

CLINICAL REVIEW

High pretreatment neutrophil-to-lymphocyte ratio as a predictor of poor survival prognosis in head and neck squamous cell carcinoma: Systematic review and meta-analysis

Lin Yang MD | Yu Huang MD | Lie Zhou MD | Yuhong Dai MD | Guangyuan Hu MD

Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Correspondence

Guangyuan Hu, Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Road, Wuhan 430030, Hubei, China.
Email: h.g.y.121@163.com

Funding information

Contract grant sponsor: This Study was supported by the Natural Science Foundation of Hubei Province (2015CFB541)

Section Editor: David W. Eisele, MD

Abstract

Background: The prognostic roles of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been reported in head and neck squamous cell carcinoma (HNSCC), but their results remain controversial.

Methods: A total of 25 literatures with 28 cohorts involving 6847 HNSCC patients were included. The hazard ratio (HR) was pooled with 95% confidence interval (CI) using fixed-effects or random-effects models.

Results: High pretreatment NLR predicted poor overall survival (OS: HR = 1.68; 95% CI = 1.39-2.03; $P < .001$), disease-free survival (DFS: HR = 1.76; 95% CI = 1.42-2.17; $P < .001$), progression-free survival (PFS: HR = 1.53; 95% CI = 1.09-2.14; $P = .014$), and cancer-specific survival (CSS: HR = 1.45; 95% CI = 1.23-1.71; $P < .001$) in HNSCC. However, the association between PLR and OS or DFS was not statistically significant.

Conclusion: The NLR can serve as a potential prognostic biomarker for patients with HNSCC.

KEYWORDS

head and neck squamous cell carcinoma, meta-analysis, neutrophil-to-lymphocyte ratio, platelet-to lymphocyte ratio, prognosis

1 | INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cancer by incidence worldwide, causing more than 200 000 deaths per year.¹ HNSCC occurs in various sites within the head and neck region, including oral cavity, oropharynx, hypopharynx, and larynx.² Although treatments for HNSCC progress rapidly, the 5-year survival rate is still less than 50%, which represents a therapeutic challenge.^{3,4} Local recurrence and distant metastasis are main reasons leading to treatment failure. Therefore, it is crucial to identify patients with poor prognosis and strengthen their treatment. The clinical TNM classification system is most frequently used for prognostic evaluation. However, this

system only focuses on the anatomic extent of tumor and is insufficient to predict prognosis precisely. Patients with the same TNM classification often have different outcomes. Recently, several new prognostic biomarkers have been explored in HNSCC, such as human papillomavirus (HPV) infection status,⁵ cancer stem cell markers,⁶ and peripheral blood cell counts and ratios.⁷ Accumulated evidence suggests that inflammation plays an essential role in tumorigenesis and tumor progression, which is now included as a hallmark of cancer.^{8,9} The peripheral inflammatory cells and calculated ratios, especially neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been demonstrated as independent prognostic biomarkers in various cancers, including breast cancer,¹⁰ esophageal

carcinoma,¹¹ colorectal carcinoma,¹² and lung cancer.¹³ Opposing to the TNM staging system, which only represents the status of tumor, NLR and PLR could reflect the inflammatory status of host and supplement the TNM staging system. Several studies have assessed the association between level of NLR or PLR and clinical outcomes in HNSCC.^{7,14,15} However, the results remain controversial, because of variation in study design, limited sample size and single-institution.

A published meta-analysis, including 100 studies of patients with unselected solid tumors, revealed that elevated NLR was associated with worse overall survival (OS) in all disease sites, subgroups, and stages.¹⁶ However, this meta-analysis only included two studies on NPC, and no studies on non-nasopharyngeal HNSCC. As is well known, NPC has distinct genotype, clinical phenotype, and prognosis from HNSCC, which is more sensitive to regular chemotherapy and radiotherapy.¹⁷ Besides this, there have been several meta-analyses reporting the association between the NLR and the prognosis in NPC.^{17–19} Thus, a more comprehensive meta-analysis to evaluate the prognostic role of NLR and PLR on non-nasopharyngeal HNSCC is warranted.

Moreover, NLR and PLR are cost-effective and easily available in pretreatment evaluation of the blood test compared with other prognostic factors.

In the present meta-analysis, we collected and pooled the related literatures to quantify the predictive impact of peripheral blood NLR and PLR on survival prognosis in patients with HNSCC.

2 | PATIENTS AND METHODS

2.1 | Search strategy

The databases of PubMed, Embase, Web of Science and the Cochrane library literature were thoroughly searched up to July 3, 2017. Only English literatures were considered. The searching strategy was randomly combing the following terms: HNSCC (“head and neck squamous cell” or “oral” or “larynx*” or “pharynx*” or “tongue” or “oropharynx*” or “hypopharynx*”), cancer (“carcinoma” or “tumor” or “neoplasm”) and NLR (“neutrophil lymphocyte ratio” or “neutrophil to lymphocyte ratio” or “neutrophil-to-lymphocyte ratio”) or PLR (“platelet lymphocyte

