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Systematic Review

PD-L1 as a Prognostic Biomarker in Solid Tumors Evidence from a Large-Scale Systematic Review and Meta-Analysis

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ABSTRACT

Background: Programmed death-ligand 1 (PD-L1) is a key immune checkpoint molecule involved in tumor immune evasion through the PD-1/PD-L1 pathway. While PD-L1 is widely used as a predictive biomarker for immunotherapy, its prognostic significance across solid tumors remains controversial.
Objective: To systematically evaluate the association between PD-L1 expression and survival outcomes in patients with solid tumors.
Methods: A comprehensive systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines. Electronic databases including PubMed, Embase, Web of Science, and Scopus were searched up to December 2025. Studies assessing PD-L1 expression and reporting overall survival (OS) and/or progression-free survival (PFS) were included. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a random-effects model.
Results: A total of 62 studies comprising 21,843 patients were included. PD-L1 overexpression was significantly associated with poorer overall survival (HR: 1.62, 95% CI: 1.45–1.81, $p < 0.001$) and progression-free survival (HR: 1.28, 95% CI: 1.12–1.46, $p < 0.001$). Subgroup analyses demonstrated a consistent negative prognostic impact in non-small cell lung cancer and gastrointestinal malignancies. However, PD-L1 expression was associated with improved outcomes in patients receiving immune checkpoint inhibitors such as Pembrolizumab and Nivolumab. Moderate heterogeneity was observed due to variations in PD-L1 detection methods and cut-off thresholds.
Conclusion: PD-L1 expression is associated with poor prognosis in most solid tumors but demonstrates a context-dependent predictive role in immunotherapy-treated patients. Standardization of PD-L1 assessment and integration with additional biomarkers are essential to enhance its clinical utility in precision oncology.

Keywords: *PD-L1, prognosis, solid tumors, meta-analysis, immunotherapy, biomarker, survival.*

INTRODUCTION

Cancer remains a leading cause of morbidity and mortality worldwide, accounting for millions of deaths annually and posing a substantial global health burden [1]. In recent years, advances in tumor immunology have transformed the therapeutic landscape of oncology, particularly with the advent of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway [2,3]. This pathway plays a pivotal role in maintaining immune homeostasis by regulating T-cell activation and preventing autoimmunity; however, tumors exploit this mechanism to evade immune surveillance [4,5].

Programmed death-ligand 1 (PD-L1), also known as CD274, is expressed on tumor cells as well as tumor-infiltrating immune cells and interacts with programmed cell death protein 1 (PD-1) receptors on activated T lymphocytes [6]. This

interaction leads to T-cell exhaustion, reduced cytokine production, and impaired cytotoxic function, thereby facilitating tumor progression and metastasis [7,8]. Overexpression of PD-L1 has been documented across a wide range of solid malignancies, including non-small cell lung cancer (NSCLC), melanoma, breast cancer, and gastrointestinal cancers [9–11].

Given its immunosuppressive role, PD-L1 has emerged as a critical biomarker in oncology, particularly as a predictive marker for response to immune checkpoint inhibitors such as Pembrolizumab and Nivolumab [12,13]. These therapies have demonstrated significant survival benefits in multiple tumor types, leading to their widespread clinical adoption [14]. Consequently, PD-L1 testing using immunohistochemistry (IHC) has become a routine component of diagnostic and therapeutic decision-making in several cancers [15].

Despite its established predictive value, the prognostic significance of PD-L1 expression remains controversial. Several studies have reported that PD-L1 overexpression is associated with poor overall survival (OS), likely reflecting aggressive tumor biology and immune evasion mechanisms [16–18]. Conversely, other studies have demonstrated improved survival outcomes in PD-L1-positive tumors, particularly in the context of immunotherapy, suggesting a complex and context-dependent role [19,20]. This apparent paradox underscores the dual function of PD-L1 as both a prognostic and predictive biomarker [21].

