Technology in Cancer Research & Treatment
Volume 21: 1-11

DOI: 10.1177/15330338211070140
journals.sagepub.com/home/tct
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Prognostic and Clinicopathologic Significance of Neutrophil-to-Lymphocyte Ratio in Esophageal Cancer: An Update Meta-Analysis

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Abstract

Background: Esophageal cancer is one of the most common cancers with significant morbidity and mortality. It is important to predict the prognosis of patients. The purpose of this study was to comprehensively assess the prognostic and clinicopathologic significance of NLR in patients with esophageal cancer. **Methods:** A systematic literature search was performed using PubMed, Cochrane Library, Embase, Web of Science, MEDLINE, and CNKI. This meta-analysis was conducted in accordance with PRISMA guidelines. Hazard ratio (HR) with 95% confidence interval (CI) was used as the effect estimation to evaluate the prognostic role of NLR. Odds ratio (OR) was used to evaluate the relation between NLR and clinicopathologic characteristics. **Results:** A total of 8431 patients from 32 studies were included in this meta-analysis. The pooled results showed that elevated NLR might predict poor prognosis: The factors considered included overall survival (OS) (HR, 1.57; 95% CI, 1.40-1.75; $P < .001$), cancer-specific survival (CSS) (HR, 1.28; 95% CI, 1.09-1.49; $P < .001$), progression-free survival (PFS) (HR, 1.45; 95% CI, 1.29-1.72; $P < .001$), and disease-free survival (DFS) (HR,1.58; 95% CI, 1.27-1.97; $P < .001$). High NLR was also associated with tumor differentiation, tumor length, tumor invasion depth, lymph node metastasis, and clinical stage. No significant association was observed between NLR and metastasis stage (OR, 1.69; 95% CI, 0.98-2.98; $P = .058$). **Conclusions:** The results of this meta-analysis suggest that elevated NLR value might predict poor prognosis (OS, CSS, PFS, and DFS), according to abnormal clinicopathologic parameters.

Keywords

esophageal cancer, inflammation, meta-analysis, neutrophil-to-lymphocyte ratio, progression

Received: July 15, 2021; Revised: December 7, 2021; Accepted: December 12, 2021.

Introduction

Esophageal cancer stands at the eighth most common cancer with significant morbidity and mortality.[1] Due to late diagnosis, rapid progression, and high rate of recurrence, treatment results of patients with esophageal cancer are usually less optimistic. To take timely and effective treatment strategies against esophageal cancer, it is important for us to explore available predictive factors for prognosis and clinicopathologic characteristics of esophageal cancer patients.

Host inflammatory responses had been reported as correlating with tumor initiation and development, and increased inflammatory response often indicates poor prognosis.[2] Inflammatory response may alter the relative levels of circulating white blood cells. In particular, the level of neutrophils increases, while that of lymphocytes declines.[3]

In previous studies, neutrophil-to-lymphocyte ratio (NLR) was proven to be a useful indicator in prostate cancer, gastric cancer and lung cancer.[4–6] There were also studies that examined the relation between NLR and prognosis in patients with esophageal cancer.[7–9] However, these studies were all limited to small study numbers and had different results. Recently, more and more clinical trials have been done to evaluated the relationship of NLR and esophageal cancer. We have a chance to systematically assess the prognostic role of NLR on

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oncologic outcomes of esophageal cancer. Oncologic outcomes include overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), and disease-free survival (DFS). Clinicopathologic parameters include tumor length, tumor differentiation, tumor invasion depth, lymph node metastasis, metastasis stage and tumor-node-metastasis (TNM) stage.

Materials and Methods

This study followed the guidelines of the Meta-analysis of Observational Studies in Epidemiology group (MOOSE).[10] PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[11] were used for study design, search strategy, screening and Reporting. Our protocol for this study has been registered with INPLASY (registration number: INPLASY2021100111).

Literature Search

A systematic literature search was performed using PubMed, Cochrane Library, Embase, Web of Science, MEDLINE, and CNKI up to January 12, 2020. Terms "NLR" (or "neutrophil lymphocyte ratio," "neutrophil to lymphocyte ratio," "neutrophil-to-lymphocyte ratio") AND "esophageal cancer" (or "esophageal Neoplasm," "esophageal carcinoma") AND "prognosis" (or "prognoses," "prognostic," "survival") AND "inflammation" were used in the literature search. Related articles and reference were also reviewed.

Inclusion and Exclusion Criteria

Studies were selected according to the following criteria: 1) esophageal cancer was diagnosed with pathology; 2) NLR was measured before treatment from serum with a clear cutoff value; 3) the association between NLR and prognosis (OS, CSS, PFS, and DFS) or clinicopathologic parameters was evaluated.

Articles were excluded when the following situations existed: 1) abstract, letter, editorial, expert opinion, review, case report, concerned nonhuman research, or full text was not available; 2) studies did not directly report hazard ratios (HRs) or odds ratio (OR) or corresponding 95% confidence intervals (CIs), and there was no sufficient data to estimate; and 3) studies contained duplicate data or repeated analysis.

Assessment of Study Quality and Risk of Bias

The Newcastle-Ottawa Scale (NOS) was used for assessing quality of the non-randomized studies. NOS includes three aspects of evaluation: selection, comparability, and outcome in the case and control groups.[12] A star system was used with a total score ranging from zero to nine stars. Studies with a score of 7 stars or greater were regarded as high-quality researches.

Data Extraction

Data were collected and extracted independently by two reviewers to avoid inconsistent evaluation and extractor bias. If the reviewers had any disagreements, those disagreements were resolved by a third reviewer. The following items were recorded for each study: authors, year of publication, country, study period, number of participants, gender, mean age, survival type, cutoff value for NLR, treatment strategy, pathological type, TNM stage, hazard ratio (HR) or OR with corresponding 95% CI (confidence interval) and its statistical method.

