Int J Clin Exp Med 2015;8(9):14595-14603
www.ijcem.com /ISSN:1940-5901/IJCEM0012192

Review Article

Clinicopathological and prognostic value of programmed death ligand-1 (PD-L1) in renal cell carcinoma: a meta-analysis

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Received June 30, 2015; Accepted August 27, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: Background: Recently, the association of immunological checkpoint marker programmed death ligand-1 (PD-L1) and the prognosis of various cancers has always been a research hotspot. The objective of this study is to assess the clinical value of PD-L1 as a novel prognostic biomarker of renal cell carcinoma (RCC). Methods: Medline/PubMed, EMBASE, the Cochrane Library databases and Grey literature were searched up to 30 March 2015 for eligible studies of the association between PD-L1 expression and cancer-specific survival (CSS) in RCC. The risk ratio (RR) and its 95% confidence interval (CI) were calculated from the included studies. Moreover, the odds ratio (OR) was also extracted to evaluate the association between the clinicopathological parameters of participants and PD-L1 expression. Results: Five studies involving 1073 patients were included in the meta-analysis. The pooled results showed that positive/higher PD-L1 expression was a negative predictor for CSS with RR of 2.90 (95% CI: 1.64-5.13; $P_{heterogeneity.} \leq 0.001$). Additionally, increased PD-L1 was found to be significantly associated with large tumor size (OR = 2.28, 95% CI: 1.61-3.23; $P_{heterogeneity.} = 0.645$), high TNM stage (OR = 4.37, 95% CI: 2.99-6.39; $P_{heterogeneity.} = 0.676$), poor nuclear grade (OR = 7.58, 95% CI: 5.26-10.92; $P_{heterogeneity.} = 0.203$) and present tumor necrosis (OR = 6.77, 95% CI: 4.73-9.71; $P_{heterogeneity.} = 0.111$) in renal cell carcinoma patients. Conclusion: The meta-analysis suggested that PD-L1 could act as a significant biomarker in the worse prognosis and adverse clinicopathologic features of renal cell carcinoma.

Keywords: PD-L1, renal cell carcinoma, prognosis, meta-analysis

Introduction

In 2015, an estimated 61,560 new cases in the United States will be diagnosed with cancers of the kidney and renal pelvis, the vast majority of which are renal cell carcinoma (RCC), with an estimated 14,080 deaths [1]. To date, as RCC appeared to be one of the most therapy-resistant malignancies, responding very poorly or not at all to hormonal therapy, radiotherapy and chemotherapy. This led investigators to focus on the new immunotherapeutic strategies [2]. Immune checkpoint blockade with antibodies that target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein 1 pathway has shown to mediate tumor shrinkage, extend overall survival and demonstrate promise in a variety of malignancies, including RCC [3]. On the other hand, certain immunological checkpoint markers have been reported [4]. Among them, programmed death ligand-1 (PD-L1) has been the focus of research.

PD-L1, also known as B7 homolog 1 (B7-H1) or CD274, is an important member of the B7/CD28 costimulatory factor superfamily. It is a surface glycoprotein known to be expressed on a majority of tumor cells and other immune cells including conventional CD4+ and CD8+ T cells, dendritic cells (DCs), macrophages and Tregs [5]. Under normal circumstance, PD-L1 is expressed to maintain the homeostasis of immune response. However, tumor cells release some immunosuppressive cytokines such as IFN-γ, TNFα and IL-10 that up-regulate its expression to protect themselves from cytolysis by activated T cells. The co-inhibitory character-

istic of PD-L1 molecule is attributed to binding to its receptor, programmed death 1 (PD-1) on tumor specific T cells, which lead to their apoptosis and then provide an immune escape for tumor cells [6]. Accumulating evidence has shown that PD-L1 expression is associated with clinicopathological and immunological factors in various human malignancies including gastric [7], liver [8], colorectal [9], pancreatic [10], breast [11], cervical [12], lung [13], bladder [14], brain [15] and blood cancers [16]. So there is an urgent need to obtain a further understanding of the potential relationship between PD-L1 and prognosis in cancer sufferers.

Moreover, some researchers have published their data with respect to PD-L1 expression and have raised concerns about the efficacy of PD-L1 as a specific prognostic factor in cancers; however, its prognostic role in RCC is still under debate. In this study, we aimed to perform an up-to-date meta-analysis to reveal the prognostic value of PD-L1 in RCC.

