Neutrophil-to-lymphocyte ratio as a prognostic indicator in head and neck cancer: A systematic review and meta-analysis

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Abstract

Background: The purposes of this systematic review and meta-analysis were to investigate the relationship between the neutrophil-to-lymphocyte ratio (NLR) and prognosis in head and neck cancer.

Methods: A systematic review and meta-analysis were done to investigate the role of NLR in overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), and progression-free survival (PFS).

Results: For qualitative analysis, 33 cohorts with over 10,072 patients were included. For quantitative analysis, 15 studies were included with 5,562 patients. The pooled data demonstrated that an elevated NLR significantly predicted poorer OS and DSS.

Conclusion: An elevated pretreatment NLR is a prognostic marker for head and neck cancer. It represents a simple and easily obtained marker that could be used to stratify groups of high-risk patients who might benefit from adjuvant therapy.

Keywords
head and neck cancer, inflammatory markers, meta-analysis, neutrophil lymphocyte ratio (NLR), prognosis, systematic review

1 | INTRODUCTION

Head and neck cancer is one of the more common cancers worldwide,1 accounting for more than half a million new cases annually. The majority of head and neck cancers is of the squamous cell carcinoma histological subtype, and may be located in the anatomic compartments of the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. Standard therapies of head and neck cancer may be surgical, radiotherapy or chemotherapy, or a combination thereof. The mode of treatment is largely determined by the characteristics of the presenting tumor, namely the stage, grade, and location. These in turn determine the prognosis of the tumor. The other known prognostic factors for head and neck cancer include performance status, smoking and alcohol history, and human papillomavirus infection.

Recently, there has been an interest in easily obtained inflammatory biomarkers that have the potential to predict the prognosis in patients with cancer. Such markers are hypothesized to reflect the underlying complex interplay between the systemic inflammatory responses with the tumor microenvironment.2–4 Markers, such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, have been described in the literature. Of these inflammatory markers, the NLR has been widely reported. The ostensible ability of the NLR to act as a prognostic tool has been demonstrated in several meta-analyses in different cancer sites.5–7

Despite the surfeit amount of studies published, the prognostic value of the NLR in patients with head and neck cancer remains unclear, and even controversial.8 There are several meta-analyses of the NLR in nasopharyngeal cancers.
only. To the best of our knowledge, this is the first meta-analysis investigating the prognostic role of NLR in head and neck cancer in all sites. Therefore, our purpose in this study was to consolidate the published literature in order to clarify the relationship between the pretreatment NLR and the prognosis of patients with cancer in all sites of the head and neck.

2 | MATERIALS AND METHODS

2.1 | Design

Our search was performed in accordance with the Cochrane Handbook of DTA Chapter on searching. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines to identify, screen, and describe the protocols used in this systematic review. Because our systematic review and meta-analysis were performed on observational studies, we also followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist. Our search strategy was designed in collaboration with a librarian at the Hofstra Northwell School of Medicine (W.H.), and the systematic review was prospectively registered in an online systematic review database (Prospective Register of Systematic Reviews [PROSPERO] 2017:CRD42017059500).14

2.2 | Search strategy

Medline (via PubMed), EMBASE, and the Cochrane Library were searched on March 17, 2017. Scopus was searched on March 20, 2017. We searched all databases from their inception to the present with no restriction on language of publication. To gather additional literature, bibliographies were hand-searched and PubMed’s related articles search was performed on all included articles. Due to the large volume of results retrieved in Embase and Scopus, the publication type filters were used to exclude conference abstracts, letters, editorials, conference reviews, conference papers, and book chapters. Briefly, keywords used were variations of “inflammatory marker,” “neutrophil lymphocyte ratio,” “lymphocyte marker,” “cancer,” “neoplasm,” “squamous cell carcinoma,” and “head and neck cancer.” The full search strategy may be found in the Supporting Materials.

