



The prevalence and prognostic and clinicopathological value of PD-L1 and PD-L2 in renal cell carcinoma patients: a systematic review and meta-analysis involving 3,389 patients

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Background: The research of the prognostic and clinicopathologic values of programmed cell death ligand 1/2 (PD-L1/2) in renal cell carcinoma (RCC) patients has been mired by a dearth of studies and considerable controversy. We thus conducted a systematic review and meta-analysis to report the prevalence and prognostic and clinicopathological value of programmed cell death ligand 1 (PD-L1) and programmed cell death-legend 2 (PD-L2) in RCC patients.

Methods: The PubMed, Cochrane Library, EMBASE databases were searched to find human studies limited to English language literature published through October 1, 2019. Using random or fixed effects models, hazard ratios (HRs) and 95% confidence intervals (CIs) were evaluated to explore the prognostic value of PD-Ls expression, while odds ratios (ORs) and 95% CIs were evaluated to investigate clinicopathological parameters. The protocol of the study was registered in PROSPERO (CRD42019135199).

Results: After pooling all 16 eligible studies comprising 3,389 patients, we found that the overall prevalence of PD-L1 and PD-L2 in RCC patients was 27% and 39%, respectively. Furthermore, PD-L1 over-expression was a strong negative predictor for overall survival (OS), disease-free survival/progression-free survival (DFS/PFS), and cancer-specific survival (CSS) in renal cell carcinoma patients (HR =2.86, 95% CI: 1.83–4.47, P<0.001; HR =2.64, 95% CI: 1.99–3.52, P<0.001; HR =2.78, 95% CI: 2.17–3.56, P<0.001). Meanwhile, PD-L2 over-expression was only a weak negative predictor for CSS (HR =1.66, 95% CI: 1.05–2.65, P<0.05). Subgroup analysis showed that Caucasians had worse OS (HR =3.60, 95% CI: 1.77–7.33, P<0.001), PFS (HR =3.56, 95% CI: 2.44–5.18, P<0.001), and CSS (HR =3.13, 95% CI: 2.37–4.14, P<0.001) than Asians. PD-L1 was a strong indicator for worse prognosis (P<0.05 for all), while PD-L2 over-expression was only associated with sarcomatoid features (presence *vs.* absence, OR =1.80, 95% CI: 1.13–2.86, P=0.014). Notably, PD-L1 overexpression was more prevalent in women (male *vs.* female, OR =0.68, 95% CI: 0.51–0.90, P=0.006).

Conclusions: Higher PD-L1 expression is more closely associated with poor prognosis and more advanced clinicopathological features in RCC patients than PD-L2, especially in women and Caucasian patients. PD-L2 was a weak negative predictor of poor CSS of RCC and was not a prompt for the metastasis of RCC.

Keywords: Immune checkpoint; prognostic biomarker; programmed cell death ligand 1 (PD-L1); programmed cell death-legend 2 (PD-L2); renal cell carcinoma (RCC)

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Introduction

As one of the most common malignancies of the kidney, renal cell carcinoma (RCC) is not only estimated to be the 16th most common cancer in the world but also causes approximately 175,000 deaths worldwide each year (1). Clear cell RCC (ccRCC), the most common histological type of RCC, and accounts for the majority of RCC deaths (2). Half of RCC cases will eventually progress to metastatic RCC (mRCC) if not treated with a proper intervention (3,4).

Over the past decade, the mechanisms underlying the etiology and pathogenesis of tumors, along with immune checkpoint inhibitory programmed cell death (PD-1)/programmed cell death ligand 1 (PD-L1) blockade—one of the most representative breakthroughs in tumor immunology—have been extensively discussed (5,6). Different from other tumors, RCC can not only be treated with surgery, chemotherapy, and radiotherapy but also with immunotherapy, yielding significantly positive treatment outcomes (7). Anti-PD-1/PD-L1 drugs have been approved by the Food and Drug Administration (FDA) and have been widely used in clinical practice as they can strengthen anti-tumor immunity and promote immune suppression in the tumor microenvironment (8-11). It has been reported that PD-1 has 2 ligands, PD-L1 and PD-L2 (12). While PD-1/PD-L1 has been widely and comprehensively studied, with PD-L1 being assumed to have associations with poor prognosis in several types of cancers (13), PD-L2 has drawn little attention, and its function is still unclear.

Both PD-L1 and PD-L2 play a suppressive role in T cell proliferation and cytokine release by interacting with PD-1 (12). According to a number of studies, PD-L2 is expressed in various types of tumors (14,15). Previous research on the association between PD-L2 and RCC, triple-negative breast cancer, and esophageal adenocarcinoma has proven that PD-L2, as a crucial potential target, may also play a similarly dominant role as PD-L1 in tumor immunotherapy (16-18). Indeed, after achieving a greater understanding of tumor immunobiology, the next major challenge for researchers lies in clarifying the resistance of the PD-1/PD-L1 blockade and reaching a more substantive comprehension of PD-L2 (19).

Overall, using the prior knowledge in this field, we performed a novel meta-analysis to evaluate the prognostic significance of both PD-L1 and PD-L2 in RCC with the aim of providing a comprehensive summary based on the available evidence.

Methods

Data sources and search strategy

Before the literature search, a detailed inclusion criterion was made following the established reporting guidelines (20,21). We independently and systematically searched the PubMed, Cochrane Library, and EMBASE database in October 2019, with the language of publication, restricted to English. Observational studies that assessed the effect of PD-L1 or PD-L2 on renal cell carcinoma patients and relevant clinical and pathological characteristics were included. References and citations of retrieved articles were all searched and checked carefully. To ensure reliability, the search process was performed by 3 authors using the following search terms: (programmed cell death 1 ligand 2 OR PD-L2 OR B7-DC OR CD273 OR programmed cell death ligand 1 OR PD-L1 OR B7-H1 OR CD274 OR B7 homolog 1) AND (cancer OR neoplasm OR malignancy OR carcinoma OR tumor) AND (survival OR outcome OR prognosis OR prognostic) AND (renal OR kidney). The agreement in the search process was reached through discussion. The protocol of the study was registered in PROSPERO (CRD42019135199).

Inclusion and exclusion criteria

Studies were considered to be eligible if they met the following criteria: (I) studies were original articles; (II) studies were published in English; (III) studies analyzed the relationship between PD-L1 or PD-L2 and overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS), or clinicopathological characteristics in any type of renal cell carcinoma patients; (IV) hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for survival analysis were reported directly or could be derived from the given data. Studies failing to conform to the inclusion criteria above were excluded. If the same sample population was included in different studies, only the most recent analysis was included.

Data collection

The 3 authors independently read and screened the retrieved titles and abstracts. The details retrieved from each study included the first author, publication year, study design, country, patient demographics, histology of cancer, cutoff value, positive rate of PD-L1 and PD-L2, follow-up time, and survival outcomes. Any missing or unclear

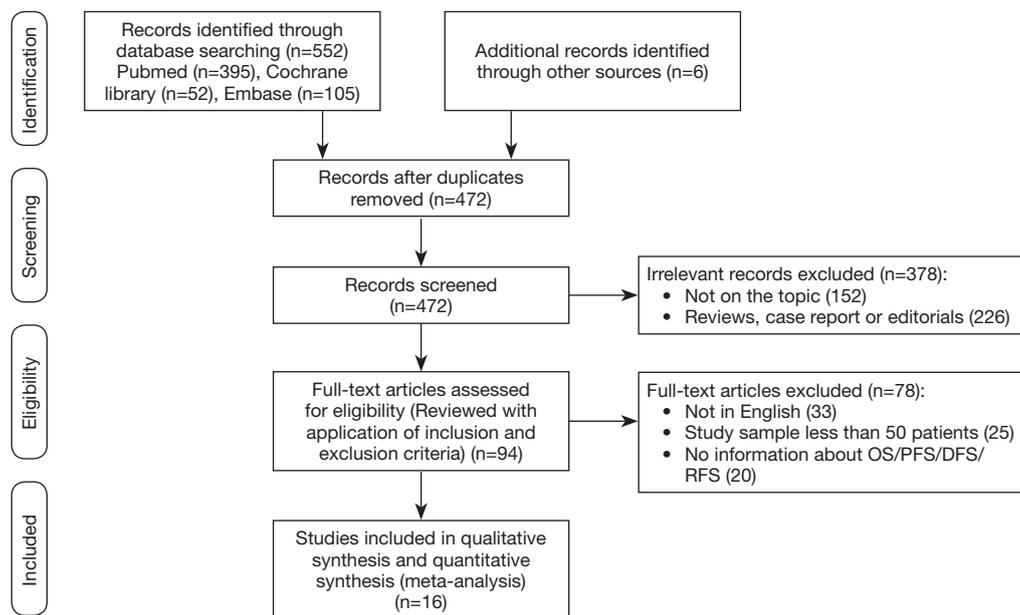


Figure 1 PRISMA flow chart of the data search. OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, relapse-free survival.

information was obtained by contacting the article authors. Information was defined as not reported if the authors did not reply. For articles that only provided survival data in a Kaplan-Meier curve, we used tools designed by Tierney and Sydes (22) to digitize and extract the HR and its 95% CI.

Risk of bias (RoB) assessment

Each of the 3 authors assessed the RoB of each included study independently. Any disagreements were resolved by consensus and communication among the 3 and with article authors. RoB of observational studies was assessed by using a modified Newcastle-Ottawa scale (NOS) (23). The scores of studies were graded from 0 to 9 according to the NOS scale for a cohort study.

