Research Article

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Clinicopathological features of programmed cell death-ligand 1 expression in patients with oral squamous cell carcinoma

https://doi.org/10.1515/med-2020-0041
received October 31, 2019; accepted January 17, 2020

Abstract: Objective: Programmed cell death-ligand 1 (PD-L1) expression has been shown to play important roles in various types of cancer. However, the role of PD-L1 expression has not been conclusively reported in patients with oral squamous cell carcinoma (OSCC). Accordingly, in this meta-analysis, we investigated the clinicopathological value of PD-L1 expression in patients with OSCC.

Methods: Google Scholar, PubMed, EMBASE, and CNKI databases were searched to find relevant studies published through to September 16, 2019. The relationships between PD-L1 expression in patients with OSCC and clinicopathological features were assessed using risk ratio (RR) and 95% confidence intervals (CIs).

Results: Sixteen studies including 1989 participants were included. The results indicated that high PD-L1 expression was correlated with sex (RR = 1.28, 95% CI: 1.16–1.42, P < 0.001), N stage (RR = 1.19, 95% CI: 1.06–1.33, P = 0.003), M stage (RR = 1.64, 95% CI: 1.01–2.66, P = 0.044), low differentiation (RR = 1.16, 95% CI: 1.01–1.33, P = 0.034), and human papilloma virus infection (RR = 1.38, 95% CI: 1.14–1.68, P = 0.001), but unrelated to TNM stage or T stage. There was no significant publication bias in the studies included in this analysis.

Conclusions: This meta-analysis revealed that high PD-L1 expression in patients with OSCC was correlated with clinicopathological features. Further large-scale studies are necessary to confirm our results.

Keywords: Oral squamous cell carcinoma; Programmed cell death-ligand 1; Clinicopathological features; Meta-analysis

1 Introduction

Oral cancer is a major public health concern worldwide; approximately 350,000 patients are newly diagnosed with oral cancer each year, and oral cancer causes approximately 170,000 deaths annually [1]. Oral squamous cell carcinoma (OSCC) accounts for nearly 90% of malignant oral carcinomas, and the 5-year survival rate is only approximately 50% [2, 3]. Owing to the high rate of metastasis in patients with OSCC, the prognosis tends to be poor [4]. Prediction of prognosis plays a critical role in the treatment of OSCC and is usually based on the tumor-node-metastasis (TNM) classification system; lymph node metastases and the presence of distant metastases are associated with a poor prognosis [5, 6]. Despite recent advancements in various therapies, including radiotherapy, chemotherapy, and surgery, the survival rates of patients with OSCC have not improved [2]. Thus, the identification of novel prognostic markers is urgently needed to improve personalized treatment approaches and clinical outcomes in patients with OSCC.

Programmed cell death-ligand 1 (PD-L1), also known as B7-H1 or CD274, is a member of the costimulatory factor superfamily [7]. PD-L1 is expressed in various types of tumor cells and in immune cells, including activated B cells and T cells, macrophages, and dendritic cells [8]. When the programmed cell death-1 (PD-1)/PD-L1 axis is highly expressed in a healthy immune system, activation of this pathway restricts autoimmunity and limits T-cell activity in an inflammatory response to infection [9]. In contrast, overexpression of PD-L1 in carcinoma cells blocks the activation of T cells, exhausts T cells, and
triggers apoptosis in effector T cells, thereby impairing cytokine production and promoting tumor growth [10-12].

Previous studies have reported the prognostic value of PD-L1 expression in many types of malignant solid tumors, such as pancreatic carcinoma [13], non-small cell lung carcinoma [14], prostate cancer [15], gastric carcinoma [16], and breast cancer [17]. Moreover, although several studies have investigated the associations between PD-L1 expression and clinicopathological characteristics in patients with OSCC, the results remain contradictory [18-32]. For example, Straub and colleagues found that PD-L1 overexpression is closely related to lymph node metastasis and is correlated with poor overall survival in patients with OSCC [24]. In contrast, Hong et al. revealed that high PD-L1 expression is associated with better prognosis in patients with OSCC [19]. In a study by Cho and colleagues, however, PD-L1 expression does not affect survival rates in patients with OSCC [32].

