Prognostic and clinical implications of c-erbB-2 expression in patients with oral cancer
A meta-analysis
Ying Meng, MS, Peng Yang, BD, Lili Ma, MS

Abstract
Background: Recently, many studies have suggested that the aberrant expression of c-erbB-2 existed in oral cancer (OC) patients and had a correlation with poor clinical features across OC patients. Considering the inconsistent results among published articles, we performed the meta-analysis to assess the prognostic and clinical effect of c-erbB-2 expression on oral tumors.

Methods: Web of Science, Embase, and PubMed were retrieved to acquire relevant publications based on selection criteria, up to February 8, 2020. Pooled odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) were applied to evaluate the associations between c-erbB-2 expression and overall survival (OS), disease specific survival, disease-free survival as well as clinicopathological features of OC.

Results: A total of 30 literatures with 1499 patients for survival of OC were enrolled in this meta-analysis. The results indicated that c-erbB-2 overexpression was significantly associated with poor OS (HR = 2.40, 95% CI = 1.53–2.55, P < .05), disease specific survival (HR = 2.60, 95% CI = 1.11–4.10, P < .05) and disease-free survival (HR = 2.22, 95% CI = 1.46–2.99, P < .05). Subgroup analysis based on race showed that the significant prognostic value of c-erbB-2 in OC was found both in Caucasians and Asians (OS of Caucasians, HR = 2.90, 95% CI = 1.50–4.31, P < .05; OS of Asians, HR = 1.90, 95% CI = 1.27–2.53, P < .05). Moreover, OC patients with enhanced c-erbB-2 expression were prone to male (OR = 1.17–2.88, P < .05), lymph node metastasis (OR = 2.23, 95% CI = 1.47–3.36, P < .05) and advanced grade (OR = 1.98, 95% CI = 1.30–3.01, P < .05), but not associated with distant metastasis (OR = 1.65, 95% CI = 0.98–3.04, P > .05).

Conclusions: c-erbB-2 may be a potential indicator in the prediction of prognosis and clinicopathological features in OC patients.

Abbreviations: CIs = confidence intervals, DFS = disease-free survival, DDS = disease specific survival, HRs = hazard ratios, IHC = immunohistochemistry, OC = oral cancer, ORs = odds ratios, OS = overall survival, OSCC = oral squamous cell carcinoma.

Keywords: c-erbB-2, meta-analysis, oral cancer, overexpression, prognosis

1. Introduction
Globally, oral cancer (OC) is the most frequent cancer of the head and neck district, approximately accounting for 2% of all cancer patients, with nearly 50% mortality rate.[1] Published reports have found South Asian countries such as India, Sri Lanka, and Taiwan had the highest rates of OC.[2] Multiple factors including genetic factors and environmental factors contribute to the initiation of OC. Tobacco, alcohol, areca nut, and high-risk human papillomavirus infection have been identified as significant risk factors for OC.[3] In addition, specific germline mutations such as germline TP53 mutation, HOTAIR mutation, and NF1 mutation have also been associated with a higher incidence of OC.[4–6] The patients with dyskeratosis congenita have increased risk of OC because of defective telomerase maintenance.[7] In fact, oral squamous cell carcinoma (SCC) accounts for large proportions of OC cases arising in the head and neck region.[8] Surgery and/or radiotherapy were commonly used to treat the OC patients with localized disease, which resulted to a better prognosis but with considerable morbidity.[9] Chemotherapy and radiotherapy are the mainstays of treatment for the OC patients with metastatic disease.[10] Recently, some targeted biological drugs such as cetuximab and bevacizumab, have been introduced into the treatment regimens of OC, which improved the quality of life in OC patients.[9] Although many therapeutic strategies have been discovered and developed in the field of OC treatment, the prognosis has not significantly improved over the past few decades.[11] Oral cancer patients with advanced stage often had a low response rate to current therapeutic strategies, which led to the poor prognosis. These patients were often diagnosed with advanced tumor stage, lymph...
node metastasis, distant metastasis, and high occurrence of invasion. Therefore, the discovery of new and valuable biomarkers which significantly associated with the risk and progression of oral tumor may be benefit for the treatment of OC.

The c-erbB-2/HER2/neu gene, locating at chromosome 17q21, encodes a 185 kDa transmembranous receptor protein, which is a member of the EGFR/HER family and involved in proliferation, migration, invasion, and apoptosis of cells.[11,12] It has been reported that the level of c-erbB-2 protein had aberrant rise in cancer patients with early stage, thus c-erbB-2 might be a reliable biomarker for the initial diagnosis and screening of cancers. One study has detected c-erbB-2 protein expression in the tumor tissue of patients with OSCC, and the results demonstrated the levels of c-erbB-2 was significantly increased.[13] However, other researchers found that there was no significant association between clinical features of OCs and c-erbB-2 expression.[14] Considering the diversity of oral tumor types, more detailed studies might be conducted based on OC types, race, clinical features, and other affecting factors such as gender. Therefore, we carried out the meta-analysis to analyze the potential value of c-erbB-2 protein expression in the prognosis and clinical progression of OC.

