Research Article

Yong-Xin Cui, Xian-Shuang Su*

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 carcinom; 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

***Corresponding author: Xian-Shuang Su,** Department of Stomatology, The Second Hospital of Shandong University, Jinan, 250033, Chin, Email: xiansdstoma@yeah.net
Yong-Xin Cui, Department of Stomatology, The Second Hospital of Shandong University, Jinan, 250033, China

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 I^2 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

describing sex (1947 patients; female versus male), T stage (1768 patients; T3/T4 versus T1/T2), N stage (1663 patients; N1–N3 versus N0), M stage (581 patients; M1 versus M0), TNM stage (1351 patients; III/IV versus I/II), histological grade (1486 patients; poorly/moderately versus well differentiated), recurrence status (333 patients; yes versus no), and human papilloma virus (HPV) status (935 patients; positive versus negative) were included. Among the 16 studies, eight studies evaluated Asians, and eight studies evaluated Caucasians. The total sample size was 1989, ranging from 24 to 305. The included articles were published between 2011 and 2019. The expression level of PD-L1 in patients with OSCC was detected using immunohistochemistry. The quality of the included studies was evaluated by the NOS, and the scores for the included literature ranged from 6 to 9, indicating that the enrolled studies were of a relatively high quality. Detailed information for the included studies is presented in Table 1.