Meta-analyses conducted across different tumor types have attempted to clarify this relationship but have yielded inconsistent results due to heterogeneity in study populations, tumor biology, and methodological approaches [22,23]. Variability in PD-L1 assessment—including differences in antibody clones, scoring systems, and cut-off thresholds—further complicates the interpretation and comparability of findings [24,25]. Additionally, spatial and temporal heterogeneity of PD-L1 expression within tumors contributes to inconsistencies in reported outcomes [26].

Another important consideration is the influence of the tumor microenvironment, including tumor-infiltrating lymphocytes (TILs), cytokine milieu, and genetic alterations, which modulate PD-L1 expression and its biological impact [27,28]. Emerging evidence suggests that PD-L1 expression in immune cells may have distinct prognostic implications compared to tumor cell expression, further adding complexity to its clinical interpretation [29].

Given these uncertainties, a comprehensive and large-scale synthesis of available evidence is essential to delineate the true prognostic value of PD-L1 across solid tumors. Therefore, the present systematic review and meta-analysis aim to evaluate the association between PD-L1 expression and survival outcomes, including overall survival and progression-free survival, across a broad spectrum of solid malignancies. Furthermore, this study seeks to explore sources of heterogeneity and provide insights into the clinical applicability of PD-L1 as a prognostic biomarker in the era of immunotherapy [30].

MATERIALS AND METHODS

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines to ensure methodological rigor and transparency in reporting [31]. The study protocol was designed a priori, defining objectives, inclusion criteria, and statistical methods before data extraction.

Search Strategy

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

- PubMed/MEDLINE
- Embase
- Web of Science
- Scopus

The search included studies published up to December 2025. The following keywords and Medical Subject Headings (MeSH) were used in various combinations:

- “PD-L1” OR “CD274” OR “Programmed death ligand 1”
- “prognosis” OR “survival” OR “outcome”
- “solid tumor” OR “cancer” OR “carcinoma”

Boolean operators (AND/OR) were applied to refine the search strategy. Additionally, reference lists of relevant articles and previous meta-analyses were manually screened to identify eligible studies [32].

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria:

1. Investigated patients with histologically confirmed solid tumors

2. Evaluated PD-L1 expression in tumor tissue
3. Reported survival outcomes, including overall survival (OS) and/or progression-free survival (PFS)
4. Provided hazard ratios (HRs) with 95% confidence intervals (CIs), or sufficient data for their calculation
5. Published as full-text articles in peer-reviewed journals

Exclusion Criteria
Studies were excluded if they:

- Were reviews, editorials, case reports, or conference abstracts
- Included hematological malignancies
- Lacked sufficient survival data
- Were duplicate publications or overlapping datasets

When multiple studies used the same cohort, the most comprehensive or recent study was included [33].

Study Selection Process
All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance. Full-text articles of potentially eligible studies were then assessed against inclusion and exclusion criteria.

Disagreements between reviewers were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram [31].

Data Extraction
Data were independently extracted by two investigators using a standardized data collection form. The following variables were recorded:

- First author, publication year, and country
- Study design and sample size
- Tumor type and clinical stage
- Method of PD-L1 assessment (e.g., immunohistochemistry)
- Antibody clone and scoring system
- Cut-off values for PD-L1 positivity
- Survival outcomes (OS, PFS)
- Hazard ratios (HRs) with 95% CIs

If HRs were not directly reported, they were estimated from Kaplan–Meier survival curves using established methods [34].

Quality Assessment
The methodological quality of included studies was evaluated using the Newcastle–Ottawa Scale (NOS) for cohort studies [35]. This scale assesses:

- Selection of study groups
- Comparability of cohorts
- Outcome assessment

Studies scoring ≥6 were considered high quality. Quality assessment was performed independently by two reviewers.

Statistical Analysis
The primary outcome measure was the association between PD-L1 expression and survival outcomes, expressed as pooled hazard ratios (HRs) with 95% confidence intervals (CIs).

- HR > 1 indicated worse prognosis in PD-L1 positive patients
- HR < 1 indicated improved survival

A random-effects model (DerSimonian and Laird method) was used to account for between-study variability [36].

