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ORIGINAL ARTICLE

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Meta-analysis of the prognostic value of the neutrophil-to-lymphocyte ratio in oral squamous cell carcinoma

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Background: A number of studies have assessed the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in oral squamous cell carcinoma (OSCC), but their results regarding the predictive value of NLR in OSCC are inconsistent. We therefore performed a meta-analysis to clarify the association between NLR and clinical outcome in OSCC.

Methods: We searched the MEDLINE and Web of Science to identify potential studies investigating the association between NLR and survival in OSCC.

Results: A total of 10 studies, enrolling 2135 patients with OSCC, were included. A higher NLR was a negative predictor for both disease-specific survival (hazard ratio [HR] = 1.93, 95% CI: 1.47-2.54) and overall survival (HR = 1.56, 95% CI: 1.28-1.90).

Conclusion: This suggests a higher NLR is predictive of a poorer prognosis in OSCC. Because determination of NLR is non-invasive and cost-effective, it could be widely used for predicting prognosis in OSCC.

KEYWORDS
meta-analysis, mouth neoplasms, neutrophil-to-lymphocyte ratio, oral cancer, prognosis

1 | INTRODUCTION

Oral cancer is one of the most frequently occurring human tumors, accounting for 409 000 new cases and 135 000 deaths worldwide in 2013,[1] and its incidence is increasing.[2,3] Oral squamous cell carcinoma (OSCC) is a predominant histological type of oral cancer.[4] Although much progress has been made in the treatment of OSCC in recent years, the prognosis remains poor, with a 5-year survival rate of <50%.[5] At present, the prognosis and treatment of OSCC are based mainly on the American Joint Committee on Cancer (AJCC) TNM classification which was based on tumor's size, spread to lymph nodes and metastasis.[6] However, a major limitation of this classification is that it is not perfectly accurate, and a combination of other factors is more predictive of prognosis than traditional tumor staging in patients with OSCC.[7]

Systemic inflammation plays a key role in tumor development and progression.[8] Inflammatory markers such as the circulating neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and C-reactive protein level are used as predictive markers for various tumors.[9-11] These inflammation markers are not only easy to acquire; they also have strong predictive value with oncologic patients.[9] Several studies have investigated the use of inflammatory markers as indicators to predict OSCC progression.[7,12-20] However, the results of these studies

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regarding use of the NLR as a prognostic marker for OSCC are controversial, due largely to the limited sample sizes and variation in study designs. Therefore, the aim of this meta-analysis was to assess the prognostic value of NLR among patients with OSCC.

2 | METHODS

2.1 | Literatures search

This meta-analysis was conducted in accordance with guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[21] A search of the MEDLINE and Web of Science electronic databases was performed, and studies published up to December 31, 2017, were considered. The key words in our literature search were as follows: "(NLR OR neutrophil to lymphocyte ratio OR neutrophil lymphocyte ratio OR neutrophil-lymphocyte-ratio) AND (mouth OR oral OR lip (delete) OR tongue OR buccal OR palate OR gingiva OR gingival OR mouth floor) AND (tumor OR neoplasm OR cancer OR carcinoma) AND (survival OR prognosis OR prognostic)". We also screened the reference lists in the included studies and relevant reviews to find additional potentially relevant articles.

2.2 | Selection and exclusion criteria

The following eligibility criteria were used: (i) investigating the prognostic value of NLR; (ii) reporting the hazard ratio (HR) with estimates of 95% CIs (or data available for calculation); and (iii) patients were diagnosed with oral cancer. The following exclusion criteria were applied: (i) conference abstracts, case reports, letters, editorials, and reviews; (ii) duplicate publications or unpublished studies; and (iii) papers in a language other than English.

2.3 | Data extraction and quality assessment

All the potential studies were reviewed, and the data were independently extracted by 2 authors (Yue Wang and Peng-fei Wang). Missing data were requested from the corresponding author(s) by e-mail in prior. The HR with 95% CIs was estimated from Kaplan-Meier curves according to a previous method.[22] Two investigators (Yue Wang and Peng-fei Wang) independently assessed the risk of bias in the included studies using the method of Newcastle-Ottawa Scale (NOS).[23] The following components were assessed: sequence generation, allocation concealment, incomplete outcome data, and other sources of bias. Disagreements were resolved through discussion.

2.4 | Statistical analysis

Study-specific HRs and 95% CIs were used to calculate pooled HRs. The HR (95% CI) for NLR predicting survival was available in the papers or was requested by e-mail. Study-specific log RRs or log ORs were weighted using the inverse of their variances. We present pooled ORs in random-effect models, which provide pooled results that are less precise, but provide correct coverage instead. The heterogeneity among the studies was assessed using the method of DerSimonian and Laird. We quantified the heterogeneity using I^2. To investigate the potential origin of the heterogeneity, we performed subgroup analyses. Small trail bias was assessed using Begg's test and Egger's test.