Materials and methods

Search strategy

We searched several international databases including Medline/PubMed, EMBASE, the Cochrane Library databases and Grey literature up to 30 March 2015. The key terms employed for literature retrieval included “PD-L1” or “B7-H1” or “CD274” or “B7 homolog 1” or “programmed death ligand-1” and “renal cell cancer” or “renal cell carcinoma” or “renal cell tumor” or “kidney tumor” and “survival” or “outcome” or “prognosis”. To obtain additional relevant manuscripts, conference summaries and reference lists missed in the retrieval were identified. We even contacted the corresponding authors to get additional information if necessary.

Selection criteria

Studies were selected if they met the following criteria: (a) they focused on renal cell carcinoma; (b) all selected cancer patients were pathologically confirmed; and (c) correlation between PD-L1, clinicopathological features and prognosis was described.

Articles were excluded from the analyses based on the following criteria: (a) non-English papers; (b) non-human experiments; (c) review articles, case reports or letters; (d) duplicate publication; and (e) insufficient data to report the risk ratios (RR) and 95% confidence interval (95% CI), or the Kaplan-Meier curve could not be extracted.

Data extraction

All data were extracted by two independent reviewers (FX and GSF). The quality of the selected articles was assessed according to the Newcastle-Ottawa Scale(NOS) [17]. Data tables were generated to extract all relevant data from texts, tables and figures, including: author, year of publication, country, patient number, cancer type, specimen, detection method, analysis method, the cut-off value, risk ratio, duration of follow-up as well as positive rates of PD-L1 overexpression. For articles that only provided survival data in a Kaplan-Meier curve, the RR and its 95% CI were digitized and extracted using the software designed by Jayne F Tierney and Matthew R Sydes [18]. To reach a consensus, any disagreement on a conflicting study was resolved by full discussion.

Statistical analysis

The statistical analysis was performed according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE) [19]. RR with 95% CI was calculated using Stata SE12.0 (Stata Corporation, TX, USA). Odds ratios (ORs) and their 95% CIs were used to assess correlations between PD-L1 expression and the clinicopathological features of renal cell cancer, including tumor size, TNM stage, nuclear grade and tumor necrosis. The heterogeneity among studies was measured using the Q and I^2 tests. A probability value of $P < 0.1$ and $I^2 \geq 50\%$ indicated the existence of significant heterogeneity [20]. If there was no significant heterogeneity among studies, the pooled RRs of each study were calculated by the fixed-effects model. If heterogeneity was indicated, the random-effects model was adopted. The potential for publication bias was assessed using the Begg’s funnel plot and the Egger linear regression test. P value < 0.05 was considered statistically significant. All P values are two-tailed.

Results

Search results

The initial search returned a total of 149 manuscripts utilizing the search strategy above. From

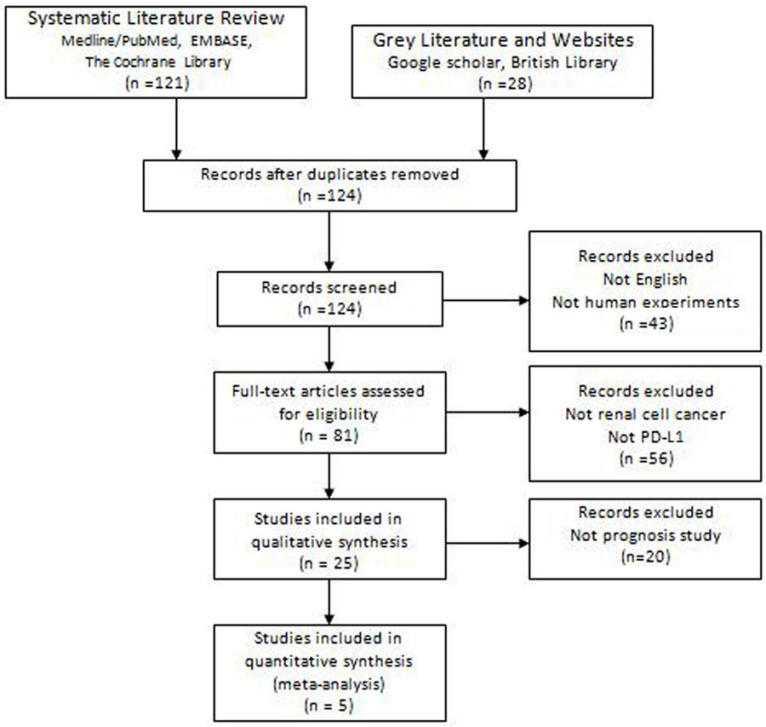


Figure 1. PRISMA flow chart of the literature search.

the title and abstract review, 144 of the articles were excluded due to non-English papers, non-human experiments, non-renal cell cancer-related studies, non-prognostic researches or non-original articles (e.g., review, letter, case report). Finally, a total of 5 studies were included in the meta-analysis. All of these enrolled studies comprehensively assessed the expression of PD-L1 and the survival rate (**Figure 1**).