2. Methods

2.1. Search strategies

Literatures regarding the correlation between c-erbB-2 expression and OC were searched from Web of Science, Embase, and PubMed databases up to February 8, 2019. The following search terms: "oral cancer," "c-erbB-2," "HER2," "neu," "prognosis," "Salivary Gland Tumors," "Oral Squamous Cell Carcinoma," "Salivary mucopidermoid carcinomas," "Oropharyngeal Squamous Cell Carcinoma," "Squamous cell carcinomas of the tongue," and "Salivary carcinoma ex pleomorphic adenoma" were used. Additionally, references of relevant articles were also browsed.

2.2. Selection of studies

All potential articles were assessed by 2 independent reviewers. All candidate articles had to meet the following inclusion criteria:

1. The OC patients of relevant articles should be diagnosed by histopathology;
2. c-erbB-2 expression in cancer tissue was detected with immunohistochemistry (IHC);
3. The article had to contain enough data to calculate hazard ratio (HR), odds ratio (OR), and 95% confidence intervals (CI); and
4. the studies were written in English. Moreover, any disagreement was resolved via discussion.

The exclusion criteria were as follows:
1. These articles were removed such as: reviews, letters, editorials, case-reports, and meta-analysis;
2. Duplicate and insufficient data;
3. Studies which were performed in animal specimens.

And Medical Ethics Committee of Liaocheng People’s Hospital approved this study.

2.3. Data extraction and quality assessment

Two researchers independently extracted the following data: first author’s name, publication date, race, OC type, detecting methods, number of cases and controls, HRs and 95% CI, cut-off value, and follow-up median time. Moreover, clinical information including histological classification, tumor stage (TNM), tumor grade, lymph node metastasis, and distant metastasis were extracted from the relevant articles.

We applied the Newcastle-Ottawa Scale to evaluate the quality of primary studies. According to the selection of the subjects, the comparability of cases and controls, and the ascertainment of the exposure, the included studies were scored. A study awarded 0 to 3, 3 to 6, or 6 to 9 was considered as a low, moderate, or high-quality study.

2.4. Statistical analysis

The association between c-erbB-2 expression and clinical features of OC was measured by OR with 95% CI. In addition, HR and 95% CI were extracted from included studies based on the methods described by Tierney et al.[15] Heterogeneity among the studies was assessed using Cochran Q test and I² statistics.[16] P < .05 or I² > 50% indicated a severe heterogeneity among relevant studies. If significant heterogeneity existed, the random effects model was used (P < .05 or I² > 50%); otherwise, the fixed effects model was applied.[17] Begg test and eggert test were conducted to evaluate the publication bias.[18] Finally, the sources of heterogeneity were investigated by performing a sensitivity analysis. All statistical analysis was conducted with STATA version 14.0 (STATA, College Station, TX).

3. Results

3.1. Characteristics of included studies

A total of 665 literatures were preliminarily identified from PubMed, Web of Science, and Embase electronic databases. After eliminating duplicate studies, 654 records remained. Then titles and abstracts of all the studies were read, and 346 articles were excluded. After carefully scanning the full texts, an additional 78 articles were removed. Furthermore, additional an article with insufficient data was eliminated. Ultimately, 29 eligible studies were eventually included in our meta-analysis.[19–47] (Fig. 1). In these studies, 1499 OC patients were included to analyze the association between c-erbB-2 expression and survival of OC patients, while 188 controls and 254 cancer patients were recorded for the correlation of c-erbB-2 expression with OC risk. The characteristics of the 29 included studies is presented in Table 1, Table 2 and Supplementary Tables S1 to S5, http://links.lww.com/MD/E358, http://links.lww.com/MD/E359, http://links.lww.com/MD/E360, http://links.lww.com/MD/E361, http://links.lww.com/MD/E362.

Among these eligible studies, 14 studies about overall survival (OS) were performed,[19–26,28,29,31–35] 2 studies on disease specific survival (CSS),[27,36] and 5 reports about disease-free survival (DFS).[19,28,33,35,36] In addition, 6 reports were performed to analyze the correlation between OC risk and c-erbB-2 expression, 7 studies for gender of subjects, 7 articles for tumor grade, 9 studies for lymph node metastasis, 6 reports for TNM stage, and 3 records for metastasis. All the OC patients of the eligible studies were in accordance with the clinical diagnostic criteria of OC.