2.3 | Article selection

Articles were selected independently by 2 of the authors (T. T. and Y.B.) in 2 phases. In the first phase, we screened a list of titles and abstracts for full-text retrieval. During the first phase (title and abstract screening), our inclusion criteria was any study that reported a description of NLR in head and neck cancer, either in the title or abstract. If the content of the abstract was not clear, we selected the study for full-text review. Articles that passed the first phase of screening were selected for full-text retrieval and were assessed in a second phase of screening.

In the second phase, we screened full text articles using predetermined inclusion/exclusion criteria. Disagreements were resolved via consensus. For the second phase of the screening (full text retrieval), the following inclusion and exclusion criteria were applied. Inclusion criteria: (1) the article reports on prognostic impact of peripheral blood NLR in head and neck cancer and associated subsites; (2) the NLR was treated as a categorical variable; (3) the NLR was collected before treatment; (4) the NLR hazard ratio (HR)/risk ratio (RR) for overall survival (OS), disease-specific survival (DSS), with or without disease-free survival (DFS), with or without progression-free survival (PFS); (5) there is 95% confidence interval (CI) for survival statistic, with or without the P value; (6) is available as full text publication; (7) is in the English language; and (8) is a clinical trial, cohort, or case control. Exclusion criteria: (1) case report, conference proceeding, letters, or reviews/meta analyses; (2) thyroid and endocrine tumors; (3) animal studies; (4) laboratory studies; (5) duplicate literature and duplicate data; when multiple reports describing the same population were published, only the most recent or complete report was included; (6) metastatic cancers only; and (7) incomplete data (no NLR HR for OS/DSS). Studies with incomplete data (for example, studies that included Kaplan-Meier curves only, or without HR with 95% CI), were not excluded initially. In these cases, we contacted the corresponding authors in attempt to obtain their original data.

The PRISMA flow chart of the systematic review can be found in Figure 1. An initial search done using the search strategy (Supporting Materials) obtained an initial 900 results. De-duplication was then performed, which reduced the number of results to 500. The first phase of screening was performed next on the titles and abstracts, which reduced the number of results to 65. The agreement was good for the first phase with a kappa of 0.7. The second phase of screening resulted in the exclusion of a further 33 results. The agreement was very good for the second phase of screening with a kappa of 0.85. Thus, a total of 32 studies (33 cohorts) remained for quality assessment (Supporting Materials).

2.4 | Controlling for methodological heterogeneity

During quality assessment, we discovered there was significant methodological heterogeneity in the 32 initially selected articles. There was a wide range of NLR cutoffs as well as inconsistent methodologies of obtaining the cutoffs. The NLR cutoff range for OS and DSS was 1.92 to 5.56 and 1.9
to 5, respectively, with cutoffs unavailable from 2 studies. The NLR cutoffs were obtained from receiver operating characteristic (ROC) curve analysis or training sets in 15 studies, based on previous literature in 5 studies, median value in 5 studies, and percentile in 3 studies, and not mentioned in 4 studies.

In order to decrease the methodological heterogeneity of our dataset, we decided to only include studies that had (a) reported NLR cutoff and (b) NLR cutoff derived from ROC curve analysis or equivalent statistical method. To control for the wide range of NLR cutoffs, we performed further stratified analyses by excluding studies in the extreme 12.5% or 25% tails of the cutoff distribution (keeping the central 75% or 50% of studies for pooled analysis). Thus, we were able to perform quantitative analysis in 11 studies for OS, 5 studies for DSS, and 3 studies for PFS. There were insufficient studies of methodological similarity in DFS/recurrence-free survival (RFS) in order to perform a pooled quantitative analysis. The list of excluded articles with the reasons for exclusion may be found in the Supporting Materials.

