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 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 PD-L1 and 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; PD-L1; 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).

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
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 I² >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).

Figure 1 PRISMA flow chart of the data search.
**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 ≥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, I² =96.7%) and an overall prevalence of PD-L2 of 39% (random effect, 95% CI: 0.24 to 0.55, I² =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 mccRCC was associated with worse PFS (HR =2.69, 95% CI: 2.03–3.56, P<0.001, I² =38.2%) and CSS (HR =2.86, 95% CI: 2.20–3.72, P<0.001, I² =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, I² =29.8%), PFS (HR =3.56, 95% CI: 2.44–5.18, P<0.001, I² =0.0%), and CSS (HR =3.13, 95% CI: 2.37–4.14, P<0.001, I² =0.0%). Subgroup analysis stratified by NOS score showed a worse OS (HR =5.97, 95% CI: 2.46–14.47, P<0.001, I² =0.0%), PFS (HR =2.71, 95% CI: 1.91–3.83, P<0.001, I² =0.0%) and CSS (HR =2.93, 95% CI: 2.18–3.95, P<0.001, I² =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-L2...
<table>
<thead>
<tr>
<th>PD-Ls</th>
<th>Study (first author, year)</th>
<th>Study type</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Gender</th>
<th>Histology of cancer</th>
<th>Cutoff value</th>
<th>Positive PD-L1/2 (%)</th>
<th>Follow-up (months), medium (range)</th>
<th>Survival</th>
<th>Model (adjusted/unadjusted)</th>
<th>Method</th>
<th>NOS</th>
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<td>Shin 2015</td>
<td>RC</td>
<td>Korea</td>
<td>Asian</td>
<td>91</td>
<td>Mixed</td>
<td>mccRCC</td>
<td>Scores 2–3</td>
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<td>34.6 (2.3–171.7) OS, PFS</td>
<td>Unadjusted</td>
<td>IHC 5</td>
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<td>Asian</td>
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<td>36.0</td>
<td>58.7 (1.4–202.1) CSS, PFS</td>
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<td>mccRCC</td>
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<td>20.9</td>
<td>64.7 (0.3–188.8) OS</td>
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<td>IHC 8</td>
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<td>81.6 (0–180) CSS, PFS</td>
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<td>Mixed</td>
<td>mccRCC</td>
<td>&gt;0</td>
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<td>115.7 (0–180) OS</td>
<td>Adjusted</td>
<td>IHC 7</td>
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<td>RC</td>
<td>USA</td>
<td>Caucasian</td>
<td>101</td>
<td>Mixed</td>
<td>nccRCC</td>
<td>≥5%</td>
<td>10.9</td>
<td>60 (0–102) OS</td>
<td>Unadjusted</td>
<td>IHC 6</td>
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<td>Caucasian</td>
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<td>nccRCC</td>
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<td>46.4</td>
<td>77.5 (0–176) OS, CSS</td>
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<td>IHC 7</td>
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<td>RC</td>
<td>Japan</td>
<td>Asian</td>
<td>102</td>
<td>Mixed</td>
<td>pRCC</td>
<td>&gt;0</td>
<td>28.4</td>
<td>CSS, PFS</td>
<td>Unadjusted</td>
<td>IHC 6</td>
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<td>Caucasian</td>
<td>101</td>
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<td>chRCC</td>
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<td>13.6</td>
<td>40.5 (1–226) OS</td>
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<td>37.2</td>
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<td>23.9</td>
<td>134.4 (0–180) CSS, PFS</td>
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<td>IHC 6</td>
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<td>RC</td>
<td>France</td>
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<td>mccRCC</td>
<td>&gt;0</td>
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<td>RC</td>
<td>Korea</td>
<td>Asian</td>
<td>351</td>
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<td>mccRCC</td>
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<td>RC</td>
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<td>Asian</td>
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<td>mccRCC</td>
<td>Staining intensity ≥1+</td>
<td>32.5</td>
<td>36 (16–70) OS, PFS</td>
<td>Adjusted</td>
<td>IHC 8</td>
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<td>PD-L1</td>
<td>Chipollini 2019</td>
<td>RC</td>
<td>Latin America and the United States</td>
<td>Caucasian</td>
<td>738</td>
<td>NA</td>
<td>nccRCC</td>
<td>≥5%</td>
<td>8.3</td>
<td>34 (3–118) OS, RFS</td>
<td>Adjusted</td>
<td>IHC 8</td>
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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>
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<tr>
<th>Study (first author, year)</th>
<th>Study design</th>
<th>Selection</th>
<th>Outcome of interest was not present at start of study</th>
<th>Comparability (study adjusts for PD-1, PD-L1, PD-2, PD-L2)</th>
<th>Outcomes</th>
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RC, retrospective cohort; NOS, Newcastle-Ottawa Scale.
Table 3  Survival outcomes pooled by PD-Ls type

