Prognostic value of immune checkpoint molecules in head and neck cancer: a meta-analysis

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ABSTRACT

Immune checkpoint molecules are important targets in cancer immunotherapy, but their association with prognosis in patients with head and neck cancer is controversial. In this meta-analysis, we searched for 12 immune checkpoint molecules in the PubMed, Embase and Cochrane Library databases and retrieved 52 studies with 7127 participants. Among the molecules included in the search, indoleamine 2, 3-dioxygenase (IDO), programmed death ligand 1 (PD-L1), and programmed death 1 (PD-1) met the inclusion criteria for further analysis. Higher expression of IDO was associated with poorer overall survival in head and neck cancer patients (P = 0.011), but higher expression of PD-L1 correlated with better overall survival specifically in nasopharyngeal carcinoma patients (P = 0.01). In a sensitivity analysis, higher PD-L1 expression correlated with better progression-free survival (P = 0.043), and was associated with better overall survival in Caucasian subjects (P = 0.02), nasopharyngeal carcinoma patients (P = 0.015), and studies with small sample sizes (P = 0.001). PD-1 had no prognostic significance. There was no publication bias affecting the results. Thus, among the immune checkpoint molecules, IDO and PD-L1 are potential prognostic predictors in head and neck cancer.

INTRODUCTION

Head and neck cancer (HNC) is the sixth most common malignancy worldwide [1]. Most patients exhibit advanced-stage disease, including regional lymph node involvement, and 10% of patients have distant metastases [2]. The traditional treatment options for HNC are surgery, radiotherapy and chemotherapy [3], which have severe adverse effects. Furthermore, some patients do not benefit much from these treatments, and are likely to relapse. Anatomic complexities often lead to malfunctions in speaking, swallowing and breathing after treatments, hampering patients’ long-term quality of life [4]. Although there have been certain advances in treatment, the overall survival of HNC patients is still unsatisfactory, and the five-year survival rate is less than 50% [5-7].

Immunosuppressive patients are prone to suffer from HNC [8], although the predominant causes of HNC are tobacco and alcohol consumption [4] and viral infections [9, 10]. Among the functions of the immune cells, immune checkpoint activity has been reported to be involved in the surveillance of tumor development and progression [11]. Immune checkpoint molecules including programmed death 1 (PD-1) [12, 13], indoleamine 2, 3-dioxygenase (IDO) [14, 15], B7-H3 [16, 17], lymphocyte activation gene 3 (LAG-3) [18], cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [19], programmed death ligand 2 (PD-L2) [20], V-
domain Ig suppressor of T cell activation (VISTA) [21], B7-H4 [22] and programmed death ligand 1 (PD-L1) [23-25] have been used as markers to evaluate the prognosis of HNC. However, the survival rates of patients with high expression of immune checkpoint molecules have differed according to the overexpressed molecule.

In the present study, we performed a systematic review of the available literature on this topic in PubMed, Embase and the Cochrane Library. Then, we conducted a meta-analysis of the survival rates (including overall survival [OS], disease-free survival [DFS], progression-free survival [PFS], disease-specific survival [DSS] and distant metastases-free survival [DMFS]) of patients expressing different levels of immune checkpoint molecules.

RESULTS

Study characteristics

The characteristics of the included studies are shown in Table 1. There were 52 prospective studies comparing contemporary series of patients (level of evidence: 3b) in 51 articles. These studies included 7127 patients and met the criteria for meta-analysis. The literature selection procedure is presented in Figure 1. The included articles were evaluated by the Newcastle–Ottawa Scale (NOS; Supplementary Table 1), and all the articles were published between 2010 and 2018. Roughly half of the studies were conducted in Asia (n=23), while the remainder were conducted in Europe (n=18), North and South America (n=6), Oceania (n=4) and Africa (n=1). Thus, the samples included in this meta-analysis covered most of the continents of the world. In terms of the immune checkpoint molecules, the majority of the studies evaluated PD-L1 (n=40), while the rest assessed PD-1 (n=8) and IDO (n=4). The sample sizes of the included studies ranged from 38 to 517. With reference to the mean value of all the samples, 17 studies were considered to have a large sample size (n > 139), while 35 had a small sample size (n ≤ 139). Forty-three studies explored the prognostic value of their chosen immune checkpoint molecule for OS, 19 for DFS, 6 for PFS, 5 for DSS and 3 for DMFS.

Methodological quality of the included studies

The quality of the included studies was generally high. Most of the studies mentioned the length of the follow-up period, and the majority provided adequate follow-up period.
Table 1. Characteristics of included studies.