2.5 Data extraction

Data forms were developed a priori as recorded in the PROSPERO registry. Two authors (T.T. and Y.B.) jointly
reviewed all of the full text articles together for the data extraction process. If there were disagreements about data points, a third author (P.C.) was consulted to adjudicate and resolve the disagreement. The following data points were collected: first author’s name; year of publication; country (region) of the population studied; sample size; age; sex; demographic data; follow-up period; tumor data, including histology, stage, grade and metastasis; survival data HR/RR OS, DSS, RFS, DFS, and/or PFS, with the associated 95% CI P value; survival data reported with univariate or multivariate analysis; cutoff value used to define “elevated NLR”; method of obtaining the cutoff value; and subgroup and covariate information.

For the analysis of the relationship between NLR and clinicopathological parameters, HR/RR and 95% CI were combined as the effective value. If several estimates of NLR HR for OS/DSS were reported in the same article, we chose the most powerful one (multivariate analysis was superior to univariate analysis, and the latter one weighted over unadjusted Kaplan-Meier analysis). If the method of NLR cutoff was by done by dividing the continuous NLR data into percentile cutoffs, the highest NLR percentile cutoff was chosen for data extraction. We attempted contacting authors if the information in their article was not sufficiently detailed to be extracted, such as details on adjusted regression analysis, information on NLR cutoff, or the method of obtaining the cutoff.48–50 If the HR for OS was reported as an HR of a patient with NLR below a specific cutoff experiencing the endpoint of death (vs HR of a patient with NLR above a specific cutoff experiencing the endpoint of death), we took the reciprocal of the reported HR in order to make it comparable with the other studies.50,69,72,74

2.6 | Statistical analysis

The logarithm of the HR with SE was used as the primary summary statistic. To obtain the log(HR) and SE, the HR with 95% CI was extracted directly from the studies. Additional calculation to obtain the HR was required if the study reported the reciprocal of the HR. Estimates of log(HR) were weighted and pooled using the generic inverse-variance.11 Because of anticipated heterogeneity, a more conservative approach applying the random effects model (the DerSimonian and Laird method) was chosen for all analyses. Forest plots were constructed for all outcomes displaying the random-effects model of the summary effect measure and 95% CI. Heterogeneity was assessed using Cochrane’s Q and Higgins’s I². Cochrane’s Q P value of < .1 and I² > 50% were considered as markers of significant heterogeneity. For survival statistics that showed heterogeneity, we additionally report the 95% prediction interval. The 95% prediction interval takes into account heterogeneity and is the statistic of choice when interpreting pooled results that show heterogeneity.79,80 All analyses was done using the RevMan version 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark)81 and Meta Essentials (ERASMUS Research Institute, Rotterdam, Netherlands).82 All statistical tests were 2-sided, and a P value of < .05 was considered statistically significant. No correction was made for multiple testing.

2.7 | Publication bias

To assess publication bias, Begg’s funnel plot and Egger’s bias indicator tests were used, if appropriate. If publication bias was detected, the influence of bias on the overall effect was assessed by Duval’s “Trim and fill” method.83 A Fail-safe N measure was also calculated with the methods described by Rosenthal.84 Due to the small number of studies reporting DSS and PFS, the funnel plots are presented with the omission of advanced publication bias tests. This is because publication bias tests have been described to be underpowered with <10 studies.85 Tests for publication bias were performed by Meta-Essentials (ERASMUS Research Institute, Rotterdam, Netherlands).82

3 | RESULTS

3.1 | Study characteristics

A total of 15 studies published between 2013 and 2016 were included in our meta-analysis, with sample sizes ranging from 104 to 1895 patients.18,65–78 The characteristics of the included studies are summarized in Table 1.18,65–78 Nine studies were from China, 2 from Japan, 1 each from Korea, India, Italy, and Austria. Of 15 studies, only 1 was a prospective cohort study. The rest of the studies were retrospective studies. With regard to the survival outcomes reported, 11 reported OS, 5 reported DSS, and 3 reported PFS. The NLR cutoffs were obtained from ROC curve analysis or equivalent means in all studies.

