

Prognostic and clinicopathologic significance of neutrophil-to-lymphocyte ratio in esophageal squamous cell carcinoma: evidence from a meta-analysis

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Purpose: Evidence from an increasing number of studies has demonstrated that the neutrophil-to-lymphocyte ratio (NLR) is a prognostic factor for various cancers. However, it is unclear whether NLR predicts prognosis in esophageal squamous cell carcinoma (ESCC). We conducted a meta-analysis to investigate the prognostic and clinicopathologic significance of NLR in patients with ESCC.

Patients and methods: Selected studies were identified by searches in PubMed, Embase, and Web of Science databases and filtered using our prepared criteria. The hazard ratio (HR) and odds ratio were chosen as effect measures to assess the prognostic role of NLR and its clinicopathologic significance in ESCC. In total, nine studies containing 2,513 patients were enrolled.

Results: We demonstrated that elevated NLR was associated with worse overall survival in ESCC patients (pooled HR = 1.314; 95% confidence interval, 1.164–1.484; $P < 0.001$). Elevated NLR was also associated with unfavorable characteristics regarding depth of tumor invasion, tumor size, clinical stage, and differentiation degree.

Conclusion: The results of our meta-analysis suggest that a high NLR value might represent a poor prognosis and worse clinicopathologic characteristics for patients with ESCC.

Keywords: ESCC, NLR, prognosis, meta-analysis, inflammation

Introduction

Esophageal cancer has a high incidence and a low 5-year survival rate. According to the latest Global Cancer Statistics, esophageal cancer is the seventh most prevalent and sixth highly mortal human cancer in male. In case of female, it is the ninth most common cause of mortality. An estimated 455,800 new esophageal cancer cases and 400,200 deaths occur globally per year.¹ Esophageal squamous cell carcinoma (ESCC) is the most common histologic subtype, especially in Asian countries. Despite intensive therapies, the prognosis of ESCC remains poor. In patients treated with radical surgical intervention, the reported 5-year survival rate remained about 30%.^{2–4} Various prognostic factors including tumor stage and genetic polymorphism have been reported,^{3,4} and more recently, certain serum biomarkers, such as inflammation factors, were also suggested to have predictive potential. Such biomarkers are easily assessable and provide important information for clinicians regarding preventive and therapeutic strategies for ESCC patients.^{5–7}

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Inflammatory reactions play a significant role in the occurrence and development of cancer.^{8–10} Levels of inflammation factors, such as neutrophils and C-reactive protein, have been reported to be elevated in many cancers.^{11–13} The neutrophil-to-lymphocyte ratio (NLR), calculated as serum neutrophil counts divided by serum lymphocyte counts, is a common indicator of inflammation. This index was proven to be a significant prognostic factor in many cancers, including colorectal cancer, gastric cancer, and lung cancer.^{14–16} Accumulated data also suggested that elevated NLR was associated with poor prognosis in ESCC patients.¹⁷ However, some research failed to confirm the NLR as a significant predictor, and the result concerning the prognostic value of NLR in ESCC is still controversial.¹⁸ Therefore, it was essential to perform a meta-analysis to confirm the effect of NLR on the prognosis of ESCC. Here, we assessed the prognostic value of increased NLR in ESCC using a meta-analysis and analyzed the relationship between NLR and clinicopathologic features in patients with ESCC.

Methods

Search method

We searched three major databases, PubMed, Embase, and Web of Science, for all relevant studies. Search items were as follows: “Prognosis” (“Prognoses”, “prognostic”, “survival”), NLR (“neutrophil lymphocyte ratio”, “neutrophil to lymphocyte ratio”, “neutrophil-to-lymphocyte ratio”), and ESCC (“Esophageal Neoplasm”, “Esophageal cancer”, “Esophageal carcinoma”, “Esophageal squamous cell carcinoma”). The cutoff date for the search was September 1, 2016.

Inclusion and exclusion criteria

Studies were selected for inclusion in the meta-analysis according to the following criteria: 1) pretreatment NLR (baseline NLR) was measured from serum; 2) all included patients were diagnosed with ESCC by pathology and did not have any other tumor subtypes; and 3) correlation of NLR with overall survival (OS) was studied. Exclusion criteria were as follows: 1) studies were reviews, letters, abstracts, case reports, or nonclinical types; 2) hazard ratio (HR) and 95% confidence interval (CI) were not included or could not be calculated; 3) studies were not written in English; and 4) studies reported HRs based on continuous NLR without a clear cutoff point.