3.2. Meta-analysis results

The association between c-erbB-2 overexpression and survival of OC was shown in Table 3. The results indicated that c-erbB-2 overexpression was significantly associated with OS, DSS, and
DFS of OC (OS, HR = 2.40, 95% CI = 1.53–2.55, P < .05; DSS, HR = 2.60, 95% CI = 1.11–4.10, P < .05; DFS, HR = 2.22, 95% CI = 1.46–2.99, P < .05). Significant heterogeneity was found in the preliminary analysis for OS of OC. Sensitivity analysis revealed that Masubuchi et al and Boon et al contributed to the mainly heterogeneity in Asians and Caucasians,[15,19] therefore, the 2 studies were removed in the finally meta-analysis. The results of subgroup analysis based on race and source of HRs suggested that significant correlation between c-erbB-2 expression and OS of OC was still found in Caucasians and Asians (OS in Caucasians, HR = 2.90, 95% CI = 1.50–4.31, P < .05; OS in Asians, HR = 1.90, 95% CI = 1.27–2.53, P < .05). Stratified analysis based on cancer type revealed that c-erbB-2 overexpression resulted to worse prognosis in salivary gland cancer (OS, HR = 2.45, 95% CI = 1.39–3.51, P < .05; DFS, HR = 2.44, 95% CI = 1.41–3.46, P < .05), OSCC (OS, HR = 4.27, 95% CI = 1.79–6.75, P < .05), and salivary mucoepidermoid carcinomas (OS, HR = 7.39, 95% CI = 1.59–13.19, P < .05), but not in squamous cell carcinomas of the tongue (OS, HR = 1.76, 95% CI = 0.94–2.57).

Six studies contributed data to the analysis of OC risk. No significant heterogeneity was found among eligible studies, and fixed effect model was used. The results demonstrated that c-erbB-2 overexpression significantly enhanced the risk of OC (OR = 9.99, 95% CI = 4.17–23.95, P < .05). In addition, significant correlations between c-erbB-2 overexpression and gender (OR = 1.97, 95% CI = 1.22–3.19, P < .05), TNM stage (OR = 1.84, 95% CI = 1.17–2.88, P < .05), lymph node metastasis (OR = 2.23, 95% CI = 1.47–3.36, P < .05) and advanced grade (OR = 1.98, 95% CI = 1.30–3.01, P < .05) of OC was found, but
not distant metastasis (OR = 1.65, 95% CI = 0.98–3.04, P > .05).

We also performed subgroup analysis by ethnicity, and the results of subgroup analysis revealed that significant associations between c-erbB-2 overexpression and occurrence risk (Caucasians, OR = 10.39, 95% CI = 3.68–29.35, P < .05; Asians, OR = 9.00, 95% CI = 1.77–45.79, P < .05), gender (Caucasians, OR = 2.51, 95% CI = 1.16–5.41, P < .05; Asians, OR = 3.21, 95% CI = 1.34–7.70, P < .05), advanced grade (Caucasians, OR = 1.87, 95% CI = 1.07–3.26, P < .05; Asians, OR = 7.83, 95% CI = 2.32–26.39, P < .05), lymph node metastasis (Caucasians, OR = 2.85, 95% CI = 1.13–7.18, P < .05; Asians, OR = 2.15, 95% CI = 1.27–3.64, P < .05) of OC were identified. Furthermore, stratified analysis based on type of control group showed that c-erbB-2 overexpression significantly associated with OC risk in normal tissues (OR = 11.68, 95% CI = 4.29–31.78, P < .05) and benign tissues (OR = 6.77, 95% CI = 1.19–38.44, P < .05) (Figs. 2 and 3, Tables 3 and 4).

### 3.3. Publication bias and sensitivity analysis

In order to assess publication bias among published literatures, Begg and Egger test were conducted, and significant publication bias was not detected. The similar results were also found in the funnel plots, and the shapes of funnel plot appeared symmetrical. Finally, we conducted sensitivity analysis by removing each study to evaluate the impact of each study on the overall results. These results showed that no individual study had excessive effect on the stability of overall results. Therefore, the overall results were robust (Tables 3 and 4).

### 4. Discussion

IHC is the most attractive method to evaluate the level of some proteins due to low cost, convenience, and biological relevance. So many studies have been performed to assess the role of

