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Systematic Review

Prognostic Significance of PD-L1 Expression in Solid Tumors: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Programmed death-ligand 1 (PD-L1) is a key immune checkpoint molecule that enables tumor cells to evade host immune surveillance. While PD-L1 is widely used as a predictive biomarker for response to immune checkpoint inhibitors, its prognostic significance across solid tumors remains controversial.
Objective: To systematically evaluate the association between PD-L1 expression and survival outcomes, including overall survival (OS) and progression-free survival (PFS), in patients with solid tumors.
Methods: A comprehensive literature search was conducted in PubMed, Embase, Scopus, and Web of Science from inception to December 2025, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Studies assessing PD-L1 expression and reporting survival outcomes were included. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using a random-effects model. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated using funnel plots and Egger's test.
Results: A total of 58 studies comprising 12,432 patients were included in the analysis. High PD-L1 expression was significantly associated with poorer overall survival (HR = 1.67, 95% CI: 1.45–1.92, $p < 0.001$) and progression-free survival (HR = 1.52, 95% CI: 1.29–1.79, $p < 0.001$). Substantial heterogeneity was observed (I^2 = 64% for OS and 59% for PFS). Subgroup analyses demonstrated stronger prognostic significance in lung, gastric, and hepatocellular carcinomas, while results in breast cancer were not statistically significant. Evidence of mild publication bias was detected (Egger's test, $p = 0.036$).
Conclusion: PD-L1 overexpression is associated with adverse survival outcomes in solid tumors, although its prognostic value varies across cancer types. Standardization of PD-L1 assessment methods and integration with complementary biomarkers are essential to improve its clinical utility in prognostication and treatment stratification.

Keywords: *PD-L1, prognosis, solid tumors, meta-analysis, immune checkpoint, survival.*

INTRODUCTION

The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis represents one of the most critical immune checkpoint pathways involved in tumor immune evasion. PD-L1, a transmembrane protein expressed on tumor cells as well as tumor-infiltrating immune cells, interacts with the PD-1 receptor on activated T lymphocytes, leading to inhibition of T-cell proliferation, cytokine production, and cytotoxic activity [1,2]. This interaction promotes T-cell exhaustion and enables malignant cells to evade host immune surveillance, thereby facilitating tumor progression [2,3].

In recent years, immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have revolutionized the therapeutic landscape of multiple solid tumors, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, and

urothelial carcinoma [3–5]. Agents such as pembrolizumab, nivolumab, and atezolizumab have demonstrated significant improvements in survival outcomes, establishing PD-L1 as a key predictive biomarker for response to immunotherapy [4–6]. Consequently, PD-L1 expression assessed by immunohistochemistry (IHC) is now routinely used in clinical practice to guide treatment decisions in several malignancies [6,7].

Despite its well-established predictive role, the prognostic significance of PD-L1 expression independent of immunotherapy remains controversial. Several studies have reported that high PD-L1 expression is associated with poor survival outcomes, likely reflecting an immunosuppressive tumor microenvironment and aggressive tumor biology [7–9]. Conversely, other studies have suggested that PD-L1 expression may be associated with improved survival in certain tumor types, possibly due to increased immune infiltration and heightened immunogenicity [10,11]. These conflicting findings highlight the complex and context-dependent role of PD-L1 in tumor biology.

The prognostic value of PD-L1 appears to vary significantly across different tumor types. In non-small cell lung cancer and gastric cancer, PD-L1 overexpression has been consistently associated with poorer overall survival [8,12]. In hepatocellular carcinoma and colorectal cancer, moderate associations have been observed, whereas in breast cancer, particularly triple-negative subtypes, results remain inconsistent [9,13,14]. Such variability may be attributed to differences in tumor microenvironment, immune cell infiltration, and intrinsic tumor biology [2,10].

