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Predictive values of PD-L1 expression for survival outcomes in patients with cervical cancer: a systematic review and meta-analysis

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ABSTRACT

Objectives: Cervical cancer is one of the most common cancers in women worldwide. Although mortality has declined over the past 30 years in high-income areas, it remains a problem in several countries. Given that the prognosis of patients with recurrent or metastatic disease is poor, it is necessary to identify valuable predictive indicators to estimate survival outcomes in patients with cervical cancer.

Material and methods: We searched electronic databases such as PubMed, Web of Science, Embase, Ovid MEDLINE, and the Cochrane Central Register of Controlled Trials, and investigated the relationship between Programmed death-ligand 1(PD-L1) expression and prognosis. Chi squared tests and I^2 were utilized to assess study heterogeneity, and publication bias was estimated using Begg's funnel plot and Egger linear regression test.

Results: Thirteen eligible studies with 1422 patients were included. Generally, high PD-L1 expression was conclusively associated with poor overall survival (OS) (HR: 1.31; 95% CI 1.03–1.66, p = 0.025). However, PD-L1 expression demonstrated no association with progression-free survival (HR: 0.93; 0.73–1.19, p = 0.57). High PD-L1 expression with a sample size over 100 indicated a shorter OS (HR: 1.51; 95% CI 1.13–2.01). High expression of PD-L1 in Asians represented a lower OS (HR: 1.52; 1.14–2.03). Overexpression of PD-L1 in tumor cells (HR: 1.57; 1.29–2.10) and tumor-infiltrating immune cells (HR: 1.75; 1.02-2.99) predicted poor OS. High PD-L1 expression (HR: 4.04; 2.58–6.31) showed a lower effect on OS with a cut-off value of 5%.

Conclusions: Our results indicate that high PD-L1 expression could be a valuable biomarker for predicting clinical outcomes in patients with cervical cancer.

Key words: biomarkers; cervical cancer; diagnosis; immune cells; PD-L1

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INTRODUCTION

Cervical cancer is one of the most frequent cancers in women and the fourth primary cause of cancer-associated fatalities worldwide. In total, 604127 women are diagnosed with cervical cancer every year, which has led to 341831 deaths in 2020 [1]. With the popularization of human papillomavirus-based screening programs and the development of new diagnostic methods and therapies, the incidence and mortality of cervical cancer has declined by more than half over the last 30 years in high-income areas. However, mortality remains high in low-income countries [2]. The mortality rates differ in patients with early-stage cervical cancer, although the prognosis for patients with recurrent or metastatic disease remains poor. Considering chemotherapy resistance in cervical cancer, it is necessary to identify patients at high risk of poor responses and offer more appropriate treatments to improve OS using predictive biomarkers [3]. According to previous studies, several prognostic biomarkers have been identified. However, the lack of specificity and sensitivity in their prediction power prevents these biomarkers from being clinically suitable. Therefore, it is imperative to identify novel predictive indicators to estimate survival outcomes in patients with cervical cancer.

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PD-L1 or B7-H1 is the ligand of programmed cell death protein 1 (PD-1), which is expressed on immune cells, such as activated T cells, B cells, dendritic cells, macrophages, and various tumor cells, and is involved in the immune checkpoint pathway [4, 5]. In the normal immune system, PD-L1 expression sustains the homeostasis of the immune reactions, and the PD-1/PD-L1 pathway plays a key role in restricting autoimmunity and in the negative regulation of cytokine production and T lymphocyte proliferation in the case of inflammatory response to infections [6].

PD-L1 is expressed on tumor cells or tumor-infiltrating immune cells (TICs) that bind to PD-1 on T cells and inhibit effector T cells [5, 7, 8]. Suppression of CD8+ T cells markedly decrease the effect of cytotoxicity, allowing cancer cells to avoid immune surveillance of T cells [9]. These findings suggest that PD-L1 could be a potential biomarker for estimating disease progression, prognosis, and therapeutic efficiency. Wang et al. [10] analyzed nine studies of breast cancer and discovered that overexpression of PD-L1 was associated with shorter OS. Accumulating evidence on the prognostic value of PD-L1 has been studied in solid cancers, such as non-small lung cancer, pancreatic cancer, and prostate cancer [11–14]. Since the predictive value of PD-L1 expression in cervical cancer remains controversial, we gathered eligible data and performed a meta-analysis to determine the prognostic and clinical value of PD-L1 in cervical cancer [15, 16].