Statistical analysis

The correlations between PD-L1/2 expression and the clinicopathological features of RCC (gender, invasion depth, grade, distant metastasis, lymph metastasis, vascular invasion, tumor necrosis, sarcomatoid features) were assessed by OR and 95% CIs. Hazard ratio (HR) with a 95% CI was pooled to reveal the correlation between PD-L1/2 expression and prognosis. The incidence of PD-L1/2 expression was also pooled. According to the DerSimonian

and Laird method (24), random-effect models were used when we found significant heterogeneity ($P < 0.05$ in Cochrane Q-test) and $I^2 > 50\%$. Otherwise, fixed-effect models were used for calculations. We conducted Begg's test and created funnel plots to assess the publication bias and small-study effects. Statistical analyses were performed using RevMan 5.3 (The Cochrane Centre) and STATA 12.0 (Stata-Corp.). The significance level was set as a two-tailed P value < 0.05 in all data analyses.

Results

Literature search

By searching the electronic databases (PubMed, Embase, and the Cochrane Library) with the search strategy mentioned above and reviewing the reference lists of the retrieved studies, we identified 558 records after removing 86 duplicated records. Another 378 records were excluded because they were case reports, reviews, editorials, or not relevant topics. In the remaining 94 records, 78 of records were excluded because they were study samples, not published in English, or did not have sufficient information for OS, PFS, DFS, or relapse-free survival (RFS) calculation. After screening for the form of data reporting, 16 retrospective cohort studies (3,389 patients) (25-40) were pooled in the final meta-analysis (shown in *Figure 1*).

Characteristics of included studies

The main features of the 16 studies are presented in *Table 1*. We included 3,389 patients in the study and all 16 studies in the review were retrospective studies. The publication dates ranged from 2004 to 2019, with 3 studies being published between 2004 and 2007 and the others being published between 2014 to 2019. According to the articles, all patients received resection. These studies were conducted across 7 countries, with 4 in Germany, 1 in China, 3 in Korea, 4 in the USA, and 1 in each of Brazil, Japan, and France. For histological type, 9 studies examined ccRCC, 1 study reported both ccRCC and non-ccRCC, and 5 studies reported non-RCC (2 reported chRCC and 1 reported pRCC; 2 studies did not report the exact type, just non-ccRCC). The mean follow-up time varied from 10 to 134.4 months. All the studies detected PD-L1/2 expression in tumor tissue using immunohistochemistry (IHC), and the cut-off values of high PD-L1/2 expression varied greatly across different studies, but $\geq 5\%$ was the most common criterion. None of the patients received any type of treatment, such as chemotherapy, radiotherapy, and neoadjuvant radiotherapy before surgery. The prognostic value of PD-L1/2 for OS was mentioned in 8 studies. The correlation between PD-L1/2 expression and PFS or cancer-specific survival (CSS) was reported in 10 studies, respectively. Eight studies reported HRs adjusted for PD-L1/2 expression, and 8 studies did not make adjustments. All the studies had NOS grades ≥ 5 , which showed that all the studies were designed with high methodological quality (*Table 2*).

Prevalence of PD-L1/2 expression in RCC

The prevalence of PD-L1 and PD-L2 expression among RCC patients in the eligible studies ranged from 6.0–70.4% and 22.4–66.2%, respectively (*Table 1*).

The pooled analysis results gave an overall prevalence of PD-L1 of 27% (random effect, 95% CI: 0.20 to 0.34, $I^2 = 96.7\%$) and an overall prevalence of PD-L2 of 39% (random effect, 95% CI: 0.24 to 0.55, $I^2 = 95.2\%$) (*Figure 2*).

Prognostic value of PD-L1/2 for OS, PFS, and CSS

Survival outcomes, including OS, PFS, and CSS, were pooled and synthesized according to the PD-L type (summarized in *Table 3*).

Eight studies, with 1631 individuals, reported OS. Six of them revealed a correlation between PD-L1 expression and

OS. We found that PD-L1 over-expression was a strong negative predictor for OS in renal cell carcinoma patients (HR =2.86, 95% CI: 1.83–4.47, $P < 0.001$). Two studies reported a correlation between PD-L2 expression and OS. Our study revealed that high PD-L2 expression had no predictive role for OS in renal cell carcinoma patients (HR =1.86, 95% CI: 0.55–6.27, $P = 0.315$) (*Figure 3*).

The impact of PD-L1/2 on PFS was mentioned in 10 studies comprising 2069 patients. The forest plot (*Figure 4*) showed that higher PD-L1 expression was significantly associated with poor PFS (HR =2.64, 95% CI: 1.99–3.52, $P < 0.001$), while no significant association was observed between PD-L2 over-expression and PFS (HR =1.46, 95% CI: 0.91–2.34, $P = 0.120$).

Ten studies comprising 1886 cases evaluated the impact of PD-L1/2 on CSS. The forest plot (*Figure 5*) showed that higher PD-L1 expression was significantly associated with poor CSS (HR =2.78, 95% CI: 2.17–3.56, $P < 0.001$). We also found that PD-L2 overexpression was a weak negative predictor for CSS among renal cell carcinoma patients (HR =1.66, 95% CI: 1.05–2.65, $P < 0.05$).

Subgroup analysis

Table 4 summarizes the results of subgroup analyses between PD-L1 expression and survival outcomes according to the histology of cancer, year of publication, ethnicity, and NOS score. Synthetic analysis showed that mcrRCC was associated with worse PFS (HR =2.69, 95% CI: 2.03–3.56, $P < 0.001$, $I^2 = 38.2\%$) and CSS (HR =2.86, 95% CI: 2.20–3.72, $P < 0.001$, $I^2 = 48.9\%$) than nccRCC. Subgroup analysis by ethnicity revealed that Caucasians had worse OS (HR =3.60, 95% CI: 1.77–7.33, $P < 0.001$, $I^2 = 29.8\%$), PFS (HR =3.56, 95% CI: 2.44–5.18, $P < 0.001$, $I^2 = 0.0\%$), and CSS (HR =3.13, 95% CI: 2.37–4.14, $P < 0.001$, $I^2 = 0.0\%$). Subgroup analysis stratified by NOS score showed a worse OS (HR =5.97, 95% CI: 2.46–14.47, $P < 0.001$, $I^2 = 0.0\%$), PFS (HR =2.71, 95% CI: 1.91–3.83, $P < 0.001$, $I^2 = 0.0\%$) and CSS (HR =2.93, 95% CI: 2.18–3.95, $P < 0.001$, $I^2 = 49.2\%$) in studies with an NOS score of 6. Due to the small number of studies reporting the association between PD-L2 and prognostic outcomes, no further analysis was conducted although some of them showed significant heterogeneity.

Association between PD-L1/2 expression and clinicopathological of RCC

We comprehensively assessed the role of PD-L1 and PD-

Table 1 Characteristics of included studies

PD-Ls	Study (first author, year)	Study type	Country	Ethnicity	Sample size	Gender	Histology of cancer	Cutoff value	Positive PD-L1/2 (%)	Follow-up (months), medium (range)	Survival	Model (adjusted/unadjusted)	Method NOS
PD-L2	Erlmeier 2017	RC	Germany	Caucasus	81	Mixed	chRCC	> median values	28.4	40.5 (1–226)	OS	Unadjusted	IHC 6
PD-L2	Shin 2015	RC	Korea	Asian	91	Mixed	mccRCC	Scores 2–3	39.6	34.6 (2.3–171.7)	OS, PFS	Unadjusted	IHC 5
PD-L2	Shin 2015 (1)	RC	Korea	Asian	214	Mixed	mccRCC	Scores 2–3	36.0	58.7 (1.4–202.1)	CSS, PFS	Adjusted	IHC 6
PD-L2	Shin 2015 (1)	RC	Korea	Asian	201	Mixed	pRCC	Scores 2–3	66.2	58.7 (1.4–202.1)	CSS, PFS	Adjusted	IHC 6
PD-L2	Zhang 2019	RC	China	Asian	163	Mixed	mccRCC/ nccRCC	≥1%	26.4	36 (16–70)	OS, PFS	Adjusted	IHC 8
PD-L1	Shin 2015	RC	Korea	Asian	91	Mixed	mccRCC	Scores 2–3	17.6	34.6 (2.3–171.7)	OS, PFS	Adjusted	IHC 5
PD-L1	Shin 2015 (1)	RC	Korea	Asian	214	Mixed	mccRCC	Scores 2–3	12.6	58.7 (1.4–202.1)	CSS, PFS	Adjusted	IHC 6
PD-L1	Shin 2015 (1)	RC	Korea	Asian	201	Mixed	pRCC	Scores 2–3	6.0	58.7 (1.4–202.1)	CSS, PFS	Adjusted	IHC 6
PD-L1	Abbas 2016	RC	Germany	Caucasus	177	Mixed	mccRCC	≥1%	20.9	64.7 (0.3–188.8)	OS	Adjusted	IHC 8
PD-L1	Krambeck 2007	RC	USA	Caucasus	298	Mixed	mccRCC	≥5%	23.5	81.6 (0–180)	CSS, PFS	Adjusted	IHC 8
PD-L1	Leite 2015	RC	Brazil	Caucasus	115	Mixed	mccRCC	>0	56.5	115.7 (0–180)	OS	Adjusted	IHC 7
PD-L1	Choueir 2014	RC	USA	Caucasus	101	Mixed	nccRCC	≥5%	10.9	60 (0–102)	OS	Unadjusted	IHC 6
PD-L1	Abbas 2016	RC	Germany	Caucasus	56	Mixed	nccRCC	>5%	46.4	77.5 (0–176)	OS, CSS	Adjusted	IHC 7
PD-L1	Motoshima 2017	RC	Japan	Asian	102	Mixed	pRCC	>0	28.4	CSS, PFS	Unadjusted	IHC 6	
PD-L1	Erlmeier 2016	RC	Germany	Caucasus	101	Mixed	chRCC	≥5%	13.6	40.5 (1–226)	OS	Unadjusted	IHC 6
PD-L1	Thompson 2004	RC	USA	Caucasus	196	NA	mccRCC	≥10%	37.2	24 (0–49.2)	CSS	Unadjusted	IHC 6
PD-L1	Thompson 2006	RC	USA	Caucasus	306	NA	mccRCC	≥5%	23.9	134.4 (0–180)	CSS, PFS	Unadjusted	IHC 6
PD-L1	Kammerer 2016	RC	France	Caucasus	98	Mixed	mccRCC	>0	70.4	10	CSS	Unadjusted	IHC 7
PD-L1	Kim 2017	RC	Korea	Asian	351	Mixed	mccRCC	Scores 2–3	30.8	NA	OS, CSS, RFS	Adjusted	IHC 8
PD-L1	Zhang 2019	RC	China	Asian	163	Mixed	mccRCC/ nccRCC	Staining intensity ≥1+	32.5	36 (16–70)	OS, PFS	Adjusted	IHC 8
PD-L1	Chipollini 2019	RC	Latin America and the United States	Caucasus	738	NA	nccRCC	≥5%	8.3	34 (3–118)	OS, RFS	Adjusted	IHC 8