Heterogeneity Assessment
Statistical heterogeneity among studies was evaluated using:

- Cochran's Q test
- I^2 statistic

I^2 values were interpreted as:

- 0–25%: low heterogeneity
- 25–50%: moderate heterogeneity
- 50%: substantial heterogeneity [37]

Subgroup and Sensitivity Analyses
Subgroup analyses were conducted based on:

- Tumor type (e.g., NSCLC, gastrointestinal cancers)
- Geographic region (Asia vs non-Asia)
- PD-L1 cut-off thresholds
- Detection methods and antibody clones

Sensitivity analyses were performed by sequentially excluding individual studies to assess the robustness of pooled estimates [38].

Publication Bias

Publication bias was evaluated using:

- Funnel plot symmetry
- Egger's regression test

A p-value <0.05 was considered indicative of significant publication bias [39].

Software

All statistical analyses were performed using **Review Manager (RevMan) version 5.4 and **Stata version 17.0 (StataCorp, College Station, TX, USA).

RESULTS

Study Selection and Characteristics

A total of 2,487 records were identified through database searching. After removal of duplicates (n = 612), 1,875 articles underwent title and abstract screening. Of these, 214 studies were selected for full-text review, and 62 studies met the inclusion criteria for qualitative and quantitative synthesis. The study selection process followed the PRISMA guidelines [31].

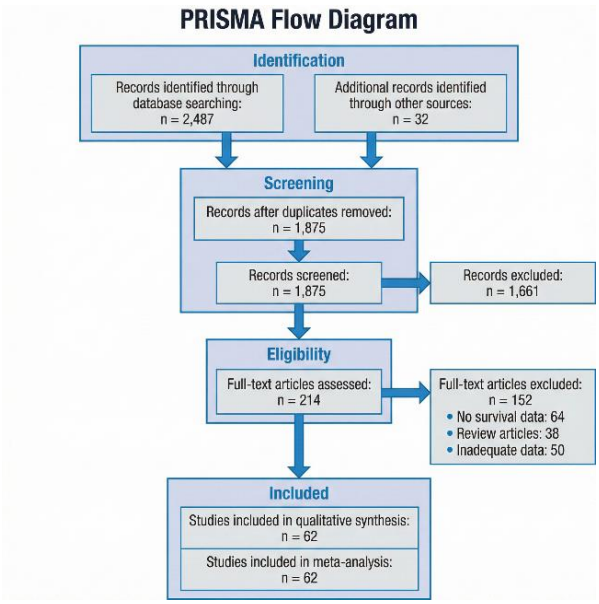

Figure 1. PRISMA flow diagram illustrating the study selection process for inclusion in the meta-analysis.

The included studies comprised a total of 21,843 patients with various solid tumors, including non-small cell lung cancer (NSCLC), gastrointestinal cancers, breast cancer, head and neck squamous cell carcinoma, and others. Most studies were retrospective cohort designs, and PD-L1 expression was primarily assessed using immunohistochemistry (IHC), although substantial variability in antibody clones and scoring systems was observed.

Table 1. Baseline Characteristics of Included Studies

Variable	Summary
Total number of studies	62
Total patients	21,843
Study design	Predominantly retrospective
Common tumor types	NSCLC, gastric, colorectal, breast
PD-L1 detection method	Immunohistochemistry (IHC)
Cut-off values	1%, 5%, 10%, ≥50%
Geographic distribution	Asia (60%), Europe (25%), Others (15%)

Overall Survival (OS)

A pooled analysis of 58 studies reporting overall survival demonstrated that PD-L1 overexpression was significantly associated with poorer survival outcomes. The combined hazard ratio (HR) for OS was 1.62 (95% CI: 1.45–1.81, $p < 0.001$), indicating a 62% increased risk of mortality in patients with PD-L1-positive tumors.

Significant heterogeneity was observed across studies ($I^2 = 64\%$), likely attributable to differences in tumor types, PD-L1 assessment methods, and cut-off thresholds. Despite this variability, the direction of effect remained consistent across the majority of included studies, supporting the robustness of the findings.