Study selection and characteristics

All features of the 5 eligible studies are listed in **Table 1** [21-25]. The publication years of the eligible studies ranged from 2004 to 2014. All five studies were conducted in USA. The number of patients in each study ranged from 101 to 306 (mean sample size, 215 patients). The quality of the enrolled studies varied from 5 to 8, with a mean of 7. The clinicopathological features including tumor size, TNM stage, nuclear grade and tumor necrosis were reported in 3 studies. PD-L1 expression levels were measured in tumor tissue or blood. In addition, tissue immunochemistry staining (IHC) for PD-L1 expression was utilized in 4 studies. The remaining one study applied enzyme linked immunosorbent assay (ELISA) to detect circulating PD-L1 expression. The mean length of follow-up ranged from 2 to 11.2 years (**Table 1**). In all studies, none of the patients received neo-adjuvant radio- or chemotherapy prior to surgery.

Main results

As shown in **Figure 2**, we found that elevated PD-L1 had significant association with an enhanced mortality risk of RCC patients in the random-effects model (combined RR 2.90, 95% CI 1.64-5.13), despite the exhibition of heterogeneity among studies (I^2 = 84.9%, P < 0.001). To explore the potential source of heterogeneity among studies, "metareg" STATA command was conducted utilizing variables as year of publication, detection method (IHC vs. ELISA) and analysis method (Univariable vs. Mutivariable). The results showed that no variable included in the meta-regression contributed to the heterogeneity.

In addition, the relationship between elevated PD-L1 and clinicopathological parameters (reported in at least 3 studies) was explored (**Figure 3**). In renal cell carcinoma, increased PD-L1 was found to be significantly associated with large tumor size (OR = 2.28, 95% CI: 1.61-3.23; $P_{heterogeneity.}$ = 0.645) (**Figure 3A**), high TNM stage (OR = 4.37, 95% CI: 2.99-6.39; $P_{heterogeneity.}$ = 0.676) (**Figure 3B**), poor nuclear grade (OR = 7.58, 95% CI: 5.26-10.92; $P_{heterogeneity.}$ = 0.203) (**Figure 3C**) and present tumor necrosis (OR = 6.77, 95% CI: 4.73-9.71; $P_{heterogeneity.}$ = 0.111) (**Figure 3D**) using fixed effect model. As mentioned above, there was no heterogeneity existed. However, no significant relationship was detected between PD-L1 overexpression and other clinical characteristics in RCC due to limited studies (n ≤ 2).

Sensitivity analysis

The selected studies were sequentially removed to investigate whether any single study could

Table 1. Main characteristics of the studies included in this meta-analysis

Authors	Year	Number of patients	Country	Cancer type	Specimen	Detection method	Analysis method	Cut-off (positive/High expression)	Risk ratio	Follow up (years)	P-value	Quality assessment (score)
Thompson	2004	196	USA	RCC	Tissue	IHC	Univariable	≥ 10% tumor cells staining (37.2%)	4.53 (1.94-10.56)	2 (0-4.1)	< 0.001	7
Thompson	2006	306	USA	RCC	Tissue	IHC	Mutivariable	≥ 5% tumor cells staining (63.1%)	2.00 (1.27-3.05)	11.2 (0-15)	0.003	5
Krambeck	2007	298	USA	ccRCC	Tissue	IHC	Univariable	≥ 5% tumor cells staining (23.5%)	4.13 (2.74-6.22)	11.2 (0-15)	< 0.001	8
Frigola	2011	172	USA	ccRCC	Blood	ELISA	Mutivariable	Median (57.1%)	1.41 (1.08-1.83)	3.6 (0.1-7.3)	0.010	7
Choueiri	2014	101	USA	Non-ccRCC	Tissue	IHC	Univariable	≥ 5% tumor cell membrane staining (10.9%)	6.41 (2.17-18.88)	5	< 0.001	8

RCC: Renal cell carcinoma; ccRCC: Clear cell renal cell carcinoma; IHC: Immunohistochemistry; ELISA: Enzyme linked immunosorbent assay.