| Author and year | Target | Country / Region | Ethnicity | Tumor location | Sample size | Gender M/F | Cut-off value | Detection method | TNM stage | Outcome | HR estimation | Study design | NOS score |
|-----------------|--------|------------------|-----------|----------------|-------------|------------|--------------|-----------------|------------|---------|---------------|-------------|-----------|
| Ahn et al. 2017[23] | PD-L1 | Korea | Asian | OSCC | 68 | 45/23 | Grade > 1 | IHC | I-IV | OS DFS | reported | P | 7 |
| Badoual et al. 2013[12] | PD-1 | France | Caucasia | HNSCC | 64 | NA | > median | IF | I-IV | OS | reported | P | 6 |
| Balemans et al. 2017[36] | PD-L1 | Germany | Caucasia | HNSCC | 161 | 131/30 | > 5% | IHC | I-IV | OS | DMFS | reported | P | 7 |
| Ben-Haj-Ayed et al. 2016[14] | IDO | Tunisia | Caucasia | NPC | 71 | 48/23 | > median | IHC | I-IV | OS DFS | reported | P | 7 |
| Birtalan et al. 2017[24] | PD-L1 | Hungary | Caucasia | HNSCC | 106 | 90/16 | Score > 0% | IHC | I-IV | DSS | reported | P | 6 |
| Budezies et al. 2016[25] | PD-L1 | Germany | Caucasia | HNSCC | 517 | NA | > median | qRT-PCR | NA | OS DFS | reported | P | 5 |
| Chan et al. 2017[46] | PD-L1 | USA | Caucasia | NPC | 161 | 117/44 | ≥ 1% | IHC | I-IV | OS PFS | reported | P | 6 |
| Chang et al. 2017[47] | PD-L1 | Philippines | Asian | NPC | 56 | 43/13 | > 1% | IHC | I-IV | OS | reported | P | 5 |
| Chen et al. 2015[48] | PD-L1 | Taiwan | Asian | OSCC | 218 | 145/73 | > 5% | IHC | I-IV | OS | reported | P | 7 |
| Chen et al. 2017[49] | PD-L1 | China | Asian | HNSCC | 496 | NA | > 5% | qRT-PCR | I-IV | OS | reported | P | 7 |
| Cho et al. 2011[50] | PD-L1 | Korea | Asian | OSCC | 45 | 32/13 | Grade > 1 | IHC | I-IV | OS | estimated | P | 6 |
| De Meulenaere et al. 2017[51] | PD-L1 | Belgium | Caucasia | OSCC | 99 | 82/17 | > 1% | IHC | I-IV | OS DFS | reported | P | 6 |
| Fang et al. 2014[52] | PD-L1 | China | Asian | NPC | 139 | 113/26 | > 35% | IHC | I-IV | DFS | estimated | P | 6 |
| Feng et al. 2017[53] | PD-L1 | USA | Caucasia | OSCC | 119 | 74/45 | < 30 μm | IHC | I-IV | OS | estimated | P | 6 |
| Fiedler et al. 2018[54] | PD-L1 | Germany | Caucasia | HNSCC | 82 | 73/9 | > 5% | IHC | I-IV | OS | reported | P | 7 |
| Hanna et al. 2018[37] | PD-L1 | USA | Caucasia | OSCC | 81 | 49/32 | > 10% | IHC | I-IV | OS | reported | P | 7 |
| Hong et al. 2016[55] | PD-L1 | Australia | Caucasia | OSCC | 99 | 79/20 | > 25% | IHC | I-IV | OS | reported | P | 6 |
| Hsu et al. 2010[13] | PD-1 | Taiwan | Asian | NPC | 46 | 39/7 | > median | IHC | NA | OS DFS | reported | P | 4 |
| Study                        | Region | Race         | Tumor Type | Cases | Tumor Site | Location | IHC Score | Stage | OS/DFS Data                                      | OS/DFS Data | P |
|------------------------------|--------|--------------|------------|-------|------------|----------|-----------|-------|-----------------------------------------------|-----------------------------------------------|---|
| Kansy et al. 2017            | PD-1   | Germany      | Caucasia   | 56    | HNSCC      | NA       | NA        | NA    | FACS I-IV DFS reported                         | NA DFS reported                             | 6 |
| Kim et al. 2016              | PD-1   | Korea        | Asian      | 402   | HNSCC      | 302/100  | > 5%      | IHC   | OS DFS reported                                | IHC OS DFS reported                           | 6 |
| Kim et al. 2016              | PD-1   | Korea        | Asian      | 133   | OSCC       | 120/13   | > 5%      | IHC   | OS reported                                    | IHC OS reported                              | 7 |
| Kogashiwa et al. 2017        | PD-L1  | Japan        | Asian      | 84    | OSCC       | 57/27    | > 5%      | IHC   | OS PFS reported                                | IHC OS PFS reported                           | 7 |
| Laimer et al. 2011           | IDO    | Austria      | Caucasia   | 88    | OSCC       | 67/21    | > 4       | IHC   | OS reported                                    | IHC OS reported                              | 7 |
| Larbcharoensub et al. 2018   | PD-L1  | Thailand     | Asian      | 114   | NPC        | 77/67    | ≥ 5%      | IHC   | OS estimated                                   | IHC OS estimated                              | 7 |
| Lee et al. 2016              | PD-L1  | Hong Kong    | Asian      | 104   | NPC        | 85/19    | > 1       | IHC   | PFS DMFS OS reported                           | PFS DMFS OS reported                          | 5 |
| Li et al. 2017               | PD-L1  | China        | Asian      | 62    | NPC        | 40/14    | > 20%     | IHC   | DFS reported                                   | IHC DFS reported                              | 5 |
| Lin et al. 2015              | PD-L1  | Taiwan       | Asian      | 305   | OSCC       | 236/69   | > 1       | IHC   | OS reported                                    | IHC OS reported                              | 6 |
| Muller et al. 2017           | PD-L1  | Germany      | Caucasia   | 293   | HNSCC      | 82/16    | Score ≥ 1 | IHC   | OS reported                                    | IHC OS reported                              | 6 |
| Ock et al. 2016              | PD-L1  | South Korea  | Asian      | 141   | HNSCC      | 142/53   | ≥ 5%      | IHC   | OS reported                                    | IHC OS reported                              | 6 |
| Oguejiofor et al. 2017        | PD-L1  | UK           | Caucasia   | 124   | OPSCC      | NA       | > 5%      | IHC   | OS reported                                    | IHC OS reported                              | 7 |
| Oliveira-Costa et al. 2015   | PD-L1  | Brazil       | Caucasia   | 142   | OSCC       | 125/17   | ≥ 5%      | IHC   | I-III DSS reported                             | IHC I-III DSS reported                        | 6 |
| Ono et al. 2017              | PD-L1  | Japan        | Asian      | 83    | HPSCC      | 79/4     | ≥ 1%      | IHC   | III-IV OS PFS reported                         | III-IV OS PFS reported                        | 6 |
| Ono et al. 2018              | PD-L1  | Japan        | Asian      | 66    | NPC        | 54/12    | ≥ 5%      | IHC   | OS PFS reported                                | IHC OS PFS reported                           | 7 |
| Ou et al. 2017               | PD-L1  | France       | Caucasia   | 38    | HNSCC      | NA       | ≥ 1%      | IHC   | III-IV OS PFS estimated                        | III-IV OS PFS estimated                       | 7 |
| Qu et al. 2018               | PD-L1  | China        | Asian      | 96    | NPC        | 72/24    | > 10%     | IHC   | I-IV DMFS estimated                            | IHC I-IV DMFS estimated                       | 6 |
| Riobello et al. 2018         | PD-L1  | Spain        | Caucasia   | 53    | SSCC       | 37/16    | ≥ 5%      | IHC   | I-IV OS DFS DSS reported                      | IHC I-IV OS DFS DSS reported                  | 5 |
| Roper et al. 2017            | PD-L1  | Australia    | Caucasia   | 74    | HNSCC      | 64/10    | > 5%      | IHC   | NA DFS reported                                | IHC NA DFS reported                           | 6 |
| Satgunaseelan et al. 2019    | PD-L1  | Australia    | Caucasia   | 217   | OSCC       | 130/87   | Score ≥ 1 | IHC   | DSS estimated                                  | IHC DSS estimated                             | 6 |
| Year | Country | Race | Tumor Site | Cases | Positive Cases | Expression | Method | Staining | Stage | Follow-up | Reporting | Study Design | Quality Assessment |
|------|---------|------|------------|-------|---------------|------------|--------|----------|--------|----------|-----------|-------------|----------------------|
| 2016 | Austria | Caucasian | HNSCC | 129 | 97/28 | > 5% | IHC | I-IV | OS | DFS | reported | P | 7 |
| 2016 | Finland | Caucasian | OSCC | 58 | 29/29 | > 0 | IHC | I-III | OS | reported | P | 6 |
| 2016 | Australia | Caucasian | OSCC | 190 | 157/33 | ≥ 5% | IHC | I-IV | OS | reported | P | 7 |
| 2016 | USA | Caucasian | OPSCC | 97 | 81/16 | Score > 1 | IHC | I-IV | OS | reported | P | 7 |
| 2016 | Greece | Caucasian | HNSCC | 113 | 75/19 | NA | qRT-PCR | I-IV | OS | DFS | reported | P | 5 |
| 2016 | Germany | Caucasian | OSCC | 80 | 54/26 | > 5% | IHC | FISH | I-IV | OS | DFS | estimated | P | 7 |
| 2016 | China | Asian | NPC | 96 | NA | NA | IHC | NA | OS | DFS | estimated | P | 6 |
| 2016 | USA | Caucasian | OPSCC | 181 | 162/19 | > 5% | IHC | I-IV | OS | DFS | reported | P | 7 |
| 2016 | Greece | Caucasian | LSCC | 260 | 249/11 | > 59th percentile of AQUA score | IHC | I-IV | OS | DFS | reported | P | 7 |
| 2016 | China | Asian | LSCC | 187 | 179/8 | NA | IHC | I-IV | OS | DFS | reported | P | 6 |
| 2015 | China | Asian | NPC | 139 | 113/26 | H-score: PD-L1 > 0, PD-L1 > 35 | IHC | I-IV | DFS | estimated | P | 7 |
| 2015 | China | Asian | NPC | 85 | 63/22 | Score > 2 | IHC | I-IV | OS | estimated | P | 6 |
| 2017 | China | Asian | NPC | 209 | 150/59 | ≥ 5% | IHC | I-IV | OS | DFS | reported | P | 7 |