Data extraction and quality evaluation

Two authors (YH and SXZ) evaluated and extracted all candidate studies independently. The full text was examined if the study could not be categorized by its title or abstract.

If the authors failed to reach a consensus, outstanding disagreements were resolved through discussion with a third author (YS). Information on the authors, year of publication, country, study design, study period, number of participants, sex, mean age, cutoff values for NLR, treatment strategy, and HR with 95% CI was obtained from selected studies for the meta-analysis. NLR was calculated from complete blood counts by dividing the absolute neutrophil count by the absolute lymphocyte count. To ensure study quality, two reviewers (PP and WS) assessed the included studies using the Newcastle–Ottawa Scale (NOS).¹⁹ Studies with NOS scores ≥ 6 were considered high-quality research.

Statistical analysis

HR and 95% CI for OS, disease-free survival (DFS), and progression-free survival (PFS) were either obtained directly from each published study or calculated from the data provided. If univariate and multivariate analyses were both reported in the same study, multivariate-adjusted HRs and their corresponding standard errors were used for the meta-analysis. Odds ratios (ORs) and 95% CIs were used to evaluate the relationship between NLR and clinicopathologic factors. We measured heterogeneity using χ^2 -based Q test and Higgins’ I^2 statistic. We applied the fixed-effects model (Mantel–Haenszel method) when the P -value for Q test was >0.10 or I^2 was $<50\%$, suggesting no significant heterogeneity. We chose the random-effects model (DerSimonian–Laird method) for cases with $P < 0.10$ for Q test or $I^2 > 50\%$. We used subgroup analysis to explore possible heterogeneity among different results. Sensitivity analyses were performed to confirm the robustness of the study. Egger’s linear regression test and Begg’s funnel plot test were used to assess the publication bias. Differences were considered statistically significant for P -values < 0.05 .

Results

Study characteristics

A total of 110 studies were selected from the databases after discarding duplicates, and 89 of these studies were excluded after browsing the titles and abstracts. The full texts of the remaining 21 studies were further reviewed, and 12 studies were excluded for the following reasons: one study performed survival analysis using a continuous NLR level and did not describe a clear cutoff value for NLR; two studies used data with a repeated population; three studies were not related to OS; four studies contained patients who were pathologically diagnosed with adenocarcinoma or other tumor subtypes; and two studies did not report the association with survival. The detailed selection processes are shown in Figure 1.

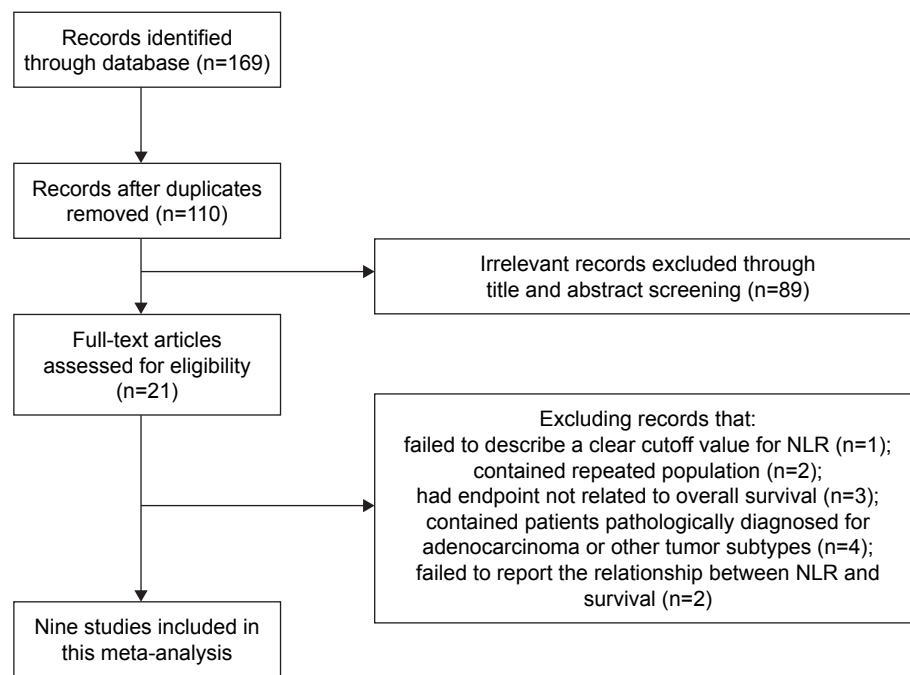


Figure 1 The flow diagram of the included studies.