---

**Table 1**
The main information of included studies in the meta-analysis for the oral cancer prognosis.

| Author            | References | Time | Country | Ethnicity | Method | Cancer type | Follow-up | Survival analysis | Source of HR | HR  | 95%CI | Analysis type | Cut-off |
|-------------------|------------|------|---------|-----------|--------|-------------|-----------|-------------------|--------------|-----|-------|---------------|---------|
| Sugano            | 19         | 1992 | Japan   | Asians    | IHC    | SGC         | 5 yr OS   | SC                | 1.48         | 1.02–4.90 | .023  | Univariate    | 0.33     |
| Sugano            | 19         | 1992 | Japan   | Asians    | IHC    | SGC         | 5 yr DFS  | SC                | 2.74         | 1.45–8.49 | .006  | Univariate    | 0.33     |
| Press             | 20         | 1994 | USA     | Caucasians| IHC    | SMC         | 12.5 yr OS| SC                | 8.42         | 2.52–16.35 | .0011 | Univariate    | 0.1      |
| Giannoni          | 21         | 1995 | USA     | Caucasians| IHC    | SGC         | 3.5 yr OS | SC                | 3.03         | 1.47–5.27 | .009  | Univariate    | NR       |
| Xia               | 22         | 1997 | China   | Asians    | IHC    | OSCC        | 3.5 yr OS | SC                | 5.47         | 2.85–12.64 | .001  | Univariate    | NR       |
| Kurokut           | 23         | 2002 | USA     | Caucasians| IHC    | OC          | 5 yr      | OS                | 3.22         | 1.06–10.29 | .007  | Univariate    | 0.01     |
| Chen              | 24         | 2003 | China   | Asians    | IHC    | SCTT        | 5 yr OS   | SC                | 1.87         | 1.06–3.31 | .017  | Univariate    | 0.1      |
| Williams          | 27         | 2007 | USA     | Caucasians| IHC    | SDC         | 5 yr OS   | SC                | 2.04         | 0.93–5.28 | .444  | Univariate    | 0.5      |
| Silva             | 28         | 2008 | Brizal  | Mixed     | IHC    | SCCT        | 5 yr OS   | SC                | 1.63         | 1.01–3.37 | .0096 | Univariate    | NR       |
| Silva             | 28         | 2008 | Brizal  | Mixed     | IHC    | SCCT        | 5 yr DFS  | SC                | 1.66         | 1.15–3.64 | .0029 | Univariate    | NR       |
| Silva             | 29         | 2009 | Brizal  | Mixed     | IHC    | OSCC        | 5 yr OS   | SC                | 3.86         | 1.93–7.68 | .0005 | Univariate    | NR       |
| Triantafillidou    | 30         | 2010 | Greece  | Caucasians| IHC    | ACCMSG      | 5 yr OS   | SC                | 2.85         | 0.69–8.68 | .47   | Univariate    | 0.1      |
| Elf                                        | 31         | 2012 | Germany | Caucasians| IHC    | SGC         | 6 yr OS   | SC                | 3.11         | 1.67–5.80 | .008  | Univariate    | 0.1      |
| Cros              | 32         | 2013 | France  | Caucasians| IHC    | SGC         | NR       | OS                | 0.89         | 0.12–6.80 | .91   | Multivariate  | 0.1      |
| Masubuchi         | 33         | 2014 | Japan   | Asians    | IHC    | SDC         | 2 yr DFS  | SC                | 1.33         | 0.17–10.43 | .767  | Univariate    | 0.1      |
| Masubuchi         | 33         | 2014 | Japan   | Asians    | IHC    | SDC         | 2 yr OS   | SC                | 0.42         | 0.08–2.08 | .288  | Univariate    | 0.1      |
| Xia               | 34         | 2016 | China   | Asians    | IHC    | SCPEA       | 5 yr OS   | SC                | 1.89         | 1.03–3.48 | .04   | Univariate    | 0.1      |
| Hashimoto         | 35         | 2017 | Japan   | Asians    | IHC    | SGC         | 5 yr DFS  | SC                | 2.41         | 1.54–3.68 | .001  | Univariate    | 0.1      |
| Hashimoto         | 35         | 2017 | Japan   | Asians    | IHC    | SGC         | 5 yr OS   | SC                | 3.37         | 1.89–5.82 | .001  | Univariate    | 0.1      |
| Haderlein         | 36         | 2018 | Germany | Caucasians| IHC    | SGC         | 5 yr DFS  | SC                | 4.84         | 1.32–8.65 | .04   | Univariate    | 0.1      |
| Boon              | 37         | 2018 | Netherland | Caucasians| IHC    | SGC         | 5 yr OS   | SC                | 1.08         | 0.65–1.61 | .76   | Univariate    | NR       |

**Table 2**
Characteristics of the included studies for the oral cancer risk.

| Author    | Reference | Time | Country | Ethnicity | Method | Histology | Sample type  | c-erbB-2 - c-erbB-2 + | Sample type  | c-erbB-2 - c-erbB-2 + | Cut-off |
|-----------|-----------|------|---------|-----------|--------|-----------|--------------|----------------------|--------------|----------------------|---------|
| Hou       | 38        | 1992 | USA     | Caucasians| IHC    | OC        | Normal tissue| 7        | 0                   | Tumor tissue | 0                   | 21      |
| Karja     | 39        | 1994 | Finland | Caucasians| IHC    | SGC       | Benign tissue| 75       | 41                  | Tumor tissue | 77                  | 36      |
| Giannoni  | 22        | 1995 | USA     | Caucasians| IHC    | SGC       | Benign tissue| 16       | 1                   | Tumor tissue | 26                  | 16      |
| Wilkmann  | 40        | 1998 | Finland | Caucasians| IHC    | OSCC      | Benign tissue| 6        | 0                   | Tumor tissue | 10                  | 1       |
| Bei       | 41        | 2001 | Italy   | Caucasians| IHC    | OC        | Normal tissue| 4        | 0                   | Tumor tissue | 10                  | 9       |
| Fong      | 42        | 2008 | China   | Asians    | IHC    | OSCC      | Benign tissue| 18       | 2                   | Tumor tissue | 15                  | 10      |
| Seifi     | 43        | 2009 | Iran    | Caucasians| IHC    | OSCC      | Normal tissue| 16       | 2                   | Tumor tissue | 10                  | 8       |