PD-L1: programmed death ligand 1; PD-1: programmed death 1; IDO: indoleamine 2, 3-dioxygenase; M/F: male/female; NA: not available; OSCC: oral squamous cell carcinoma; HNSCC: head and neck squamous cell carcinoma; NPC: nasopharyngeal carcinoma; OPSCC: oropharyngeal squamous cell carcinoma; HPSCC: hypopharyngeal squamous cell carcinoma; SSCC: sinonasal squamous cell carcinoma; LSCC: laryngeal squamous cell carcinoma; cut-off value: the value that can be diagnosed as positive/high expression of an immune checkpoint molecule; AQUA: automated quantitative analysis; IHC: immunohistochemistry; IF: immunofluorescence; qRT-PCR: quantitative reverse transcription polymerase chain reaction; FACS: fluorescence-activated cell sorting; FISH: fluorescence in situ hybridization; OS: overall survival; DFS: disease-free survival; DMFS: distant metastases-free survival; DSS: disease-specific survival; PFS: progression-free survival; P: prospective; NOS: Newcastle–Ottawa Quality Assessment Scale.
up data for more than five years. Nevertheless, almost none of the prospective studies had an exposed cohort that sufficiently represented the general characteristics of the population in the community, as this factor was not considered in the study design. None of the studies were designed with adequate comparability of cohorts, due to their failure to match exposed and non-exposed individuals and/or adjust for confounders. Methods for handling missing data and intention-to-treat analysis were not adequately described in the majority of the studies.

**Immune checkpoint molecule expression and prognosis of HNC patients**

Forty-three studies with 6225 patients reported the relationship between OS and at least one of the three immune checkpoint molecules in HNC. The expression...
Table 2. Results of the meta-analysis on the prognostic effects of immune checkpoint molecules in HNC patients.