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

In total, nine studies^{6,7,17,18,20–24} were finally enrolled, and 2,513 ESCC patients were included in the meta-analysis. The studies were all from Asian countries (China: n=6; Japan: n=3). Six studies recruited <300 patients, and three studies involved >300 patients. NLR cutoff values presented in these studies varied, ranging from 1.7 to 3.612. Six studies had a cutoff value >2.5, and three studies used a value ≤2.5.

Detailed information on the selected studies is summarized in Table 1. All of the research studies had an NOS score ≥6.

NLR and OS in ESCC

Nine studies with 2,513 ESCC patients reported the association between elevated NLR and OS. We found that high NLR was positively associated with poor OS (pooled

Table 1 Main characteristics of all the studies included in the meta-analysis

Study	Year	Study design	Country	Study period	No (male/female)	Mean age ± SD (years)	Survival type	CV	Treatment	Stage	HR
Feng et al ²³	2014	R	People's Republic of China	2005–2008	483 (411/72)	59.1±8.0 (34–80)	OS	3.5	Surgery	NR*	M/U
Hirahara et al ¹⁸	2015	R	Japan	2006–2014	141 (127/14)	NR (≥70, n=46; <70, n=95)	OS	2.5	Surgery	I–III	U
Han et al ²⁴	2015	R	People's Republic of China	2007–2008	218 (177/41)	60.5 (32–84)	OS, DFS	2.6	Mix	I–III	M/U
Shao et al ⁶	2015	R	People's Republic of China	2002–2012	633 (484/149)	60 (37–83)	OS	1.7	Surgery	I–III	M/U
He et al ¹⁷	2016	NR	People's Republic of China	2000–2010	317 (268/49)	60 (37–77)	OS, DFS	3.3	Mix	I–IV	M
Ji et al ²²	2016	R	People's Republic of China	2009–2012	41 (38/3)	56.6±7.2	OS, PFS	5	Mix	I–III	M/U
Kosumi et al ²¹	2016	R	Japan	2005–2011	283 (248/35)	NR (≥65, n=165; <65, n=118)	OS	1.94	Mix	I–IV	M/U
Toyokawa et al ⁷	2016	R	Japan	2000–2014	185 (152/33)	64 (59–70)	OS	3.612	Mix	I–IV	M
Zhang et al ²⁰	2016	R	People's Republic of China	2006–2011	212 (166/46)	60 (37–81)	OS, PFS	3	Chemoradiotherapy	NR**	M

Notes: R: retrospective study; M: HR from multivariate analysis; U: HR from univariate analysis; Mix: mixed treatment with at least two anticancer methods including chemotherapy, surgery, radiotherapy, or chemoradiotherapy. *No patients had metastasis. **A few patients had metastasis.

Abbreviations: CV, cutoff value; HR, hazard ratio; OS, overall survival; NR, not reported; DFS, disease-free survival; PFS, progression-free survival; SD, standard deviation.

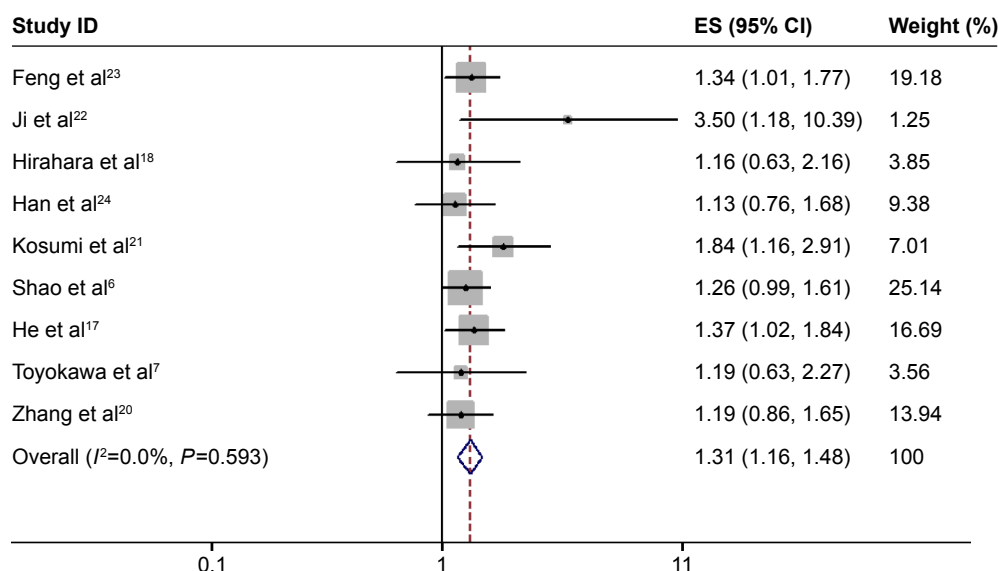


Figure 2 Meta-analysis of the association between NLR and OS in ESCC. Results are presented as individual and pooled HR, and 95% CI.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; ES, effect size.