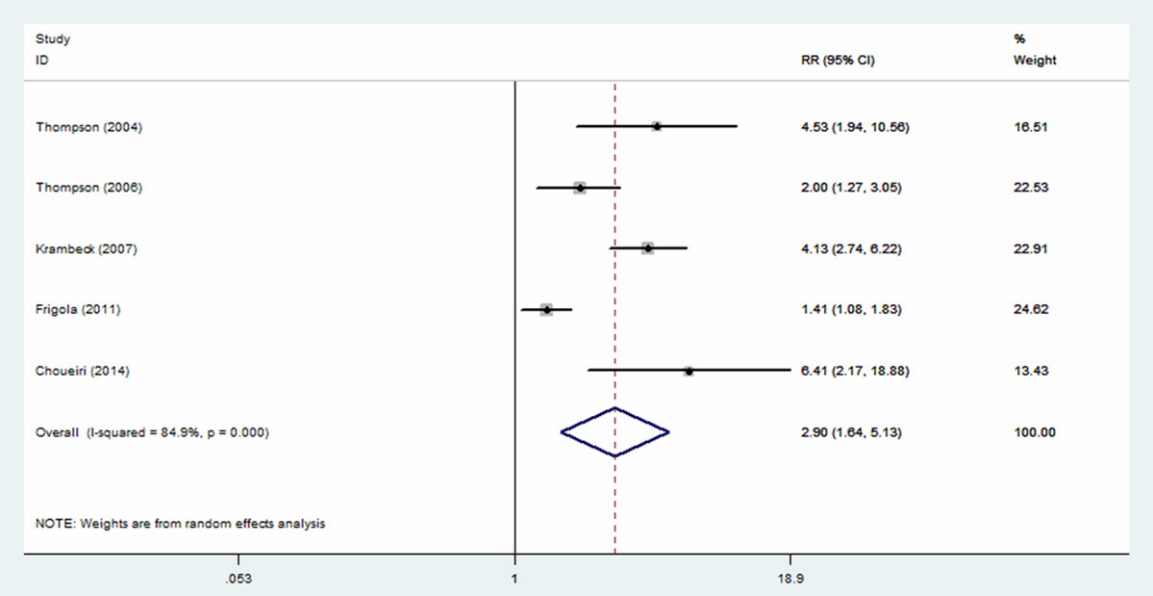


Figure 2. Forest plots of studies evaluating risk ratios (RRs) of PD-L1 for cancer specific survival.

have an influence on the pooled results. As shown in **Figure 4**, the stable pooled RR was found to be not significantly affected by each individual study.