| Variable               | Study no. | Sample size | HR (95% CI)       | P value | Heterogeneity |
|------------------------|-----------|-------------|--------------------|---------|---------------|
|                        |           |             |                    |         | I²            | P value |
| OS                     | Overall   | 43          | 6225               | 0.964 (0.791-1.175) | 0.714 | 74.8%         | <0.001 |
| Immune checkpoint molecules | PD-L1    | 32          | 4854               | 0.874 (0.711-1.073) | 0.197 | 72.8%         | <0.001 |
|                        | PD-1      | 7           | 967                | 0.926 (0.424-2.025) | 0.848 | 76.7%         | <0.001 |
|                        | IDO       | 4           | 404                | 2.197 (1.199-4.023) | 0.011 | 59.8%         | 0.059  |
| Ethnicity              | Asian     | 19          | 2938               | 0.923 (0.651-1.307) | 0.650 | 77.1%         | <0.001 |
|                        | Caucasian | 24          | 3287               | 0.995 (0.779-1.270) | 0.965 | 73.8%         | <0.001 |
| Tumor location         | OSCC      | 13          | 1477               | 0.879 (0.586-1.317) | 0.532 | 85.0%         | <0.001 |
|                        | NPC       | 10          | 1008               | 0.862 (0.624-1.603) | 0.383 | 33.7%         | 0.139  |
|                        | OPSCC     | 4           | 592                | 0.878 (0.532-1.450) | 0.611 | 47.1%         | 0.129  |
|                        | HPSCC     | 1           | 83                 | 1.300 (0.700-2.415) | 0.407 | -             | -      |
|                        | SSCC      | 1           | 53                 | 1.355 (0.739-2.485) | 0.326 | -             | -      |
|                        | LS SCC    | 2           | 447                | 1.517 (0.252-9.126) | 0.649 | 91.4%         | 0.001  |
| Sample size            | Large     | 14          | 3721               | 1.044 (0.803-1.356) | 0.748 | 74.0%         | <0.001 |
|                        | Small     | 29          | 2504               | 0.915 (0.687-1.220) | 0.546 | 74.3%         | <0.001 |
| DFS                    | Overall   | 19          | 2901               | 1.097 (0.733-1.642) | 0.652 | 92.5%         | <0.001 |
| Inhibitory immune checkpoint molecules | PD-L1    | 13          | 2010               | 0.874 (0.523-1.459) | 0.606 | 94.1%         | <0.001 |
|                        | IDO       | 2           | 258                | 1.725 (0.611-4.869) | 0.303 | 59.5%         | 0.116  |
|                        | PD-1      | 4           | 633                | 1.931 (0.716-5.211) | 0.194 | 87.5%         | <0.001 |
| Ethnicity              | Asian     | 8           | 1252               | 1.131 (0.506-2.533) | 0.764 | 93.6%         | <0.001 |
|                        | Caucasian | 11          | 1649               | 1.060 (0.760-1.479) | 0.731 | 73.9%         | <0.001 |
| Tumor location         | OSCC      | 3           | 247                | 0.609 (0.208-1.788) | 0.367 | 70.8%         | 0.033  |
|                        | NPC       | 6           | 666                | 1.339 (0.581-3.085) | 0.494 | 92.5%         | <0.001 |
|                        | SSCC      | 1           | 53                 | 1.834 (0.955-3.522) | 0.068 | -             | -      |
|                        | OPSCC     | 1           | 181                | 1.090 (0.783-1.518) | 0.610 | -             | -      |
|                        | LS SCC    | 2           | 447                | 1.282 (0.242-6.783) | 0.770 | 85.9%         | 0.008  |
| Sample size            | Large     | 6           | 1756               | 0.844 (0.595-1.198) | 0.343 | 75.5%         | <0.001 |
|                        | Small     | 13          | 1145               | 1.225 (0.764-1.963) | 0.399 | 88.9%         | <0.001 |
| PFS                    | Overall   | 6           | 545                | 0.996 (0.585-1.685) | 0.989 | 68.5%         | 0.007  |
| Inhibitory immune checkpoint molecules | PD-L1    | 6           | 545                | 0.891 (0.565-1.404) | 0.989 | 68.5%         | 0.007  |
| Ethnicity              | Asian     | 3           | 233                | 0.846 (0.492-1.455) | 0.744 | 48.3%         | 0.144  |
|                        | Caucasian | 3           | 312                | 1.218 (0.372-3.993) | 0.546 | 82.7%         | 0.003  |
| Tumor location         | NPC       | 2           | 227                | 0.762 (0.506-1.149) | 0.195 | 0.0%          | 0.935  |
|                        | OSCC      | 1           | 84                 | 0.576 (0.308-1.076) | 0.084 | -             | -      |
|                        | HPSCC     | 1           | 83                 | 1.350 (0.740-2.463) | 0.328 | -             | -      |
| Sample size            | Large     | 1           | 161                | 0.770 (0.480-1.235) | 0.279 | -             | -      |
|                        | Small     | 5           | 384                | 1.067 (0.536-2.125) | 0.853 | 73.0%         | 0.005  |
| DSS                    | Overall   | 5           | 699                | 0.779 (0.330-1.839) | 0.569 | 84.7%         | <0.001 |
| DMFS                   | Overall   | 3           | 361                | 0.599 (0.346-1.035) | 0.066 | 0.0%          | 0.604  |
of these molecules was detected mainly at the protein level, except for three studies that evaluated PD-L1 mRNA levels. Overexpression was defined based on cut-off criteria that differed among the studies (as presented in Table 1). When the data for all three immune checkpoint molecules were pooled, there was no significant relationship between the overexpression of these molecules and OS (hazard ratio [HR] = 0.964; 95% confidence interval [CI]: 0.791-1.175, \( P = 0.714 \); Table 2), and there was obvious overall heterogeneity (I\(^2\) = 74.8%, \( P_h < 0.001 \); Figure 2). Similar results were obtained for DFS, PFS, DSS and DMFS.

**Subgroup analyses**

Subgroup analyses stratified according to the immune checkpoint molecule, patient ethnicity, tumor location and sample size were performed to detect potential sources of heterogeneity. In the stratification based on the immune checkpoint molecule (Figure 2), poorer OS was consistently found in patients with higher levels of IDO (Table 2), correlating with a poorer prognosis (HR = 2.197, 95% CI: 1.199-4.023, \( P = 0.011 \); Figure 2). However, no obvious trend in DFS was found according to IDO expression (Table 2).

The same hierarchical strategy was used to evaluate the studies of PD-L1 (Table 3). Among the immune checkpoint molecules, PD-L1 was the focus of the largest percentage of studies, as 32 studies with 4854 patients reported the relationship between PD-L1 expression and OS (Figure 3). There was a possible trend for a better prognosis in patients overexpressing PD-L1 (HR = 0.874; 95% CI: 0.711-1.073, \( P = 0.197 \)).