HR=1.314; 95% CI, 1.164–1.484; $P<0.001$; Figure 2), and there was no significant heterogeneity ($I^2=0\%$, $P_h=0.593$; Table 2). Subgroup analysis by cutoff values revealed that the combined HR was 1.345 (95% CI, 1.098–1.647; $P=0.004$; $I^2=12.2\%$, $P_h=0.32$) for cutoff value ≤ 2.5 , whereas the HR was 1.297 (95% CI, 1.114–1.51; $P=0.001$; $I^2=0\%$, $P_h=0.531$) for patients with a cutoff value >2.5 . Subgroup analysis by

sample size revealed that the combined HR was 1.316 (95% CI, 1.083–1.598; $P=0.006$; $I^2=20.4\%$, $P_h=0.28$) for sample size <300 and 1.313 (95% CI, 1.124–1.534; $P=0.001$; $I^2=0\%$, $P_h=0.905$) for studies with sample size >300 . Subgroup analysis according to treatment method showed that the combined HR was 1.283 (95% CI, 1.077–1.528; $P=0.005$) for patients undergoing surgery alone and 1.404

Table 2 Summary of the meta-analysis results

Factor	No of studies	No of patients	Effects model	HR (95% CI)	P-value	Heterogeneity	
						I ² (%)	P _h
OS							
Overall	9	2,513	Fixed	1.314 (1.164–1.484)	<0.001	0	0.593
Country							
People's Republic of China	6	609	Fixed	1.291 (1.132–1.472)	<0.001	0	0.533
Japan	3	1,904	Fixed	1.463 (1.063–2.015)	0.02	0	0.394
Treatment							
Surgery	3	1,257	Fixed	1.283 (1.077–1.528)	0.005	0	0.902
Mixed	5	1,044	Fixed	1.404 (1.152–1.71)	0.001	26.4	0.245
Cutoff value							
≤2.5	3	1,057	Fixed	1.345 (1.098–1.647)	0.004	12.2	0.32
>2.5	6	1,456	Fixed	1.297 (1.114–1.51)	0.001	0	0.531
Sample size							
<300	6	1,080	Fixed	1.316 (1.083–1.598)	0.006	20.4	0.28
>300	3	1,433	Fixed	1.313 (1.124–1.534)	0.001	0	0.905
Survival analysis							
Univariate	6	1,799	Fixed	1.335 (1.149–1.55)	<0.001	16	0.311
Multivariate	8	2,372	Fixed	1.321 (1.167–1.495)	<0.001	0	0.502
DFS							
Overall	2	525	Fixed	1.268 (1.01–1.592)	0.041	0	0.845
PFS							
Overall	2	253	Fixed	1.221 (0.9–1.655)	0.2	0	0.484

Note: P_h : P-value of Q test for heterogeneity.

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; No, number.

Table 3 Meta-analysis of the association between NLR and clinicopathologic features of ESCC

Variable	No of studies	No of patients	OR (95% CI)	P-value	Heterogeneity		Publication bias Begg's P
					I^2 (%)	P_h	
TNM stage (III–IV vs I–II)	3	576	1.578 (1.11–2.243)	0.011	0	0.623	1
Tumor differentiation (poor vs moderate/high)	4	1,059	1.51 (1.106–2.061)	0.01	35.1	0.202	0.734
Depth of invasion (T3–T4 vs T1–T2)	4	954	2.742 (1.997–3.765)	<0.001	14.9	0.318	0.734
Tumor size (>3 cm vs <3 cm)	3	1,018	2.825 (1.675–4.764)	<0.001	62.9	0.067	1
Lymph node metastasis (yes vs no)	5	1,271	1.424 (0.862–2.355)	0.168	68.9	0.012	0.806
Vascular invasion (yes vs no)	2	524	1.383 (0.859–2.228)	0.182	0	0.336	1

Note: P_h : P-value of Q test for heterogeneity.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; ESCC, esophageal squamous cell carcinoma; OR, odds ratio; CI, confidence interval; TNM, tumor node metastasis; No, number.

