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Review Article

Correlation between neutrophil/lymphocyte ratio (NLR) and prognosis in patients with resectable oesophageal cancer: a meta-analysis

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Abstract: Objectives: Esophageal cancer ranks among the most prevalent malignant tumours. Numerous studies have established the neutrophil-to-lymphocyte ratio (NLR) as a pivotal inflammatory biomarker in tumour development and progression. Methods: This meta-analysis reviewed literature from PubMed, Embase, Cochrane and Web of Science to elucidate the prognostic value of NLR in esophageal cancer patients. We analyzed 33 research cohorts from 32 articles, encompassing 10,089 patients. Results: Our findings indicate that elevated NLR correlates with poor overall survival (OS), disease-free survival (DFS), and cancer-specific survival (CSS)/disease-specific survival (DSS). In patients who received neoadjuvant therapy before surgery, had a blood sample taken within one to two weeks, and were younger than 60 years, NLR demonstrated a stronger predictive value for OS. NLR also showed high prognostic value for DFS across different pathological subtypes, irrespective of neoadjuvant therapy or study site. Japanese male patients with high NLR exhibited worse CSS/DSS. Conclusion: NLR is a reliable prognostic marker for patients with resectable esophageal cancer.

Keywords: NLR, resectable esophageal cancer, meta-analysis

Introduction

In 2018, 18.1 million new cancer cases were diagnosed globally, resulting in 9.6 million cancer-related deaths. Esophageal cancer accounted for 572,000 of these new cases, raising its incidence rank from eighth to seventh [1]. Despite significant advances in diagnosis and treatment of esophageal cancer in recent years, the late onset of typical clinical symptoms often leads to delayed presentation, rapid disease progression, high recurrence rates and poor prognosis.

There is mounting evidence of a strong causal relationship between inflammation and cancer. Inflammation affects all aspects of tumorigenesis and development, either promoting or inhibiting tumour progression, angiogenesis and metastasis, suppressing tumour immunity and affecting response to systemic therapy [2-5].

Recent insights into the interplay between inflammatory responses and tumours, coupled with the accessibility of peripheral blood samples, underscore the value of peripheral blood in reflecting the body's inflammatory state. This is particularly evident in inflammatory cell ratios such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR). Numerous clinical studies have examined the relationship between systemic inflammatory response indices and the prognosis of various solid tumours [6-15].

Elevated neutrophil levels are frequently observed in patients with advanced cancers, including melanoma, renal cancer and lung

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cancer, and are typically associated with a poor prognosis [16-19]. Recent extensive research has demonstrated that the neutrophil-to-lymphocyte ratio (NLR) is a valuable marker for assessing the prognosis of malignant tumours and the efficacy of different treatments [7, 20, 21].

In several cancers, including hepatocellular carcinoma, non-small cell lung cancer, colorectal cancer, breast cancer and gastric cancer, high NLR levels correlate with lower survival rates and poor treatment response [19].

The prognosis of esophageal cancer patients is influenced by multiple factors, such as lifestyle habits [22], age [23], clinical symptoms [24], pathological conditions (including lymph node metastasis, tumour size, tumour invasion depth and distant metastasis) [25, 26] and molecular biological markers (such as heat shock protein2 and cyclin D1) [27, 28].

This study aims to synthesize the existing clinical research to further investigate the impact of NLR on the prognosis of resectable esophageal cancer patients and to evaluate the feasibility of using NLR as a prognostic indicator for patients treated with esophagectomy. This study has been registered with PROSPERO under ID: CRD42020207872.

Methods

Search strategy

We utilized a combination of subject terms and free text keywords to search the PubMed, Embase, Cochrane and Web of Science databases for relevant studies, with a publication cut-off date of 10 March 2023. Additionally, we reviewed references from related articles and topic reviews.

Inclusion criteria

The inclusion criteria for the literature were as follows: (1) studies on NLR and prognosis of esophageal cancer treated with esophagectomy; (2) all patients had a confirmed pathological diagnosis of esophageal cancer; (3) the studies categorized patients into two independent groups based on NLR; and (4) the selected prognostic indicators included overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), and cancer-specific survival (CSS), providing hazard ratios (HR) and 95% confidence intervals (95% CI) or data from survival curves.

Exclusion criteria

Exclusion criteria for the literature were as follows: (1) exclusion of inappropriate literature types such as case reports, reviews, and conference abstracts; (2) if multiple studies included the same cohort, we selected the most comprehensive study and excluded those with fewer samples; and (3) exclusion of studies with a sample size of less than 20 cases.

Data extraction

Two independent researchers (Lan LYU and Yu Zhang) screened all studies identified by the search and resolved any disagreements by discussion. Data extracted included first author, publication date, sample size, patient sex, disease stage, treatment method, follow-up period, NLR cut-off, outcome indicators and their HR and 95% CI.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). Studies with a NOS score of less than 5 were considered to be of low quality and were excluded from the meta-analysis.

Statistical analysis

We combined HR and 95% CI to assess the effect of NLR on prognosis. Heterogeneity was assessed by Q test and I^2 test. In cases of significant heterogeneity, a random-effects model was used; otherwise, a fixed-effects model was used. Subgroup and meta-regression analyses were performed to further explore sources of heterogeneity. Sensitivity analyses assessed the stability of the combined results. Begg's and Egger's tests were used to detect publication bias. All statistical analyses were performed using STATA 12.0.