MATERIAL AND METHODS

Literature search strategy

We searched for relevant studies in electronic databases, including PubMed, Web of Science, Embase, Ovid MEDLINE, and the Cochrane Central Register of Controlled Trials up to 2021. The following Medical Subject Headings (MeSH) terms: "PD-L1" OR "programmed cell death ligand-1" OR "B7-H1" OR "CD274" AND "cervical carcinoma" OR "cervical cancer" OR "cervical tumor" OR "expression" were used in our electronic search. We reviewed relevant review articles, reference lists of published trials, and conference abstracts [American Society of Clinical Oncology (ASCO), Annual Meetings, and the European Cancer Conference (ECCO)] were manually reviewed for potentially eligible studies.

Inclusion and exclusion Criteria

Studies were considered qualified if they met the following criteria: 1) patients were histologically identified as cervical cancer; 2) detection samples of PD-L1 expression were selected before PD-1/PD-L1 checkpoint inhibitor treatment; 3) PD-L1 expression was measured by immunohistochemistry (IHC) staining of tumor cells and tumor-infiltrating lymphocytes (TILs); 4) the studies analyzed and demonstrated a relationship between PD-L1 expression and prognosis (such as OS, progression-free survival [PFS]); 5) hazard ratio (HR) or relative risks (RR) values could be extracted directly or calculated indirectly through Kaplan– Meier curves; and 6) articles were published in English. Studies that did not meet the inclusion criteria included literature reported in reviews, case reports, animal studies, and letters, and these were excluded. Two investigators (HW and XC) independently checked whether each study met the inclusion criteria, and discrepancies were resolved by judgement from a third, additional reviewer.

Data extraction and quality assessment

The investigators (XW and SX) extracted all information, including author name(s), publication year, study design, country, patient's demographics, prognostic endpoint, treatment, International Federation of Gynecology and Obstetrics (FIGO) stage, IHC stained cells, and cut-off value of PD-L1 expression. Any disagreements were resolved by consensus. The primary endpoints were OS and PFS.

Quality assessment

Study quality assessment was estimated separately by two researchers (TH and XW) based on the Newcastle-Ottawa Scale (NOS). Total scores ranged from 0 to 9 points; trials considered 'high quality' were scored higher than 6.

Statistical analysis

Statistical analyses were performed using Stata statistical software (version 13.0; Stata Corp., College Station, TX, USA). The HRs and 95% CIs were used to evaluate the association between PD-L1 expression and prognosis. RR was used to analyze the relationship between PD-L1 expression and clinicopathological features. Chi-square tests and I^2 were used to assess study heterogeneity. The Begg's funnel plot and Egger linear regression test were used to investigate the possibility of publication bias [17, 18]. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Literature selection

A total of 1209 relevant references were checked after the initial literature search. Among these, 1096 publications were excluded as 628 were review articles and other ineligible types of references, 165 were non-English language articles, 236 included experiments on non-human species, and 67 articles were duplicates (Fig. 1). The remaining 30 articles were retrieved for a more detailed assessment. After screening the full text, 17 studies were removed because the authors: explored other types of cancers (n = 6), presented insufficient data (n = 6), and did not use immunohistochemistry (n = 5). Finally, 13 studies were included in this meta-analysis [15, 19–30].