3 | RESULTS

3.1 | Literature search and study characteristics

The flowchart for the literature searches is shown in Figure 1. An initial search identified 108 papers, of which 46 were excluded as duplications. Sixty-two papers were retained after screening the titles and abstracts, as they were not related to topic of the study. Eight additional papers were excluded after full-text evaluation because of our inclusion/exclusion criteria. Chen et al.[20] investigated the prognostic value of the NLR and provided 2 cutoffs; therefore, with more than 1 HR, it was excluded from the analysis.

Consequently, 10 studies consisting of 2135 patients with oral cancer were included in this meta-analysis.[7,12-19,24] All of the included studies were published in English between 2013 and 2017 and were performed in China, India, Austria, Japan, and South Korea. The sample sizes ranged from 69 to 471 patients (Table 1). All the studies except one provided a cutoff value for NLR[16] (delete). The prognostic value of NLR was evaluated based on overall survival (OS) in 6 studies and on disease-specific survival (DSS) in 6 studies. The median NOS was 7.5 (standard deviation 1).[23]

3.2 | Disease-specific survival

It is accepted that DSS may better reflect outcomes in oral cancer than OS. Six studies, enrolling a total of 1161 patients, provided HRs

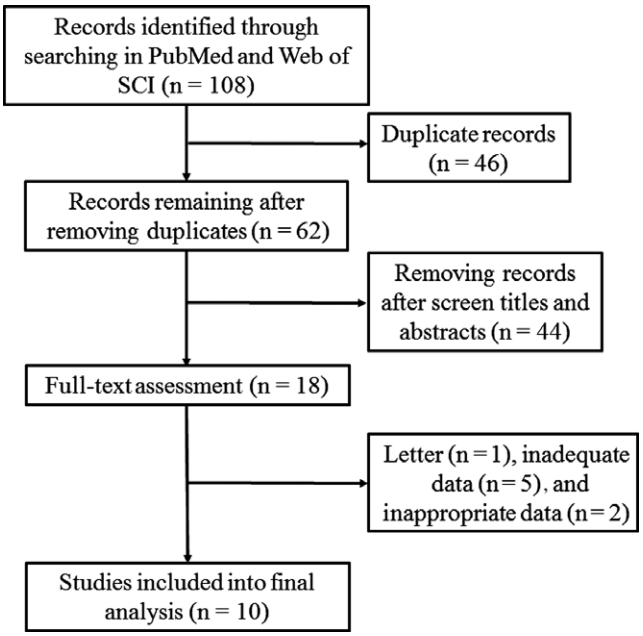

FIGURE 1 Flow chart of the included studies

TABLE 1 Description of included studies investigating the prognostic value of NLR in patients with oral cancer

Study	Country	Study design	Sample size	Cutoff value for NLR	Survival analysis	HR (95% CI)	Multivariate analysis factors adjusted in the analysis	NOS
Fang, 2013	China	Retrospective	226	2.44	OS	2.040 (1.036-4.014)	Univariate analysis	6
Perisanidis, 2013	Austria	Retrospective	97	1.9	DSS	10.37 (1.28-84.08)	Perineural invasion, TNM stage	8
Tsai, 2014	China	Retrospective	213	5	DSS	2.41 (0.51-8.76)	Univariate analysis	7
Nakashima1, 2016	Japan	Retrospective	124	2.4	DSS, OS	DSS: 1.733 (0.739-4.415) OS: 1.963 (0.879-4.734)	Primary site, T/N stage, differentiation, pathological response	8
Christina EC, 2016	Austria	Retrospective	144	1.9	OS	1.16 (0.65-2.06)	Univariate analysis	8
Ong, 2016	China	Retrospective	133	na	OS	1.585 (1.016-2.754)	Histologic grading, neutrophil count, lymphocyte count, platelet count, PLR, and LMR	7
Bobdey, 2017	India	Retrospective	471	2.38	OS	1.392 (1.045-1.855)	TNM stage, lymph node mets, and monocyte	7
Lee, 2017	China	Retrospective	396	2.37	DSS	1.74 (1.23-2.46)	TNM stage, perineural invasion	8
Wu, 2017	China	Retrospective	262	2.95	DSS, OS	DSS: 2.106 (1.007-4.405) OS: 2.292 (1.326-3.962)	Lymph node density, tumor thickness, extranodal extension	8
Park et al.	South Korea	Retrospective	69	2.29	DSS	2.65 (1.01-6.93)	Univariate analysis	7