Outcome Measures

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. OS was defined as the time between curative treatment and patient death or date of last follow-up. CSS was defined as the percentage of people who have not died from esophageal cancer in a defined period of time; which usually begin at the time of diagnosis or at the start of treatment and ended at the time of death (patients who died from causes other than the esophageal cancer being studied are were not counted in this study). PFS was defined as the length of time during and after the treatment of esophageal cancer. DFS was estimated from the day of treatment until the detection of cancer recurrence.

Statistical Analysis

HRs and 95% CIs were used to analyze the relation between NLR and prognosis (OS, CSS, PFS, and DFS). If univariate and multivariate analysis were both reported in the same study, multivariate-adjusted HRs and 95% confidence intervals were used with priority. ORs and 95% CIs were used to evaluate the relation between NLR and clinicopathologic factors. Between-study heterogeneity was assessed by χ^2-based Q test and Higgins' I^2 statistic. *P*-value for Q test was >.10 and I^2 was <50%. These suggested that there was no significant heterogeneity and therefore fixed-effects model was used to calculate overall estimate of effect. If there was any heterogeneity, random-effects model would be used instead. Subgroup analysis was used to explore possible heterogeneity. Robustness of data included was tested by sensitivity analysis. Publication bias was assessed by Begg's funnel plot and Egger's linear regression test. Differences were considered statistically significant for *P*-values <.05. Statistical analysis was conducted with Stata version 14.1 (Stata Corporation). All *P*-values were two-sided.

Results

Study Characteristics

A total of 154 abstracts were selected in the initial search. After discarding duplicates, 137 abstracts remained, and then 68 articles were excluded after reading the titles and abstracts, as they were views, letters, abstracts, case reports, or nonclinical types. The remaining 69 articles were further reviewed with full texts. After that, 37 studies were excluded as theyfor the following reasons: did not providing provide sufficient data, involved continuous NLR without a clear cutoff point, or were repeated repeated

reporteds. Figure 1 showed the detailed screening process. Finally, 32 studies were included in this meta-analysis.[13–44] All those studies were retrospective observational cohort studies, all reports were published between 2011 and 2017. The 32 articles involved a total of 8431 patients. Among them, 6569 suffered from squamous cell carcinoma, and 1862 suffered from adenocarcinoma and other malignant tumors. NLR cutoff values in these studies varied, ranging from 1 to 5. Of all those studies, 15 had a cutoff value ≤2.5, and 17 had a value >2.5. Detailed information on the selected studies was summarized in Table 1. All the studies had an NOS score ≥7.

Overall Survival of Esophageal Cancer

21 Studies involving 5630 patients evaluated the association between NLR and OS (Table 2). High pretreatment NLR predicted a poor OS with a pooled HR of 1.57 (95% CI = 1.40-1.75, $P < .001$, Figure 2). Significant between-study heterogeneity was found ($I^2 = 42.7\%$, $P = .021$) and random-effect model was used.

For further investigation, subgroup analysis of OS was performed, and the detailed information was shown in Table 2. Subgroup analysis by country showed that the combined HR was 1.49 (95% CI = 1.31-1.69, $P < .001$, $I^2 = 47.2\%$, $P_{heterogeneity} = 0.030$, Figure S1A within Supplemental) for China and 1.68 (95% CI = 1.30-2.17, $P < .001$, $I^2 = 14.8\%$, $P_{heterogeneity} = 0.319$) for Japan. Subgroup analysis according to sample size revealed that the combined HR was 1.52 (95% CI = 1.34-1.71, $P < .001$, $I^2 = 37.2\%$, $P_{heterogeneity} = 0.121$) for sample size >250 and 1.68 (95% CI = 1.35-2.09, $P < .001$, $I^2 = 49.8\%$, $P_{heterogeneity} = 0.025$) for sample size ≤250 (Figure S1B within Supplemental). Subgroup analysis also showed that high NLR was correlated with poor OS for different therapy, different cutoff values, different survival analyses (univariate or multivariate analysis) and different histology (Table 2, Supplemental Figure S1C-S1F).

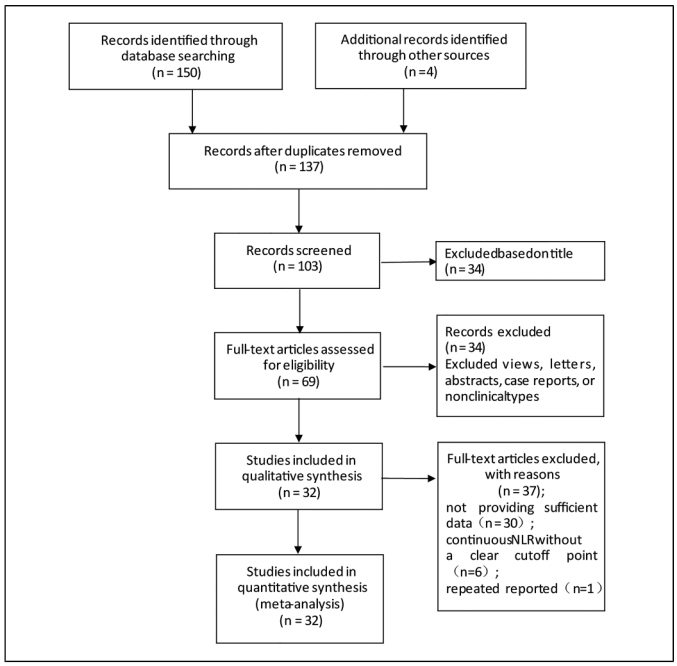

Figure 1. Flow diagram of search strategy and study selection. NLR, neutrophil-to-lymphocyte ratio.