Results

Study characteristics

Following the screening process, we included 33 research cohorts from 32 articles encom-

Table 1. Main characteristics and result of the eligible studies

Study	Year	Country	Sample size	Gender (M/F)	Age (year) (median, range)	NLR (time)	Histology	Treatment	Neoadjuvant treatment	Median Follow-up (median month)	Cut-off value	Survival analysis	Study design	Method	NOS score
Chen L	2019	China	107	104/3	55 (29-80)	NA	ESCC	S	No	65	2.5	OS, DFS	Retro	UV	6
Feng J	2020	China	372	284/88	59.3±8.0*	NA	ESCC	S, C, R	No	NA	6	CSS	Retro	UV	6
Fu X	2019	China	357	279/78	57 (34-77)	1 w	ESCC	S, C, R	NA	58	2.27	OS	Retro	UV	6
Han F	2018	China	354	267/87	NA	NA	ESCC, A, other	S	NA	43	1.88	OS, DFS	Retro	MV	7
He Y	2015	China	317	268/49	60 (37-77)*	1 w	ESCC	S, C, R	No	NA	3.3	OS, DFS	Retro	MV	7
Gao Q	2018	China	153	128/25	61.93±6.72*	3 d	ESCC	S, C, R	No	NA	2.1	OS	Retro	UV	6
Gao Y	2019	China	468	376/92	59.5 (36-81)	5 d	ESCC	S	No	49.1#	2.27	OS, DFS	Retro	MV	7
Geng Y1	2018	China	542	416/126	54*	NA	ESCC	S, C, R	NA	NA	1.5	OS	Retro	MV	7
Geng Y2	2018	China	374	280/94	51*	NA	ESCC	S, C, R	NA	NA	1.5	OS	Retro	MV	7
Hirahara1	2016	Japan	147	132/15	NA	1 w	ESCC	S	NA	42	1.6	OS, CSS	Retro	UV	6
Hirahara2	2016	Japan	148	132/16	NA	NA	ESCC	S	NA	NA	3.5	CSS	Retro	UV	5
Hu J	2020	China	556	420/136	59 (28-84)	1 w	ESCC	S	NA	35#	2.43	OS, DFS	Retro	MV	8
Ikeguchi	2016	Japan	84	73/11	66 (49-78)	NA	ESCC	S, C	C	35.5	3	DFS	Retro	MV	6
Ji W	2015	China	41	38/3	56.6±7.2*	NA	ESCC	S, C	CRT	35	5	OS, PFS	Retro	MV	7
Keisuke	2015	Japan	283	248/35	NA	NA	ESCC	S, C, R	C, R	33.6	1.94	OS, CSS	Retro	MV	7
Miyazaki	2016	Japan	192	173/19	65.8 (42-86)*	2 w	ESCC	S	No	26.5#	3.49	OS	Retro	MV	6
Nakamura	2017	Japan	245	249/26	NA	NA	ESCC, A, other	S, C, R	NA	37.2	2.42	OS, DFS	Retro	MV	7
Jung	2015	Korea	119	112/7	63.64±8.42*	1w	ESCC	S, C	No	28.68	2.97	OS, DFS	Retro	UV	6
Sakai	2020	Japan	105	93/12	64.75 (42-81)*	NA	NA	S, C, R	No	NA	1.594	OS	Retro	UV	5
Sugawara	2020	Japan	378	321/57	NA	NA	ESCC, A, other	S, C	C	66.5	2.57	OS	Retro	MV	6
Tan Z	2017	China	1135	888/247	58 (28-88)	2 w	ESCC	S	No	NA	NA	OS	Retro	MV	6
Wang Y	2017	China	129	85/44	60 (39-78)	1 w	ESCC, SCC	S, C, R	No	67.5	2.97	OS	Retro	MV	7
Xiao Q	2016	China	121	106/15	62 (30-76)	1 w	BSCC	S, Imun, C, R	NA	28	1.77	OS, RFS	Retro	MV	7
Xie X	2014	China	317	244/73	58.1 (34-76)*	10 d	ESCC	S, C	No	46	2.1	DSS	Retro	MV	7
Xu G	2018	China	419	328/91	NA	1 w	ESCC	S, C, R	No	NA	2.998	CSS	Retro	MV	7
Yang Y	2018	China	515	418/97	61 (33-92)	2 w	ESCC	S, C	No	35	1.2	OS	Retro	MV	7
Yin N	2020	China	267	219/48	60 (44-79)	1 w	ESCC	S, C	No	36	NA	OS	Retro	MV	6
Yoon	2020	Korea	248	248/0	63.46±7.63*	NA	ESCC	S, C, R	CRT	26.3	NA	OS	Retro	UV	6
Zhang H	2018	China	655	537/118	61 (27-88)	2 w	ESCC	S	No	36	1.87	OS	Retro	MV	7
Zhao Q	2017	China	329	287/42	NA	1 w	ESCC	S, C, R	No	34	4	CSS	Retro	UV	6
Zhou S	2018	China	119	87/32	63 (46-78)	1 w	ESCC	S, C, R	NA	18	3.33	OS	Retro	MV	7
Ohaswa	2022	Japan	163	137/26	63.4±7.9*	NA	ESCC	S, C, R	CRT	NA	4.5	OS, PFS	Retro	MV	7
Powell	2021	UK	330	250/44	69 (62-74)	NA	A	C	C	60	2.5	OS, DFS	Retro	MV	7

NA: not available; M/F: male/female ratio; OS: overall survival; DFS: disease free survival; CSS: cancer specific survival; DSS: disease specific survival; 1/2 w: 1/2 week before treatment; 3/5/10 d: 3/5/10 days before treatment; ESCC: squamous carcinoma; BSCC: basaloid squamous cell carcinoma; A: adenocarcinoma; SCC: small cell cancer; S: surgery; C: chemotherapy; R: radiotherapy; no: no neoadjuvant therapy; CRT: concurrent radiochemotherapy; MV: Multivariate analysis; UV: Univariate analysis; *: mean age, ± standard deviation or range; #: mean follow-up; Retro: retrospective study.

