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PD-L1 and prognosis in patients with malignant pleural mesothelioma: a meta-analysis and bioinformatics study

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Abstract

Background: The prognostic value of programmed death-ligand 1 (PD-L1) expression in patients with malignant pleural mesothelioma (MPM) has been controversial according to previous investigations. Therefore, we conducted a meta-analysis to assess the potential prognostic significance of PD-L1 expression in MPM.

Methods: PubMed, Embase, Web of Science, Scopus, and the Cochrane Library were thoroughly searched for relevant original articles published before 9 April 2020. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of overall survival (OS) and progression-free survival (PFS) were calculated. The results of the meta-analysis were verified using The Cancer Genome Atlas (TCGA) dataset.

Results: In total 16 studies were included in our meta-analysis. A high PD-L1 expression was associated with a poor OS (HR = 1.53, 95% CI = 1.28–1.83, $p < 0.001$), but not a grave PFS (HR = 1.07, 95% CI = 0.82–1.39, $p = 0.643$) in MPM. Furthermore, the PD-L1 expression correlated with the sarcomatoid + biphasic type of MPM (odds ratio = 4.32, 95% CI = 2.16–8.64, $p < 0.001$). TCGA data indicated that PD-L1 was a significant prognostic factor for OS (HR = 2.069, 95% CI = 1.136–3.769, $p = 0.0175$), but not for PFS (HR = 1.205, 95% CI = 0.572–2.539, $p = 0.624$), which was in accordance with the results of the meta-analysis.

Conclusion: A high PD-L1 expression is a significant prognostic factor for poor OS of patients with MPM. We therefore suggest that PD-L1 expression levels can be used to predict the clinical outcomes of patients with MPM in the future.

Keywords: cancer risk, evidence-based medicine, malignant pleural mesothelioma, meta-analysis, PD-L1

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Introduction

Malignant pleural mesothelioma (MPM) is a rare cancer of the pleura with increasing incidence worldwide.[1] MPM is associated with asbestos exposure, which is responsible for 80% of the diagnosed cases,[2] and is an aggressive cancer with a grim prognosis.[1] The median survival period of patients with MPM is 8–14 months[3] and the 5-year overall survival (OS) rate is 8.5%.[4] For localized disease of MPM, the mainstay therapeutic strategies are surgical resection with or without radiotherapy and/or chemotherapy, whereas for patients with unresectable disease, multimodality therapy including radiotherapy and chemotherapy is usually selected.[5] Moreover, immunotherapy with checkpoint blockade has emerged as a promising new treatment for unresectable MPM.[6–8] KEYNOTE-028 was the first clinical trial to show the benefit of immune checkpoint inhibition (ICI) in patients with MPM.[9] Although revolutionary advancements have been achieved in the treatment of MPM in the last decade, the prognosis for MPM has not substantially improved. Biomarkers are important for the early

determination of prognosis for patients with MPM. Therefore, it is necessary to identify novel and effective prognostic factors for MPM.

Programmed death-ligand 1 (PD-L1) is a 40 kDa surface glycoprotein molecule that is expressed in a variety of immune cells and tumor cells.[10] PD-L1 plays a vital role in immune suppression. The interaction of PD-L1 with programmed cell death 1 (PD-1) negatively regulates T cell-mediated immune responses.[11] The activation of the PD-1/PD-L1 signal pathway inhibits effector T cell function and protects cancer cells from immune surveillance.[12] Many studies have demonstrated the prognostic role of PD-L1 expression in diverse solid tumors, including hepatocellular carcinoma,[13] colorectal cancer,[14] breast cancer,[15] lung cancer,[16] and pancreatic cancer.[17] The potential prognostic value of tumor PD-L1 expression in patients with MPM has also been investigated; however, the results are inconsistent.[18–23] In addition, there is no consensus on whether PD-L1 expression can predict the efficiency of ICI treatments and the outcomes for patients receiving them.[6] Therefore, we performed a meta-analysis to incorporate current evidence to assess the prognostic significance of PD-L1 expression for MPM. In addition, we also validated the results of the meta-analysis using The Cancer Genome Atlas (TCGA) to confirm the reliability of the data.

Methods

Study guidelines and ethics

We carried out the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24] As our research was based on data extracted from previously published studies, ethical approval was not required.

Search strategy

Electronic platforms such as PubMed, Embase, Web of Science, Scopus, and the Cochrane Library were thoroughly searched using the following terms: PD-L1, programmed death ligand-1, PDL1, B7-H1, B7 homolog 1, CD274, programmed cell death ligand 1, mesothelioma, MPM, and malignant pleural mesothelioma. The search was conducted up to 9 April 2020. The search strategies for PubMed are shown in the Supplemental Material online. Searches were limited to English-language publications. In addition, the reference lists of the retrieved articles were examined for potential eligible studies.