3.2 | Neutrophil-to-lymphocyte ratio and overall survival in head and neck cancer

Data from 11 studies were synthesized in the meta-analysis for NLR and OS in patients with head and neck cancer (Table 2).18,65–74 An elevated NLR value was found to be significantly associated with poorer OS with HR of 1.51 (95% CI 1.32-1.73; P < .001). The test for heterogeneity showed an I² value of 0%, P = .68, which represented no detectable heterogeneity. The forest plot and corresponding funnel plot are represented in Figure 2.18,65–74

Begg’s funnel plot for HR of OS indicated that there was evidence of publication bias, with fewer negative small studies reporting negative results than would be expected.
Therefore, we further performed Duval’s “trim and fill” analysis of OS data. It was estimated that an additional 4 studies remain unpublished. The filled meta-analysis for the effect of NLR in OS upheld our pooled results (adjusted HR 1.41; 95% CI 1.25-1.58; P < .001). A classic Failsafe N value was also calculated that showed that an additional 82 negative studies are needed to invalidate the current results. Last, we performed a sensitivity analysis on the dataset and the pooled results were not significantly changed (Supporting Materials).

### Table 1 Summary of included studies

| Author   | Year | Country | Study design | Site          | Follow-up (months) | Age (years) | Total no. | Stage I+II, no. | Stage III+IV, no. | Treatment modality | Outcomes |
|----------|------|---------|--------------|---------------|-------------------|-------------|------------|-----------------|-------------------|-------------------|----------|
| Bobdey65 | 2016 | India   | RCS OC       | Mean (22)     | Mean (50)         | 471         | 124        | 347             | N/A              | Surgery, RT, CT   | OS       |
| Chen66   | 2016 | China   | PC OC        | Not specified | Not specified     | 402         | 177        | 225             |                  | Surgery, RT, CT   | OS       |
| Fu67     | 2016 | China   | RCS L        | Not specified | Median (60)       | 420         | 0          | 420             |                  | Surgery, RT, CT   | OS, DSS  |
| Sun68    | 2016 | China   | RCS NP       | Median (50)   | Median (46)       | 251         | 46         | 205             | RT, CT            | OS, PFS           |
| Kano69   | 2016 | Japan   | RCS OP, HP   | Median (61.2) | Median (61)       | 285         | 63         | 222             | RT, CT            | OS               |
| Kawakita18 | 2016 | Japan   | RCS SG       | Median (39.6) | Median (64)       | 140         | N/A        | N/A             | Surgery, RT, CT   | OS, PFS           |
| Kim70    | 2016 | Korea   | RCS OP, HP, OC, L | Median (39) | Median (58)       | 104         | 0          | 104             | RT, CT            | OS, PFS           |
| Tu71     | 2015 | China   | RCS L        | Median (51) mean (54) | Median (59) | 141         | 80         | 61              | Surgery           | OS, RFS           |
| Turri-Zanoni72 | 2016 | Italy   | RCS PS       | Median (39) mean (51.1) | Median (65) mean (61.6) | 215 | N/A | N/A | Surgery, RT, CT | OS, RFS |
| Wang73   | 2016 | China   | RCS L        | N/A           | Mean (60.6)       | 120         | 39         | 81              | Surgery, RT, CT   | OS, RFS           |
| Li74     | 2016 | China   | RCS NP       | Median (45)   | Median (45)       | 409         | 77         | 332             | RT, CT            | OS               |
| An75     | 2010 | China   | RCS NP       | Median (62)   | Mean (47)         | 363         | 95         | 268             | RT, CT            | DSS              |
| Chang76  | 2013 | China   | RCS NP       | Not specified | Not specified     | 1895        | 766        | 1129            | RT, CT            | DSS              |
| Li77     | 2016 | China   | rPC NP       | Not specified | Not specified     | 249         | 32         | 217             | RT, CT            | DSS              |
| Perisanidis78 | 2013 | Austria | RCS OC       | Median (44.4) | Not specified     | 97          | 0          | 97              | Surgery, RT, CT   | DSS              |

