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Review Article

The prognostic significance of the neutrophil-to-lymphocyte ratio in esophageal cancer patients undergoing chemoradiotherapy: a meta-analysis

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Abstract: Objective: Recent research increasingly highlights the association between inflammation and esophageal cancer, with radiotherapy and chemotherapy being crucial in treatment of advanced stages. This meta-analysis aims to investigate the association between the neutrophil-to-lymphocyte ratio (NLR) and the prognosis of esophageal cancer patients undergoing chemoradiotherapy. Methods: A systematic search of PubMed, Embase, Web of Science, and Cochrane was performed. Data were extracted and analyzed using STATA 12.0 to consolidate effect sizes, test heterogeneity, and assess sensitivity for publication bias and heterogeneity sources. Results: Elevated NLR was significantly associated with shorter overall survival (OS) (HR: 1.515, 95% CI: 1.278-1.795) and progression-free survival (PFS) (HR: 1.419, 95% CI: 1.003-2.009). This association was particularly strong in male patients (HR: 1.755, 95% CI: 1.373-2.245) and those with cervical esophageal cancer (HR: 1.876, 95% CI: 1.280-2.751). Sensitivity analysis confirmed the robustness of these findings, and no significant publication bias was detected. Heterogeneity in the OS group may be attributed to variations in treatment (P=0.02) and data analysis methods (P=0.007). Conclusion: NLR is a readily available, cost-effective, and reliable prognostic marker for esophageal cancer patients undergoing chemoradiotherapy, especially in male patients with cervical esophageal cancer.

Keywords: Neutrophil-to-lymphocyte ratio, esophageal cancer, chemoradiotherapy, meta-analysis

Introduction

Esophageal cancer is a significant global health burden, ranking eighth in incidence and sixth in mortality, with over 450,000 new cases reported annually worldwide [1, 2]. Despite recent advances in understanding its mechanisms, diagnosis, and treatment, the 5-year survival rate remains low at 20-30%. The primary pathological types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. In Western countries, both types occur with similar frequency, with adenocarcinoma on the rise. However, in Eastern countries like China, squamous cell carcinoma remains predominant [3, 4].

Early-stage esophageal cancer is often asymptomatic, leading to late-stage diagnosis and poor prognosis in most patients [2, 5-8]. Tumor-node-metastasis (TNM) staging is the current gold standard for predicting cancer prognosis, focusing on tumor invasion depth, lymph node involvement, and distant metastasis. However, there is increasing recognition of the importance of systemic inflammatory responses in cancer progression and prognosis [9].

Recent studies have emphasized the role of inflammation in cancer progression, prompting investigations into inflammation-related prognostic markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR),

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neutrophils, platelets, and C-reactive protein (CRP) [10-12].

Numerous studies have demonstrated that the neutrophil-to-lymphocyte ratio (NLR) holds significant prognostic value for patients with esophageal cancer. Kosumi et al. identified NLR as an independent prognostic factor in esophageal squamous cell carcinoma patients undergoing surgery [13]. Kijima et al. found that elevated pre-treatment NLR and fibrinogen levels were associated with poor prognosis in advanced esophageal squamous cell carcinoma [14]. Similarly, Duan et al. demonstrated that preoperative NLR effectively predicts survival in operable esophageal cancer patients [9, 15].

Despite these findings, the prognostic value of NLR in patients with esophageal cancer undergoing chemoradiotherapy remains underexplored, with existing studies often limited by small sample sizes. Therefore, we conducted a meta-analysis to consolidate effect sizes and clarify the relationship between NLR and prognosis in these patients.

Methods

Search strategy

A systematic search of PubMed, Cochrane, Web of Science, and Embase was conducted using a combination of medical subject heading (MeSH) terms and free-text keywords, including "esophageal neoplasms", "oesophageal neoplasms", "neutrophil-lymphocyte ratio", and "neutrophil/lymphocyte ratio". The search was completed by August 31, 2020, with additional searches of references in the included studies to ensure comprehensiveness. Our study has been registered on the PROSPERO database (ID: CRD42020207873).

Inclusion criteria

Studies were included if they met the following criteria: (1) investigated the relationship between NLR and prognosis in patients with advanced esophageal cancer receiving chemoradiotherapy, (2) confirmed the diagnosis of esophageal cancer by pathology, (3) categorized patients based on NLR levels, (4) provided extractable or calculable prognostic outcomes with 95% confidence intervals (95% CI), and (5) were randomized controlled trials or cohort studies.

Exclusion criteria

Studies were excluded if they: (1) were conference abstracts, case reports, or reviews, (2) lacked full text availability, (3) had a sample size of less than 20 cases, or (4) were duplicate publications from the same cohort, in which case the study with the smaller sample size was excluded.

Data extraction

Two investigators (Lan Lyu and Hongmei Nie) independently extracted data, including study characteristics, cohort details, treatment interventions, and prognostic effect sizes with 95% CIs. Disagreements were resolved by group discussion led by the study coordinator (Yu Zhang).

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies, with studies scoring ≤5 considered low quality.

Statistical analysis

Statistical analyses were performed using STATA 12.0, including effect size pooling (using random and fixed effect models), heterogeneity testing (I^2 test, and Galbraith test), heterogeneity exploration (meta-regression and subgroup analysis), sensitivity analysis, and publication bias assessment.

