PD-L1 Expression in Glioblastoma, the Clinical and Prognostic Significance: A Systematic Literature Review and Meta-Analysis

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Running title: Prognostic value of PD-L1 expression in glioblastoma: A meta-analysis

Keywords: glioblastoma, PD-L1, prognostic, clinicopathological, meta-analysis
Abstract

Background: Programmed death-ligand 1, PD-L1, the clinical and prognostic value of programmed death-ligand 1, PD-L1, in glioblastoma (GBM) remains controversial. The present study aimed to identify the expression of PD-L1 for its prognostic value in glioblastoma.

Methods: A comprehensive literature search was performed using the PubMed and CNKI databases. The overall survival (OS) and disease-free survival (DFS) of GBM was analyzed based on Hazard ratios (HRs) and 95% confidence intervals (CIs). Furthermore, Odds ratios (ORs) and 95% CIs were summarized for clinicopathological parameters. The statistical analysis was using RevMan 5.3 software.

Results: The meta-analysis was performed by using total nine studies including 806 patients who had glioblastoma. The pooled results indicated that PD-L1 expression in tumour tissues was significantly related to a poor OS (HR=1.63, 95%CI: 1.19-2.24, P=0.003, random effects model) with heterogeneity (I2=51%). In subgroup analyses, PD-L1 positivity was significantly associated with a worse OS for patients of American and Asian regions, but not for those of European regions. Moreover, PD-L1 expression implied a trend toward the mutation status of the IDH1 gene (coding the Isocitrate Dehydrogenase (NADP(+))-1 protein) (HR=9.92, 95%CI: 1.85-53.08, P=0.007, fixed effects model). However, the prediction overall survival (OS) of the patients showed that PD-L1 expression was independent from other clinicopathological features, such as gender, age and tumour progression/recurrence.

Conclusions: Our analyses indicated that high expression of PD-L1 in glioblastoma tumour tissues is associated with poor survival of patients, and PD-L1 may act as a prognostic predictor and an effective therapeutic target for glioblastoma.

INTRODUCTION

Glioblastoma (GBM) represents the most commonly seen primary malignant brain tumour in adults, characterized by high aggressive behaviour and high recurrence rate (Alifieris and Trafalis, 2015). Multimodality therapies that have been suggested and practiced according to NCCN Guidelines, including surgical resection, radiotherapy with alkylating agents such as temozolomide (TMZ) and adjuvant TMZ chemotherapy. However, the outcomes of the treatment
are far from satisfactory with the 5-year overall survival being less than 10% (Komotar et al., 2008; Affronti et al., 2009; Ostrom et al., 2015).

Differently from many other tumours, molecularly targeted therapies for glioblastoma produced very limited advances in prolonging life expectancies of the patients, reasons at least partly attributable to the poor penetration of the Blood Brain Barrier (BBB) by therapeutic agents or by rapidly developing drug resistance (Schlageter et al., 1999; Ramirez et al., 2013). In the recent years, it is increasingly recognized that there is an the central nervous system (CNS) interacts actively with the systemic immune system has offered a new exciting theoretical basis and promising opportunities for brain tumour immunotherapy (Prins et al., 2011; Fecci et al., 2014; Garber et al., 2016; Cloughesy et al., 2019).

Tumour cells can display immune evasion that weaken antitumor immunity by activating the so-called immune Checkpoint molecules (ICs) (Topalian et al., 2015). Programmed cell death ligand-1 (PD-L1), a “classic” IC molecule, has the effect on induction of T-cell-mediated immune tolerance in tumour local microenvironment, leading to tumour immune escape and tumour growth stimulation, by combination with programmed cell death-1 (PD-1) located on the surface of activated T cells (Wei et al., 2013). PD-L1 has been shown to be upregulated in various cancer cells and associated with unfavorable prognosis. Over the past decade, immunotherapies targeting PD-1/PD-L1 axis have made a series of remarkable breakthroughs in prognosis improvement of hard-to-treat solid tumours (including head and neck squamous cell carcinoma, non-small cell lung cancer, gastric cancer, urothelial cancer, cervical cancer, and melanoma) and have entered in the standard clinical practice (Wu et al., 2006; Schalper et al., 2014; Faghfuri et al., 2015; Reck et al., 2016; Zhu et al., 2017; Rotte et al., 2018). Recently, the expression of PD-L1 on glioma cells has been documented (Berghoff et al., 2015; Heiland et al., 2017). Researches have increasingly concerned over the prognostic evaluation of PD-L1 in patients with glioblastoma. However, whether PD-L1 expression correlates with prognosis in GBM patients remains controversial. Therefore, we assessed the consistency and magnitude of the prognostic and clinical significance of PD-L1 in GBM patients through a systematic review and meta-analysis.