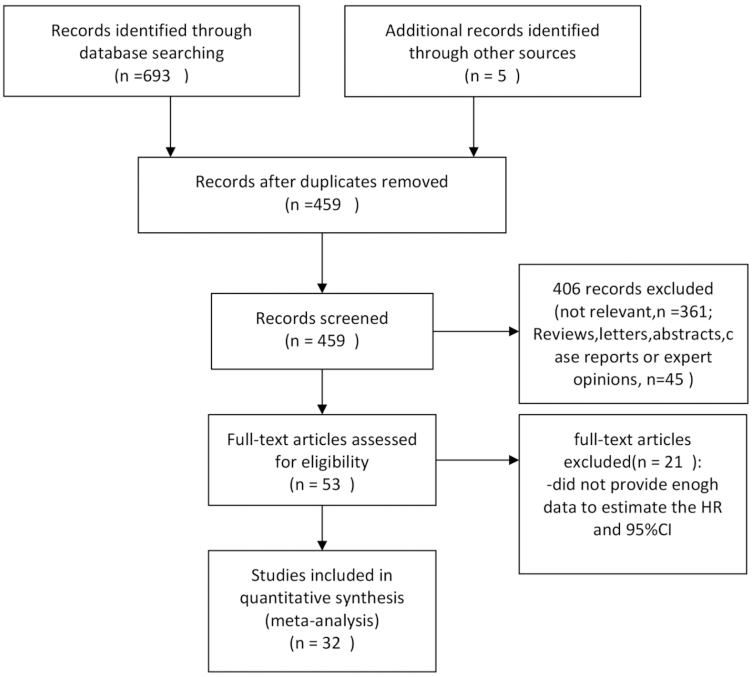

Figure 1. Flow chart of the included studies.

passing 10,089 patients [29-60]. The Geng Y study divided patients into two groups, which we named Geng Y1 and Geng Y2. The pathological type was esophageal squamous cell carcinoma (ESCC) in 26 research cohorts, mixed ESCC and other types in five cohorts, adenocarcinoma in one cohort, and one cohort did not specify the pathological type. Patients in seven trials received neoadjuvant treatment, including radiotherapy or chemotherapy. There were 27 study cohorts with overall survival (OS) as an outcome measure, 9 with disease-free survival (DFS), and 6 with cancer-specific survival (CSS) or disease-specific survival (DSS). Detailed information about the included trials is presented in **Table 1**. The literature screening process is illustrated in **Figure 1**.

NLR and OS

Due to significant heterogeneity between studies (I^2 = 49.1%, P < 0.01; H = 1.4, 95% CI: 1.1-1.8), we used random effects models to combine effect sizes. The combined hazard ratio (HR) for the OS group was 1.349 (95% CI: 1.223-1.489) (**Figure 2**), indicating that higher NLR was associated with poorer OS in patients with esophageal cancer.

NLR and DFS

Significant heterogeneity was observed between studies (I^2 = 80.3%, P < 0.001; H = 2.3, 95% CI: 1.7-3.1). Therefore, we used the random effects model to combine effect sizes. High NLR was associated with shorter DFS (HR = 1.785, 95% CI: 1.380-2.308) (**Figure 3**), and the results were statistically significant.

NLR and CSS/DSS

The combined effect size from the random effects model showed that NLR was associated with CSS/DSS (HR = 1.824, 95% CI: 1.441-2.308) (**Figure 4**). Significant heterogeneity between studies was observed (I^2 = 45%, P = 0.10; H = 1.4, 95% CI: 1.0-2.1).

Heterogeneity and subgroup analyses

Meta-regression analysis was used to identify sources of heterogeneity. In the OS group, sample size (P = 0.095), country (P = 0.502), neoadjuvant therapy (P = 0.868), univariate or multivariate analysis (P = 0.60), year of study (P = 0.683), and NOS score (P = 0.204) were not significant sources of heterogeneity. In the DFS group, pathological type (P = 0.002) was a significant source of heterogeneity, whereas cut-off (P = 0.141), sample size (P = 0.159), sex (P = 0.453), country (P = 0.642), treatment modality (P = 0.600), and NOS score (P = 0.314) were not. In the CSS/DSS group, sample size (P = 0.398), sex (P = 0.376), cut-off (P = 0.848), NOS score (P = 0.986), country (P = 0.957), treatment (P = 0.654), and univariate or multivariate analysis (P = 0.619) were not significant sources of heterogeneity.

Based on the meta-regression results, we further explored heterogeneity through subgroup analysis. When blood sampling occurred within one or two weeks before treatment, the mean or median age of patients was less than 60 years, or when neoadjuvant therapy was not administered before surgery, the heterogeneity between studies was low, and a high NLR was