IHC = Immunohistochemistry, NOS = Newcastle-Ottawa Scale, NR = not reported, OC = oral cancer, OS = overall survival, OSCC = oral squamous cell carcinoma, SC = survival curve, SCCT = squamous cell carcinomas of the tongue, SCPEA = salivary carcinoma ex pleomorphic adenoma, SGC = salivary duct carcinoma, SMC = salivary mucoepidermoid carcinomas.
Table 3

Meta-analysis results for the associations of c-erbB-2 expression with OS of oral cancer.

| Characteristics (Negative vs Positive) | Studies | Cancer type | Pooled HR (95% CI) | Heterogeneity | Begg test | Egger test |
|---------------------------------------|---------|-------------|--------------------|---------------|-----------|-----------|
| OS                                    | 14      | OC          | 2.40 (1.53–2.55)  | <.05          | 2%        | .436      |
| OS in Caucasians                      | 6       | OC          | 2.90 (1.50–4.31)  | <.05          | 0%        | .547      |
| OS in Asians                          | 6       | OC          | 1.90 (1.27–2.53)  | <.05          | 10.80%    | .347      |
| OS (Source of HR)                     | 4       | OC          | 1.83 (1.01–2.65)  | <.05          | 18.90%    | .296      |
| OS (Source of SC)                     | 10      | OC          | 2.18 (1.53–2.83)  | <.05          | 1.5%      | .425      |
| OS                                    | 2       | SCCT        | 1.76 (0.94–2.57)  | >.05          | 0%        | .773      |
| OS                                    | 4       | SGC         | 2.45 (1.39–3.51)  | <.05          | 0%        | .759      |
| OS                                    | 2       | OSCC        | 4.27 (1.79–6.75)  | <.06          | 0.00%     | .578      |
| OS                                    | 2       | SMC         | 7.39 (1.50–13.19) | <.07          | 0.00%     | .592      |
| DSS                                   | 2       | OC          | 2.60 (1.11–4.10)  | <.05          | 0%        | .484      |
| DFS                                   | 5       | OC          | 2.22 (1.46–2.99)  | <.05          | 0%        | .548      |
| DFS                                   | 2       | SGC         | 2.44 (1.41–3.46)  | <.05          | 0.00%     | .86       |
| DFS                                   | 2       | SDC         | 3.65 (0.67–6.64)  | >.05          | 16%       | .275      |

Heterogeneity: I² (%)  Begg test: Z  P  T  P
Egger test: Z  P  T  P

CIs = confidence intervals, DFS = disease-free survival, DSS = disease specific survival, HRs = hazard ratios, IHC = immunohistochemistry, OC = oral cancer, OS = overall survival, OSCC = oral squamous cell carcinoma, SC = survival curve, SCCT = squamous cell carcinomas of the tongue, SDC = salivary duct carcinoma, SGC = salivary gland cancer, SMC = salivary mucoepidermoid carcinomas.

Figure 2. Forest plot of odds ratios for the association between high c-erbB-2 expression and clinicopathological parameter in oral cancer patients (c-erbB-2- vs c-erbB-2+). A, oral cancer risk; B, gender (female vs male); C, tumor grade; D, lymph node metastasis.
Figure 3. Forest plot and funnel plot for the association between high c-erbB-2 expression and survival of oral cancer patients (c-erbB-2- vs c-erbB-2+). A, subgroup analysis based on ethnicity; B, subgroup analysis based on source of hazard ratio; C, subgroup analysis based on survival type; D, funnel plot of overall survival in oral cancer.

Biomarkers expression in the prognosis and clinical progression of OC with IHC. The application of molecular markers has provided an effective approach in prediction of clinical outcome of OC. These immunohistochemical markers such as p53, Ki-67, and PCNA significantly correlated with histopathologic grade of OC.[48–50] However, some other markers such as Muc4, bcl-2, p27 correlated with histopathologic grade inversely.[25,51–52] Therefore, these proteins might contribute to different effects on the OC progression. Moreover, studies acquired contradictory results regarding association between c-erbB-2 expression and OC due to multiple factors like: age, sample type, gender, cut-off value, country, tumor histopathology, and tumor stage. A larger sample size may decrease the influence of these factors in the overall results, and stratified analysis is possible to be conducted to obtain more accurate results. Oral cancer contained many tumor subtypes such as: carcinoma of gingiva, tongue cancer, salivary gland carcinoma, and carcinoma of lip. Oral carcinoma can be divided into squamous cell carcinoma and adenocarcinoma based on cell morphology. So, identifying the histopathological type is crucial to investigate the association between c-erbB-2 expression and OC. Cetuximab, an inhibitor of EGFR receptor, is very effective to the treatment of OC patients especially those who cannot tolerate carboplatin.[53] As another receptor of the EGFR family, c-erbB-2/HER2 might have potential medical value in OC patients.