DSS, disease-specific survival; HR, hazard ratio; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NOS, Newcastle-Ottawa Scale; OS, overall survival; PLR, platelet-to-lymphocyte ratio.

for DSS. Two of those studies reported non-significant HRs. In the remaining 3 studies, a higher NLR was associated with poorer DSS (HR = 1.93, 95% CI: 1.47-2.54; Figure 2). A fixed-effect model was used because there was no obvious heterogeneity. Next, subgroup analyses were carried out taking into consideration the cutoff value, univariable or multivariable analysis, cases and NOS. In these analyses, NLR continued to appear as a prognostic marker, except when the number of patients is <200 (Table 2). We found no publication bias with Begg's test (P = .060, Figure S1A) or Egger's tests (P = .050, Figure S1B).

3.3 | Overall survival

There were 6 studies, enrolling 1360 patients, included in this analysis. Two studies reported non-significant HRs. The pooled HR for OS was 1.56, and the 95% CI was 1.28-1.90 (Figure 3). Because no significant heterogeneity was observed, a fixed-effect model was used together with subgroup analysis. NLR continued to appear as a prognostic marker independent of variation in other factors (Table 2). We detected no publication bias with Begg's test (P = .707, Figure S1C) or Egger's tests (P = .266, Figure S1D).

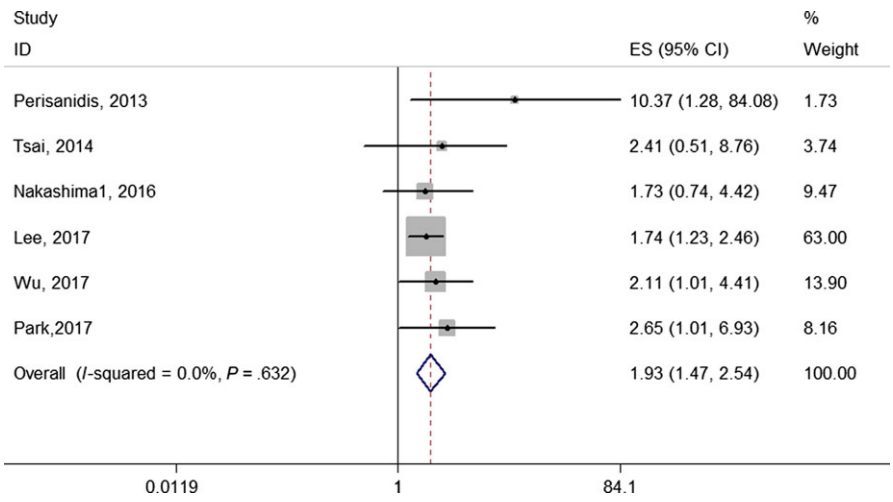

FIGURE 2 Forest plot showing neutrophil-to-lymphocyte ratio hazard ratios for disease-specific survival in oral squamous cell carcinoma (OSCC)

TABLE 2 Subgroup analysis of the prognostic value of neutrophil-to-lymphocyte ratio in oral squamous cell carcinoma

Factor	No. of studies	No. of cases	Pooled hazard ratio with 95% CI	I^2, %	$P_{heterogeneity}$
Disease-specific survival					
Cutoff (<5)	5	948	1.913 (1.445-2.532)	0.00	.502
Multiple analysis	4	879	1.856 (1.385-2.488)	0.00	.413
Cases >200	3	871	1.826 (1.344-2.480)	0.00	.833
Cases ≤200	3	280	0.889 (0.263-1.514)	17.60	.297
Newcastle-Ottawa Scale (NOS) ≥8	4	879	1.856 (1.385-2.488)	0.00	.413
Overall survival					
Multiple analysis	4	990	1.582 (1.271-1.968)	0.00	.427
Cases >200	3	959	1.603 (1.264-2.034)	34.50	.217
Cases ≤200	3	401	1.470 (1.042-2.074)	0.00	.552
NOS ≥8	3	530	1.711 (1.195-2.451)	32.00	.230
NOS <8	3	830	1.499 (1.187-1.893)	0.00	.577

