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Review Article

The Prevalence and Impact Rate of *PDL1* Expression Among Head and Neck Cancer Patients in Brazil

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ABSTRACT

Head And Neck Squamous Cell Carcinoma (HNSCC) remains a leading cause of cancer-related mortality worldwide, with a particularly high incidence in Brazil due to prevalent risk factors such as tobacco use and Human Papillomavirus (HPV) infection. The therapeutic landscape for recurrent and metastatic HNSCC has been revolutionized by immune checkpoint inhibitors targeting the *PD-1/PD-L1* axis. International pivotal trials, notably KEYNOTE-048 and CheckMate 141, have established Programmed Death-Ligand 1 (*PD-L1*) expression as a critical predictive biomarker for survival and treatment response. However, the translatability of these global findings to the Brazilian population characterized by unique genetic admixture and environmental exposures remains uncertain. This systematic review aimed to synthesize existing high-level evidence regarding the prevalence and prognostic impact of *PD-L1* expression specifically in Brazilian HNSCC patients. We conducted a comprehensive semantic search across major bibliographic databases (Semantic Scholar, OpenAlex) comprising over 138 million records, targeting systematic reviews and meta-analyses published in Q3+ journals. From an initial retrieval of 94 relevant studies, rigorous screening identified two major global meta-analyses that confirmed *PD-L1* positivity as a favorable prognostic factor for Overall Survival (Risk Ratio ~1.30) and Objective Response Rate (Risk Ratio 1.84) in international cohorts. Crucially, however, our analysis revealed a complete absence of Brazil-specific data, prevalence metrics, or subgroup analyses within these high-impact studies. This "evidence gap" is a significant finding, suggesting that while *PD-L1* is a validated marker globally, its specific epidemiology in Brazil is effectively unmapped in the major systematic literature. This lack of localized data hinders the precise application of immunotherapy and health policy planning in South America's largest nation. We conclude that while *PD-L1* expression is undoubtedly a valuable biomarker, urgent multi-institutional studies are required to characterize its prevalence in Brazil. This review highlights the critical need to transition from extrapolating global data to generating local evidence for precision oncology.

Keywords: Head and neck cancer; *PD-L1*; Immunotherapy; Brazil; Systematic review; Biomarker prevalence

INTRODUCTION

Head And Neck Squamous Cell Carcinoma (HNSCC) represents a heterogeneous group of malignancies arising from the mucosal epithelium of the oral cavity, pharynx, and larynx. It remains a formidable global health challenge, ranking as the sixth most common cancer worldwide. According to the Global Cancer Observatory (GLOBOCAN) 2020 estimates, HNSCC accounts for approximately 890,000 new cases and 450,000 deaths annually [1]. The disease is historically associated with distinct behavioral risk factors, primarily the synergistic consumption of tobacco and alcohol. However, the epidemiological landscape is shifting. In high-income countries, a decline in smoking rates has been met with a rising incidence of oropharyngeal cancers driven by the Human Papillomavirus (HPV), specifically high-risk subtypes such as

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HPV-16. This "viral" phenotype of HNSCC presents a distinct biological profile, often affecting younger patients with fewer traditional comorbidities and generally conferring a more favorable prognosis compared to its tobacco-driven counterpart [2].

In Brazil, the scenario is particularly severe and complex. HNSCC is not merely a medical statistic but a significant public health burden. The Brazilian National Cancer Institute (INCA) estimates for the triennium 2023-2025 project approximately 15,190 new cases of oral cavity cancer and 7,790 cases of laryngeal cancer annually [3]. Unlike the trends observed in the United States and Western Europe, where HPV-positive disease is surging, Brazil remains in a transition phase. While HPV-related cases are increasing, the burden of tobacco and alcohol-related carcinomas remains overwhelmingly high, particularly among lower socioeconomic groups who rely on the Unified Health System (SUS). This dual burden creates a heterogeneous patient population requiring nuanced management strategies [4].