PD-L1, programmed cell death-legend 1; PD-L2, programmed cell death-legend 2; RC, retrospective cohort; NA, not available; RCC, renal cell carcinoma; mccRCC, metastatic clear cell RCC; nccRCC, non-clear cell RCC; chRCC, chromophobe; pRCC, papillary RCC; OS, overall survival; PFS/DFS, progression-free survival/disease-free survival; CSS, cancer-specific survival; RFS, recurrence-free survival; NOS, Newcastle-Ottawa Scale; IHC, immunohistochemistry. (1), refer to reference 34.

Table 2 The Newcastle-Ottawa scale (NOS) quality assessment of the included studies.

Study (first author, year)	Study design	Selection			Outcome of interest was not present at start of study	Comparability (study adjusts for PD-1, PD-L1, PD-2, PD-L2)	Outcomes		Total scores
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure			Assessment of outcome	Follow-up long enough	
Erimeier2017	RC	0	1	1	1	0	1	1	6
Shin 2015	RC	0	1	1	0	0	1	1	5
Shin 2015 (1)	RC	0	1	1	0	1	1	1	6
Abbas 2016	RC	1	1	1	1	1	1	1	8
Krambeck 2007	RC	1	1	1	1	1	1	1	8
Leite 2015	RC	0	1	1	1	1	1	1	7
Choueir 2014	RC	0	1	1	1	0	1	1	6
Abbas 2016	RC	0	1	1	1	1	1	1	7
Motoshima 2017	RC	0	1	1	1	0	1	1	6
Erimeier2016	RC	0	1	1	1	0	1	1	6
Thompson 2004	RC	0	1	1	1	0	1	1	6
Thompson 2006	RC	1	1	1	0	0	1	1	6
Kammerer 2016	RC	1	1	1	1	0	1	1	7
Kim 2017	RC	1	1	1	1	1	1	1	8
Zhang 2019	RC	1	1	1	1	1	1	1	8
Chipollini 2019	RC	1	1	1	1	1	1	1	8

RC, retrospective cohort; NOS, Newcastle-Ottawa Scale.

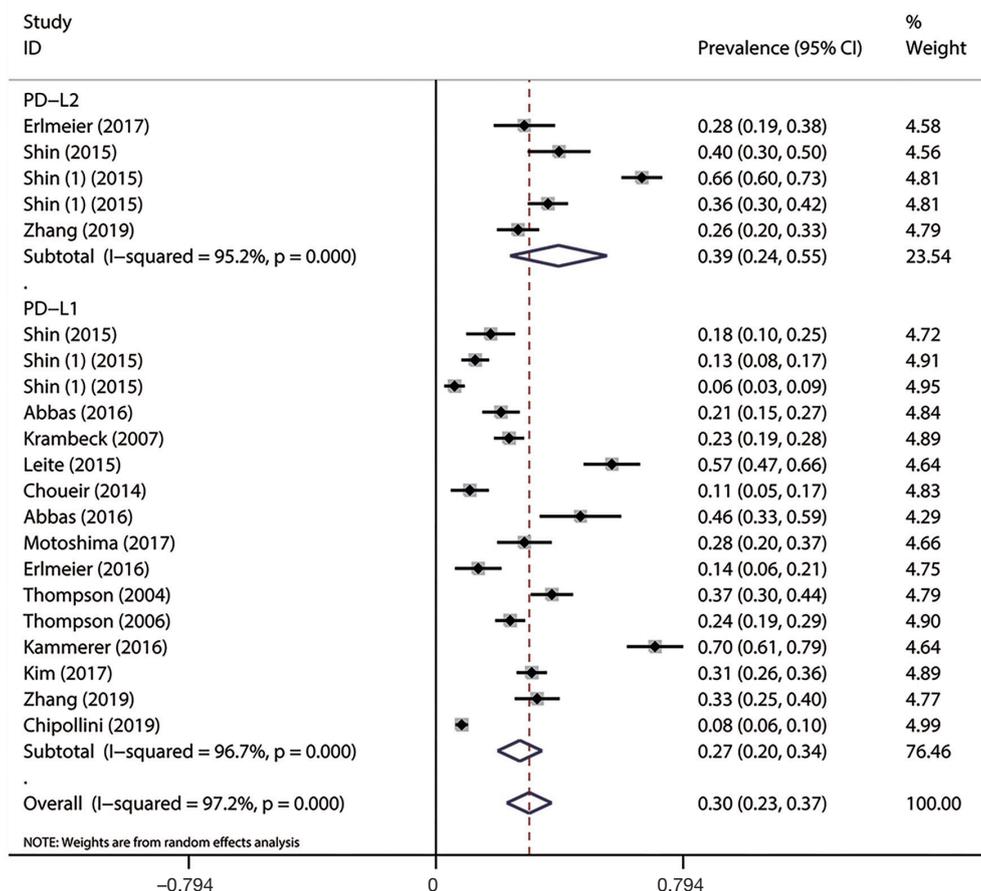


Figure 2 Prevalence of PD-L1 and PD-L2 expression in RCC. PD-L1, programmed cell death-legend 1; PD-L2, programmed cell death-legend 2; RCC, renal cell carcinoma

Table 3 Survival outcomes pooled by PD-Ls type

PD-Ls	OS					PFS					CSS				
	No. of studies	Pooled HR (95% CI)	P value	Heterogeneity I ² (%) P value		No. of studies	Pooled HR (95% CI)	P value	Heterogeneity I ² (%) P value		No. of studies	Pooled HR (95% CI)	P value	Heterogeneity I ² (%) P value	
PD-L1	6	2.86 (1.83, 4.47)	0.000	48.8	0.082	7	2.64 (1.99, 3.52)	0.000	10.6	0.349	8	2.78 (2.17, 3.56)	0.000	29.6	0.192
PD-L2	2	1.86 (0.55, 6.27)	0.315	55.4	0.134	3	1.46 (0.91, 2.34)	0.120	46.9	0.152	2	1.66 (1.05, 2.65)	0.032	0.0	0.589
Total	8	2.54 (1.60, 4.05)	0.001	65.7	0.005	10	2.10 (1.53, 2.87)	0.000	52.5	0.028	10	2.48 (2.17, 3.56)	0.000	35.1	0.127

PD-L1, programmed cell death-legend 1; PD-L2, programmed cell death-legend 2; OS, overall survival; PFS/DFS, progression-free survival/disease-free survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence intervals.