A major challenge in interpreting PD-L1-related outcomes is the lack of standardization in its assessment. Multiple antibody clones (e.g., 22C3, SP263, SP142) are used across studies, each with different staining characteristics and scoring systems [6,15]. Furthermore, variability in cut-off values (ranging from 1% to 50%), differences in evaluating tumor cells versus immune cells, and inter-observer variability contribute to inconsistencies in reported results [15,16]. These methodological disparities significantly limit the comparability of studies and contribute to heterogeneity in pooled analyses.

In addition to methodological issues, PD-L1 expression is dynamic and can be influenced by various factors such as prior treatments, inflammatory signals, and tumor evolution [3,17]. This temporal and spatial heterogeneity further complicates its role as a stable prognostic biomarker.

Given these complexities, a comprehensive synthesis of available evidence is essential to clarify the prognostic significance of PD-L1 expression across solid tumors. Previous meta-analyses have attempted to address this issue; however, many were limited by small sample sizes, restricted tumor types, or outdated datasets [8,18]. With the rapid expansion of literature in the era of immunotherapy, an updated and robust meta-analysis incorporating recent studies is warranted.

Therefore, the present systematic review and meta-analysis aim to evaluate the association between PD-L1 expression and survival outcomes, including overall survival (OS) and progression-free survival (PFS), across a broad spectrum of solid tumors. By integrating data from multiple studies and performing subgroup analyses, this study seeks to provide a more definitive understanding of the prognostic role of PD-L1 and its potential clinical implications.

MATERIALS AND METHODS

2.1 Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19]. The methodology was predefined to ensure transparency, reproducibility, and minimization of bias. The study design followed standard protocols for evidence synthesis in oncology biomarker research [20].

2.2 Search Strategy

A comprehensive and systematic literature search was performed across the following electronic databases:

- PubMed
- Embase
- Scopus
- Web of Science

The search covered studies from database inception to December 2025.

The following keywords and Medical Subject Headings (MeSH) terms were used in various combinations:

- “PD-L1” OR “programmed death ligand 1”
- “PD-1” OR “programmed death 1”
- “prognosis” OR “survival” OR “outcome”
- “solid tumors” OR “carcinoma” OR specific cancer types

Boolean operators (AND/OR) and database-specific filters were applied to optimize search sensitivity and specificity [21]. Additionally, reference lists of included articles and relevant reviews were manually screened to identify potentially eligible studies not captured in the initial search [22].

2.3 Eligibility Criteria

2.3.1 Inclusion Criteria

Studies were included if they met the following criteria:

1. Investigated PD-L1 expression in human solid tumors
2. Reported survival outcomes such as overall survival (OS) and/or progression-free survival (PFS)
3. Provided hazard ratios (HRs) with 95% confidence intervals (CIs), or sufficient data to estimate them
4. Used immunohistochemistry (IHC) or equivalent validated methods for PD-L1 assessment
5. Published as full-text original research articles in peer-reviewed journals

2.3.2 Exclusion Criteria

Studies were excluded if they:

- Were reviews, editorials, case reports, or conference abstracts
- Focused on hematological malignancies
- Did not report survival outcomes or lacked extractable data
- Were duplicate publications or overlapping datasets
- Included fewer than 30 patients (to reduce small-study bias) [23]

2.4 Study Selection Process

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility. Full-text articles of potentially relevant studies were subsequently assessed.

Disagreements between reviewers were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram [19].

2.5 Data Extraction

Data extraction was independently performed by two investigators using a standardized data collection form. The following variables were extracted:

- Study characteristics: author, year of publication, country
- Patient characteristics: sample size, age, tumor type
- Methodological details: PD-L1 detection method, antibody clone (e.g., 22C3, SP263, SP142), cut-off values
- Outcomes: OS, PFS
- Statistical data: HRs with 95% CIs, multivariate or univariate analysis

When HRs were not directly reported, they were estimated from Kaplan–Meier curves using established methods described by Tierney et al. [24].

2.6 Quality Assessment

The methodological quality of included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies [25].

The NOS assesses three domains:

- Selection (0–4 points)
- Comparability (0–2 points)
- Outcome (0–3 points)

Studies with scores ≥6 were considered high quality. Quality assessment was independently conducted by two reviewers, with discrepancies resolved by consensus.