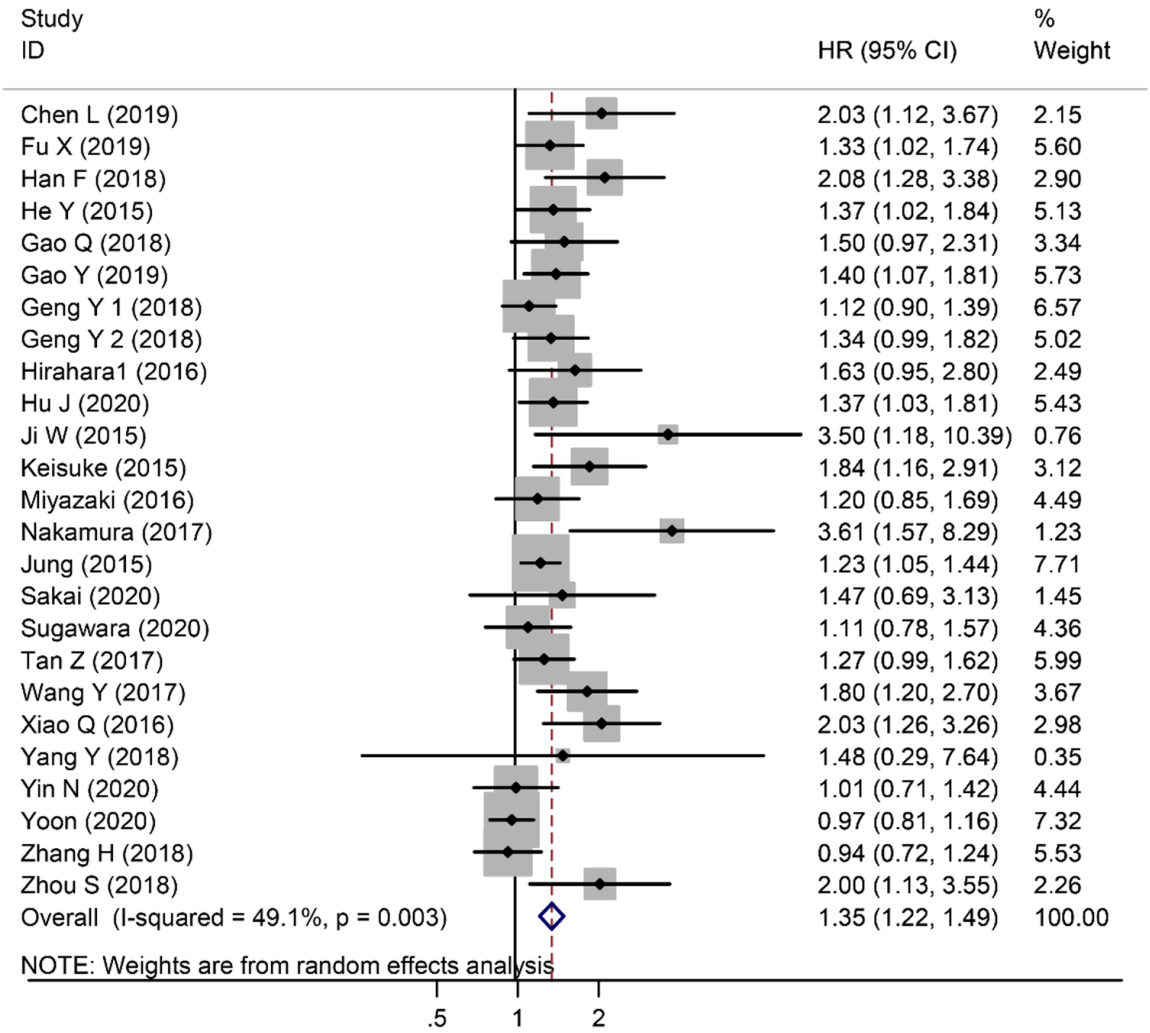

Figure 2. Forest plot of the association between NLR and OS of all patients.

associated with poor OS. In the DFS group, regardless of the pathological type of esophageal squamous cell carcinoma, whether the pathological type was undifferentiated, and whether neoadjuvant therapy was administered, a high NLR predicted poor prognosis with low between-group heterogeneity in studies from China or Japan. In the CSS/DSS group, studies conducted in Japan with a male-to-female ratio greater than 7 and univariate analysis showed less heterogeneity, and NLR values were associated with CSS/DSS. Detailed results of the subgroup analyses are shown in **Table 2**.

Sensitivity analysis

Sensitivity analysis showed that excluding any study in the OS group did not significantly change the combined effect size, indicating low sensitivity and stable results (**Figure 5**). Similar results were obtained in the sensitivity analyses for the DFS group (**Figure 6**) and the CSS/DSS group (**Figure 7**).

Publication bias

Begg's test revealed significant publication bias in the OS group (P = 0.002) (**Figure 8**), while the DFS (P = 0.118) (**Figure 9**) and CSS/DSS (P = 0.452) (**Figure 10**) groups did not show significant publication bias. Eggers test showed similar results: OS (P < 0.001), DFS (P = 0.017) and CSS/DSS (P = 0.837). To assess the impact of publication bias in the OS group on the meta-analysis results, we used the trim and fill method. The combined effect size (random: HR = 1.204, 95% CI: 1.080-1.341) did not