| Abbreviations: CT, chemotherapy; DSS, disease-specific survival; HP, hypopharynx; L, larynx; N/A, not available; NP, nasopharynx; OC, lip and oral cavity; OP, oropharynx; OS, overall survival; PC, prospective cohort; PFS, progression-free survival; PS, paranasal sinus; RCS, retrospective cohort study; RFS, recurrence-free survival; rPC, retrospectively collected data on prospective cohort; RT, radiotherapy; SG, salivary gland. |
| Categorical descriptions given for the types of treatments given to the patients. |
| Data on breakdown not described in the article. |
| TNM classification used. |

3.3 Neutrophil-to-lymphocyte ratio and disease-specific survival in head and neck cancer

Data from 5 studies were synthesized in the meta-analysis for NLR and DSS in patients with head and neck cancer...
An elevated NLR value was found to be significantly associated with poorer DSS with HR of 1.50 (95% CI 1.23-1.83; \( P < .001 \)). The test for heterogeneity showed an \( I^2 \) value of 27\%, \( P = .24 \), which did not represent heterogeneity of results. The forest plot and corresponding funnel plot are represented in Figure 3.67,75–78 The NLR cutoffs for DSS ranged from 1.9 to 3.73. After exclusion of NLR cutoffs in the extreme 25\% tails, the DSS cutoff range was 2.50 to 2.59, and the pooled HR for DSS was 1.39 (95% CI 1.20-1.62; \( P < .001 \)) with no detectable heterogeneity (\( I^2 = 0\% \); \( P = .58 \)).

### 3.4 Neutrophil-to-lymphocyte ratio and disease-free survival/recurrence-free survival and progression-free survival in head and neck cancer

There were insufficient studies of methodological similarity in DFS/RFS in order to perform a pooled quantitative analysis. There were 3 eligible studies reporting PFS but the results showed significant statistical heterogeneity (\( I^2 = 63\% \); \( P = .07 \)), therefore, the pooled result was not interpreted (Supporting Materials).

### 4 DISCUSSION

This meta-analysis aimed to examine the relationship among NLR and OS, DSS, DFS/RFS, and PFS in head and neck cancer. The initial studies selected from the screening process had significant methodological heterogeneity. After a further round of exclusion, 15 studies of similar methodological design remained for meta-analyses.

The pooled data demonstrated that an elevated pretreatment NLR significantly predicted poorer OS (HR 1.51; 95% CI 1.23-1.83; \( P < .001 \)), DSS (HR 1.50; 95% CI 1.23-1.83) of patients with head and neck cancer. Of note, there was no detectable heterogeneity in OS (\( I^2 = 0\% \); \( P = .58 \)) or DSS (\( I^2 = 27\% \); \( P = .24 \)). There were insufficient studies of methodological similarity to pool DFS/RFS data. We were able to pool the results of 3 studies for PFS, however, because the statistical heterogeneity was high (\( I^2 = 63\% \); \( P = .07 \)), the pooled result is not reported.