Because of the significance heterogeneity, sensitivity analysis was done to estimate the influence of each individual study on the overall estimate of effect, and the data proved that the results calculated were reliable and stable (Figure 3A).

Other Survival Indicators of Esophageal Cancer

The association between NLR and CSS, PFS and DFS were evaluated and shown in Table 2. Patients with elevated NLR was notably correlated with poorer CSS (HR = 1.28, 95% CI = 1.09-1.49, $P < .001$, Figure S2A), without between-study heterogeneity ($I^2 = 3.8\%$, $P = .397$). Impact of NLR on PFS was also examined. The results revealed that higher NLR was related with poorer PFS (HR = 1.45, 95% CI = 1.29 −1.72, $P < .001$, Figure S2B), and no significant heterogeneity was found ($I^2 = 0.0\%$, $P = .464$). The meta-analysis also revealed that NLR had prognostic role for DFS of esophageal cancer; the combined HR was 1.58 (95% CI = 1.27-1.97, $P < .001$, Figure S2C) with high heterogeneity ($I^2 = 50.2\%$, $P = .074$).

Sensitivity analysis was done to evaluate the influence of single study on overall estimate of effect, and the results showed that the pooled HR was reliable (Supplemental Figure S3).

Tumor Length of Esophageal Cancer

Significant association was observed between high NLR and large tumor size (OR = 2.85, 95%CI = 2.32-3.50, $P < .001$). No statistical heterogeneity was found among these studies ($I^2 = 37.7\%$, $P = .141$, Figure 4A).

Subgroup analysis by tumor length cutoff value revealed that combined OR was 2.28 (95% CI = 1.72-3.01, $P < .0001$, $I^2 = 0.0\%$, $P_{heterogeneity} = 0.960$, Supplemental Figure S4) for tumor length cutoff value of 5, and 3.62 (95% CI = 2.66-4.94, $P < .0001$, $I^2 = 43.5\%$, $P_{heterogeneity} = 0.150$, Supplemental Figure S4) for tumor length cutoff value of 3.

Tumor Differentiation of Esophageal Cancer

The associations between NLR and clinicopathologic parameters were shown in Table 3. Pooling data (from 12 studies with 3686 patients) showed that NLR was higher in patients with poor tumor differentiation (OR = 1.43, 95%CI = 1.10-1.85). The random-effects model was adopted to determine the significance of heterogeneity ($P = .028$, $I^2 = 49.0\%$, Figure 4C).

We next investigated whether heterogeneity resulted from NLR cutoff value. The results suggested that elevated NLR was associated with high tumor differentiation for cases with NLR cutoff value >2.5 (OR = 1.41, 95% CI = 1.02-1.95, $P = .037$, $I^2 = 48.3\%$, $P_{heterogeneity} = 0.071$, Figure S5A within

Table 1. Main Characteristics of Relevant Studies.

Study	Country	Study period	No (male/female)	Mean age ± SD (years)	Survival type	NLR CV	Treatment	Histology	TNM stage	HR
Zhou 2017[13]	China	2006 to 2010	517(407/110)	65(36-74)	OS PFS	5	MIX	ESCC	II-IV	M
Zhang 2017[14]	China	2007 to 2011	109(88/21)	59(39-79)	OS	2.5	MIX	ESCC	I-III	M
Nakamura et al. 2017[15]	Japan	2005 to 2016	245(219/26)	NR	OS DFS	2.42	MIX	ESCC	NR	M
Hirahara et al.2017[16]	Japan	2006 to 2014	147(132/15)	NR	OS CSS	1.6	Surgery	ESCC	I-III	U
He et al.2017[17]	China	2000 to 2010	317(268/49)	60(37-77)	OS DFS	3.3	MIX	ESCC	I-IV	M
Zhu et al.2016[18]	China	2013 to 2015	114(88/26)	NR	-	3	MIX	ESCC	I-IV	U
Zhang et al.2016[19]	China	2006 to 2011	212(166/46)	60(37-81)	OS PFS	3	CRT	ESCC	NR	M
Xiao et al.2016[20]	China	2007 to 2014	121(106/15)	62(30-76)	OS	1.77	Surgery	ESCC	I-III	M
Toyokawa et al.2016[21]	Japan	2000 to 2014	185(152/33)	64(59-70)	OS	3.612	MIX	ESCC	I-IV	M
Miyazaki et al.2016[22]	Japan	2004 to 2014	192(173/19)	65.8(42-86)	OS	3.49	MIX	ESCC	I-III	M
Liu et al.2016[23]	China	2012 to 2013	147(118/29)	63.1(38-74)	OS PFS	2.46	CRT	ESCC	II-III	M
Kosumi et al.2016[24]	Japan	2005 to 2011	283(243/35)	NR	OS CSS	1.94	MIX	ESCC	I-IV	M
Ji et al.2016[25]	China	2009 to 2012	41(38/3)	56.6 ± 7.2	OS PFS	5	MIX	ESCC	I-III	M
Hirahara et al.2016[26]	Japan	2006 to 2015	147(132/15)	NR	CSS	1.6	Surgery	ESCC	I-III	U
Yutong et al.2015[27]	China	2007 to 2008	820(526/294)	60.0 ± 9.3	OS	3.5	MIX	EC	I-IV	M
Wu and Yu2015[28]	China	2008 to 2011	149(86/63)	NR	-	3	Radiotherapy	ESCC	NR	NR
Su et al.2015[29]	China	2003 to 2009	345(213/132)	NR	OS DFS	2.21	MIX	EC	I-IV	M
Shao et al.2015[30]	China	2002 to 2012	633(484/149)	60(37-83)	OS	1.7	Surgery	ESCC	I-III	M
Liu et al.2015[31]	China	2006 to 2008	326(283/43)	59.2 ± 7.9	-	3.45	Surgery	ESCC	NR	M
Hirahara et al.2015[32]	Japan	2006 to 2014	141(127/14)	NR	OS	2.5	Surgery	ESCC	I-III	U
Han et al.2015[33]	China	2007 to 2008	218(177/41)	60.5(32-84)	OS DFS	2.6	MIX	ESCC	I-III	M
Hao et al.2015[34]	China	2000 to 2007	371(276/95)	57	CSS	3	Surgery	ESCC	I-III	M
Xie et al2016[35]	China	2008 to 2010	317(244/73)	58.1 ± 8.9	CSS	2.1	MIX	ESCC	I-III	M
Yoo et al.2014[36]	South Korea	2005 to 2010	138(132/6)	67.6 ± 7.7	OS PFS	2	CRT	EC	II-III	M
Wang et al.2014[37]	China	2007 to 2007	90(72/18)	60.5(42-78)	OS DFS	1	Surgery	ESCC	I-III	U
Feng et al.2014[38]	China	2005 to 2008	483(411/72)	59.1 ± 8.0	OS	3.5	Surgery	ESCC	NR	M
Chen and 2014[39]	China	2007 to 2008	475(382/93)	NR	OS	2.5	MIX	ESCC	I-III	M
Jifeng et al.2013[40]	China	2001 to 2010	43(30/13)	58.7 ± 7.8	OS	3.5	MIX	ESCC	NR	NR