<table>
<thead>
<tr>
<th>PD-Ls</th>
<th>No. of studies</th>
<th>Pooled HR (95% CI)</th>
<th>OS Heterogeneity</th>
<th>Weight</th>
<th>PFS Heterogeneity</th>
<th>CSS Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>6</td>
<td>2.86 (1.83, 4.47)</td>
<td>48.8 0.082</td>
<td></td>
<td>7</td>
<td>2.64 (1.99, 3.52)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.000</td>
<td>10.6 0.349</td>
<td></td>
<td>8</td>
<td>2.78 (2.17, 3.56)</td>
</tr>
<tr>
<td>PD-L2</td>
<td>2</td>
<td>1.86 (0.55, 6.27)</td>
<td>55.4 0.134</td>
<td></td>
<td>3</td>
<td>1.46 (0.91, 2.34)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>0.001</td>
<td>52.5 0.028</td>
<td></td>
<td>3</td>
<td>2.48 (0.000, 0.000)</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>2.54 (1.60, 4.05)</td>
<td>65.7 0.005</td>
<td></td>
<td>10</td>
<td>2.10 (1.53, 2.87)</td>
</tr>
</tbody>
</table>

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 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.
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.
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. TII+TIII, 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
Table 4 Subgroup analyses between PD-L1 expression and survival outcomes

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>OS</th>
<th>Pooled HR (95% CI)</th>
<th>P value</th>
<th>Heterogeneity</th>
<th>Pooled HR (95% CI)</th>
<th>P value</th>
<th>Heterogeneity</th>
<th>CSS</th>
<th>Pooled HR (95% CI)</th>
<th>P value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies</td>
<td></td>
<td></td>
<td>i² (%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Overall</td>
<td>6</td>
<td>2.86 (1.83, 4.47)</td>
<td>0.000</td>
<td>48.8</td>
<td>0.082</td>
<td>7</td>
<td>2.64 (1.99, 3.52)</td>
<td>0.000</td>
<td>10.6</td>
<td>0.349</td>
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<tr>
<td></td>
<td>Histology of cancer</td>
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<td></td>
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<td></td>
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<tr>
<td>mccRCC</td>
<td>3</td>
<td>2.31 (1.18, 4.52)</td>
<td>0.015</td>
<td>71.7</td>
<td>0.029</td>
<td>5</td>
<td>2.69 (2.03, 3.56)</td>
<td>0.000</td>
<td>38.2</td>
<td>0.167</td>
<td>5</td>
</tr>
<tr>
<td>nccRCC</td>
<td>3</td>
<td>5.97 (2.46, 14.47)</td>
<td>0.000</td>
<td>0.0</td>
<td>0.820</td>
<td>2</td>
<td>2.56 (1.14, 5.76)</td>
<td>0.023</td>
<td>0.0</td>
<td>0.635</td>
<td>3</td>
</tr>
<tr>
<td>Year of publication</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Before 2016</td>
<td>2</td>
<td>4.03 (2.75, 5.89)</td>
<td>0.000</td>
<td>0.0</td>
<td>0.368</td>
<td>5</td>
<td>2.94 (2.21, 3.92)</td>
<td>0.000</td>
<td>0.0</td>
<td>0.544</td>
<td>5</td>
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<tr>
<td>2016 and after</td>
<td>4</td>
<td>1.99 (1.02, 3.89)</td>
<td>0.045</td>
<td>38.3</td>
<td>0.198</td>
<td>2</td>
<td>1.56 (0.78, 3.10)</td>
<td>0.206</td>
<td>0.0</td>
<td>0.360</td>
<td>3</td>
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<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Caucasus</td>
<td>4</td>
<td>3.60 (1.77, 7.33)</td>
<td>0.000</td>
<td>29.8</td>
<td>0.241</td>
<td>2</td>
<td>3.56 (2.44, 5.18)</td>
<td>0.000</td>
<td>0.0</td>
<td>0.863</td>
<td>5</td>
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<tr>
<td>Asian</td>
<td>2</td>
<td>2.22 (0.72, 6.86)</td>
<td>0.164</td>
<td>85.0</td>
<td>0.010</td>
<td>5</td>
<td>2.02 (1.40, 2.94)</td>
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<td>0.0</td>
<td>0.680</td>
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<td>NOS score</td>
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<tr>
<td>5</td>
<td>1</td>
<td>3.77 (2.51, 5.66)</td>
<td>0.000</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>2.53 (1.22, 5.25)</td>
<td>0.013</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>5.97 (2.46, 14.47)</td>
<td>0.000</td>
<td>0.0</td>
<td>0.820</td>
<td>4</td>
<td>2.71 (1.91, 3.83)</td>
<td>0.000</td>
<td>0.0</td>
<td>0.495</td>
<td>5</td>
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<tr>
<td>7</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1.68 (0.89, 3.16)</td>
<td>0.108</td>
<td>31.6</td>
<td>0.227</td>
<td>2</td>
<td>2.69 (1.65, 4.39)</td>
<td>0.000</td>
<td>76.7</td>
<td>0.038</td>
<td>1</td>
</tr>
</tbody>
</table>

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

the meta-analysis were reliable (Figure 7).