Selection criteria

Eligible studies were selected based on the following inclusion criteria: (1) patients' MPM diagnoses were pathologically and/or histologically confirmed; (2) the studies recorded sufficient data to calculate the hazard ratio (HR) with 95% confidence interval (CI) for overall survival (OS) and/or progression-free survival (PFS); (3) PD-L1 expression in tumor tissue was detected using immunohistochemistry (IHC) staining; (4) PD-L1 expression was stratified into high and low groups using a definite cut-off value; and (5) the studies were published in English. The exclusion criteria were as follows: (1) duplicate reports, meeting abstracts, correspondences, letters, and reviews; (2) studies without sufficient data for meta-analysis; and (3) animal studies and basic research. OS was calculated from diagnosis of malignancy until death due to any cause or until the date of last follow-up visit for still alive patients. PFS was calculated from diagnosis of malignancy until disease progression.

Data extraction

Two independent researchers (LJ and WG) extracted data in a standardized form from the included studies, and any disagreements were resolved *via* discussion with a third investigator (ZC). The information extracted from each study included the first author, country, year of publication, number of cases, enrollment duration, treatment, sex, median or mean age of patients, study design, survival endpoints, follow-up, cut-off values for high PD-L1 expression, HR estimate, and HR with 95% CI.

Qualitative assessment

Two investigators (XL and LX) independently assessed the methodological quality of all the included studies, using the Newcastle–Ottawa Scale (NOS).[25] The NOS includes three domains: selection (0–4 stars), comparability (0–2 stars), and outcome (0–3 stars). The maximum score of the NOS is nine points and studies with NOS scores $\geqslant$6 are considered high-quality studies. Any discrepancies were discussed by all the researchers in the group, to reach a consensus.

Bioinformatics study using TCGA data

The RNA-sequencing data and corresponding survival analysis of patients with MPM were analyzed using TCGA data. We accessed the datasets through cBioPortal (http://www.cbioportal.org/). The "TCGA, PanCancer Atlas" dataset was selected, and 87 patients with available data were included. This dataset was selected because it contained the largest sample size in mesothelioma type of cancer. We requested mRNA expression with a z-score threshold of ± 1.4, based on the median value and referring to previous literature.[26] Analyses of OS and PFS were conducted using Kaplan–Meier plots.

Statistical analysis

The prognostic value of PD-L1 for OS and PFS was calculated by pooling the HR and 95% CI values. The odds ratios (ORs) and 95% CIs were calculated to evaluate the association between PD-L1 expression and clinicopathological characteristics of MPM. The heterogeneity among the studies was detected using Cochran's Q test and the I^2 test. If the heterogeneity was significant ($p < 0.1$ or $I^2 > 50\%$), a random-effects model (REM) (the Mantel–Haenszel method) was used; otherwise, a fixed-effects model (the DerSimonian and Laird method) was applied. We also conducted subgroup analyses to detect potential sources of heterogeneity. A survival analysis (using TCGA) of 87 patients was conducted in cBioPortal, using the Kaplan–Meier curve. Publication bias was analyzed using the Begg's test. All the calculations were performed using Stata version 12.0 (StataCorp LP, TX, USA). A two-sided p-value < 0.05 was considered to indicate statistical significance.

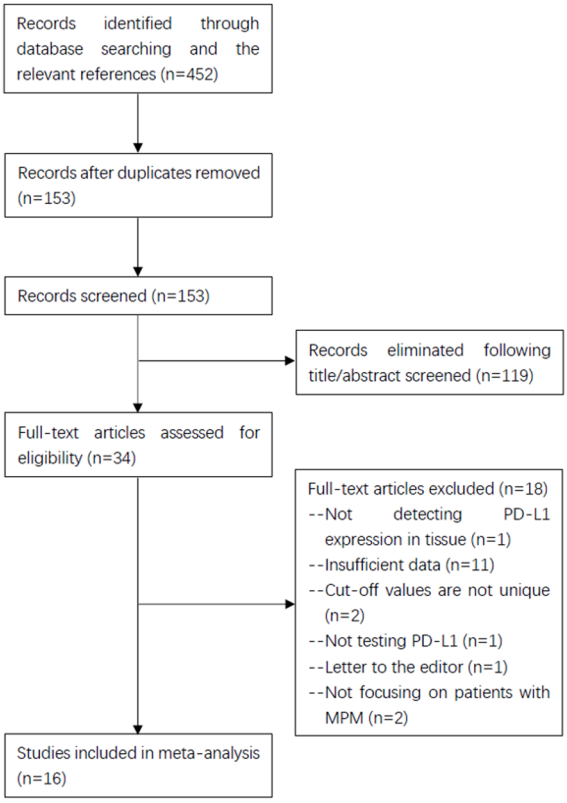

Figure 1. Flow chart of included studies for the meta-analysis.
MPM, malignant pleural mesothelioma; PD-L1, programmed death-ligand 1.

