

# Prognostic significance of neutrophil-to-lymphocyte ratio in esophageal cancer: a meta-analysis

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**Background:** The neutrophil-to-lymphocyte ratio (NLR) is a useful predictive factor in several cancers. However, the prognostic value of NLR in patients with esophageal cancer (EC) is still controversial. Therefore, it was necessary for us to perform a meta-analysis to evaluate the prognostic value of NLR in patients with EC.

**Methods:** A systematic literature search was performed by using Web of Science, PubMed Central, and Medline to evaluate the prognostic value of NLR in patients with EC. The deadline of our primary search was July 10, 2014. This meta-analysis was conducted in accordance with PRISMA guidelines. Pooled hazard ratio (HR) with 95% confidence interval (CI) was used to assess the association of NLR and overall survival (OS) and disease-free survival (DFS).

**Results:** Six studies involving 1,633 patients were included in our meta-analysis. Our pooled results demonstrated that high NLR was associated with poor OS (HR: 1.54, 95% CI: 1.32–1.80,  $I^2=25.3%$ ,  $P=0.254$ ) and DFS (HR: 1.74, 95% CI: 1.25–2.43,  $I^2=63.9%$ ,  $P=0.096$ ). Subgroup analysis between NLR and OS was performed in a further investigation. When the patients were segregated according to country, sample size, and pathological type, high NLR was also significantly correlated with OS.

**Conclusion:** High NLR is associated with poor prognosis in patients with EC. NLR may be a significant predictive biomarker in patients with EC.

**Keywords:** esophageal cancer, neutrophil-to-lymphocyte ratio, prognosis, meta-analysis, overall survival, disease-free survival

## Introduction

Esophageal cancer (EC) is one of the most common cancers worldwide.<sup>1</sup> Although there is a significant improvement in the treatment of patients with EC, the prognosis is still poor due to late diagnosis, rapid progression, and high rate of recurrence.<sup>2,3</sup> Therefore, it is important for us to identify better predictive factors, especially serum predictive biomarkers, for prognosis in patients with EC.

In recent years, systemic inflammatory response has been shown to correlate with prognosis in various cancers.<sup>4,5</sup> Various inflammatory biomarkers, such as cytokine, C-reactive protein (CRP), and Glasgow prognostic score, have been investigated in a variety of cancers.<sup>6–9</sup> Recent studies have demonstrated that neutrophil-to-lymphocyte ratio (NLR) is associated with prognosis in various cancers.<sup>10–12</sup> However, due to the inconsistent results, the prognostic value of NLR in EC remains controversial.<sup>13–20</sup> Therefore, it was necessary for us to perform a meta-analysis to evaluate the prognostic value of NLR in patients with EC.

In this study, we conducted a meta-analysis to evaluate the prognostic value of NLR for survival in patients with EC. To the best of our knowledge, this is the first

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meta-analysis to investigate the prognostic role of NLR in patients with EC.

## Materials and methods

### Literature search

A systematic literature search was performed by using Web of Science, PubMed, and Medline to evaluate the prognostic value of NLR in patients with EC. The search strategy was based on combinations of the following search terms: (“neutrophil-lymphocyte ratio” or “neutrophil-to-lymphocyte ratio” or “neutrophil lymphocyte ratio” or “NLR”) and (“esophageal cancer” or “esophageal carcinoma” or “EC”). The deadline of our primary search was July 10, 2014. Only human research was included in our meta-analysis. In addition, the reference lists of identified studies were also checked for further relevant studies.

### Inclusion/exclusion criteria

Inclusion criteria were as follows: 1) patients were diagnosed as having EC by pathology; 2) the NLR was measured before treatment; 3) the NLR was measured by serum-based methods; 4) the relationship between NLR and prognosis (overall survival [OS] and disease-free survival [DFS]) was evaluated; 5) full-text studies without language limits. The exclusion criteria were 1) review, letter, case report, or nonhuman research; 2) insufficient data to extract the hazard ratios (HRs) and the 95% confidence intervals (CIs).

### Data extraction

Data from each study were extracted independently by two authors (Yang and Huang). If the results reported had possible overlap, only the most recent or the most complete study was included in this study. The following data were collected for each study: author, year, sample, country, treatment, pathological type, cutoff level, TNM stage, follow-up, and HRs and 95% CIs for the correlation between NLR and prognosis.