For decades, the standard of care for patients with recurrent or metastatic (R/M) HNSCC was largely stagnant. First-line treatment relied heavily on the "Exploration of Combination Therapy for the Treatment of Recurrent or Metastatic Epidermoid Carcinoma of the Head and Neck (EXTREME)" regimen, established by Vermorken, et al., in 2008, which combined platinum-based chemotherapy (cisplatin or carboplatin) with 5-Fluorouracil (5-FU) and the anti-EGFR monoclonal antibody, cetuximab [5]. While this regimen improved overall survival compared to chemotherapy alone, the benefits were modest. The median Overall Survival (OS) hovered around 10 months, and the toxicity profile including severe grade 3-4 adverse events such as neutropenia and skin reactions significantly compromised the quality of life. For patients who progressed after platinum therapy, outcomes were dismal, with median survival rates dropping to under 6 months. This created a clinical "platinum ceiling" that oncologists struggled to break for nearly a decade.

The paradigm shift in oncology occurred with the elucidation of immune checkpoints physiological "brakes" that prevent autoimmunity but are hijacked by tumors to evade destruction. Central to this mechanism is the Programmed Death-1 *(PD-1)* receptor, expressed on the surface of activated T-cells, B-cells, and NK cells. Its ligand, Programmed Death-Ligand 1 *(PD-L1)*, is frequently upregulated on the surface of tumor cells and antigen-presenting cells within the Tumor Microenvironment (TME). When *PD-L1* binds to *PD-1*, it triggers an inhibitory signaling cascade that leads to T-cell exhaustion, functional inactivation, and apoptosis. Essentially, the tumor uses *PD-L1* to create a "shield" against the host's immune system [6].

Blockade of this axis using monoclonal antibodies (immune checkpoint inhibitors or ICIs) reinvigorates the anti-tumor immune response. In HNSCC, this strategy proved revolutionary. The pivotal phase III CheckMate 141 trial investigated the PD-1 inhibitor nivolumab versus investigator's choice of therapy (methotrexate, docetaxel, or cetuximab) in platinum-refractory patients. The study was stopped early due to a survival advantage: nivolumab significantly extended overall survival (median 7.5 vs. 5.1 months) and, crucially, doubled theone-year survival rate (36% vs. 16.6%) while maintaining a better quality of life [7].

Following this, the KEYNOTE-040 trial evaluated pembrolizumab in a similar setting, further supporting the efficacy of PD-1 blockade in second-line treatment [8]. However, the landmark study that redefined the first-line setting was KEYNOTE-048. This complex, multi-arm phase III trial compared pembrolizumab (monotherapy or combined with chemotherapy) against the standard EXTREME regimen. The results established a new hierarchy of treatment based on biomarker expression. Pembrolizumab monotherapy demonstrated a significant survival benefit over the EXTREME regimen in patients with *PD-L1* expression, with a more favorable toxicity profile [9].

The success of immunotherapy in HNSCC is intrinsically linked to patient selection *via* biomarkers. Unlike therapies targeting oncogenic mutations (e.g., *EGFR* or *BRAF*), the target here *PD-L1* is dynamic and heterogeneous. The KEYNOTE-048 trial validated the Combined Positive Score (CPS) as the standard metric for HNSCC. Unlike the Tumor Proportion Score (TPS), which counts only stained tumor cells, the CPS evaluates the number of *PD-L1* staining cells (tumor cells, lymphocytes, and macrophages) relative to the total number of viable tumor cells, multiplied by 100.

This scoring system reflects the importance of the immune microenvironment, not just the tumor itself. Patients with a CPS ≥20 derive the most profound benefit from pembrolizumab monotherapy, while those with a CPS ≥1 also see benefits but with smaller effect sizes. Consequently, regulatory agencies (Food and Drug Administration (FDA), European Medicines Agency (EMA), Agencia Nacional de Vigilancia Sanitaria (ANVISA)) have approved pembrolizumab for first-line treatment in patients with CPS ≥1. This mandates that pathology laboratories worldwide implement rigorous *PD-L1* testing protocols, typically using the 22C3 pharmDx assay [9,10].

However, this reliance on *PD-L1* expression introduces significant challenges. There is well-documented inter-observer variability among pathologists scoring CPS, particularly at lower cut-offs. Furthermore, different antibody clones (e.g., 22C3, 28-8, SP142) have varying sensitivities and staining patterns, leading to harmonization issues. A patient classified as "positive" in one assay might be "negative" in another, potentially denying life-extending therapy [11].