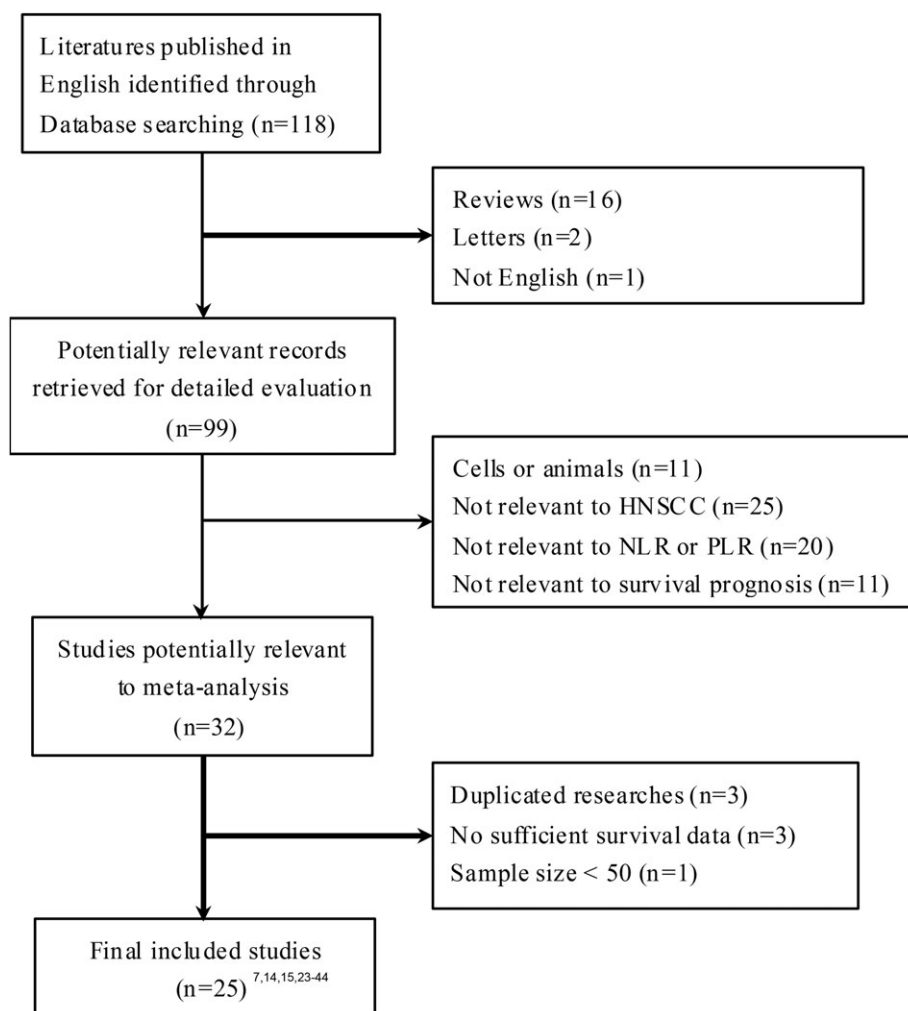


FIGURE 1 Flow chart of studies selection procedure

TABLE 1 Characteristics of studies included in this meta-analysis

Author	Year	Country	Sample size	Tumorsite	Tumor stage	NLR cutoff	PLR cutoff	Outcome	HR/model	NOS score
Fang ²³	2013	China	226	OC	I-IV	2.44	–	OS, DFS	R/U	7
Tsai ²⁴	2014	China	202	OC	NA	5	–	CSS	R/U	8
Young ²⁵	2014	UK	251	OP	I-IV	5	–	OS	E/U	8
Moon ²⁶	2015	Korea	153	HN	I-IV	NA	–	OS, PFS, CSS	R/M	8
Rassouli ⁷	2015	Canada	273	HN	NA	4.2	170	DFS	E/U	8
Salim ²⁷	2015	Turkey	79	HN	IV	2.93	–	OS, PFS	E/M	6
Selzer ¹⁴	2015	Austria	318	HN	I-IV	5	150-300	OS	R, E/M	7
Song ²⁸	2015	China	146	HP	NA	2.3	–	OS	E/U	7
Tu ²⁹	2015	China	141	L	I-IV	2.17	–	OS, DFS	R/M	7
Charles ³⁰	2016	Australia	145	HN	I-IV	5	–	OS	R/M	7
Rachidi ³¹	2016	America	543	HN	I-IV	2.36-4.39	–	OS	R/M	8
Zeng ³²	2016	China	125	L	III-IV	3	–	OS, PFS	R/M	7
Nakashima ³³	2016	Japan	124	OC	III-IV	2.4	–	DFS	R/M	7
Ong ³⁴	2016	China	133	OC	I-II	NA	129	OS, DFS	R/M	7
Wong ¹⁵	2016	UK	140	L	I-IV	1.78-2.41-3.1	–	OS, DFS	R/M	8
Kano ³⁵	2016	Japan	285	HN	I-IV	1.92	125	OS, DFS	R,E/U	8
Fu ³⁶	2016	China	420	L	III-IV	2.59	–	OS, CSS	R/M	7
Kim ³⁷	2016	Korea	104	HN	III-IV	3	–	OS, PFS	R/M	7
Nakahira ³⁸	2016	Japan	100	HP	I-IV	3	150	CSS	R/U	7
Rosculet ³⁹	2017	America	123	HN	I-IV	2.7	–	OS	R/U	8
Lo ⁴⁰	2017	China	105	HP	III-IV	3.22	–	OS, DFS	R/M	7
Ikeguchi ⁴¹	2016	Japan	59	HP	III-IV	5	–	OS	R/M	6
Hsueh ⁴²	2017	China	979	L	I-IV	1.62-2.4	81.62-111	DFS, CSS	R/M	8
Bobdey ⁴³	2017	India	471	OC	I-IV	2.38	–	OS	R/U	7
Chen ⁴⁴	2016	China	1202	OC	I-IV	1.94-3.66	–	OS	R/M	7

Abbreviations: CSS, cancer-specific survival; DFS, disease-free survival; E: reported in text; E, estimated; HN, head and neck; HP, hypopharynx; HR, hazard ratio; L, larynx; M: multivariate; NA: not available; NOS, Newcastle-Ottawa Quality Assessment Scale; OC, oral cavity; OP, oropharynx; OS: overall survival; PFS, progression-free survival; U: univariate.

ratio” or “platelet to lymphocyte ratio” or “platelet-to-lymphocyte ratio”). All candidate publications and their bibliographies were manually inspected by two reviewers independently for potential relevant articles. Discrepancies were resolved in consensus.

2.2 | Eligibility criteria

The eligibility criteria were listed as follows: (1) the diagnosis of HNSCC was proved based on histological result, and NPC was excluded; (2) articles evaluated the relationship between NLR or PLR and survival prognosis; (3) the hazard ratio (HR) and their 95% confidence interval (CI) were provided or could be calculated from the original article; (4) articles were published as original research in English. To duplicated publications or overlapped data, only the most recent or more comprehensive article was included. The exclusion criteria were: (1) reviews, letters, meeting abstract; (2) nonhuman studies; (3) articles including only NPC; (4) sample size <50 patients. Two independent reviewers assessed the eligibility of article independently. Any discrepancy was discussed and resolved by consensus.

2.3 | Information extraction

Two reviewers extracted the following information from the included studies independently: first author's last name, year of publication, study country, sample size, tumor location, clinico-pathological parameters, cutoff value of NLR and PLR, survival data (OS, disease-free survival [DFS], progression-free survival [PFS], cancer specific survival [CSS], loco-regional recurrence-free survival [LRRFS], metastases-free survival [MFS], recurrence-free survival [RFS], and disease-specific survival [DSS]). If univariate and multivariate HRs were both reported, multivariate data were used. Consensus was reached by discussion when inconsistent results exist.

2.4 | Extraction of HR

If HRs and their 95% CIs were described in literatures, they were extracted directly. Otherwise, they were calculated from raw data or survival curves by methods of Parmar and Tierney.^{20,21}

2.5 | Quality assessment

The quality of included literatures was evaluated independently by two reviewers according to the Newcastle-Ottawa

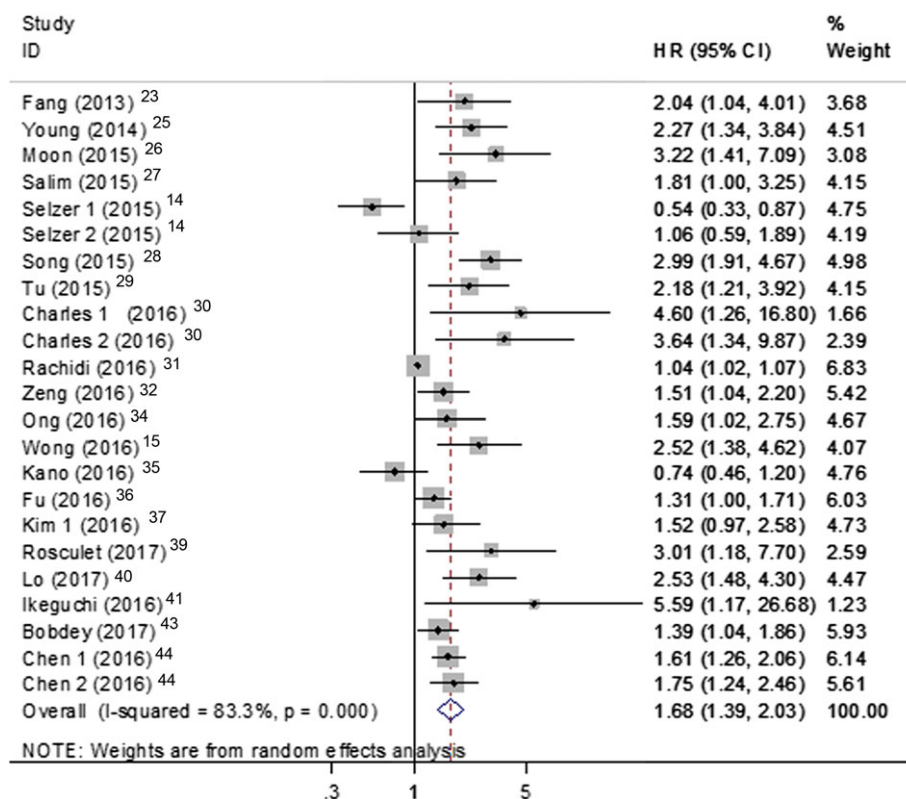


FIGURE 2 Forest plot of hazard ratio (HR) for the impact of NLR on overall survival (OS). NLR, neutrophil-to-lymphocyte ratio; CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

Scale (NOS).²² Studies with NOS score ≥ 6 were defined as high quality. Disagreements were resolved by discussion.