Results

Literature search

A total of 452 records were identified through literature retrieval and reference list examination. Then, 299 duplicate publications were excluded, and 153 studies were screened by title and abstract. Subsequently, 119 studies were discarded and 34 studies[9,18–23,27–53] were left for eligibility assessment by full-text examination. Eighteen studies were excluded for different reasons: one study did not detect PD-L1 expression in sera samples other than tumor tissues,[37] 11 studies did not present sufficient data for meta-analysis,[9,38,39,42–48,52] two studies did not use unique cut-off value,[40,50] one study did not test PD-L1 expression,[41] one study was a letter to the editor,[49] and two studies recruited patients with pleural and peritoneal mesothelioma tumors other than MPM.[51,53] Finally, 16 studies were included in our meta-analysis.[18–23,27–36] The flow chart of the article screening process is shown in Figure 1.

Characteristics of eligible studies

The baseline features of the 16 included studies are summarized in Table 1. The studies were published from 2014 to 2020. The sample size of the individual studies ranged from 27 to 329, and our meta-analysis eventually included 1899 patients. Two studies were prospective studies[19,23] and 14 were of retrospective design.[18,20–22,27–36] All 16 studies[18–23,27–36] provided data on the association between PD-L1 and OS, whereas only two studies reported data on PFS.[19,30] With respect to treatment, seven studies enrolled patients receiving surgery,[18,27–29,31,35,36] three studies recruited patients receiving chemotherapy[19,33] or immunotherapy,[30] and six studies included patients receiving mixed treatments (chemotherapy, radiotherapy,

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

Study	Sample size	Country	Enrollment period	Sex, male/female	Treatment	Line of therapy	Age, years Median (range)	Detection method	Cut-off value	Follow-up, months	Survival analysis	Study design	NOS score
Ahmadzada *et al.*[18]	67	Australia	1992–2007	55/12	Surgery	First	65 (42–83)	IHC	5%	NR	OS	Retrospective	8
Brosseau, *et al.*[19]	214	France	2008–2014	160/54	Chemotherapy	First	66.85 (34.7–75.9)	IHC	1%	NR	OS, PFS	Prospective	9
Cedres *et al.*[20]	27	Spain	2000–2014	20/7	Surgery + chemotherapy	First	68 (53–83)	IHC	1%	14 (0.6–47.3)	OS	Retrospective	7
Cedres *et al.*[21]	119	Spain	2002–2014	85/34	Surgery + chemotherapy	First	69 (42–90)	IHC	1%	15.1 (0.2–99)	OS	Retrospective	7
Combaz-Lair *et al.*[22]	58	France	1993–2014	45/13	Surgery + chemotherapy	First	69 (39–84)	IHC	1%	To Dec 2014	OS	Retrospective	8
de Perrot *et al.*[23]	69	Canada	2008–2016	57/12	Radiotherapy + surgery	First	65 (41–82)	IHC	1%	To Oct 2018	OS	Prospective	9
Inaguma *et al.*[27]	175	USA	NR	101/74	Surgery	First	59.2	IHC	5%	120	OS	Retrospective	6
Kao *et al.*[28]	72	Australia	1992–2007	58/14	Surgery	First	NR	IHC	5%	NR	OS	Retrospective	8
Mansfield *et al.*[29]	106	USA	1987–2003	90/16	Surgery	First	66.5	IHC	5%	120	OS	Retrospective	7
Metaxas *et al.*[30]	93	Switzerland, Australia	2015–2017	85/8	Immunotherapy	⩾Second	68 (25–94)	IHC	5%	9	OS, PFS	Retrospective	7
Muller *et al.*[31]	319	USA	1989–2010	237/82	Surgery	First	64 (29–85)	IHC	1%	12	OS	Retrospective	8
Nguyen *et al.*[32]	58	Australia	2006–2016	49/9	Chemotherapy + radiotherapy	First	73	IHC	1%	NR	OS	Retrospective	8
Patil *et al.*[33]	99	Italy	2003–2012	66/33	Chemotherapy	First	67 (46–82)	IHC	1%	20.7 (3–130)	OS	Retrospective	7
Sobhani *et al.*[34]	62	Italy	2005–2016	51/11	Surgery + chemotherapy/ radiotherapy	First	76.3 (37–92)	IHC	Score 1	NR	OS	Retrospective	8
Thapa *et al.*[35]	329	Australia	1988–2014	274/55	Surgery	First	NR	IHC	5%	NR	OS	Retrospective	6
Watanabe *et al.*[36]	32	Japan	1992–2016	27/5	Surgery	First	60.5 (34–79)	IHC	1%	13.5 (2–117)	OS	Retrospective	7

IHC, immunohistochemistry staining; MPM, malignant pleural mesothelioma; NR, not reported; OS, overall survival; PFS, progression-free survival.

Table 2. Immunohistochemical methods for PD-L1 detection in the studies included in this meta-analysis.