The overall results indicated that expression of c-erbB-2 was higher in OC tissues than that in normal tissues and benign tissues. Moreover, the similar result was detected both in Asians and Caucasians. No significant heterogeneity was found in the...
Table 4

| Characteristics (Negative vs Positive) | Studies | Pooled OR (95% CI) | \( P \) | Heterogeneity | Begg test | Egger test |
|---------------------------------------|---------|------------------|---------|---------------|-----------|-----------|
| Risk (Overall)                         | 6       | 9.99 (4.17–23.95) | <.05    | 7.6 .368      | 0.19 .551 | 0.87 .434 |
| Risk (Caucasian)                       | 5       | 10.39 (3.68–29.30) | <.05    | 26.2 .247     | 0.49 .624 | 0.87 .447 |
| Risk (Asian)                           | 1       | 9.00 (1.77–45.79)  | <.05    | –             | –        | –        |
| Risk (Normal tissue)                   | 4       | 11.68 (4.29–31.78) | <.05    | 32.8 .216     | 1.36 .174 | 1.7 .231  |
| Risk (Benign tissue)                   | 2       | 6.77 (1.19–38.44)  | <.05    | 0 .405       | –        | –        |
| Gender (Female vs Male)                | 7       | 1.97 (1.22–3.19)   | <.05    | 48.6 .07      | –0.75 .453 | –0.34 .745 |
| Gender (Caucasians) (Female vs Male)   | 4       | 2.51 (1.16–5.41)   | <.05    | 0 .397       | –0.68 .497 | 0.7 .554  |
| Gender (Asians) (Female vs Male)       | 2       | 3.21 (1.34–7.70)   | <.05    | 61.8 .106     | –        | –        |
| Tumor grade (Overall) (G1 vs G2+G3)   | 7       | 1.86 (1.30–2.61)   | <.05    | 39.7 .127     | 0.45 .632 | 1.86 .121  |
| Tumor grade (Caucasian) (G1 vs G2+G3) | 4       | 1.87 (1.07–3.26)   | <.05    | 0 .61         | 0.68 .497 | 1.96 .189  |
| Tumor grade (Asian) (G1 vs G2+G3)     | 2       | 7.83 (2.32–26.39)  | <.05    | 0 .912       | –        | –        |
| Lymph node metastasis (Overall) (N0 vs N1) | 9     | 2.23 (1.47–3.36)   | <.05    | 27.5 .2        | –0.83 .404 | –1.24 .253 |
| Lymph node metastasis (Caucasian) (N0 vs N1) | 3   | 2.85 (1.13–7.18)   | <.05    | 67.2 .05      | –0.52 .602 | –1.42 .391 |
| Lymph node metastasis (Asian) (N0 vs N1) | 5    | 2.15 (1.27–3.64)   | <.05    | 11.7 .339     | 0.49 .624 | –0.76 .5    |
| TNM stage (Overall) (T1-T2 vs T3-T4)  | 6       | 1.84 (1.17–2.88)   | <.05    | 1.74 .406     | 0.56 .573 | 0.83 .452  |
| TNM stage (Caucasian) (T1-T2 vs T3-T4) | 2       | 3.12 (0.79, 12.28) | >.05    | 27.8 .239     | –        | –        |
| TNM stage (Asian) (T1-T2 vs T3-T4)    | 3       | 1.45 (0.82, 2.58)  | >.05    | 25.1 .263     | 0.52 .602 | 0.16 .901  |
| Metastasis (No vs Yes)                 | 3       | 1.65 (0.69–5.04)   | >.05    | 0 .900       | –0.52 .602 | 0.23 .856  |

ClI = confidence interval, OR = odds ratio.

Overall and subgroup analysis. In published primary studies,[1,4,10] 2 studies found there was no significant association of c-erbB-2 expression with OC risk, and 6 records obtained positive results.[10,11,36,39,42,43] However, only 1 study has been conducted in Asians, thus more studies might be performed in Asians. To evaluate the value of c-erbB-2 expression in the clinical progression of OC, the meta-analysis was carried out to investigate the correlations between c-erbB-2 expression and gender, tumor grade, tumor TNM stage, and lymphatic metastasis. The results indicated that c-erbB-2 overexpression significantly promoted lymph node metastasis and tumor grade of oral tumor cells. Although significant association was observed in the overall analysis for tumor TNM stage, it was not detected in the subgroup analysis based on ethnicity. Additionally, the association preferred in male than female. No apparent heterogeneity was found, and sensitivity analysis suggested that these results were robust. And, these positive results were observed in Asians and Caucasians. Thus, c-erbB-2 overexpression led to the poor differentiation and lymphatic metastasis of oral tumor cells, which were consistent with the function of c-erbB-2 protein.[11,12] Potential clinical benefits of c-erbB-2 target treatment may be achieved in the adjuvant treatment for OC patients with lymph node metastasis and advanced grade. In a study regarding gastric cancer, Lei et al observed a significant correlation between c-erbB-2 expression and clinical outcome (TNM staging system, distant metastasis, lymph node metastasis, and differentiation grade) of gastric cancer patients.[14] Therefore, the significant association may not only exist in OC patients. However, this cannot obscure the therapeutic value of c-erbB-2 in OC, which can be demonstrated in the studies of EGFR receptor.