![Figure 3. Overall forest plot of stratified analysis based on the tumor location for the association between PD-L1 and OS.](image-url)
Table 3. Results of the meta-analysis on the prognostic effects of PD-L1 in HNC patients.

| Variable | Study no. | Sample size | HR (95% CI) | P value | Heterogeneity |
|----------|-----------|-------------|-------------|---------|---------------|
|          |           |             | I²          | P value |
| OS       | Overall   | 32          | 4854        | 0.874 (0.711-1.073) | 0.197 | 72.8% | <0.001 |
| Ethnicity|           |             |             |         |               |
| Asian    | 14        | 2074        | 0.792 (0.537-1.168) | 0.240 | 78% | <0.001 |
| Caucasian| 18        | 2780        | 0.91 (0.716-1.158) | 0.444 | 68.2% | <0.001 |
| Tumor location | | | | | |
| OSCC     | 10        | 1198        | 0.726 (0.470-1.121) | 0.148 | 84.7% | <0.001 |
| NPC      | 7         | 795         | 0.692 (0.523-0.915) | 0.01 | 0.0% | 0.855 |
| OPSCC    | 3         | 495         | 0.975 (0.771-1.234) | 0.835 | 0.0% | 0.403 |
| HPSCC    | 1         | 83          | 1.300 (0.700-2.415) | 0.407 | - | - |
| SSCC     | 1         | 53          | 1.355 (0.739-2.485) | 0.326 | - | - |
| LSCC     | 1         | 260         | 0.635 (0.393-1.025) | 0.063 | - | - |
| Sample size | | | | | |
| Large    | 12        | 3132        | 1.022 (0.790-1.321) | 0.87 | 71.4% | <0.001 |
| Small    | 20        | 1722        | 0.77 (0.575-1.031) | 0.08 | 66.6% | <0.001 |
| DFS      | Overall   | 13          | 2011        | 0.874 (0.523-1.465) | 0.607 | 93.9% | <0.001 |
| Ethnicity|           |             |             |         |               |
| Asian    | 5         | 617         | 0.824 (0.290-2.338) | 0.716 | 94.2% | <0.001 |
| Caucasian| 8         | 1394        | 0.883 (0.638-1.221) | 0.451 | 62.4% | 0.009 |
| Tumor location | | | | | |
| OSCC     | 3         | 247         | 0.610 (0.208-1.793) | 0.369 | 70.5% | 0.034 |
| NPC      | 4         | 549         | 1.042 (0.349-3.111) | 0.941 | 94.9% | <0.001 |
| SSCC     | 1         | 53          | 1.834 (0.955-3.522) | 0.068 | - | - |
| OPSCC    | 1         | 181         | 1.090 (0.783-1.518) | 0.610 | - | - |
| LSCC     | 1         | 260         | 0.591 (0.350-0.997) | 0.048 | - | - |
| Sample size | | | | | |
| Large    | 4         | 1167        | 0.829 (0.597-1.151) | 0.263 | 57.5% | 0.07 |
| Small    | 9         | 844         | 0.900 (0.454-1.785) | 0.762 | 91.7% | <0.001 |
| PFS      | Overall   | 7           | 630         | 0.996 (0.632-1.569) | 0.986 | 62.1% | 0.015 |
| Ethnicity|           |             |             |         |               |
| Asian    | 4         | 318         | 0.879 (0.585-1.321) | 0.534 | 24.2% | 0.266 |
| Caucasian| 3         | 312         | 1.219 (0.372-3.997) | 0.744 | 82.6% | 0.003 |
| Tumor location | | | | | |
| OSCC     | 2         | 169         | 0.706 (0.416-1.197) | 0.196 | 7.8% | 0.298 |
| HPSCC    | 1         | 83          | 1.350 (0.737-2.473) | 0.331 | - | - |
| NPC      | 2         | 227         | 0.762 (0.503-1.154) | 0.200 | 0.0% | 0.935 |
| Sample size | | | | | |
| Large    | 1         | 161         | 0.770 (0.476-1.246) | 0.287 | - | <0.001 |
| Small    | 6         | 469         | 1.058 (0.600-1.876) | 0.845 | 66.2% | 0.011 |
| DSS      | Overall   | 5           | 699         | 0.779 (0.330-1.839) | 0.569 | 84.7% | <0.001 |
| DMFS     | Overall   | 3           | 361         | 0.599 (0.346-1.035) | 0.066 | 0.0% | 0.604 |
In nasopharyngeal carcinoma (NPC) patients, the OS was better for those expressing higher levels of PD-L1 (HR = 0.692, 95% CI: 0.523-0.915, \( P = 0.010 \)). However, no obvious trend in DFS, PFS, DSS or DMFS was found according to PD-L1 expression. In laryngeal squamous cell carcinoma patients, higher PD-L1 expression was associated with better DFS (HR = 0.591, 95% CI: 0.350-0.997, \( P = 0.048 \)).

### Sensitivity analysis and publication bias

A sensitivity analysis of the association between the expression of PD-L1 and the prognosis of HNC patients was performed for high-quality studies (NOS score ≥ 7, Table 4). The overall HRs and 95% CIs followed the same trends as those in the previous analysis. Higher levels of PD-L1 exhibited a trend of correlation with better OS (HR = 0.754, 95% CI: 0.568-1.002, \( P = 0.051 \), Figure 4A) and were associated with better PFS (HR = 0.618, 95% CI: 0.388-0.985, \( P = 0.043 \), Figure 4B) in the high-quality studies. As in the previous analysis, the OS of NPC patients was better in the high-PD-L1 group (HR = 0.649, 95% CI: 0.458-0.920, \( P = 0.015 \), Figure 4A). The heterogeneity among the studies decreased slightly for OS, but it remained statistically significant (\( I^2 = 76.6\% \), \( P_\text{h} < 0.001 \); Table 4). In addition, subgroup analyses revealed that higher PD-L1 levels were associated with better OS in Caucasian patients (HR = 0.742, 95% CI: 0.578-0.954, \( P = 0.020 \)) and in studies with small sample sizes (HR = 0.582, 95% CI: 0.426-0.796, \( P < 0.001 \), Table 4).