Study	Detection method	Primary antibody						Cut-off value
		Antibody source	Antibody type	Antibody	Antibody clone	Antibody dilution	Antibody company	
Ahmadzada *et al.*[18]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	1:75	Cell Signaling Technology, Danvers, MA, USA	5%
Brosseau *et al.*[19]	IHC	NR	NR	Anti-PD-L1	E1L3N	1:400	CST/Ozyme	1%
Cedres *et al.*[20]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	1:1200	Cell Signaling Technology, Danvers, MA, USA	1%
Cedres *et al.*[21]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	1:1200	Cell Signaling Technology, Danvers, MA, USA	1%
Combaz-Lair *et al.*[22]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	1:100	Cell Signaling Technology, Danvers, MA, USA	1%
de Perrot *et al.*[23]	IHC	NR	NR	Anti-PD-L1	28.8	1:200	Abcam Inc., Toronto, Ontario, Canada	1%
Inaguma *et al.*[27]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	1:200	Cell Signaling Technology, Danvers, MA, USA	5%
Kao *et al.*[28]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	1:75	Cell Signaling Technology, Danvers, MA, USA	5%
Mansfield *et al.*[29]	IHC	Mouse	MAB	Anti-B7-H1	5H1-A3	1:300	NR	5%
Metaxas *et al.*[30]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	NR	Cell Signaling Technology, Danvers, MA, USA	5%
Muller *et al.*[31]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	1:100	Cell Signaling Technology, Danvers, MA, USA	1%
Nguyen *et al.*[32]	IHC	Rabbit	MAB	Anti-PD-L1	SP263	NR	VENTANA	1%
Patil *et al.*[33]	IHC	NR	NR	Anti-PD-L1	SP142	1:30	Genentech/Ventana Roche	1%
Sobhani *et al.*[34]	IHC	NR	MAB	Anti-PD-L1	22c3	1:50	DAKO	Score 1
Thapa *et al.*[35]	IHC	Rabbit	MAB	Anti-PD-L1	E1L3N	NR	Cell Signaling Technology, Danvers, MA, USA	5%
Watanabe *et al.*[36]	IHC	NR	NR	Anti-PD-L1	SP142	NR	Ventana Medical Systems, Tucson, AZ, USA	1%

IHC, immunohistochemistry staining; MAB, monoclonal antibody; NR, not reported; PD-L1, programmed death-ligand 1.

and surgery).[20–23,32,34] The detailed information of antibody used in IHC for included studies is shown in Table 2. The NOS indicated that all the included studies were of high quality (score $\geq$6); the detailed scores are shown in Table 3.

Prognostic value of PD-L1 for OS and PFS

The data derived from 16 studies comprising 1899 patients were used to investigate the prognostic significance of PD-L1 for OS. The pooled results were as follows: HR = 1.53, 95% CI = 1.28–1.83, $p < 0.001$ (Table 4; Figure 2). As the heterogeneity was significant ($I^2 = 63.4\%$, $p < 0.001$), the REM was applied for calculation. For PFS, two studies consisting of 307 cases provided relevant data. The combined HR and 95% CI (HR = 1.07, 95% CI = 0.82–1.39, $p = 0.643$) indicated that the association between PD-L1 expression and PFS was not significant (Table 4; Figure 3). We then conducted a subgroup analysis of OS for further investigations (Table 4). The results showed that

Table 3. The Newcastle–Ottawa scale quality assessment of the enrolled studies.

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest	Control for factor	Assessment of outcome	Follow-up long enough	Adequacy of follow-up of cohorts	
Ahmadzada *et al.*[18]	★	★	★	★	★★	★	–	★	8
Brosseau *et al.*[19]	★	★	★	★	★★	★	★	★	9
Cedres *et al.*[20]	★	★	–	★	★★	★	–	★	7
Cedres *et al.*[21]	★	–	–	★	★★	★	★	★	7
Combaz-Lair *et al.*[22]	★	★	–	★	★★	★	★	★	8
de Perrot *et al.*[23]	★	★	★	★	★★	★	★	★	9
Inaguma *et al.*[27]	★	–	–	★	★★	★	–	★	6
Kao *et al.*[28]	★	★	–	★	★★	★	★	★	8
Mansfield *et al.*[29]	★	★	–	★	★★	★	–	★	7
Metaxas *et al.*[30]	★	★	–	★	★★	★	–	★	7
Muller *et al.*[31]	★	★	★	★	★★	★	–	★	8
Nguyen *et al.*[32]	★	★	–	★	★★	★	★	★	8
Patil *et al.*[33]	★	–	★	★	★★	★	–	★	7
Sobhani *et al.*[34]	★	★	–	★	★★	★	★	★	8
Thapa *et al.*[35]	★	–	–	★	★★	★	–	★	6
Watanabe *et al.*[36]	★	–	★	★	★★	★	–	★	7

Table 4. Summary of subgroup analysis in studies that reported overall survival and progression-free survival stratified by programmed death-ligand 1 status in patients with malignant pleural mesothelioma.

