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Evaluation of PD-L1 biomarker for immune checkpoint inhibitor (PD-1/PD-L1 inhibitors) treatments for urothelial carcinoma patients: A meta-analysis

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ABSTRACT

Introduction: Newly published results of clinical trials has demonstrated immune checkpoint inhibitors as robust antitumor agents for urothelial carcinoma patients. However, searching for predictive biomarkers is still on the way. Previous clinical trials used PD-L1 as biomarkers, however, whether it can predict the objective response rate and overall survival is controversial. This is the first and latest study to pool the newest data in order the evaluate PD-L1 biomarker.

Result: Nine studies were included and 1,436 urothelial carcinoma patients were included. We evaluated PD-L1 biomarker for atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab treatments. Patients with higher PD-L1 expression have significantly higher objective response rate compared with the lower ones. PD-L1 predicted the one year overall survival of PD-L1 inhibitors but not PD-1 inhibitors. Only one year overall survival of durvalumab was significantly associated with PD-L1 expression.

Conclusion: PD-L1 can be used as a biomarker for objective response rate, while PD-L1 cannot predict the overall survival.

1. Background

The promising anti-tumor effect of monoclonal antibodies blocking the immune checkpoints led to fast approvals of these drugs for the treatment of a variety of malignancies [1]. PD-1, PD-L1, and CTLA-4 are three key molecules which play essential roles in the niche of tumor [2]. Inhibiting these three molecules can prevent their interaction at the tumor-immune cell interface, thus significantly improving the survival of solid cancer patients according to the current research [3]. Non-small cell lung cancer patients and melanoma patients can now get treated with immune checkpoint inhibitors (ICIs) due to the FDA's approving. However, among urothelial carcinoma patients, most clinical trials of ICIs are at the state of phase I or II. There is still no solid evidence showing whether PD-1/PD-L1 inhibitors are safe and their predictive biomarkers are still lacking [3].

The PD-1 and PD-L1 signal pathways are dynamic, where PD-L1 molecule may get up-regulated or down-regulated depending on specific factors such as cytokines. Previous evidence showed that PD-L1 is strongly correlated with the adaptive immune system. This protein is expressed on a variety of immune cell types including CD8 positive T cells and CD4 positive T cells, B cells, NK cells, etc. [4]. PD-1 itself is expressed on T cells and inhibits them by binding to its ligands [4]. Blocking those molecules can re-stimulate the immune system and hence generate robust antitumor effects [4]. The clinical trials and approvals made ICIs promising agents as for cancer patients.

Looking for the proper biomarkers is a heated topic and an unsolved problem in this field [5–7]. Previous research was focused on the PD-L1 molecule, and, numerous researchers have been devoted to find more biomarkers for ICIs [5–7]. Recently, a group found that B cells can predict adverse events of immune checkpoint therapy [8], which showed that high-grade immune-related adverse events might be leveraged to improve the patients' monitoring. Interestingly, another group discovered that CD137 molecule on circulating CD8 positive T cells was in correlation with the disease-free survival of melanoma patients after ipilimumab (CTLA-4 inhibitor) plus nivolumab (PD-1 inhibitor) [9]. Of date, a computational research highlight the significance of epithelial–mesenchymal transition (EMT) in tumor immunity [10]. They interestingly showed that higher EMT score correlates with the response to ICI and overall survival of all patients. In another phase II clinical trial for advanced melanoma patients, scientists evaluated the predictive value of pre-treatment serum cytokine profiles [11]. And it was proved to correlate with the efficacy of nivolumab (PD-1 inhibitor).

