figure 3. Egger's publication bias plot for assessment of potential publication bias in studies. Abbreviations: SE, standard error; HR, hazard ratio.

Publication bias

The reliability of results was evaluated by publication bias estimation. We performed Egger's test and Begg's tests for precise assessment (Egger's test, $P = 0.718$; Begg's test, $P = 1.000$), which implied no publication bias. As shown in **Figure 3**, Egger's publication bias plot revealed no evidence of publication bias for pooled HR.

Discussion

The relationship between PD-L1 expression and NSCLC has been investigated extensively, but the results are inconsistent. Using a meta-analysis, we investigated the association between PD-L1 expression and clinicopathological features. The pooled data indicated that PD-L1 expression was positively correlated with histology type, differentiation, and tumor stage but not with gender, the presence or absence of lymph node metastasis and smoking status. We saw that PD-L1 expression may be associated with tumor progression.

Subsequently, we assessed the potential prognosis role of PD-L1 expression in NSCLC patients but found no statistically significant difference between PD-L1 expression and prognosis in NSCLC. Different studies exhibited various consequences. Velcheti et al [26], Lin et al [29], Cooper et al [31] and Yang et al [32] reported that higher PD-L1 level was associated with a significant better prognosis. However, Azuma et al [27], Mao et al [28], Shimoji et al [34] and Song et al [35] showed completely reverse results, which indicated PD-L1 overexpression was associated with a significant shorter OS. In the remaining included studies, we couldn't obtain a significant correlation between PD-L1 expression and OS. Indeed, the differences in the definition of PD-L1-positivity/negativity, therapeutic regimen and many other discordance in these studies may affect the final conclusion.

Owing to the significant heterogeneity, we conducted subgroup analysis to explore the relationship between PD-L1 expression and OS according to different regions, sample size, histology types, detection methods, antibody source and type. We found that PD-L1 higher expression was significantly associated with good prognosis in Western patients and no heterogeneity was found in this subgroup. Patents in the west may be more likely to accept the immune therapy and PD-LI expression may be a fine curative effect biomarker for anti-PD-LI/PD-1 monoclonal antibodies therapy [36]. We couldn't find any other statistical relationship between PD-L1 expression and NSCLC prognosis to identify the source of heterogeneity. Various factors may be barriers to a pooled analysis to illustrate the prognostic significance of PD-L1 in NSCLC, such as differences in the baseline characteristics of the patients, the sole dependence on immunohistochemical analysis of PD-L1 expression, the definition of positive/high PD-L1 expression, treatment, the duration of follow-up and so on.

A potential association between PD-L1 expression and the prognosis of patients with NSCLC has been assessed in previous meta-analysis. Zhou et al [37], Pan et al [38] and Wang et al [39] showed NSCLC patients with raised PD-L1 expression exhibited poor OS. Zhong et al [40] Hu et al [41] performed updated meta-analysis later, but found no statistically significant difference between PD-L1 expression and prognosis for patients with NSCLC. However, several drawbacks existed in the precious meta-analy-

sis. Firstly, the combined sample size of the former three analyses were relatively small such that the results may not be representative. Our meta-analysis enrolled 3000 NSCLC patients, which far exceeded their sample size. Furthermore, we brought several up-to-date studies into our meta-analysis and our data were fresh compared to theirs. Secondly, several HRs in their studies were extracted from Kaplan-Meier curves, which may not be accurate. To enhance it, eligible studies had to clearly provide adjusted data of HR for OS with 95% CI. Thirdly, the majority of studies they included were performed in china, while we included studies with a wider range of population distribution.

Although we conducted a systematical and comprehensive analysis, there still exists several limitations, such as variations of the baseline characteristics of patients, the difference of cut-off value for judging high PD-L1 expression, the quality of primary antibody and dilution, the sole dependence on immunohistochemical analysis of PD-1 and PD-L1 expression and so on. But we don't have adequate data to perform subgroup analysis on these factors. Besides, we assessed the publication bias and did not find significant deviation though a positive result is easier to be published as we all know.

In conclusion, our meta-analysis indicated that PD-L1 expression is positively correlated with histology type, poor differentiation, and high tumor stage. There is no statistically significant relationship between PD-L1 expression and the prognosis of NSCLC patients. PD-L1 may not be a good predictive biomarker for NSCLC outcome. Nevertheless, more large scale research is needed to accurately support the relationship between PD-L1 expression and prognosis for NSCLC patients.

Disclosure of conflict of interest

None.