Subgroups	Studies, *n*	Patients, *n*	Heterogeneity		HR (95% CI)	*p*-value	Effects model
			I^2, %	*p*			
Overall survival							
Total	16	1899	63.4	<0.001	1.53 (1.28–1.83)	<0.001	REM
Study design							
Retrospective	14	1616	67.8	<0.001	1.63 (1.32–2.01)	<0.001	REM
Prospective	2	283	0	0.504	1.21 (0.92–1.59)	0.178	FEM
Sample size							
$n < 80$	8	445	13.0	0.329	1.83 (1.41–2.37)	<0.001	FEM
$n \geqslant 80$	8	1454	64.9	0.006	1.37 (1.13–1.66)	0.001	REM
Treatment method							
Surgery	7	1100	67.4	0.005	1.48 (1.15–1.90)	0.003	REM
Chemotherapy or immunotherapy	3	406	37.8	0.200	1.38 (1.12–1.71)	0.002	FEM
Mixed	6	393	0	0.425	1.87 (1.39–2.53)	<0.001	FEM
Cut-off value							
1% and other	10	1057	61.6	0.005	1.47 (1.18–1.85)	0.001	REM
5%	6	842	52.4	0.062	1.64 (1.19–2.26)	0.003	REM
Progression-free survival							
Total	2	307	0	0.467	1.07 (0.82–1.39)	0.643	FEM

CI, confidence interval; FEM, fixed-effects model; HR, hazard ratio; REM, random-effects model.

PD-L1 overexpression significantly correlated with poor OS irrespective of the sample size, treatment method, or PD-L1 cut-off value.

Relationship between PD-L1 expression and clinicopathological characteristics in MPM

A total of five studies with 840 patients explored the connection between PD-L1 and four clinical factors, namely, smoking (yes *versus* no),[21,29] clinical stage (III–IV *versus* I–II),[21,35] sex (male *versus* female),[19,21,28,29,35] and pathological type (sarcomatoid + biphasic *versus* epithelial).[19,21,28,29,35] The pooled ORs and 95% CIs (Figure 4) demonstrated that PD-L1 overexpression correlated with the sarcomatoid + biphasic type of MPM (OR = 4.32, 95% CI = 2.16–8.64, $p < 0.001$). However, the association between PD-L1 and smoking (OR = 1.06, 95% CI = 0.56–2.05, $p = 0.855$), clinical stage (OR = 1.17, 95% CI = 0.76–1.81, $p = 0.478$), and sex (OR = 1.02, 95% CI = 0.67–1.54, $p = 0.944$) was not significant.

Publication bias

Begg's funnel plot was applied to assess the publication bias of the literature. The plot (Begg's test: $p = 0.964$ for OS and 0.317 for PFS) demonstrated that there was no significant publication bias in the meta-analysis (Figure 5).

TCGA dataset validation of prognostic value of PD-L1 expression in MPM

To further validate and confirm the prognostic significance of PD-L1 expression for OS and PFS

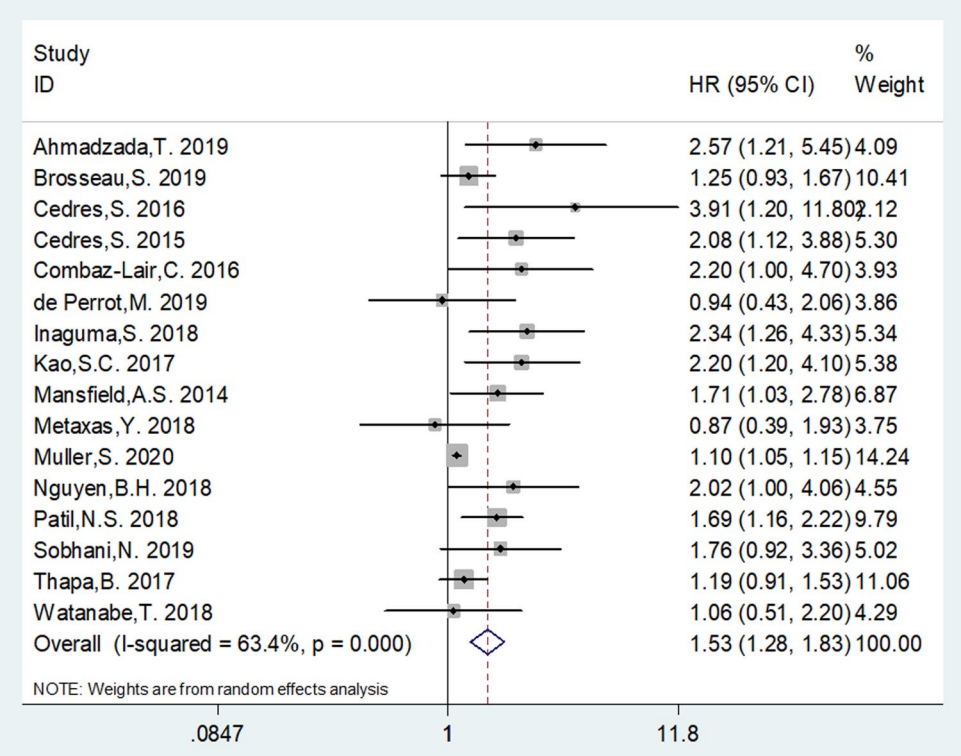

Figure 2. Forest plot of pooled hazard ratio for association between programmed death-ligand 1 and overall survival in patients with malignant pleural mesothelioma.
CI, confidence interval; HR, hazard ratio.