(continued)

Table 1. (continued)

Study	Country	Study period	No (male/female)	Mean age ± SD (years)	Survival type	NLR CV	Treatment		Histology	TNM stage HR
Feng et al.2013[41]	China	2001 to 2010	483(411/72)	59.1 ± 8.0	OS	3.5	Surgery	ESCC	I-III	M
Sharaiha et al.2011[42]	US	1996 to 2009	295(237/58)	62.8	OS DFS	5	MIX	EC	I-IV	M
Miyata et al.2011[43]	Japan	2000 to 2008	152(132/20)	62.5 ± 8.4	OS	4	MIX	EC	II-IV	M
Dutta et al.2011[44]	UK	1996 to 2008	112(85/27)	NR	CSS	2.5	MIX	EC	I-IV	U

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; the dashes represent no data.
Abbreviations: CV, cutoff value; HR, hazard ratio; NR, not reported; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; CSS, cancer-specific survival; SD, standard deviation; TNM, tumor node metastasis; NLR, neutrophil-to-lymphocyte ratio; CRT, chemoradiotherapy; ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer including adenocarcinoma, esophageal squamous cell carcinoma and other types esophageal carcinoma; No, number.

Supplemental), but not for those with NLR cutoff value ≤2.5 (OR = 1.47, 95% CI = 0.91-2.37, $P = .119$, $I^2 = 59.9\%$, $P_{heterogeneity} = 0.041$). Both subgroups showed high heterogeneity. Sensitivity analysis showed that the pooled OR was steady (Supplemental Figure S5B).

Depth of Invasion of Esophageal Cancer

A total of 16 studies were accessed to calculate a pooled OR and 95% CI for depth of invasion of esophageal cancer. As heterogeneity was detected ($I^2 = 52.8$, $P = .007$), random-effect model was used. Significant associations were observed between high

Table 2. Summary and Subgroup Analysis of the Association Between NLR and Prognosis of EC.

Factor	Number of studies	Number of patients	Model	HR (95% CI)	Overall effect *P*-value	Heterogeneity I^2 (%)	Heterogeneity *P*
OS							
Overall	21	5630	Random	1.57 (1.40-1.75)	<.0001	42.7%	.021
Country							
China	13	4044	Random	1.49 (1.31-1.69)	<.0001	47.2%	.030
Japan	6	1153	Random	1.68 (1.30-2.17)	<.0001	14.8%	.319
Sample size							
> 250	9	3831	Random	1.52 (1.34-1.71)	<.0001	37.2%	.121
≤ 250	12	1799	Random	1.68 (1.35-2.09)	<.0001	49.8%	.025
NLR CV							
≥ 2.5	13	3628	Random	1.54 (1.33-1.79)	<.0001	51.5%	.016
< 2.5	8	2002	Random	1.61 (1.35-1.93)	<.0001	31.0%	.180
Therapy							
Mix	12	3182	Random	1.73 (1.47-2.03)	<.0001	48.2%	.031
Surgery	7	2098	Random	1.36 (1.19-1.55)	<.0001	0.0%	.689
CRT	2	350	Random	1.51 (0.87-2.62)	.142	65.5%	.089
Histology							
ESCC	17	4700	Random	1.54 (1.35-1.75)	<.0001	45.4%	.022
EC	4	930	Random	1.72 (1.34-2.22)	<.0001	34.6%	.204
Survival analysis							
Univariate	3	378	Random	1.37 (1.00-1.89)	.052	0.0%	.700
Multivariate	18	5252	Random	1.60 (1.41-1.81)	<.0001	49.6%	.009
CSS							
Overall	7	1703	Fixed	1.28 (1.09-1.49)	.002	3.8%	.397
DFS							
Overall	6	1510	Random	1.58 (1.27-1.97)	<.0001	50.2%	.074
PFS							
Overall	4	908	Fixed	1.45 (1.29-1.72)	<.0001	0.00%	.464

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; EC, esophageal carcinoma including adenocarcinoma, esophageal squamous cell carcinoma and other types esophageal carcinoma; HR, hazard ratio; CI, confidence interval; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival; PFS, progression-free survival; Mix: mixed treatment with at least two anticancer methods including chemotherapy, surgery, radiotherapy, or chemoradiotherapy; CRT, chemoradiotherapy; ESCC, esophageal squamous cell carcinoma; CV, cutoff value.