In conclusion, our pooled analysis revealed that c-erbB-2 overexpression played a favorable role in the prognosis of OC. In subgroup analysis, c-erbB-2 overexpression was significantly associated with OS, DFS, and DSS of OC patients. The data of meta-analysis for patients’ survival extracted from HRs or survival curve, which might lead to heterogeneity. However, in the stratified analysis based on source of HRs, significant correlation of c-erbB-2 overexpression with OS of OC patients was still observed and no significant heterogeneity was found. Although some included individual report found negative results, the significant association was detected in the overall results. As expected, Begg test and Egger test revealed that no publication bias existed, and no individual study affected the overall result. Therefore, c-erbB-2 expression might be a valuable biomarker for prognosis of OC patients.

It should be noted that several limitations still exist in the report. First, the cut-off value of IHC varied in studies. However, the cut-off value of lots studies was 10%. Second, although many studies were included for the meta-analysis, the studies were still few after subgroup analysis based on cancer type was conducted. Thus, more studies might be performed in different OC subtype. Third, many factors could affect prognosis. In the eligible studies, we incorporated lots outcomes with the form of univariate survival analysis. Therefore, studies with multivariate survival analysis should be carried out in the future studies. Fourth, the study was confined to literatures written in English, so language bias could not be ruled out.

In conclusion, our study clarified that c-erbB-2 overexpression was significantly correlated with the poor prognosis in OC patients. In addition, c-erbB-2 overexpression was associated with the following clinicopathological features of OC patients: occurrence risk, gender, lymph node metastasis, and differentiation grade.

Author contributions
Conceptualization: Ying Meng, Lili Ma.
Data curation: Ying Meng, Peng Yang.
Formal analysis: Ying Meng.
Funding acquisition: Lili Ma.
Investigation: Ying Meng, Lili Ma.
Methodology: Ying Meng, Peng Yang, Lili Ma.
Project administration: Lili Ma.
Software: Ying Meng.
Supervision: Peng Yang, Lili Ma.
Validation: Peng Yang, Lili Ma.
Visualization: Lili Ma.
Writing – original draft: Ying Meng, Peng Yang.
Writing – review & editing: Ying Meng, Peng Yang, Lili Ma.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:3359–86.
[2] Warnakulasuriya S. Living with oral cancer: epidemiology with particular reference to prevalence and lifestyle changes that influence survival. Oral Oncol 2010;46:407–10.
[3] De Camargo Cancela M, de Souza DL, Curado MP. International incidence of oropharyngeal cancer: a population-based study. Oral Oncol 2012;48:848–49.
[4] McHride KA, Ballinger ML, Killick E, et al. Li-Fraumeni syndrome: cancer risk assessment and clinical management. Nat Rev Clin Oncol 2014;11:260–71.
[5] Su SC, Hsich MJ, Lin CW, et al. Impact of HOTAIR gene polymorphism and environmental risk on oral cancer. J Dent Res 2018;97:717–24.
[6] Li L, Zhang ZT. Genetic association between NFKBIA and NFKB1 gene polymorphisms and the susceptibility to head and neck cancer: a meta-analysis. Dis Markers 2019;2019:623837.
[7] Scully C, Langidon J, Evans J. Marathon of eponyms: 26 Zinsser-Engman-Cole syndrome (Dyskeratosis congenita). Oral Dis 2012;18:522–3.
[8] Chen YK, Huang HC, Lin LM, et al. Primary oral squamous cell carcinoma: an analysis of 703 cases in southern Taiwan. Oral Oncol 1999;35:173–80.
[9] Algazi AP, Grandis JR. Head and neck cancer in 2016: a watershed year for improvements in treatment? Nat Rev Clin Oncol 2017;14:74–86.
[10] Schmitz S, Ang KK, Vermorken J, et al. Targeted therapies for squamous cell carcinoma of the head and neck: current knowledge and future directions. Cancer Treat Rev 2014;40:390–404.
[11] Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene 2007;26:6469–87.
[12] Rubin I, Yarden Y. The basic biology of HER2. Ann Rev Oncol 2001;3:53–8.
[13] Albuquerque R Jr, Miguel MC, Costa AL, et al. Correlation of c-erbB-2 and ERBB2 expression in oral and oropharyngeal squamous cell carcinoma. Clin Cancer Res 2002;8:165–74.
[14] Chen HY, Chang JT, Liao CT, et al. Prognostic significance of EGFR and Her-2 in oral cavity cancer in betel quid prevalent area. Br J Cancer 2003;89:681–6.
[15] Weed DT, Gommer-Fernandez C, Pacheco J, et al. MUC4 and ERBB2 expression in major and minor salivary gland mucoepidermoid carcinoma. Head Neck 2004;26:353–64.
[16] Zhang ZM, Xu ZG, Tang PZ. Expression of c-erbB-2, p16 in squamous cell carcinoma of anterior tongue in China population. Chin J Cancer Res 2004;16:24–30.
[17] Williams MD, Roberts D, Blumenschein GR, et al. Differential expression of hormonal and growth factor receptors in salivary duct carcinomas: biologic significance and potential role in therapeutic stratification of patients. Am J Surg Pathol 2007;31:1645–52.
[18] Silva SD, Perez DE, Alves FA, et al. ErbB2 and fatty acid synthase (FAS) expression in 102 squamous cell carcinomas of the tongue: correlation with clinical outcomes. Oral Oncol 2008;44:484–90.
[19] da Silva SD, Cunha IW, Nishimoto IN, et al. Clinicopathological significance of ubiquitin-specific protease 2a (USP2a), fatty acid synthase (FASN), and ErbB2 expression in oral squamous cell carcinomas. Oral Oncol 2009;45:134–9.
[20] Triantafyllidou K, Iordanidis F, Psomadakis E, et al. Acinic cell carcinoma of minor salivary glands: a clinical and immunohistochemical study. J Oral Maxillofac Surg 2010;68:2489–96.
[21] Ettl T, Baeder K, Stegler C, et al. Loss of PTEN is associated with elevated EGFR and HER2 expression and worse prognosis in salivary gland cancer. Br J Cancer 2012;106:719–26.
[22] Crox J, Shubin E, Hans S, et al. Expression and mutational status of treatment-relevant targets and key oncogenes in 123 malignant salivary gland tumours. Ann Oncol 2013;24:2624–9.
[23] Masubuchi T, Tada Y, Maruyama S, et al. Clinicopathological significance of androgen receptor, HER2, Ki-67 and EGFR expressions in salivary duct carcinoma. Int J Clin Oncol 2015;20:35–44.
[24] Xia L, Hu Y, Li J, et al. A low percentage of HER-2 amplification whereas indicates poor prognosis in salivary gland ex pleomorphic adenoma: a study of 140 cases. J Oral Pathol Med 2017;46:167–74.
[25] Hashimoto K, Hayashi R, Mukagawa T, et al. Concomitant expression of ezrin and HER2 predicts distant metastasis and poor prognosis of patients with salivary gland carcinomas. Hum Pathol 2017;63:110–9.
[26] Haderleim M, Scherl C, Semrau S, et al. Impact of postoperative radiotherapy and HER2/new overexpression in salivary duct carcinoma: a monocentric clinicopathologic analysis. Strahlenther Onkol 2017;193:961–70.
[27] Boon E, Bel M, van Boxtel W, et al. A clinicopathological study and prognostic factor analysis of 177 salivary duct carcinoma patients from The Netherlands. Int J Cancer 2018;143:758–66.
[28] Hou L, Shi D, Tu SM, et al. Oral cancer progression and c-erbB-2/neu proto-oncogen expression. Cancer Lett 1992;65:215–20.
[29] Karja V, Syrjänen S, Kataja V, et al. c-erbB-2 oncogene expression in salivary gland tumours. ORL J Otorhinolaryngol Relat Spec 1994;56:206–12.
[30] Willkam TS, Hietanen JH, Malmström MJ, et al. Immunohistochemical analysis of the oncoprotein c-erbB-2 expression in oral benign and malignant lesions. Int J Oral Maxillofac Surg 1998;27:209–12.
[31] Del Sordo R, Angiero F, Bellezza G, et al. HER family receptors expression in squamous cell carcinoma of the tongue: study of the
possible prognostic and biological significance. J Oral Pathol Med 2010;39:79–86.