MATERIALS AND METHODS

Literature Search Strategy
The implementation of this systematic review and meta-analysis followed the guideline of PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We systematically reviewed the literature published in the PubMed and CNKI (China National Knowledge Infrastructure) databases (dated to July 2019). The following key words were adopted: ("glioblastoma" OR “GBM” OR “glioma” OR “brain tumour” OR “brain cancer” OR “cerebral tumour” OR “intracranial tumour”) AND (“CD 274” OR “PD-L1” OR “Programmed Cell Death 1 Ligand 1”) without restrictions on languages, regions and publication types.

**Inclusion and exclusion criteria**

The study adopted the following inclusion criteria: (1) All patients were diagnosed with GBM by pathological or histological examination; (2) Hazard ratio (HR) and 95% confidence intervals (CIs) could be available; or the association between PD-L1 and overall survival (OS) or disease-free survival (DFS) with sufficient data were provided.

The study excluded the following: (1) conference abstracts, case reports, reviews, basic research, clinical trials; (2) studies missing available data.

**Data extraction and quality assessment**

Two investigators independently reviewed potentially relevant studies in order to minimize bias. A third reviewer was brought in where and when there were disagreements. We extracted the following data from the included studies: authors, name of the journal, year of publication and ethnicity, number of enrolled patients, tumour histology, PD-L1 expression level, cut off value, detection area, detection methods, and follow-up.

If only survival curves were available, the data could be extracted from the Kaplan Meier curves. The quality of each retrieved article was assessed independently by two assessors according to the Newcastle-Ottawa Quality Assessment Scale (NOS). A total score of 0-9 was assigned to each included study, and studies with a NOS score ≥5 were considered to be of high quality (Stang, 2010).

**Statistical analysis**

The association between PD-L1 expression with OS and DFS of patients with GBM was evaluated according to the HR and 95%CI. Statistical heterogeneity among studies was quantified with the Cochran’s Q test and the $I^2$ statistic. We used a random-effects model to pool the data when evidence suggested significant heterogeneity ($I^2>50\%$ or $P$-value <0.1), while a fixed-effects model was applied when heterogeneity was negligible.
model was conducted otherwise. Subgroup analyses and sensitivity analyses were attempted to explain the origin of heterogeneities. The potential publication bias was estimated by the Begg’s and Egger’s tests with significance of \( P \)-value <0.05. Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK) and STATA 15 were statistical packages used in the study.