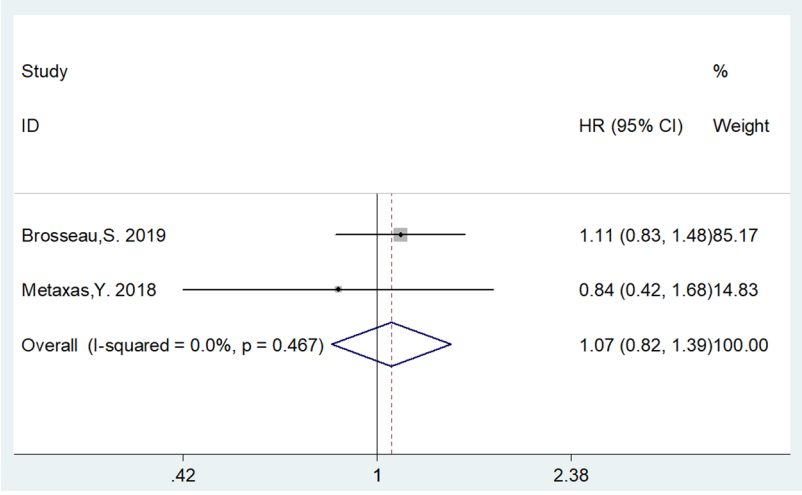

Figure 3. Forest plot of pooled hazard ratio for association between programmed death-ligand 1 and progression-free survival in patients with malignant pleural mesothelioma.
CI, confidence interval; HR, hazard ratio.

of patients with MPM, we evaluated the expression using TCGA data. The mRNA levels of PD-L1 were tested. A total of 87 samples were analyzed, with 86 and 84 samples accessible for OS and PFS analysis, respectively. The maximum follow-up period was 92 months. For the OS analysis, 86 patients were included; 14 and 72 patients exhibited high and low PD-L1 expression, respectively. In the PD-L1 overexpression group, 13 patients died, with a median

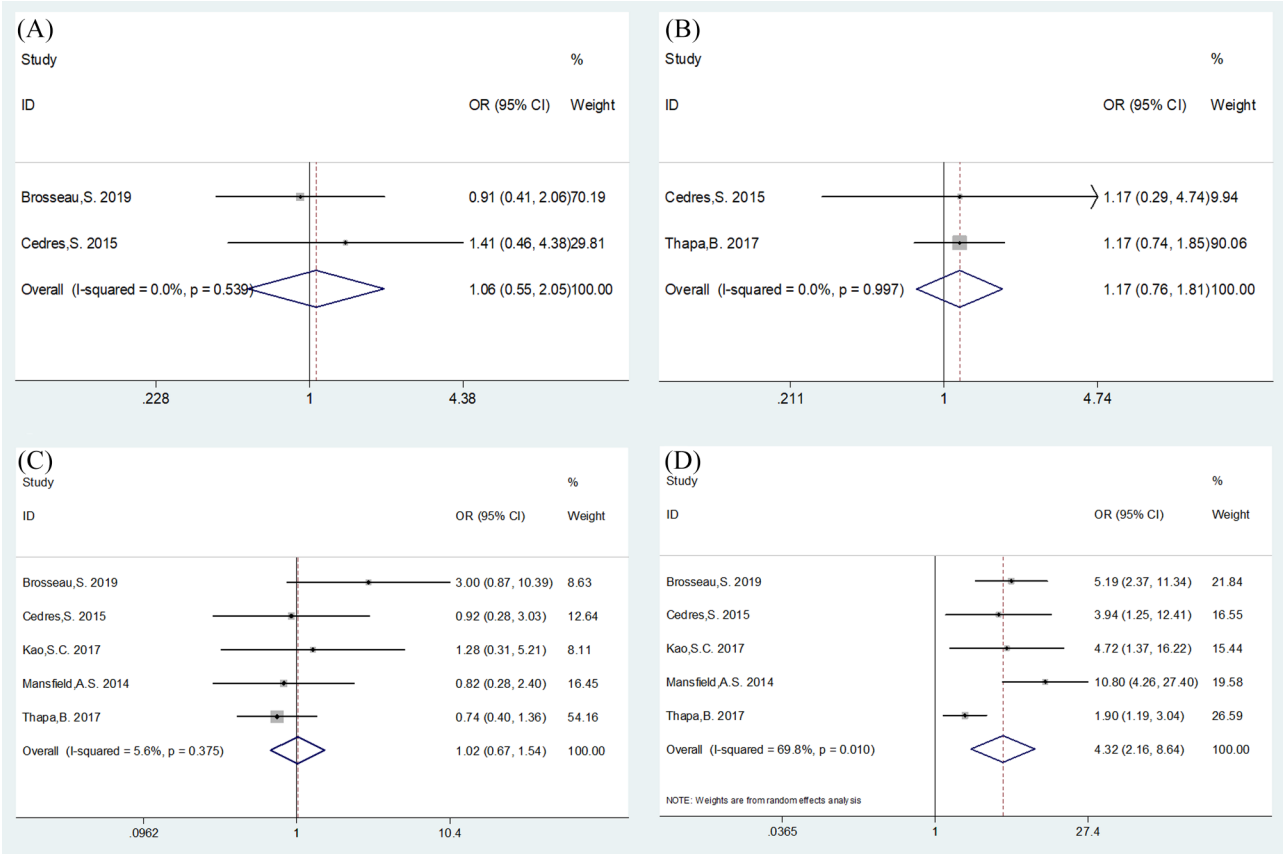

Figure 4. Meta-analysis of the association between programmed death-ligand 1 and (A) smoking (yes *versus* no), (B) clinical stage, (C) sex, and (D) pathological type in malignant pleural mesothelioma.
CI, confidence interval; HR, hazard ratio.

