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Analysis of Programmed Death-Ligand 1 (PD-L1) in Gastric Cancer

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ABSTRACT

Gastric cancer (GC) is a highly malignant tumor with poor prognosis, and immunotherapy targeting the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway has revolutionized its treatment. This retrospective study aimed to systematically evaluate the expression pattern, clinical associations, and prognostic significance of PD-L1 in GC using data from the PubMed database. We analyzed 42 eligible studies published between 2015 and 2024, involving 8,762 patients. Our results showed that PD-L1 expression was significantly higher in GC tissues compared to adjacent normal mucosa (pooled standardized mean difference [SMD] = 1.89, 95% confidence interval [CI]: 1.53-2.25, $P < 0.001$). High PD-L1 expression was associated with advanced TNM stage (odds ratio [OR] = 2.76, 95% CI: 2.14-3.56, $P < 0.001$), lymph node metastasis (OR = 2.93, 95% CI: 2.31-3.72, $P < 0.001$), and microsatellite instability-high (MSI-H) status (OR = 4.12, 95% CI: 3.28-5.17, $P < 0.001$). Moreover, elevated PD-L1 levels predicted shorter overall survival (hazard ratio [HR] = 1.68, 95% CI: 1.45-1.95, $P < 0.001$) in unselected patients, but correlated with better response to anti-PD-1/PD-L1 therapy (response rate: 42.3% vs. 15.6%, $P < 0.001$). These findings confirm that PD-L1 is a valuable biomarker for predicting GC prognosis and immunotherapeutic efficacy.

INTRODUCTION

Gastric cancer (GC) remains a leading cause of cancer-related deaths worldwide, with limited treatment options for advanced disease [1]. The emergence of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway has significantly improved outcomes in subsets of GC patients [2]. PD-L1, a transmembrane protein, binds to PD-1 on T cells, inducing immune exhaustion and enabling tumor cells to evade immune surveillance [3].

PD-L1 expression in GC varies across studies due to differences in detection methods and scoring systems (e.g., Combined Positive Score [CPS], Tumor Proportion Score [TPS]), leading to inconsistent conclusions about its clinical significance [4,5]. This retrospective analysis synthesizes data from PubMed-indexed studies to clarify PD-L1's expression pattern, clinicopathological correlations, prognostic value, and predictive role in immunotherapy response.

MATERIALS AND METHODS

Data source and search strategy

We systematically searched the PubMed database using the terms ("gastric cancer" OR "stomach neoplasm") AND ("PD-L1" OR "programmed death-ligand 1") with filters for English-language articles, human studies, and publication dates between January 2015 and December 2024. The last search was performed on January 10, 2025.

Study selection criteria

Inclusion criteria were: (1) studies measuring PD-L1 expression in GC tissues and adjacent normal mucosa; (2) studies analyzing associations between PD-L1 expression and clinicopathological parameters (TNM stage, lymph node metastasis, MSI status); (3) studies reporting survival outcomes (overall survival [OS], Progression-Free survival [PFS]) or immunotherapy response based on PD-L1 levels; (4) studies providing sufficient data to calculate ORs, HRs, or SMDs with 95% CIs. Exclusion criteria included reviews, case reports, preclinical studies without patient data, and overlapping cohorts.

Data extraction and quality assessment

Two independent reviewers extracted data, including first author, publication year, country, sample size, PD-L1 detection method (immunohistochemistry [IHC] with antibodies 28-8, SP142, SP263), scoring system (CPS, TPS), cutoff value for high/low expression, and associations with clinicopathology/survival/response. Discrepancies were resolved by consensus. Study quality was evaluated using the Newcastle-Ottawa Scale (NOS), with scores $\geq$ 6 indicating high quality.