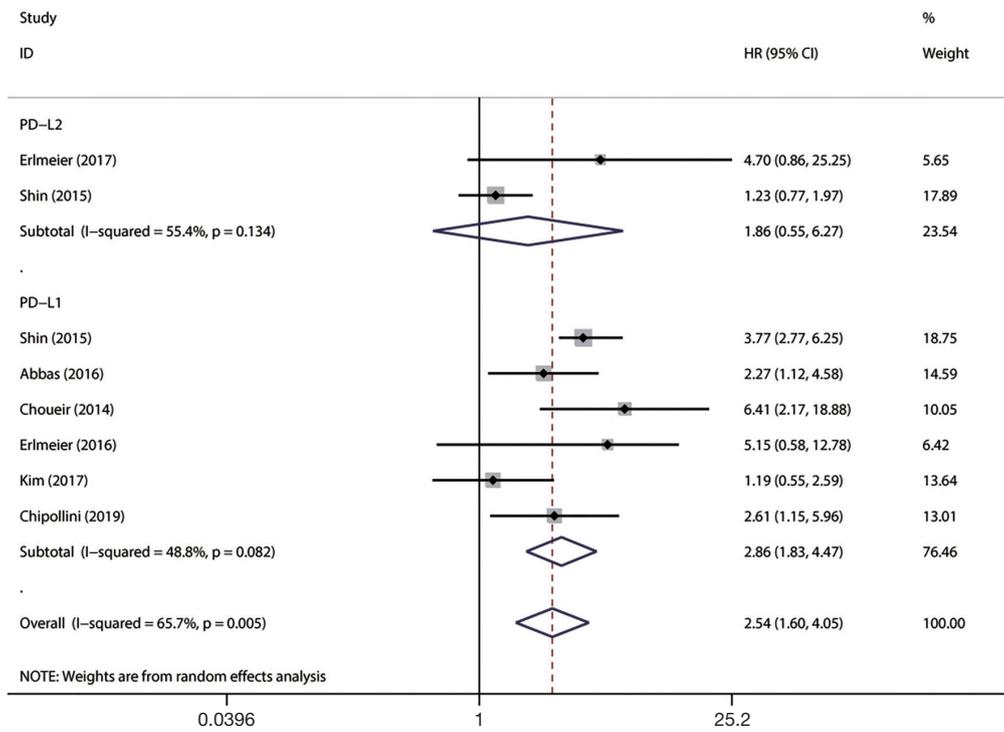


Figure 3 Prognostic value of PD-L1 and PD-L2 for OS. PD-L1, programmed cell death-legend 1; PD-L2, programmed cell death-legend 2.

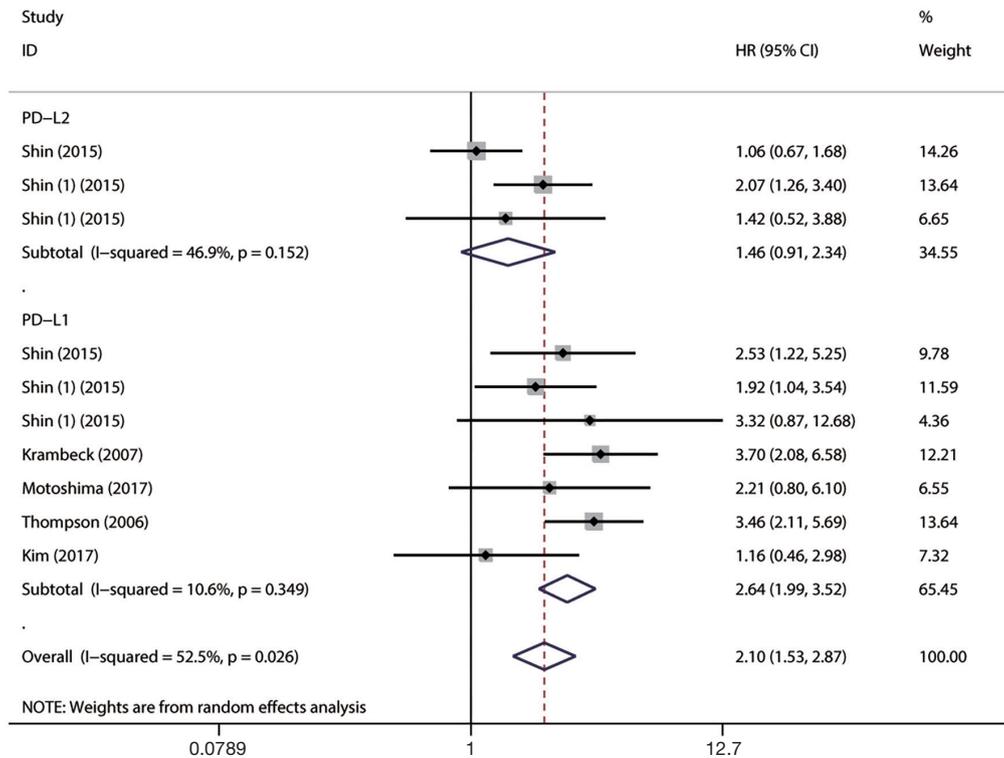


Figure 4 Prognostic value of PD-L1 and PD-L2 for PFS/DFS. PD-L1, programmed cell death-legend 1; PD-L2, programmed cell death-legend 2; PFS/DFS, progression-free survival/disease-free survival.

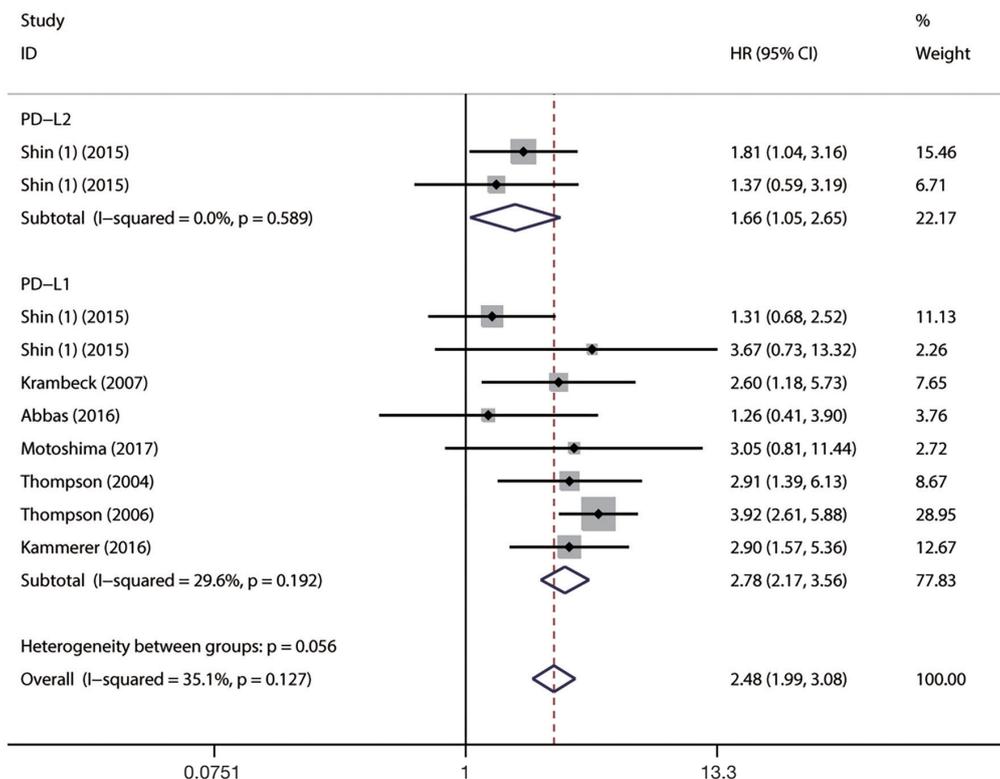


Figure 5 Prognostic value of PD-L1 and PD-L2 for CSS. PD-L1, programmed cell death-legend 1; PD-L2, programmed cell death-legend 2; CSS, cancer-specific survival.

L2 as a biochemical marker in renal cell carcinoma by studying the correlation between PD-L1/2 expression and the clinicopathology of RCC (presented in *Table 5* and *Figures S1-S8*). A total of 15 studies including 3,389 individuals were pooled in the correlation analysis. From the results, we found that PD-L1 was a strong indicator for worse prognosis: lymphatic metastasis (presence *vs.* absence, OR =1.98 95% CI: 1.36–2.89, P=0.004), depth of invasion (TIII + TIV *vs.* TI + TII, OR =2.52, 95% CI: 1.56–4.08, P=0.013), histopathological stage (III + IV *vs.* I + II, OR =2.83, 95% CI: 1.76–4.54, P=0.007), tumor metastasis (presence *vs.* absence, OR =2.67, 95% CI: 1.73–4.12, P=0.000), vascular invasion (presence *vs.* absence, OR =1.65, 95% CI: 1.07–2.56, P=0.024), necrosis (presence *vs.* absence, OR =3.09, 95% CI: 1.78–5.36, P=0.000), sarcomatoid feature (presence *vs.* absence, OR =5.59, 95% CI: 3.37–9.25, P=0.000). Notably, we found that PD-L1 overexpression was more prevalent in women (male *vs.* female, OR =0.68, 95% CI: 0.51–0.90, P=0.006). It seemed that PD-L2 was not associated with these items, except for

sarcomatoid features (presence *vs.* absence, OR =1.80, 95% CI: 1.13–2.86, P=0.014).

Publication bias

Begg’s funnel plot and Egger’s test were conducted to analyze the publication bias. No significant publication bias was found (OS: Begg’s test, P=0.824; Egger’s test, P=0.558 (*Figure 6A*); PFS: Begg’s test, P=0.548; Egger’s test, P=0.310 (*Figure 6B*); CSS: Begg’s test, P=0.858; Egger’s test, P=0.331 (*Figure 6C*).

Sensitivity analysis

We conducted a sensitivity analysis to evaluate the effects of a single study on the pooled results. We deleted each included study in each analysis to see whether the individual data might influence the pooled results. The results showed that the pooled results were not significantly affected by a single individual, suggesting that the combined results of the meta-analysis were reliable (*Figure 7*).