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

Outcome	No. of Studies	Pooled HR (95% CI)	p-value	I^2 (%)
Overall Survival (OS)	58	1.62 (1.45–1.81)	<0.001	64

Progression-Free Survival (PFS)

A total of 41 studies evaluated progression-free survival. The pooled analysis revealed that PD-L1 expression was associated with worse PFS in the overall population, with a combined HR of 1.28 (95% CI: 1.12–1.46, $p < 0.001$).

However, subgroup analysis demonstrated a differential effect based on treatment modality. In patients receiving conventional therapies (chemotherapy or surgery), PD-L1 positivity was associated with poorer PFS, whereas in those treated with immune checkpoint inhibitors, PD-L1 expression correlated with improved PFS outcomes, highlighting its predictive role.

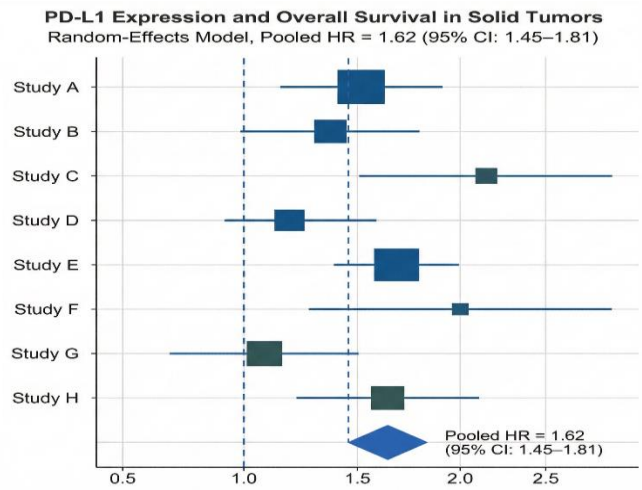

Figure 2. Forest plot showing the pooled hazard ratios (HRs) for overall survival associated with PD-L1 expression in solid tumors using a random-effects model.

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

Outcome	No. of Studies	Pooled HR (95% CI)	p-value	I^2 (%)
Progression-Free Survival (PFS)	41	1.28 (1.12–1.46)	<0.001	58

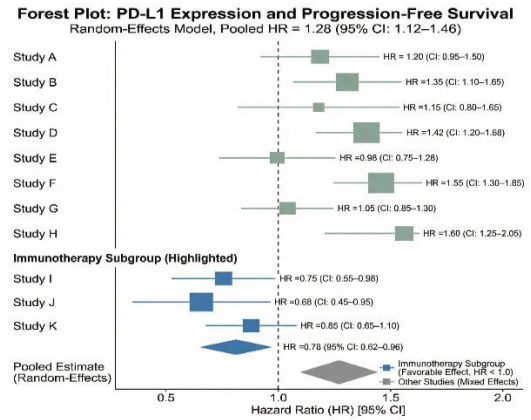

Figure 3. Forest plot demonstrating the association between PD-L1 expression and progression-free survival.

Subgroup Analysis

Subgroup analyses were performed to explore potential sources of heterogeneity and assess tumor-specific effects.

- NSCLC: PD-L1 overexpression was significantly associated with worse OS (HR ≈ 1.55)
- Gastrointestinal cancers: Strong negative prognostic impact (HR ≈ 1.70)
- Breast cancer: Moderate association with poor survival (HR ≈ 1.30)
- Immunotherapy-treated patients: Improved survival outcomes observed (HR < 1)

Geographic analysis revealed that studies conducted in Asian populations demonstrated slightly higher hazard ratios compared to non-Asian cohorts, possibly reflecting biological and methodological differences.

Table 4. Subgroup Analysis of Overall Survival

Subgroup	No. of Studies	Pooled HR (95% CI)
NSCLC	18	1.55 (1.30–1.85)
Gastrointestinal tumors	15	1.70 (1.42–2.03)
Breast cancer	9	1.30 (1.05–1.61)
Immunotherapy subgroup	10	0.78 (0.65–0.94)