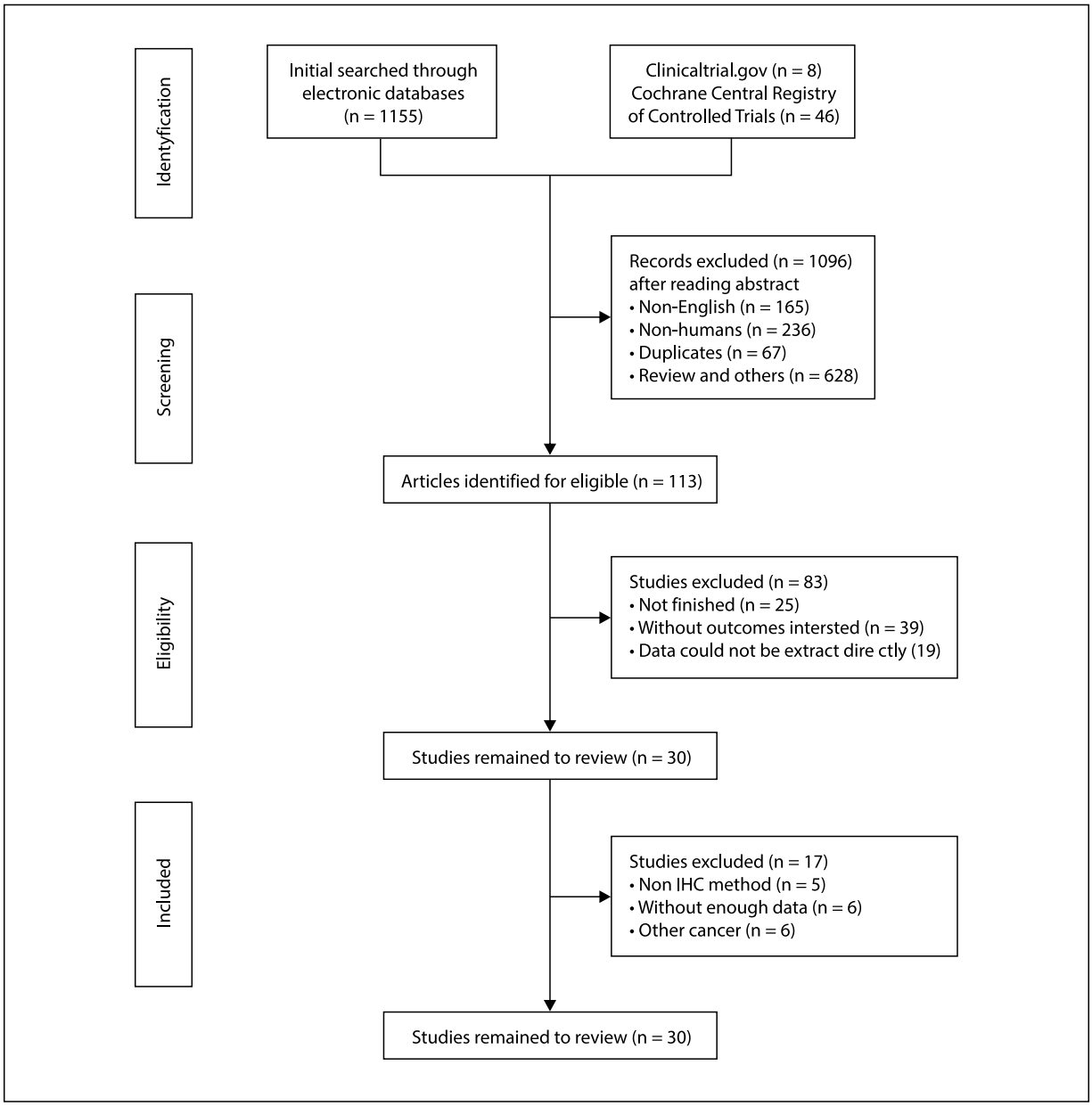

Figure 1. Diagram of including studies selection procedures; IHC — immunohistochemistry

Characteristics of patients and studies

Thirteen eligible studies with 1422 patients were included in this study, all of which were published between 2009 and 2020. Four studies were performed in China, three in Japan, two in Korea, one in Canada, one in the USA, one in Brazil, and one in Belgium. Thirteen studies provided information on OS as an endpoint, and eight studies used PFS as the endpoint. Clinical points such as FIGO stage, tumor size, vascular invasion, and lymph node metastasis were also explored to determine the relationship with PD-L1 expression. All the included studies were of high quality and scored over 6. We treated PD-L1 expression in the area of tumor cells and TICs as two different IHC staining areas; thus, we extracted the information as two independent groups, which led to one study being analyzed twice (Tab. 1).