### Statistical analysis

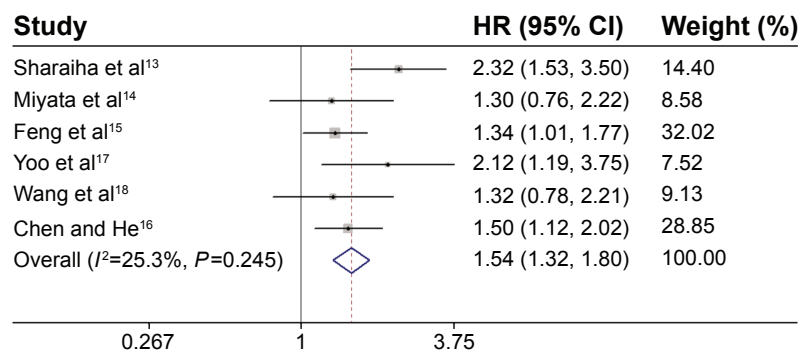
Pooled HRs and 95% CIs were used to analyze the relationship between NLR and prognosis (OS and DFS). The heterogeneity of combined HRs was initially evaluated by  $\chi^2$ -square test and expressed by inconsistency index  $I^2$ . A significant heterogeneity was defined as  $P < 0.10$  or  $I^2 > 50\%$ .<sup>21</sup> A combined HR  $> 1$  indicated a worse OS, and it was considered statistically significant if the 95% CI for the HR did not overlap. Publication bias was assessed using Begg’s funnel plot and Egger’s linear regression test. All statistical analyses

**Table 1** Characteristics of included studies

Author	Country	Sample size (M/F)	Treatment	Survival analysis	Pathological type	HR (95% CI)	Cutoff level	Follow-up (M)*	TNM stage
Sharaiha et al <sup>3</sup>	USA	295 (85/27)	C/R + S	OS, DFS	SCC + AC	2.32 (1.53–3.50) 2.26 (1.44–3.56)	5.0	31 (13–61)	I–IV
Miyata et al <sup>4</sup>	Japan	152 (132/20)	C + S	OS	SCC	1.30 (0.76–2.22)	4.0	60.2 (20.1–120.8)	II–IV
Feng et al <sup>5</sup>	People’s Republic of China	483 (411/72)	S	OS	SCC	1.339 (1.015–1.768)	3.5	45 (3–84)	I–III
Yoo et al <sup>7</sup>	South Korea	138 (132/6)	C/R	OS	SCC + AC	2.115 (1.193–3.749)	2.0	39.5 (1.1–93.4)	II–III
Wang et al <sup>8</sup>	People’s Republic of China	90 (72/18)	S	OS, DFS	SCC	1.316 (0.783–2.214) 1.279 (0.780–2.097)	1.0	NA	I–III
Chen and He <sup>6</sup>	People’s Republic of China	475 (382/93)	S + C/R	OS	SCC	1.50 (1.12–2.02)	2.5	44.9 (2–84.4)	I–III

**Notes:** \*Data shown as mean (minimum-maximum).

**Abbreviations:** M/F, male/female; S, surgery; C/R, chemotherapy/radiotherapy; OS, overall survival; DFS, disease-free survival; SCC, squamous cell carcinoma; AC, adenocarcinoma; NA, not available; M, months.



**Figure 1** Forest plot of the association between NLR and OS in EC.

**Abbreviations:** HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; EC, esophageal cancer.

were conducted with Stata version 12.0 (Stata Corporation, College Station, TX, USA).

## Results

According to the search strategies, a total of six eligible studies, including 1,633 patients with EC, were included in this meta-analysis.<sup>13–18</sup> Sato et al<sup>19</sup> demonstrated the correlation between NLR and the response to neoadjuvant chemotherapy. Thus, we excluded it from this study. Rashid et al<sup>20</sup> reported the opposite conclusion. However, we could not extract the data from the manuscript because of insufficient data. Therefore, we excluded Rashid's study as well. The main characteristics of the six included studies are listed in Table 1.