### Table 2 Summary of neutrophil-to-lymphocyte ratio endpoint data

| Author        | NLR cutoff | Method of obtaining cutoff | HR (95% CI)       | \( P \) value | Type of analysis |
|---------------|------------|----------------------------|-------------------|---------------|-----------------|
| OS            |            |                            |                   |               |                 |
| Bobdey\textsuperscript{65} | 2.38       | ROC curve analysis using same dataset | 1.392 (1.045-1.855) | .024          | M               |
| Chen\textsuperscript{66}      | 3.66       | Generated through training set using X-tile program based on \( P \) values | 1.94 (1.16-3.27) | .012          | M               |
| Fu\textsuperscript{67}        | 2.59       | ROC curve analyses using training dataset | 1.31 (1-1.71) | .046          | M               |
| Sun\textsuperscript{68}       | 2.6        | ROC curve analysis using same dataset | 1.87 (0.89-3.95) | .99           | M               |
| Kane\textsuperscript{69}      | 1.92       | ROC curve analysis using same dataset | 1.348 (0.831-2.183)\textsuperscript{a} | .228          | M               |
| Kawakita\textsuperscript{18}  | 2.5        | ROC curve analysis using same dataset | 1.8 (1.05-3.08) | .032          | M               |
| Kim\textsuperscript{70}       | 3          | ROC curve analysis using same dataset | 1.52 (0.97-2.58) | .156          | M               |
| Tu\textsuperscript{71}        | 2.17       | ROC curve analysis using same dataset | 2.177 (1.208-3.924) | .010          | M               |
| Turri-Zanoni\textsuperscript{72} | 5.56   | ROC curve analysis using same dataset | 2.17 (1.04-4.55)\textsuperscript{a} | .08           | M               |
| Wang\textsuperscript{73}      | 2.79       | ROC curve analysis using same dataset | 1.994 (1.089-3.649) | .025          | U               |
| Li\textsuperscript{74}        | 2.48       | ROC curve analysis using same dataset | 1.15 (0.683-1.938) | .598          | M               |
| DSS            |            |                            |                   |               |                 |
| Fu\textsuperscript{67}        | 2.59       | ROC curve analyses using training dataset | 1.42 (1.06-1.91) | .018          | M               |
| An\textsuperscript{75}        | 3.73       | ROC curve analysis using same dataset | 1.74 (1.15-2.62) | .008          | M               |
| Chang\textsuperscript{76}     | 2.5        | ROC curve analysis using same dataset | 1.351 (1.128-1.618) | .001         | M               |
| Li\textsuperscript{77}        | 2.5        | ROC curve analysis using same dataset | 1.939 (1.004-3.761) | .049          | M               |
| Perisanidis\textsuperscript{78} | 1.9       | ROC curve analysis using same dataset | 10.37 (1.28-84.06) | .0290        | M               |
| PFS            |            |                            |                   |               |                 |
| Sun\textsuperscript{68}       | 2.6        | ROC curve analysis using same dataset | 2.01 (1.23-3.29) | .005          | M               |
| Kawakita\textsuperscript{18}  | 2.5        | ROC curve analysis using same dataset | 1 (0.63-1.59) | .994          | M               |
| Kim\textsuperscript{70}       | 3          | ROC curve analysis using same dataset | 1.12 (0.97-1.47) | .156          | M               |

Abbreviations: CI, confidence interval; DSS, disease-free survival; HR, hazard ratio; M, multivariate; OS, overall survival; PFS, progression-free survival; ROC, receiver operator characteristic; U, univariate.

\( a \)The reciprocal of the reported value was used to be able to compare against other studies.
In order to investigate the effect of the wide range of NLR cutoffs, we also performed additional stratified analyses by excluding studies that used NLR cutoffs in either the extreme 12.5% or 25% of the NLR cutoff distribution (therefore, the central 75% and 50% of cutoffs remained for analysis). For the OS analysis, the resultant NLR cutoff ranges were much narrower after excluding cutoff values at the extreme 12.5% or 25%, at ranges of 2.17 to 3 and 2.38 to