Result

Study characteristics

Fifteen articles comprising 18 independent research cohorts with a total of 3,216 patients were included [14, 16-29]. Fourteen cohorts were from eastern countries or regions, and four were from western countries. Twelve cohorts had a sample size more than 100. The pathological type was squamous cell carcinoma in 14 studies. All studies reported overall survival (OS) as a prognostic outcome, and five cohorts also reported progression-free survival (PFS). All studies had a Newcastle-Ottawa Scale (NOS) score of ≥6. **Table 1** summarizes

Table 1. Main characteristics and results of the eligible studies

Study	Year	Region	Sample size	Gender (M/F)	Age (year) (median)	Location	Treatment	Histology	Median Follow-up (month)	Cut-off value	Survival analysis	Method	NOS score
Cox S	2017	UK	257	144/113	NA	NA	dCRT	ESCC, EAC, Other	46.2	2.029	OS	MV, UV	8
Dai Y	2019	China	106	79/27	58	C	dRT/dCRT	ESCC	19	2.1	OS	UV	7
Gabiatti T1	2019	Brazil	51	45/6	56.1*	T	dCRT	ESCC, EAC	10.1	2.8	OS, PFS	MV	6
Gabiatti T2	2019	Brazil	72	63/9	61.6*	T	dCRT	ESCC, EAC	10.1	2.8	OS, PFS	MV	6
Kijima T	2017	Japan	98	86/12	64.9*	T	CRT/CT	ESCC	15.4	3	OS	UV	7
Li K	2019	China	204	171/33	65.8	T	CCRT	ESCC	11.5	2.64	OS	MV, UV	7
Liu X	2018	China	147	118/29	63	T, GEJ	dCRT	ESCC	NA	2.46	OS, PFS	MV, UV	7
Luo H	2020	China	567	413/154	64	C, T	dRT/dCRT	ESCC	67.4	3.25	OS	MV, UV	8
Mclaren P	2017	USA	60	48/12	66	NA	neoCRT+S	EAC, SCC	NA	3.17	OS	MV	6
Miao C	2017	China	168	134/34	67.15*	T	CRT	ESCC	NA	3.34	OS	UV	7
Sato Y1	2017	Japan	110	NA	65.3	NA	CRT	ESCC	NA	3	OS	UV	6
Sato Y2	2017	Japan	150	NA	63.6	NA	CT	ESCC	NA	3	OS	UV	6
Wu C1	2018	Taiwan	63	61/2	58	C	CCRT	ESCC	NA	2.5	OS	UV	7
Wu C2	2018	Taiwan	63	61/2	58	T	CCRT	ESCC	NA	2.5	OS	MV, UV	7
Wu Y	2019	Taiwan	105	98/7	57.69*	T	CCRT	ESCC	19.5	4.35	OS	MV, UV	7
Zhang H	2019	China	266	172/94	67	T	CCRT/RT	ESCC	NA	3.06	OS	MV, UV	7
Zhang P	2016	China	212	166/46	60	T	CCRT	ESCC	17	3	OS, PFS	MV	7
Zhou X	2017	China	517	407/110	65	T	dCRT	ESCC	17	5	OS, PFS	MV, UV	8
Teseng R	2022	Taiwan	420	397/23	55	T	CCRT	ESCC	NA	3.5	OS, DSS	UV	6
Hsueh	2022	Taiwan	123	114/9	56	T	CCRT	ESCC, EAC	56	3.1	OS	UV	7
Koh	2021	Korea	68	64/4	66	T	CCRT	ESCC	11.4	2.5	OS	MV	7
Yoo E	2014	Korea	138	132/6	67.6	T	CCRT	ESCC, EAC	39.5	2.0	OS, PFS	MV, UV	7

C: cervical cancer; T: thoracic cancer; *: mean or average age; CT: chemotherapy; RT: radiotherapy; CRT: chemoradiotherapy; dCRT/dRT: definitive chemoradiotherapy/radiotherapy; CCRT: concurrent chemoradiotherapy; neoCRT: neoadjuvant chemoradiotherapy; GEJ: gastroesophageal junction; S: surgery; ESCC: esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma; SCC: small cell cancer; OS: overall survival; PFS: progression free survival; MV: Multivariate analysis; UV: Univariate analysis; NA: not available.