All these six studies presented data on NLR and OS,<sup>13–18</sup> but only two studies reported data on NLR and DFS.<sup>13,17</sup> Our pooled results showed that high NLR was associated with poor OS (HR: 1.54, 95% CI: 1.32–1.80,  $I^2=25.3%$ ,  $P=0.245$ ) (Figure 1) and DFS (HR: 1.74, 95% CI: 1.25–2.43,  $I^2=63.9%$ ,  $P=0.096$ ) (Figure 2).

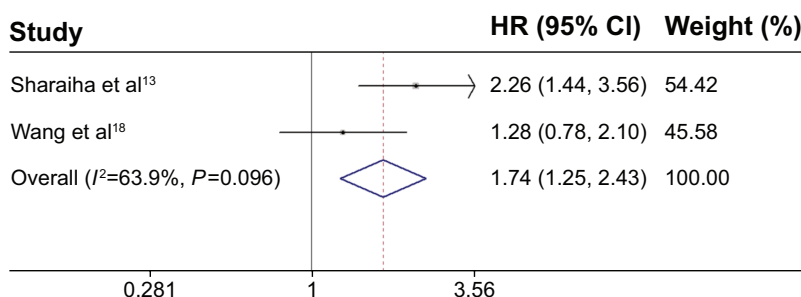
In a further investigation, subgroup analyses were performed (Figure 3). When stratified by “sample size,” the “>300” group yielded a HR of 1.41, and the 95% CI was 1.15–1.73 (Figure 3A). The “≤300” group yielded a HR

of 1.76, and the 95% CI was 1.38–2.26 (Figure 3B). In the subgroup analysis by “country,” we found that no matter the patients were Chinese (Figure 3C) or non-Chinese (Figure 3D), high NLR was still a poor predictor for OS. The subgroup analysis by “pathological type” showed that high NLR still yielded a worse OS (Figure 3E and F).

Sensitivity analysis showed that no single study could affect the pooled HRs in the present meta-analysis (Figure 4A). The Begg's funnel plot and Egger's linear regression test were performed to analyze the publication bias. There was no significant publication bias in our study (Begg's test:  $P=0.707$ , Egger's test:  $P=0.521$ ) (Figure 4B and C).