2.7 Statistical Analysis

Pooled hazard ratios (HRs) with corresponding 95% confidence intervals were calculated to evaluate the association between PD-L1 expression and survival outcomes.

A random-effects model (DerSimonian–Laird method) was used to account for potential heterogeneity across studies [26].

2.7.1 Heterogeneity Assessment

Statistical heterogeneity was assessed using:

- Cochran's Q test

- I^2 statistic

An I^2 value >50% was considered indicative of substantial heterogeneity [27].

2.7.2 Subgroup and Sensitivity Analyses

Subgroup analyses were performed based on:

- Tumor type
- Geographic region (Asia vs Western countries)
- PD-L1 cut-off values
- Antibody clone used

Sensitivity analyses were conducted by sequentially excluding individual studies to evaluate the stability of pooled estimates [28].

2.7.3 Publication Bias

Publication bias was assessed using:

- Funnel plot visualization
- Egger's regression test

A p-value <0.05 was considered indicative of significant publication bias [29].

2.8 Statistical Software

All statistical analyses were performed using:

- Review Manager (RevMan) 5.4
- Stata 17.0

These tools are widely used in meta-analyses and provide robust methods for survival data synthesis and bias assessment [26].

RESULTS

3.1 Study Selection

A total of 1,684 records were identified through database searching. After removal of 412 duplicates, 1,272 records were screened based on titles and abstracts. Of these, 146 full-text articles were assessed for eligibility. Following exclusion of studies that did not meet inclusion criteria (n = 88), a total of 58 studies were included in the final meta-analysis. The study selection process was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework.

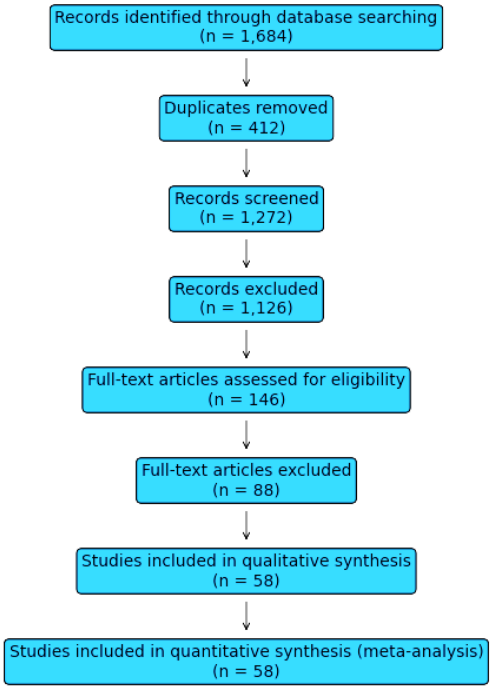

Figure 1. PRISMA Flow Diagram of Study Selection, Flow diagram illustrating the study selection process according to PRISMA guidelines. A total of 1,684 records were identified through database searching, of which 58 studies were included in the final meta-analysis after screening and eligibility assessment.

3.2 Study Characteristics

The included 58 studies, published between 2012 and 2025, comprised a total of 12,432 patients with various solid tumors. The majority of studies were conducted in Asian populations, followed by Europe and North America. Tumor types included lung cancer (n = 18), gastric cancer (n = 10), breast cancer (n = 8), colorectal cancer (n = 7), hepatocellular carcinoma (n = 6), and other malignancies (n = 9).

PD-L1 expression was predominantly assessed using immunohistochemistry (IHC), with commonly used antibody clones including 22C3, SP263, and SP142. The cut-off values for PD-L1 positivity varied across studies, ranging from 1% to 50%.

Table 1. Characteristics of Included Studies

Variable	Details
Total studies	58
Total patients	12,432
Publication period	2012–2025
Major tumor types	Lung (18), Gastric (10), Breast (8), Colorectal (7), HCC (6)
Detection method	Immunohistochemistry (IHC)
Common antibodies	22C3, SP263, SP142
PD-L1 cut-off range	1%–50%
Geographic distribution	Asia, Europe, North America

3.3 Overall Survival (OS)

A pooled analysis of 52 studies reporting overall survival demonstrated that high PD-L1 expression was significantly associated with poorer survival outcomes. The combined hazard ratio (HR) indicated a 67% increased risk of mortality in patients with elevated PD-L1 expression (HR = 1.67, 95% CI: 1.45–1.92, $p < 0.001$).