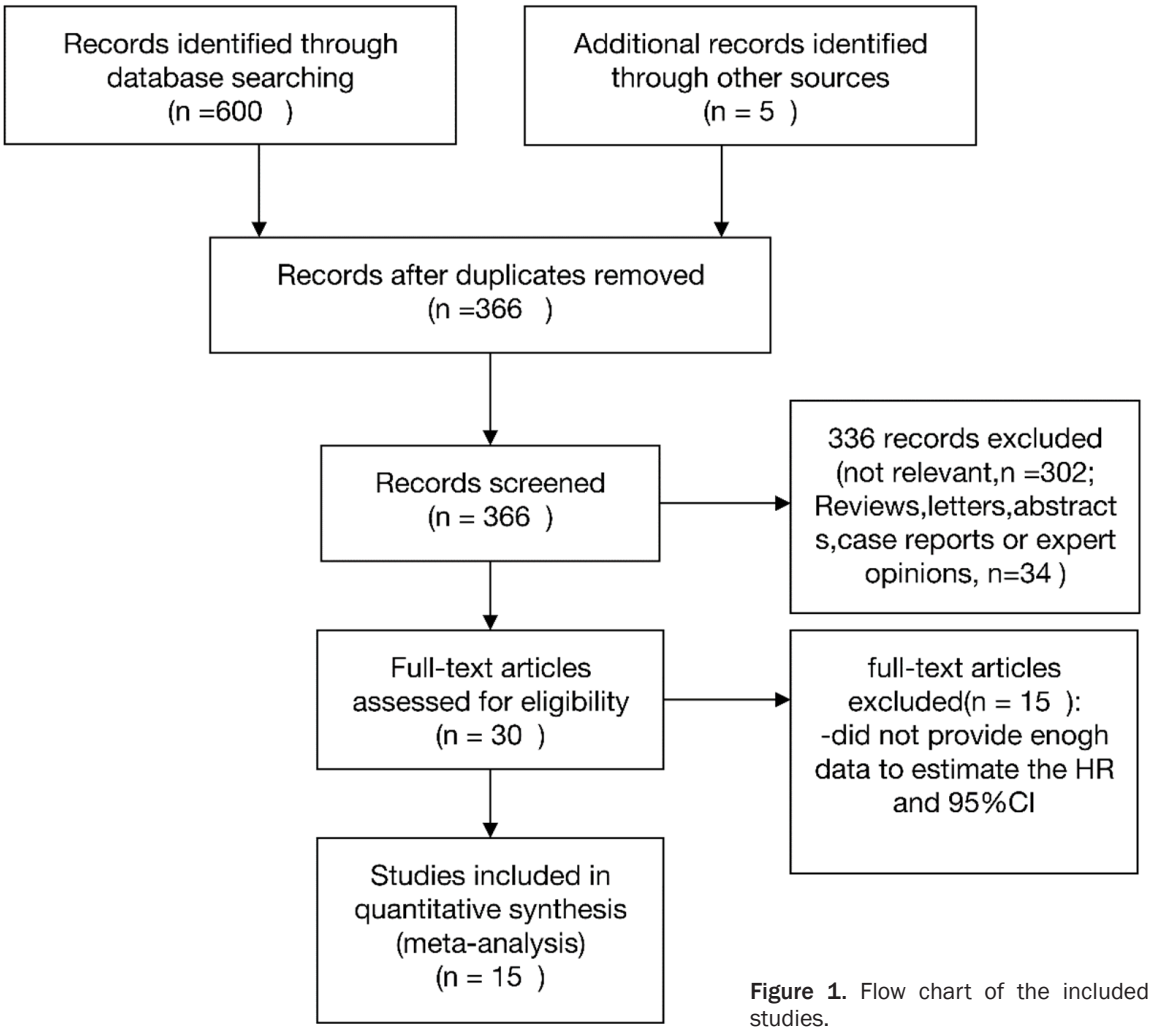

Figure 1. Flow chart of the included studies.

the basic characteristics of the included studies, and the literature screening process is illustrated in **Figure 1**.

NLR and OS

Significant heterogeneity was observed among studies (H test: H=2.3, 95% CI: 1.8-2.8; I^2=80.6%), leading to the use of a random effects model. The pooled analysis showed that a high NLR was associated with shorter OS (HR=1.515, 95% CI: 1.278-1.795) (**Figure 2**).

NLR and PFS

The heterogeneity test results for PFS (H=2.5, 95% CI: 1.7-3.8; I^2=84.2%) also required a random effects model. The analysis showed that a high NLR correlated with shorter PFS (HR=1.419, 95% CI: 1.003-2.009) (**Figure 3**).

Heterogeneity and subgroup analyses

Meta-regression identified treatment method (P=0.02) and data analysis method (P=0.007) as sources of heterogeneity in the OS group, while region, sample size, cut-off value, and NOS score were not significant factors. In the PFS group, none of the evaluated variables, including region, location, pathology type, sample size, male/female ratio, age, cut-off value, and NOS score, independently explained the heterogeneity, suggesting mixed factors as contributors.

Subgroup analysis for OS showed that high NLR was associated with poor prognosis in cohorts with a male/female ratio ≥5 (HR=1.755, 95% CI: 1.373-2.245) with low heterogeneity (I^2= 25.3%, P=0.236) (**Figure 4**). Elevated NLR levels in patients with cervical esophageal cancer