**RESULTS**

**Characteristics of included studies**

A total of 201 potentially relevant records were obtained according to the search strategy mentioned above. One hundred and eighty-eight studies were rejected after screening the titles and abstracts. Thirteen studies were included for further evaluation, of which 4 articles without eligible survival data were excluded. Finally, nine studies with 806 patients fulfilled the criteria and entered the meta-analysis. The selection flowchart and the baseline information of the studies are respectively displayed in Figure-1 and Table-1.
**Table 1:** General characteristics of included studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
<th>Country</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>Methods</th>
<th>Cut-off point (high/low)</th>
<th>HR estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al., 2013</td>
<td>Neuro Biology of Disease</td>
<td>2013</td>
<td>Denmark</td>
<td>17</td>
<td>Surgery</td>
<td>IFC</td>
<td>Score ≥ 2</td>
<td>OS</td>
</tr>
<tr>
<td>Berghoff et al., 2015</td>
<td>Neuro-Oncology</td>
<td>2015</td>
<td>Austria</td>
<td>135</td>
<td>Surgery</td>
<td>IHC</td>
<td>5%</td>
<td>OS</td>
</tr>
<tr>
<td>Nduom et al., 2016</td>
<td>Neuro-Oncology</td>
<td>2016</td>
<td>USA</td>
<td>94</td>
<td>Surgery</td>
<td>IHC</td>
<td>5%</td>
<td>OS</td>
</tr>
<tr>
<td>Zeng et al., 2016</td>
<td>Oncotarget</td>
<td>2016</td>
<td>China</td>
<td>229</td>
<td>Surgery</td>
<td>IHC</td>
<td>Median</td>
<td>OS +DFS</td>
</tr>
<tr>
<td>Han et al., 2017</td>
<td>Journal of Pathology and Translational Medicine</td>
<td>2017</td>
<td>Korea</td>
<td>54</td>
<td>Surgery</td>
<td>IHC</td>
<td>Median</td>
<td>OS +DFS</td>
</tr>
<tr>
<td>Miyazaki et al., 2017</td>
<td>Journal of Neuro-Oncology</td>
<td>2017</td>
<td>Japan</td>
<td>16</td>
<td>Surgery</td>
<td>IHC</td>
<td>Median</td>
<td>OS +DFS</td>
</tr>
<tr>
<td>Lee et al., 2018</td>
<td>Journal of Neuro-Oncology</td>
<td>2017</td>
<td>Korea</td>
<td>115</td>
<td>Surgery</td>
<td>IHC</td>
<td>5%</td>
<td>OS</td>
</tr>
<tr>
<td>Pratt et al., 2019</td>
<td>Neurosurgery</td>
<td>2018</td>
<td>USA</td>
<td>125</td>
<td>Surgery</td>
<td>IHC</td>
<td>5%</td>
<td>OS</td>
</tr>
<tr>
<td>Hwang et al., 2018</td>
<td>Journal of Neuro-Oncology</td>
<td>2018</td>
<td>South Korea</td>
<td>21</td>
<td>Surgery</td>
<td>IHC</td>
<td>Score ≥ 2</td>
<td>OS</td>
</tr>
</tbody>
</table>
Association Between PD-L1 Expression and Prognostic Parameters

PD-L1 Expression and the Overall Survival (OS) of the patients

For OS, nine studies presented OS data (n=806). Significant heterogeneity existed amongst studies included in the analyses (I²=51%, P=0.04). Pooled result by a random-effects model revealed a significantly inverse correlation between PD-L1 overexpression OS patients with GBM (HR=1.63, 95%CI: 1.19–2.24, P=0.003) (Fig.2).

PD-L1 Expression and association with the Diseases Free Survival (DFS)

As shown in Fig.3, three studies (n=299) focused on DFS and no heterogeneity was existed amongst the studies (I²=10%, P=0.33). However, pooled analysis by fixed model did not reveal any significant link between PD-L1 and DFS of patients (HR=0.82, 95% CI: 0.58–1.15, P=0.25).

PD-L1 Expression and Clinicopathological Characteristics

Age

Two studies, consisting of 246 patients, assessed the correlation between age and PD-L1 expression. As shown in Fig.4-A, 90 (51.14%) of 176 younger patients (whose age defined as younger than 50 yrs) showed PD-L1 expression, compared with and 57.14% (40 of 70) of older patients (equal or greater than 50 years of age) who had PD-L1 overexpression. PD-L1 expression did not correlate significantly with age (OR=0.92, 95%CI: 0.51–1.65, P=0.78).

Gender

The dependability between PD-L1 expression and gender was assessed in three studies involving 300 patients. Eighty-five (52.47%) of 162 male patients and 64 (46.38%) of 138 female patients were PD-L1 overexpression. The results indicated that PD-L1 overexpression had no significant association with gender (OR=1.20, 95%CI: 0.75–1.92, P=0.44; Fig.4-B).