Connections between PD-L1 expression and survival indicators in cervical cancer patients

Thirteen studies explored the association between PD--L1 expression and OS. The results showed that high PD-L1 expression predicts poor survival in OS (HR: 1.31; 95% CI 1.03–1.66, P = 0.025), as the heterogeneity was high (I^2 = 81.3%, p = 0.00), random effects were chosen (Fig. 2). In the analysis of the association between PD-L1 expression

Table 1. Characteristics of including studies

Study	Country	No. of patients	Age	FIGO stage	Endpoint	PD-L1 expression		NOS score
						Area by IHC	Cut-off value	
Karim 2009 [19]	USA	115	47 (24–87)	I–II	OS	TICs	> 0%	9
Enwere 2017 [20]	Canada	120	44 (39–49)	IB–IVA	OS, PFS	Tumor cells	tAQUA score	9
Kim 2017 [15]	Kroea	27	46 (36–71)	IB1–IIA	OS, PFS	Tumor cells	1%	9
Feng 2018[21]	China	219	49 (26–75)	I–IV	OS	Tumor cells, TICs	5%	9
Kawachi 2018 [22]	Japan	148	45 (30–72)	I–II	OS	Tumor cells	5%	9
Wang 2018 [23]	China	90	46 (23–71)	IB1–IIA2	OS, PFS	Tumor cells	H-score of 100	8
Grochot 2019 [25]	Brazil	155	44	I–IVB	OS, PFS	Tumor cells	> 0%	7
Chung 2019 [24]	Korea	98	46 (24–75)	II–IVB	OS, PFS	Tumor cells + TICs	Combined positive score	7
Taruma 2019 [26]	Japan	20	50 (32–68)	III–IV	OS, PFS	Tumor cells	1%	7
Chen 2020 [27]	China	222	49 (21–75)	I–II	OS, DFS	Tumor cells, TICs	Tumor cells > 1% TICs > 5%	8
Lijima 2020 [28]	Belgium	33	N.A	IIB–IVA	OS, PFS	Tumor cells	1%	9
Miyasaka 2020 [29]	Japan	71	60 (28–88)	IB–IVA	OS, PFS	Tumor cells	1%	8
Tsuchiya 2020 [30]	Japan	104	46 (26–77)	I–IV	OS	Tumor cells, TICs	Score(tumor cells,0; TICs,3)	9

FIGO — The International Federation of Gynecology and Obstetrics; IHC — immunohistochemistry; NOS — Newcastle-Ottawa Scale; OS — overall survival; PFS — progress-free survival; TICs — tumor-infiltrating immune cells