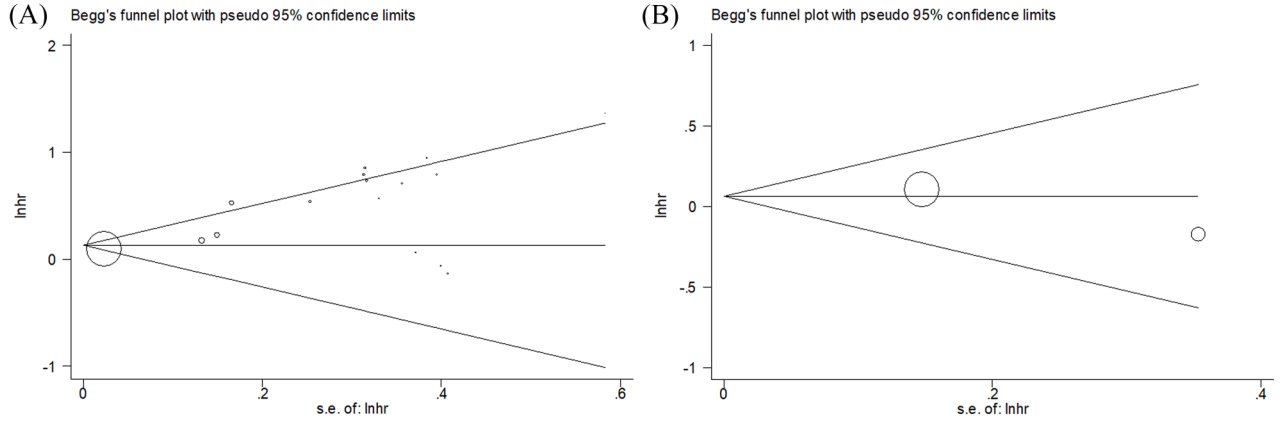

Figure 5. Begg's funnel plot for the assessment of potential publication bias. (A) For overall survival; (B) for progression-free survival.
CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; s.e.of: lnhr, standard error of ln(HR).

survival period of 6.08 months. In the PD-L1 underexpression group, 60 patients died at the end of follow-up, with a median survival period of 19.99 months. The HR was 2.069, with 95% CI = 1.136–3.769 and $p = 0.0175$ (Figure 6). For the PFS analysis, 84 patients were included; 12 and 72 patients exhibited high and low expression of PD-L1, respectively. Eight patients in the

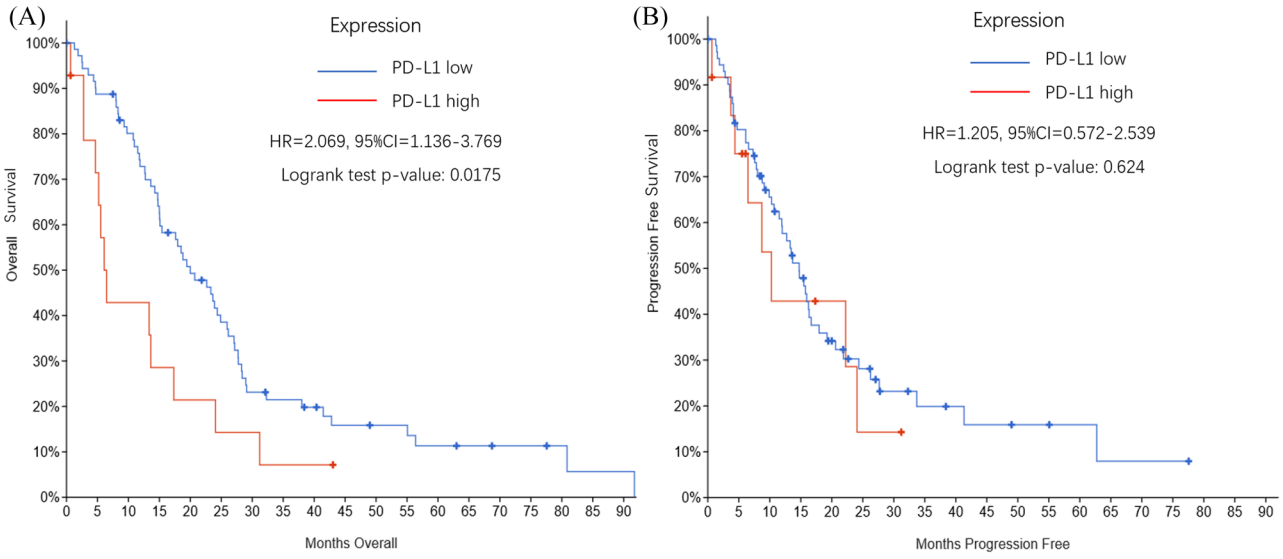

Figure 6. Kaplan–Meier plotter showing the prognostic role of PD-L1 mRNA expression for (A) overall survival and (B) progression-free survival in malignant pleural mesothelioma. Data were derived from The Cancer Genome Atlas dataset.
CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1.