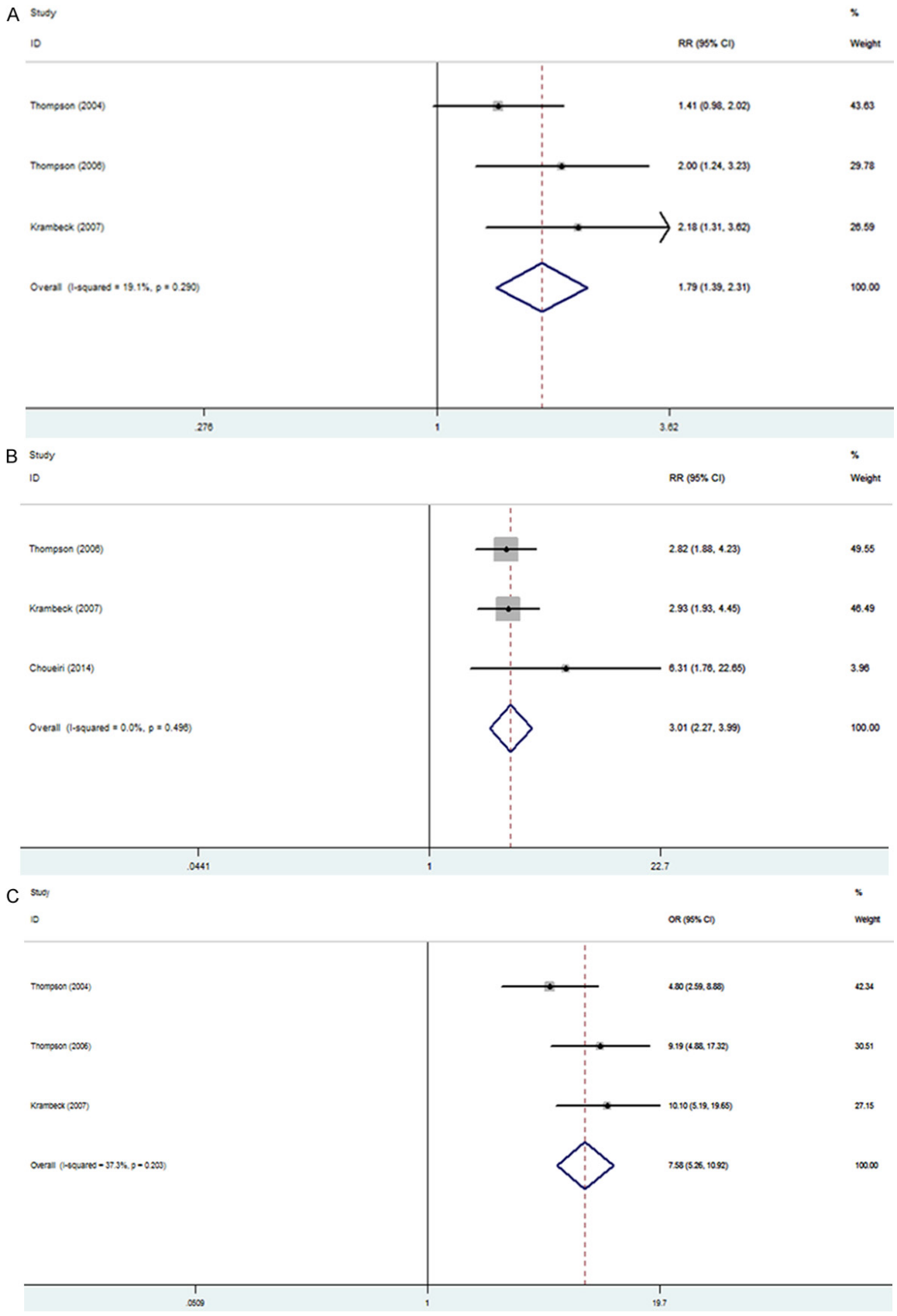
Publication bias

The figure of the Bgger's funnel plot did not show any evidence of obvious asymmetry (P = 0.462; **Figure 5**). Then, the Egger's linear regression was performed and publication bias was not detected either (P = 0.135).

Discussion

Up to now, the relationship between PD-L1 and the outcome of tumor sufferers remains inconclusive. Our current study chiefly concerned with the prognostic role of PD-L1 in renal cell cancer. To the best of our knowledge, it is the first meta analysis to investigate the clinicopathological feature and prognostic role of PD-L1 in RCC. The pooled RR for cancer-specific survival (CSS) was 2.90 (95% CI: 1.64-5.13; $P_{heterogeneity.} \leq 0.001$), indicating that positive/higher PD-L1 expression significantly predicted poorer CSS compared with negative/lower PD-L1 expression. Significant heterogeneity was observed and could not be eliminated even after using random effect model. Further, meta-regression was performed to investigate the source of heterogeneity. However, none of the variables including year of publication, detection method and analysis method contributed to the heterogeneity in our meta-analysis. Additionally, when the clinicopathological features were considered, the combined odds ratio (OR) was found to be significantly associated with large tumor size, high TNM stage, poor nuclear grade and present tumor necrosis of renal cell carcinoma. However, the association of PD-L1 and other clinicopathological features was explored in few studies enrolled in our analysis. These findings might strengthen the sensitivity and specificity of PD-L1 in predicting the clinical survival of renal cell carcinoma.