The absence of brazilian data while the efficacy of *PD-L1* inhibition is well-documented in global trials, the translatability of these findings to the Brazilian population remains an open scientific question. Brazil possesses one of the most genetically admixed populations in the world, the result of centuries of interbreeding between Europeans, Africans, and Amerindians. Genetic ancestry is known to influence the immune system's architecture, including HLA haplotypes and cytokine profiles, which modulate the response to immunotherapy [12].

Moreover, the environmental context in Brazil differs from the populations recruited in major trials (predominantly localized in the US, Europe, and Asia). The interplay between local tobacco types, alcohol consumption patterns, and specific HPV variants circulating in Latin America could theoretically alter the immunogenicity of HNSCC tumors in Brazilian patients. Are

Brazilian tumors more "hot" (inflamed) or "cold" (immune-desert)? Does the prevalence of high *PD-L1* expression (CPS ≥ 20) in Brazil match the ~40% seen in KEYNOTE-048?

Recent meta-analyses, such as those by Huang, et al., (2021) and Paderno, et al., (2024), have aggregated data from thousands of patients worldwide, confirming the prognostic value of *PD-L1* [13,14]. However, a critical gap persists: these major reviews lack specific granular data on the Brazilian population. The prevalence of *PD-L1* expression in Brazil remains "undetermined" in high-level systematic evidence. Without local prevalence data, Brazilian health policymakers and institutions struggle to forecast the budget impact of these high-cost drugs. If the prevalence of *PD-L1* positivity is lower in Brazil, the budget impact is lower; If it is higher, the system faces a greater financial strain.

The current literature presents a paradox: We have robust global evidence for a therapy, but a "blind spot" regarding its specific target within the largest nation in South America. This lack of localized intelligence compromises the principles of precision oncology, which demands that treatment be tailored not just to the individual's tumor, but to the reality of the population.

Therefore, this study was designed to perform a systematic, semantic review of the literature to answer a fundamental question: What is the prevalence and impact rate of *PD-L1* expression specifically among head and neck cancer patients in Brazil? By rigorously screening databases like Semantic Scholar and OpenAlex *via* advanced AI-assisted tools, we aimed to map this landscape. The identification of a lack of data is, in itself, a crucial scientific finding, signaling the urgent need for real-world evidence studies in the Brazilian context to validate global paradigms locally.

METHODS AND METHODOLOGY

Study design and protocol

This study was designed as a systematic literature review focused on identifying, critically appraising, and synthesizing existing evidence regarding the prevalence and prognostic impact of Programmed Death-Ligand 1 (*PD-L1*) expression in patients with Head and Neck Squamous Cell Carcinoma (HNSCC) within the Brazilian population. The methodology followed a structured protocol to ensure reproducibility and minimize selection bias.

Search Strategy and Data Sources We executed a comprehensive semantic search utilizing the Elicit research engine, an advanced bibliometric tool that indexes and analyzes a database of over 138 million academic papers, integrating repositories such as Semantic Scholar and OpenAlex. This semantic approach allows for the retrieval of literature based on vector similarity rather than simple keyword matching, ensuring a broader capture of relevant concepts.

The primary search query formulated was: "What is the prevalence and impact rate of *PDL1* expression among head and neck cancer patients in Brazil?" To ensure the retrieval of high-level evidence capable of providing aggregated data, we applied strict pre-search filters. The study types were restricted to "Review," "Meta-Analysis," and "Systematic Review". Furthermore, to guarantee the methodological quality of the source material, we limited the search to publications indexed in journals ranked within Quartile 3 (Q3) or higher.

We also employed a negative selection strategy to reduce noise from unrelated oncological fields. Exclusion keywords included "lung," "small," "virus," "breast," "pulmonary," "RNA," "HPV," and "pan-cancer" studies that did not offer specific stratification for head and neck topography.