To date, newly-published results of several clinical trials for

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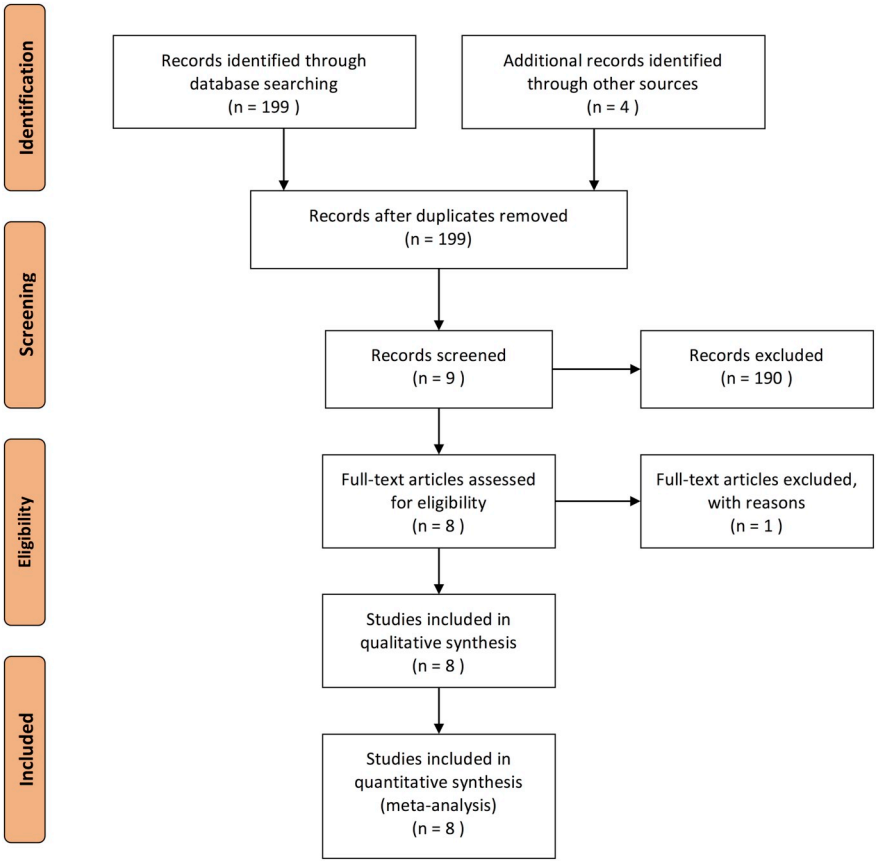

Fig. 1. Study screening process of this meta-analysis.

urothelial carcinoma patients were promising [12–19]. Emerging evidence manifested that ICIs are powerful antitumor drugs as second-line therapies in patients with disease that progressed after platinum-based chemotherapy. In some trials, PD-1 inhibitors and PD-L1 inhibitors were even selected as the first-line therapy [19]. In general, all these trials used PD-L1 molecule as a potential biomarker. However, it still remains controversial whether PD-L1 is a predictive and reliable biomarker, especially in urothelial carcinoma.

In this study, we attempted to assess whether PD-L1 molecule can be used as a reliable biomarker. To the best of our knowledge, this is the first study with a focus on urothelial carcinoma, closely following the novel published data of clinical trials in 2018. We hope this analysis could improve our understanding of the biomarkers for ICI treatment, and thus providing evidence-based support to help the oncologists for their clinical decisions.

2. Methods

2.1. Strategy of study screening

In order to screen all eligible studies of PD-L1 biomarkers, we performed a systematic search of clinical trials of immune checkpoints inhibitors for urothelial carcinoma strongly following the screening criterial. We identified original articles on PubMed and Google Scholar before March 2018. We also reviewed the references of published original papers and related review articles. As for the literature search, following keywords was used, including PD-1 inhibitor, CTLA-4 inhibitor, PD-L1, immune checkpoint inhibitor, PD-L1, biomarker, overall survival, progression-free survival, objective response rate, clinical trial, atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab (anti-PD-1).

2.2. Selection criteria

We strongly followed the PICOS selection standard to conduct the inclusion work. Firstly, only studies of urothelial carcinoma patients will be included. Patients should be divided into two groups (PD-L1 high expression group and PD-L1 low expression group). Secondly, interventions of immune checkpoint inhibitors will be included. That is, all included studies should report the results of atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab. Thirdly, trials should report the objective response rate and overall survival of urothelial carcinoma patients. Fourthly, trials should report the PD-L1 grouping data of urothelial carcinoma patients. Finally, only clinical trials will be included. If the paper was not published in English, it would get excluded.

2.3. Data extraction

Data was extracted by one reviewer (Xin Rui) and reviewed

Table 1
Characteristics of included studies.