Progress/Recurrence

Regarding the progression or recurrence, subgroup analysis by three studies showed that the PD-L1 positive tumours were seen in 41.89% (62/148) patients with progression or recurrence and 44.07% (119/270) patients without progression or recurrence, respectively. There were no significant links between PD-L1 and cancer progression or recurrence (OR=0.86, 95%CI: 0.55–1.35, P=0.52; see Fig.4-C).

Ethnicity

In ethnicity subgroup, the stratified analysis revealed PD-L1 positivity was linked to unfavorable OS in patients from the Asian regions (five studies with 435 cases: HR=3.01, 95%CI:1.21–7.48,
and the American regions (two studies with 219 cases: HR=2.09, 95%CI:1.48–2.94, 
\( P=0.02 \)) and the American regions (two studies with 219 cases: HR=2.09, 
95%CI:1.48–2.94, \( P<0.0001 \)), but not in patients from the European studies (two studies with 152 cases: HR=1.78, 
95%CI:0.55–5.81, \( P=0.34 \)) (Fig.5).

**IDH1 (Isocitrate Dehydrogenase (NADP(+) )-1 coding gene) status**

Two separate studies, encompassing 209 patients in total, evaluated a possible connection between 
IDH1 mutation (namely \( IDH1 \)-wild type vs with \( IDH1 \)mutation) and PD-L1 was evaluated. Of 
the 183 tumours which displayed \( IDH1 \)-wild type, 67 (36.61%) were PD-L1 positive. Of the 26 
tumours which had \( IDH1 \)-mutation, one (3.85%) was PD-L1 positive expression. The pooled OR 
indicated that PD-L1 positivity was closely related to IDH1 status (OR=9.92, 95%CI: 1.85–53.08, 
\( P=0.007 \)) (Fig.6).

In a subgroup analysis using a random effects model, heterogeneity was revealed in relation to 
PD-L1 and ethnicity of the patients (\( P<0.00001 \), \( I^2=91\% \)).

**Sensitivity Analysis and Publication bias**

Finally, we found no significant publication bias in the nine studies entered the current analysis, 
by respectively applying the Begg’s test and the Egger’s test (\( P=0.917 \) and \( P=0.527 \), respectively) 
(Fig.7).

**DISCUSSION**

PD-L1 is a coinhibitory ligand expressed on many types of tumour cells. It has been indicated that 
the binding of PD-L1 to its receptor PD-1 induces T cell dysfunction and apoptosis which plays a 
crucial role in tumour immune evasion. Gliomas have been recognized as immunosuppressive 
tumour. The current understanding of glioma-mediated immune suppression have generated 
increasing interest in the correlations between PD-L1 expression and survival for gliomas, 
particularly glioblastomas (GBMs). However, the published results glioblastomas (GBMs) remain 
controversial. In 2013 Liu et al. first reported that the expression of PD-L1 in seventeen patients 
with glioblastoma is a possible indicator for poor clinical outcome(Liu et al., 2013). Using level 3 
Illumina RNASeq, Nduom et al. also found PD-L1 gene overexpression was indicative of shorter 
survival time in 149 patients with GBM from (data from the Cancer Genome Atlas (TCGA) 
dataset)(Nduom et al., 2016). Various other studies showed similar relationship (Han et al., 
2017;Lee et al., 2018;Pratt et al., 2019). However, in a retrospective study of 117 newly diagnosed
GBMs as well as a TCGA database analysis comprising 446 GBM patients, Berghoff et al. did not find a significant connection between PD-L1 and the overall survival (Berghoff et al., 2015). The similar views were also taken in several other analyses (Zeng et al., 2016; Miyazaki et al., 2017). To clarify a reasonable evidence-based conclusion, a meta-analysis including 9 studies with a total of 806 patients was performed. The present meta-analysis showed that PD-L1 positive expression was significantly associated with poor OS (HR=1.63, 95%CI: 1.19–2.24, \( P=0.003 \)) in GBM patients after surgery; however, there were insufficient evidence to suggest that PD-L1 was related to DFS (HR=0.82, 95% CI: 0.58–1.15, \( P=0.25 \)). These results suggested that PD-L1 positive expression might be a negative prognostic factor in glioblastomas (GBMs).