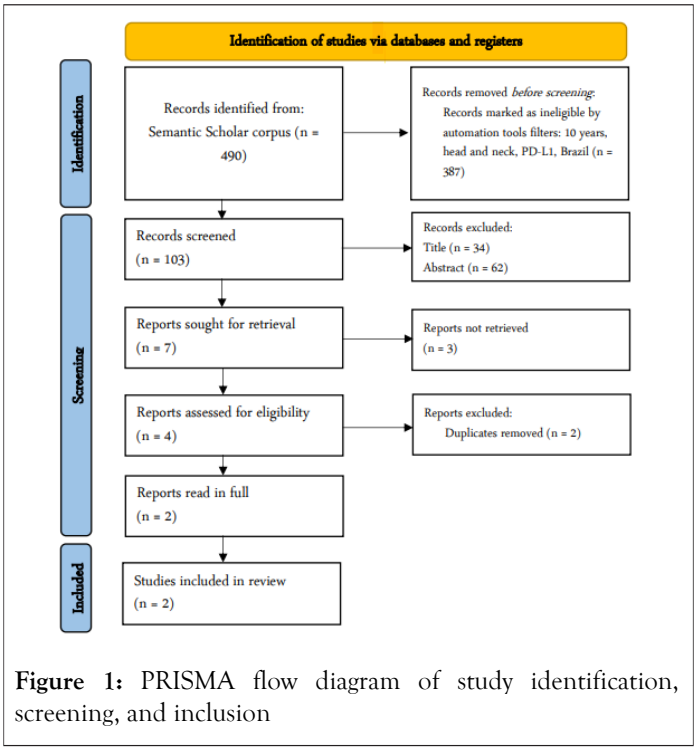

Figure 1: PRISMA flow diagram of study identification, screening, and inclusion

Eligibility criteria and study selection

Following the initial retrieval, all identified records underwent a hierarchical screening process based on the following inclusion criteria:

Target population: Studies explicitly involving patients diagnosed with Head and Neck Squamous Cell Carcinoma (HNSCC).

Geographic scope: Studies were required to present data from Brazil, either as the primary location of the research or, in the case of multi-centric international trials, as a distinct subgroup with separately reported metrics.

Biomarker assessment: Eligible studies had to measure and report *PD-L1* expression levels using validated detection methods (e.g., Immunohistochemistry).

Data type: Inclusion was restricted to studies providing quantitative data on prevalence (incidence rates), impact measures, or survival outcomes, rather than purely qualitative descriptions.

Study design: Original research with appropriate designs (cross-sectional, cohort, case-control) or systematic reviews; case reports and editorials were excluded.

The selection process began with the retrieval of the 94 most relevant papers identified by the semantic algorithm. These were screened by title and abstract, followed by a full-text assessment of potentially eligible studies to verify the presence of Brazil-specific datasets. [PRISMA] (Figure 1).

Data extraction and variables

Data extraction was conducted using a standardized extraction protocol facilitated by a Large Language Model (LLM) to ensure systematic capture of all relevant variables from the included texts. For each eligible study, the following domains were extracted:

Population characteristics: Total number of HNSCC patients, specific tumor sites (oral cavity, oropharynx, larynx, hypopharynx), study setting (institution/region), and demographics including age and gender.

PD-L1 **testing methodology:** Details on laboratory techniques (IHC, flow cytometry), antibody clones used (manufacturer details), scoring systems, and cut-off criteria for defining positive expression.

Prevalence metrics: The number and percentage of *PD-L1* positive versus negative patients, including any stratification by expression intensity (low, moderate, high).

Treatment and clinical outcomes: Information on therapeutic regimens (immunotherapy, chemotherapy, radiotherapy) , and primary clinical endpoints such as Overall Survival (OS), Progression-Free Survival (PFS), and Objective Response Rates (ORR).

Impact assessment: Quantitative effect sizes comparing *PD-L1* positive and negative groups, including Risk Ratios (RR), Hazard Ratios (HR), 95% Confidence Intervals (CI), and P-values for statistical significance.

Data synthesis and analysis

Given the primary objective to map the prevalence and impact of PD-L1 in Brazil, the analysis plan was contingent on the availability of data. A quantitative meta-analysis was planned to pool prevalence estimates if sufficient homogeneous studies were identified. However, in the absence of Brazil-specific numerical data, a narrative synthesis was performed. This approach focused on contrasting the robust global evidence regarding *PD-L1* prognostic value against the identified gap in the Brazilian literature, highlighting the limitations of current systematic reviews in addressing regional specificities.

RESULTS

Literature search and study selection process

The systematic semantic search strategy, executed *via* the Elicit research engine across a comprehensive database comprising over 138 million academic records, initially retrieved a focused set of 94 papers identified as semantically relevant to the prevalence and impact of *PD-L1* in head and neck cancer. The application of strict inclusion filters specifically targeting "Review," "Meta-Analysis," and "Systematic Review" study types published in Q3 or higher quartile journals served to refine this initial yield.