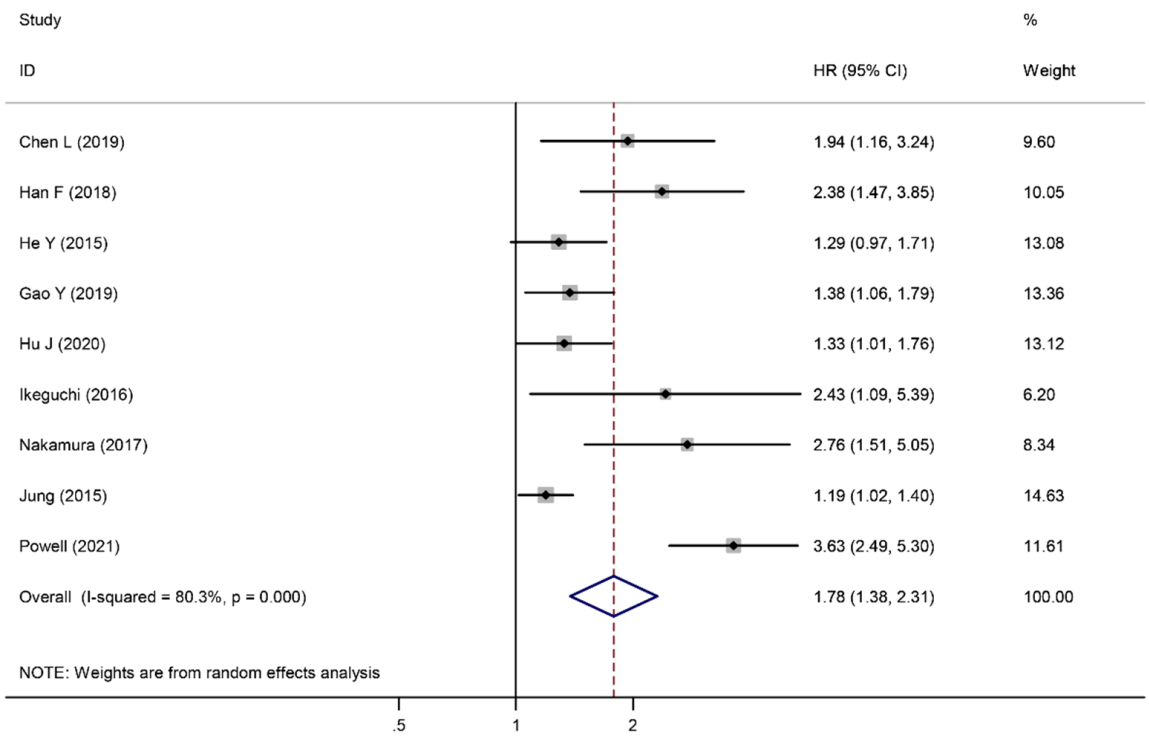

Figure 3. Forest plot of the association between NLR and DFS of all patients.

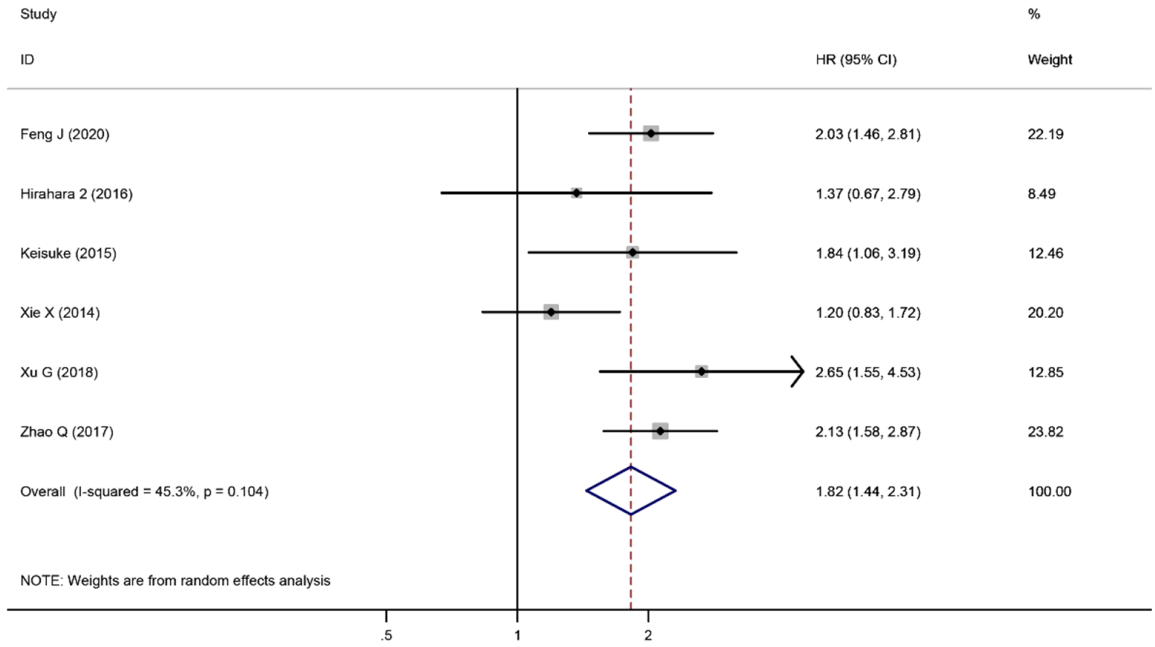

Figure 4. Forest plot of the association between NLR and CSS/DSS of all patients.

change significantly after adjustment for publication bias, suggesting minimal impact on the OS group results. Similar conclusions were drawn for the DFS (Random: HR = 1.330, 95% CI: 1.001-1.768) and CSS/DSS (Random: HR = 1.824, 95% CI: 1.441-2.308) groups.

Table 2. Table of subgroup analysis results

Outcome	Grouping strategy	No of studies	Random-effect		Fixed-effect		Heterogeneity	
			HR (95% CI)	P	HR (95% CI)	P	I^2 (%)	Ph
OS	NLR time							
	1 week	11	1.371 (1.239-1.517)	< 0.001	1.354 (1.237-1.482)	< 0.001	13.1	0.320
	2 week	4	1.132 (0.963-1.329)	0.132	1.132 (0.963-1.329)	0.132	0	0.434
	Age							
	≥ 60	14	1.469 (1.211-1.782)	< 0.001	1.260 (1.158-1.371)	< 0.001	75.4	< 0.001
	< 60	8	1.317 (1.180-1.470)	< 0.001	1.132 (1.182-1.455)	0	8.3	0.366
	Neo therapy							
	No	12	1.271 (1.146-1.409)	< 0.001	1.261 (1.155-1.377)	< 0.001	17.3	0.274
	Yes	6	1.902 (1.163-3.109)	0.01	1.282 (1.118-1.471)	< 0.001	88.3	< 0.001
DFS	Histology							
	ESCC	6	1.326 (1.167-1.506)	< 0.001	1.304 (1.169-1.454)	< 0.001	16.4	0.308
	ESCC + other	3	3.021 (2.313-3.945)	< 0.001	3.021 (2.313-3.945)	< 0.001	0	0.378
	Neo therapy							
	No	4	1.297 (1.130-1.488)	< 0.001	1.281 (1.136-1.443)	< 0.001	15.5	0.314
	Yes	2	3.371 (2.394-4.747)	< 0.001	3.371 (2.394-4.747)	< 0.001	0	0.372
	Country							
	Japan	2	2.633 (1.626-4.266)	< 0.001	2.633 (1.626-4.266)	< 0.001	0	0.801
	China	5	1.491 (1.231-1.806)	< 0.001	1.447 (1.253-1.671)	< 0.001	38.3	0.166
CSS/DSS	M/F							
	≥ 7	2	1.648 (1.066-2.547)	0.025	1.648 (1.066-2.547)	0.025	0	0.519
	< 7	4	1.885 (1.385-2.566)	< 0.001	1.871 (1.567-2.235)	< 0.001	64.4	0.038
	Country							
	Japan	2	1.648 (1.066-2.547)	0.025	1.648 (1.066-2.547)	0.025	0	0.519
	China	4	1.885 (1.385-2.566)	< 0.001	1.871 (1.567-2.235)	< 0.001	64.4	0.038
	Method							
	MV	3	1.741 (1.074-2.824)	0.024	1.600 (1.229-2.082)	< 0.001	67.3	0.047
	UV	3	2.008 (1.627-2.479)	< 0.001	2.008 (1.627-2.479)	< 0.001	0	0.532