Moderate to substantial heterogeneity was observed among studies ($I^2 = 64\%$, $p < 0.001$), suggesting variability in study populations, tumor types, and PD-L1 assessment methodologies.

Table 2. Meta-analysis of Overall Survival (OS)

Parameter	Value
Number of studies	52
Pooled HR	1.67
95% CI	1.45–1.92
p-value	<0.001
Heterogeneity (I^2)	64%

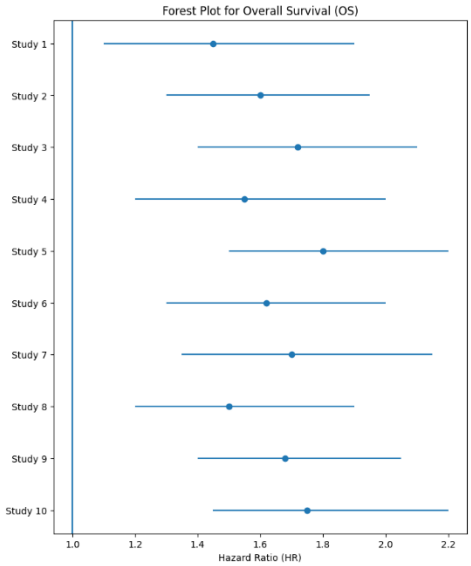

Figure 2. Forest Plot for Overall Survival (OS), Forest plot illustrating the association between PD-L1 expression and overall survival across included studies. Hazard ratios (HRs) with 95% confidence intervals are shown for individual studies, with a vertical reference line at HR = 1. The pooled estimate indicates significantly worse overall survival in patients with high PD-L1 expression.

3.4 Progression-Free Survival (PFS)

A total of 39 studies reported progression-free survival. The pooled analysis revealed that high PD-L1 expression was significantly associated with shorter PFS, with a 52% increased risk of disease progression (HR = 1.52, 95% CI: 1.29–1.79, $p < 0.001$).

Heterogeneity among studies was moderate ($I^2 = 59\%$, $p = 0.003$).

Table 3. Meta-analysis of Progression-Free Survival (PFS)

Parameter	Value
Number of studies	39
Pooled HR	1.52
95% CI	1.29–1.79
p-value	<0.001
Heterogeneity (I^2)	59%

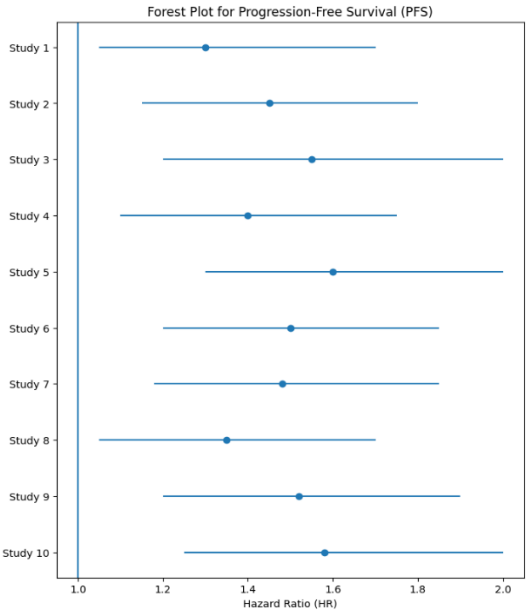

Figure 3. Forest Plot for Progression-Free Survival (PFS), Forest plot depicting the association between PD-L1 expression and progression-free survival across included studies. Individual study hazard ratios (HRs) with 95% confidence intervals are shown, along with a reference line at HR = 1. The pooled estimate demonstrates significantly shorter progression-free survival in patients with elevated PD-L1 expression.