Funnel plots of OS were created for all the studies (Figure 5A), for the studies on PD-L1 (Figure 5B) and for the high-quality studies on PD-L1 (Figure 5C). For all three plots, the studies were distributed uniformly around the axis, manifesting no obvious publication bias (\( P = 0.509, 0.876 \) and 0.868 for all the studies, the studies on PD-L1 and the high-quality studies on PD-L1, respectively).

### Table 4. Sensitivity analysis results for high-quality studies on the prognostic effects of PD-L1 in HNC patients.

| Variable     | Study no. | Sample size | HR (95% CI)          | \( P \) value | Heterogeneity |
|--------------|-----------|-------------|----------------------|---------------|---------------|
|              |           |             | \( I^2 \)              | \( P \) value |               |
| OS           | Overall   | 17          | 2581                 | 0.754 (0.568-1.002) | 0.051 | 76.6% <0.001 |
| Ethnicity    | Asian     | 7           | 1255                 | 0.720 (0.385-1.348) | 0.305 | 88.1% <0.001 |
|              | Caucasian | 10          | 1326                 | 0.742 (0.578-0.954) | 0.020 | 46.1% 0.054 |
| Tumor location | OSCC     | 5           | 531                  | 0.653 (0.292-1.462) | 0.300 | 90.7% <0.001 |
|              | NPC       | 3           | 389                  | 0.649 (0.458-0.920) | 0.015 | 0.0% 0.744  |
|              | OPSCC     | 3           | 495                  | 0.975 (0.771-1.234) | 0.835 | 0.0% 0.403  |
|              | LSCC      | 1           | 260                  | 0.635 (0.393-1.025) | 0.063 | - -         |
| Sample size  | Large     | 7           | 1715                 | 0.984 (0.659-1.468) | 0.936 | 79.5% <0.001 |
|              | Small     | 10          | 866                  | 0.582 (0.426-0.796) | 0.001 | 50.3% 0.034 |
| DFS          | Overall   | 7           | 1066                 | 0.928 (0.618-1.392) | 0.717 | 69.4% 0.003 |
| Ethnicity    | Asian     | 3           | 416                  | 0.809 (0.241-2.720) | 0.732 | 85.8% 0.001 |
|              | Caucasian | 4           | 650                  | 0.938 (0.663-1.328) | 0.719 | 43.6% 0.150 |
| Tumor location | OSCC     | 2           | 148                  | 0.699 (0.114-4.263) | 0.697 | 78.4% 0.032 |
|              | NPC       | 2           | 348                  | 1.215 (0.288-5.133) | 0.791 | 91.0% 0.001 |
|              | OPSCC     | 1           | 181                  | 1.090 (0.783-1.518) | 0.610 | - -         |
|              | LSCC      | 1           | 260                  | 0.591 (0.351-0.996) | 0.048 | - -         |
| Sample size  | Large     | 3           | 650                  | 0.753 (0.485-1.171) | 0.208 | 66.8% 0.049 |
|              | Small     | 4           | 416                  | 1.146 (0.536-2.450) | 0.725 | 71.0% 0.016 |
| PFS          | Overall   | 3           | 188                  | 0.618 (0.388-0.985) | 0.043 | 0.0% 0.867 |
Figure 4: Overall forest plots of sensitivity analysis. (A) Stratified analysis based on the tumor location for the association between PD-L1 and OS. (B) Overall forest plots of sensitivity analysis for the association between PD-L1 and PFS.
Figure 5: Begg's funnel plots of publication bias on the relationships between immune checkpoint molecules and OS in all studies (A), PD-L1-associated studies (B) and high-quality studies on PD-L1 (C).
DISCUSSION

As immune checkpoint molecules could be involved in the immune surveillance of tumor development and progression and the clearance of tumors [11], anti-immune-checkpoint drugs such as pembrolizumab [3, 19], nivolumab [26, 27] and ipilimumab [28] have been approved to treat melanoma, non-small cell lung cancer, renal cell carcinoma, prostate cancer and HNC. Recent studies have examined how immune checkpoint molecules, especially PD-L1, influence the prognosis of cancer patients, and a large number of updated reports have been published in the past two years. However, no consensus has been reached on the effects of immune checkpoint molecules on the prognosis of HNC.

This meta-analysis on the prognostic value of immune checkpoint molecules included 52 studies with a total of 7127 patients. The expression of immune checkpoint molecules was found to be a controversial prognostic factor for the OS, DFS, PFS, DSS and DMFS of HNC patients. Although the current view is that immune checkpoint molecules may be important predictors of a poor prognosis in HNC [17-19, 22, 29-31], our subgroup analysis stratified according to the immune checkpoint molecule revealed that different molecules had different associations with the patient prognosis. Thus, our results require careful attention.

Higher IDO expression was associated with a poorer prognosis for HNC patients in our study. Similarly, high IDO expression has been reported to correlate with a poor prognosis in patients with melanoma, breast cancer and colon cancer [32-34]. However, in our study, higher expression of PD-L1 tended to be associated with better OS. Kogashiwa et al. [35] found that higher expression of PD-L1 was associated with a higher number of CD8+ tumor-infiltrating lymphocytes, leading to better OS for HNC patients. Balermapas et al. and Hanna et al. [36, 37] also reported higher levels of tumor-infiltrating lymphocytes in HNC patients expressing higher levels of PD-L1, which could explain the improved OS of these patients.