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

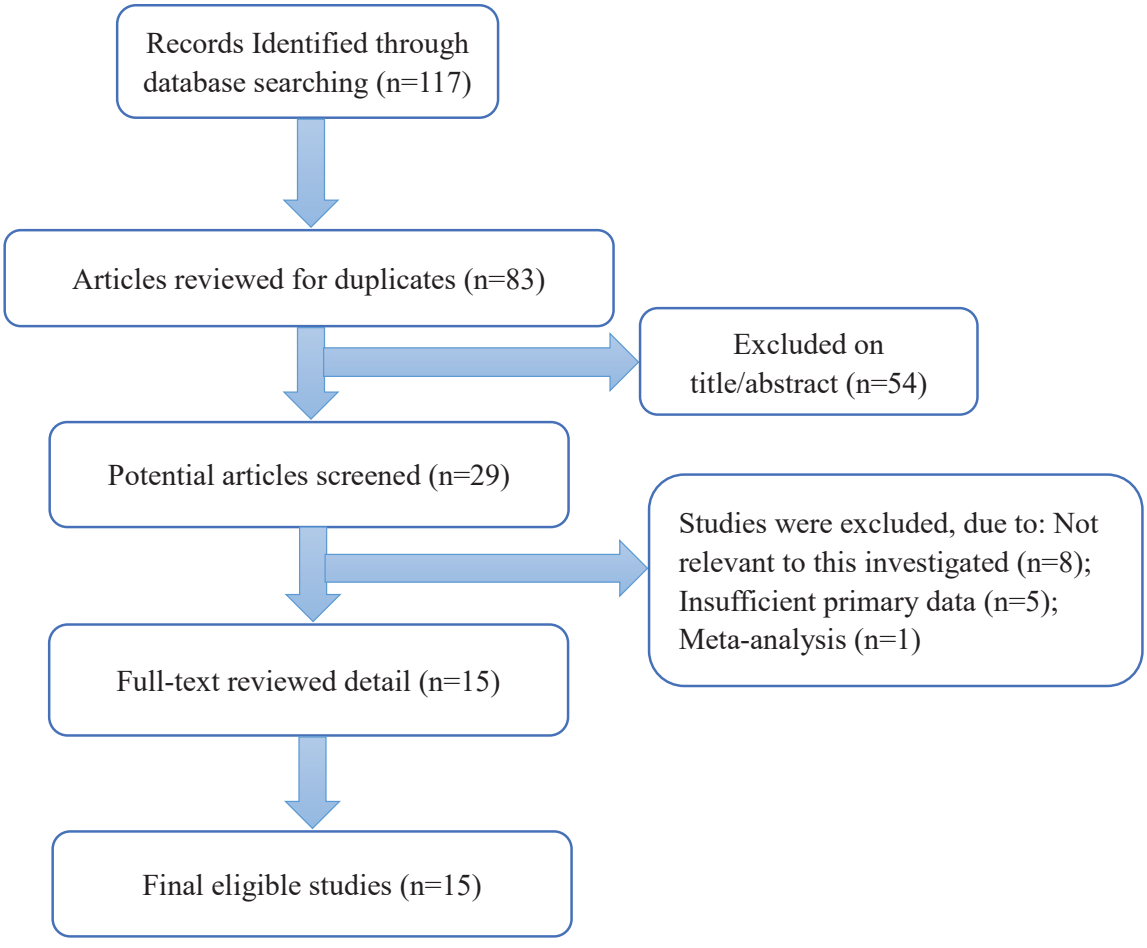

Figure 1: Flow chart of study identification.

Table 1: Characteristics of included studies.

Author	Year	Country	Ethnicity	Total (n)	TNM stage	PD-L1 expression			NOS
						Detection method	Positive	Negative	
Cho	2011	Korea	Asian	45	I-IV	IHC	26	19	6
Ukpo	2013	USA	Caucasian	181	I-IV	IHC	84	97	7
Lin	2015	China	Asian	305	I-IV	IHC	133	172	7
Oliveira-Costa	2015	Brazil	Caucasian	142	I-III	IHC	47	49	8
Hong	2016	Australia	Caucasian	99	I-IV	IHC	69	30	7
Kim	2015	Korea	Asian	133	I-IV	IHC	90	43	9
Ock(a)	2016	Korea	Asian	50	I-IV	IHC	32	18	8
Ock(b)	2016	Korea	Asian	91	I-IV	IHC	59	32	8
Satgunaseelan	2016	Australia	Caucasian	217	NA	IHC	40	177	9
Straub	2016	Germany	Caucasian	80	I-IV	IHC	36	44	7
Meulenaere	2017	Belgium	Caucasian	99	I-IV	IHC	22	72	8
Hirai	2017	Japan	Asian	24	I-IV	IHC	13	11	7
Kogashiwa	2017	Japan	Asian	84	I-IV	IHC	44	40	7
Troeltzsch	2016	Germany	Caucasian	88	I-IV	IHC	26	62	8
Hong	2019	Australia	Caucasian	214	I-IV	IHC	145	69	9
Sato	2019	Japan	Asian	137	I-IV	IHC	81	56	8