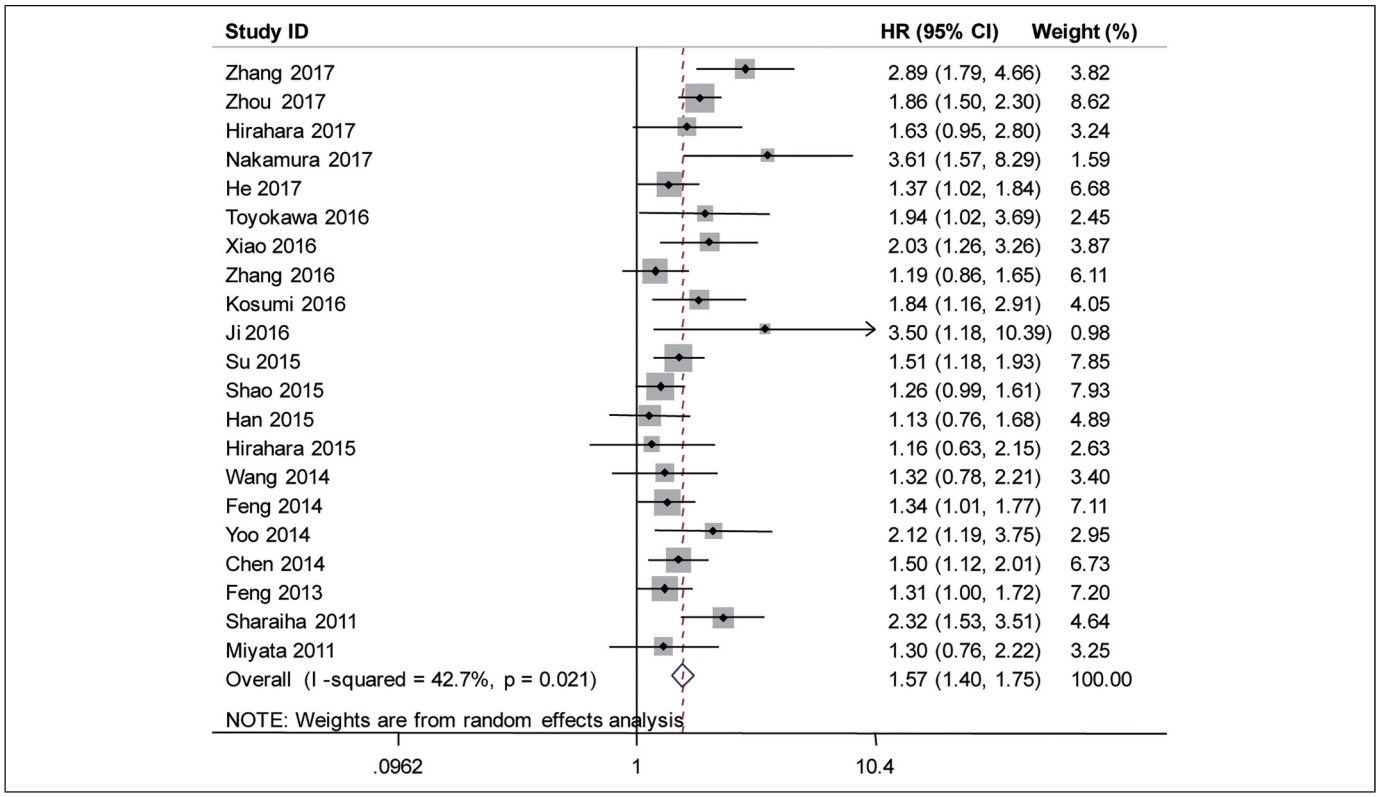

Figure 2. Forest plots of studies evaluating hazard ratios of NLR for OS.
NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; CI, confidence interval.

NLR and deeper invasion (T3-T4) (pooled OR = 1.82, 95% CI = 1.38-2.41, $P < .001$, Figure 4D).

Due to the presence of heterogeneity, we performed stratified analysis by NLR cutoff value. Combined OR was 1.29 (95% CI = 0.94-1.77, $P = .111$, $I^2 = 24.2\%$, $P_{heterogeneity} = 0.244$, Supplemental Figure S6A) for NLR cutoff value ≤ 2.5 and 2.73 (95% CI = 2.14-3.49, $P < .0001$, $I^2 = 0.0\%$, $P_{heterogeneity} = 0.445$) for NLR cutoff value > 2.5. The results revealed that, NLR was associated with depth of invasion only for NLR cutoff value > 2.5. Significant heterogeneity was not observed