Recently, the early clinical experience of large phase I studies targeting PD-L1 pathway with monoclonal antibodies has received substantial attention. A multicenter phase I trial utilized the PD-L1 inhibitor BMS-936559 in patients with RCC in 2012 [26]. Durable tumor regression was noted with an objective response Rate (ORR) observed in 2 of 17 (12%; 95% CI, 2-36) for RCC lasting 4 and 17 months. Seven additional patients (41%) had stable disease lasting at least 24 weeks. Herbst and his colleagues [27] evaluated 175 solid tumors including 56 patients with RCC using the anti-PD-L1 antibody MPDL3280A. The overall ORR was 13%. Responses were seen in both clear-cell and non-clear-cell histology and were observed in patients with tumors expressing high levels of PD-L1, especially when PD-L1 was expressed


A
Study
ID
RR (95% CI)
%
Weight
Thompson (2004)
1.41 (0.98, 2.02)
43.63
Thompson (2006)
2.00 (1.24, 3.23)
29.78
Krambeck (2007)
2.18 (1.31, 3.62)
26.59
Overall (I-squared = 19.1%, p = 0.290)
1.79 (1.39, 2.31)
100.00
.276
1
3.62
B
Study
ID
RR (95% CI)
%
Weight
Thompson (2006)
2.82 (1.88, 4.23)
49.55
Krambeck (2007)
2.93 (1.93, 4.45)
46.49
Choueiri (2014)
6.31 (1.76, 22.65)
3.96
Overall (I-squared = 0.0%, p = 0.496)
3.01 (2.27, 3.99)
100.00
.0441
1
22.7
C
Study
ID
OR (95% CI)
%
Weight
Thompson (2004)
4.80 (2.59, 8.88)
42.34
Thompson (2006)
9.19 (4.88, 17.32)
30.51
Krambeck (2007)
10.10 (5.19, 19.65)
27.15
Overall (I-squared = 37.3%, p = 0.203)
7.58 (5.26, 10.92)
100.00
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1
19.7

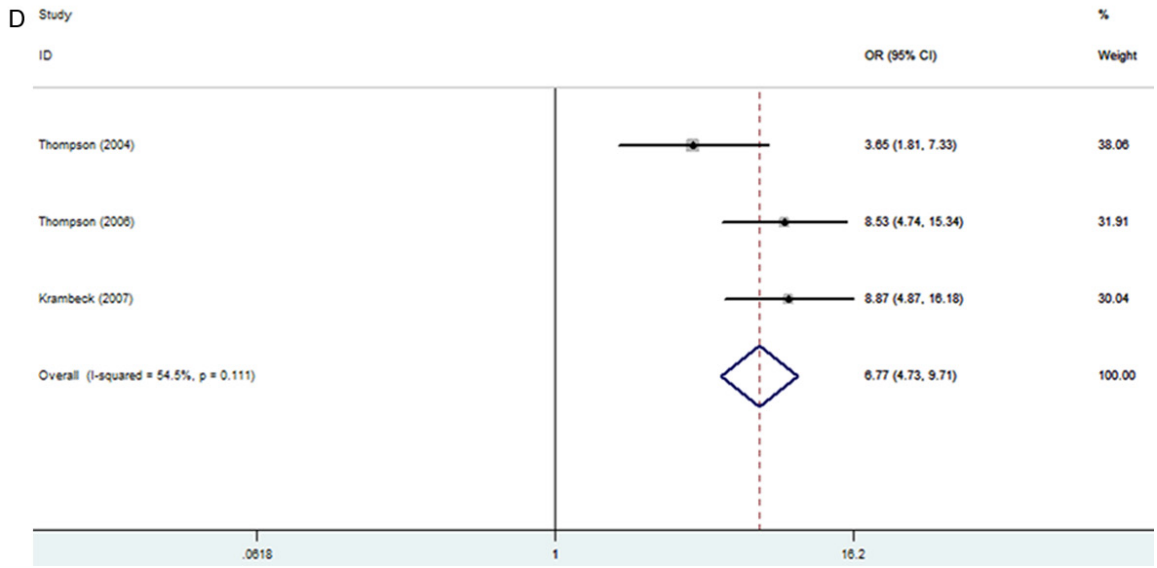

Figure 3. Forest plots of studies evaluating the association between PD-L1 and clinical parameters in renal cell carcinoma. A. Tumor size (≥ 5 cm vs. < 5 cm). B. TNM stage (III/IV vs. I/II). C. Nuclear grade (3, 4 vs. 1, 2). D. Tumor necrosis (present vs. absent).