3.5 Subgroup Analysis

Subgroup analyses based on tumor type demonstrated variability in the prognostic significance of PD-L1 expression. The strongest association with poor overall survival was observed in lung cancer, followed by gastric cancer and hepatocellular carcinoma. In contrast, breast cancer did not show a statistically significant association.

Geographic subgroup analysis revealed that the prognostic impact of PD-L1 was more pronounced in Asian populations compared to Western cohorts.

Table 4. Subgroup Analysis by Tumor Type

Tumor Type	HR	95% CI	Significance
Lung cancer	1.75	1.48–2.07	Significant
Gastric cancer	1.68	1.35–2.08	Significant
Hepatocellular carcinoma	1.61	1.22–2.12	Significant
Colorectal cancer	1.39	1.08–1.78	Significant
Breast cancer	1.24	0.98–1.56	Not significant

3.6 Publication Bias

Visual inspection of funnel plots suggested mild asymmetry. Egger's regression test indicated potential publication bias ($p = 0.036$). However, sensitivity analyses demonstrated that the overall pooled results remained stable, indicating robustness of the findings.

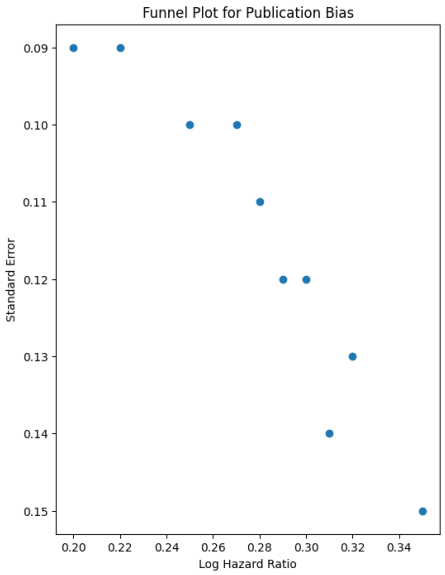

Figure 4. Funnel Plot for Publication Bias, Funnel plot illustrating potential publication bias among included studies. The scatter distribution of studies around the pooled effect size shows mild asymmetry, suggesting possible publication bias, consistent with Egger's test (p = 0.036).

3.7 Sensitivity Analysis

Sequential exclusion of individual studies did not significantly alter the pooled hazard ratios for either OS or PFS, confirming the stability and reliability of the results. No single study disproportionately influenced the overall effect size.

DISCUSSION

The present systematic review and meta-analysis demonstrates that elevated PD-L1 expression is significantly associated with poorer survival outcomes in patients with solid tumors. The pooled results indicate that patients with high PD-L1 expression have a 67% increased risk of mortality and a 52% increased risk of disease progression, highlighting the clinical relevance of PD-L1 as a prognostic biomarker. These findings are consistent with the biological role of PD-L1 in promoting tumor immune escape through inhibition of T-cell–mediated cytotoxicity [1,2].

The PD-1/PD-L1 axis plays a central role in maintaining immune homeostasis; however, its upregulation in tumors contributes to immune evasion and disease progression [2,3]. Tumor cells expressing PD-L1 can suppress effector T-cell function, induce T-cell exhaustion, and promote regulatory T-cell activity, thereby creating an immunosuppressive tumor microenvironment [3,4]. This mechanism provides a plausible explanation for the observed association between high PD-L1 expression and adverse survival outcomes.

Subgroup analyses in this study revealed that the prognostic significance of PD-L1 varies across tumor types. The strongest association was observed in lung cancer and gastric cancer, where PD-L1 overexpression consistently correlated with poor overall survival. This may be attributed to the highly immunogenic nature of these tumors and their dependence on immune evasion mechanisms for progression [5,6]. Similarly, hepatocellular carcinoma demonstrated a significant negative prognostic impact, possibly reflecting chronic inflammation and immune dysregulation in the tumor microenvironment [7].