Author	Trial	Drug	Molecule	Disease and treatment
Petrylak 2018	NCT01375842	Atezolizumab	PD-L1	Second-line anti–PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy
Balar 2016	NCT02108652	Atezolizumab	PD-L1	First-line anti–PD-L1/PD-L1 therapies in cisplatin-ineligible patients
Sharma 2016	NCT01928394	Nivolumab	PD-1	Second-line anti–PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy
Sharma 2017	NCT02387996	Nivolumab	PD-1	Second-line anti–PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy
Powles 2017	NCT01693562	Durvalumab	PD-L1	Second-line anti–PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy
Patel 2018	NCT01772004	Avelumab	PD-L1	Second-line anti–PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy
Rosenberg 2016	NCT02108652	Atezolizumab	PD-L1	Second-line anti–PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy
Balar 2017	NCT02335424	Pembrolizumab	PD-1	First-line anti–PD-L1/PD-L1 therapies in cisplatin-ineligible patients

independently by another investigator (Ting-Ting Gu). The following information from the clinical trials was extracted: Year of publication, first author, number of patients, type of immune checkpoint inhibitor (atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab), PD-L1 expression cutoffs, objective response rate, and 1-year overall survival.

2.4. Risk of publication bias assessment and sensitivity analysis

The Egger's algorithm and Begg's algorithm was conducted by using STATA software. Sensitivity analysis was performed to assess the potential bias in our study by using STATA software.

2.5. Statistical analysis

Statistical analyses were conducted through Stata SE 14 (Stata Corp, College Station, TX, USA). Relative risks (RRs) were used for evaluation and 95% confidence intervals (CIs) were calculated for each effect size. A P value which was < 0.05 would be treated as statistically significant. Heterogeneity was considered low, moderate or high for I-square values if the I-square value was $< 25\%$, 25 to 50%, and over 50%, respectively [20]. If the I-square was not over 50%, We will analyze through the fixed-model. If the I-square value was over 50%, A random-model would be used.

3. Results

3.1. Patients characteristics and eligible studies

Fig. 1 depicted the whole search screening process of this study. In all, 8 studies were included and 1,436 patients were analyzed [12–19]. All the reviewers strongly followed the screening criteria as is described in the Method section. According to our screening criteria, all the included studies reported the expression of PD-L1 and evaluated the effectiveness of ICIs in urothelial carcinoma patients (Table 1). In general, five different drugs were analyzed, including atezolizumab (anti-PD-L1), nivolumab (anti-PD-1), durvalumab (anti-PD-L1), avelumab (anti-PD-L1), and pembrolizumab (anti-PD-1). First-line anti-PD-L1/PD-L1 therapies in cisplatin-ineligible patients and second-line anti–PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy were included. Most included studies are the latest published data.

3.2. PD-L1 can predict the objective response rate

All trials report the objective response rate (ORR). First, we assess the heterogeneity of the analysis of ORR. I-square value of 16.1% reveals that a fixed effect analysis model should be used. Then, we evaluated the overall predictive value of PD-L1. In general, PD-L1 can serve as the ORR biomarker for ICI in urothelial carcinoma patients (RR: 0.53, 95% CI: 0.43–0.65, $P < 1 \times 10^{-8}$) as is depicted in Fig. 1. Urothelial carcinoma patients with higher PD-L1 expression treated with PD-1/PD-L1 agents have significantly higher ORR compared with the lower ones. Then, subgroup analyses by the type of blocking targets and the type of drugs were conducted. Our results manifested that PD-L1 both predicts the ORR of PD-1 inhibitors (RR: 0.45, 95% CI: 0.33–0.61, $P < 1 \times 10^{-6}$) and PD-L1 inhibitors (RR: 0.63, 95% CI: 0.47–0.83, $P = 0.001$). The detailed information was visualized in Figs. 2 and 3. PD-L1 can predict the ORR of atezolizumab, durvalumab, and pembrolizumab. However, we found that PD-L1 is not an ideal biomarker for nivolumab (RR: 0.71, 95% CI: 0.47–1.09, $P = 0.110$) and avelumab (RR: 0.60, 95% CI: 0.29–1.27, $P = 0.176$).