Table 4 Subgroup analyses between PD-L1 expression and survival outcomes

Subgroup analysis	OS					PFS					CSS				
	No. of studies	Pooled HR (95% CI)	P value	I ² (%)	Heterogeneity P value	No. of studies	Pooled HR (95% CI)	P value	I ² (%)	Heterogeneity P value	No. of studies	Pooled HR (95% CI)	P value	I ² (%)	Heterogeneity P value
Overall	6	2.86 (1.83, 4.47)	0.000	48.8	0.082	7	2.64 (1.99, 3.52)	0.000	10.6	0.349	8	2.78 (2.17, 3.56)	0.000	29.6	0.192
Histology of cancer															
mccRCC	3	2.31 (1.18, 4.52)	0.015	71.7	0.029	5	2.69 (2.03, 3.56)	0.000	38.2	0.167	5	2.86 (2.20, 3.72)	0.000	48.9	0.098
nccRCC	3	5.97 (2.46, 14.47)	0.000	0.0	0.820	2	2.56 (1.14, 5.76)	0.023	0.0	0.635	3	2.19 (1.05, 4.58)	0.038	0.0	0.438
Year of publication															
Before 2016	2	4.03 (2.75, 5.89)	0.000	0.0	0.368	5	2.94 (2.21, 3.92)	0.000	0.0	0.544	5	2.88 (2.17, 3.83)	0.000	49.6	0.094
2016 and after	4	1.99 (1.02, 3.89)	0.045	38.3	0.198	2	1.56 (0.78, 3.10)	0.206	0.0	0.360	3	2.48 (1.51, 4.09)	0.000	0.0	0.421
Ethnicity															
Caucasus	4	3.60 (1.77, 7.33)	0.000	29.8	0.241	2	3.56 (2.44, 5.18)	0.000	0.0	0.863	5	3.13 (2.37, 4.14)	0.000	0.0	0.407
Asian	2	2.22 (0.72, 6.86)	0.164	85.0	0.010	5	2.02 (1.40, 2.94)	0.000	0.0	0.680	3	1.75 (1.01, 3.01)	0.045	17.6	0.297
NOS score															
5	1	3.77 (2.51, 5.66)	0.000	-	-	1	2.53 (1.22, 5.25)	0.013	-	-	-	-	-	-	-
6	2	5.97 (2.46, 14.47)	0.000	0.0	0.820	4	2.71 (1.91, 3.83)	0.000	0.0	0.495	5	2.93 (2.18, 3.95)	0.000	49.2	0.096
7	-	-	-	-	-	-	-	-	-	-	2	2.40 (1.40, 4.11)	0.001	38.4	0.203
8	3	1.68 (0.89, 3.16)	0.108	31.6	0.227	2	2.69 (1.65, 4.39)	0.000	76.7	0.038	1	2.60 (1.18, 5.73)	0.018	-	-

OS, overall survival; PFS/DFS, progression-free survival/disease-free survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence intervals; -, not available.

Discussion

Recently, much attention has been paid to the advancement and progress of studies investigating the implication of PD-L1/2 in tumor immunity. However, significant disagreement still exists among these studies. PD-L1, which was first introduced in 1999 by Dong and colleagues (41), is a normally expressed protein on the cell surface. The mechanisms of these critical molecules in cancer immunotherapy has been well illustrated in previous research (41-48). Furthermore, antibodies to

PD-1/PD-L1 have been approved for treating several types of malignancies, such as skin melanoma, bladder cancer, etc., representing significant progress on the road to cancer treatment (49). PD-L2, a new but seldom discussed protein, functions mainly by adjusting the T helper type 2 (Th2) cell response (50), and research on PD-L2 may also provide new insights into solving the drug resistance of PD-1/PD-L1 blockade (19).

Overall, this is the newest and the most comprehensive meta-analysis reporting the prevalence and prognostic and

Table 5 Association between PD-L1/2 expression and clinicopathological of RCC

Items	PD-Ls	No. of studies	Pooled OR (95% CI)	P value	Overall OR (95% CI)	P value	I ² (%)	P value	Model
Gender (male vs. female)	PD-L1	8	0.68 (0.51, 0.90)	0.006	0.90 (0.73, 1.16)	0.333	32.1	0.119	Fixed
	PD-L2	4	1.35 (0.96, 1.90)	0.085					
Depth of invasion (TIII+TIV vs. T1+TII)	PD-L1	8	2.52 (1.56, 4.08)	0.013	1.94 (1.28, 2.95)	0.001	64.5	0.068	Random
	PD-L2	3	1.20 (0.80, 1.80)	0.767					
Histopathological stage (III+IV vs. I+II)	PD-L1	9	2.83 (1.76, 4.54)	0.007	2.11 (1.39, 3.21)	0.000	66.5	0.000	Random
	PD-L2	3	1.11 (0.75, 1.66)	0.596					
Lymphatic metastasis (presence vs. absence)	PD-L1	9	1.98 (1.36, 2.89)	0.004	1.83 (1.32, 2.89)	0.001	11.5	0.327	Fixed
	PD-L2	3	1.51 (0.82, 2.78)	0.185					
Tumor metastasis (presence vs. absence)	PD-L1	7	2.67 (1.73, 4.12)	0.000	1.99 (1.36, 2.89)	0.000	37.5	0.119	Fixed
	PD-L2	2	0.79 (0.35, 1.75)	0.556					
Vascular invasion (presence vs. absence)	PD-L1	4	1.65 (1.07, 2.56)	0.024	1.34 (0.99, 1.82)	0.062	0.0	0.681	Fixed
	PD-L2	2	1.09 (0.71, 1.69)	0.685					
Necrosis (presence vs. absence)	PD-L1	8	3.09 (1.78, 5.36)	0.000	2.05 (1.19, 3.56)	0.000	84.2	0.000	Random
	PD-L2	3	0.87 (0.42, 1.82)	0.715					
Sarcomatoid feature (presence vs. absence)	PD-L1	5	5.59 (3.37, 9.25)	0.000	3.04 (2.17, 4.24)	0.000	46.7	0.051	Fixed
	PD-L2	3	1.80 (1.13, 2.86)	0.014					

PD-L1, programmed cell death-legend 1; PD-L2, programmed cell death-legend 2; OR, odds ratio; CI, confidence intervals; RCC, renal cell carcinoma.

clinicopathological value of PD-L1 and PD-L2 in RCC patients. A past meta-analysis had investigated the impact of PD-L1 expression alone on overall survival (OS) and the association between PD-L1 and clinicopathological features, such as tumor stage, lymph node involvement, distant metastases, nuclear grade, and histologic necrosis (51). We included 16 eligible and high-quality studies with 3,389 patients, performed further subgroup analysis, and introduced more details to the review and meta-analysis. Notably, we are the first to report a correlation between PD-L1/2 expression and gender; it is also the first time that the correlation between the over-expression of PD-L2 and survival outcomes has been evaluated and that clinically significant comparisons between PD-L1 and PD-L2 have been made.

Based on the pooled results, the prevalence of PD-L1 and PD-L2 was 27% and 39%, respectively. The high variations in studies for the prevalence of PD-L1/2 might be attributed to the differences of IHC techniques, including the definition of cut-off values and primary antibody species etc. Previous studies have shown that PD-

L1/2 is commonly expressed in RCC patients (34,35). The pooled results might be influenced by the low number of studies reporting PD-L2 expression in RCC patients. More studies investigating PD-L1/2 expression and their relations with prognostic outcomes are thus required.

Another meta-analysis by Yang and colleagues investigated the association between PD-L2 and solid tumors, revealing that PD-L2 over-expression predicts poor PFS in RCC patients (16). According to our pooled results, PD-L1 was a strong negative predictor for OS, DFS/PFS, and CSS in RCC patients, and PD-L2 had only a weak negative prognostic value for CSS. It seems that PD-L1 is a more powerful prognostic predictor for survival outcomes in RCC patients. These results, however, might be limited by a dearth of eligible PD-L2 studies. More research investigating the prognostic values of PD-L2 might be needed to explore this matter more extensively. Subgroup analysis revealed that the prognostic significance of PD-L1 varied according to ethnicity, histology, and other factors. PD-L1 overexpression in Caucasians showed poorer survival outcomes in OS, PFS/DFS, and CSS than in

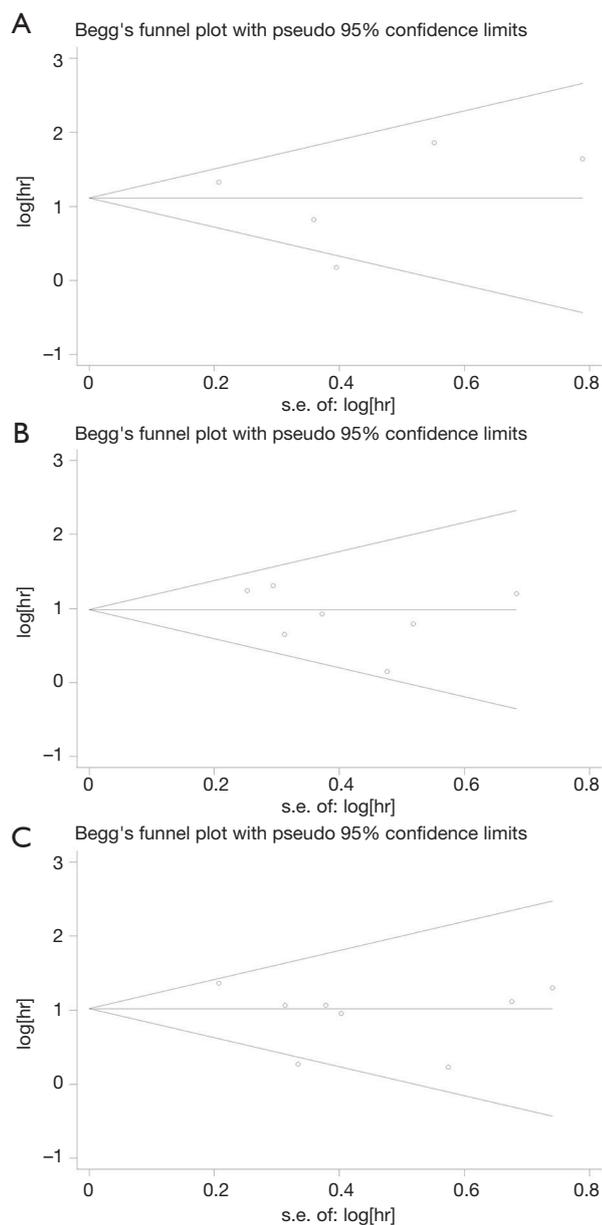


Figure 6 Funnel plots based on PD-L1 for overall survival (A), disease-free survival (B) and cancer-specific survival (C). PD-L1, programmed cell death-legend 1.