Random-effect: random-effect models; Fixed-effect: fixed-effect models; HR: hazard ratio; 95% CI: 95% confidence interval; Ph: *P* value of Q test for heterogeneity test; OS: Overall survival; DFS: Disease free survival; 1/2 week: 1/2 week before treatment; Neo therapy: neoadjuvant therapy; M/F: male/female ratio; ESCC: esophageal squamous-cell carcinoma; MV: Multivariate analysis; UV: Univariate analysis.

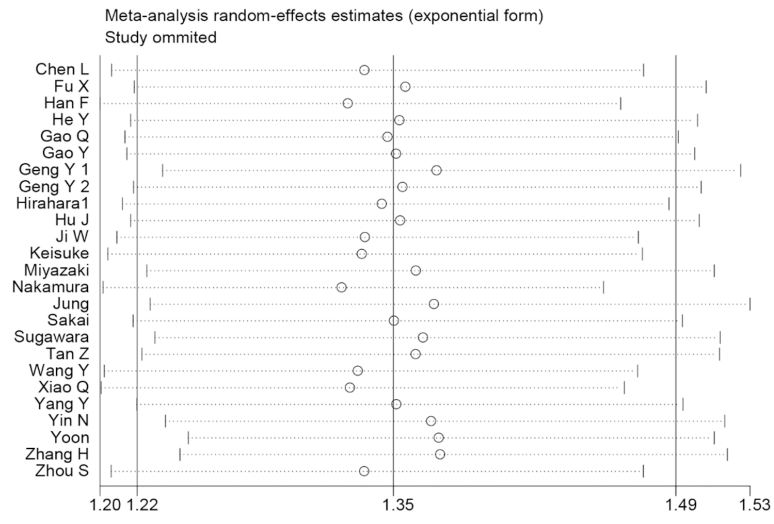

Figure 5. Sensitivity analysis of the publication in the OS group.

Discussion

Our study demonstrated that a high neutrophil-to-lymphocyte ratio (NLR) is a significant predictor of poor overall survival (OS), disease-free survival (DFS) and cancer-specific survival/disease-specific survival (CSS/DSS). Notably, in patients younger than 60 who received neoadjuvant therapy within one to two weeks before surgery, NLR showed superior predictive accuracy for OS. For DFS, a high NLR indicated a poor prognosis, irrespective of the

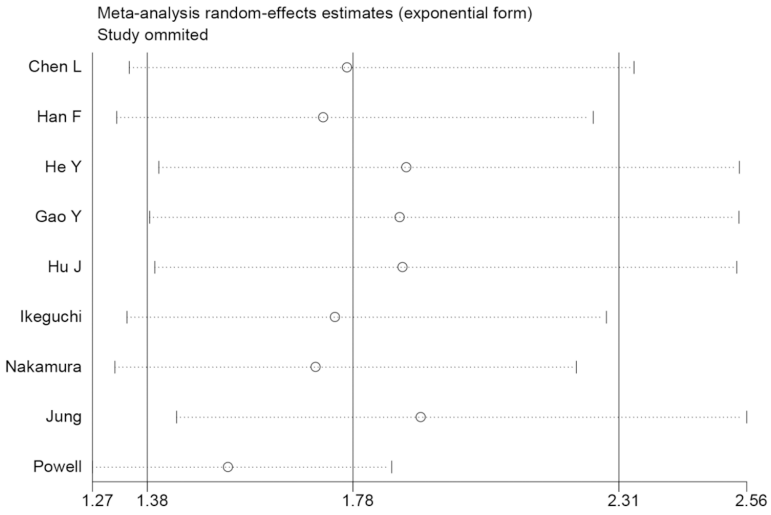

Figure 6. Sensitivity analysis of the publication in the DFS group.

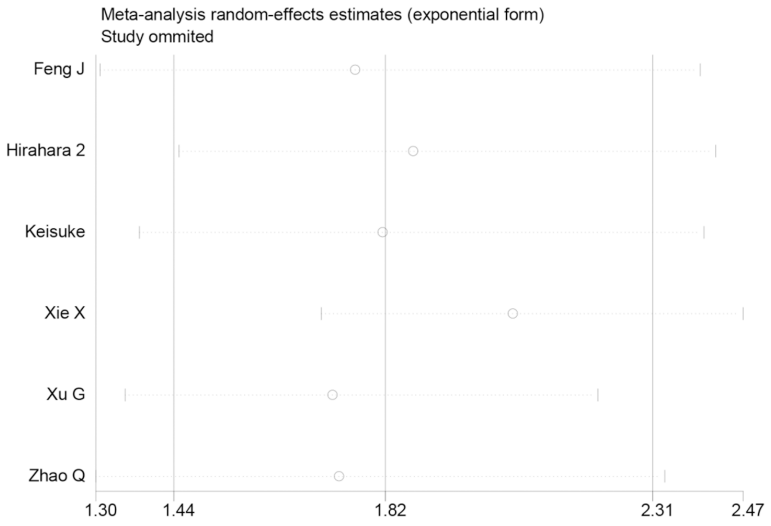

Figure 7. Sensitivity analysis of the publication in the CSS/DSS group.

pathological type, whether esophageal squamous cell carcinoma, undifferentiated, or the administration of neoadjuvant therapy. In male patients from Japan, univariate analysis revealed that elevated NLR levels correlated with poor CSS/DSS.