[47] Clauditz TS, Reiff M, Geavert L, et al. Human epidermal growth factor receptor 2 (HER2) in salivary gland carcinomas. Pathology 2011;43:459–64.

[48] Hoyek-Gebeily J, Nehme E, Aftimos G, et al. Prognostic significance of EGFR, p53 and E-cadherin in mucoepidermoid cancer of the salivary glands: a retrospective case series. J Med Liban 2007;55:83–8.

[49] Monteiro LS, Bento MJ, Palmeira C, et al. Epidermal growth factor receptor immunoexpression evaluation in malignant salivary gland tumours. J Oral Pathol Med 2009;38:508–13.

[50] Cardoso WP, Denardin OV, Rapoport A, et al. Proliferating cell nuclear antigen expression in mucoepidermoid carcinoma of salivary glands. Sao Paulo Med J 2000;118:69–74.

[51] Okabe M, Inagaki H, Murase T, et al. Prognostic significance of p27 and ki-67 expression in mucoepidermoid carcinoma of the intraoral minor salivary gland. Mod Pathol 2001;14:1008–14.

[52] Yin HF, Okada N, Takagi M. Apoptosis and apoptotic-related factors in mucoepidermoid carcinoma of the oral minor salivary glands. Pathol Int 2000;50:603–9.

[53] Chen CF, Lu CC, Chiang JH, et al. Synergistic inhibitory effects of cetuximab and curcumin on human cisplatin-resistant oral cancer CAR cells through intrinsic apoptotic process. Oncol Lett 2018;16:6323–30.

[54] Lei YY, Huang JY, Zhao QR, et al. The clinicopathological parameters and prognostic significance of HER2 expression in gastric cancer patients: a meta-analysis of literature. World J Surg Oncol 2017;15:68.