2.6 | Statistical analysis

A pooled HR > 1 and 95% CI not overlap 1 ($P < .05$) represented worse survival prognosis for high NLR or PLR group in HNSCC. The heterogeneity among the included studies was assessed by the Cochran Q -test and I^2 test. Cochran Q -test's $P \leq .10$ or I^2 value $\geq 50\%$ in I^2 test indicated significant heterogeneity among studies and random-effects models were used to calculate the pooled HR and 95% CI. Otherwise, fixed-effects models were performed. Stratified analyses were carried out to explore the factors potentially influencing the predictive value of NLR or PLR on HNSCC. Sensitivity analysis was applied to verify the stability of the pooled results. To evaluate publication bias, a funnel plot with Begg's and Egger's test was conducted. And $P > .05$ was considered as no publication bias. All statistical analyses were performed by STATA Statistical Software, version 12.0 (Stata Corporation, College Station, Texas).

3 | RESULTS

3.1 | Characteristics of eligible studies

A flowchart showed the detailed study election procedure (Figure 1). A total of 118 relevant publications in English were

initially identified by our search strategy. Through title and abstract screening, 86 articles were excluded. Subsequently, by full text review, 3 articles were further excluded because the same cohorts of patients were used in other selected literatures, 3 articles were excluded because of insufficient survival data to extract HR, and 1 article was excluded due to sample size < 50 . Finally, 25 studies with 28 cohorts fulfilled the criteria and were eligible in this meta-analysis.^{7,14,15,23-44} All of them are retrospective observation studies.

As shown in Table 1, the characteristics of the included studies were summarized, which were conducted from 2013 to June 2017. Among them, 8 studies (1872 cases) were performed in non-Asians and 17 studies (4975 cases) in Asians. All studies recorded the pretreatment NLR or PLR, except for one study, which reported both the pretreatment and the post-treatment NLR.³⁷ The data from the post-treatment NLR were omitted. Cutoff values for high NLR was defined as from 1.62 to 5 (≥ 2 in 19 studies, < 2 in 4 studies, and unknown in 2 studies), for high PLR was from 81.62 to 300. Seven studies included patients with TNM stage III-IV, 14 studies included patients with mixed TNM stage (I-IV), 1 study included patients with I-II, and 3 studies did not describe the status of TNM classification.

The numbers of studies reporting the effect of NLR on LRRFS, MFS, RFS, and DSS were no more than two. Thus, only OS, DFS, CSS and PFS were selected as the endpoints of NLR-related meta-analysis. No study reported the effect of PLR on PFS, LRRFS, MFS, RFS and DSS, and only

TABLE 2 Main results of the subgroup analyses for the impact of NLR on OS

Subgroup analysis	No. of Cohorts	No. of Patients	HR (95% CI)	P	Heterogeneity test	
					I ²	P
OS						
Overall	23	5169	1.68 (1.39, 2.03)	<.001	83.3%	<.001
Tumor location						
Oral cavity	5	2032	1.59 (1.36, 1.85)	<.001	0.0%	.799
Oropharynx	3	396	2.70 (1.74, 4.18)	<.001	0.0%	.494
Hypopharynx	3	310	2.88 (2.06, 4.03)	<.001	0.0%	.624
Larynx	4	826	1.65 (1.24, 2.19)	.001	43.2%	.152
Ethnicity						
Asian	14	3570	1.69 (1.41, 2.02)	<.001	57.2%	.004
Non-Asian	9	1599	1.65 (1.12, 2.43)	.012	81.4%	<.001
Sample size						
≥200	10	3716	1.26 (1.02, 1.56)	.032	81.3%	<.001
<200	13	1453	2.17 (1.79, 2.63)	<.001	20.4%	.238
Cutoff value						
<2	4	1627	1.50 (1.02–2.22)	.041	75.0%	.007
≥2	17	3256	1.70 (1.35–2.14)	<.001	82.7%	<.001
TNM classification						
III-IV	6	892	1.64 (1.29-2.09)	<.001	34.4%	.178
Mix(I-IV)	15	3998	1.58 (1.25-2.01)	<.001	83.1%	<.001
Uni/multivariate						
Univariate	6	1502	1.79 (1.16-2.76)	.008	77.3%	.001
Multivariate	17	3667	1.63 (1.32-2.03)	<.001	82.0%	<.001

Abbreviations: CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; No, number; OS, overall survival.

2 studies on CSS. Therefore, for PLR, only OS and DFS were adopted as the endpoints. NOS scores of the included studies ranged from 6 to 9, suggesting high quality.

3.2 | Impact of NLR on OS

For all 20 studies (23 cohorts) reporting the effect of NLR on OS, the heterogeneity test suggested a high heterogeneity ($I^2 = 83.3\%$; $P < .001$). Consequently, the random-effect model was used and the combined HR was 1.68 (95% CI, 1.39-2.03; $P < .001$), indicating that high NLR was significantly associated with poor OS in HNSCC (Figure 2).

Subgroup analysis was stratified according to tumor location, ethnicity, sample size, cutoff value of NLR, TNM classification, and statistical model (univariate or multivariate), which correlated with patient's prognosis or the NLR, and might bring heterogeneity to the overall analysis. As listed in Table 2, the prognostic value of high NLR on poor OS was significant in squamous cell carcinoma of oral cavity (HR = 1.59; 95% CI, 1.36-1.85; $P < .001$), oropharynx (HR = 2.70; 95% CI, 1.74-4.18; $P < .001$), hypopharynx (HR = 2.88; 95% CI, 2.06-4.03; $P < .001$) and Larynx (HR = 1.65; 95% CI, 1.24-2.19; $P < .001$). Moreover, the heterogeneity in individual subgroups reduced to be mild

(oral cavity, $I^2 = 0.0\%$; $P = .799$; oropharynx, $I^2 = 0.0\%$; $P = .494$; hypopharynx, $I^2 = 0.0\%$; $P = .624$; larynx, $I^2 = 43.2\%$; $P = .152$), which demonstrated that tumor location was a major cause of the high heterogeneity. In term of sample size, ethnicity, TNM classification, and statistical model, subgroup analyses revealed the significant prognostic role of the NLR on OS in all subgroups, suggesting the reliability of our findings. As shown in Table 2, the stratified analysis by cutoff point of NLR revealed that the significant association between high NLR and poor OS existed in both NLR ≥ 2 subgroup (HR = 1.70; 95% CI = 1.35-2.14; $P < .001$) and NLR < 2 subgroup (HR = 1.50; 95% CI = 1.02-2.22; $P = .041$). However, the association in NLR < 2 subgroup tended to be mild.