(95% CI, 1.152–1.71; $P=0.001$) for patients with multimodal treatment. No significant heterogeneity was observed (Table 2). Subgroup analyses conducted by country and survival analyses (univariate and multivariate analysis) are also shown in Table 2.

Our study also examined the impact of NLR on PFS and DFS. Two cohorts revealed that elevated NLR was notably correlated with poorer DFS (HR=1.268; 95% CI, 1.01–1.592; $P=0.041$) with no heterogeneity ($I^2=0\%$, $P_h=0.845$). However, the pooled data of another two cohorts, also using a fixed-effects model, revealed that NLR had no prognostic role in PFS for ESCC (HR=1.221; 95% CI, 0.9–1.655; $P=0.2$; $I^2=0\%$, $P_h=0.484$) (Table 2).

NLR and clinicopathologic parameters of ESCC

We also examined the relationship between NLR and clinicopathologic characteristics. Five studies^{17,20,22–24} reported the association of NLR with clinicopathologic features such as

lymph node metastasis, tumor node metastasis stage, tumor differentiation, depth of tumor invasion, tumor size, and vascular invasion. Our results showed that higher NLR was positively associated with depth of tumor invasion ($n=4$; OR=2.742; 95% CI, 1.997–3.765; $P<0.001$), tumor size ($n=3$; OR=2.825; 95% CI, 1.675–4.764; $P<0.001$), clinical stage ($n=3$; OR=1.578; 95% CI, 1.11–2.243; $P=0.011$), and poor differentiation ($n=4$; OR=1.51; 95% CI, 1.106–2.061; $P=0.01$). Elevated NLR was not correlated with lymph node metastasis or vascular invasion (Table 3).

Publication bias and sensitivity analysis

We used the Begg's test and Egger's test to evaluate publication bias. The results revealed that there was no significant publication bias in OS ($P=0.348$ for Begg's test and $P=0.225$ for Egger's test respectively). Furthermore, there was no significant bias in the analysis of the relationship between NLR and clinicopathologic characteristics (Table 3). The results of sensitivity analysis demonstrated that the combined HR

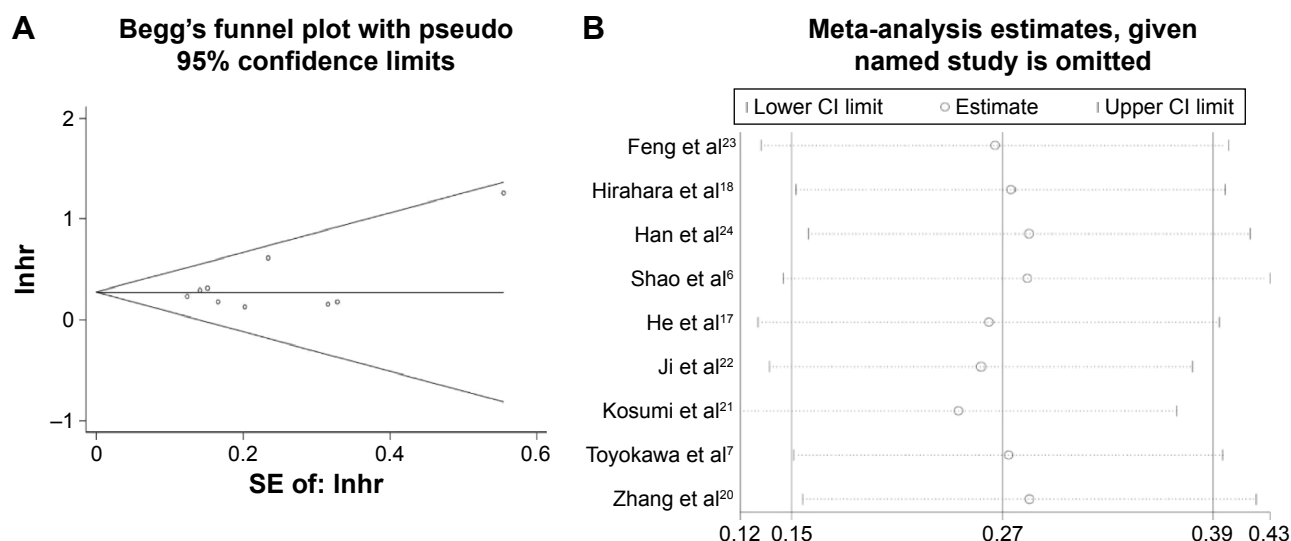


Figure 3 (A) Begg's funnel plot for the assessment of potential publication bias. (B) Sensitivity analysis of the relationship between NLR and OS.