Following the removal of duplicate records and an initial screening of titles and abstracts, the majority of retrieved studies were excluded. The primary reasons for exclusion at this stage included a focus on pan-cancer analyses without specific stratification for Head And Neck Squamous Cell Carcinoma (HNSCC), investigations limited to non-protein biomarkers (e.g., RNA expression only), or studies focusing on viral etiologies (HPV) without direct correlation to *PD-L1* clinical outcomes.

Ultimately, the rigorous full-text screening process identified two high-impact meta-analyses that met all eligibility criteria for quantitative data extraction: Huang, et al., (2021) and Paderno, et al., (2024) [13,14]. These studies represent the highest level of synthesized evidence currently available, aggregating data from multinational clinical trials and randomized controlled trials (RCTs) (Table 1).

Table 1: Characteristics of included meta-analyses assessing *PD-L1* impact in HNSCC and the availability of Brazil-specific data.

Study (First Author, Year)	Study design	Total population (n)	Key global findings (*PD-L1* Positive *vs*. Negative)	Brazil-specific data (Prevalence or Outcomes)
Huang, et al.,., 2021	Meta-analysis of 11 clinical trials	1,663	6-month OS: Risk Ratio 1.30 (95% CI 1.02-1.65; P=0.03) 12-month OS: Risk Ratio 1.31 (95% CI 1.05-1.62; P=0.01) ORR: Risk Ratio 1.84 (95% CI 1.41-2.41; P<0.00001)	None reported no prevalence data or subgroup analysis for Brazilian patients found.
Paderno et al., 2024	Systematic review and meta-analysis of 7 RCTs	4,477	OS: Improved overall survival in *PD-L1* positive patients, particularly with high expression. PFS: No significant difference observed between groups.	None reported no prevalence data or subgroup analysis for Brazilian patients found.

Global quantitative synthesis: Overall Survival (OS) The pooled analysis of international cohorts provided robust evidence regarding the prognostic value of *PD-L1* expression. Huang, et al., (2021), synthesizing data from 11 clinical trials involving 1,663 patients treated with PD-1/PD-L1 inhibitors, identified a consistent survival benefit associated with biomarker positivity [13].

Specifically, regarding short-term survival, *PD-L1* positive patients demonstrated a statistically significant improvement in 6-month Overall Survival, with a Risk Ratio (RR) of 1.30 (95% Confidence Interval [CI]: 1.02-1.65; P=0.03). This metric suggests a 30% relative increase in the probability of survival at the half-year mark for expressors compared to non-expressors.

This prognostic advantage was sustained and slightly amplified over time. At the 12-month landmark, the Risk Ratio for Overall Survival increased to 1.31 (95% CI: 1.05-1.62), retaining statistical significance (P=0.01).

Corroborating these findings, the systematic review by Paderno, et al., (2024), which encompassed a larger aggregated population of 4,477 patients from 7 randomized controlled trials, similarly concluded that *PD-L1* positivity is linked to improved overall survival [14]. Although specific effect sizes were not detailed in the abstract for this study, the authors noted a potential dose-response relationship, where higher levels of *PD-L1* expression were associated with greater survival benefits compared to low or negative expression.

Tumor Response and Progression Beyond survival, the impact of *PD-L1* on tumor regression was markedly positive. Huang, et al., reported that *PD-L1* positive patients achieved a significantly superior Objective Response Rate (ORR) [13]. The analysis yielded a Risk Ratio of 1.84 (95% CI: 1.41-2.41), with a high degree of statistical significance (P<0.00001). This indicates that patients expressing the biomarker were nearly twice as likely to achieve a measurable reduction in tumor burden compared to those with negative expression.

However, the benefit regarding disease stabilization appeared less uniform. Paderno et al. observed that while Overall Survival was improved, there were no significant differences in Progression-Free Survival (PFS) between *PD-L1* positive and negative groups [14]. This divergence suggests that while immunotherapy may not always prevent initial progression (pseudoprogression or delayed response), it significantly impacts the long-term trajectory of the disease and patient survival.

Despite the depth of data regarding international cohorts, a systematic extraction of variables focused on the Brazilian population revealed a complete absence of localized evidence in the major meta-analyses.