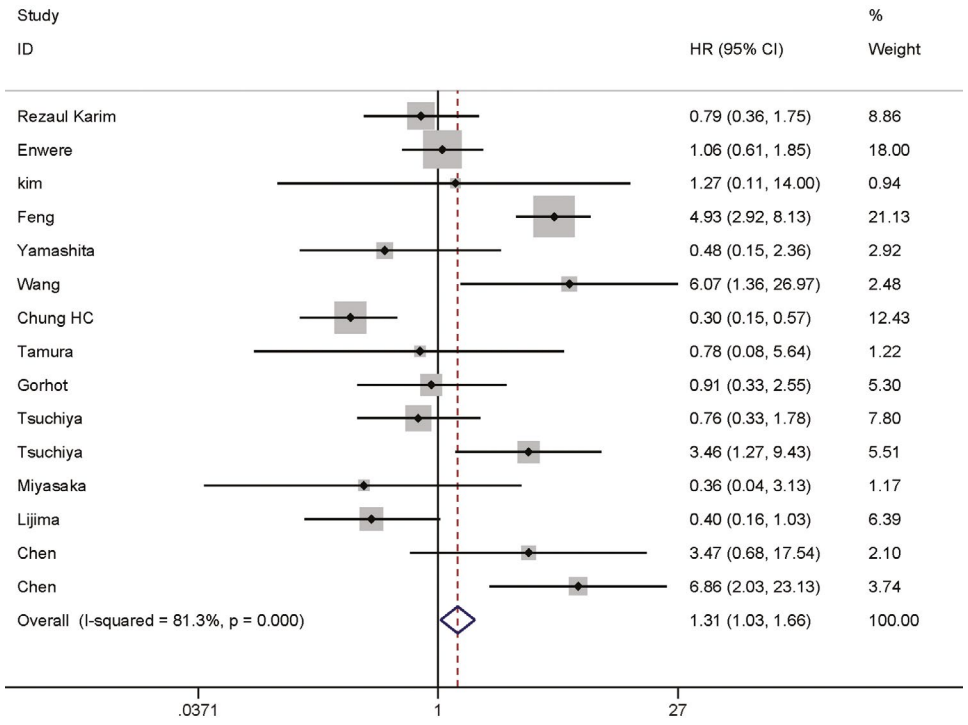

Figure 2. Forest plots showing the significant relationship between high level of PD-L1 expression and a shorter overall survival (OS) in cervical cancers patients, analysis results are reported by hazard ratio (HR); CI — confidence interval

and PFS, the combined effect measures identified no conclusive association between the level of PD-L1 expression and PFS (HR: 0.93; 0.73-1.19, p = 0.57) (Fig. 3).

Subgroup analysis

We performed subgroup analysis of OS based on sample size (> 100 or ≤ 100), race (Asian or non-Asian), IHC staining area (tumor cells, TICs, or tumor cells + TICs), and cut-off values (1%, 5% and others). According to the results, high levels of PD-L1 expression with a sample size of over 100 indicated a shorter OS (HR: 1.51; 95% CI 1.13–2.01). As for race, high level expression of PD-L1 in Asians represented a lower OS (HR: 1.52; 1.14–2.03). Overexpression of PD-L1 in tumor cells (HR: 1.57; 1.29–2.10) and TICs (HR: 1.75; 1.02–2.99) predicted poor OS. High levels of PD-L1 expression (HR: 4.04; 2.58–6.31) showed a lower effect of OS with a cut-off value of 5% (Tab. 2). However, in the subgroup analysis of PFS, PD-L1 expression showed no significant prognostic value in relation to sample size, race, IHC staining area, and cut-off value (Tab. 3).