To further explore the potential sources of heterogeneity in the relationship of PD-L1 and overall survival in GBM, we utilized subgroup analyses. The results confirmed that the significance of PD-L1 in OS was not affected by gender, age and tumour progression/recurrence, collectively suggesting that this relationship is independent of these factors in this tumour type. The influence of PD-L1 on the OS of multiethnic patients was also explored. Patients were classified as from Asia, America and Europe. Different combined HRs and P-values for OS were shown in different ethnic groups: PD-L1 overexpression was significantly associated with poor OS for patients from Asia and America, while no significant association for the survival of patients from Europe survival, which suggested that racial differences may be a potential origin of heterogeneity in GBM. This "ethnic biasedness" of PD-L1 has been observed in several clinical studies for patients with certain other types of solid tumours. KEYNOTE-181, a phase 3 trial of Pembrolizumab (P) vs chemotherapy (paclitaxel, docetaxel or irinotecan) in patients with oesophageal squamous cell carcinoma, showed that P was superior to chemotherapy for OS in patients with PD-L1 positive expression (CPS \( \geq 10 \)) in the global cohort, especially in the Chinese subgroup (J. Chen et al., 2019). Similarly, in the KEYNOTE-062 (a study of Pembrolizumab vs chemotherapy in patients who had advanced gastric or gastro-oesophageal junction cancer), P didn't bring significant survival benefits as the first-line treatment for PD-L1-positive (CPS \( \geq 1 \)) population in the full global cohort (Tabernero J and et al.). However, in further ethnicity subgroup analysis, P showed lower risk of death in Asians with PD-L1 positive expression (CPS \( \geq 1 \)) when compared to chemotherapy, but not in Europeans, Americans and Australians. The findings in stratified analyses that PD-L1 has a prognostic role in different ethnic groups may have potential
implications to help stratify patients for immunotherapy and prognostication. It is possible that the immunogenetics might to some extent differ in different races (Zhang et al., 2019). So the subgroup analysis stratified by ethnicity may be necessary to accurately assess the potential prognostic value of PD-L1 and the efficacy of relevant immunotherapy drugs in further clinical studies for GBM.

Although the traditional classification according to histological analysis and the degree of malignancy remains essential in the diagnosis of gliomas, molecular markers which were incorporated in the updated 2016 World Health Organization (WHO) classification of diffuse gliomas strongly improved our understanding of glioma biology and gliomagenesis (Louis et al., 2016; Wirsching and Weller, 2016). Isocitrate dehydrogenase (IDH), a key rate-limiting enzyme in the Krebs cycle, has been considered as one of the important molecular biomarkers of glioma subtypes that has diagnostic, prognostic and predictive application (Yen et al., 2010; Kloosterhof et al., 2011; van Lith et al., 2014; Chen et al., 2017). Studies have reported the mutations in genes encoding 2 of the isoforms of IDH (IDH1 and IDH2) are present in gliomas (Hartmann et al., 2009; Cohen et al., 2013). GBMs that are hotspot mutation in IDH1 generally have a significantly better prognosis compared with IDH1-wildtype GBMs (Ohgaki and Kleihues, 2013; Kaminska et al., 2019; Korshunov et al., 2019). Moreover, the expression of PD-L1 in diffuse gliomas might be directly influenced by IDH1 mutational status (Wang et al., 2016; Berghoff et al., 2017; Lee et al., 2018). Therefore, the relation between PD-L1 expression and IDH1 status was further investigated in the stratified analysis. We found that IDH1-wildtype status in GBM was PD-L1 expression positive. The result confirmed recent findings of a PD-L1/IDH1-wildtype association. Studies have shown that IDH1-wildtype patients exhibited higher PD-L1 gene expression than IDH1-mutant counterparts. The hypothesis about its mechanism of this connection was that IDH1 mutation can result in the PD-L1 promoter hypermethylation that downregulates the expression of PD-L1 (Mu et al., 2018; Rover et al., 2018). Compared with IDH1-mutant gliomas, gliomas with IDH1-wildtype status were considered to have lower sensitivity to chemo/radiation therapy and more unfavorable clinical outcome (Turkalp et al., 2014). Given the result that the PD-L1 overexpression was linked with poor OS and IDH1-wildtype status, it would help to provide a valuable clinical reference for appropriate use of PD-L1 immune checkpoint blockers in radio/chemo-resistant IDH1-wildtype GBMs. While in further clinical trials for patients with
IDH1-mutant GBMs, the PD-L1 inhibitors might not be advisable because of the low PD-L1 expression.

