Review Article

Prognostic Role of Long Noncoding RNAs in Oral Squamous Cell Carcinoma: A Meta-Analysis

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Long noncoding RNAs (lncRNAs) have emerged as critical regulators of tumor progression, and lncRNA expression levels could serve as a potential molecular biomarker for the prognosis and diagnosis of some cancers. However, the prognostic value of lncRNAs in oral squamous cell carcinoma (OSCC) remains unclear. Thus, a meta-analysis was conducted to explore the potential prognostic value of lncRNAs in OSCC. We systematically searched PubMed, EBSCO, Web of Science, and Elsevier from 2005 to 2021 to identify all published studies that reported the association between lncRNAs and prognosis in OSCC. Then, we used meta-analytic methods to identify the actual effect size of lncRNAs on cancer prognosis. The hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated to assess the strength of the association. The reliability of those results was then examined using measures of heterogeneity and testing for selective reporting biases. According to the inclusion and exclusion criteria, a total of 17 studies were eligible in our meta-analysis, involving 1384 Asian patients. The results identified a statistically significant association of high lncRNA expression with poor overall survival [adjusted pooled hazard ratio (AHR) = 1.52; 95% confidence interval (CI): [1.26–1.84], p ≤ 0.001]. The present meta-analysis demonstrated that lncRNA expression might be used as a predictive prognostic biomarker for Asian patients with OSCC.

1. Introduction

Oral squamous cell carcinoma (OSCC) is a significant subgroup of head and neck squamous cell carcinomas [1, 2]. OSCC is characterized by invasive growth, frequent metastases, and high recurrence, and its incidence is increasing, with more than 274,000 new patients with OSCC every year worldwide [3–5]. Although considerable developments in diagnosis and combined treatments have been made in recent years, the 5-year survival rate among OSCC patients has not improved and remains less than 50% [6–8]. Therefore, it is essential to identify useful biomarkers and therapeutic targets to improve the prognosis of OSCC.

Long noncoding RNAs (lncRNAs), a class of regulatory transcripts, are synthesized by RNA polymerase II and have lengths greater than 200 nucleotides [8–10]. Recent studies have shown that dysregulated lncRNAs play essential roles in tumor cellular processes of cell proliferation, differentiation, and invasion during cancer development and progression and play essential roles in tumorigenesis and progression of ovarian [11], colorectal [11], gastrointestinal [12], and lung cancers [13]. lncRNAs are regarded as essential therapeutic targets [14, 15].

Some studies have shown that abnormal lncRNAs contribute to biological behaviors, clinical diagnosis, prognosis, and treatment options in OSCC. HOX antisense intergenic
RNA (HOTAIR) is a transacting IncRNA that was the first identified IncRNA [16]. HOTAIR is located at chromosome 12q13.13, which is a regulatory boundary in the HOXC cluster [17]. The expression level of HOTAIR was significantly associated with metastasis, tumor differentiation, malignant degree, and prognosis of the patients. In addition, the upregulation of HOTAIR expression promoted OSCC cell proliferation, invasion, metastasis, and angiogenesis by binding to EZH2 and H3K27me3 and ultimately E-cadherin gene silencing [18]. H19 acts as an oncogene in OSCC by competing with miR-138 and releasing EZH2, thereby playing a role in cell proliferation, migration, invasion, apoptosis, and epithelial-mesenchymal transition (EMT), and high expression of H19 was correlated with TNM stage, lymph node metastasis, and poor prognosis outcome [19]. One study demonstrated that the low expression of IncRNA AC012456.4 contributed to poor disease-free survival (DFS) and indicated that IncRNA AC012456.4 remarkably correlated with the JNK-STAT and MAPK signaling pathways in tumorigenesis and functioned as a novel target for the diagnosis, clinical treatment, and outcome of OSCC [20]. Due to varying diagnostic accuracy, limitations in sample size, different IncRNA types, and research methods, a single-center study may be inaccurate and inadequate. Based on the current research situation, the present study was aimed at clarifying the clinical feasibility of IncRNAs as potential biomarker candidates by systematically summarizing all eligible articles.

2. Materials and Methods

2.1. Search Strategy. We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. A systematic literature review was searched from the PubMed, EBSCO, Elsevier, Web of Science, and Elsevier databases for papers online from 2005 to 2021. The search was performed by two independent researchers (YW and XL). The following search terms were used: (oral squamous cell carcinoma or OSCC) and (IncRNA or (long noncoding RNA) or (long noncoding RNAs)) and (prognosis or prognostic or survival). In addition, the cited references in the eligible studies were also searched and reviewed.