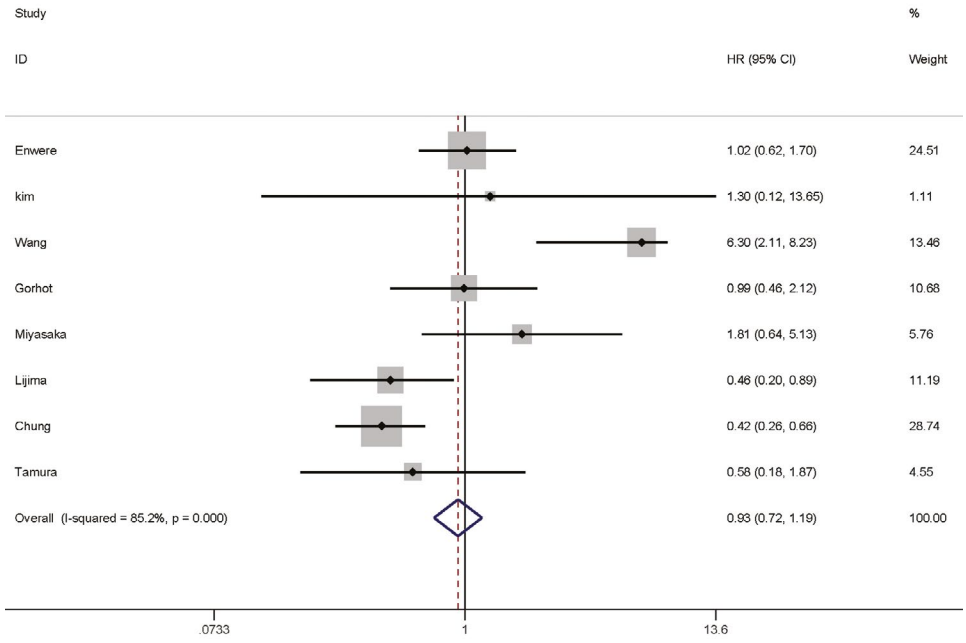

Figure 3. Forest plots showing no association between high PD-L1 expression and progress-free survival (PFS) in cervical cancers patients; HR — hazard ratio; CI — confidence interval

Table 2. Subgroup analysis of overall survival

Subgroup		HR (95% CI)	P_z-value	I^2	P_H-value
Number	> 100	1.51 (1.13, 2.01)	0.05	81%	0.00
	≤ 100	1.38 (0.71, 2.68)	0.35	60.5%	0.02
Race	Asian	1.52 (1.14, 2.03)	0.82	0%	0.00
	Non-Asian	0.95 (0.63, 1.44)	0.00	84.5%	0.83
IHC area	Tumor cells	1.57 (1.19, 2.10)	0.00	77.9%	0.00
	TICs	1.75 (1.02, 2.99)	0.04	76.1%	0.00
	Tumor cells + TICs	0.30 (0.15, 0.57)	0.00	–	–
Cut off value of PD-L1 expression	other	0.82 (0.62, 1.10)	0.18	73.8%	0.00
	1%	1.28 (0.47, 3.51)	0.63	0.0%	0.40
	5%	4.04 (2.58, 6.31)	0.00	80.9%	0.00

HR — hazard ratio; IHC — immunohistochemistry; TICs — tumor-infiltrating immune cells; CI — confidence interval

Table 3. Subgroup analysis of progress-free survival

Subgroup		HR (95% CI)	P_z-value	I^2	P_H-value
Number	> 100	1.01 (0.66, 1.54)	0.96	0%	0.95
	≤ 100	0.89 (0.65, 1.21)	0.46	89.4%	0.00
Race	Asian	0.89 (0.65, 1.21)	0.96	89.4%	0.00
	Non-Asian	1.01 (0.66, 1.54)	0.46	0%	0.95
ICH area	Tumor cells	1.24 (0.91, 1.69)	0.17	84%	0.00
	TICs	1.81 (0.64, 5.12)	0.26	0%	–
	Tumor cells + TICs	0.42 (0.26, 0.69)	0.00	0%	–
Cut off value of PD-L1 expression	other	1.25 (0.74, 1.43)	0.98	92.8%	0.00
	1%	1.48 (0.47, 4.66)	0.22	37%	0.19

HR — hazard ratio; IHC — immunohistochemistry; TICs — tumor- infiltrating immune cells; CI — confidence interval

Table 4. Relations between PD-L1 expression and clinical points

Clinical point	Studies Number	RR (95% CI)	P_Z	I^2	P_H
Tumor size (≥ 4 cm vs < 4 cm)	4	0.99 (0.77, 1.26)	0.93	27.3%	0.24
Lymph nodes	8	1.02(0.82, 1.26)	0.90	35.9%	0.12
FIGO stage	4	0.88(0.73, 1.06)	0.18	76%	0.02
Vascular invasion	5	0.90(0.75, 1.07)	0.45	0%	0.18

FIGO — International Federation of Gynecology and Obstetrics; RR — relative risk; CI — confidence interval

Relationship between PD-L1 expression and clinical-pathological characteristics

We investigated tumor size, FIGO stage, lymph node status, and vascular invasion to determine the effect of PD-L1 expression on clinicopathological characteristics. We found no significant associations with these characteristics (Tab. 4).

Publication bias

We assessed publication bias using Begg's funnel plots and Egger's linear regression test and found no publication bias in OS (Begg's p = 0.59, Egger's p = 0.79) and PFS (Begg's p = 0.62; Egger's p = 0.61). The details are shown in Table 5.