As PD-L1 attracted the most attention of the included immune checkpoint molecules, and a large number of updated studies reported the relationship between high levels of PD-L1 and the prognosis of HNC in 2017 and 2018, we considered it important to conduct a further meta-analysis solely on this molecule. We found that higher PD-L1 expression was associated with better OS in NPC patients, although for HNC overall there was only a positive trend, rather than a concrete link (Figure 3). A sensitivity analysis revealed the same trends in OS. In addition, higher PD-L1 expression was found to correlate with better PFS. The results of the sensitivity analysis may be more dependable than the former results, as all the included studies were of high quality. Furthermore, the same relationship between PD-L1 expression and OS was confirmed in Caucasian subjects, NPC patients and studies with small sample sizes.

Tumors can develop adaptive immune resistance, which is one of the two mechanisms regulating tumor PD-L1 expression (the second being intrinsic immune resistance) [38]. While the intrinsic mechanism leads to PD-L1 expression after oncogenic mutation [39], the adaptive mechanism causes tumor cells to express PD-L1 after they have been stimulated by interferon gamma secreted by CD8+ T cells [40, 41]. Therefore, tumor-membranous PD-L1 levels could partly reflect the amount of tumor-infiltrating lymphocytes, especially cytotoxic T cells, accounting to some extent for the better survival of patients with higher PD-L1 levels.

There are several limitations to this meta-analysis. Firstly, the overall heterogeneity was high, so random effects models were required for the analysis, and there was less sensitivity to detect significant differences. Secondly, all the included studies were prospective, and the majority of studies did not have adequate random sequences or comparable cohorts, increasing the risk of bias. Thus, the quality of the included studies was not perfect. Lastly, the study populations were all of Asian or Caucasian ethnicity, which may have caused a population selection bias.

Our meta-analysis indicated that different immune checkpoint molecules correlated with different prognoses in HNC patients: higher IDO expression predicted a poorer prognosis, while higher PD-L1 expression was associated with a better prognosis. Furthermore, our study revealed that higher expression of PD-L1 was associated with significantly better OS in Caucasian subjects, NPC patients and studies with small sample sizes. In summary, our study suggested that the immune checkpoint molecules IDO and PD-L1 have potential prognostic value and applicability to immune therapy for HNC.

METHODS

Literature-search strategy

This literature search was performed on August 10, 2018 without any restrictions in region, publication type, journal or language. The databases of PubMed, Embase and the Cochrane Library were thoroughly searched with the following strategy: ((((((((((((head and neck cancer [Title/Abstract]) OR head and neck squamous cell
The inclusion and exclusion criteria

The available prospective comparative studies (cohort studies) were included in this study based on their conformance to the following inclusion criteria: 1) the association of immune checkpoint marker expression with OS/DFS/PFS/DSS/DMFS in HNC was reported; 2) the diagnosis of HNC was made based on pathological examination; 3) HRs and 95% CIs were provided or could be estimated from the text; 4) only the more recent or complete article was selected when multiple reports described the same population, to avoid the duplicate inclusion of data; and 5) articles were published as original research.

The exclusion criteria were: 1) reviews, meeting abstracts, letters; 2) animal model studies; 3) sample size < 30 patients; 4) insufficient data to estimate the HR and 95% CI; 5) the main type of tumor was not SCC; 6) the number of studies on a single molecule was less than three; and 7) the study design was not prospective.

Data extraction and quality assessment

Two reviewers (Y.Q.J. and B.Y.) extracted the following information independently from the included studies: author, year of publication, study country or region, sample ethnicity, tumor location, follow-up period, sample size, gender, cut-off values of immune checkpoint molecules, detection method, TNM stage, and survival data such as OS, DFS, PFS, DSS and DMFS. The HR and 95% CI were either reported or calculated from the $P$ value or Kaplan-Meier survival curve [42, 43]. Disagreements were resolved by a senior reviewer (Z.W.).

Two reviewers (L.L.W. and W.X.M.) independently assessed the quality of the included studies by the NOS. A score of 0–9 was given to each study, and studies with NOS scores ≥ 7 were defined as high-quality. Consensus was reached by discussion with senior reviewers (B.C. and Z.W.) when there were inconsistent results. Importantly, the procedure of assessing the quality of the studies was blinded to the reviewers who extracted the data (Y.Q.J. and B.Y.).

Statistical analysis

This meta-analysis was performed in accordance with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines [44, 45]. The HR was used as a summary statistic for censored outcomes (OS, DFS, PFS, DSS and DMFS). The HR and 95% CI were either reported or calculated from the $P$ value or Kaplan-Meier survival curve [42, 43]. Disagreements were resolved by a senior reviewer (Z.W.).

Heterogeneity among the primary studies was evaluated by Cochrane’s $Q$ statistic and the $I^2$ statistic. A $P$ value < 0.10 in Cochrane’s $Q$ test or an $I^2$ value > 50% indicates substantial heterogeneity among studies, so a random effects model was used to calculate the pooled HR and 95% CI in such cases. Otherwise, a fixed effects model was applied.

We used the mean sample size as the boundary between studies with large and small sample sizes. Subgroup analyses were carried out according to the immune checkpoint molecule, ethnicity, sample size and tumor location. Sensitivity analysis was applied to high-quality studies (NOS ≥ 7). Begg’s funnel plots were used to assess publication bias. All statistical analyses
were conducted with STATA 12.0 statistical software (Stata Corporation, College Station, TX, USA). A two-tailed $P$ value < 0.05 was considered statistically significant.

**Abbreviations**

PD-L1: programmed death ligand 1; PD-1: programmed death 1; LAG-3: lymphocyte activation gene 3; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; PD-L2: programmed death ligand 2; IDO: indoleamine 2, 3-dioxygenase; VISTA: V-domain Ig suppressor of T cell activation; HR: hazard ratio; M/F: male/female; NA: not available; HNC: head and neck cancer; HNSCC: head and neck squamous cell carcinoma; OSCC: oral squamous cell carcinoma; NPC: nasopharyngeal carcinoma; OPSCC: oropharyngeal squamous cell carcinoma; LSCC: laryngeal squamous cell carcinoma; cut-off value: the value that can be diagnosed as positive/high expression of an immune checkpoint molecule; AQUA: automated quantitative analysis; IHC: immunohistochemistry; IF: immunofluorescence; qRT-PCR: quantitative reverse transcription polymerase chain reaction; FACS: fluorescence-activated cell sorting; FISH: fluorescence in situ hybridization; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; DMFS: distant metastases-free survival; CI: confidence interval.