3.3 | Impact of NLR on DFS

Among the 9 studies reporting the role of NLR on DFS, results indicated that high NLR could predict poor DFS (HR = 1.76; 95% CI, 1.42-2.17; $P < .001$) using the random-effect model, as high heterogeneity was detected ($I^2 = 44.6\%$; $P = .071$) (Figure 3A).

Stratified analysis was conducted by tumor location, ethnicity, sample size, cutoff value of NLR, TNM classification, and statistical model. Results also suggested significant prognostic effect of high NLR on poor DFS in squamous cell carcinoma of oral cavity (HR = 1.69; 95% CI, 1.24-2.30; $P = .001$) and larynx (HR = 1.36; 95% CI, 1.13-1.63; $P = .001$) (Table 3). Due to limited studies, the subgroup analyses in squamous cell carcinoma of hypopharynx and oropharynx could not be carried out. Similarly, the heterogeneity decreased to be acceptable in oral cavity ($I^2 = 0.0\%$; $P = .817$) and larynx ($I^2 = 0.0\%$; $P = .404$) subgroups. As shown in Table 3, stratified analyses based on sample size, cutoff value of NLR, tumor TNM classification, and statistical model showed that these factors had no significant effect on the association between high NLR and poor DFS. However, the subgroup analysis by ethnicity revealed that high NLR could predict poor DFS in Asians (HR = 1.64; 95% CI, 1.35-1.98; $P < .001$), but not in non-Asians (HR = 2.55; 95% CI, 0.78-8.36; $P = .122$) (Table 3). Given only two studies included non-Asian patients, this conclusion need to be verified further.

3.4 | Impact of NLR on PFS

There were 4 studies reporting the impact of NLR on PFS. Since high heterogeneity ($I^2 = 60.0\%$; $P = .058$) was evaluated, meta-analysis using the random-effect model showed significant association between high NLR and poor PFS (HR = 1.53; 95% CI, 1.09-2.14; $P = .014$) (Figure 3B). Due to insufficient studies, subgroup analysis could not be performed.

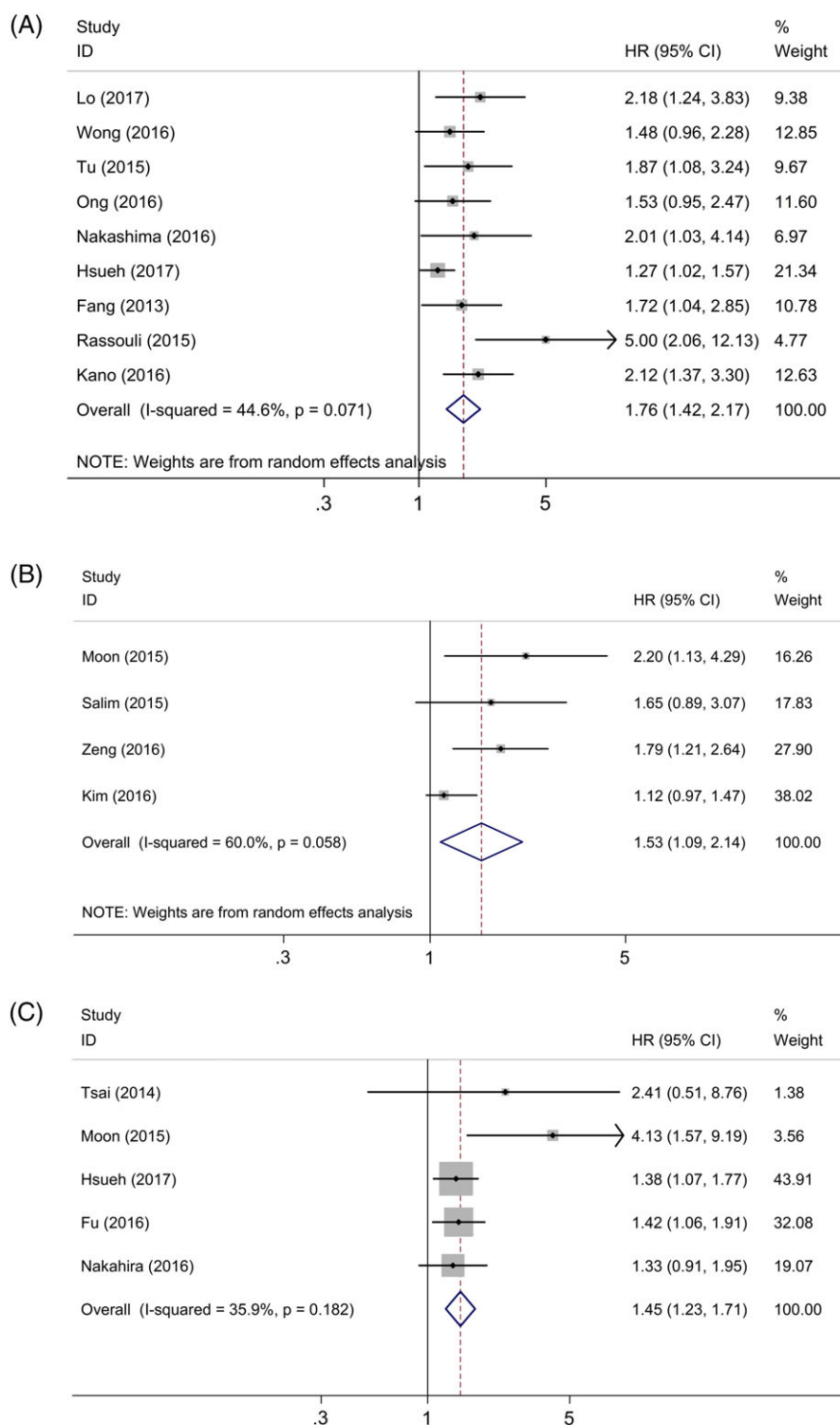


FIGURE 3 Forest plot of HR for the impact of NLR on A, DFS; B, PFS; C, CSS. HR, hazard ratio; CI, confidence interval; CSS, cancer-specific survival; DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | Impact of NLR on CSS

Five studies with mild heterogeneity ($I^2 = 35.9%$; $P = .182$), which reported the predictive effect of the NLR on CSS, were combined by the fixed-effect model. And results indicated that high NLR was significantly correlated with worse CSS in HNSCC (HR = 1.45; 95% CI, 1.23-1.71; $P < .001$) (Figure 3C). Given limited studies, no subgroup analysis was conducted.

3.6 | Impact of PLR on OS and DFS

Regarding PLR, 4 literatures reported the predictive effect of PLR on OS and 3 literatures on DFS. The random-effects models were used because of significant heterogeneity (OS: $I^2 = 75.9%$; $P = .006$; DFS: $I^2 = 84.5%$; $P = .002$). And results indicated no significant association between PLR and OS (HR = 0.94; 95% CI, 0.65-1.36; $P = .743$) or DFS (HR = 1.26; 95% CI, 0.94-1.68; $P = .119$) in HNSCC. (Figure 4A,B).