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

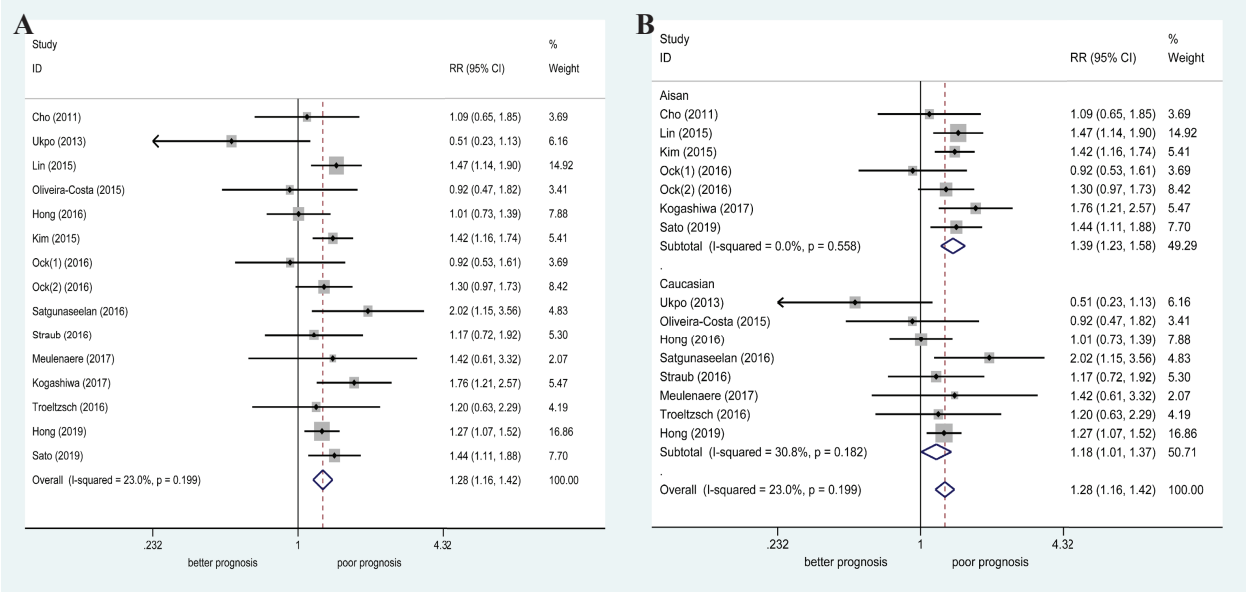

Figure 2: Forest plot of RRs and 95% CIs for the association between PD-L1 expression and sex. (A) Overall population; (B) stratified by ethnicity.

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).

Table 2: Correlation between clinical variables and PD-L1 expression in OSCC.

		Heterogeneity		Association			
Clinical variables	**Studies**	**I2**	**p-value**	**RR**	**95%CI**	**p-value**	**Egger's**
Gender	14	23	0.199	1.28	1.16-1.42	<0.001	0.203
Asian	6	0	0.558	1.39	1.23-1.58	<0.001	
Caucasian	8	30.8	0.182	1.18	1.01-1.37	0.039	
T stage	14	13.2	0.309	1.03	0.94-1.13	0.546	0.879
Asian	6	0	0.9	0.93	0.80-1.07	0.295	
Caucasian	8	29.1	0.196	1.12	0.98-1.27	0.094	
N stage	13	40.6	0.063	1.19	1.06-1.33	0.003	0.575
Asian	5	0	0.639	0.98	0.82-1.18	0.845	
Caucasian	8	40.4	0.109	1.34	1.16-1.56	<0.001	
M stage	3	68.7	0.041	1.64	1.01-2.66	0.044	0.12
TNM stage	9	49.6	0.037	0.9	0.75-1.08	0.252	0.264
Asian	5	63.5	0.018	0.92	0.70-1.20	0.537	
Caucasian	4	19.2	0.294	0.86	0.68-1.10	0.235	
Differentiation	11	0	0.624	1.16	1.01-1.33	0.034	0.942
Asian	4	0	0.72	1.16	0.94-1.43	0.168	
Caucasian	7	13	0.331	1.16	0.97-1.39	0.106	
Recurrence	4	0	0.585	0.75	0.57-1.00	0.046	0.291
HPV-Positive	7	59.6	0.015	1.38	1.14-1.68	0.001	0.953
Asian	2	0	0.713	1.22	1.02-1.46	0.011	
Caucasian	5	70.8	0.008	1.54	1.10-2.14	0.027	

PD-L1, programmed cell death ligand 1; CI, confidence interval; RR, relative risks.

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)