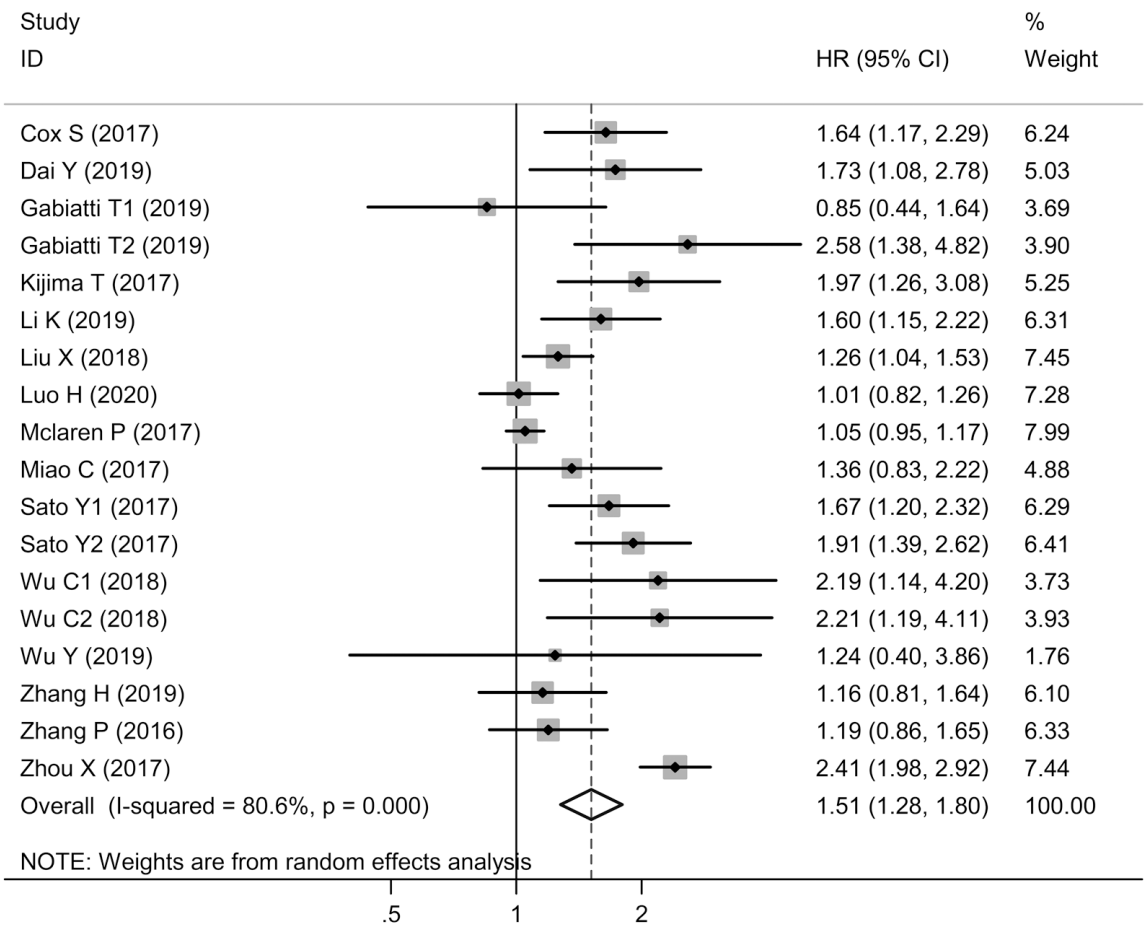

Figure 2. Forest plot of the association between NLR and OS of all patients. NLR: neutrophil-to-lymphocyte ratio; OS: overall survival.

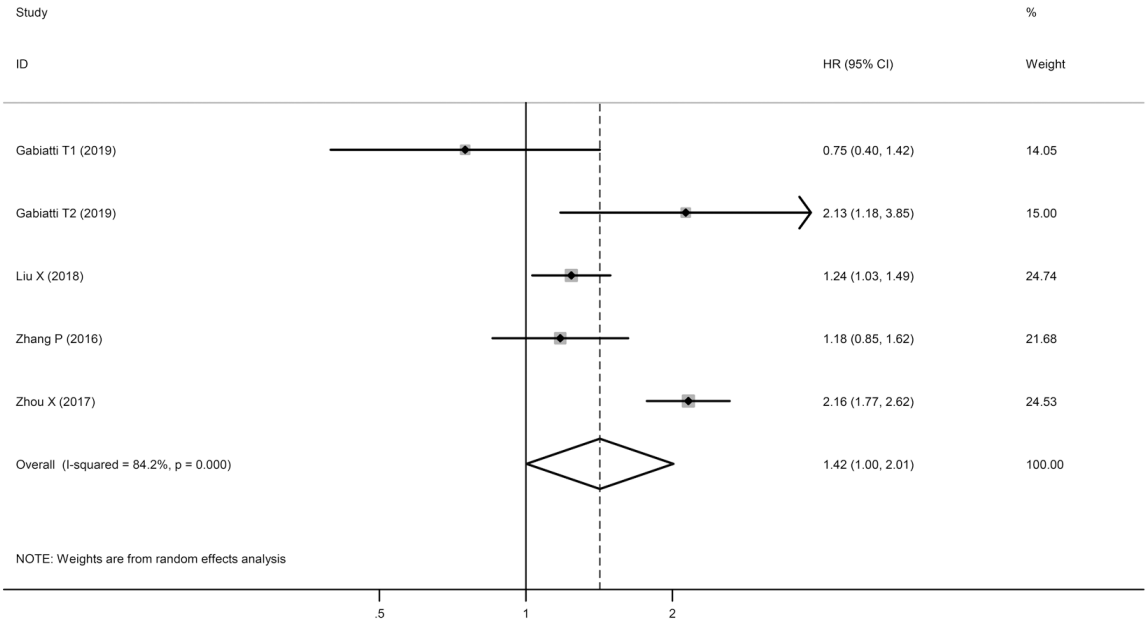

Figure 3. Forest plot of the association between NLR and PFS of all patients. PFS: progression-free survival.