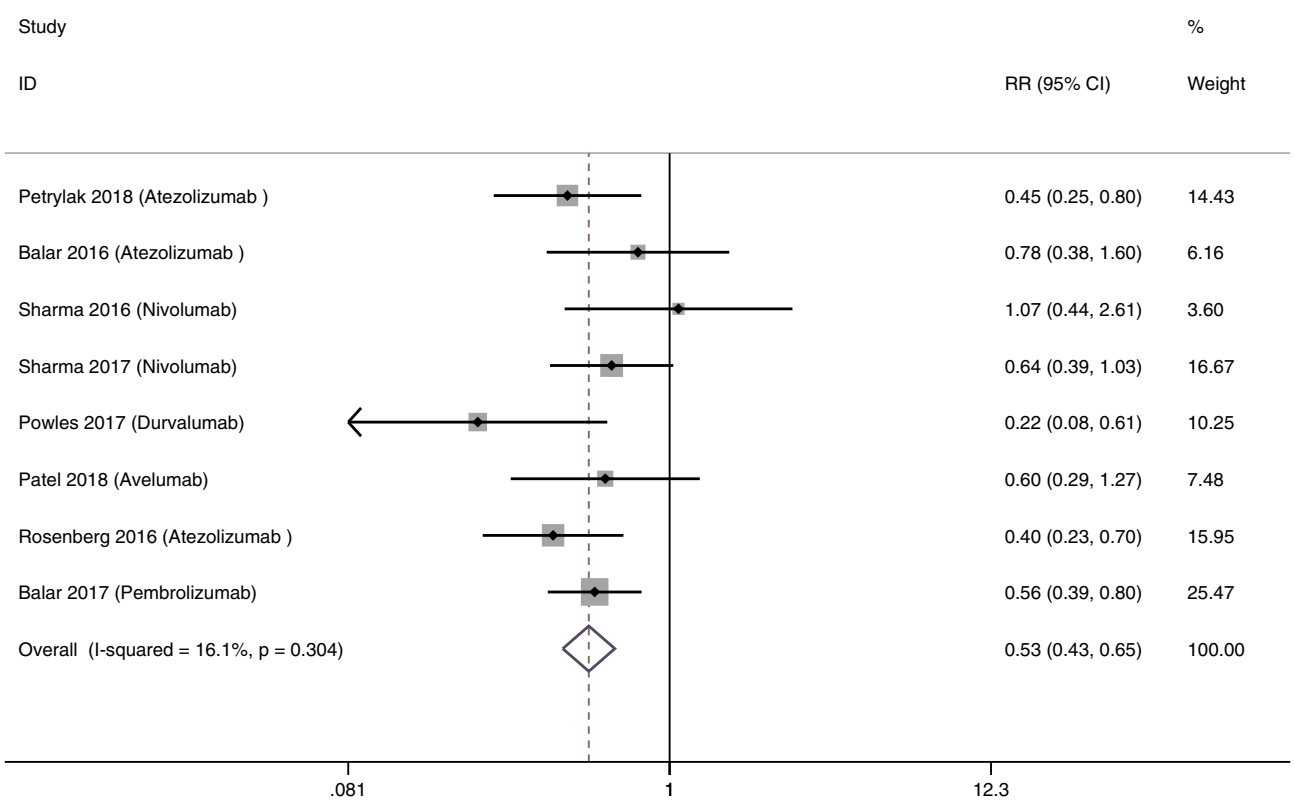

Fig. 2. Meta-analysis of PD-L1 biomarker for objective response rate.

3.3. PD-L1 cannot predict the 1-year overall survival rate except durvalumab

One year overall survival (OS) rate is a key indicator in ICI trials. We extracted the 1 year overall survival rate from the literature, and only 6 trials reported the 1-year OS rate. Heterogeneity result with the I-square value of 32.3% reveals that a fixed effect analysis model should get used. In all, PD-L1 predicts the 1-year OS in urothelial carcinoma patients (RR: 0.70, 95% CI: 0.54–0.91, P = 0.007) as is visualized in Fig. 4. Then, subgroup analyses by the type of blocking targets and the type of drugs were conducted, which was similar to the ORR analysis. The technical process was fully described in the method part. We found that PD-L1 predicted the OS of PD-L1 inhibitors (RR: 0.70, 95% CI: 0.54–0.91, P = 0.007). Nevertheless, as for PD-1 inhibitor (Fig. 5), PD-L1 expression is not a good predictive tool for overall survival (RR: 0.57, 95% CI: 0.10–3.38, P = 0.542). In order to fetch the detailed predictive value of PD-L1 in each drugs, we performed the subgroup analysis of different agents. It was observed that 1-year OS of atezolizumab, nivolumab, and avelumab was not correlated with PD-L1 expression (RR: 0.79, 95% CI: 0.59–1.06, P = 0.115; RR: 0.57, 95% CI: 0.10–3.38, P = 0.542; RR: 0.73, 95% CI: 0.33–1.59, P = 0.441; respectively). Only 1-year OS of patients treated with durvalumab was significantly associated with PD-L1 expression (RR: 0.28, 95% CI: 0.10–0.80, P = 0.016; Fig. 5).