Recent research has showed that tumour cells in gliomas can regulate PD-L1 expression via 2 major mechanisms to mediate immune evasion, “adaptive resistance” mechanism and “innate resistance” mechanism(Xue et al., 2017). The former is for extrinsic induction of PD-L1. IFN-γ, a proinflammatory cytokine primarily produced by tumour infiltrating lymphocytes (TILs), can induce PD-L1 upregulation via NF-κB /PKD2 signal pathway(Chen et al., 2012; Gowrishankar et al., 2015; Qian et al., 2018). The latter is proved to mediate intrinsic induction of PD-L1. When there is a lack of TILs, PD-L1 induction in glioma cells might depend on multiple oncogenic signaling pathways (such as JAK/STAT 3, PI3K/Akt/mTOR/S6K1 and EGFR/MAPK pathway) or oncogene mutations (such as ALK, EGFR and PTEN)(Parsa et al., 2007; Marzec et al., 2008; Crane et al., 2009; Green et al., 2010; Akbay et al., 2013; Topalian et al., 2015; Lastwika et al., 2016; Zhao et al., 2019). However, further research demonstrated that cellular components with PD-L1 expression in tumour microenvironment may also be a significant factor affecting the process of immunosuppression and the prognostic value of PD-L1, such as activated microglia and peripheral-derived myeloid cells(Bloch et al., 2013; Nduom et al., 2015; Antonios et al., 2017; Qian et al., 2018). Additionally, the evaluation of PD-L1 as a biomarker for prediction of prognosis in glioma may be affected by certain factors. Analyses of TCGA datasets have produced variable results, which may be due to the difference of source material and constitution of cases(Berghoff et al., 2015; Nduom et al., 2016). Furthermore, methods of patient separation may also influence the prognostic assessment of PD-L1, which was demonstrated in part by Zeng and Colleagues. In their study, patients were divided in two groups, those with longer follow up or overall survival (≥12 months) and those with shorter follow up or survival (<12 months). The authors found a significant association between PD-L1 and poor prognosis in glioblastoma in the long-time survival or follow up. In contrast, in patients with a short follow up or overall survival, there appears to be an opposite, namely favorable link between PD-L1 and patients prognosis(Zeng et al., 2016). It is clear that more works are required here, particularly in a much larger cohort in order to decipher these intimate connections.

Some of the recent studies have indicated that PD-L1 may be a valuable therapeutic target in cancer immunotherapy (Chen and Han, 2015; Garber et al., 2016). Recently, promising preclinical
data in murine models of glioma have provided support for PD-L1 checkpoint inhibitors implementation in GBM patients (Zeng et al., 2013; Wainwright et al., 2014; Huang et al., 2015). However, early clinical trials on the effectiveness of PD-L1 blockade agents are still limited and elusive. A combination between Anti-PD-L1 mAb durvalumab and bevacizumab is now being tested in a phase 2 open label, non-randomized clinical trial for GBM (cohort B, NCT02336165)(Reardon DA et al., 2017). Interim results of durvalumab monotherapy revealed low SAE (severe adverse events) rate of 10% and efficacy with OS-6 of 42% and PFS-6 (progression-free survival) of 20%. Trials for other cohorts (cohort A: newly diagnosed MGMT-promoter unmethylated GBM, cohort C: refractory recurrent GBM) are still ongoing. Atezolizumab, a humanized antibody to PD-L1 that has been approved for second-line treatment for patients with advanced or metastatic NSCLC (non-small cell lung cancer) and urothelial cancer, is also being studied in a phase 1a clinical trial for multiple solid tumours, including GBM (PCD4989g; NCT01375842)(Lukas et al., 2018). Results showed that Atezolizumab was safe and well tolerated in patients with GBM. Glioblastoma was considered a type of “immunologically cold tumour” due to the relative lack of tumour infiltrating T cells in the tumour micro-environment (TME) and high selectivity of BBB(Suter et al., 2003; Muldoon et al., 2013; Colli et al., 2016). The “cold” phenotype of GBM may limit immunotherapy efficacy. Combinatorial treatment approaches targeting immune-suppression or BBB permeability may help shift the “cold” microenvironment and enhance response to immune checkpoint blockade in GBM, including radiation therapy, chemotherapy, other immunotherapies (e.g. Chimeric antigen receptor T-cells, oncolytic virus), and bevacizumab(O'Rourke et al., 2017; Gupta and Burns, 2018).

