Association between PD-L1 expression and head and neck cancer prognosis: a meta-analysis

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Abstract

Background: Programmed cell death ligand 1 (PD-L1) plays an important role in tumor cell immune escape, and it has been extensively studied in head and neck cancer. However, its prognostic impact on patients with head and neck cancer remains controversial, so we sought to investigate this issue through a comprehensive meta-analysis.

Methods: To assess the significance of PD-L1 on the survival of patients with head and neck cancer, we collected articles reported in PubMed, EMBASE, and Cochrane Library, until January 31, 2019. We also used the Newcastle Ottawa Scale (NOS) for literature quality evaluation.

Results: The study included a total of 4551 patients affected by 6 different types of head and neck cancer reported in 26 articles. Our study found that the association between the expression of PD-L1 and the prognosis of head and neck tumors was highly heterogeneous ($P < 0.00001$, $I^2 = 80.0\%$); therefore, the random effects model was applied to combine the effect sizes. Based on the combined hazard ratios (HR) of 1.15 (95% CI: 0.88 to 1.50, $P = 0.32$), the expression of PD-L1 in head and neck tumors may not be a factor associated with poor prognosis.

Conclusions: Our results suggest that PD-L1 expression cannot predict the overall survival of patients with oral, nasopharyngeal, or esophageal cancer. Through subgroup analysis, we found that the expression of PD-L1 may be a poor prognostic factor for some head and neck cancers.

Background

Head and neck cancer (HNC) is the sixth most common cancer in the world [1]. More than 500,000 people worldwide are diagnosed with HNC each year, and approximately 380,000 people die from this disease each year [2]. HNC may affect the nasopharynx, oropharynx, oral cavity, larynx, hypopharyngeal and esophageal cavity, nasal and paranasal cavity, temporal bone, salivary glands and so on, and most of these subtypes are squamous cell carcinoma. The global incidence of HNC has been increasing for decades, but the reasons are not fully understood [3]. Due to the absence of early symptoms and lack of effective screening techniques, most patients are diagnosed with advanced cancer [1].

Programmed death factor 1 (PD-1) and its ligands are currently one of the research focuses of tumor targeted therapy. When PD-1 binds to the ligand PD-L1, the function of T cells is reduced by various mechanisms, including antagonizing T cell receptors to inhibit their signal transduction, changing the normal metabolism of T cells to inhibit their differentiation, and reducing the antioxidant function of T cells to inhibit their killing [4,5]. At present, several PD-1 inhibitors and PD-L1 inhibitors have entered clinical trials, and some are used in cancer treatment. Nivolumab was the first PD-L1 inhibitor to be marketed and approved by the FDA for the treatment of metastatic melanoma, non-small cell lung cancer and advanced renal cell carcinoma [6].

To better prolong the survival of patients with HNC, the selection of effective immunological molecular biomarkers and immunotherapy programs will open up new strategies for the treatment of advanced HNC.

Many studies have found that high expression of PD-L1 in HNC patients is associated with poor prognosis and does not depend on the tumor origin. PD-L1 is considered to be a prognostic biomarker [7]. Therefore, we conducted this meta-analysis to determine the prognostic impact of PD-L1 on patients with HNC.

Method

Search method

All articles were searched in the PubMed, EMBASE, and Cochrane Library databases, up to January 31, 2019. We used the search terms ("head and neck tumor" OR "oral" OR "tonsil" OR "parathyroid" OR "thyroid" OR "laryngeal" OR "ear" OR "nose" OR "tongue" OR "salivary gland" OR "esophageal" OR "facial" OR "nasopharyngeal" OR "hypopharyngeal") and ("pd-l1" OR "b7-h1" OR "programmed death ligand 1" OR "cd274" OR "b7homolog1" OR "pdl1") and ("cancer" OR "carcinoma" OR "adenocarcinoma"). Selected publications were all written in the English language. In addition, the references included in the articles were manually reviewed to obtain other potentially relevant articles.

Inclusion criteria

The inclusion criteria included that the clinical and pathological data of all cases were complete, and the pathological examination confirmed the diagnosis of HNC. Additionally, immunohistochemistry (IHC) staining for the detection of PD-L1 expression in tumor tissues, and raw data about PD-L1 expression and HR and 95% CI for the prognostic correlation in cancer patients were provided in the study.

Exclusion criteria

The exclusion criteria consisted of non-original research articles, such as reviews, abstracts, letters, and case reports; copying reports or similar data; Newcastle-Ottawa Scale (NOS) scores <5 points and other unusable documents; the subjects were not human patients; the sample size was less than 30; and the full text could not be obtained.

Data extraction

Data extraction and quality assessment were performed by two of the authors. The data included in each study were extracted independently. The authors extracted the author's name, publication year, country in which the study was conducted, sample size, cancer type, and critical criteria for over expression (the definition of positive PD-L1), hazard ratios (HRs) and 95% confidence intervals (CI).