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; SE, standard error; Inhr, natural logarithm of hazard ratio; CI, confidence interval.

for OS was not markedly changed, indicating the reliability of our results (Figure 3B).

Discussion

Results of this meta-analysis of nine studies with 2,513 ESCC patients suggested that elevated NLR significantly correlated with poor OS (pooled HR =1.314; 95% CI, 1.164–1.484; $P<0.001$) in patients with ESCC. Subgroup analyses also showed that high NLR was correlated with poor OS in ESCC for different treatment methods and different countries. Elevated NLR was associated with poor DFS, but had no prognostic role for PFS. In addition, elevated NLR was correlated with large tumor size, deep depth of tumor invasion, late stage, and poor differentiation in ESCC patients. Overall, these findings suggest that NLR might be used as an effective serum biomarker in the prognosis of ESCC.

An increasing number of studies have proved that inflammation plays a critical role in cancer progression and prognosis. Control and regulation of the inflammatory response is a potential therapeutic strategy in cancer treatment that may provide an opportunity to improve patient outcome.^{25,26} Recently, the associations of inflammation-based markers with the prognosis of various cancers have been actively explored.^{14–16} The combined index of NLR, which could partially reflect the inflammatory status of patients, is a promising marker for assessing the systemic inflammatory changes. Various studies have proved that an elevated NLR is positively correlated with poor prognosis in many cancer types.^{15,27,28} Accumulating data have demonstrated that lymphocytes can prevent tumor development from immune compartments and that lymphocytes express recombined antigen receptors to regulate the immunosurveillance process.²⁹ Existing studies show that CD8⁺ and CD4⁺ T lymphocytes play a critical role in cell-mediated immunity. Tumor-infiltrating CD8⁺ and CD4⁺ T lymphocytes have been proved to have antitumor activity and could be an indicator to predict prognosis in many cancer patients.^{30–32} In contrast, neutrophils have been recognized as an important element in tumor progression. Bidirectional cross talk between neutrophils and tumor cells results in changes that eventually lead to tumor-infiltrating (associated) neutrophils (TANs) equipped with various tumor-promoting features. Growing evidence indicates that TANs might be associated with a poor prognosis through the promotion of angiogenesis, cell mobility, and migration.^{33–35} Thus, a high value of NLR in the serum is a valuable index to evaluate the level of inflammation and is ultimately correlated with prognosis. Importantly, the NLR is easy to measure at very low cost. Together, these characteristic features suggest that NLR might be a useful

tool for clinicians when performing clinical therapy and evaluating the outcomes.

Two previous meta-analyses have reported the relationship between NLR and survival in esophageal cancer;^{36,37} however, the prognostic role of NLR in ESCC required more investigation. To our knowledge, our research is the first to identify the prognostic and clinicopathologic significance of peripheral blood NLR in ESCC. However, this meta-analysis has some limitations. First, all studies included in this meta-analysis were from Asian countries. It is well known that the pattern of pathology of the esophageal cancer is quite different between Western and Asian countries; adenocarcinoma of the esophagus and the gastroesophageal junction is prevalent in the West, whereas ESCC is more prevalent in Asia.^{1,4} Although some articles have reported the relationship between esophageal cancer and NLR in Western countries, including both esophageal adenocarcinoma and squamous cell carcinoma,^{38,39} we failed to get sufficient data for the ESCC subgroup, and these studies were excluded from our analysis. Therefore, our results may have limited value in other geographic regions. Second, the cutoff values of NLR varied among studies, which may lead to heterogeneity. In addition, there may have been a lack of uniformity. Third, some articles evaluated the relationship between NLR and cancer-specific survival, but not OS.^{40,41} We did not include these articles because of the small numbers involved. Fourth, all of the studies enrolled in our meta-analysis were retrospective and published in English. Therefore, the pooled HR estimates should be interpreted with caution.

Conclusion

In summary, we found that a high value of NLR might be a negative factor when estimating prognosis of ESCC patients. Furthermore, elevated NLR might be a predictor of deeper tumor invasion, advanced stage, and poor differentiation. Further well-designed and large prospective studies are needed to confirm our results. In addition, additional research should focus on anti-inflammatory interventions for patients with ESCC.

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Disclosure

The authors report no conflicts of interest in this work.

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