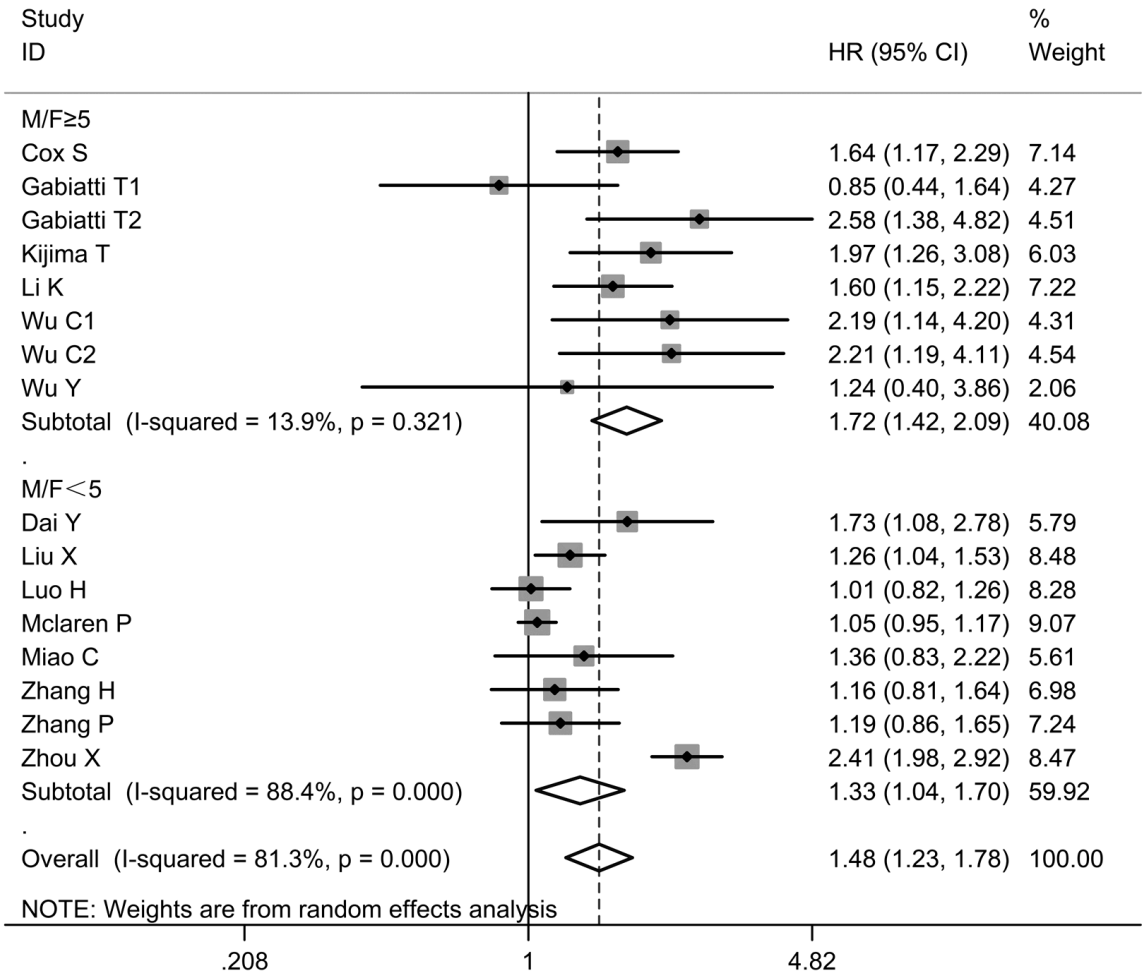

Figure 4. Forest plot of the association between NLR and OS in male/female ratio subgroup.

were also associated with shorter OS (HR= 1.876, 95% CI: 1.280-2.751) with no significant heterogeneity (I^2=0, P=0.566) (**Figure 5**).

Sensitivity analysis

Sensitivity analysis confirmed the robustness of the results, as removal of a single study did not change the results for either OS (**Figure 6**) or PFS (**Figure 7**).

Publication bias

In the OS group, Begg's test (P=0.649) (**Figure 8**), Egger's test (P=0.062) (**Figure 9**), and the trim-and-fill method (**Figure 10**) indicated no significant publication bias. Similarly, in the PFS group, Begg's test (P=1.000) (**Figure 11**), Egger's test (P=0.684) (**Figure 12**), and the trim-and-fill method (**Figure 13**) showed no significant bias.

Discussion

Our study shows that a high neutrophil-to-lymphocyte ratio (NLR) is significantly associated with shorter overall survival (OS) and progression-free survival (PFS) in patients with esophageal cancer. The association appears to be particularly strong in male patients and in those with cervical esophageal cancer. Sensitivity analyses confirmed the stability of our findings, and no significant publication bias was identified in the included studies. The heterogeneity in the OS group may be attributed to differences in treatment and data analysis methods, indicating that future trials should focus on these variables.

Inflammation is recognized as a key factor in cancer progression, where inflammatory cells and mediators can promote tumour growth,