So far as we are aware, the present study is the first meta-analysis, to systematically estimate the correlation between PD-L1, and clinical outcomes and clinicopathological factors in glioblastoma. While some limitations need attention. Firstly, different analysis strategy of IHC and inconsistent cut-off values of PD-L1 expression may lead to heterogeneity between studies. Thus, a standardized approach for protein expression should be set up to improve consistency and veracity in the measurement of PD-L1 for future studies. Secondly, some subgroups, such as the IDH1 status group, had small sample sizes. Thirdly, the investigation about the correlations between PD-L1 and clinical features, including as tumour size, tumour site and surgical approach are not performed due to the deficiency of related original information.
In conclusion, our meta-analysis shows that high PD-L1 expression is strongly correlated with unfavorable prognosis for GBM patients. PD-L1 may present itself as a valuable target for Immunotherapy in clinical practice. Additional high-quality, larger-scale prospective studies are needed to provide validate the potential value of PD-L1 for the prognosis and treatment of GBM patients in the future.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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Fig 1. Flow chart of the selection process of studies for
**Fig. 2** Forest plot of 9 studies evaluating the association between PD-L1 expression and overall survival.

**Fig. 3** Forest plot of 3 studies evaluating the association between PD-L1 expression and DFS.
Fig. 4 Forest plots for the association of PD-L1 expression with clinicopathological features in GBM patients. 

### Table: Clinicopathological Features

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Male Events</th>
<th>Male Total</th>
<th>Female Events</th>
<th>Female Total</th>
<th>Weight</th>
<th>Odds Ratio M-H Fixed 95% CI</th>
<th>Odds Ratio M-H Fixed 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>162</td>
<td>138</td>
<td>64</td>
<td></td>
<td></td>
<td>1.20 [0.75, 1.92]</td>
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<tr>
<td>Progress</td>
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<tr>
<td>No PD-L1 positive</td>
<td>148</td>
<td>270</td>
<td>100%</td>
<td></td>
<td></td>
<td>0.86 [0.55, 1.35]</td>
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<tr>
<td>PD-L1 positive</td>
<td>22</td>
<td>40</td>
<td>18.8%</td>
<td></td>
<td></td>
<td>0.94 [0.80, 1.08]</td>
<td></td>
</tr>
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<td>PD-L1 negative</td>
<td>4</td>
<td>12</td>
<td>18.8%</td>
<td></td>
<td></td>
<td>0.94 [0.80, 1.08]</td>
<td></td>
</tr>
<tr>
<td>Progress</td>
<td></td>
<td></td>
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<td>No PD-L1 positive</td>
<td>148</td>
<td>270</td>
<td>100%</td>
<td></td>
<td></td>
<td>0.86 [0.55, 1.35]</td>
<td></td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>22</td>
<td>40</td>
<td>18.8%</td>
<td></td>
<td></td>
<td>0.94 [0.80, 1.08]</td>
<td></td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>4</td>
<td>12</td>
<td>18.8%</td>
<td></td>
<td></td>
<td>0.94 [0.80, 1.08]</td>
<td></td>
</tr>
</tbody>
</table>