Inflammation is pivotal at various stages of tumour development, including initiation, progression, malignant transformation, invasion and metastasis [61]. Tumor-associated inflammation fosters an inflammatory microenvironment that supports tumor growth by disrupting the homeostasis of surrounding tissues. The tumour microenvironment (TME) is critical for tumor development, with the inflammatory response being a key component [62]. Inflammatory cells are central to this process as the TME comprises numerous innate immune cells, tumour cells, surrounding matrix (fibroblasts, endothelial cells, pericytes and mesenchymal cells) and regulatory immune cells (T and B lymphocytes) [61, 62]. The TME is known to inhibit tumor cell apoptosis, facilitate immune escape, and promote proliferation, angiogenesis, invasion and metastasis [3, 61, 62].

Neutrophils, the most abundant inflammatory cells in the peripheral blood, are essential for pathogen defense and can enter various tissues through the circulation [19]. However, prolonged neutrophil aggregation and activation can be harmful, as seen in cancer-related inflammation. The antimicrobial and immunomodulatory mediators produced by neutrophils can alter the tissue microenvironment, ultimately promoting tumor development, angiogenesis, progression and metastasis [63-65].

Lymphocytes are critical for humoral and cellular immune responses, possessing immune recognition functions and regulating immune surveillance through recombinant antigen receptors expression [66]. Tumour-infiltrating lymphocytes (TILs) within the TME exhibit potent and specific antitumour effects [67, 68]. Cytotoxic lymphocytes (CTLs) can recognize specific antigens on the tumour cell surfaces, initiating tumor immunity and leading to targeted cell death [69, 70]. In several tumour types, the presence of CD8+ CTLs in the TME is often associated with a favorable prognosis and prolonged DFS [70].

Tumor cells recruit neutrophils into the tumor microenvironment, where they differenti-

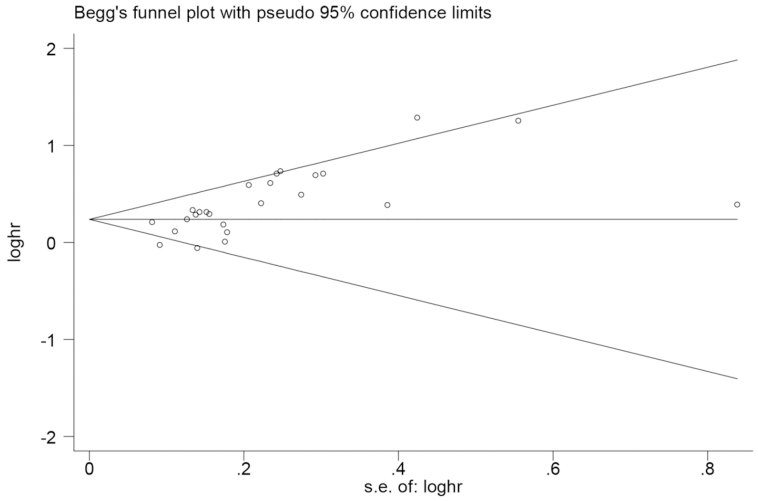

Figure 8. Begg funnel plot estimating the publication bias of the included studies in the OS group.

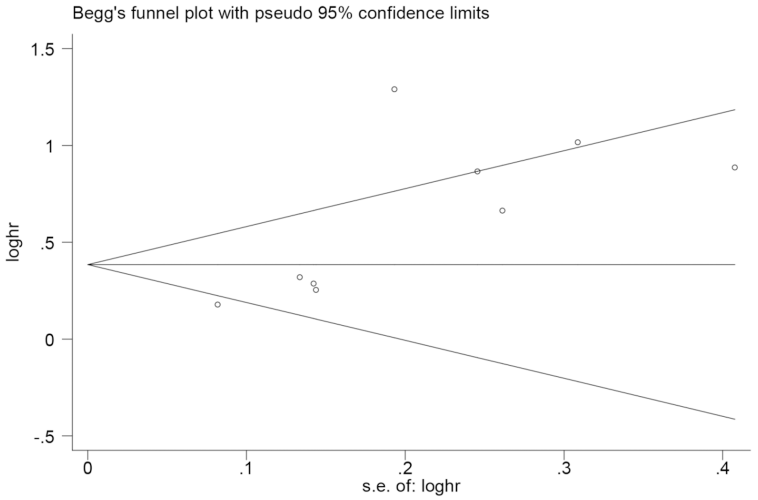

Figure 9. Begg funnel plot estimating the publication bias of the included studies in the DFS group.