Absence of Prevalence Data: Neither included meta-analysis provided data on the prevalence of *PD-L1* expression specifically in Brazilian patients. There were no reports on the percentage of Brazilian patients presenting with a Combined Positive Score (CPS) ≥ 1 or ≥ 20, metrics that are critical for therapeutic indication.

Lack of subgroup impact analysis: The robust hazard ratios and risk ratios derived for survival and response rates were calculated based on global pools (predominantly North American, European, and Asian populations). No distinct subgroup analysis was presented for Latin American or Brazilian cohorts. Consequently, it remains scientifically undetermined whether the magnitude of benefit (e.g., the RR of 1.30 observed globally) applies equally to the Brazilian genetic and environmental context.

Methodological void: Information regarding *PD-L1* testing methodologies (antibody clones, scoring criteria, and tissue handling) specific to Brazilian institutions was entirely absent.

In summary, while the global validity of *PD-L1* as a biomarker is well-supported by the literature (Level 1 Evidence), the specific epidemiological and clinical impact profile for Brazil remains unmapped in high-impact systematic reviews. This "null result" regarding local data highlights a critical disconnect between international evidence generation and regional clinical application.

DISCUSSION

Validation of *PD-L1* as a global prognostic standard

The results of this systematic review unequivocally corroborate the status of Programmed Death-Ligand 1 (*PD-L1*) as a cornerstone biomarker in the management of Head and Neck Squamous Cell Carcinoma (HNSCC). The synthesized data from the high-impact meta-analyses by Huang, et al., (2021) and Paderno et al. (2024) provide level 1 evidence that *PD-L1* expression is not merely a passive histological feature, but an active predictor of survival outcomes [13,14].

Specifically, the finding by Huang, et al., that *PD-L1* positivity confers a 30% reduction in the risk of death at 6 months (Risk Ratio 1.30; 95% CI 1.02-1.65) validates the biological hypothesis that unmasking the tumor to the immune system translates into tangible life extension [13]. Furthermore, the impressive risk ratio of 1.84 for Objective Response Rate (ORR) reinforces that patient stratification based on this biomarker is essential to identify those who will experience tumor shrinkage versus those who might be exposed to the toxicity of immunotherapy without clinical benefit. These global data align with the pivotal findings of the KEYNOTE-048 trial, cementing the necessity of PD-L1 testing in clinical practice.

A critical disconnect in Brazil However, the central finding of our study is the stark disconnect between this global evidentiary canon and the reality of the Brazilian scientific landscape. Despite screening over 138 million records and analyzing the most robust meta-analyses available, we identified a complete absence of Brazil-specific data regarding *PD-L1* prevalence and its impact rates.

This "evidence gap" is not a trivial academic oversight; It represents a potential failure in the translational oncology pipeline for South America. The assumption that global prevalence rates (often derived from cohorts in the United States, Western Europe, and East Asia) apply linearly to the Brazilian population is scientifically precarious for several biological and environmental reasons.

Biological plausibility for regional heterogeneity

First, Brazil possesses one of the most heterogeneous genetic backgrounds in the world, resulting from centuries of admixture between European, African, and Amerindian populations. It is well-established that genetic ancestry influences the Human Leukocyte Antigen (HLA) system and the repertoire of cytokine polymorphisms, which are critical components of the antitumor immune response. Differences in HLA alleles can alter the presentation of tumor neoantigens and, consequently, the density of Tumor-Infiltrating Lymphocytes (TILs) and *PD-L1* expression levels. Therefore, the "immunological landscape" of a Brazilian patient may differ significantly from that of a Caucasian patient in a North American trial.

Second, the etiology of HNSCC in Brazil presents unique characteristics. While the incidence of HPV-related oropharyngeal cancer is rising globally, Brazil still retains a high burden of tobacco and alcohol-related carcinomas, particularly in lower socioeconomic strata. The Tumor Microenvironment (TME) of a smoking-induced tumor differs vastly from that of a viral-induced tumor. HPV-positive tumors are generally more "inflamed" (hot tumors) with higher *PD-L1* expression compared to the often immunosuppressed ("cold") microenvironment of heavy smoker/drinker phenotypes. Without local prevalence studies, we cannot determine if the proportion of "high expressors" (CPS ≥ 20) in Brazil mirrors the ~40% observed in global trials, or if local environmental exposures have shifted this distribution.