Quality assessment

According to the NOS, the quality of each of the included studies was evaluated [8]. The total score was 9 points, and articles with scores below 5 points were deemed to be of low-quality. The evaluation process

was independently conducted by 2 authors, and differences in evaluation were resolved by negotiation. When the opinions were inconsistent, a 3rd author made the assessment. Finally, the appropriate literature was selected for meta-analysis.

Statistical analysis

HR and CI were used to assess the association between PD-L1 expression levels and head and neck tumor prognosis. Heterogeneity testing was performed using Revman 5.3 software. The Chi-square test was to estimate the between-study heterogeneity. When $P \geq 0.1$ and $I^2 \leq 50\%$, the studies were considered homogeneous, and the fixed effect model was selected and analyzed. When $P < 0.1$ and $I^2 > 50\%$, the studies were considered to be heterogeneous, and the source of heterogeneity was further analyzed by subgroup analysis or sensitivity analysis. If the heterogeneity could not be eliminated, the random effects model was chosen. Additionally, a funnel plot was drawn to test the publication bias of the assessment study [9].

Results

Description of trials included in the meta-analysis

A total of 320 articles were retrieved from the relevant databases, all the documents were saved to Endnote and evaluated, and 111 duplicates were excluded. After reading the titles and abstracts of the articles, 80 preliminary screenings were obtained. After reading the full text, according to the inclusion and exclusion criteria, 26 articles were selected [10–35], which included 4551 patients. The flow diagram of literature selection is summarized in Fig. 1. Twenty-six articles were used for meta-analysis of the survival data. The quality of the literature was evaluated according to the NOS, and only articles with 5 points or more were included. The vast majority of the studies were based on Asian populations, including 13 Chinese population studies, 3 Japanese population studies, and 4 Korean population studies; the sample size of 7 studies was below 100, and the sample size of 19 studies was greater than 100. There were 7 studies on nasopharyngeal carcinoma, 6 on oral cancer, 8 on esophageal cancer, and 2 on thyroid cancer. The indicators of 23 studies were overall survival (OS), and the other three were progression-free survival (PFS), disease-free survival (DFS), disease-specific survival (DSS), The characteristics of the included studies are summarized in Table 1.

Prognosis

A total of 26 studies reported that the levels of PD-L1 expression were associated with prognosis. Twelve studies showed that PD-L1 over expression is associated with poor prognosis in HNC. Our analysis showed that the expression level of PD-L1 was not associated with prognosis in HNC (HR = 1.15, 95% CI = 0.88–1.50, $P = 0.32$, random effect) (Fig. 2).

Subgroup analysis

Further subgroup analysis was based on the patient's origin (China and not China), the IHC assessment of PD-L1 percentage cutoff, and the cancer type. The conclusions from the subgroup analysis were similar to those of the overall analysis (more details are listed in Table 3, 4 and 5.). However, we found that PD-L1 may be a poor prognosis factor for oral squamous cell carcinoma and other types of head and neck cancer.

FIGURE 3 Meta-analysis forest plot of the subgroups of HNC survival in different regions.

Prognostic study publication bias and sensitive analysis

The funnel plot test evaluated the publication bias. The result shows incomplete symmetry (Fig. 6), suggesting that there may be publication bias in the prognostic study. Sensitive analysis did not change the results.

Discussion

The study included a total of 4551 patients affected by 6 different types of head and neck cancer reported in 26 articles. Our study found that the association between PD-L1 expression and head and neck tumor prognosis is highly heterogeneous; therefore, a random effects model was applied. We found that the expression of PD-L1 in head and neck tumors may not be a factor in poor prognosis. Through subgroup analysis, we found that the expression of PD-L1 was not related with the prognosis of oral cancer, esophageal cancer, and nasopharyngeal carcinoma, but it may be a poor prognostic biomarker for other types of head and neck cancer.

Many meta-analyses report the prognostic value of PD-L1 in various types of cancer [36–39], and a large number of studies have reported the association between PD-L1 and the prognosis of head and neck tumors [10–35], but the results are not completely consistent. Therefore, this paper used a meta-analysis to explore the association between PD-L1 and HNC prognosis. Head and neck tumors consists mainly of head and neck squamous cell carcinoma. Recently, yang [40] reported that PD-L1 expression by IHC is not recommended as a predictor of HNSCC survival and that positive PD-L1 expression may predict better PFS in patients with advanced HNSCC. Our study collected more studies for meta-analysis to investigate the association between PD-L1 and HNC prognosis, and similar results were obtained. It should be emphasized that the heterogeneity of the results cannot be ignored. Heterogeneity may be due to different sample sizes of the included studies, the different relevant detection methods, including antibody selection, standardized definition of outcome indicators and differences in population characteristics and types and sources of cancer. The most important is the different standards for PD-L1 expression. During our research, we found that the cut-off value was not standardized. There are two ways to define the cut-off value in the study. One method is the integral comprehensive measurement method; the value corresponding to each positive intensity $\times$ the percentage of the intensity cells, and then sum again. The second method is to use the value corresponding to the percentage of positive cells. Therefore, based on the cut-off value, we performed a subgroup analysis. We found that the heterogeneity of the cutoff group of 5% is small (Fig. 4). In addition, we performed a subgroup analysis based on the type of cancer and found that for other types of head and neck cancers, it seems that PD- L1 expression was associated with prognosis.