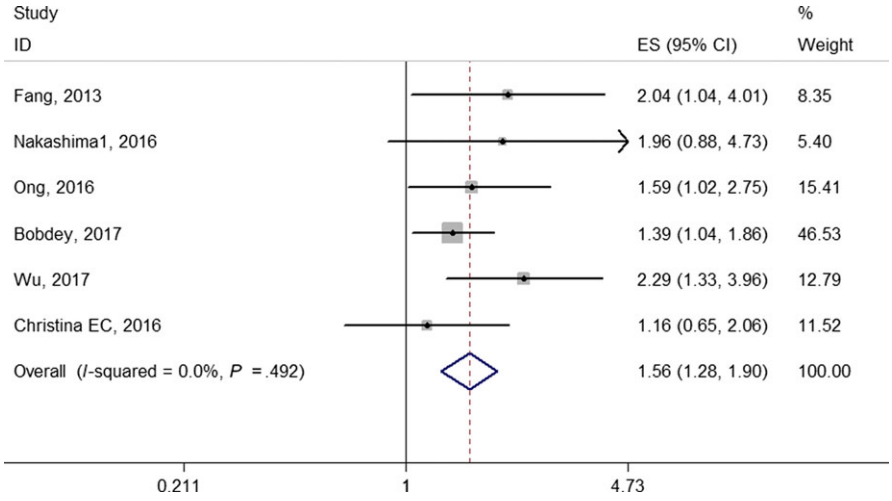

FIGURE 3 Forest plot showing neutrophil-to-lymphocyte ratio hazard ratios for overall survival in oral squamous cell carcinoma (OSCC)

4 | DISCUSSION

The present meta-analysis of 10 studies in which 2135 patients were enrolled indicates that a high NLR is associated with a poor prognosis in patients with OSCC. A recently published meta-analysis showed that a higher NLR is associated with a poorer clinical outcome in patients with advanced tumors.[9] However, our meta-analysis is the first to assess the prognostic value of NLR in patients with OSCC.

Our results are consistent with those of a large prospective study investigating the prognostic role of NLR in OSCC.[20] That study was not included in our meta-analysis, although its results support our conclusion and show that a high NLR is associated with a worse prognosis in patients with OSCC. The value of NLR as a prognostic marker has also been shown for other cancers, including colorectal and pancreatic cancers, among others.[9] In Mei et al.'s[9] analysis, the cutoff value for NLR divided by 5 was predictive of clinical outcome in advanced cancers. The cutoff in most of our included studies was all <5 and suggested a lower NLR was associated with improved OS and DSS. That Tsai obtained non-significant results when the cutoff for NLR was set at 5[14] suggests the optimal cutoff value should <5 for oral cancers. Interestingly, a significant association was observed between NLR and TNM stage in oral cancers.[7,12,14] In our study, however, most cases were not advanced stage cancers, which may also explain why the optimal cutoff for NLR varied.

The mechanism underlying the prognostic value of NLR in patients with OSCC likely involves inflammation.[8,25] There is a close relationship between inflammation and tumor progression, immune function, and treatment response.[8] The key role of inflammation was further confirmed by observations that other inflammation markers, such as the platelet-lymphocyte ratio and the serum C-reactive protein level, are also prognostic in OSCC.[12,26,27] Moreover, tumor-infiltrating lymphocytes (TILs) and immune checkpoint inhibitors programmed death ligand-1 (PD-L1) are involved in tumor immunosuppression in OSCC.[28,29] PD-L1 is also reportedly prognostic in OSCC.[29] These results suggest a complicated mechanism of

immunosuppression in OSCC, which involves systemic inflammation, TILs, and PD-L1. Thus, a comprehensive evaluation of immune status in OSCC would be necessary to fully assess prognosis.

Although our meta-analysis showed the prognostic value of NLR in OSCC, it has several limitations. First, only limited number of studies was assessed. It was not necessary to assess publication bias when the number of studies was small. Nevertheless, we assessed the bias and found no heterogeneity. Second, all included studies were retrospective and contained recall bias. Third, cutoff levels reported these studies varied, and the HRs for NLR were calculated using different methods. From these data, therefore, it is difficult to produce a generalized cutoff that can be applied clinically to predict prognosis in OSCC. Fourth, although the included studies dealt with oral cancers at different stages managed using varied treatment strategies, the prognostic value of NLR for a specific cancer stage or treatment strategy was not evaluated. Finally, differing cutoff values were used in the included studies, but most were around 2.5. While the subgroup analysis confirmed the prognostic value of NLR with different cutoff values, it was a problem for doctors to obtain an optimal value for individual patients in practice.

Our study demonstrated the prognostic value of NLR in oral cancers, but the work is not finished. The conclusion should be confirmed through a large prospective study employing a standardized cutoff value. The immunophenotypes of blood neutrophils and lymphocytes were identified by Caldeira et al.,[30] but the immune checkpoints expressed by $CD4^+$ or $CD8^+$ cells should be analyzed in oral cancers, as they might negatively influence antitumor immunity. Moreover, there were little data on neutrophils or lymphocytes in tumor tissue or saliva, and there is a need to investigate the immunophenotype and NLR within the tumor environment. Most importantly, research is needed to clarify the mechanism.

In summary, our results showed that a high NLR is a negative prognostic marker in OSCC and it can be readily introduced to clinical practice due to the ease and convenience of the measurements.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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