3.4. Evaluation of publication bias analysis and sensitivity analysis

In order to assess whether there exists the publication bias in our analysis, we performed the Egger's check and Begg's check. As a result, no significant publication bias effect was generated in our analysis, with a P value of 0.771 and 0.237 in the Egger's check and Begg's check respectively. Next, sensitivity analysis was performed to assess the potential bias in our study. And no significant results were observed which reveals there was no sensitivity bias. The detailed technical process was in detail in the method part.

4. Discussion

Newly published results of clinical trials have demonstrated immune checkpoint inhibitors as robust antitumor agents for urothelial carcinoma patients. Almost all the studies selected PD-L1 as the biomarker in the trials. However, whether PD-L1 is predictive still remains largely unknown. In this study, we attempted to assess whether PD-L1 can predict the objective response rate and 1-year overall survival for urothelial carcinoma patients. By using fixed effect model, we found that PD-L1 can serve as a biomarker of objective response rate for ICI treatments. To the best of our knowledge, this is the first study regarding the role of PD-L1 for predicting ICI responses with a focus on urothelial carcinoma patients.

Whether PD-L1 can be used as a biomarker is controversial in the field of tumor immunotherapy [21]. Refining existing biomarkers and identifying new biomarkers is essential for applying these agents in the clinical practice [22]. To date, credible evidence is still lacking and a combinational meta-analysis is needed. PD-L1 molecule is a key protein not only for targeting but also for predicting. As for adjuvant chemotherapy, immunohistochemistry-assessed PD-L1 expression was