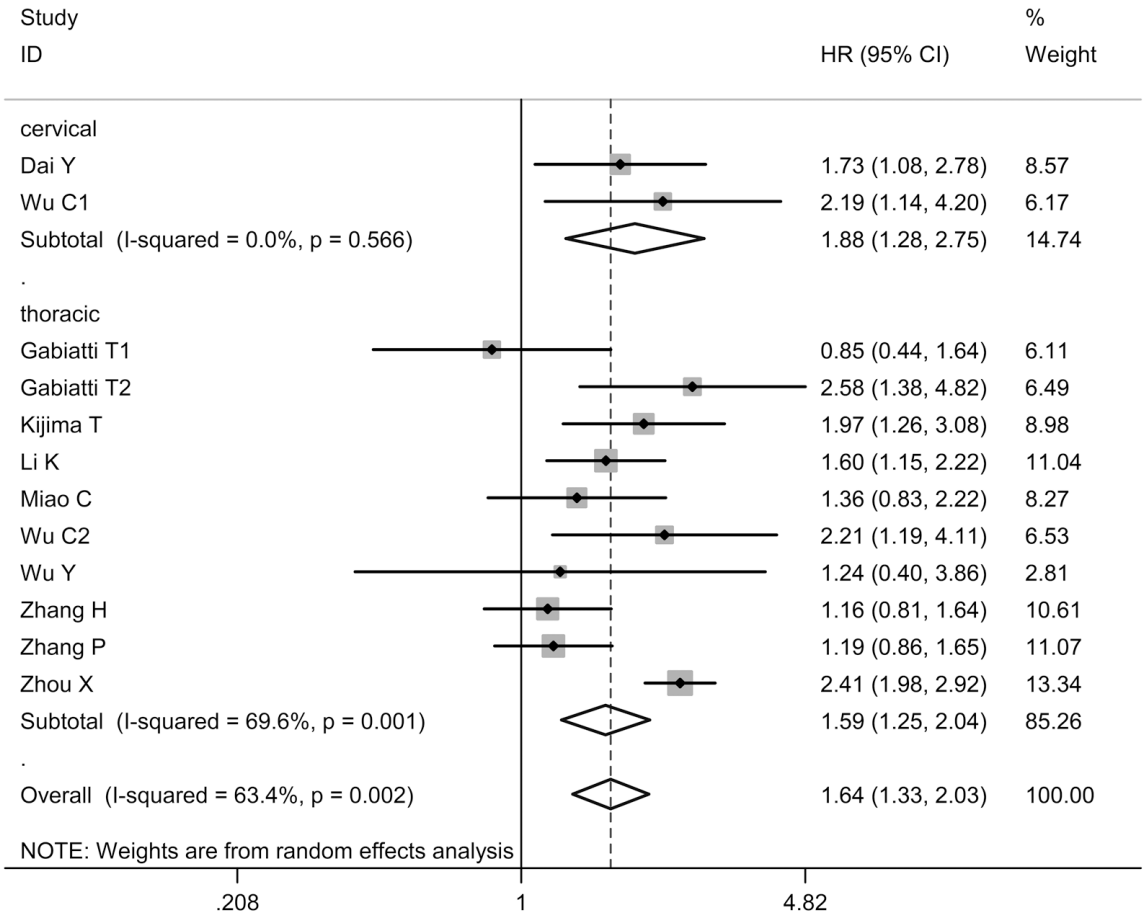

Figure 5. Forest plot of the association between NLR and OS in tumor location subgroup.

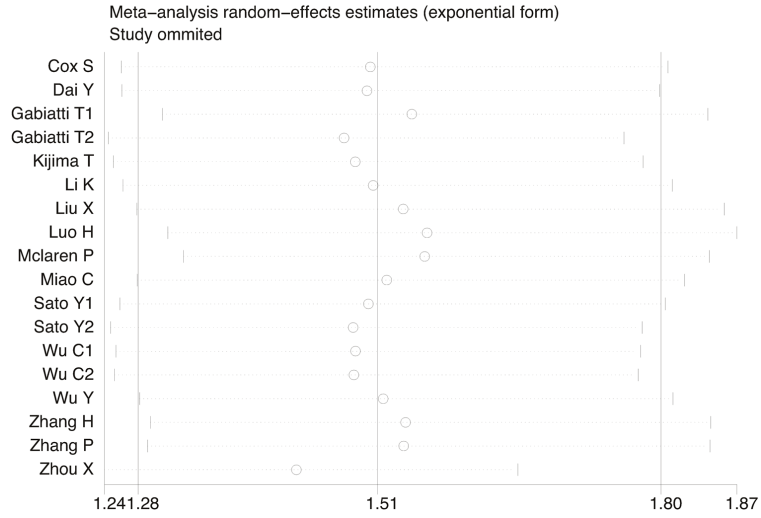

Figure 6. Sensitivity analysis of the publication in the OS group.

recurrence and metastasis, adversely affecting patient survival [30, 31]. Studies have shown that the infiltrating inflammatory cells and inflammatory factors in the esophageal epithelium can cause the release of large amounts of inflammatory mediators, which can promote epithelial cell proliferation and cancer [32, 33].

In esophageal cancer patients, environmental exposures can induce chronic inflammation, leading to the structural activation of pro-inflammatory signaling pathways, thereby promoting tumor cell proliferation. Reduced anti-tumor immune function, such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), and immune checkpoints such as programmed death ligand

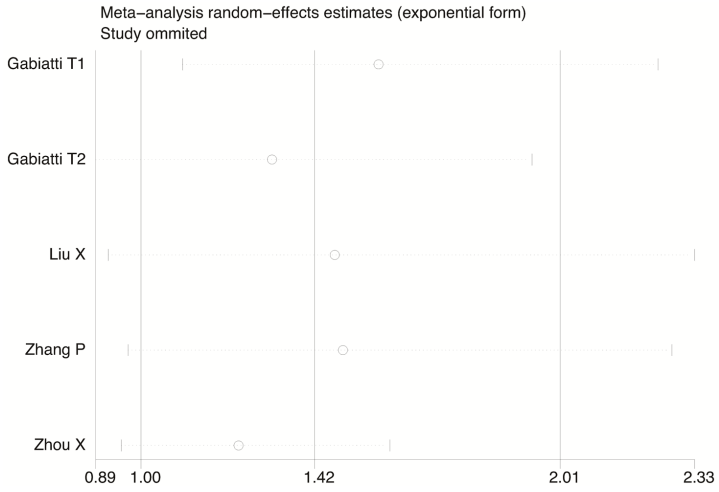

Figure 7. Sensitivity analysis of the publication in the PFS group.

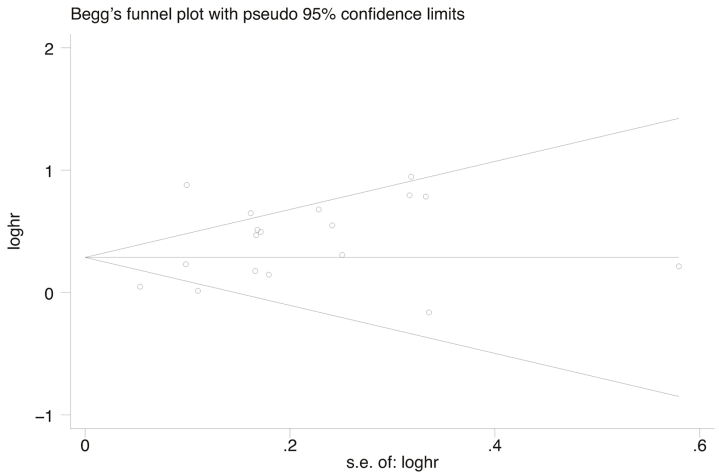

Figure 8. Begg funnel plot estimating the publication bias of the included studies in the OS group.