TABLE 3 Main results of the subgroup analyses for the impact of NLR on DFS

Subgroup analysis	No. of cohorts	No. of patients	HR (95%CI)	P	Heterogeneity test	
					I ²	P
DFS						
Overall	9	2406	1.76 (1.42, 2.17)	<.001	44.6%	.071
Tumor location						
Oropharynx	3	483	1.69 (1.24, 2.30)	.001	0.0%	.817
Larynx	3	1260	1.36 (1.13, 1.63)	.001	0.0%	.404
Ethnicity						
Asian	7	1993	1.64 (1.35, 1.98)	<.001	22.9%	.254
Non-Asian	2	413	2.55 (0.78, 8.36)	.122	82.9%	.016
Sample size						
≥200	4	1763	1.93 (1.23, 3.03)	.004	75.1%	.007
<200	5	643	1.72 (1.36, 2.18)	<.001	0.0%	.800
Cutoff value						
<2	2	425	1.77 (1.24-2.51)	.002	60.1%	.028
≥2	6	1848	1.89 (1.36-2.63)	<.001	23.4%	.253
TNM classification						
III-IV	2	229	2.11 (1.36-3.27)	.001	0.0%	.862
Mix(I-IV)	5	1771	1.55 (1.26-1.91)	<.001	27.7%	.237
Uni/multivariate						
Univariate	3	784	2.33 (1.44-3.78)	.001	52.7%	.121
Multivariate	6	1622	1.47 (1.25-1.74)	<.001	3.5%	.394

Abbreviations: CI, confidence interval; DFS, disease free-survival; HR, hazard ratio; No, number; NLR, neutrophil-to-lymphocyte ratio.

3.7 | Publication bias and sensitivity analysis

The publication bias was assessed using Begg's funnel plot and Egger's test. Among the 20 studies reporting the effect of NLR on OS, Begg's test found acceptable publication bias ($P = .291$), whereas Egger's test detected a publication bias ($P = .044$). In terms of the 9 studies reporting the impact of NLR on DFS, both Begg's test ($P = .048$) and Egger's test ($P < .001$) revealed significant publication bias. The shapes of the Begg's funnel plot also seemed not so symmetrical by visual inspection (Figure 5A,B). Since limited studies were included in other analyses, the evaluation of publication bias was not conducted.

Subsequently, sensitivity analyses were performed to evaluate the reliability of the meta-analysis results by sequentially removing individual study from pooled analysis. Results demonstrated that omission of single study did not statistically change the results of the impact of NLR on OS (Table 4) and DFS (Table 5), which suggested the stability of our results.

4 | DISCUSSION

To the best of our knowledge, this is the most comprehensive meta-analysis investigating the prognostic value of NLR and PLR in HNSCC. Our results from 25 literatures

with 28 cohorts involving 6847 HNSCC patients confirmed that high level of pretreatment NLR was significantly associated with poor OS, DFS, PFS, and CSS. By contrast, PLR was evaluated to have no significant predictive role on either OS or DFS in HNSCC.

Recently, a meta-analysis published by Takenaka et al. investigated the prognostic role of NLR in HNSCC.⁴⁵ However, in the present meta-analysis, we included more studies (25 vs 19 studies in Takenaka's) and greater number of HNSCC patients (6847 vs 3770 patients in Takenaka's). Moreover, we conducted more comprehensive analysis on the association between both the NLR and PLR, and OS, DFS, PFS, and CSS. Takenaka et al. only focused on the relationship between NLR and OS, or DSS. Importantly, the similar results of the two meta-analyses further support the potential prognostic role of NLR in HNSCC.

It remains poorly understood for the mechanisms underlying the association between NLR or PLR and oncologic prognosis. For neutrophil, first, it has been verified to promote angiogenesis, cell growth, tumorigenesis, and tumor progression by secreting vascular endothelial growth factor, hepatocyte growth factor, IL-6, IL-8, and matrix metalloproteinases.^{46–50} Second, neutrophil has been demonstrated to suppress the cytotoxic activity of lymphocytes, natural killer cells, and activated T cells through producing reactive oxygen species, arginase, and nitric oxide.^{51,52} Therefore, elevated neutrophil counts are frequently associated with poor prognosis in cancer. Whereas, for lymphocyte, it is essential to activate effective antitumor response in host immune system.⁵³ Decreased lymphocyte counts often indicate suppression of lymphocyte-mediated antitumor immunity and poor clinical outcome. NLR has been widely assumed as a marker of upregulated host inflammation to promote the progression of tumor.⁵⁴ Meanwhile, platelet is considered to promote tumor cell growth and metastases via contacting cancer cells directly and secreting bioactive proteins relevant to tumor angiogenesis and osteoclast resorption.⁵⁵ PLR also has emerged as an independent prognostic factor in various cancers.^{7,56,57}

Notably, HNSCC is a heterogeneous disease, including squamous cell carcinoma from oral cavity, oropharynx, larynx, and hypopharynx. Tumor location is an important factor, which influences the survival prognosis of HNSCC. In subgroup analyses based on tumor location, NLR showed significant association with OS and DFS in all subpopulations. Moreover, the heterogeneity among studies in individual subgroups reduced to be acceptable, suggesting that tumor location is the main cause of high heterogeneity in the overall meta-analysis. In addition, it represents the robustness and stability of our results about the impact of NLR on OS and DFS. Subgroup analyses stratified by ethnicity and sample size also suggested the similar results in all subgroups, except for DFS in non-Asians. Due to only two studies including non-Asian patients, future large-scale

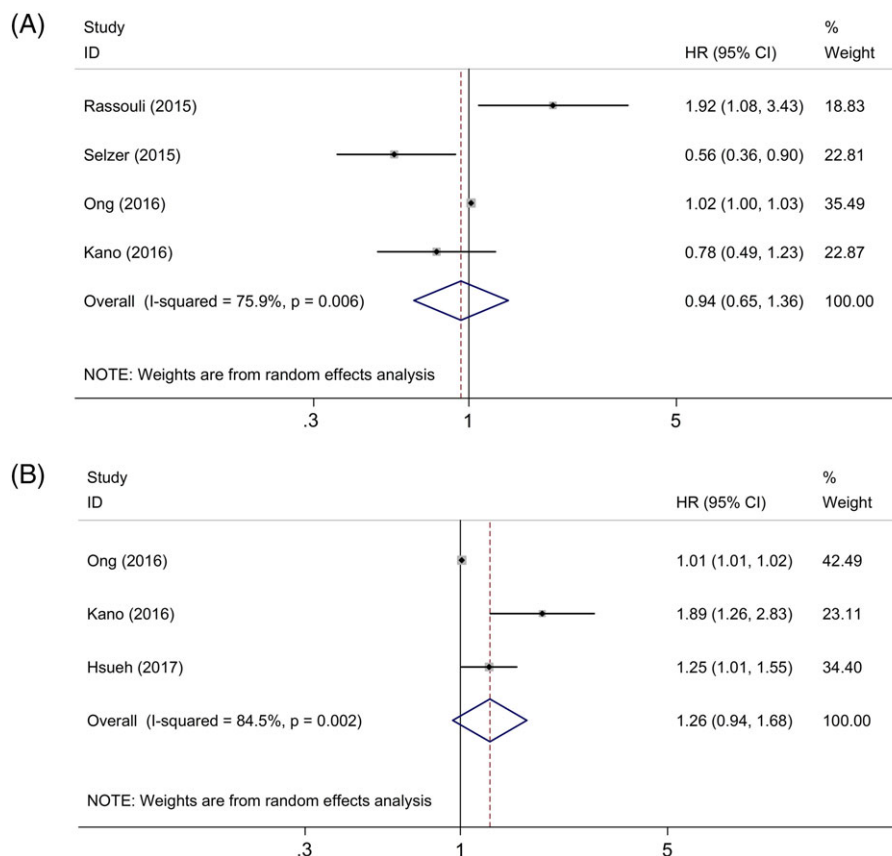


FIGURE 4 Forest plot of HR for the impact of PLR on A, OS; B, DFS. CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio [Color figure can be viewed at wileyonlinelibrary.com]

prospective trials are required before a definite conclusion can be made.