PD-L1 overexpression group and 51 patients in the PD-L1 underexpression group exhibited disease progression with median PFS periods of 10.26 and 14.73 months, respectively. The HR of PFS was 1.205, with 95% CI = 0.572–2.539 and $p = 0.624$ (Figure 6).

Discussion

The prognostic value of PD-L1 expression in patients with MPM has been controversial according to previous investigations. We therefore carried out a meta-analysis to identify the exact significance of PD-L1 expression for the prognosis of MPM. Our meta-analysis indicated that high PD-L1 expression is a significant prognostic factor for poor OS, but not for PFS, of patients with MPM. The prognostic value of PD-L1 for OS was further confirmed using TCGA data. Moreover, overexpression of PD-L1 was associated with sarcomatoid and biphasic histology of MPM.

The PD-L1/PD-1 pathway is the prominent mechanism of peripheral tolerance in the immune system. PD-L1 was the first reported ligand of PD-1, and the binding of PD-L1/PD-1 could promote inhibition, the proliferation of T cells, and cytokine production.[54] PD-L1 is significantly expressed in different types of immune cells, including macrophages, B cells, T cells, myeloid DCs, and NK cells.[55] The PD-L1/PD-1 immune checkpoints can disrupt the PD-1 axis to reverse T-cell suppression and enhance endogenous antitumor immunity in various types of cancer.[11] There are several ongoing clinical trials to evaluate the efficiency and safety of single-agent and combination ICIs in MPM treatment.[9] An anti-PD-1 monoclonal antibody (mAb), nivolumab, showed clinical activity and an acceptable safety profile as a second-line treatment for recurrent MPM.[42] The NIBIT-MESO-1 study also demonstrated that the combination of anti-CTLA4 mAb (tremelimumab) and anti-PD-L1 mAb (durvalumab) was active, with a good safety profile in patients with mesothelioma.[46] In those studies, PD-L1 expression did not correlate with the outcome in patients receiving ICI treatments. Herein, we have shown the prognostic value of PD-L1 for poor OS of patients who underwent surgery, chemotherapy/immunotherapy, and systemic treatment. However, only one study involving patients who received pembrolizumab was included in this meta-analysis.[30] Considering that ICIs are promising therapeutic strategies for MPM, further studies are needed to identify the prognostic value of PD-L1 expression for MPM patients receiving immunotherapy.

Many recent meta-analyses have also demonstrated the prognostic value of PD-L1 expression in solid tumors.[12,13,56,57] Zeng *et al.* showed that PD-L1 expression was associated with the prognosis of diffuse large B-cell lymphoma (DLBCL) (HR = 1.70, 95% CI = 1.05–2.74, $p = 0.031$).[56] Li *et al.* reported

that a high PD-L1 expression was associated with a shorter OS period of patients with hepatocellular carcinoma.[13] In addition, a recent meta-analysis indicated that PD-L1 overexpression could predict poor survival outcomes related to bladder cancer.[58] Through our meta-analysis, we found a significant prognostic value of PD-L1 overexpression for poor OS, but not for PFS. The non-significant association between PD-L1 and PFS may be due to the limited number of studies included in the analysis. Therefore, the prognostic significance of PD-L1 for PFS should be verified *via* further studies. Moreover, in future prospective clinical trials, the prognostic impact of PD-L1 should be verified. It is also suggested to include PD-L1 testing in the diagnostic pathway of patients with malignant disease like MPM.

Some limitations of this meta-analysis need to be noted. First, the heterogeneity among the studies is significant and cannot be ignored. Study design, treatment methods, and other factors can result in heterogeneity among studies. Second, non-English studies and studies with negative results were not included in our meta-analysis; this may have caused publication bias. Third, studies from the USA and Europe accounted for the majority of the included studies, which may have limited the applicability of the results to other regions of the world. Fourth, the studies for PFS analysis were too limited, because only two studies[19,30] were eligible. Although we did not restrict the treatment of eligible studies, the sample size for PFS analysis was relatively small. We suggested that more clinical trials investigating PFS should be validated, especially using various treatment methods including surgery, chemotherapy, and immunotherapy.

Conclusion

In summary, this meta-analysis shows that high PD-L1 expression is a significant prognostic factor for poor OS of patients with MPM; this has been verified using TCGA data. We therefore suggest that PD-L1 expression levels can be used to predict the clinical outcomes of MPM patients in the future.

Author contributions

LJ and WG collected, extracted, performed quality assessment of articles; LJ, XL, and LX analyzed the data; WG and LW conceived and designed this study and wrote the paper. ZC reviewed the final manuscript. LJ and LX revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

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