2.2. Inclusion and Exclusion Criteria. Inclusion criteria are as follows: (1) the research design was a prospective or retrospective study, (2) the paper researched the relationship between IncRNA and the prognosis of survival in OSCC, (3) the hazard ratio and 95% CI of overall survival were reported or could be calculated from the study, (4) more than 20 cases were included, and (5) studies were published in the English language. Two researchers (YW and XL) decided the ultimate eligible studies, and disagreements were resolved by consulting a third researcher (XBC). The exclusion criteria were as follows: (1) studies without sufficient or usable data; (2) reviews, laboratory articles, letters, unpublished data, and conference abstracts; and (3) duplicate publications.

2.3. Data Extraction and Quality Evaluation. Two investigators (YW and PW) perused the full text of the included articles and extracted relevant data independently from the eligible studies. Extracted information included the name of the first author, published year, regions, sample size, IncRNA types, HR and 95% CI, case number, outcome, HR estimation, and cutoff value [22]. The Newcastle–Ottawa quality assessment scale (NOS) was used to assess the quality of the included studies [23]. NOS scores of 1–3, 4–6, and 7–9 were designated as low, medium, and high quality, respectively. The quality evaluation was conducted by XL and PW independently, and disagreements were resolved through group discussion with a third investigator (XLZ).

2.4. Statistical Methods. p < 0.05 was considered statistically significant for comparing the groups with high and low expression of IncRNAs regarding survival of OSCC patients. p ≥ 0.05 was identified as no statistically significant difference between the two groups in OSCC patients.

HRs (HRs and 95% CIs) were calculated using a reported method [24] and used to evaluate the overall survival effect. If included articles reported the HR and 95% CI or did not directly provide the HR, but they reported the O-E value (observed value minus expected value), the 95% CI or the log-rank p value, we could calculate accurate HRs. If only the total number of cases, the number of each group, and the log-rank p value were reported, the approximate HRs could be calculated as described previously [24]. Additionally, if only valid data were provided in the form of survival curves, the data from Kaplan–Meier survival curves could be used to calculate HRs by Parmar’s method [25].

Statistical heterogeneity within studies was detected by the Q statistic and I² statistics. If I² ≤ 50% identified lower heterogeneity, a fixed-effect model was used. If I² > 50% showed higher heterogeneity, the random-effect model was used [26]. Subsequently, Egger’s method was used to detect
publication bias and observed in the form of a funnel plot [27]. If publication bias was found, then the HRs were adjusted by the method of Duval and Tweedie’s trim-and-fill [28].

### 3. Results

#### 3.1. Literature Search and Characteristics of the Included Studies

As shown in Figure 1, 631 articles were searched in the databases of PubMed, Web of Science, EBSCO, and Elsevier. After removing duplicate studies and ineligible studies, 405 studies remained. After reading the title, abstract, and keywords and further excluding irrelevant studies (n = 358), 47 eligible articles were downloaded and analyzed in detail. Seventeen articles were excluded because HR could not be calculated, and 13 articles were excluded because they did not focus on our area of interest. In the end, 17 studies were included in this review [19, 20, 29–43]. The necessary information and data from the included studies are shown in Tables 1 and 2. The studies enrolled 1384 participants, with a maximum sample size of 252 and a minimum sample size of 30 patients. Eligible studies published from 2013 to 2021 reported an association between lncRNA expression level and overall survival, and all participants’ ethnic backgrounds were Asian. In addition, lncRNAs and relevant targets in oral squamous cell carcinoma are shown in Table 3.

#### 3.2. Quality Evaluation

The data were extracted from all 17 eligible studies. According to the NOS quality assessment system, 9 studies were of high quality, 6 studies were of medium quality, and 2 studies were of low quality (Table 1). The average score of all included studies was 6.53. In addition, four studies were based on multivariate analysis, and 13 studies were based on univariate analysis. HR and 95% CI of each study are shown in Table 2.

#### 3.3. Meta-Analysis

The meta-analysis data of pooled HRs of overall survival were extracted from the 17 included studies. The results showed a pooled HR of 1.52 (95% CI, 1.26–1.84; p < 0.001) with statistically significant heterogeneity (Q-statistic, 75.00; I² = 71.80%, p value < 0.001, random-effect model) (Figures 2(a) and 2(b)). Compared with the decreased lncRNA expression group, upregulated lncRNA expression was correlated with poor prognosis.

Most of the lncRNAs were investigated in a single study; only NEAT1 was investigated in two studies. We then conducted a meta-analysis to assess the relationship between NEAT1 expression and overall survival (OS) in OSCC patients. We noted that the heterogeneity was significant (I² = 71.05%, p = 0.06). Therefore, a random-effect model was applied, and the results of the analysis showed that NEAT1 was not significantly associated with OS (HR: 2.49, 95% CI: 0.73–8.51; p = 0.15) (Figure 3).