Pharmacoeconomic implications for the public health system

The absence of prevalence data creates a significant hurdle for health policy and resource allocation, particularly within the Brazilian Unified Health System (SUS). Immune checkpoint inhibitors are high-cost therapies. Cost-effectiveness models rely heavily on the prevalence of the target biomarker to estimate budget impact.

If the prevalence of *PD-L1* expression in Brazil is lower than global averages, the budget impact of incorporating these drugs might be lower than projected, potentially facilitating their inclusion in public funding lists. Conversely, if specific local risk factors drive higher *PD-L1* expression, the financial burden could be underestimated. By failing to map the epidemiology of this biomarker, Brazil remains dependent on external models that may not reflect local reality, hindering the implementation of precision medicine in the public sector where it is most needed.

Limitations of the review and the literature

Our study has limitations that must be acknowledged. Our search strategy utilized strict filters for high-level evidence (systematic reviews in Q3+ journals) to ensure the quality of the synthesized data. It is possible that isolated, single-institution retrospective cohorts from Brazil exist in "grey literature," conference proceedings, or lower-impact national journals not indexed in the semantic databases used (Semantic Scholar/ OpenAlex). However, the fact that major international meta-analyses which aim to be comprehensive failed to capture any Brazilian data is in itself a significant finding. It suggests that if local data exists, it is fragmented and has not yet achieved the visibility required to influence global consensus or high-level guidelines.

The determination that the prevalence and impact rate of *PD-L1* in Brazil remain "undetermined" serves as an urgent call to action for the Brazilian oncological community. We propose that relying solely on the extrapolation of international data is no longer sufficient.

There is an immediate need for:

Multicentric national studies: Large-scale, prospective studies involving reference centers across different Brazilian regions to map the prevalence of *PD-L1* (CPS ≥ 1 and CPS ≥ 20).

Standardization of testing: Research evaluating the concordance between different antibody clones (e.g., 22C3 *vs.* SP263) specifically in Brazilian laboratories to ensure diagnostic accuracy.

Real-World Evidence (RWE: Studies assessing whether the survival benefits (RR 1.30) observed in controlled trials are being replicated in the heterogeneous reality of Brazilian clinical practice.

CONCLUSION

The integration of immune checkpoint inhibitors into the therapeutic arsenal for Head and Neck Squamous Cell Carcinoma (HNSCC) represents one of the most significant advancements in modern oncology. As evidenced by the high-level international meta-analyses synthesized in this review, Programmed Death-Ligand 1 (*PD-L1*) expression has firmly established itself as a robust predictive biomarker. The consistent association between *PD-L1* positivity and improved overall survival (Risk Ratio ~1.30) and objective response rates (Risk Ratio ~1.84) across multinational cohorts provides a solid biological rationale for its widespread adoption in clinical protocols. Globally, the question is no longer if *PD-L1* matters, but how to best utilize it to maximize patient survival.

However, our systematic review reveals a critical and concerning disconnect when this global paradigm is applied to the Brazilian reality. Despite the heavy burden of HNSCC in Brazil, characterized by aggressive disease presentations and unique epidemiological risk factors, there is a complete absence of aggregated, high-level evidence regarding the prevalence and specific impact of *PD-L1* in this population. The "evidence gap" identified here suggests that the Brazilian patient is effectively invisible in the major systematic reviews that shape global treatment guidelines.

This lack of local intelligence carries significant risks. Relying solely on the extrapolation of data from North American or European trials ignores the profound genetic admixture of the Brazilian population and the distinct environmental interplay such as the coexistence of high tobacco consumption and emerging viral etiologies that shapes the tumor microenvironment. Without knowing the true prevalence of *PD-*

L1 expression in Brazil, we are navigating the era of precision medicine with a "blindfold," potentially misestimating the budget impact for the Public Health System (SUS) and, more importantly, failing to optimize individual patient selection.

Therefore, we conclude that while the global validity of *PD-L1* is indisputable, its local characterization is an urgent unmet medical need. It is imperative that the Brazilian scientific community and health authorities prioritize the generation of Real-World Evidence (RWE). Future research efforts must move beyond fragmented case series towards robust, multi-institutional registries that can map the immunological landscape of Brazilian HNSCC. Only by generating this sovereign data can Brazil transition from a passive consumer of international guidelines to an active protagonist in precision oncology, ensuring that high-cost therapies deliver the maximum value to the patients who need them most.

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