Asians. A multi-year randomized-controlled trial conducted by Horn *et al.* has demonstrated that PD-1/PD-L1-related immunotherapy in treating non-small-cell lung cancer (NSCLC) provides long-term clinical benefits and favorable tolerability with no observed differences among different ethnicities (52). Thus, whether the prognostic value of PD-L1/2 in RCC patients differs across ethnic types, and

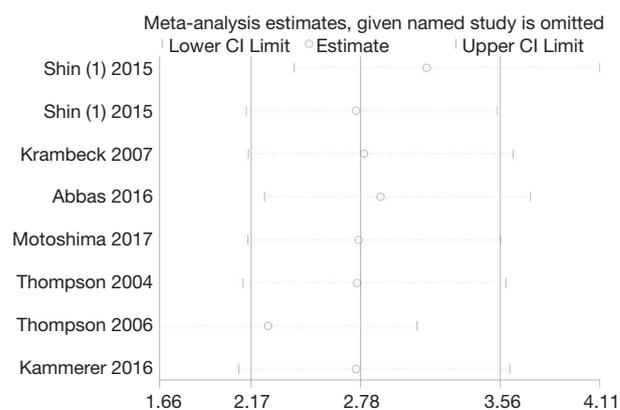


Figure 7 Sensitivity analysis (PD-L1 for disease-free survival). PD-L1, programmed cell death-legend 1.

what effects these differences might entail, remains to be discovered.

Additionally, higher PD-L1 expression implied more advanced clinicopathological features, such as depth of invasion, histopathological stage, lymphatic metastasis, tumor metastasis, vascular invasion, tumor necrosis, and sarcomatoid features; however, tumors with high PD-L2 expression displayed only a weak trend of sarcomatoid features. Meng *et al.* found PD-L1 over-expression to be associated with poor clinical characteristics (53), which is consistent with our findings. Further investigations into the mechanisms of the PD-L2 effect in RCC immunity are required to understand the role of PD-L2. It is also worth noting that PD-L1 overexpression was more prevalent in women with RCC, which, to our knowledge, is the first time this finding has been reported. A former published article (54) emphasized that the immune treatment efficacy differences between different gender in melanoma and non-small-cell lung cancer. Further well-designed, large cohort studies need to be conducted in order to confirm this trend. Additionally, as was revealed in a previous study (40), PD-L1 status was associated with the prognosis of kidney cancer patients which could help stratify patients for stricter surveillance.

Some limitations of this meta-analysis should be addressed. (I) IHC techniques were used extensively in these studies, and inconsistency in the definition of cutoff values and primary antibody species, etc. might have contributed to heterogeneity. A uniform standard is required to explore this issue better. (II) With the extensively heterogenous cutoff values of PD-L1/2, no further subgroup analysis according to cut-off values, was performed. (III) Finally, the

number of eligible studies related to PD-L2 and including RCC patients was relatively small. Thus, no detailed subgroup analysis of PD-L2 could be completed. We, therefore, recommend this as an inducement to researchers to design more large-cohort clinical trials.

Conclusions

The prevalence of PD-L1 and PD-L2 expressed in RCC was 27% and 39%, respectively. Higher PD-L1 expression is associated with poorer prognosis and more advanced clinicopathological features in RCC patients than PD-L2, especially in women and Caucasian patients. Furthermore, PD-L2 is a weak negative predictor of poor CSS of RCC and is not a good indicator of RCC metastasis.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau.2020.01.21>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the procedures performed were in full accordance with the ethical standards of the appropriate national and institutional committees on human experimentation and with the Helsinki Declaration. Ethics approval was obtained from Tianjin Medical University General Hospital ethics committee. The need for consent to participate was waived by Ethics Commission of Tianjin Medical University General Hospital.

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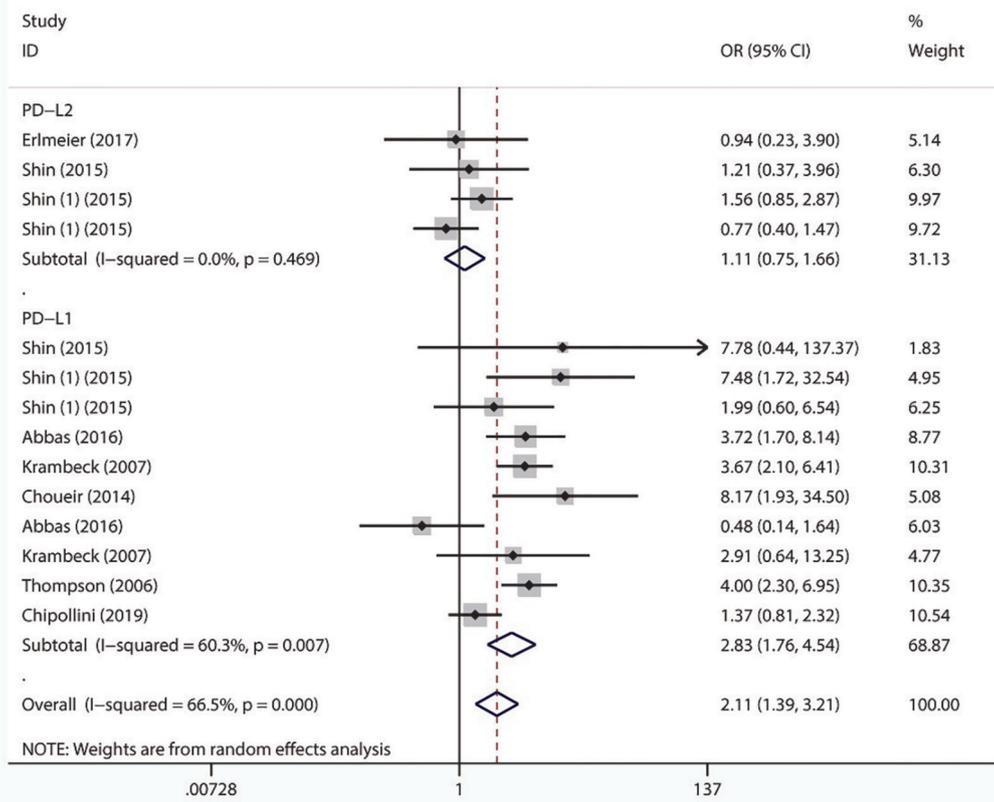


Figure S1 Correlation between PD-L1/2 expression and histopathological stage of RCC. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.

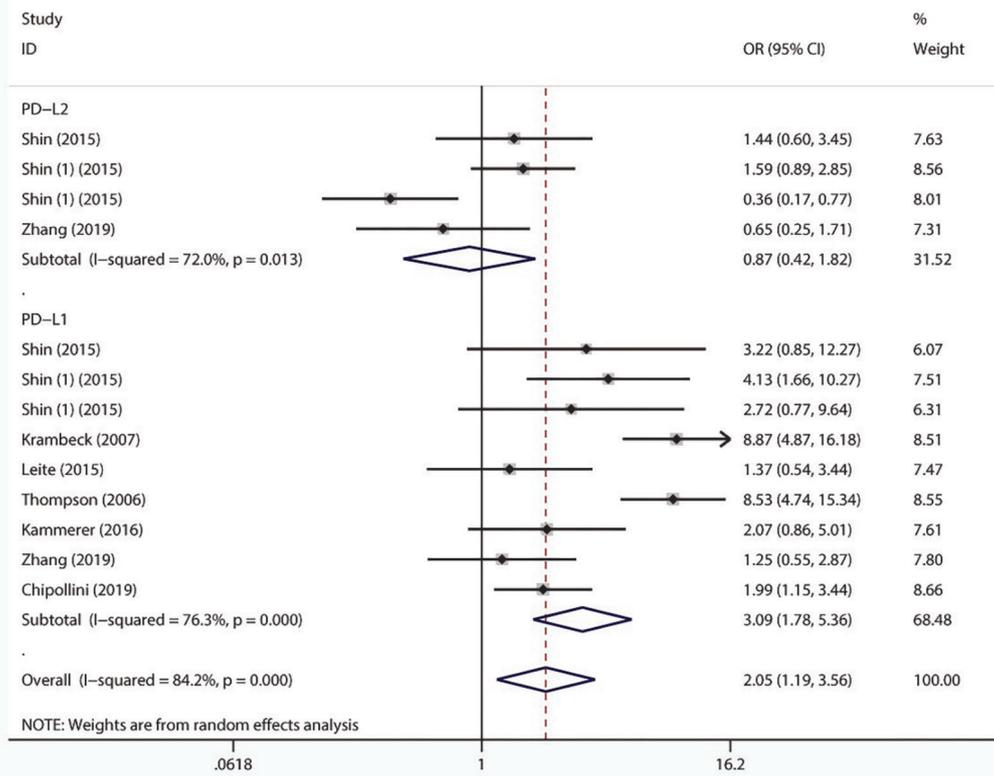


Figure S2 Correlation between PD-L1/2 expression and necrosis of RCC. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.