### Fig. 4 Details:
- **Total events**: 176 for <50 years and 120 for ≥50 years.
- **Heterogeneity**: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%.
- **Test for overall effect**: Z = 0.28 (P = 0.78).
Fig. 5 Forest plot for the association of PD-L1 expression with clinicopathological feature of region in GBM patients.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>America</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drew Pratt 2018</td>
<td>0.89738395</td>
<td>0.20100087</td>
<td>15.2%</td>
<td>2.45 [1.66, 3.64]</td>
<td></td>
</tr>
<tr>
<td>Edjah K. Nduom 2016</td>
<td>0.5467244</td>
<td>0.22299899</td>
<td>15.0%</td>
<td>1.73 [1.12, 2.67]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>30.2%</td>
<td>2.09 [1.48, 2.94]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.02; Chi^2 = 1.37, df = 1 (P = 0.24); I^2 = 27%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 4.20 (P &lt; 0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiheun Han Yongkilhong 2017</td>
<td>0.54801961</td>
<td>0.86532931</td>
<td>7.4%</td>
<td>1.73 [0.32, 9.43]</td>
<td></td>
</tr>
<tr>
<td>Jing Zong 2016</td>
<td>0.80200463</td>
<td>0.67549076</td>
<td>9.4%</td>
<td>2.23 [0.59, 8.38]</td>
<td></td>
</tr>
<tr>
<td>Khwanh Hwang 2018</td>
<td>2.47821091</td>
<td>4.36105209</td>
<td>0.5%</td>
<td>11.92 [0.00, 61433.83]</td>
<td></td>
</tr>
<tr>
<td>Kyu Sang Lee 2018</td>
<td>0.647246</td>
<td>0.250656</td>
<td>14.7%</td>
<td>1.91 [1.17, 3.12]</td>
<td></td>
</tr>
<tr>
<td>Tsubasa Miyazaki 2017</td>
<td>1.91063646</td>
<td>0.09888109</td>
<td>16.0%</td>
<td>6.70 [5.57, 8.20]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>48.9%</td>
<td>3.91 [1.21, 7.48]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.64; Chi^2 = 25.74, df = 4 (P &lt; 0.0001); I^2 = 84%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.37 (P = 0.02)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anna Sophie Berghoff 2015</td>
<td>0.21006263</td>
<td>0.22211599</td>
<td>15.0%</td>
<td>1.23 [0.80, 1.91]</td>
<td></td>
</tr>
<tr>
<td>Yawei Liu 2013</td>
<td>1.56526906</td>
<td>0.94143093</td>
<td>6.7%</td>
<td>4.78 [0.76, 30.28]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>21.8%</td>
<td>1.78 [0.55, 5.81]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.45; Chi^2 = 1.96, df = 1 (P = 0.16); I^2 = 49%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.96 (P = 0.34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>2.42 [1.29, 4.53]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.63; Chi^2 = 85.78, df = 8 (P &lt; 0.0001); I^2 = 91%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.77 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroups differences: Chi^2 = 0.64, df = 2 (P = 0.72); I^2 = 0%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 6 Forest plot for the association of PD-L1 expression with clinicopathological feature of IDH1 status in GBM

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>IDH Wt Events</th>
<th>IDH Mut Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H. Fixed, 95% CI</th>
<th>M-H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drew Pratt 2018</td>
<td>30</td>
<td>81</td>
<td>1</td>
<td>13</td>
<td>66.0% 7.06 [0.87, 57.03]</td>
<td></td>
</tr>
<tr>
<td>Kyu Sang Lee 2016</td>
<td>37</td>
<td>102</td>
<td>0</td>
<td>13</td>
<td>34.0% 15.46 [0.89, 267.52]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>183</strong></td>
<td><strong>26</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>9.92 [1.85, 53.08]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>67</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.66 (P = 0.007)
Fig. 7 Egger’s plot for assessing publication bias for the impact of PD-L1 expression on OS in GBM patients.