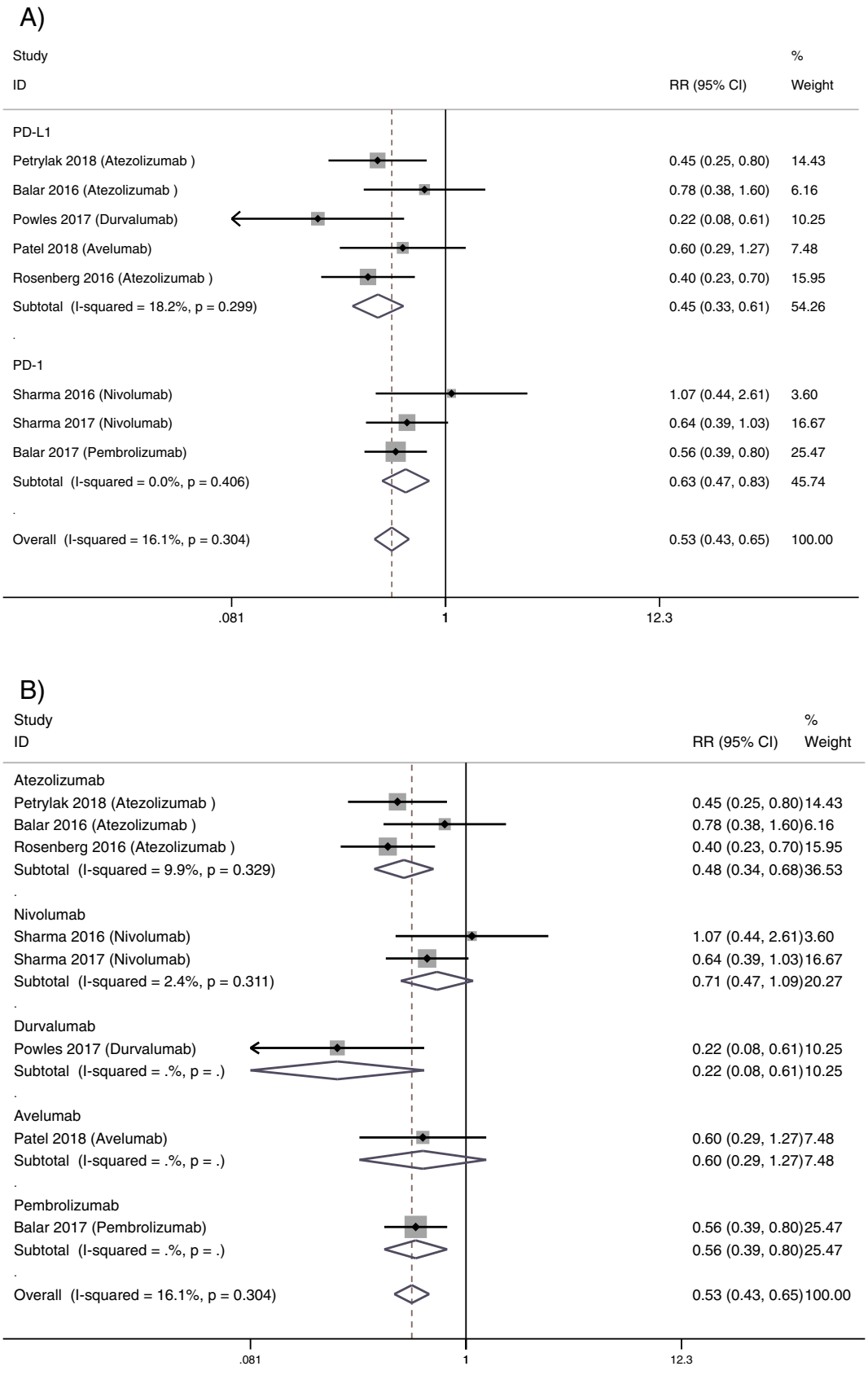

Fig. 3. Subgroup analysis of PD-L1 biomarker for objective response rate by checkpoint inhibition types (A), and drug types (B).