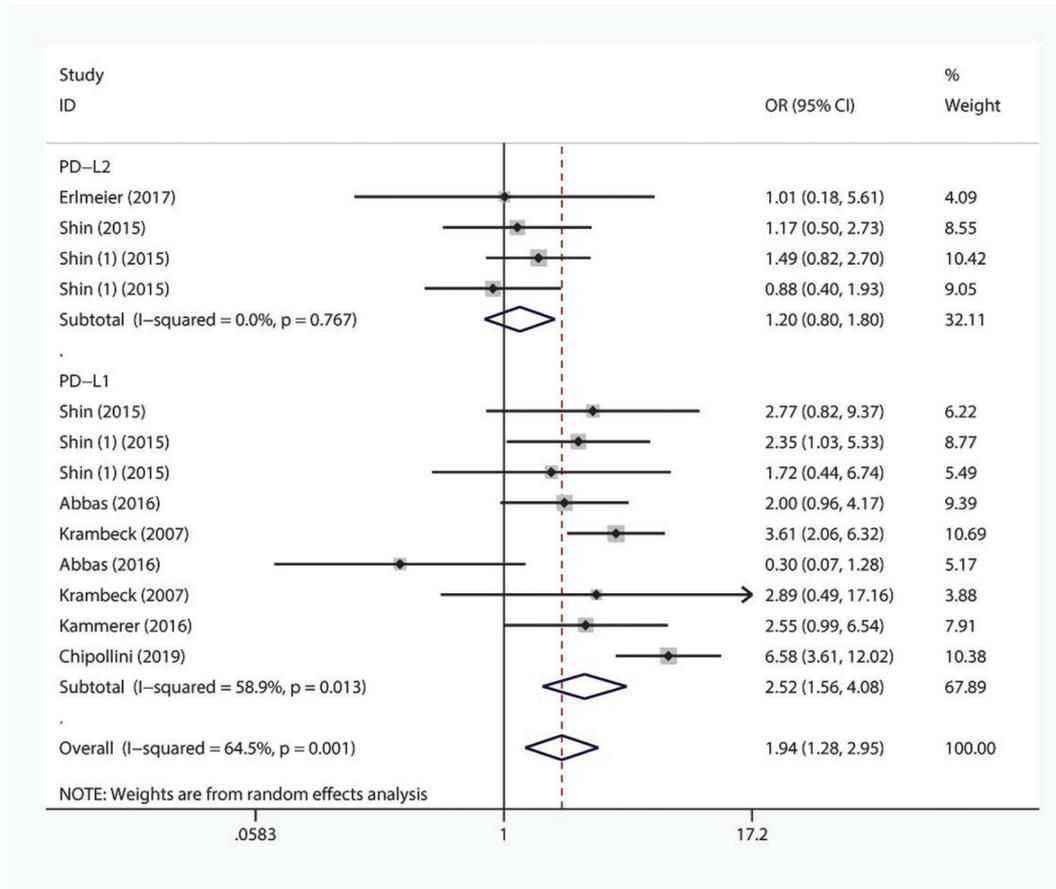


Figure S3 Correlation between PD-L1/2 expression and depth of invasion of RCC. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.

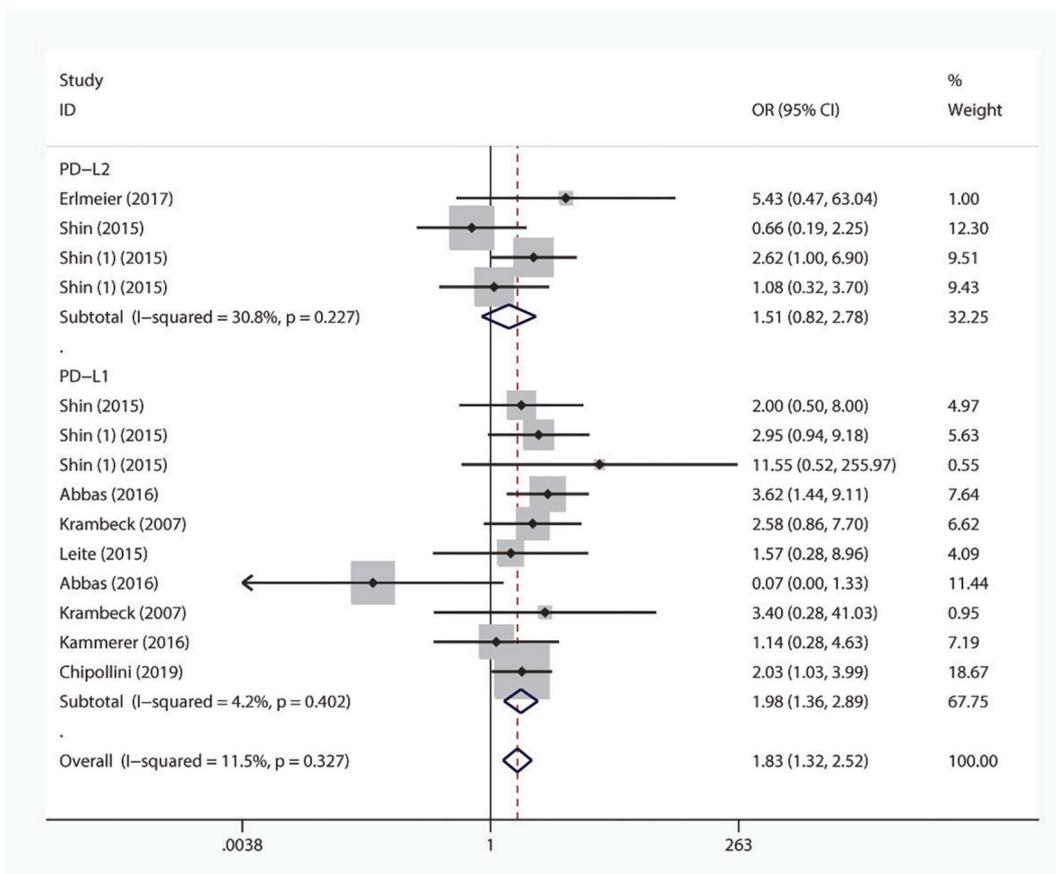


Figure S4 Correlation between PD-L1/2 expression and lymph metastasis of RCC. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.

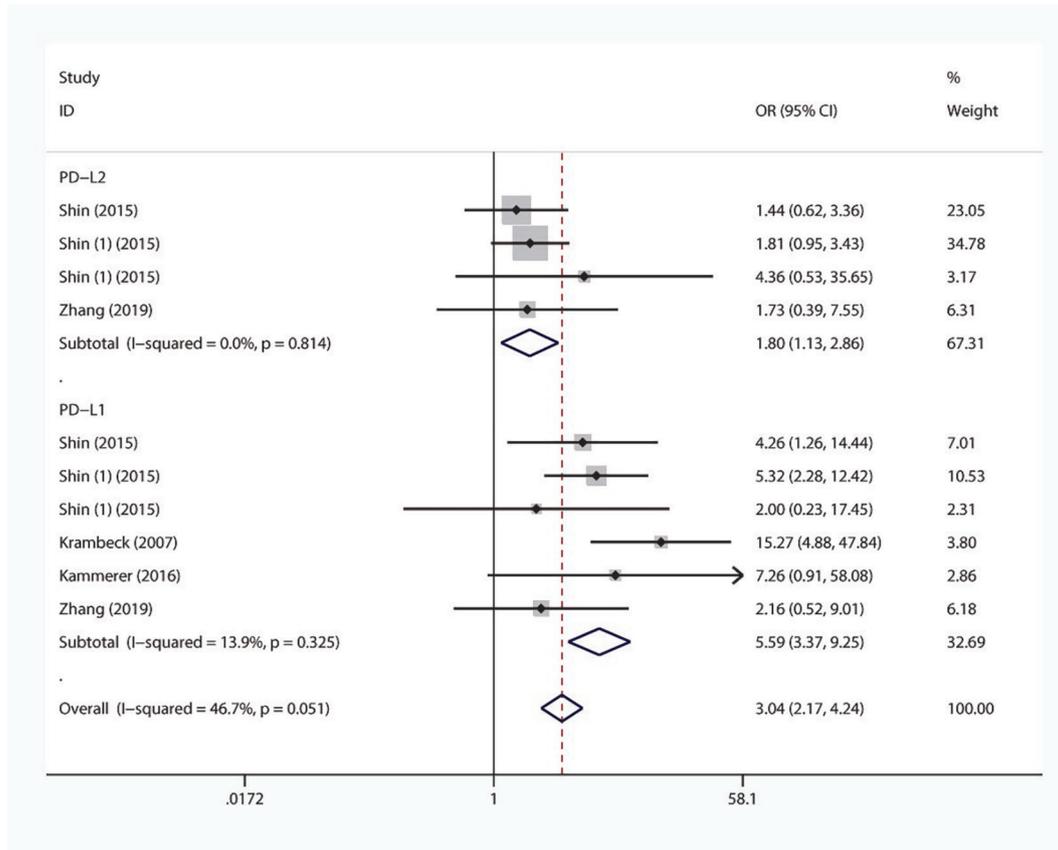


Figure S5 Correlation between PD-L1/2 expression and sarcomatoid feature of RCC. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.