Treatment strategy and clinical stage also have been manifested to be crucial prognostic factors in HNSCC. Nowadays, comprehensive treatment is standard in HNSCC, which is utilized in majority of the included studies. Therefore, the issue whether individual treatment strategy influences the correlation between NLR or PLR and survival prognosis could not be investigated in our study. In terms of tumor stage, due to the limited information in the included literatures, we could not separate the patients precisely. Consequently, only TNM stage III-IV subgroup and mixed stage (I-IV) subgroup were divided. And the results of stratified analysis revealed that the high NLR predicted poor OS and DFS in both subgroups (Tables 2 and 3), which is warranted be explored further in the future studies.

Another well-documented prognostic factor for HNSCC is HPV status.⁵ What is more, HPV infection could modulate the host immune response to the tumor and influence the NLR.³⁹ Consequently, the impact of HPV status on the predictive role of NLR or PLR should be taken into account. However, only two included studies reported the HPV status and concluded conversely.^{31,39} Rachidi et al. revealed that the NLR predicted survival regardless of HPV status.³¹ Whereas, Rosculet et al. suggested that the NLR does not have independent prognostic significance in the favorable

prognostic HNSCC patients with HPV-positive tumor. The conflict findings call for more in-depth investigation. Given limited studies, the impact of HPV status on the relationship between NLR and survival prognosis in HNSCC were not further explored here.

As well known, the NLR and PLR are nonspecific parameters, which could be influenced by many other conditions, such as age, infection, hypertension, inflammatory diseases, and medications.^{58,59} Its nonspecificity for using it as a prognostic marker comes into doubt. However, another nonspecific parameter lactate dehydrogenase, which also could be affected by infection, liver injury, and cancer,^{60,61} is an important item in the widely assumed international prognostic index for Non-Hodgkin's lymphoma. Actually, Templeton et al. have already cooperated the NLR in a simple score in metastatic castration-resistant prostate cancer to help predict prognosis and tailor therapy.⁶² All these suggest that it is available and reasonable to add NLR in establishing prognostic system for cancer.

As a literature-based meta-analysis, some limitations of our study should be noticed. First, all of the included studies were retrospective and observational. Potential selection bias may exist. Therefore, prospective randomized controlled studies are warranted to confirm our findings. Second, there was evidence of publication bias, potentially indicating bias towards publication of positive

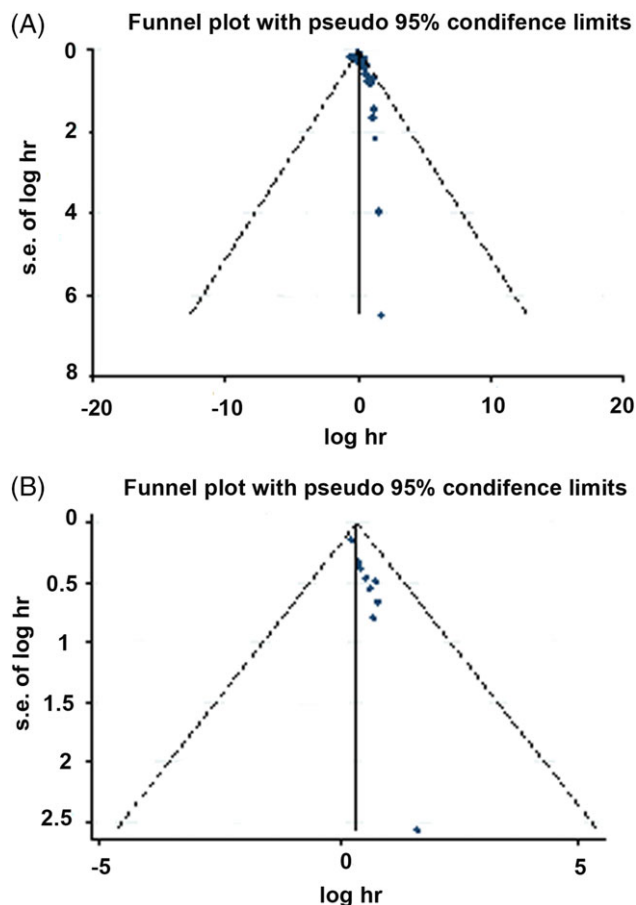


FIGURE 5 Funnel plot for included studies in the meta-analysis. A, Studies for the impact of NLR on OS. B, Studies for the impact of NLR on DFS. DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival [Color figure can be viewed at wileyonlinelibrary.com]

studies. And language limitations in the inclusion criterion might also account for the bias. However, sensitivity analysis verified the reliability of our findings. Third, in several studies, the HRs and CIs had to be calculated from survival curves, given no parameters reported directly, which might bring in small errors. But the stable results of our sensitivity analyses suggested that the effects of such errors were limited. Fourth, most of the included studies (17 studies out of 25 studies) with 4975 cases (out of 6847 patients) were performed in Asians, the results about non-Asians should be concluded carefully and need to be verified further. At last, there are no standard cutoff values for NLR and PLR among the included studies, with NLR ranged from 1.62 to 5 and PLR from 81.62 to 300. However, Templeton et al. considered that the range of NLR cutoffs was considered narrow and unlikely to influence the association between NLR and reported HR for survival,¹⁶ which was in consistent with our results. Since the association between the NLR and OS prognosis decreased to be mild in cutoff value of NLR < 2 subgroup (HR = 1.50; 95% CI = 1.02-2.22; *P* = .041), we suggested that the cutoff value of NLR should be set up more than 2 in future studies.

TABLE 4 Sensitivity analysis of HR for the impact of NLR on OS

Study omitted	HR (95% CI)	<i>P</i>	<i>I</i> ²	<i>P</i> _H
Moon ²⁶	1.64 (1.35, 1.99)	<.001	83.1%	<.001
Salim ²⁷	1.67 (1.37, 2.03)	<.001	83.6%	<.001
Kim ³⁷	1.69 (1.38, 2.06)	<.001	83.8%	<.001
Rosculet ³⁹	1.65 (1.36, 2.00)	<.001	83.4%	<.001
Song ²⁸	1.61 (1.34, 1.95)	<.001	81.1%	<.001
Lo ⁴⁰	1.64(1.35, 1.99)	<.001	82.7%	<.001
Ikeguchi ⁴¹	1.65 (1.36, 2.00)	<.001	83.5%	<.001
Tu ²⁹	1.66(1.36, 2.01)	<.001	83.3%	<.001
Zeng ³²	1.69(1.39, 2.07)	<.001	83.6%	<.001
Wong ¹⁵	1.65 (1.36, 2.00)	<.001	83.0%	<.001
Charles 1 ³⁰	1.65 (1.36, 1.99)	<.001	83.4%	<.001
Charles 2 ³⁰	1.64 (1.36, 1.99)	<.001	83.3%	<.001
Ong ³⁴	1.68 (1.38, 2.05)	<.001	83.7%	<.001
Selzer 1 ¹⁴	1.77 (1.46, 2.15)	<.001	83.1%	<.001
Selzer 2 ¹⁴	1.71 (1.41, 2.09)	<.001	84.0%	<.001
Rachidi ³¹	1.72 (1.43, 2.07)	<.001	66.4%	<.001
Kano ³⁵	1.75 (1.44, 2.13)	<.001	83.8%	<.001
Fu ³⁶	1.71 (1.40, 2.11)	<.001	83.7%	<.001
Young ²⁵	1.65 (1.36, 2.00)	<.001	83.0%	<.001
Fang ²³	1.66 (1.37, 2.02)	<.001	83.6%	<.001
Bobdey ⁴³	1.71 (1.39, 2.09)	<.001	83.6%	<.001
Chen 1 ⁴⁴	1.69 (1.38, 2.07)	<.001	82.6%	<.001
Chen 2 ⁴⁴	1.67 (1.37, 2.04)	<.001	83.0%	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; *P*_H, the *P* value of Cochran *Q*-test for heterogeneity.