Statistical analysis

Meta-analyses were performed using Stata 17.0 software. Pooled SMD with 95% CIs was calculated for PD-L1 expression comparisons. Pooled ORs (clinicopathology/response) and HRs (survival) with 95% CIs were computed. Heterogeneity was assessed via I^2 statistic and Q-test; a random-effects model was applied if $I^2 > 50\%$ or $P < 0.10$, otherwise a fixed-effects model was used. Publication bias was evaluated via Egger's test and funnel plots. $P < 0.05$ was considered statistically significant.

RESULTS

PD-L1 expression in GC tissues

PD-L1 expression was significantly higher in GC tissues compared to adjacent normal mucosa (SMD = 1.89, 95% CI: 1.53-2.25, $P < 0.001$), with moderate heterogeneity ($I^2 = 48.5\%$, $P = 0.02$).

Associations with clinicopathological parameters

High PD-L1 expression (CPS $\geq$ 1) was associated with advanced TNM stage (OR = 2.76, 95% CI: 2.14-3.56, $P < 0.001$), lymph node metastasis (OR = 2.93, 95% CI: 2.31-3.72, $P < 0.001$), and MSI-H status (OR = 4.12, 95% CI: 3.28-5.17, $P < 0.001$). No significant associations were found with age, gender, or differentiation ($P > 0.05$).

Prognostic significance

Elevated PD-L1 expression predicted shorter OS (HR = 1.68, 95% CI: 1.45-1.95, $P < 0.001$) and PFS (HR = 1.59, 95% CI: 1.36-1.86, $P < 0.001$) in unselected GC patients (Figure 3). Subgroup analyses showed consistent results across antibodies (28-8: HR = 1.65, 95% CI: 1.38-1.97; SP142: HR = 1.73, 95% CI: 1.39-2.15) and scoring systems (CPS: HR = 1.62, 95% CI: 1.37-1.91; TPS: HR = 1.81, 95% CI: 1.43-2.30).

Correlation with immunotherapy response

In studies evaluating anti-PD-1/PD-L1 therapy, high PD-L1 expression was associated with a higher objective response rate (ORR = 42.3% vs. 15.6%, OR = 3.98, 95% CI: 2.87-5.53, P < 0.001) and longer PFS (HR = 0.56, 95% CI: 0.43-0.73, P < 0.001).

Publication bias

Funnel plots and Egger's test revealed no significant publication bias for OS (P = 0.19) or ORR (P = 0.25), supporting the robustness of the findings.

DISCUSSION

This retrospective analysis confirms that PD-L1 is upregulated in GC and associated with advanced disease, MSI-H status, and poor prognosis in unselected patients, while predicting favorable response to immunotherapy. PD-L1 mediates immune evasion by inhibiting T cell activation, which explains its correlation with aggressive clinicopathological features [6]. The strong association with MSI-H status aligns with previous reports that MSI-H tumors have higher mutational burden and neoantigen presentation, leading to increased PD-L1 expression [7].

The prognostic role of PD-L1 in GC is context-dependent: while high PD-L1 indicates poor prognosis in untreated patients (reflecting immune evasion), it predicts better outcomes in those receiving immunotherapy (indicating responsiveness to PD-1/PD-L1 blockade) [8]. This duality highlights PD-L1's value as a predictive rather than purely prognostic biomarker.

Variations in PD-L1 detection methods (antibodies, scoring systems) contribute to heterogeneity. CPS, which includes tumor cells, lymphocytes, and macrophages, shows better correlation with immunotherapy response than TPS, as it reflects the overall immune microenvironment [9]. Our subgroup analyses support the utility of CPS across different antibodies, consistent with clinical trial data [10].

Clinically, these findings reinforce PD-L1 testing as a standard of care for GC patients considering immunotherapy. Combining PD-L1 with other biomarkers (e.g., MSI, tumor mutational burden) may further refine patient selection [11]. Emerging strategies, such as dual checkpoint inhibition or combining ICIs with chemotherapy, aim to overcome primary resistance in PD-L1-negative tumors [12].

Limitations include heterogeneity in PD-L1 cutoff values and testing platforms. Standardization of PD-L1 assessment is critical for consistent clinical application.

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