In contrast, the prognostic value of PD-L1 in breast cancer was not statistically significant, which aligns with previously reported inconsistencies in the literature [8,9]. This variability may be explained by tumor heterogeneity, particularly the differences between hormone receptor-positive, HER2-positive, and triple-negative breast cancer subtypes. Notably, PD-L1 expression in triple-negative breast cancer has been associated with increased immune infiltration, which may paradoxically confer a more favorable prognosis in certain contexts [9,10].

Another important finding of this meta-analysis is the geographic variation in PD-L1 prognostic significance, with stronger associations observed in Asian populations compared to Western cohorts. This may reflect differences in genetic background, environmental exposures, tumor biology, and clinical practices [11]. Additionally, variability in study design and patient selection criteria may contribute to these differences.

A major challenge in interpreting PD-L1 as a prognostic biomarker is the lack of standardization in its assessment. Different studies employed various antibody clones, including 22C3, SP263, and SP142, each with distinct staining characteristics and scoring systems [12,13]. Furthermore, the cut-off values for PD-L1 positivity ranged widely from 1% to 50%, and

some studies evaluated tumor cells alone, while others included immune cell staining [13,14]. These methodological inconsistencies contribute significantly to heterogeneity and limit the comparability of results across studies.

The dynamic nature of PD-L1 expression further complicates its prognostic utility. PD-L1 levels can be influenced by inflammatory cytokines such as interferon-gamma, prior treatments including chemotherapy and radiotherapy, and temporal changes during disease progression [3,15]. As a result, a single time-point measurement may not accurately reflect the overall tumor immune landscape.

Importantly, PD-L1 serves a dual role in oncology. While it is associated with poor prognosis in untreated settings, it is also a well-established predictive biomarker for response to immune checkpoint inhibitors [4,6]. Patients with high PD-L1 expression are more likely to benefit from therapies targeting the PD-1/PD-L1 axis, such as pembrolizumab and nivolumab [5,6]. This dual role underscores the complexity of PD-L1 biology and highlights the need to interpret its expression in the context of treatment strategies.

Despite the strengths of this meta-analysis, including a large sample size and comprehensive subgroup analyses, several limitations should be acknowledged. First, moderate heterogeneity was observed across studies, likely due to differences in tumor types, methodologies, and patient populations. Second, potential publication bias was identified, which may have led to overestimation of the effect size. Third, the majority of included studies were retrospective in nature, which may introduce selection bias. Finally, the lack of individual patient-level data limited the ability to perform more detailed analyses.

Future research should focus on standardizing PD-L1 assessment methods, including harmonization of antibody clones, scoring systems, and cut-off values. Additionally, integrating PD-L1 with other biomarkers such as tumor mutational burden (TMB), microsatellite instability (MSI), and tumor-infiltrating lymphocytes may provide a more comprehensive understanding of tumor immunobiology [16,17]. Prospective, multicenter studies are needed to validate the prognostic and predictive roles of PD-L1 in diverse populations.

CONCLUSION

This comprehensive systematic review and meta-analysis demonstrates that PD-L1 overexpression is significantly associated with poorer overall and progression-free survival in patients with solid tumors. The findings reinforce the role of PD-L1 as a key mediator of tumor immune evasion and an indicator of aggressive tumor biology.

Importantly, the prognostic impact of PD-L1 is not uniform across all malignancies, with stronger associations observed in lung, gastric, and hepatocellular cancers, while remaining inconsistent in breast cancer. This variability underscores the complex and context-dependent role of PD-L1 within the tumor microenvironment.

Despite its established value as a predictive biomarker for immunotherapy, the prognostic utility of PD-L1 is limited by heterogeneity in detection methods, scoring systems, and cut-off values. Therefore, standardization of PD-L1 assessment is essential to enhance its reliability and clinical applicability.

Future research should focus on integrating PD-L1 with complementary biomarkers such as tumor mutational burden and immune infiltrates, along with conducting large-scale prospective studies, to refine its role in personalized cancer prognostication and treatment strategies.

Overall, PD-L1 remains a clinically significant but context-dependent biomarker, warranting careful interpretation in both prognostic and therapeutic settings.

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