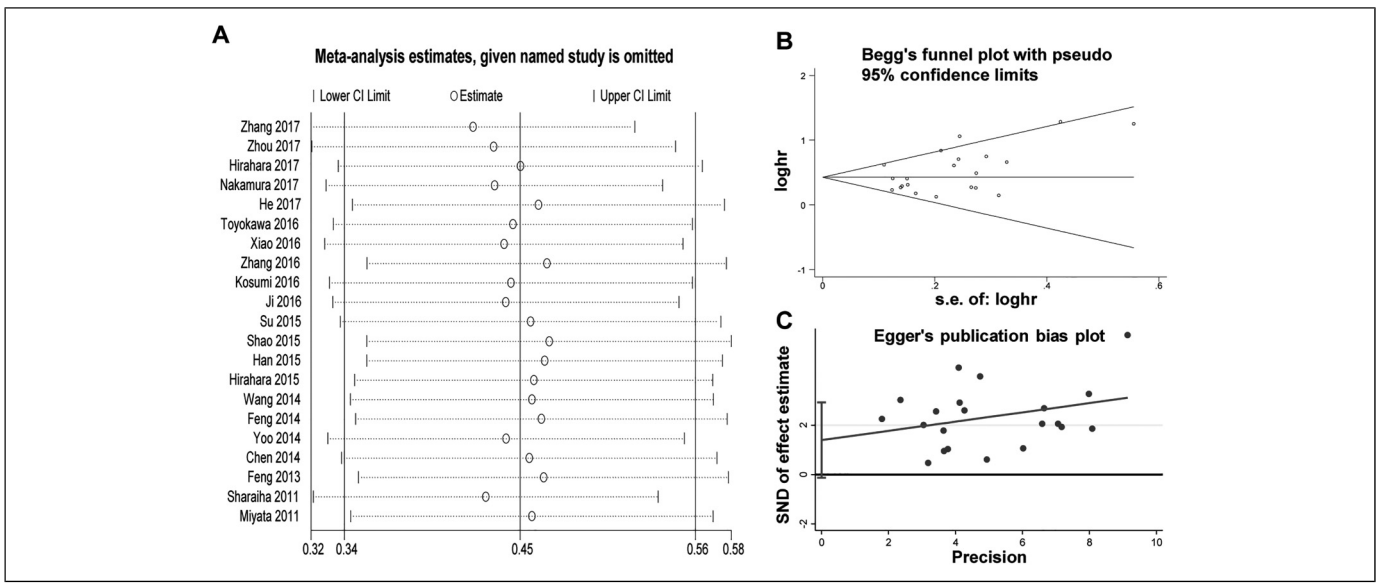

Figure 3. Sensitivity analysis (A) and publication bias of Begg's funnel plot (B) and Egger's linear regression test (C) on the relationship between NLR and OS, using Metaninf function in Stata 14.1.
NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; CI, confidence interval; HR, hazard ratio; s.e., standard error; SND, standardized.

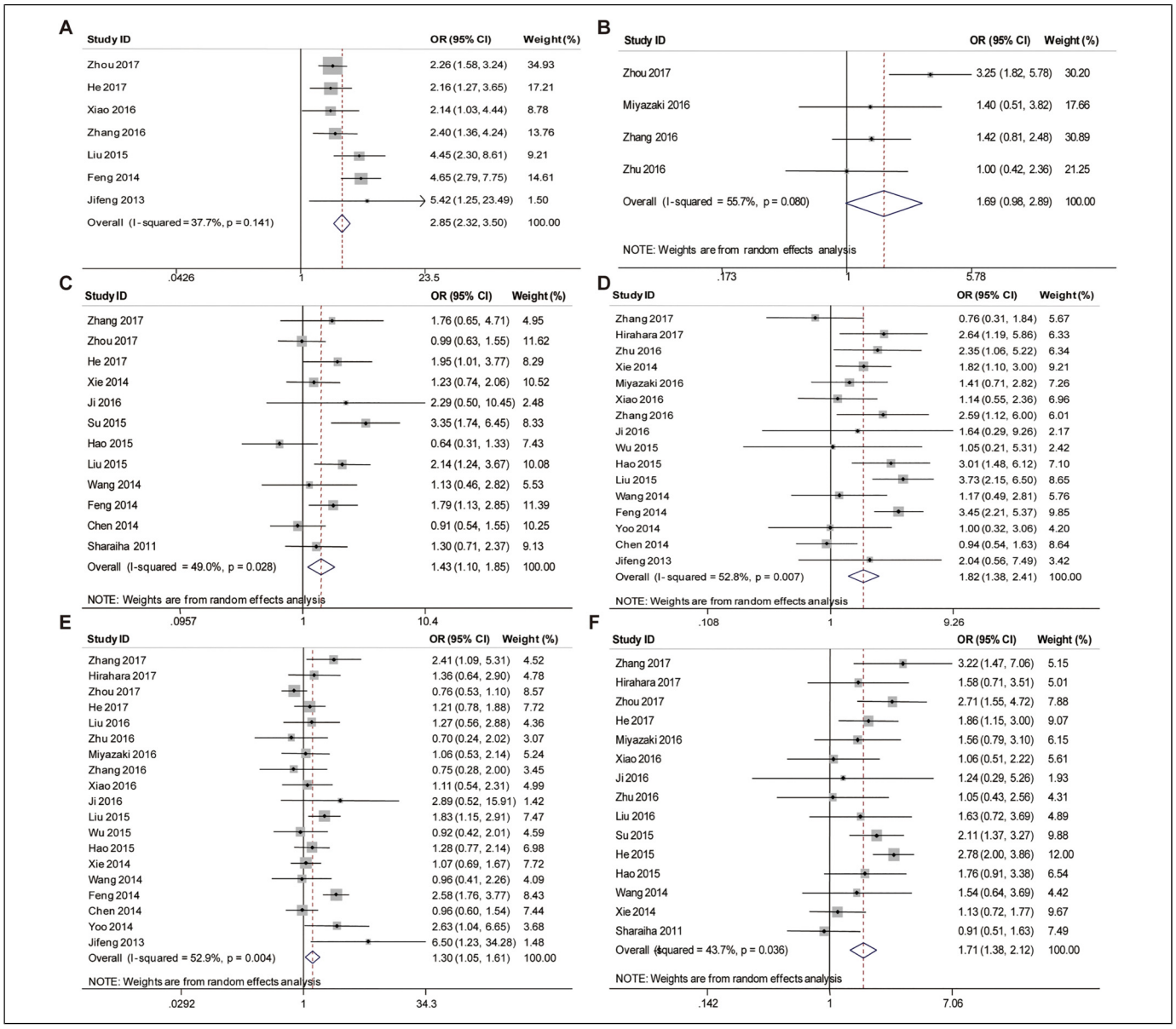

Figure 4. Forest plots of studies evaluating odds ratios of NLR for tumor length (A), metastasis stage (B), tumor differentiation (C), depth of invasion (D), lymph node metastasis (E), and TNM stage (F).
NLR, neutrophil-to-lymphocyte ratio; TNM, tumor, node, metastasis; OR, odds ratio; CI, confidence interval.