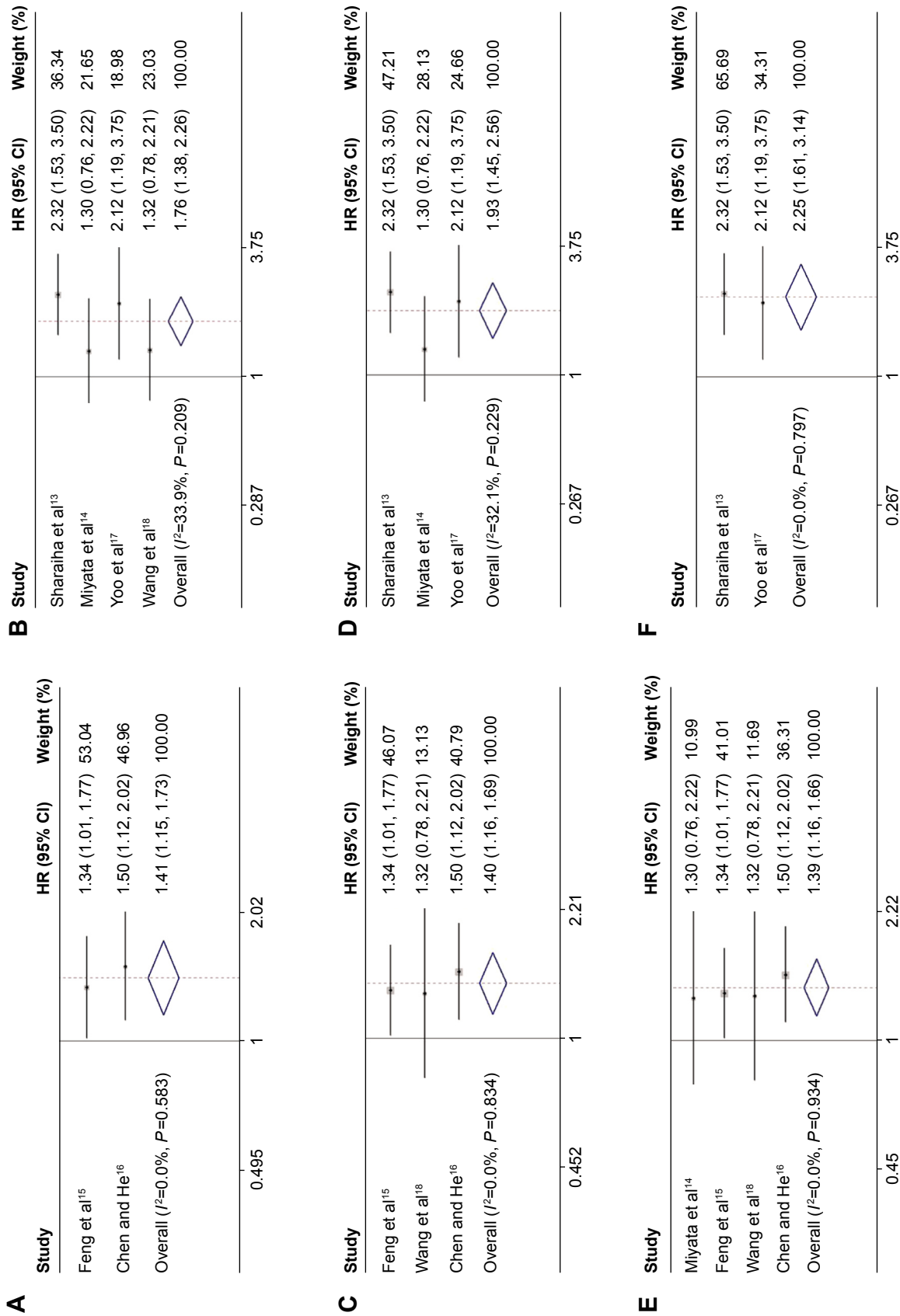
## Discussion

To the best of our knowledge, this is the first meta-analysis to investigate the prognostic role of NLR in patients with EC. In this meta-analysis, our pooled results demonstrated that high NLR was associated with poor OS (HR: 1.54, 95% CI: 1.32–1.80,  $I^2=25.3%$ ,  $P=0.245$ ) and DFS (HR: 1.74, 95% CI: 1.25–2.43,  $I^2=63.9%$ ,  $P=0.096$ ) in patients with EC. Subgroup analyses between NLR and OS were performed in a further investigation. When the patients were segregated according to country, sample size, and pathological type, high NLR was also significantly correlated with OS.



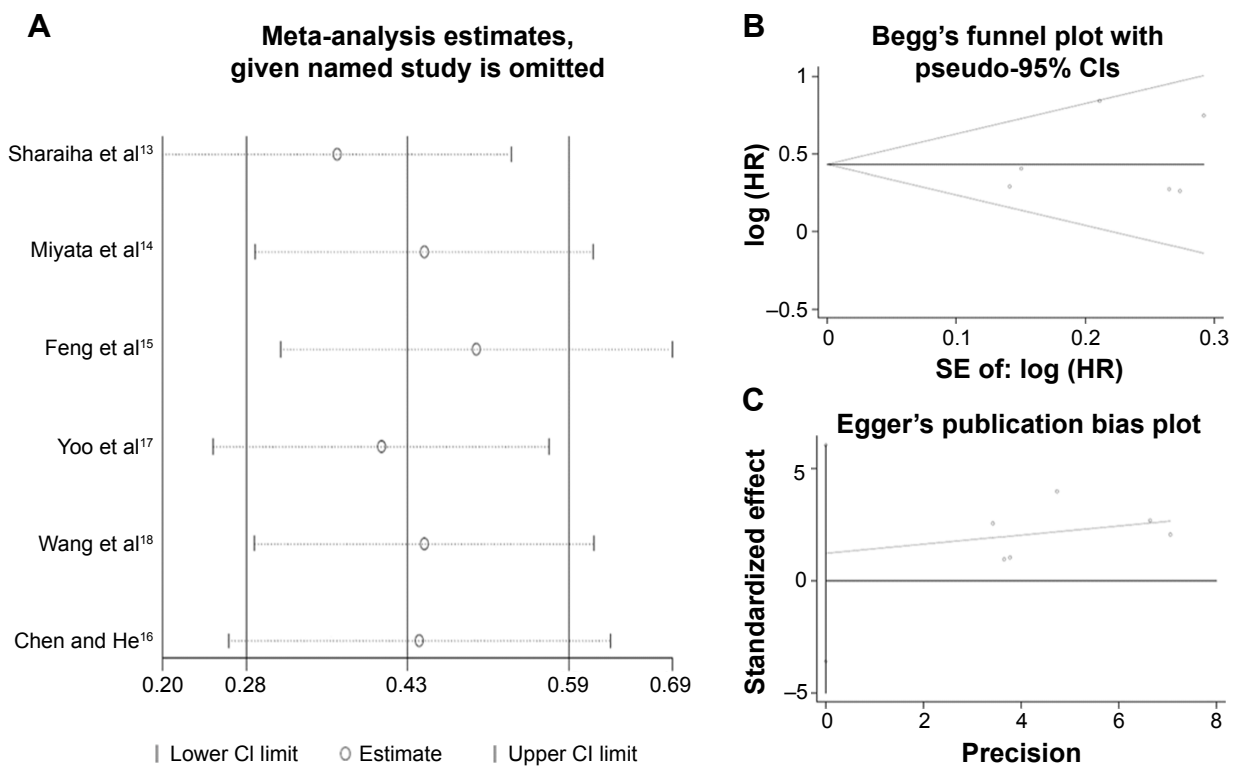
**Figure 2** Forest plot of the association between NLR and DFS in EC.