In this study, in order to clarify the role of PD-L1 in OSCC, we performed a meta-analysis of PD-L1 expression and clinicopathological features in patients with OSCC.

2 Methods

2.1 Literature search

A systematic literature search was performed of PubMed, EMBASE, Google Scholar, and CNKI up to September 16, 2019 using the following search terms: (“mouth” OR “oral”) AND (“carcinoma” OR “tumor” OR “neoplasm” OR “cancer”) AND (“B7-H1” OR “programmed cell death ligand 1” OR “PD-L1”). The study was performed according to the Statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [33].

2.2 Inclusion and exclusion criteria

The included studies met the following inclusion criterion: (a) participants were histologically diagnosed with OSCC; (b) articles were written in English or Chinese with full text available, and humans were used as the study subjects; (c) the expression level of the PD-L1 gene was estimated in OSCC tissues; (d) the relationship of PD-L1 expression with clinicopathological features was investigated in OSCC patients; (e) studies had sufficient materials to estimate relative risk (RR) with corresponding 95% confidence intervals (95% CIs). Exclusion criteria were as follows: (a) reviews, editorials, conference abstracts, and case reports; and (b) studies that had insufficient data.

2.3 Data extraction and quality assessment

The available data for the included studies were independently extracted by two authors. The following data were extracted: first author, country, ethnicity, publication year, detection method, and clinicopathological parameters. Disagreement was settled through discussion between authors. The Newcastle-Ottawa-Scale (NOS) was applied to estimate the quality of the included studies [34].

2.4 Statistical analysis

The relationships between PD-L1 expression in patients with OSCC and clinicopathological characteristics were assessed using RR and 95% CIs. Cochrane’s Q tests and the I² statistic were carried out to evaluate between-study heterogeneity. Significant heterogeneity was defined as \( P < 0.1 \) or \( I^2 > 50 \), and RR were then pooled using the random-effect model [35]; Or else, a fixed-effect model was chosen [36]. Additionally, we performed a sensitivity analysis to determine the stability of the pooled values. To estimate potential publication bias, Egger linear regression tests and Begg’s funnel plots were used [37, 38]. All analyses were performed using Stata 15.0 software (Stata Corp., College Station, TX, USA).

3 Results

3.1 Literature search results

Figure 1 shows the literature search process. In total, 117 studies were selected from our database search. Duplicates were deleted, 83 articles were screened, and 54 records were further removed. The full text of the remaining 29 articles was read. Finally, 15 articles were included in the current analysis [18-32].

3.2 Description of the included studies

Sixteen retrospective studies including 1989 participants were included in our meta-analysis of the association between PD-L1 expression and clinicopathological features in patients with OSCC. Among the 15 articles, data
3.3 Meta-analysis results

3.3.1 Sex

Fifteen studies (1947 patients; 458 women and 1489 men) were included for evaluation of the relationship between PD-L1 expression and sex in patients with OSCC. There was a low degree of heterogeneity among the studies ($I^2 = 23.0\%$, $P = 0.199$); thus, the fixed-effect model was used for pooled analysis. The results indicated a statistically significant relationship between high PD-L1 expression and female sex ($RR = 1.28$, 95% CI: 1.16–1.42, $P < 0.001$). Subgroup analysis by race indicated that high PD-L1 expression was associated significantly with women in both Caucasian and Asian populations (Table 2 and Figure 2).

3.3.2 N stage

Thirteen studies (1663 patients; 958 with N1–N3 stage and 705 with N0 stage) were included for evaluation of
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Table 1: Characteristics of included studies.