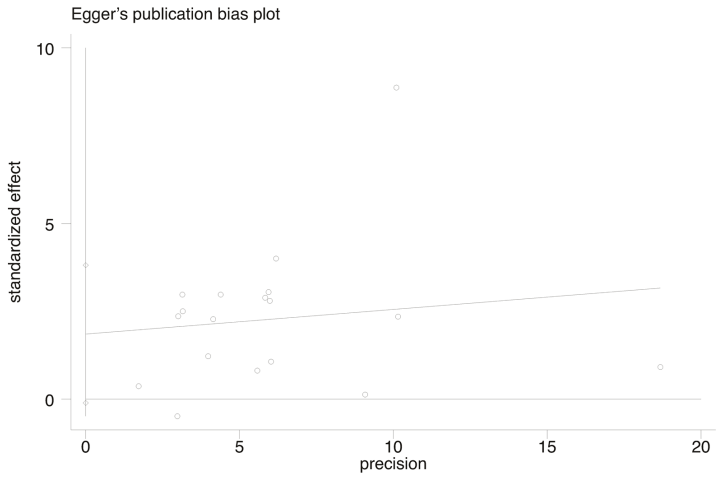

Figure 9. Egger's funnel plot estimating the publication bias of the included studies in the OS group.

(PD-1), allow tumors continue to progress [34-37].

Various factors, including smoking, alcohol consumption, gastroesophageal reflux disease (GERD), and high body mass index (BMI), adversely affect the prognosis of esophageal cancer [38-40]. Tumor invasion, TNM staging, and differentiation are crucial prognostic factors, with TNM stage being the most important predictor of survival in esophageal squamous cell carcinoma [41, 42]. However, pathological TNM staging is limited to surgically resected specimens and is not applicable to patients who are deemed unsuitable for surgery.

Blood examination has the advantages of easy operation, high reproducibility, and low cost in clinical work. Therefore, in recent years, research in the prediction of the proliferation, differentiation and metastasis by peripheral blood inflammatory indicators has been a hot spot. White blood cells, neutrophils, lymphocytes, monocytes and platelets can all participate in the inflammatory response of tumors. Since a single inflammatory cell number cannot predict the degree of systemic inflammation in a stable and standardized manner, composite indicators such as NLR, PLR and LMR are considered ideal indicators.

NLR may reflect the relationship between the body's tumor inflammatory response and anti-tumor immunity and is associated with the prognosis of non-small cell lung cancer (NSCLC) [43, 44], gastric cancer [45, 46], colon cancer [47-49], liver cancer [50, 51], thyroid cancer [52] and other solid tumors, and a higher ratio indicates a poor prognosis. Sharaiha et al. found that a high NLR (≥5.0) in peripheral blood correlated with shorter disease-free survival (DFS)

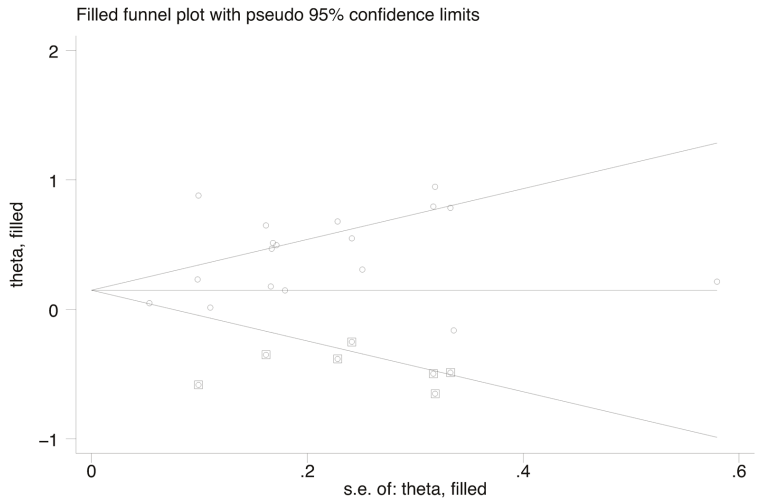

Figure 10. Trim and Fill method funnel plot estimating the publication bias of the OS group.

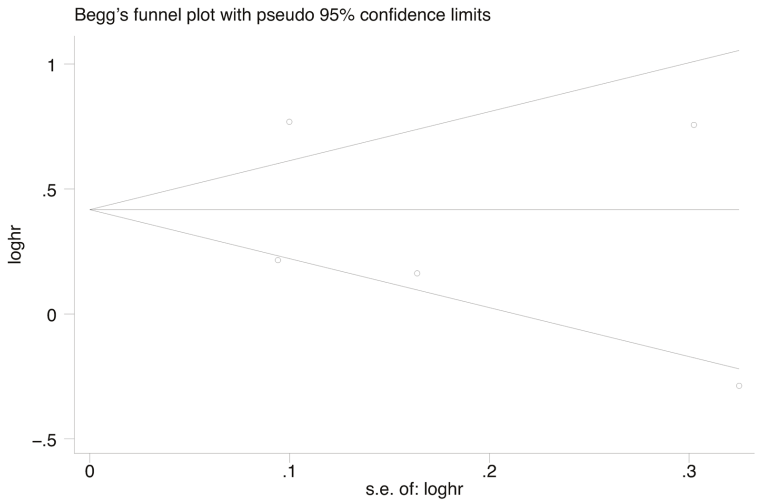

Figure 11. Begg funnel plot estimating the publication bias of the included studies in the PFS group.