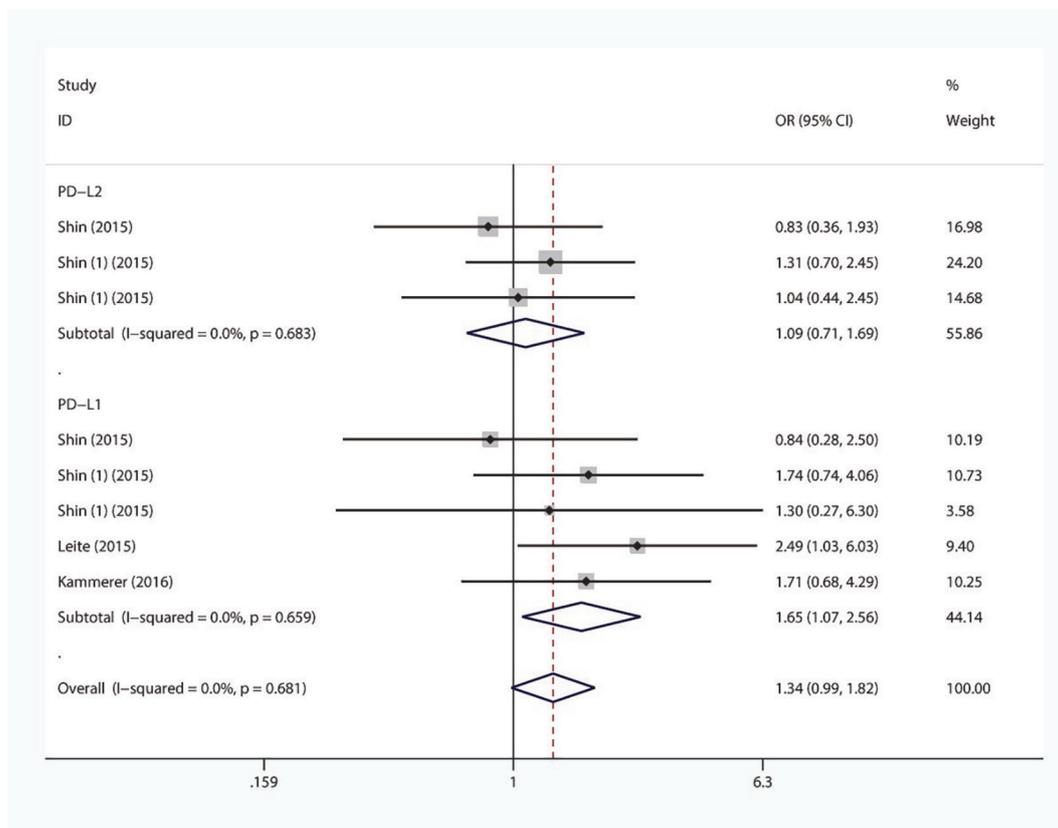


Figure S6 Correlation between PD-L1/2 expression and vascular invasion of RCC. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.

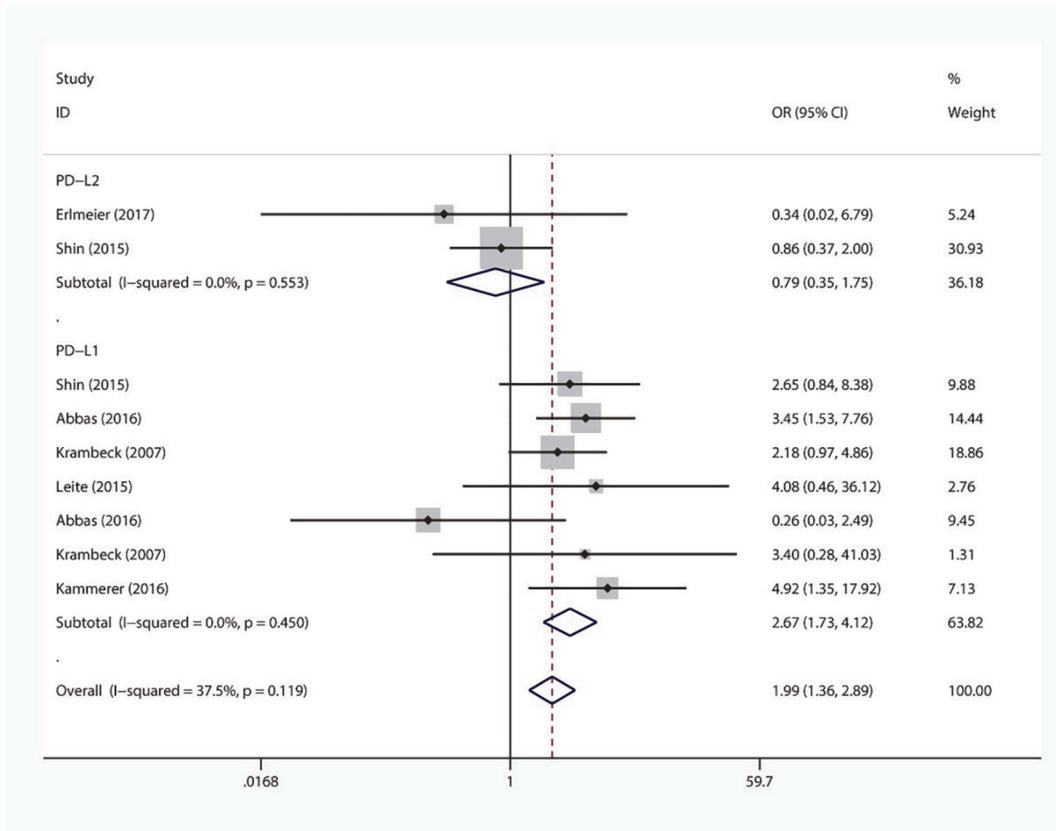


Figure S7 Correlation between PD-L1/2 expression and tumor metastasis of RCC. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.

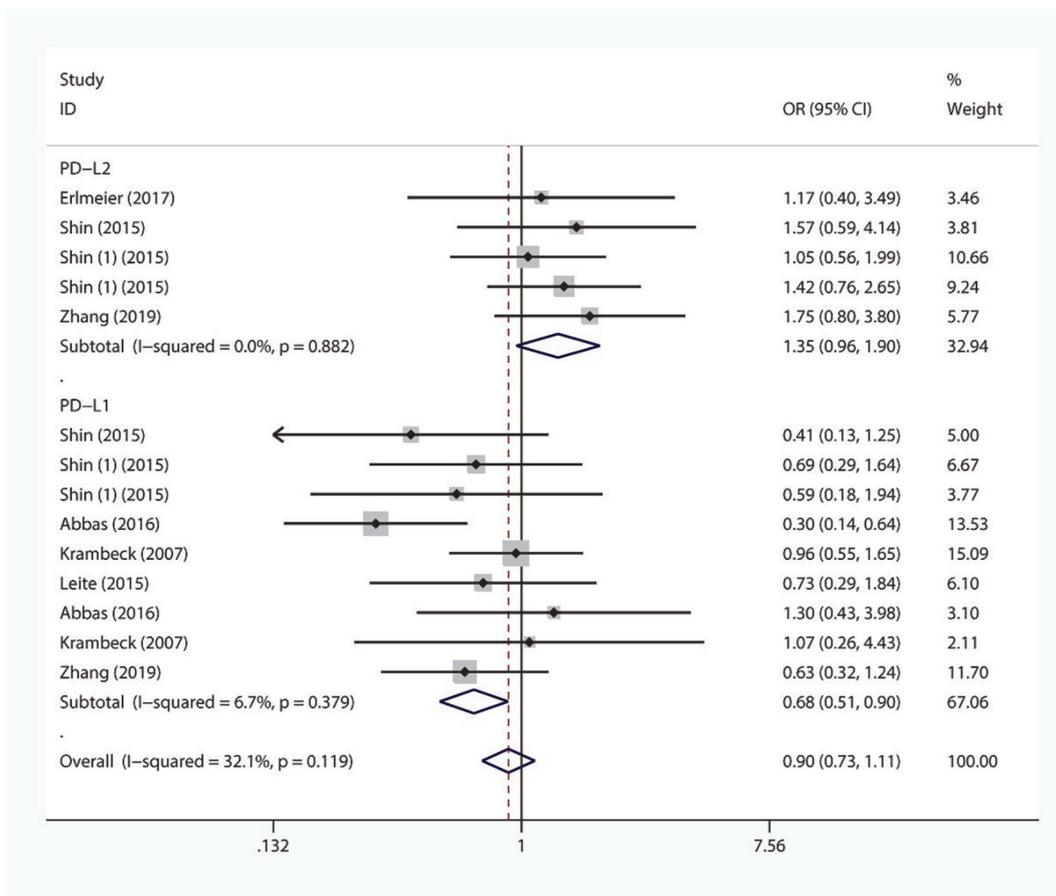


Figure S8 Correlation between PD-L1/2 expression in RCC and gender. RCC, renal cell carcinoma; PD-L1/2, programmed cell death ligand 1/2.