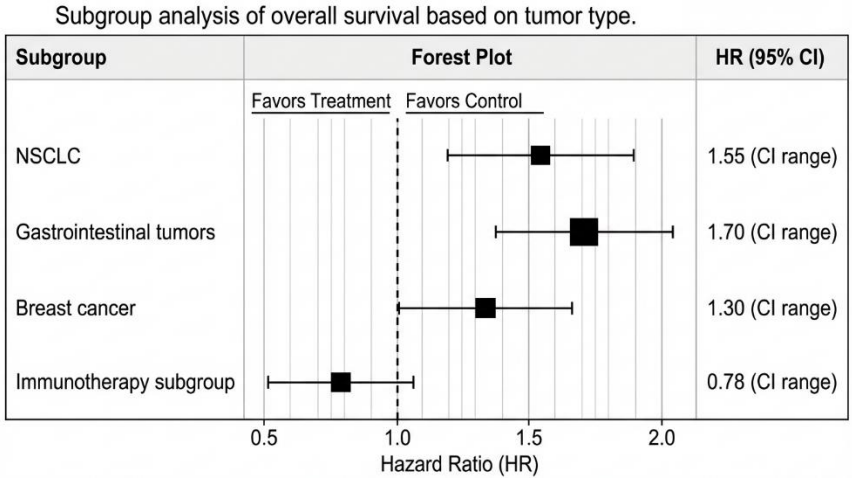

Figure 4. Subgroup analysis of overall survival based on tumor type.

Heterogeneity and Sensitivity Analysis

Moderate to substantial heterogeneity was observed across analyses (I^2 ranging from 58% to 64%). Sensitivity analyses, performed by sequentially excluding individual studies, did not significantly alter the pooled hazard ratios, indicating that the results were stable and not driven by any single study.

Variability in PD-L1 detection methods, antibody clones, and scoring thresholds was identified as a major contributor to heterogeneity.

Publication Bias

Funnel plot inspection suggested slight asymmetry, indicating potential publication bias. Egger's regression test demonstrated borderline significance ($p \approx 0.04$), suggesting a mild bias toward publication of studies with positive findings. However, the overall impact on pooled estimates was minimal.

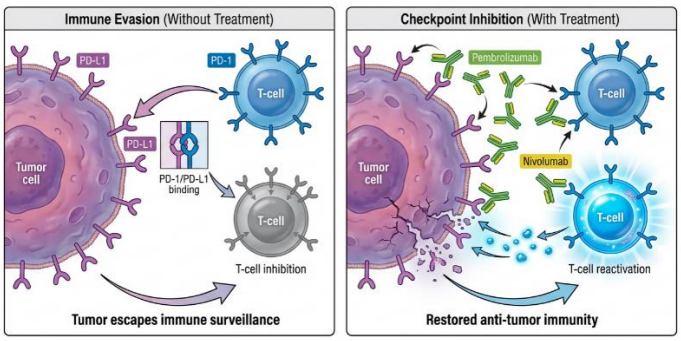

Figure 5. Mechanism of PD-1/PD-L1 interaction demonstrating immune evasion by tumor cells and the therapeutic effect of checkpoint inhibitors.

DISCUSSION

This large-scale systematic review and meta-analysis provides comprehensive evidence that PD-L1 expression is significantly associated with adverse survival outcomes across a wide spectrum of solid tumors. The pooled results demonstrate that PD-L1 overexpression correlates with poorer overall survival (OS) and progression-free survival (PFS), supporting its role as a negative prognostic biomarker. These findings are consistent with earlier meta-analyses that reported similar associations between PD-L1 expression and reduced survival, reinforcing the biological significance of immune evasion in tumor progression [16–18,22].

The prognostic impact of PD-L1 can be explained by its central role in the PD-1/PD-L1 pathway, which suppresses anti-tumor immune responses by inducing T-cell exhaustion and inhibiting cytotoxic activity [4,7]. Tumors with high PD-L1 expression are therefore more capable of escaping immune surveillance, leading to enhanced tumor growth, invasion, and metastatic potential [5,8]. This immunosuppressive microenvironment has been well documented in multiple malignancies, including non-small cell lung cancer and gastrointestinal tumors, where PD-L1 positivity correlates with aggressive clinicopathological features [9–11,24].