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**Table 1: Necessary information about the included studies.**

| Study ID       | IncRNA   | Country | Sample | Reference | Detection method | Sample size | Outcome | Source of HR | Cutoff value | NOS |
|----------------|----------|---------|--------|-----------|------------------|-------------|---------|--------------|--------------|-----|
| Jie Wu, 2015 [18] | HOTAIR   | China   | Tissues | GAPDH     | qPCR              | 100         | OS      | Log rank     | Median       | 7   |
| Yonglong Hong, 2017 [19] | H19     | China   | Tissues | GAPDH     | qPCR              | 42          | OS      | Sur curve    | NA           | 6   |
| Luyi Chai, 2018 [29]  | ANRIL    | China   | Tissues | GAPDH     | qPCR              | 130         | OS      | Sur curve    | Median       | 6   |
| Yan Guo, 2018 [30]  | CEBPA-AS1| China   | Tissues | GAPDH     | qPCR              | 60          | OS      | Reported     | Median       | 3   |
| Gang Huang, 2018 [31]   | NEAT1    | China   | Tissues | NEAT1/RGS20 | qPCR            | 30          | OS      | Sur curve    | NA           | 8   |
| Xiaohua Liu, 2018 [32]   | NEAT1    | China   | Tissues | GAPDH     | qPCR              | 58          | OS      | Sur curve    | Median       | 7   |
| Koyo Nishiyama, 2018 [33] | DLEU1   | Japan   | Tissues | ACTB (β-actin) | qPCR         | 252         | OS      | Sur curve    | Median       | 8   |
| Tingru Shao, 2018 [34]   | AC0077271.3 | China   | Tissues | GAPDH     | qPCR              | 80          | OS      | Reported     | Median       | 6   |
| Chengcao Sun, 2017 [35]  | PDIA3P   | China   | Tissues | GAPDH     | qPCR              | 58          | OS      | Sur curve    | NA           | 3   |
| Chengmei Yang, 2016 [36]  | SOX21-AS1| China   | Tissues | GAPDH     | qPCR              | 86          | OS      | Reported     | Median       | 6   |
| Chenzheng Zhang2, 2017 [37] | FTH1P3 | China   | Tissues | GAPDH/U6  | qPCR              | 70          | OS      | Log rank     | Mean         | 9   |
| Chenzheng Zhang1, 2017 [38]  | LINC00668| China   | Tissues | GAPDH/U6  | qPCR              | 50          | OS      | Log rank     | Mean         | 8   |
| Zhongzhi Jin, 2018 [39]   | MORT     | China   | Tissues | GAPDH     | qPCR              | 59          | OS      | Reported     | Median       | 7   |
| Zhe Liu, 2018 [40]       | HNF1A-AS1| China   | Tissues | GAPDH     | qPCR              | 62          | OS      | Sur curve    | Median       | 5   |
| Qian Lyu, 2019 [41]      | MNCR     | China   | Tissues | GAPDH     | qPCR              | 80          | OS      | Sur curve    | Median       | 6   |
| J, Wang, 2019 [42]       | LACAT1   | China   | Tissues | GAPDH     | qPCR              | 78          | OS      | Sur curve    | Median       | 7   |
| Yixin Yang, 2019 [43]    | CASC9    | China   | Tissues | GAPDH     | qPCR              | 84          | OS      | Reported     | Median       | 9   |
Subsequently, we conducted subgroup analyses according to univariate and multivariate analyses, NOS score evaluation, and source of HR. The results are shown in Table 4. The combined analysis showed that upregulated lncRNA expression has significant prognostic value in OSCC: univariate analysis (AHR: 1.43, 95% CI: 1.20–1.71, \( p < 0.001 \)), multivariate analysis (AHR: 2.50, 95% CI: 1.65–3.78, \( p < 0.001 \)), source of HR (reported: HR: 1.85, 95% CI: 1.51-2.26, \( p < 0.001 \); survival curve: AHR: 1.18, 95% CI: 1.10-1.27, \( p < 0.001 \)), and NOS score evaluation (high: 1.64, 95% CI: 1.38–1.96, \( p < 0.001 \); medium: 1.45, 95% CI: 1.01–2.07, \( p = 0.04 \); low: 3.78, 95% CI: 1.92-7.44, \( p < 0.001 \)).

Publication bias of the included articles was evaluated by funnel plots and Begg's bias test. The shape of the funnel plot was asymmetrical, and the \( p \) value of Begg's test was 0.002 for OS of all enrolled articles, suggesting the existence of publication bias.
of significant publication bias in the meta-analysis. Then, we use Duval and Tweedie’s trim-and-fill method to adjust the HRs. The outcome of this study was adjusted for HRs.