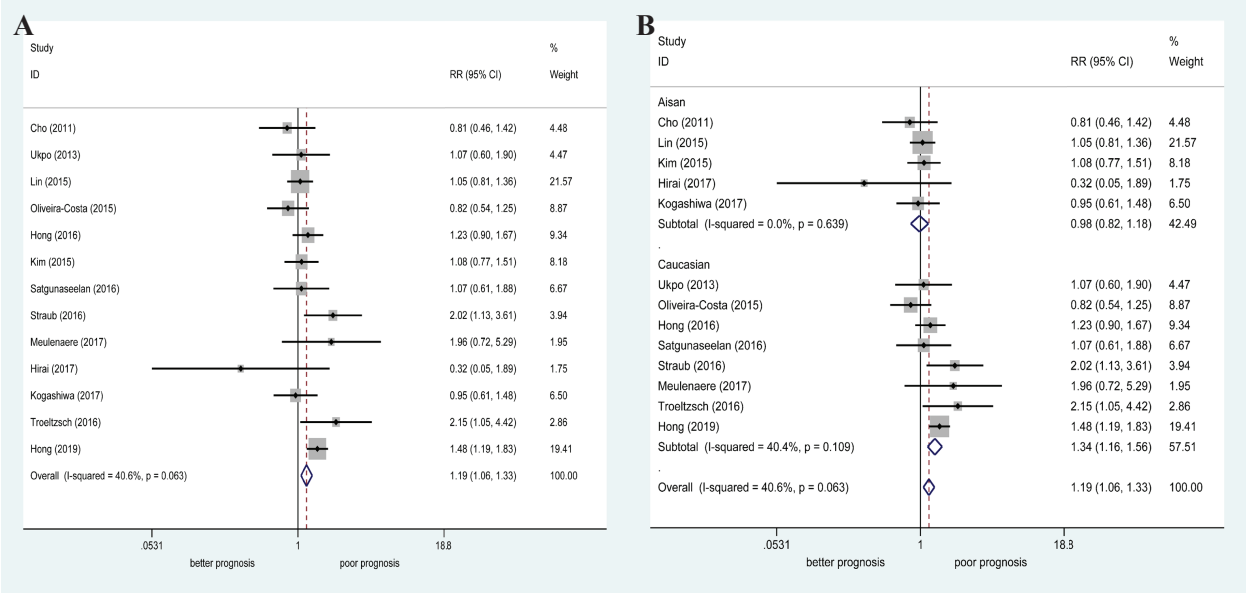

Figure 3: Forest plot of RRs and 95% CIs for the association between PD-L1 expression and N stage. (A) Overall population; (B) stratified by ethnicity.

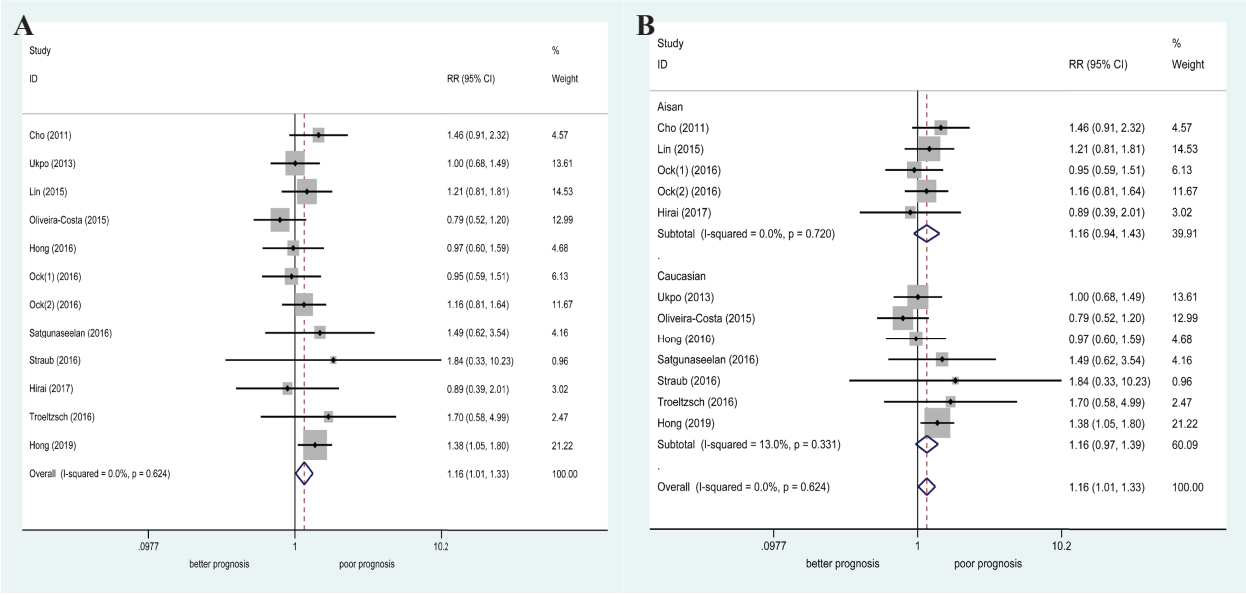

Figure 4: Forest plot of RRs and 95% CIs for the association between PD-L1 expression and histological grade. (A) Overall population; (B) stratified by ethnicity.