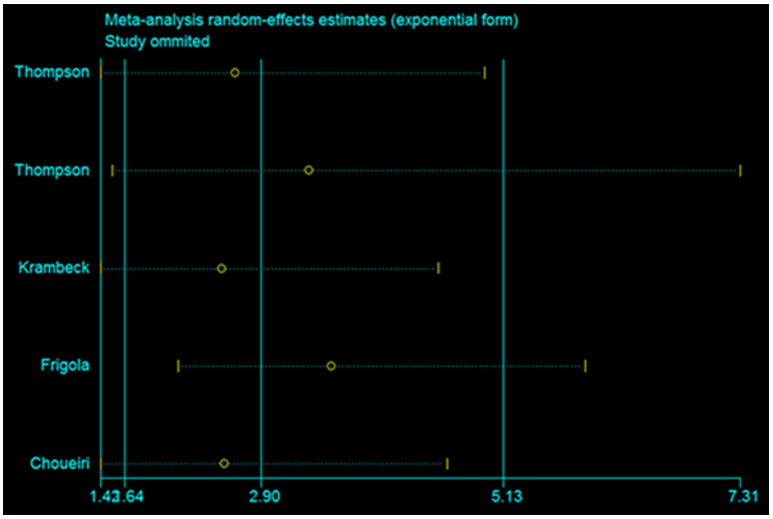

Figure 4. Effect of individual studies on the pooled RRs for PD-L1 and CSS of patients.

by tumor-infiltrating immune cells. An additional 30% of patients had stable disease. At 24 weeks, 48% of the patients were alive without disease progression. In an ongoing phase II study, MPDL3280A is being assessed either as monotherapy or in combination with antiangiogenic agents (bevacizumab or sunitinib) in previously untreated RCC (NCT01375842) [28]. Based on these studies, our results suggest that anti-PD-L1 antibodies might be preferentially carried out on patients with renal cell carcinoma in future clinical trials.

Although our results are promising, there are several limitations of this study need to be carefully taken into account. Firstly, as a novel prognostic marker in malignancies, PDL1 just loomed in recent years and nearly half of the sample size was relatively small. Secondly, all of the enrolled studies were from USA, which might contribute to publication bias. Thirdly, a majority of the selected studies measured PD-L1 expression by IHC, the distinct antibodies used, the protocol of staining, the exact cell type and the method of scoring might account for the high variability in the frequencies reported by different authors. On the other hand, we pooled RRs from different studies with a different number of cut off values, which might have caused some of the heterogeneity observed here. Although triple subsets of PD-L1 threshold values revealed the similar results, a baseline referring to PD-L1 overexpression should be set up. Finally, few studies explored the association of patient prognosis and circulating PD-L1 expression, which might provide more valuable evidence than tissue throughout the lives of the

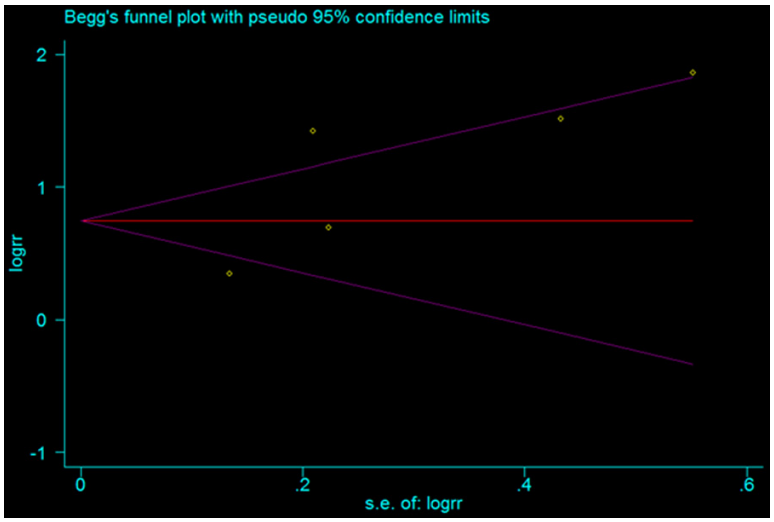

Figure 5. Begg's funnel plots for all of the included studies reported with CSS.

cancer patients. Although similar inclusion criteria were employed for each study, potential factors that were not considered might make an impact on our results.

In conclusion, the current evidence firstly shows that an elevated PD-L1 is a negative predictor for survival in renal cell carcinoma. More multicentre studies with larger sample size are needed to present more reliable results of the clinical relevance and precise molecular explanation for the abnormal expression of PD-L1 in the future.

Acknowledgements

This study was supported by the National Science and Technology Support Program of China (2013BAI04B01).

Disclosure of conflict of interest

None.

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