**AUTHOR CONTRIBUTIONS**

Y.Q.J. and B.Y. conceived and designed the research, analyzed the data and wrote the paper. Z.W. and B.C. reviewed drafts of the paper and participated in its design and coordination. L.L.W. and W.X.M. evaluated the quality of the literature and prepared the figures and tables. All the authors read and approved the final manuscript.

**CONFLICTS OF INTEREST**

The authors declare no conflict of interest.

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## Supplementary Table 1. Risk of bias in prospective studies based on the modified Newcastle-Ottawa Scale.

| Study                  | Selection | Comparability | Outcome |
|------------------------|-----------|---------------|---------|
|                        | Representativeness of the Exposed Cohort | Selection of the Non-Exposed Cohort | Ascertainment of Exposure | Demonstration That Outcome of Interest Was Not Present at Start of Study | Comparability of Cohorts on the Basis of the Design or Analysis | Assessment of Outcome | Long Enough Follow-Up for Outcomes to Occur | Adequacy of Follow-Up of Cohorts | Quality Score |
| Ahn et al. 2017        | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Badoual et al. 2013    | 0         | 1             | 1       | 1       | 1 | 1 | 0 | 1 | 6 |
| Balempas et al. 2017   | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Ben-Haj-Ayed et al. 2016 | 0        | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Birtalan et al. 2017   | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 0 | 6 |
| Budezies et al. 2016   | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 0 | 5 |
| Chan et al. 2017       | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 0 | 6 |
| Chang et al. 2017      | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 0 | 5 |
| Chen et al. 2015       | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Chen et al. 2017       | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Cho et al. 2011        | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 0 | 6 |
| De et al. 2017         | 0         | 1             | 1       | 1       | 1 | 1 | 0 | 1 | 6 |
| Fang et al. 2014       | 0         | 1             | 1       | 1       | 1 | 1 | 0 | 1 | 6 |
| Feng et al. 2017       | 1         | 1             | 1       | 1       | 1 | 1 | 0 | 1 | 6 |
| Fiedler et al. 2018    | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Hanna et al. 2018      | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Hong et al. 2016       | 0         | 1             | 1       | 1       | 1 | 1 | 0 | 1 | 6 |
| Hsu et al. 2010        | 0         | 1             | 1       | 1       | 1 | 1 | 0 | 0 | 4 |
| Kansy et al. 2017      | 0         | 1             | 1       | 1       | 1 | 1 | 0 | 1 | 6 |
| Kim et al. 2016        | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 0 | 6 |
| Kim et al. 2016        | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Kogashiwa et al. 2017  | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Laimer et al. 2017     | 0         | 1             | 1       | 1       | 1 | 1 | 1 | 1 | 7 |
| Year   | Authors                          | Score | Age   | Stress | Diet | Exercise | Cognition | Depression | Pubchem | Notes   |
|--------|----------------------------------|-------|-------|--------|------|----------|-----------|------------|---------|---------|
| 2011   | Larbcharoensub et al. 2018       | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 1       | 7       |
|        | Lee et al. 2016                  | 0     | 1     | 1      | 1    | 1        | 0         | 1          | 1       | 0       | 5       |
|        | Li et al. 2017                   | 0     | 1     | 1      | 1    | 0        | 1         | 1          | 0       | 5       |         |
|        | Lin et al. 2015                  | 0     | 1     | 1      | 1    | 0        | 1         | 1          | 1       | 6       |         |
|        | Muller et al. 2017               | 0     | 1     | 1      | 1    | 1        | 0         | 1          | 1       | 6       |         |
|        | Ock et al. 2016                  | 0     | 1     | 1      | 1    | 1        | 1         | 0          | 1       | 6       |         |
|        | Oguejiofor et al. 2017           | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Oliveira-Costa et al. 2015       | 0     | 1     | 1      | 1    | 0        | 1         | 1          | 1       | 6       |         |
|        | Ono et al. 2017                  | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 6       |         |
|        | Ono et al. 2018                  | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Ou et al. 2017                   | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Qu et al. 2017                   | 0     | 1     | 1      | 1    | 1        | 1         | 0          | 1       | 6       |         |
|        | Riobello et al. 2018             | 0     | 1     | 1      | 1    | 1        | 0         | 1          | 1       | 5       |         |
|        | Roper et al. 2017                | 0     | 1     | 1      | 1    | 0        | 1         | 1          | 1       | 6       |         |
|        | Satgunaseelan et al. 2016        | 0     | 1     | 1      | 1    | 1        | 1         | 0          | 1       | 6       |         |
|        | Schneider et al. 2018            | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Seppälä et al. 2016              | 0     | 1     | 1      | 1    | 0        | 1         | 1          | 1       | 6       |         |
|        | Solomon et al. 2018              | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Steuer et al. 2018               | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Strati et al. 2017               | 0     | 1     | 1      | 1    | 1        | 1         | 0          | 0       | 5       |         |
|        | Straub et al. 2016               | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Tang et al. 2017                 | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 0       | 6       |         |
|        | Ukpo et al. 2013                 | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Vassilakopoulou et al. 2015      | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Ye et al. 2012                   | 0     | 1     | 1      | 1    | 1        | 1         | 0          | 1       | 6       |         |
|        | Zhang et al. 2015                | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |
|        | Zheng et al. 2017                | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 0       | 6       |         |
|        | Zhu et al. 2017                  | 0     | 1     | 1      | 1    | 1        | 1         | 1          | 1       | 7       |         |