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-

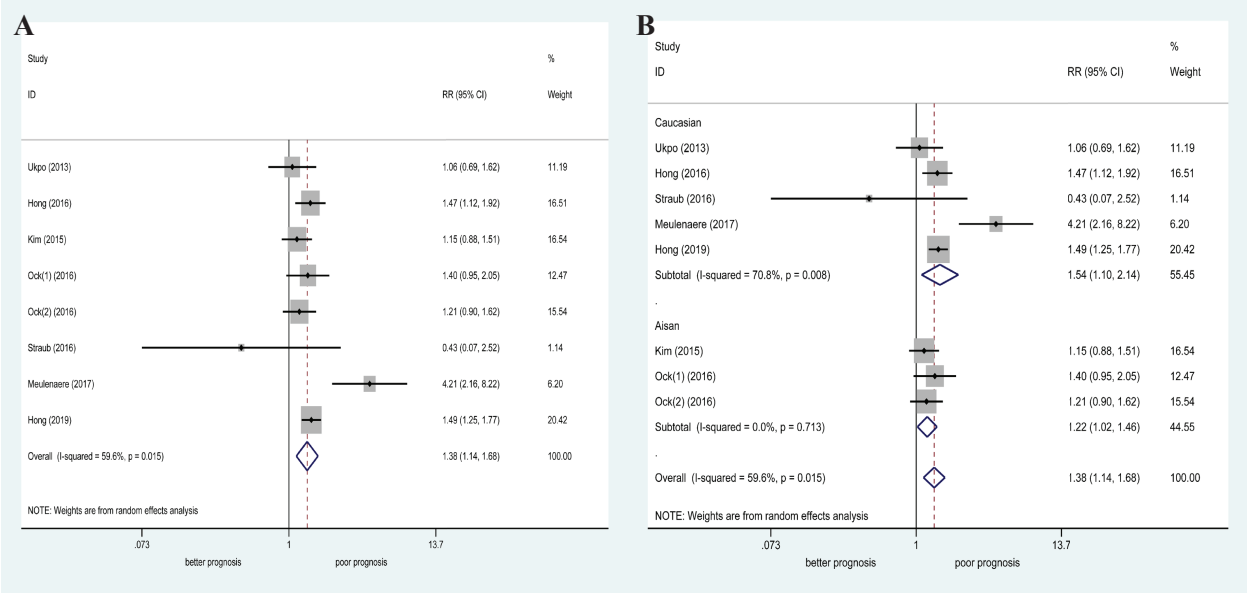

Figure 5: Forest plot of RRs and 95% CIs for the association between PD-L1 expression and HPV status. (A) Overall population; (B) stratified by ethnicity.