in both subgroups. Sensitivity analysis demonstrated that the combined OR was not markedly changed by omitting each study in turn (Supplemental Figure S6B).

Lymph Node Metastasis of Esophageal Cancer

Our pooled results showed that high NLR was associated with advanced lymph node metastasis (N1-N3). The combined OR was 1.30 (95% CI = 1.05-1.61, $P = .018$, $I^2 = 52.9\%$, $P_{heterogeneity} = 0.004$, Figure 4E), using a random-effects model.

To explore heterogeneity, subgroup analysis was done by NLR cutoff value, which revealed that the pooled OR was1.22 (95% CI = 0.97-1.55, $P = .091$, $I^2 = 2.8\%$, $P_{heterogeneity} = 0.408$, Supplemental Figure S7A) for NLR cutoff value $\leq$ 2.5 and 1.31 (95% CI = 0.93-1.83, $P = .119$, $I^2 = 67.4\%$, $P_{heterogeneity} = 0.001$) for NLR cutoff value >2.5. The results implied no significant correlation between lymph node metastasis of esophageal cancer and high- or low-NLR groups. Sensitivity analysis was done to investigate the influence of an individual study on the pooled results. The results indicated that the pooled OR showed no significant change (Supplemental Figure S7B).

Metastasis Stage of Esophageal Cancer

There were only four studies reported the correlation between NLR and metastasis stage of esophageal cancer. The pooled

Table 3. Summary and Subgroup Analysis of the Association Between NLR and Clinicopathologic Features of EC.

Factor	Number of studies	Number of patients	Model	OR (95% CI)	Overall effect *P*-value	Heterogeneity I^2 (%)	Heterogeneity *P*
Tumor differentiation (poor vs moderate/high)			random				
Overall	12	3686		1.43 (1.10-1.85)	.007	49.0%	.028
NLR CV ≤2.5	5	1336		1.47 (0.91-2.37)	.119	59.9%	.041
NLR CV >2.5	7	2350		1.41(1.02-1.95)	.037	48.3%	.071
Tumor length (cm)			fixed				
Overall	7	2019		2.85 (2.32-3.50)	<.0001	37.7%	.141
Tumor length CV = 3 cm	4	1169		3.62 (2.66-4.94)	<.0001	43.5%	.150
Tumor length CV = 5cm	3	850		2.28 (1.72-3.01)	<.0001	0.0%	.969
Depth of invasion (T3–T4 vs T1–T2)			random				
Overall	16	3328		1.82 (1.38-2.41)	<.0001	52.8%	.007
NLR CV ≤2.5	7	1397		1.29 (0.94-1.77)	.111	24.2%	.244
NLR CV >2.5	9	1931		2.73 (2.14-3.49)	<.0001	0.0%	.445
Lymph node metastasis (N1–N3 vs N0)			random				
Overall	19	4309		1.30 (1.05-1.62)	.018	52.9%	.004
NLR CV ≤2.5	8	1544		1.22 (0.97-1.55)	.091	2.8%	.408
NLR CV >2.5	11	2765		1.31 (0.93-1.83)	.119	67.4%	.001
Metastasis stage (M1 vs M0)	4	1035	random	1.69 (0.98-2.89)	.058	55.7%	.080
TNM stage (III–IV vs I–II)			random				
Overall	15	3943		1.71 (1.38-2.12)	<.0001	43.7%	.036
NLR CV ≤2.5	7	1276		1.62 (1.21-2.15)	.001	25.8%	.232
NLR CV >2.5	8	2667		1.76 (1.28-2.41)	<.0001	53.7%	.034

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; CV, cutoff value; EC, esophageal carcinoma; OR, odds ratio; CI, confidence interval; TNM, tumor node metastasis.

OR was 1.69 (95% CI = 0.98-2.98, $P = .058$, $I^2 = 55.7\%$, $P_{heterogeneity} = 0.08$, Figure 4B). This indicated that NLR was not an effective predictor for metastasis stage of esophageal cancer. But as there were only a few studies concerning this topic, sensitivity analysis was not carried out.

TNM Stage of Esophageal Cancer

High NLR was found to be significantly associated with late TNM stage (III-IV) of esophageal cancer (OR = 1.71, 95% CI = 1.38-2.12, $P < .0001$, Figure 4F) with high heterogeneity among these studies ($I^2 = 43.7\%$, $P = .036$).

Stratified analysis by NLR cutoff value showed that OR was 1.62 (95% CI = 1.21-2.15, $P = .001$, Supplemental Figure S8A) for NLR cutoff value ≤ 2.5 and 1.76 (95% CI = 1.28-2.41, $P < .0001$) for NLR cutoff value >2.5. Significant heterogeneity was observed in the high-NLR group ($I^2 = 53.7\%$, $P_{heterogeneity} = 0.034$), not in the low-NLR group ($I^2 = 25.8\%$, $P_{heterogeneity} = 0.232$).