In summary, our results suggest that the elevated NLR is significantly associated with adverse OS, DFS, PFS, and CSS in HNSCC, which can serve as a cost-effective prognostic biomarker to help stratify patients and individualize the treatments. Notably, tumor site is demonstrated to be a major cause leading to the obvious heterogeneity among the included studies. However, our results failed to identify PLR as a predictive factor on either OS or DFS in HNSCC. In the future, multicenter prospective and randomized clinical trials are warranted to confirm such findings and promote the utilization in clinic, especially in cooperation with other prognostic markers.

TABLE 5 Sensitivity analysis of HR for the impact of NLR on DFS

Study omitted	HR (95% CI)	<i>p</i>	<i>I</i> ²	<i>P</i> _H
Lo ⁴⁰	1.72 (1.37, 2.16)	<.001	46.7%	.069
Wong ¹⁵	1.83 (1.43, 2.34)	<.001	51.1%	.046
Tu ²⁹	1.76 (1.39, 2.23)	<.001	50.2%	.050
Ong ³⁴	1.81 (1.42, 2.31)	<.001	51.4%	.044
Nakashima ³³	1.75 (1.39, 2.20)	<.001	49.9%	.052
Hsueh ⁴²	1.88 (1.55, 2.27)	<.001	3.6%	.402
Fang ²³	1.78 (1.40, 2.27)	<.001	51.1%	.046
Kano ³⁵	1.71 (1.36, 2.15)	<.001	44.3%	.083
Rassouli ⁷	1.58 (1.35, 1.85)	<.001	10.5%	.349

Abbreviations: NLR, Neutrophil-to-lymphocyte ratio; DFS, disease free survival; HR, hazard ratio; CI, confidence interval; *P*_H, the *P* value of Cochran *Q*-test for heterogeneity.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

REFERENCES

- Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87-108.
- Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J Clin Oncol*. 2014;32:3930-3938.
- Braakhuis BJ, Leemans CR, Visser O. Incidence and survival trends of head and neck squamous cell carcinoma in The Netherlands between 1989 and 2011. *Oral Oncol*. 2014;50:670-675.
- Fuller CD, Wang SJ, Thomas CR Jr, Hoffman HT, Weber RS, Rosenthal DI. Conditional survival in head and neck squamous cell carcinoma: results from the SEER dataset 1973-1998. *Cancer*. 2007;109:1331-1343.
- Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*. 2008;100:261-269.
- Fan Z, Li M, Chen X, et al. Prognostic value of cancer stem cell markers in head and neck squamous cell carcinoma: a meta-analysis. *Sci Rep*. 2017;7:43008.
- Rassouli A, Saliba J, Castano R, Hier M, Zeitouni AG. Systemic inflammatory markers as independent prognosticators of head and neck squamous cell carcinoma. *Head Neck*. 2015;37:103-110.
- Palucka AK, Coussens LM. The basis of oncoimmunology. *Cell*. 2016;164:1233-1247.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674.
- Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res*. 2017;19:2.
- Yodying H, Matsuda A, Miyashita M, et al. Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis. *Ann Surg Oncol*. 2016;23:646-654.
- Zhang J, Zhang HY, Li J, Shao XY, Zhang CX. The elevated NLR, PLR and PLT may predict the prognosis of patients with colorectal cancer: a systematic review and metaanalysis. *Oncotarget*. 2017;8:68837-68846.
- Yuan C, Li N, Mao X, Liu Z, Ou W, Wang SY. Elevated pretreatment neutrophil/white blood cell ratio and monocyte/lymphocyte ratio predict poor survival in patients with curatively resected non-small cell lung cancer: results from a large cohort. *Thorac Cancer*. 2017;8:350-358.
- Selzer E, Grah A, Heiduschka G, Kornek G, Thurnher D. Primary radiotherapy or postoperative radiotherapy in patients with head and neck cancer: comparative analysis of inflammation-based prognostic scoring systems. *Strahlenther Onkol*. 2015;191:486-494.
- Wong BY, Stafford ND, Green VL, Greenman J. Prognostic value of the neutrophil-to-lymphocyte ratio in patients with laryngeal squamous cell carcinoma. *Head Neck*. 2016;38(Suppl 1):E1903-E1908.
- Templeton AJ, McNamara MG, Seruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106:dju124.
- Chua ML, Tan SH, Kusumawidjaja G, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in locally advanced nasopharyngeal carcinoma: a pooled analysis of two randomised controlled trials. *Eur J Cancer*. 2016;67:119-129.
- Su L, Zhang M, Zhang W, Cai C, Hong J. Pretreatment hematologic markers as prognostic factors in patients with nasopharyngeal carcinoma: a systematic review and meta-analysis. *Biomed Res Int*. 2017;96:e6364.
- Jin Y, Ye X, He C, Zhang B, Zhang Y. Pretreatment neutrophil-to-lymphocyte ratio as predictor of survival for patients with metastatic nasopharyngeal carcinoma. *Head Neck*. 2015;37:69-75.
- Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17:2815-2834.
- Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.
- Wells G, Shea B, O'Connell J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Health Research Institute Web site. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (2012).
- Fang HY, Huang XY, Chien HT, et al. Refining the role of preoperative C-reactive protein by neutrophil/lymphocyte ratio in oral cavity squamous cell carcinoma. *Laryngoscope*. 2013;123:2690-2699.
- Tsai YD, Wang CP, Chen CY, et al. Pretreatment circulating monocyte count associated with poor prognosis in patients with oral cavity cancer. *Head Neck*. 2014;36:947-953.
- Young CA, Murray LJ, Karakaya E, Thygesen HH, Sen M, Prestwich RJ. The prognostic role of the neutrophil-to-lymphocyte ratio in oropharyngeal carcinoma treated with chemoradiotherapy. *Clin Med Insights Oncol*. 2014;3:81-86.
- Moon H, Roh JL, Lee SW, et al. Prognostic value of nutritional and hematologic markers in head and neck squamous cell carcinoma treated by chemoradiotherapy. *Radiother Oncol*. 2016;118:330-334.
- Salim DK, Mutlu H, Eryilmaz MK, et al. Neutrophil to lymphocyte ratio is an independent prognostic factor in patients with recurrent or metastatic head and neck squamous cell cancer. *Mol Clin Oncol*. 2015;3:839-842.
- Song Y, Liu H, Gao L, et al. Preoperative neutrophil-to-lymphocyte ratio as prognostic predictor for hypopharyngeal squamous cell carcinoma after radical resections. *J Craniofac Surg*. 2015;26:e137-e140.
- Tu XP, Qiu QH, Chen LS, et al. Preoperative neutrophil-to-lymphocyte ratio is an independent prognostic marker in patients with laryngeal squamous cell carcinoma. *BMC cancer*. 2015;15:743.
- Charles KA, Harris BD, Haddad CR, et al. Systemic inflammation is an independent predictive marker of clinical outcomes in mucosal squamous cell carcinoma of the head and neck in oropharyngeal and non-oropharyngeal patients. *BMC Cancer*. 2016;16:124.
- Rachidi S, Wallace K, Wrangle JM, Day TA, Alberg AJ, Li Z. Neutrophil-to-lymphocyte ratio and overall survival in all sites of head and neck squamous cell carcinoma. *Head Neck*. 2016;38(Suppl 1):E1068-E1074.
- Zeng YC, Chi F, Xing R, et al. Pre-treatment neutrophil-to-lymphocyte ratio predicts prognosis in patients with locoregionally advanced laryngeal carcinoma treated with chemoradiotherapy. *Jpn J Clin Oncol*. 2016;46:126-131.
- Nakashima H, Matsuoka Y, Yoshida R, et al. Pre-treatment neutrophil to lymphocyte ratio predicts the chemoradiotherapy outcome and survival in patients with oral squamous cell carcinoma: a retrospective study. *BMC Cancer*. 2016;16:41.
- Ong HS, Gokavarapu S, Wang LZ, Tian Z, Zhang CP. Low pretreatment lymphocyte-monocyte ratio and high platelet-lymphocyte ratio indicate poor cancer outcome in early tongue cancer. *J Oral Maxillofac Surg*. 2017;75:1762-1774.
- Kano S, Homma A, Hatakeyama H, et al. Pretreatment lymphocyte-to-monocyte ratio as an independent prognostic factor for head and neck cancer. *Head Neck*. 2017;39:247-253.
- Fu Y, Liu W, OuYang D, Yang A, Zhang Q. Preoperative neutrophil-to-lymphocyte ratio predicts long-term survival in patients undergoing Total laryngectomy with advanced laryngeal squamous cell carcinoma: a single-center retrospective study. *Medicine*. 2016;95:e2689.
- Kim DY, Kim IS, Park SG, Kim H, Choi YJ, Seol YM. Prognostic value of posttreatment neutrophil-lymphocyte ratio in head and neck squamous cell carcinoma treated by chemoradiotherapy. *Auris Nasus Larynx*. 2017;44:199-204.
- Nakahira M, Sugawara M, Matsumura S, et al. Prognostic role of the combination of platelet count and neutrophil-lymphocyte ratio in patients with hypopharyngeal squamous cell carcinoma. *Eur Arch Otorhinolaryngol*. 2016;273:3863-3867.
- Rosculet N, Zhou XC, Ha P, et al. Neutrophil-to-lymphocyte ratio: prognostic indicator for head and neck squamous cell carcinoma. *Head Neck*. 2017;39:662-667.
- Lo WC, Wu CT, Wang CP, et al. The pretreatment neutrophil-to-lymphocyte ratio is a prognostic determinant of T3-4 hypopharyngeal squamous cell carcinoma. *Ann Surg Oncol*. 2017;24:1980-1988.
- Ikeguchi M. Glasgow prognostic score and neutrophil-lymphocyte ratio are good prognostic indicators after radical neck dissection for advanced squamous cell carcinoma in the hypopharynx. *Langenbecks Arch Surg*. 2016;401:861-866.
- Hsueh C, Tao L, Zhang M, et al. The prognostic value of preoperative neutrophils, platelets, lymphocytes, monocytes and calculated ratios in patients with laryngeal squamous cell cancer. *Oncotarget*. 2017;8:60514-60527.