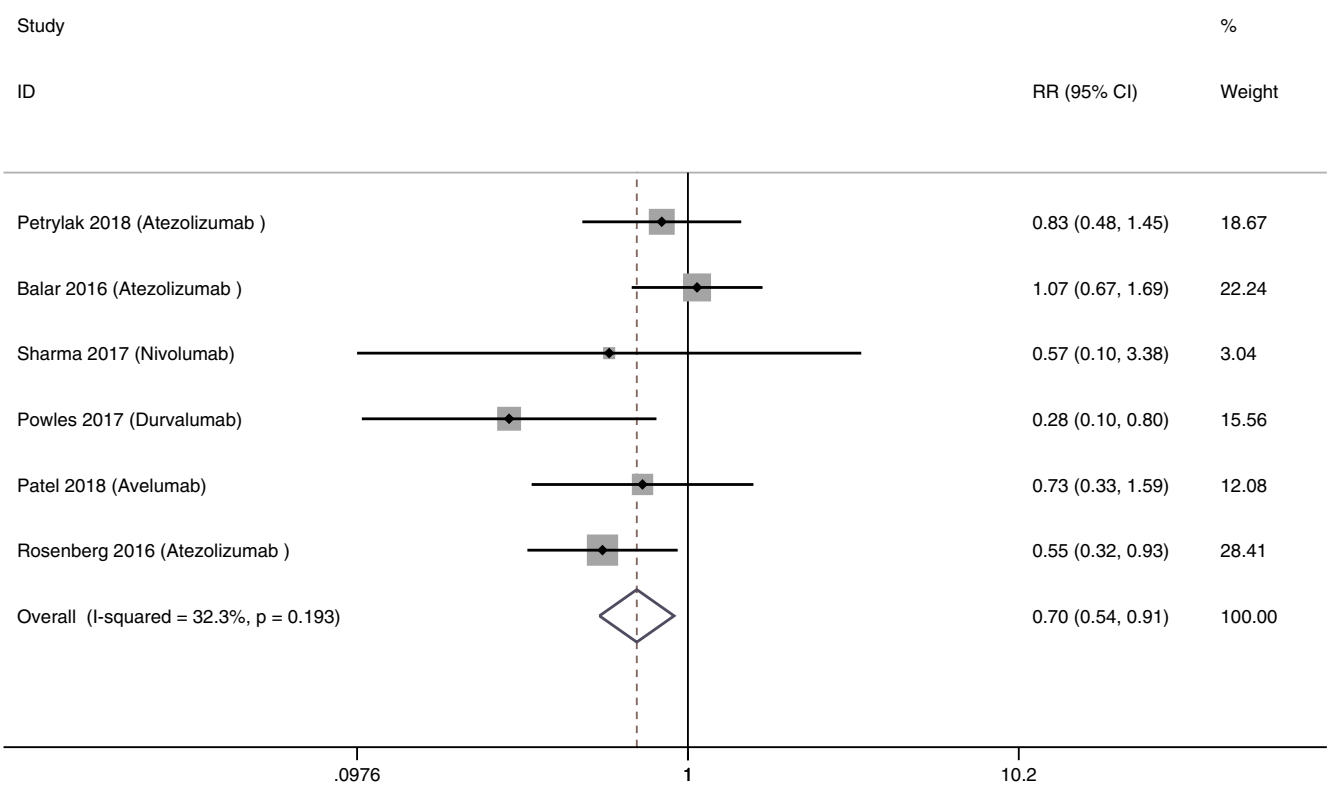

Fig. 4. Meta-analysis of PD-L1 biomarker for one year overall survival.

found to be neither prognostic nor predictive of in resected non-small cell lung cancer (NSCLC) patients [23]. Another group assesses whether PD-L1 could get used as a biomarker for immune checkpoint inhibitors in advanced NSCLC. It was observed that ORR has increased correlated with the PD-L1 expression [24]. Also, PD-L1 was found to predict the progression free survival (PFS) rate in advanced NSCLC ICI treatments. However, the conclusions suggested that PD-L1 could not be considered as a predictive biomarker, although the data are gathered three years ago. An updated research with a similar topic demonstrated that better OS, PFS, and ORR in ICI treatments [25]. They finally concluded that PD-L1 biomarker can predict the ICI response in NSCLC patients.

Searching for other robust biomarkers for ICI effectiveness prediction is a heated topic in this field [6]. Large quantities of preclinical studies attempted to find underlying mechanisms of ICI biomarkers, although only a few of them were finally tested in clinical trials [22]. PD-L1 is one of the known predictors applied in the clinical test, however, it still remains controversial whether this biomarker is useful [26]. Especially in the field of urothelial carcinoma immunotherapy, no evidence suggested whether PD-L1 biomarker can be finally used [26]. To date, we have five kinds of ICIs for urothelial carcinoma patients, including atezolizumab (anti-PD-L1), nivolumab (anti-PD-1), durvalumab (anti-PD-L1), avelumab (anti-PD-L1), and pembrolizumab (anti-PD-1). Since it is still under debate whether PD-L1 can be selected [27,28], this work represent an attempt to compare PD-L1 biomarkers across five different drugs to identify the feasibility of using PD-L1 in difference ICI treatments, which may help clinicians in their daily practice.

With a focus on urothelial carcinoma patients, our results supported that PD-L1 can predict the objective response rate for ICI treatments. This observation was in accordance with another research conducted in NSCLC patients [22]. Also, our study do not recommend using PD-L1 for predicting the overall survival. Interestingly, another independent research was also in line with our results, although their sample size of urothelial carcinoma patients are relatively lower. Our study do have some potential disadvantages. The major concern is the heterogeneity of different PD-L1 expression cut-offs. Some included studies used 1% as a cut-off, however, 5% is also used, although we have searched all available data and performed the heterogeneity test. Furthermore, we also attempted to assess whether PD-L1 can predict progression-free survival, which is widely used in the immune checkpoint inhibitor treatment, however, there are only three eligible studies that reached the screening criteria. Hence, we finally did not pool the data due to the small sample size.

Taken together, our study pooled newly published related results of PD-L1 biomarkers in the tumor immunotherapy (immune checkpoint inhibitor). This is the first study, with a focus on urothelial carcinoma, to evaluate whether PD-L1 can be selected as a useful biomarker for the efficacy of immune checkpoint inhibitors. The results strongly recommended clinicians to use PD-L1 as a biomarker for objective response rate, while PD-L1 cannot predict overall survival. These results need further investigation in the clinical practice, and searching for more predictive biomarkers is urgent in the near future.