**Abbreviations:** HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; DFS, disease-free survival; EC, esophageal cancer.



**Figure 3** Forest plot of the association between serum CRP and OS in EC by subgroup analyses.

**Notes:** Subgroup analysis by sample size (**A**: > 300, **B**: < 300), country (**C**: People's Republic of China, **D**: not People's Republic of China), and pathological type (**E**: SCC, **F**: SCC + AC). **Abbreviations:** HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; OS, overall survival; EC, esophageal cancer; SCC, squamous cell carcinoma; AC, adenocarcinoma.



**Figure 4** Sensitivity analysis (A) and funnel plot of publication biases (B and C) on the relationship between NLR and OS in EC.

**Abbreviations:** CI, confidence interval; HR, hazard ratio; SE, standard error; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; EC, esophageal cancer.

Several meta-analyses demonstrated that NLR can be used as an independent predictive factor and can predict the prognosis of various cancers, including urinary cancer,<sup>22</sup> hepatocellular carcinoma,<sup>23</sup> and colorectal cancer.<sup>24</sup> The results of our study are consistent with those of published reports. Furthermore, the sensitivity analysis showed that no single study could affect the pooled HRs in our meta-analysis. There was no significant publication bias in our study. This finding suggests that our meta-analysis was stable and reliable.

The mechanism of the prognostic value of NLR in patients with EC remains unclear. Several reports showed that NLR was associated with tumor-associated macrophages, which promote interleukin-6.<sup>25</sup> Furthermore, cancer has been shown to produce various cytokines, such as granulocyte colony-stimulating factor, tumor necrosis factor- $\alpha$ , transforming growth factor- $\beta$ , interleukin-1, and interleukin-6, which may influence tumor-related neutrophilia.<sup>26,27</sup>

There were several limitations in our study. First, the number of included studies was limited. Second, the pooled HRs in our study between NLR and OS/DFS were not strong. Empirically, a HR >2 is considered a strongly predictive factor. Therefore, the results should be regarded with caution when using NLR to predict OS/DFS in EC. Moreover, because

of the lack of a relevant prospective study, all of the included studies were retrospective. In addition, Rashid's study was important for our study. However, we excluded it due to insufficient data, which may have influenced our analysis. Therefore, more prospective studies are needed to confirm whether NLR is a prognostic factor in patients with EC.

In conclusion, our meta-analysis demonstrated that high NLR was significantly associated with poor OS and DFS in patients with EC. We conclude that NLR might serve as a useful biomarker for EC. However, further large prospective studies should be carried out to confirm whether NLR has a prognostic value in patients with EC.

## Disclosure

The authors report no conflicts of interest in this work.

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