43. Bobbey S, Ganesh B, Mishra P, Jain A. Role of monocyte count and neutrophil-to-lymphocyte ratio in survival of Oral cancer patients. *Int Arch Otorhinolaryngol*. 2017;21:21-27.
44. Chen F, Lin L, Yan L, Qiu Y, Cai L, He B. Preoperative neutrophil-to-lymphocyte ratio predicts the prognosis of Oral squamous cell carcinoma: a large-sample prospective study. *J Oral Maxillofac Surg*. 2017;75:1275-1282.
45. Takenaka Y, Oya R, Kitamiura T, et al. Prognostic role of neutrophil-to-lymphocyte ratio in head and neck cancer: a meta-analysis. *Head Neck*. 2018;40:647-655.
46. McCourt M, Wang JH, Sookhai S, Redmond HP. Proinflammatory mediators stimulate neutrophil-directed angiogenesis. *Arch Surg*. 1999;134:1325-1331. discussion 1331-1322.
47. McCourt M, Wang JH, Sookhai S, Redmond HP. Activated human neutrophils release hepatocyte growth factor/scatter factor. *Eur J Surg Oncol*. 2001;27:396-403.
48. Jablonska E, Kiluk M, Markiewicz W, Piotrowski L, Grabowska Z, Jablonski J. TNF-alpha, IL-6 and their soluble receptor serum levels and secretion by neutrophils in cancer patients. *Arch Immunol Ther Exp (Warsz)*. 2001;49:63-69.
49. Schaidt H, Oka M, Bogenrieder T, et al. Differential response of primary and metastatic melanomas to neutrophils attracted by IL-8. *Int J Cancer*. 2003;103:335-343.
50. Shamamian P, Schwartz JD, Pocock BJ, et al. Activation of progelatinase a (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: a role for inflammatory cells in tumor invasion and angiogenesis. *J Cell Physiol*. 2001;189:197-206.
51. Petrie HT, Klassen LW, Kay HD. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. *J Immunol*. 1985;134:230-234.
52. el-Hag A, Clark RA. Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system. *J Immunol*. 1987;139:2406-2413.
53. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. *Br J Cancer*. 2011;105:93-103.
54. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. *Nat Rev Cancer*. 2016;16:431-446.
55. Sharma D, Brummel-Ziedins KE, Bouchard BA, Holmes CE. Platelets in tumor progression: a host factor that offers multiple potential targets in the treatment of cancer. *J Cell Physiol*. 2014;229:1005-1015.
56. Racz JM, Cleghorn MC, Jimenez MC, et al. Predictive ability of blood neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in gastrointestinal stromal tumors. *Ann Surg Oncol*. 2015;22:2343-2350.
57. Cannon NA, Meyer J, Iyengar P, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. *J Thorac Oncol*. 2015;10:280-285.
58. Li J, Chen Q, Luo X, et al. Neutrophil-to-lymphocyte ratio positively correlates to age in healthy population. *J Clin Lab Anal*. 2015;29:437-443.
59. Balta S, Demirkol S, Unlu M, Arslan Z, Celik T. Neutrophil to lymphocyte ratio may be predict of mortality in all conditions. *Br J Cancer*. 2013;109:3125-3126.
60. Le A, Cooper CR, Gouw AM, et al. Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression. *Proc Natl Acad Sci U S A*. 2010;107:2037-2042.
61. Cassidy WM, Reynolds TB. Serum lactic dehydrogenase in the differential diagnosis of acute hepatocellular injury. *J Clin Gastroenterol*. 1994;19:118-121.
62. Templeton AJ, Pezaro C, Omlin A, et al. Simple prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil-to-lymphocyte ratio. *Cancer*. 2014;120:3346-3352.

How to cite this article: Yang L, Huang Y, Zhou L, Dai Y, Hu G. High pretreatment neutrophil-to-lymphocyte ratio as a predictor of poor survival prognosis in head and neck squamous cell carcinoma: Systematic review and meta-analysis. *Head & Neck*. 2019; 41:1525–1535. <https://doi.org/10.1002/hed.25583>