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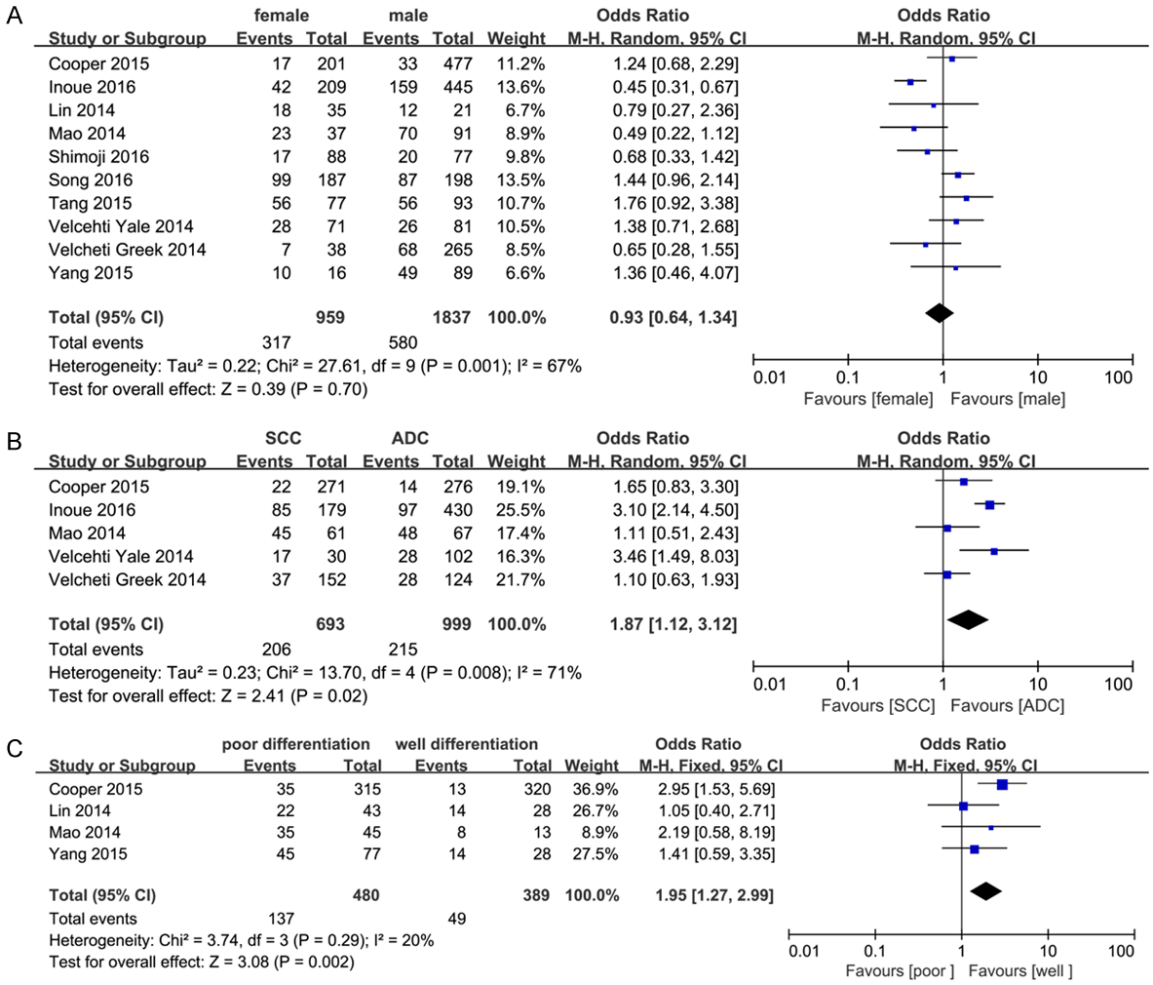
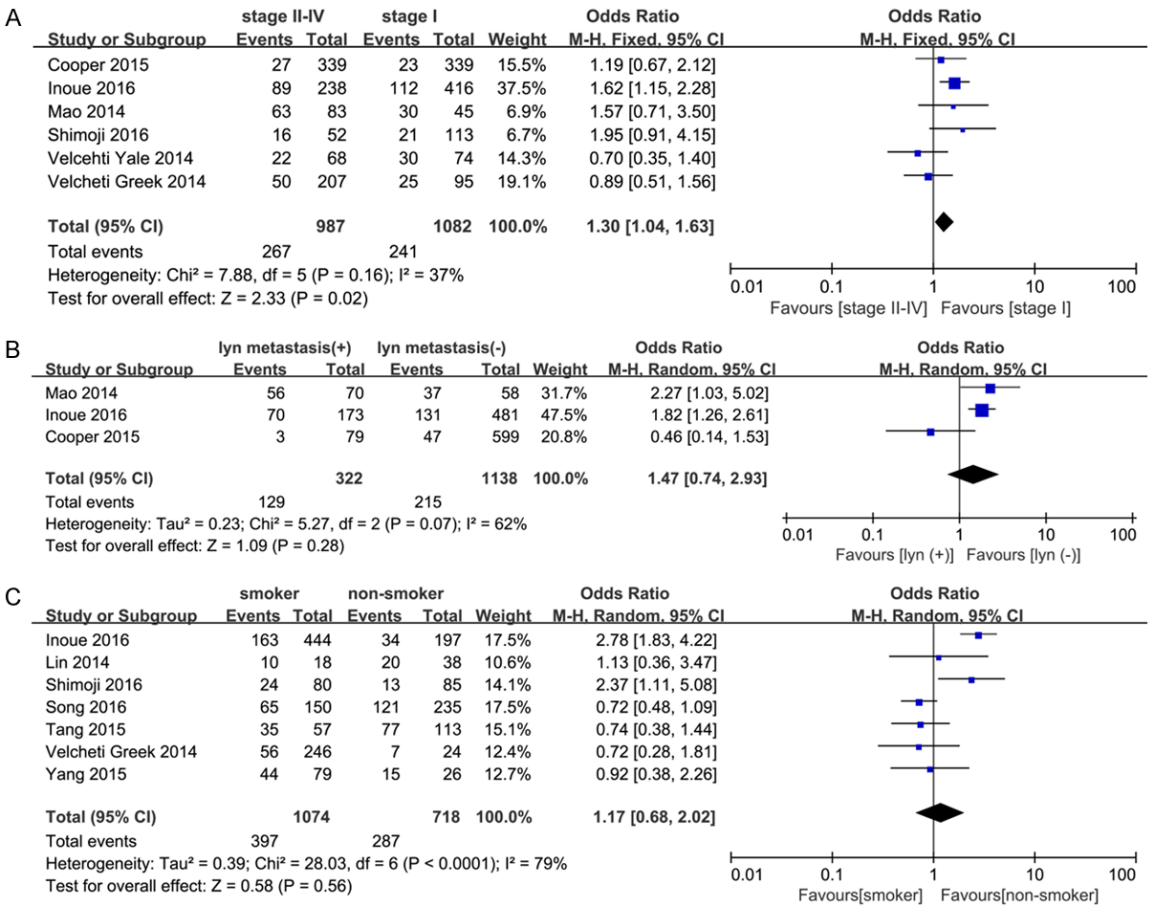
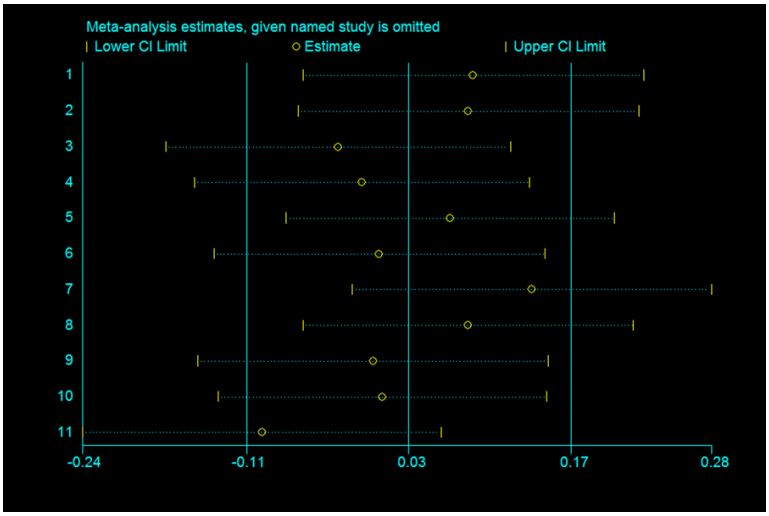


Supplementary Figure 1. Forest plots of studies evaluating the association between PD-L1 expression and clinical parameters in NSCLC. A. Gender (female versus male). B. Histology type (SCC versus ADC). C. Differentiation (poor versus well). Abbreviations: NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; CI, confidence interval; M-H, Mantel-Haenszel.



Supplementary Figure 2. Forest plots of studies evaluating the association between PD-L1 expression and clinical parameters in NSCLC. A. TNM stage (II-IV versus I). B. Lymph node metastasis (Positive vs Negitive). C. Smoking status (Smoker versus Non-smoker). Abbreviations: NSCLC, non-small cell lung cancer; CI, confidence interval; M-H, Mantel-Haenszel.



Supplementary Figure 3. Sensitivity analysis. The stable pooled HRs were not significantly affected by each individual study. Abbreviations: CI, confidence interval.