**FIGURE 2** A. Neutrophil-to-lymphocyte ratio (NLR) and overall survival (OS) in head and neck cancer. Forest plot meta-analysis of the association between elevated NLR above the cutoff and OS in head and neck cancer. Each study is shown by the last name of the first author, and the hazard ratio (HR) with 95% confidence interval (CI). The summary HR and 95% CI is also shown (according to random effect estimations). B. The NLR and OS in head and neck cancer. The funnel plot of the studies included in the meta-analysis [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3  Stratified analysis

| Stratified analysis          | Cohorts, no. | NLR cutoff range | Random effects model | Heterogeneity |
|-----------------------------|--------------|------------------|----------------------|--------------|
|                             |              |                  | HR (95% CI)          | P valueb     | I² (%) | P valuec |
| Overall pooled OS           | 11           | 1.92-5.56        | 1.51 (1.32-1.73)     | < .001       | 0  .68 |
| Extreme 12.5% of cutoffs    | 8            | 2.17-3           | 1.47 (1.27-1.71)     | < .001       | 0  .62 |
| Extreme 25% of cutoffs      | 6            | 2.38-2.79        | 1.42 (1.21-1.68)     | < .001       | 0  .63 |
| Overall pooled DSS          | 5            | 1.9-3.73         | 1.50 (1.23-1.83)     | < .001       | 27  .24 |
| Extreme 25% of cutoffs      | 3            | 2.50-2.59        | 1.39 (1.20-1.62)     | < .001       | 0  .58 |

Abbreviations: CI, confidence interval; DSS, disease-specific survival; HR, hazard ratio; I², Higgin’s test for heterogeneity; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

aForest plot and list of studies included in each subgroup may be found in the Supporting materials.

bP value of random effects model for pooled HR.
cP value of Cochrane Q test for heterogeneity.
Both stratified results upheld the overall pooled results for OS with no detectable heterogeneity ($I^2 = 0\%$). Similarly, in the DSS analysis, we excluded studies with cutoffs in the extreme 25\%, and the resultant range of NLR cutoffs was much narrower (range 2.50–2.59). The stratified DSS result upheld the overall DSS result, with a decrease in heterogeneity ($I^2 = 0\%$ from $I^2 = 27\%$).

The above findings suggest that a dichotomized cutoff for NLR that is generated through population-specific or ROC methods could be used to guide clinical stratification and decision making with regard to outcomes for OS or DSS in head and neck cancer. To the best of our knowledge, this is the first meta-analysis reporting the relationship between elevated pretreatment NLR and outcomes in head and neck cancer. A recent search on the clinicaltrials.gov database has also shown that there are several prospective clinical trials investigating NLR in head and neck cancer that are already underway (NCT02211677).

Recently, novel prognostic systems have been developed incorporating NLR, such as the combination of NLR and platelet counts in hypopharyngeal cancer, or histopathological staging and NLR in oral cancer. Other inflammatory...
markers and systems, such as the platelet-to-lymphocyte ratio,72 lymphocyte-to-monocyte ratio,69 and Glasgow Prognostic Score93 have also received interest as prognostic indicators in head and neck cancer. It remains to be seen which of these markers, or combination thereof, is the superior option for clinical use as a prognostic biomarker.

There are several weaknesses in our study that we acknowledge. First, there was a wide range of NLR cutoff values for the included studies. However, we accounted for this by excluding studies with NLR cutoffs in the extreme tails of the cutoff distribution in an additional stratified analysis. The resultant cutoffs for OS and DSS were much narrower after exclusion of the extreme tails. The results of the stratified analysis corroborated the results of the overall pooled results for OS and DSS.

Another limitation to our study is that most of the studies included were also retrospective in nature, with only 1 true prospective study. Furthermore, because of a lack of individual patient data in many of the studies, we were unable to perform meta-analyses of individual patient data. Another limitation of this article is the publication bias detected for OS, as there were significantly more articles published that reported a poorer OS for higher NLR. However, the adjusted trim and fill analysis did not change the original conclusion. Last, the primary endpoint chosen for inclusion of studies was OS/DSS; therefore, DFS and PFS data were drawn from studies that reported OS/DSS as an endpoint.

The advantages of our study were the high amount of studies included, agreement of our results with the existing literature in other cancers, and significance using the random effects model. The effect of NLR on OS was also stable after literature in other cancers, and significance using the random effects model. The effect of NLR on OS was also stable after

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