| Author          | Year | Country | Ethnicity | Total (n) | TNM stage | Detection method | PD-L1 expression | NOS |
|-----------------|------|---------|-----------|-----------|-----------|------------------|------------------|-----|
| Cho             | 2011 | Korea   | Asian     | 45        | I-IV      | IHC              | Positive         | 6   |
| Ukpo            | 2013 | USA     | Caucasian | 181       | I-IV      | IHC              | Positive         | 7   |
| Lin             | 2015 | China   | Asian     | 305       | I-IV      | IHC              | Negative         | 7   |
| Oliveira-Costa  | 2015 | Brazil  | Caucasian | 142       | I-III     | IHC              | Positive         | 8   |
| Hong            | 2016 | Australia | Caucasian | 99         | I-IV      | IHC              | Positive         | 7   |
| Kim             | 2015 | Korea   | Asian     | 133       | I-IV      | IHC              | Negative         | 9   |
| Ock(a)          | 2016 | Korea   | Asian     | 50        | I-IV      | IHC              | Positive         | 8   |
| Ock(b)          | 2016 | Korea   | Asian     | 91        | I-IV      | IHC              | Negative         | 8   |
| Satgunaseelan   | 2016 | Australia | Caucasian | 217       | NA        | IHC              | Negative         | 9   |
| Straub          | 2016 | Germany | Caucasian | 80        | I-IV      | IHC              | Positive         | 7   |
| Meulenaere      | 2017 | Belgium | Caucasian | 99        | I-IV      | IHC              | Positive         | 8   |
| Hirai           | 2017 | Japan   | Asian     | 24        | I-IV      | IHC              | Positive         | 7   |
| Kogashiwa       | 2017 | Japan   | Asian     | 84        | I-IV      | IHC              | Positive         | 7   |
| Troeltzsch      | 2016 | Germany | Caucasian | 88        | I-IV      | IHC              | Positive         | 8   |
| Hong            | 2019 | Australia | Caucasian | 214       | I-IV      | IHC              | Positive         | 9   |
| Sato            | 2019 | Japan   | Asian     | 137       | I-IV      | IHC              | Positive         | 8   |

PD-L1, programmed cell death ligand 1; NA, not available; IHC, immunohistochemical; NOS, Newcastle-Ottawa-Scale.

Figure 2: Forest plot of RRs and 95% CIs for the association between PD-L1 expression and sex. (A) Overall population; (B) stratified by ethnicity.

the relationship between PD-L1 expression and lymph node metastasis in patients with OSCC. Moderate heterogeneity was found among the studies ($I^2 = 40.6\%, P = 0.063$); thus, the fixed-effect model was used for pooled analysis. The results indicated that there was a significant relationship between high PD-L1 expression and lymph node metastasis (N1–N3; RR = 1.19, 95% CI: 1.06–1.33, P = 0.003). Subgroup analysis by race indicated that high PD-L1 expression was significantly correlated with lymph node metastasis among Caucasians (RR = 1.34, 95% CI: 1.16–1.56, P < 0.001; Table 2 and Figure 3).
3.3.3 Histological grade

Twelve studies (1486 patients; 1149 with poorly/moderately differentiated disease and 337 with well differentiated disease) were included for assessment of the association between histological grade and PD-L1 expression. No significant heterogeneity was found ($I^2 = 0\%$, $P = 0.624$); thus, the fixed-effect model was used for pooled analysis. The results revealed a significant relationship between high PD-L1 expression and advanced histological grade (poorly/moderately differentiated; RR = 1.16, 95% CI: 1.01–1.33, $P = 0.034$). In the stratification according to ethnicity, we found no significant relationship between high PD-L1 expression and different histological grades (Table 2 and Figure 4).

3.3.4 HPV status

Eight studies (935 patients; 424 with HPV-associated disease and 511 without HPV-associated disease) were included for evaluation of the relationship between HPV status and PD-L1 expression. Moderate heterogeneity was found among the studies ($I^2 = 59.6\%$, $P = 0.015$); thus, a random-effect model was used for pooled analysis. The results demonstrated a significant association between high PD-L1 expression and HPV-associated OSCC (RR = 1.38, 95% CI: 1.14–1.68, $P = 0.001$). In the subgroup analysis stratified based on ethnicity, we found that high PD-L1 expression was significant correlated with HPV-associated OSCC among Caucasian and Asian populations (Table 2 and Figure 5).
3.3.5 Other clinicopathological features

Four studies (333 patients; 85 with recurrence and 248 without recurrence) were included for evaluation of the relationship between PD-L1 expression and recurrence status in patients with OSCC. No heterogeneity was found ($I^2 = 0\%$, $P = 0.585$); thus, a fixed-effect model was used for the pooled analysis. The results revealed a significant relationship between high PD-L1 expression and recurrence (RR = 0.75, 95% CI: 0.57–1.00, $P = 0.046$). However, high expression of PD-L1 was not significantly correlated with T stage (RR = 1.03, 95% CI: 0.94–1.13, $P = 0.546$) or TNM stage (RR = 0.90, 95% CI: 0.75–1.08, $P = 0.252$; Table 2).