ate into tumor-associated neutrophils (TANs). TANs are classified into N1 and N2 phenotypes, with N1 TANs exerting anti-tumor effects during early stages and N2 TANs promoting tumor progression at later stages. N2 TANs facilitate tumor growth by secreting matrix metalloproteinase-9 (MMP-9), which regulates oncogene-induced keratinocyte hyperproliferation. Type I interferon-deficient TANs, regulated by FOXO3a, stimulate angiogenesis and tumor growth. TANs also enhance tumor cell motility and invasiveness by inducing epithelial-mesenchymal transition (EMT) through CD90-TIMP-1 signaling. Additionally, TANs contribute to tumor invasion and metastasis by producing neutrophil extracellular traps (NETs) and secreting proteolytic enzymes such as serine proteases and cathepsins, which degrade the extracellular matrix [71-75]. N2 TANs suppress immune responses by inducing CD8+ T cell apoptosis through TNF-α and nitric oxide (NO) pathways, aiding immune evasion. Together with granulocytic myeloid-derived suppressor cells (G-MDSCs), they inhibit CD8+ T cell proliferation, undermining anti-tumor immunity. Conversely, tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, play a crucial role in anti-tumor immunity by secreting interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). CD4+ T cells support CD8+ T cells and natural killer (NK) cells by activating antigen-presenting cells (APCs) through co-stimulatory molecules and cytokines, such as IL-12. They also maintain memory CD8+ T cells, ensuring sustained immune surveillance [75-78]. In certain contexts, T cells may paradoxically promote tumor progression. For instance, Th9/Th17 lymphocytes secrete IL-9 and IL-17, which induce EMT in lung cancer cells, promoting tumor migration and metastasis. Activated platelets further contribute to distant metastasis by forming protective thrombi around circulating tumor cells, shielding them from NK cell-mediated lysis. Tumor cells activate platelets via soluble mediators like ADP, thromboxane A2 (TXA2), and tissue factor (TF), triggering coagulation and subsequent platelet activation [79-83]. Thus, an elevated NLR in ESCC patients, indicative of increased neutrophils and/or decreased lymphocytes, reflects a pro-tumorigenic inflammatory state and suppressed adaptive immune response, correlating with poor prognosis, and highlighting its potential as a therapeutic target.

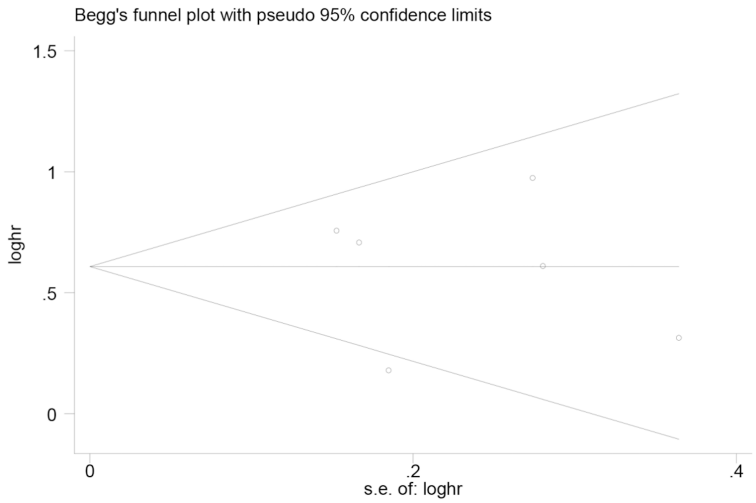

Figure 10. Begg funnel plot estimating the publication bias of the included studies in the CSS/DSS group.

Numerous studies have shown that patients with esophageal squamous cell carcinoma typically exhibit lower peripheral blood lymphocyte counts, and higher platelet counts compared to healthy individuals [51, 84]. Current theoretical research suggests that relative neutropenia and decreased lymphocyte counts are components of a cancer-induced systemic inflammatory response [85, 86]. This provides the theoretical basis for using NLR as an indicator of tumors.

Sharaiha et al. [87] categorized NLR into two groups: NLR < 5 and NLR ≥ 5. No significant differences were observed between these groups in terms of age, sex, race, pathological stage, pathological type, lesion location, tumour differentiation, use of non-steroidal anti-inflammatory drugs, and smoking history. The only significant difference was in the use of adjuvant therapy.

Xie et al. [51] reported differences in NLR levels in esophageal cancer patients based on sex, lymph node metastasis and tumor length. Feng et al. [84] observed that both NLR and platelet-lymphocyte ratio (PLR) varied with tumor size, differentiation grade, invasion depth and lymph node metastasis, with a significant positive correlation between NLR and PLR.

The clinical significance of this study extends beyond preliminary prognosis of esophageal cancer based on NLR and includes the development of clinical treatment strategies. Patients with higher NLR may benefit from neoadjuvant chemotherapy, neoadjuvant radiotherapy and treatments targeting tumor-related anti-inflammatory responses. However, these conclusions require further validation.

Wang C et al. [72] identified NLR as an independent predictor of treatment response in patients with esophageal squamous cell carcinoma (ESCC) undergoing concurrent chemoradiotherapy. Sharaiha RZ et al. [87] further discovered that preoperative NLR could serve as a potential prognostic marker for recurrence and mortality after esophagectomy. Additionally, studies by Ohsawa M [88] and Huang Y [89] demonstrated that NLR is associated with lymph node metastasis and clinical staging in esophageal cancer. More recently, research by Al Lawati Y [75] suggested that dynamic changes in NLR levels may provide more prognostic information for esophageal cancer patients than static baseline values. However, most current research focuses on the role of NLR in the prognosis of esophageal cancer patients in general, with limited attention to its specific relationship with prognosis in patients with ESCC undergoing surgical treatment. Given the significant prognostic differences between ESCC patients receiving surgical versus non-surgical treatment, this study aims to further investigate the prognostic value of NLR in ESCC patients undergoing surgery.

Our study has several limitations: 1) despite the inclusion of many studies, the predominance of retrospective studies may introduce bias; 2) most of the included studies were conducted in Eastern countries, necessitating confirmation with data from other regions; 3) we were unable to perform subgroup analyses on tumour location, differentiation and surgical approach due to insufficient data; 4) the cut-off values for NLR varied and an optimal cut-off value was not determined; 5) the exclusion of non-English documents may have introduced additional bias.

In conclusion, a high NLR is a significant risk factor for poor OS, DFS and CSS/DSS in patients with resectable esophageal cancer. However, due to the aforementioned limitations, further validation by large prospective studies is necessary to confirm our conclusions.

Disclosure of conflict of interest

None.

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; DSS, disease-specific survival; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte/monocyte ratio; NOS, Newcastle-Ottawa Scale; HR, hazard ratio; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; TME, tumor microenvironment; TILs, tumor-infiltrating lymphocytes; CILs, cytotoxic lymphocytes.

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