and OS in patients with esophageal cancer undergoing surgery [53]. Sato et al. retrospectively analyzed 83 patients with esophageal cancer who received neoadjuvant chemotherapy (cisplatin + 5-FU) and found that a pretreatment high NLR level (≥2.2) in the peripheral blood was independently associated with a low pathological remission rate [54]. Heikkila et al. conducted a retrospective study on patients with locally advanced esophageal cancer who received chemotherapy and radiotherapy. The result showed that the high NLR group (≥2.0) before treatment had shorter progression-free survival (PFS) and OS (P<0.05). However, the sensitivity to radiotherapy and chemotherapy of patients in the low NLR group was significantly higher than that of the high NLR group (P<0.05), which confirmed the reliability of NLR in predicting the sensitivity of radiotherapy and chemotherapy, but the predictive effect on survival was not ideal [55]. However, current studies have focused on investigating the role of NLR in the prognosis of esophageal cancer patients as a whole, and relatively little attention has been paid to its specific relationship in the prognosis of esophageal cancer patients receiving chemoradiotherapy. Given the significant prognostic differences between esophageal cancer patients treated with chemoradiotherapy and those treated with surgery, the results of the present study confirm the prognostic value of NLR in this group of patients.

Tumor cells recruit neutrophils into the tumor microenvironment and these differentiate into tumor-associated neutrophils (TANs). N1-type TANs possess anti-tumor properties, whereas N2-type TANs promote tumor progression. N2-type TANs promote tumor growth by secreting matrix metalloproteinase-9 (MMP-9) [56] and stimulate angiogenesis by generating FOXO3a regulation [57]. TANs also enhance tumor invasiveness by inducing epithelial-mesenchymal transition (EMT) via CD90-TIMP-1 signalling [58], and generate neutrophil extracellular traps (NETs) and secreted proteases that promote tumor metastasis [59, 60]. In addition, N2-type TANs induce apoptosis of CD8+ T cells via TNF-α and NO pathways [61] and inhibit their proliferation [62]. In contrast, tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, are essential for an effective anti-tumor response [63]. CD8+ T cells perform cytotoxic functions and enhance the immune response

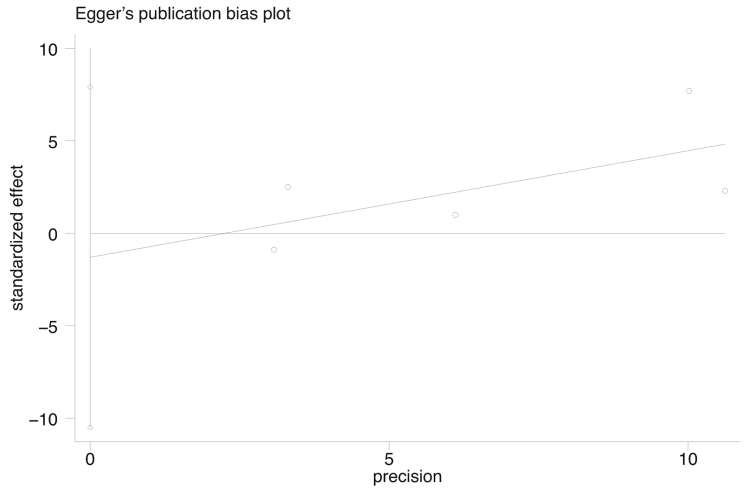

Figure 12. Egger's funnel plot estimating the publication bias of the included studies in the PFS group.

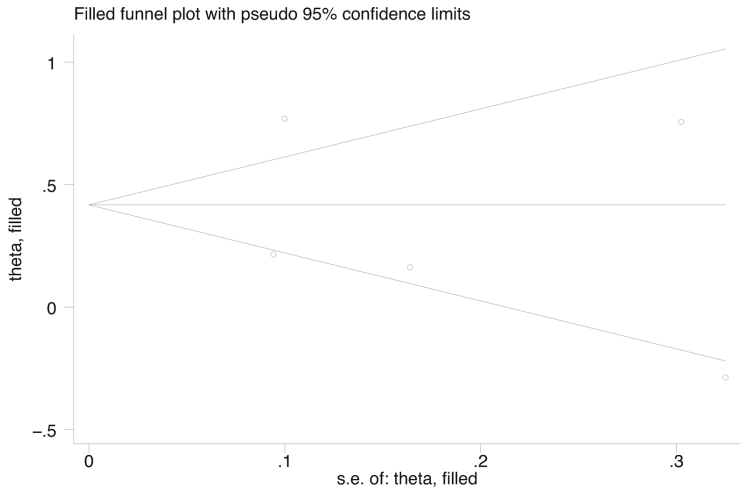

Figure 13. Trim and Fill method funnel plot estimating the publication bias of the PFS group.

through the secretion of IFN-γ and TNF-α [64]. CD4+ T cells support CD8+ T cells and NK cells through co-stimulatory molecules and cytokines, and maintain a pool of CD8+ memory T cells after antigen clearance [65]. However, certain T cells, such as Th9/Th17, can paradoxically promote tumor progression [66]. Thus, elevated NLR reflects increased neutrophils and/or decreased lymphocytes, indicating a pro-tumor inflammatory state and suppressed adaptive immune response, which correlates with poor prognosis in tumor patients.

This study does have a few limitations. Firstly, it includes only retrospective studies, which may introduce bias due to the lack of prospective data. Secondly, some effect sizes were estimated from survival curves, potentially increasing bias. Thirdly, only English-language studies were included, which may skew results towards positive findings due to publication bias. Furthermore, the sample size remains relatively small, necessitating the inclusion of recent studies to update this meta-analysis. Consequently, large-scale prospective studies are imperative to further validate these findings.

In conclusion, NLR is a readily available, cost-effective, and reliable prognostic marker for esophageal cancer patients undergoing chemotherapy and radiotherapy, particularly among male patients with cervical esophageal cancer.

Disclosure of conflict of interest

None.

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