Table 5. The publications bias of the study

Overall	Begg's p	Egger's p (95% CI)
OS	0.62	0.79 (–3.56, 2.77)
PFS	0.71	0.61 (–4.9, 1.73)
Clinical points		
tumor size	0.22	0.19 (–4.14, 1.27)
vascular invasion	1	0.93 (–3.79, 3.55)
FIGO	0.22	0.23 (–4.27, 12.02)
Lymph nodes	0.47	0.20 (–5.17, 1.27)

OS — overall survival; PFS — progress-free survival; FIGO — International Federation of Gynecology and Obstetrics

DISCUSSION

This study focused on the prognostic value of PD-L1 expression in cervical cancer. We updated the data and analyzed 13 studies with 1422 patients to identify the relationship between PD-L1 expression and survival. Our findings demonstrated that high levels of PD-L1 expression in cervical cancer were associated with poor OS survival. Moreover, in subgroup analysis, a high level of PD-L1 was associated with shorter OS in terms of race, sample size, IHC staining area, and cut-off value. According to our results, no association existed between PD-L1 expression and PFS, including estimates explored in the subgroup analysis.

Similar results were obtained in a previous study, which demonstrated that overexpression of PD-L1 had a prognostic value of lower OS [31]. However, we obtained different results in subgroup analysis, such that high PD-L1 expression indicated poor OS with sample size over 100, and we did not find that PD-L1 was a prognostic factor of PFS among Asians. Moreover, we analyzed PD-L1 expression in the IHC staining area and the connection between PD-L1 expression and cut-off values, which were not mentioned in the previous study. Overexpression of PD-L1 in tumor cells and TICs predicted a poor effect of OS, but in the mixture of TICs and tumor cells, PD-L1 expression indicated favorable

results for OS. We deduced that the differences between the two studies may be due to several reasons, the first one being sample size. We included 13 studies with 1422 patients in this research; however, the previous research only included seven studies. Larger samples may offer more evidence to prove the prognostic value of PD-L1. The second determinant may be due to the method of data extraction, as we treated PD-L1 expression in tumor cells and TICs as two different datasets. Thus, we extracted and analyzed the information as two different groups and that would result in one study being analyzed twice.

As immune checkpoint inhibitors are a hot spot in cancer therapy, an increasing number of studies are focusing on the treatment of anti PD-1/PD-L1 antibodies in cervical cancer [26, 32–38]. However, how to make immune checkpoint inhibitors more efficient is still a problem because among patients, the same therapy strategy may have different effects. Thus, it is valuable to determine the characteristics of patients with respect to PD-L1 expression. The predictive value of PD-L1 expression has been shown in other types of cancers, such as lung cancer, gastric cancer, and colorectal cancer [39, 40]. Zhang et al. [41] analyzed the association between PD-L1 expression and gynecological cancers and found that a high level of PD-L1 expression had a negative effect on OS and was not significantly associated with PFS.

Our study has several limitations. Firstly, although we performed the subgroup analysis and analyzed the data using a fixed model, we still did not find the source of heterogeneity. Given the incomplete dataset, we did not conduct further research. Secondly, as we extracted the value of HR only from Kaplan-Meier curves, different methods or software for reading the graph may produce slightly different results. Thirdly, we limited our inclusion criteria to select articles only published in English and excluded all other non-English, written literature. Thus, considering the limitations mentioned above, the results should be interpreted carefully.

CONCLUSIONS

In conclusion, this study indicated that high expression of PD-L1 is associated with poor OS and has no significant relationship with PFS in cervical cancer. These findings indicate that PD-L1 may potentially serve as a valuable prognostic indicator of cervical cancer.

Authors contributions

XW contributed to conception and design of the research. TH contributed to data collection, and data analysis. HW contributed to data analysis. XC contributed to manuscript writing. SX and XW contributed to revising the manuscript critically for important intellectual content. All authors have read and approved the manuscript.

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Conflict of interest

The authors declare no conflict of interests.

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