Conclusion

Based on the above meta-analysis, we preliminarily estimated that the expression of PD-L1 may not be significantly related to the prognosis of oral squamous cell carcinoma, nasopharyngeal carcinoma, and esophageal squamous cell carcinoma. However, for some of other HNC, we cannot deny the existence of the correlation.

Abbreviations

NA: not available; HR: Hazard ratios; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; DSS: disease-specific survival; OSCC: oral squamous cell carcinoma; MTC: medullary thyroid carcinoma; NPC: nasopharyngeal carcinoma; ESCC: esophageal squamous cell carcinoma; cSCCHN: cutaneous squamous cell carcinoma of the head and neck; SGC: salivary gland carcinoma; HNSCC: head and neck squamous cell carcinoma; PTC: papillary thyroid cancer; CI: Confidence interval; PD-1 and PD-L1: Programmed cell death protein-1 and ligand-1;

Declarations

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Authors' contributions

ZS designed the study, searched the literature, analysed and interpreted the data; LW and GZ performed the data entry, searched the literature, and wrote the manuscript; XC performed the data entry, searched the literature, and wrote the manuscript; DY searched the literature. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are included within

the article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Characteristics of the studies included for meta-analysis

First Author	Year	Country	sample size	Survival Results	Cut-off Value for PD-L1 Positivity	Cancer Type	P value	NOS Score
Ahn H	2017	Korea	68	OS	NA	OSCC	0.039	5
Bi Y	2018	China	87	OS	1%	MTC	0.083	6
Chang AMV	2016	Philippines	56	OS	5%	NPC	0.801	6
Chen TC	2015	Taiwan	218	OS	5%	OSCC	0.97	8
Chen K	2016	China	536	OS	5%	ESCC	0.293	7
de Vicente JC	2018	Spain	125	DSS	10%	OSCC	0.01	6
García-Pedrero JM	2017	Spain	100	OS	1%	cSCCHN	0.29	6
Hatogai K	2017	Japan	286	OS	1%	ESCC	0.015	6
Kim HS	2015	Korea	133	OS	5%	OSCC	0.513	7
Kim R	2016	South Korea	200	OS	H-score	ESCC	0.034	6
Li YF	2017	China	62	DFS	20%	NPC	0.006	6
Lim SH	2016	South Korea	73	OS	H-score	ESCC	0.023	6
Lin YM	2015	Taiwan	305	OS	NA	OSCC	0.0609	7
Liu YJ	2018	Taiwan	208	OS	4%	NPC	0.15	6
Loos M	2011	Germany	101	OS	NA	ESCC	p < 0.001	6
Mukaigawa T	2016	Japan	219	OS	1%	SGC	0.459	6
Ngamphaiboon	2019	Thailand	203	OS	5%	HNSCC	0.505	7
Oliveira-Costa JP	2015	Brazil	142	OS	5%	OSCC	0.27	6
Rong L	2019	China	378	OS	1%	ESCC	0.423	7
Shi RL	2017	China	260	RFS	NA	PTC	0.024	6
Tanaka K	2016	Japan	180	OS	NA	ESCC	0.011	6
Victor H.F. Lee	2016	Hong Kong	104	OS	5%	NPC	0.261	6
Yang F	2018	China	81	OS	NA	HNSCC	0.002	6
Zheng L	2017	China	85	OS	H-score	NPC	0.032	6
Zhou Y	2017	China	132	OS	H-score	NPC	0.016	7

Zhu Q	2017	China	209	OS	5%	NPC	0.693	7
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Abbreviations: NA, not available; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; DSS, disease-specific survival; OSCC, oral squamous cell carcinoma; MTC, medullary thyroid carcinoma; NPC, nasopharyngeal carcinoma; ESCC, esophageal squamous cell carcinoma; cSCCHN, cutaneous squamous cell carcinoma of the head and neck; SGC, salivary gland carcinoma; HNSCC, head and neck squamous cell carcinoma; PTC, papillary thyroid cancer.

Figures

Figure 1

Flow chart of the study selection.

Figure 2

Forest plot describing the association between PD-L1 expression and HR of patients with HNC.

Figure 3

Meta-analysis forest plot of the subgroups of HNC survival in different regions.

Figure 4

Meta-analysis forest plots of the survival subgroups of HNC with different cutoffs.

Figure 5

Meta-analysis forest plots of the survival subgroups of different types of HNC.

Figure 6

The funnel plot test evaluating the publication bias.