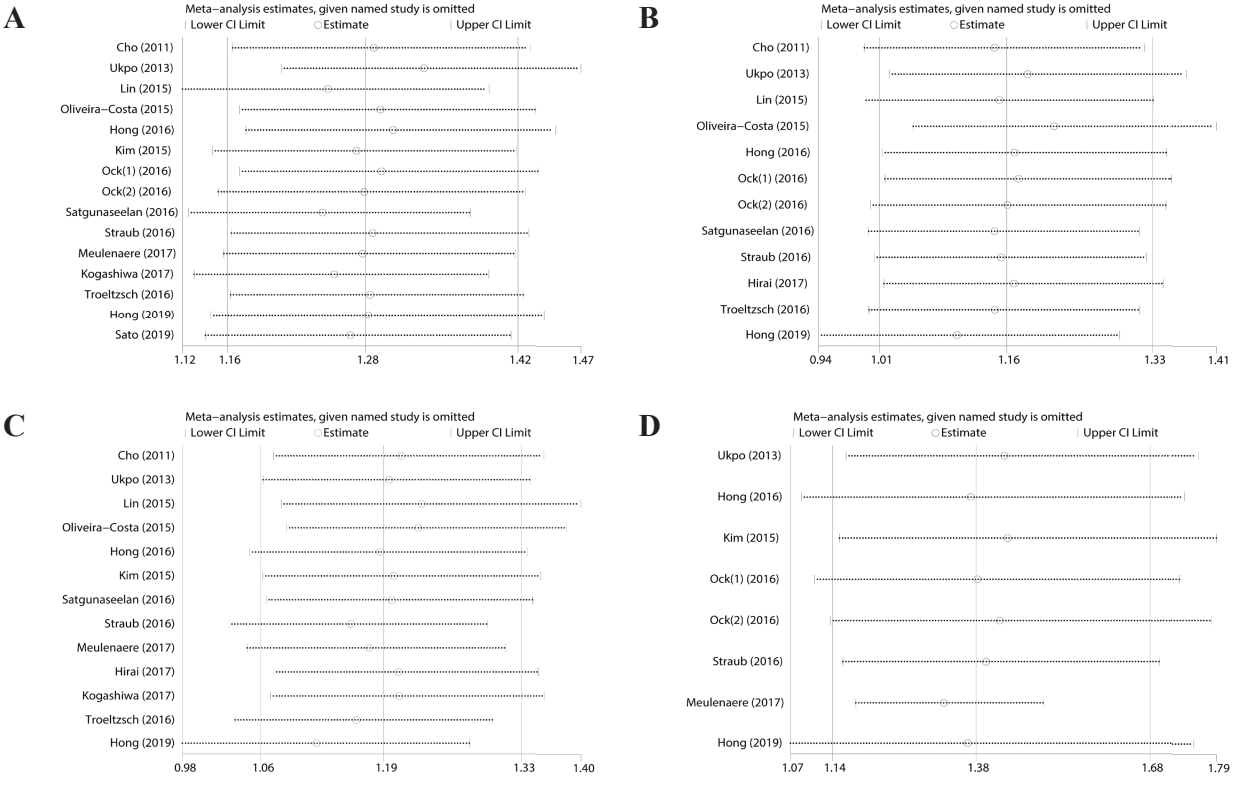

Figure 6: Sensitivity analysis for the association between PD-L1 expression and (A) sex; (B) grade; (C) N stage; and (D) HPV status.

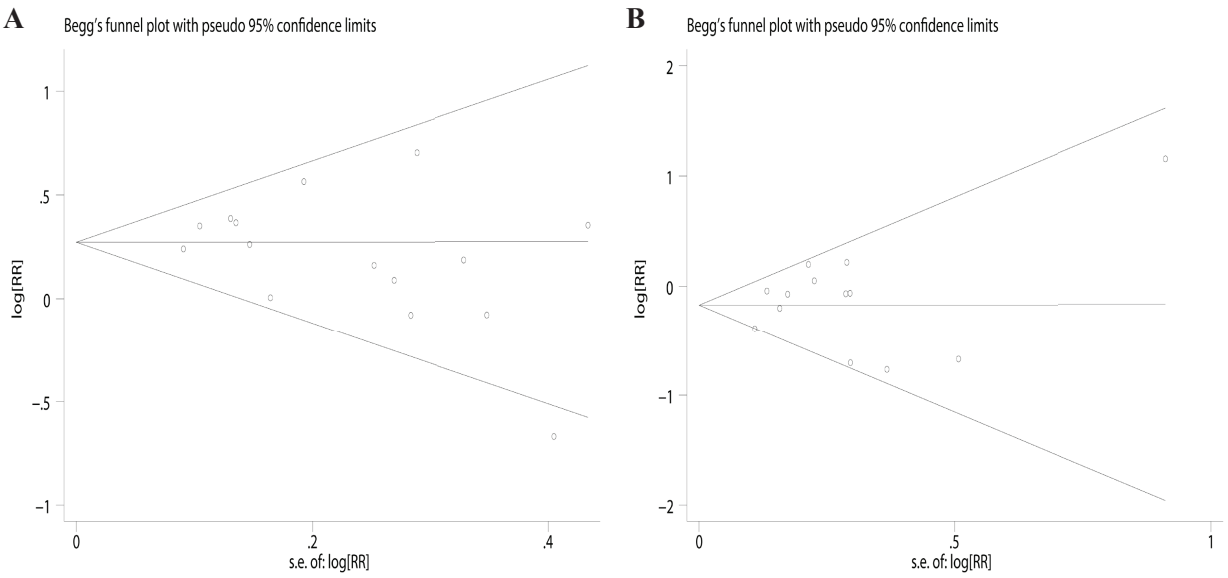

Figure 7: Begg's funnel plot for the association between PD-L1 expression and (A) sex and (B) N stage.

tial publication bias was evaluated using Egger's test and Begg's funnel. Funnel plots were largely symmetric, indicating no obvious publication bias, as shown in Figure 7 and Table 2.