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

<table>
<thead>
<tr>
<th>Items</th>
<th>PD-Ls</th>
<th>No. of studies</th>
<th>Pooled OR (95% CI)</th>
<th>P value</th>
<th>Overall OR (95% CI)</th>
<th>P value</th>
<th>I² (%)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male vs. female)</td>
<td>PD-L1</td>
<td>8</td>
<td>0.68 (0.51, 0.90)</td>
<td>0.006</td>
<td>0.90 (0.73, 1.16)</td>
<td>0.333</td>
<td>32.1</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>PD-L2</td>
<td>4</td>
<td>1.35 (0.96, 1.90)</td>
<td>0.085</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Depth of invasion (TIII+TIV vs. TII+TIII)</td>
<td>PD-L1</td>
<td>8</td>
<td>2.52 (1.56, 4.08)</td>
<td>0.013</td>
<td>1.94 (1.28, 2.95)</td>
<td>0.001</td>
<td>64.5</td>
<td>0.068</td>
</tr>
<tr>
<td></td>
<td>PD-L2</td>
<td>3</td>
<td>1.20 (0.80, 1.80)</td>
<td>0.767</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Histopathological stage (II+IV vs. I+II)</td>
<td>PD-L1</td>
<td>9</td>
<td>2.83 (1.76, 4.54)</td>
<td>0.007</td>
<td>2.11 (1.39, 3.21)</td>
<td>0.000</td>
<td>66.5</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>PD-L2</td>
<td>3</td>
<td>1.11 (0.75, 1.66)</td>
<td>0.596</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphatic metastasis (presence vs. absence)</td>
<td>PD-L1</td>
<td>9</td>
<td>1.98 (1.36, 2.89)</td>
<td>0.004</td>
<td>1.83 (1.32, 2.89)</td>
<td>0.001</td>
<td>11.5</td>
<td>0.327</td>
</tr>
<tr>
<td></td>
<td>PD-L2</td>
<td>3</td>
<td>1.51 (0.82, 2.78)</td>
<td>0.185</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor metastasis (presence vs. absence)</td>
<td>PD-L1</td>
<td>7</td>
<td>2.67 (1.73, 4.12)</td>
<td>0.000</td>
<td>1.99 (1.36, 2.89)</td>
<td>0.000</td>
<td>37.5</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>PD-L2</td>
<td>2</td>
<td>0.79 (0.35, 1.75)</td>
<td>0.556</td>
<td></td>
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<tr>
<td>Vascular invasion (presence vs. absence)</td>
<td>PD-L1</td>
<td>4</td>
<td>1.65 (1.07, 2.56)</td>
<td>0.024</td>
<td>1.34 (0.99, 1.82)</td>
<td>0.062</td>
<td>0.0</td>
<td>0.681</td>
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<tr>
<td></td>
<td>PD-L2</td>
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<td>1.09 (0.71, 1.69)</td>
<td>0.685</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis (presence vs. absence)</td>
<td>PD-L1</td>
<td>8</td>
<td>3.09 (1.78, 5.36)</td>
<td>0.000</td>
<td>2.05 (1.19, 3.56)</td>
<td>0.000</td>
<td>84.2</td>
<td>0.000</td>
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<tr>
<td></td>
<td>PD-L2</td>
<td>3</td>
<td>0.87 (0.42, 1.82)</td>
<td>0.715</td>
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<td></td>
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<tr>
<td>Sarcomatoid feature (presence vs. absence)</td>
<td>PD-L1</td>
<td>5</td>
<td>5.59 (3.37, 9.25)</td>
<td>0.000</td>
<td>3.04 (2.17, 4.24)</td>
<td>0.000</td>
<td>46.7</td>
<td>0.051</td>
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<tr>
<td></td>
<td>PD-L2</td>
<td>3</td>
<td>1.80 (1.13, 2.86)</td>
<td>0.014</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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

PD-1/PD-L1 blockade (19).

Overall, this is the newest and the most comprehensive meta-analysis reporting the prevalence and prognostic and 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
PD-L1 overexpression in Caucasians showed poorer survival outcomes in OS, PFS/DFS, and CSS than in 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 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.

Acknowledgments

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ZYYFY2018031].

Footnote

Conflicts of Interest: 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.

**Figure S2** Correlation between PD-L1/2 expression and necrosis of RCC. RCC, renal cell carcinoma.
Figure S3 Correlation between PD-L1/2 expression and depth of invasion of RCC. RCC, renal cell carcinoma.

Figure S4 Correlation between PD-L1/2 expression and lymph metastasis of RCC. RCC, renal cell carcinoma.
**Figure S5** Correlation between PD-L1/2 expression and sarcomatoid feature of RCC. RCC, renal cell carcinoma.

**Figure S6** Correlation between PD-L1/2 expression and vascular invasion of RCC. RCC, renal cell carcinoma.
Figure S7 Correlation between PD-L1/2 expression and tumor metastasis of RCC. RCC, renal cell carcinoma.

Figure S8 Correlation between PD-L1/2 expression in RCC and gender. RCC, renal cell carcinoma.