4. Discussion

Oral squamous cell carcinomas (OSCC) are often detected at an advanced clinical stage with metastasis, and poor prognosis of oral cancer may lead to high incidence [44]. Despite considerable advances being achieved in medical technologies for cancer diagnosis and treatment in the past decades, the 5-year survival rate for patients with OSCC remains less than 50% [45].

Accumulating evidence reveals that lncRNAs serve critical regulatory roles in diverse biological processes, including gene expression, cell invasion, migration, and tumorigenesis.
Previous meta-analyses have demonstrated high expression of lncRNAs to correlate with poor prognosis in patients with various cancers, such as ovarian [11], colorectal [12], gastrointestinal [12], and lung cancers [13]. However, no meta-analyses have revealed the role of lncRNAs in OSCC prognosis.

We conducted a meta-analysis to validate the accuracy and value of the theoretical results of lncRNAs as prognostic molecular markers in patients with OSCC. A total of 17 studies, including 1384 patients, were enrolled within our meta-analysis. The expression of NEAT1 was upregulated. There are no downexpression lncRNAs in participants of this analysis. The analysis showed a reliable result for upregulated lncRNA expression to correlate with poor prognosis in OSCC (HR: 1.52, 95% CI: [1.26, 1.84]; p < 0.001, random effect). Also, subgroup analysis revealed that lncRNA expression correlated with prognosis, while the analysis method, source of HR, and NOS score evaluation did not significantly affect the pooled results of this meta-analysis. By our analysis, these findings suggest that lncRNA can be developed as a prognostic and therapeutic biomarker in OSCC.

Several lncRNAs with high HR in this study have also been reported in other cancers other than OSCC accidents. For example, CEBPA-AS1 with high HRs (HR: 6.71, 95% CI: 3.61-8.73) was also reported in gastric cancer. Ke et al. found that high expression of CEBPA-AS1 has a poor prognosis patients with gastric cancer [47]. HOTAIR, as one of the most crucial lncRNA, has been extensively studied, and overexpression HOTAIR is correlated with poor survival for breast, colon, and liver cancer patients [48]. This study also showed that patients with high expression HOTAIR have a poor prognosis in OSCC. While the prognostic value of NEAT1 was assessed, and the pooled HRs were 2.49 (95% CI: 0.73-8.51, p = 0.15, random effect), the results showed that NEAT1 was not statistically significantly associated with OS. Only two studies were included in this evaluation, resulting in a low power of evidence. NEAT1 has been found to be associated with many different types of cancer prognosis.

Fu et al. identified that lncRNA NEAT1 was overexpressed in gastric cancer tissues and cell lines, and patients with high levels of NEAT1 had more reduced survival than
those with lower levels of NEAT1 [49]. Chen et al. found that high expression of NEAT1 predicts poor prognosis and has a crucial regulatory role in esophageal squamous cell carcinoma [50]. Therefore, further research needs to confirm the mechanisms of NEAT1 in the progression of OSCC.

In this study, we also collected mechanisms of lncRNAs; 9 of the included studies investigated the correlation between lncRNAs and microRNAs. It could be evidenced from these researches that the relationship between lncRNAs and microRNAs is associated with cancer incidence. The same lncRNA is associated with the occurrence and development of different cancers, but the mechanism is still unclear. In the future, research hotspots may be focused on the method of simultaneous intervention with multiple RNA by exploring the interrelationship between lncRNA and multiple types of RNA.

It should be stressed that there are several limitations in our meta-analysis. Firstly, only 17 studies were eligible in this meta-analysis, which might weaken the reliability of our results. Secondly, remarkable statistical heterogeneity ($I^2 = 71.80\%$) was observed, which may be due to the differences in cancer types, internal control, cutoff value, clinical characteristics, and sample sizes. The geographical bias may be present, as all studies were performed in Asia. As demonstrated in previous studies, people of different race/ethnicity vary in their risk of developing OCSS, and the differences in OS may link both to the genetic and the lifestyle. We hope that other countries in different regions will also conduct relevant research and reports in the future. Finally, some HRs were extracted from the survival curves, which may lead to small statistical errors.

5. Conclusion

Despite several limitations described above, the meta-analysis offers evidence that upregulated lncRNAs are significantly corrected with poor OS in Asian patients with OSCC, which demonstrated that the lncRNAs could serve as the prognostic factor for Asian patients with OSCC. However, large-scale and comprehensive studies are needed to improve the credibility of our findings and thus promote the clinical utility of lncRNAs in OSCC prognosis evaluation.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Yu Wang and Peng Wang are equal contributors and co-first authors.

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