Meta-sensitivity analysis suggested no undue influence of any single study on the pooled effect (Supplemental Figure S8B).

Publication Bias

Begg's test and Egger's test were used to evaluate publication bias. Visual inspection of Begg's funnel plots and Egger's linear regression tests indicated no significant publication bias in this meta-analysis on relation between NLR and survival indicator and clinicopathologic characteristics (Figure 3B, Figure 3C, and Supplemental Figure S9-S15). *P*-values for Begg's text and Egger's test also failed to find evidence of publication bias (Supplemental Table S1). It was not necessary to carry out tests of publication bias test was not done on the outcomes of PFS and Metastasis stage, because there were only a few studies concerning these topics.

Discussion

The results of our analysis from 32 studies with 8431 esophageal cancer patients demonstrated that pretreatment NLR was an effective serum marker to predict prognosis and associated with various clinicopathological characteristics, including tumor length, tumor invasion, clinical stage, lymph node metastasis and differentiation, except metastasis stage. In addition, subgroup analyses and sensitivity analyses provided further support for the conclusions.

A number of studies reported that inflammatory responses play crucial roles in tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis.[2,6,45,46] Our finding are consistent with those in published reports, but the mechanisms on how elevated NLR causes poor outcomes remain elusive. It was reported that neutrophils may secrete vascular endothelial growth factor to promote tumor angiogenesis, and they can promote cell proliferation, mobility, and migration.[37,47–49] On the other side, accumulating data have demonstrated that cancer produce various cytokines, such as circulating vascular endothelial growth factors, TNF-α (tumor necrosis factor-α), TGF-β (transforming growth factor-β), interleukin-1, and interleukin-6, which may

contribute to tumor-infiltrating associated neutrophils.[49,50] In view of these, pretreatment NLR may not only serve as an indicator to evaluate the level of inflammation response, but also have great potential for prediction of prognosis of patients. Measuring pretreatment NLR could guide clinical decisions for patients with esophageal cancer. Furthermore, NLR test is easy to perform, and the materials are cheap and readily available in oncological practice.

Our study showed that NLR could as an independent predictor of esophageal cancer. In addition, we should not ignore other important factors affecting the prognosis of esophageal cancer. Tumor TNM staging, which is related to doctors' judgment of the disease, guidance of treatment, prognosis estimation and screening of the best treatment plan for tumors of different stages. Other important factors include smoking,[51] alcohol consumption,[51] tumor length,[52] tumor location,[52] difficulty in swallowing,[53] and genetic mutations.[54] To esophagus cancer position, upper esophageal carcinoma patient is the most serious, followed by midpiece esophagus cancer, and lower esophageal cancer patients. The degree of tumor differentiation is also a key factor affecting prognosis. Poor tumor differentiation is associated with poor tumor prognosis. The results of this study showed that high NLR value predicted poor tumor differentiation. This finding is consistent with our results that high NLR values can predict poor outcomes in patients with esophageal cancer. In practice, clinicians are recommended to consider all those factors to make a reliable prediction on prognosis of patients with esophageal cancer.

Previous meta-analysis has reported the relation between NLR and survival of patients with esophageal cancer.[7–9] But those studies only enrolled small numbers of patients. To overcome such limitation, Different from previous studies, our research work(a) included rolled large numbers of patient with 8431 patients from 32 studies, and heterogeneity between the studies was minimized. In our work, a comprehensive analysis of the relation between NLR and esophageal cancer was made by analyzing important outcomes of esophageal cancer (CSS, PFS, lymph node metastasis, and metastasis stage). Apart from those, our work also confirmed that there is a relation between NLR and esophageal cancer. Such findings were in line with those of Yang et al..[7] But some results of Yodying et al.[8] and Huang et al.[9] were negated in our work.

This meta-analysis had some limitations, which were intrinsic to the nature of included studies and provide basis for future research. First, most of the enrolled studies were retrospective, published in English, and from Asian countries, making results more susceptible to some bias. Second, the cutoff values of NLR were lack of uniformity, ranged from 2 to 5, which may lead to heterogeneity and influence clinical application of the index, and some subgroup analysis by NLR cutoff value showed that the pooled OR had no statistical significance when NLR cutoff value $\leq$2.5. Third, there were only four studies reported the correlation between NLR and metastasis stage of esophageal cancer, making their conclusions unreliable. Fourth, NLR-related ratios were affected by some diseases, including inflammation and infection, and certain medications, including antibiotics, which could undoubtedly reduce the prognostic value of NLR. In view of these, the pooled HR and OR should be interpreted with caution. Further meta-analysis on larger sample size and other geographic regions are needed.

In summary, this study revealed that NLR was negatively correlated with prognosis in patients with esophageal cancer (OS, CSS, PFS and DFS). Elevated pretreatment NLR was related to poor differentiation, large tumor size, advanced clinical stage, deep tumor invasion and serious lymph node metastasis. Metastasis stage of esophageal cancer showed nothing to do with NLR, which need more studies and evidence to confirm its reliability. Furthermore, farther research into cancer-related inflammation should be carried out, because it might be helpful for developing better diagnostics and treatments.

Acknowledgments

There are no sources of any funding for this study. We thank for all the patients and clinical investigators who are involved in the selected studies in the meta-analysis.

Author Contributions

Binfeng Li and Sheng Wang conceived the study. Fei Xiong and Binfeng Li performed the literature search and collected the data. Binfeng Li drafted the manuscript. Fei Xiong, Shengzhong Yi and Sheng Wang assessed the study quality. Shengzhong Yi and Sheng Wang revised the manuscript and language. All authors approved the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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