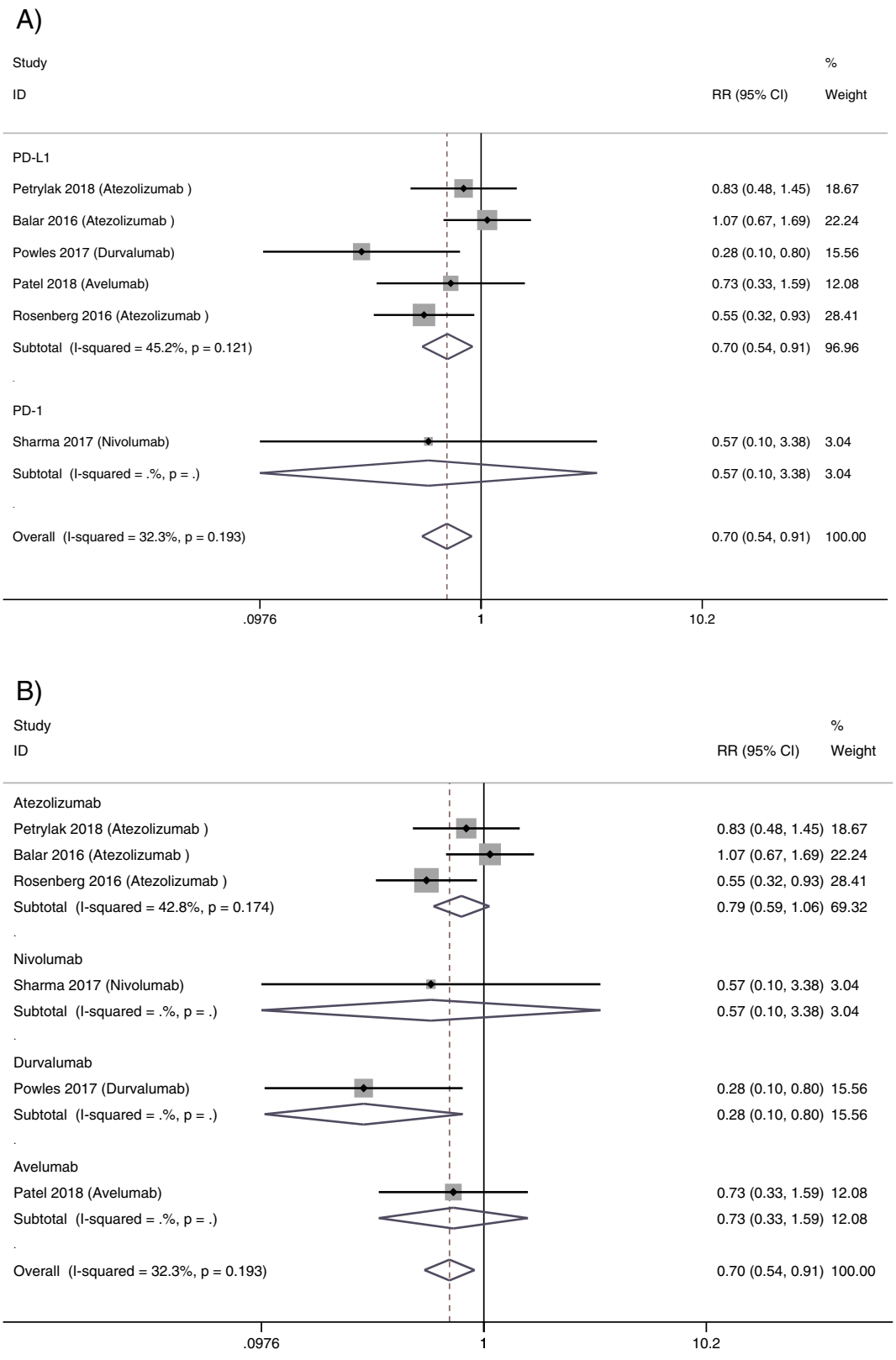

Fig. 5. Subgroup analysis of PD-L1 biomarker for one year overall survival by checkpoint inhibition types (A), and drug types (B).

Ethics approval and consent to participate

Not applicable.

Consent to publish

All the authored have agreed.

Availability of data and materials

All the data can be fetched in the cited publications and in the figures.

Competing interests

None.

Funding

None.

Authors' contributions

Data extraction: All authors. Manuscript writing: All authors. Project design: Hui-Zhi Zhang.

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