3.4 Sensitivity analysis and publication bias

We performed a sensitivity analysis by sequentially deleting each study individually; the results indicated that the pooled RR was unaffected, as shown in Figure 6. Poten-
Figure 5: Forest plot of RRs and 95% CIs for the association between PD-L1 expression and HPV status. (A) Overall population; (B) stratified by ethnicity.

Figure 6: Sensitivity analysis for the association between PD-L1 expression and (A) sex; (B) grade; (C) N stage; and (D) HPV status.
4 Discussion

PD-L1, an immunoinhibitory receptor that was first described in 1992 by Ishida, is expressed in tumor cells and various types of immune cells, including activated B cells and T cells, macrophages, and dendritic cells [8, 39]. PD-L1 is an essential regulatory molecule in the immune system and is critical for the immune escape mechanisms of many types of cancer cells [40]. Overexpression of PD-L1 results in an immunosuppressive tumor microenvironment and prevents T cells from mediating cytolysis in numerous solid tumors. In some tumor cells, PD-L1 blocks the activation of T cells, exhausts T cells, triggers apoptosis in effector T cells, and impairs cytokine production, resulting in tumor growth [10-12].

PD-L1’s immune checkpoint response has been extensively studied and plays predominant roles in immune surveillance during tumor development and immune escape of cancer cells [41]. Immune checkpoint inhibitors, including nivolumab and pembrolizumab, have been approved to treat OSCC [42-46]. Despite the importance of the immune checkpoint, the clinicopathological effects of PD-L1 expression in patients with OSCC remain unclear. In this study, we performed a comprehensive and systematic analysis of the clinicopathological significant of PD-L1 expression in patients with OSCC. Our findings showed that high PD-L1 expression was significantly correlated with certain clinicopathological parameters, including female sex, lymph node metastasis (N1–N3), and advanced histological grade (poorly/moderately differentiated), in patients with OSCC.

In a previous study by Lin et al., high PD-L1 expression was found to be associated with low overall survival in patients with OSCC, and PD-L1 was highly expressed in women [30], consistent with our results. However, there was no significant correlation between high PD-L1 expression and sex in patients with OSCC in another study [47]. Thus, it remains unclear whether sex plays a role in influencing PD-L1 expression in patients with OSCC. In our study, the results demonstrated that high PD-L1 expression was significantly related to lymph node metastasis and advanced histological grade, consistent with some previous studies [19, 32]. These characteristics suggest that deviations in the PD-L1 pathway in malignant tumors are associated with more malignant clinical conditions, including tumor prognosis and progression. Moreover, we also investigated the association between HPV status and high PD-L1 expression in patients with OSCC; the results showed that high PD-L1 expression was significantly related to HPV-associated OSCC, consistent with previous studies [19]. However, no significant relationship was found between the high PD-L1 expression and HPV status in a different study [31], potentially because of the
limited sample size. Overall, our meta-analysis revealed that high PD-L1 expression was associated with several clinicopathological features in patients with OSCC, suggesting that PD-L1 may play a role in the clinical diagnosis and prognosis of OSCC.

There were several limitations to our current results. First, although 16 studies were selected, the sample size was relatively small, with only 1899 patients included in the evaluated studies. Second, the studies were published in Chinese and English, which may have resulted in publication bias; however, we detected no publication bias in this study. Third, significant heterogeneity was observed between studies; thus, we implemented this meta-analysis using random-effect models and sensitivity analysis to verify the reliability of our results.

5 Conclusions

Our current meta-analysis indicated that high PD-L1 expression in patients with OSCC was correlated with clinicopathological features, suggesting the potential roles of PD-L1 in the diagnosis and prognosis of patients with OSCC. To verify our results, further large-scale studies are needed.

Acknowledgements: None.

Ethical approval: Not applicable.

Funding: None.

Declaration of competing interests: None.

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