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 1989 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.

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108

[2] Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell carcinoma--an update. CA Cancer J Clin. 2015;65(5):401-421

[3] Chinn SB, Myers JN. Oral Cavity Carcinoma: Current Management, Controversies, and Future Directions. J Clin Oncol. 2015;33(29):3269-3276

[4] Feller L, Lemmer JJJoct. Oral squamous cell carcinoma: epidemiology, clinical presentation and treatment. J Cancer Ther. 2012;3(04):263-268

[5] Patel SG, Shah JP. TNM staging of cancers of the head and neck: striving for uniformity among diversity. CA Cancer J Clin. 2005;55(4):242-258; quiz 261-2, 264

[6] Woolgar JA, Rogers S, West CR, Errington RD, Brown JS, Vaughan ED. Survival and patterns of recurrence in 200 oral cancer patients treated by radical surgery and neck dissection. Oral oncol. 1999;35(3):257-265

[7] Chamoto K, Al-Habsi M, Honjo T. Role of PD-1 in Immunity and Diseases. Curr Top Microbiol Immunol. 2017;410:75-97

[8] Hansen JD, Du Pasquier L, Lefranc MP, Lopez V, Benmansour A, Boudinot P. The B7 family of immunoregulatory receptors: a comparative and evolutionary perspective. Mol Immunol. 2009;46(3):457-472

[9] Wang P-F, Chen Y, Song S-Y, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. Front Pharmacol. 2017;8:730

[10] Ceeraz S, Nowak EC, Noelle RJ. B7 family checkpoint regulators in immune regulation and disease. Trends Immunol. 2013;34(11):556-563

[11] Ni L, Dong C. New checkpoints in cancer immunotherapy. Immunol Rev. 2017;276(1):52-65

[12] Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348(6230):56-61

[13] Zhuan-Sun Y, Huang F, Feng M, et al. Prognostic value of PD-L1 overexpression for pancreatic cancer: evidence from a meta-analysis. Onco Targets Ther. 2017;10:5005-5012

[14] Wang A, Wang HY, Liu Y, et al. The prognostic value of PD-L1 expression for non-small cell lung cancer patients: a meta-analysis. Eur J Surg Oncol. 2015;41(4):450-456

[15] Li C, Shen Z, Zhou Y, Yu W. Independent prognostic genes and mechanism investigation for colon cancer. Biol Res. 2018;51(1):10

[16] Gu L, Chen M, Guo D, et al. PD-L1 and gastric cancer prognosis: A systematic review and meta-analysis. PloS one. 2017;12(8):e0182692

[17] Zhang M, Sun H, Zhao S, et al. Expression of PD-L1 and prognosis in breast cancer: a meta-analysis. Oncotarget. 2017;8(19):31347-31354

[18] Sato F, Ono T, Kawahara A, et al. Prognostic impact of p16 and PD-L1 expression in patients with oropharyngeal squamous cell carcinoma receiving a definitive treatment. J Clin Pathol. 2019;72(8):542-549

[19] Hong AM, Ferguson P, Dodds T, et al. Significant association of PD-L1 expression with human papillomavirus positivity and its prognostic impact in oropharyngeal cancer. Oral Oncol. 2019;92:33–39

[20] Troeltzsch M, Woodlock T, Pianka A, et al. Is There Evidence for the Presence and Relevance of the PD-1/PD-L1 Pathway in Oral Squamous Cell Carcinoma? Hints From an Immunohistochemical Study. J Oral Maxillofac Surg. 2017;75(5):969-977

[21] Kogashiwa Y, Yasuda M, Sakurai H, et al. PD-L1 Expression Confers Better Prognosis in Locally Advanced Oral Squamous Cell Carcinoma. Anticancer Res. 2017;37(3):1417-1424