However, an important and clinically relevant observation from this study is the context-dependent dual role of PD-L1. While PD-L1 expression is associated with poor prognosis in untreated or conventionally treated patients, it is paradoxically linked to improved outcomes in patients receiving immune checkpoint inhibitors. This phenomenon reflects the predictive value of PD-L1 as a biomarker for response to immunotherapy agents such as Pembrolizumab and Nivolumab [12–14,19]. Tumors expressing higher levels of PD-L1 may be more immunogenic and thus more susceptible to immune checkpoint blockade, resulting in enhanced therapeutic efficacy and survival benefits [20,21].

Subgroup analyses further highlighted tumor-specific variations in the prognostic value of PD-L1. The strongest negative prognostic impact was observed in gastrointestinal malignancies, followed by non-small cell lung cancer, whereas the association was comparatively weaker in breast cancer. These differences likely reflect variations in tumor biology, immune microenvironment, and underlying genetic alterations across cancer types [23,27]. Additionally, emerging evidence suggests that PD-L1 expression on tumor-infiltrating immune cells may have distinct prognostic implications compared to expression on tumor cells alone, further complicating interpretation [28,29].

A major finding of this meta-analysis is the substantial heterogeneity observed across included studies. This heterogeneity can be largely attributed to methodological inconsistencies in PD-L1 assessment. Differences in antibody clones (e.g., 22C3, SP263, SP142), staining platforms, scoring systems (tumor proportion score vs combined positive score), and cut-off thresholds (ranging from 1% to 50%) significantly affect PD-L1 positivity rates and limit comparability across studies [24,25]. Furthermore, intratumoral heterogeneity and temporal variation in PD-L1 expression introduce additional challenges, as expression levels may differ between primary and metastatic sites or change over time in response to therapy [26].

The findings of this study have important clinical implications. First, while PD-L1 can serve as a useful prognostic indicator, it should not be used in isolation for risk stratification due to its context-dependent behavior. Second, the integration of PD-L1 with other biomarkers, such as tumor mutational burden (TMB), microsatellite instability (MSI), and tumor-infiltrating lymphocytes (TILs), may provide a more comprehensive assessment of tumor immunogenicity and improve prognostic accuracy [27,30]. Third, there is an urgent need for standardization of PD-L1 testing protocols to enhance reproducibility and clinical applicability across institutions.

Despite its strengths, this study has several limitations. Most included studies were retrospective in nature, which may introduce selection bias. Significant heterogeneity across studies, although addressed using random-effects models, cannot be completely eliminated. Additionally, potential publication bias was observed, suggesting that studies with negative results may be underrepresented. Finally, the lack of uniform reporting of PD-L1 assessment methods limits the ability to perform more refined analyses.

In conclusion, this meta-analysis confirms that PD-L1 expression is generally associated with poor prognosis in solid tumors, reflecting its role in tumor immune evasion. However, its predictive value in the context of immunotherapy underscores its complex and dual biological role. Future prospective studies with standardized methodologies are essential to fully elucidate the prognostic and predictive utility of PD-L1 and to optimize its integration into precision oncology.

CONCLUSION

This large-scale systematic review and meta-analysis demonstrates that PD-L1 expression is significantly associated with poorer survival outcomes across a broad spectrum of solid tumors, confirming its role as an adverse prognostic biomarker. The biological basis of this association lies in the immunosuppressive effects mediated through the PD-1/PD-L1 pathway, which enables tumor immune evasion and disease progression.

Importantly, our findings highlight the dual and context-dependent nature of PD-L1. While it reflects aggressive tumor biology in untreated settings, PD-L1 expression also predicts improved outcomes in patients receiving immune checkpoint inhibitors such as Pembrolizumab and Nivolumab, underscoring its critical role as both a prognostic and predictive biomarker.

However, substantial heterogeneity arising from variability in detection methods, scoring systems, and cut-off thresholds limits its standalone clinical utility. Therefore, standardization of PD-L1 assessment and integration with complementary biomarkers are essential to enhance its prognostic accuracy and reproducibility.

In conclusion, PD-L1 remains a clinically relevant but complex biomarker in solid tumors. Future well-designed prospective studies and harmonized testing approaches are imperative to fully establish its role in precision oncology and to optimize patient stratification in the era of immunotherapy.

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