[22] Hirai M, Kitahara H, Kobayashi Y, et al. Regulation of PD-L1 expression in a high-grade invasive human oral squamous cell carcinoma microenvironment. Int J Oncol. 2017;50(1):41-48

[23] De Meulenaere A, Vermassen T, Aspeslagh S, et al. Tumor PD-L1 status and CD8(+) tumor-infiltrating T cells: markers of improved prognosis in oropharyngeal cancer. Oncotarget. 2017;8(46):80443-80452

[24] Straub M, Drecoll E, Pfarr N, et al. CD274/PD-L1 gene amplification and PD-L1 protein expression are common

events in squamous cell carcinoma of the oral cavity. Oncotarget. 2016;7(11):12024-12034
[25] Satgunaseelan L, Gupta R, Madore J, et al. Programmed cell death-ligand 1 expression in oral squamous cell carcinoma is associated with an inflammatory phenotype. Pathology. 2016;48(6):574-580
[26] Ock CY, Kim S, Keam B, et al. PD-L1 expression is associated with epithelial-mesenchymal transition in head and neck squamous cell carcinoma. Oncotarget. 2016;7(13):15901-15914
[27] Kim HS, Lee JY, Lim SH, et al. Association Between PD-L1 and HPV Status and the Prognostic Value of PD-L1 in Oropharyngeal Squamous Cell Carcinoma. Cancer Res Treat. 2016;48(2):527-536
[28] Hong AM, Vilain RE, Romanes S, et al. PD-L1 expression in tonsillar cancer is associated with human papillomavirus positivity and improved survival: implications for anti-PD1 clinical trials. Oncotarget. 2016;7(47):77010-77020
[29] Oliveira-Costa JP, de Carvalho AF, da Silveira da GG, et al. Gene expression patterns through oral squamous cell carcinoma development: PD-L1 expression in primary tumor and circulating tumor cells. Oncotarget. 2015;6(25):20902-20920
[30] Lin YM, Sung WW, Hsieh MJ, et al. High PD-L1 Expression Correlates with Metastasis and Poor Prognosis in Oral Squamous Cell Carcinoma. PloS one. 2015;10(11):e0142656
[31] Ukpo OC, Thorstad WL, Lewis JS, Jr. B7-H1 expression model for immune evasion in human papillomavirus-related oropharyngeal squamous cell carcinoma. Head Neck Pathol. 2013;7(2):113-121
[32] Cho YA, Yoon HJ, Lee JI, Hong SP, Hong SD. Relationship between the expressions of PD-L1 and tumor-infiltrating lymphocytes in oral squamous cell carcinoma. Oral oncology. 2011;47(12):1148-1153
[33] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-269, w264
[34] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [cited 2019 Sep 20]
[35] DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015;45(Pt A):139-145
[36] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-748
[37] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-1101
[38] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634
[39] Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J. 1992;11(11):3887-3895
[40] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264.
[41] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol. 2014;27:16-25
[42] Polverini PJ, D'Silva NJ, Lei YL. Precision Therapy of Head and Neck Squamous Cell Carcinoma. J Dent Res. 2018;97(6):614-621
[43] Saâda-Bouzid E, Defaucheux C, Karabajakian A, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Ann Oncol. 2017;28(7):1605–1611.
[44] Specenier P. Nivolumab in squamous cell carcinoma of the head and neck. Expert Rev Anticancer Ther. 2018;18(5):409-420
[45] Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer. 2018;119(2):153–159.
[46] Tahara M, Muro K, Hasegawa Y, et al. Pembrolizumab in Asia-Pacific patients with advanced head and neck squamous cell carcinoma: Analyses from KEYNOTE-012. Cancer Sci. 2018;109(3):771-776
[47] Chen XJ, Tan YQ, Zhang N, He MJ, Zhou G. Expression of programmed cell death-ligand 1 in oral squamous cell carcinoma and oral leukoplakia is associated with disease progress and CD8+ tumor-infiltrating lymphocytes. Pathol Res Pract. 2019;215(6):152418