The role of pretreatment prognostic nutritional index in esophageal cancer: A meta-analysis

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Abstract
Clinicopathological characteristics and prognosis of esophageal cancer (EC) patients with decreased prognostic nutritional index (PNI) have not been well investigated. So, we conducted this meta-analysis. We performed comprehensive research in PubMed, Embase, and Cochrane databases. The effect size was hazard ratio (HR) with 95% confidence interval (CI) for overall survival (OS) and cancer-specific survival (CSS). The pooled odds ratio (OR) with 95% CI were used to assess the association between PNI and clinicopathological features. A total of 3,425 EC patients were included in the present meta-analysis. Male patients, advanced age, higher tumor stage, and lymph node metastases were associated with reduced PNI level (OR = 1.40, 95% CI: 1.10-1.79; OR = 1.35, 95% CI: 1.10-1.66; OR = 2.37, 95% CI: 1.91-2.94; OR = 1.63, 95% CI: 1.04-2.56). And, the EC patients with decreased PNI held a worse OS and CSS compared with those who carried a higher PNI (HR = 1.29, 95% CI: 1.10-1.50; HR = 2.53, 95% CI: 1.15-5.57). This meta-analysis demonstrated PNI level was associated with tumor stage and lymph nodes metastases and was an independent prognostic factor in EC.

KEYWORDS
esophageal cancer, meta-analysis, pretreatment, prognosis, prognostic nutritional index

1 INTRODUCTION

Esophageal cancer (EC), a common digestive tract neoplasm, is the world’s sixth leading cause of cancer-related deaths. And, men are more likely to suffer from EC compared with women. In 2017, approximately 17,290 Americans were diagnosed with EC, which also leads to 15,850 deaths in the United States (Siegel, Miller, & Jemal, 2018). However, there is a considerable variation in the incidence of EC among different regions, a 60-fold difference existing between high- and low-incidence areas (Corley & Buffler, 2001). The main high-prevalence regions span from Northern China through Central Asia and into Northern Iran (Torre, Siegel, Ward, & Jemal, 2016). Pathologically, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are the major histological types. The consumption of tobacco and alcohol, obesity, and high body mass have been identified as the leading risk factors of EC (Ajani et al., 2015). Although advances in treatments of EC have been achieved, the long-term outcome of patients remains unsatisfactory. Thus, biomarkers used to predict prognosis of patients are needed to guide clinical treatments (F. Liu et al., 2017).

The nutrition and immunologic status of patients have been demonstrated as significant indicators of progression and outcome of tumors (Mainous & Deitch, 1994; Mellman, Coukos, & Dranoff, 2011). Consequently, some screening tools were developed to evaluate the pretreatment nutrition and immunologic status of cancer cases, prognostic nutritional index (PNI) being one of them (Forrest, Mcmillan, Mcardle, Angerson, & Dunlop, 2004; Oh et al., 2009). The PNI, calculating as following items: 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (per mm³) in peripheral blood (Onodera, Goseki, &...
Kosaki, 1984), was proposed by Onodera et al. (1984) to assess the risk of postoperative complications and the prognosis of gastrointestinal cancer patients treated by surgery. Albumin is capable of representing the nutrition status of cases, and its predictive roles of morbidity following esophagectomy and outcomes in certain tumors have been illustrated (Seaton, 2001). Meanwhile, peripheral blood lymphocyte count is a parameter of antitumor immunity in patients. As a result, decreased lymphocyte count enables tumor cells to avoid the elimination of immune system (Gupta & Lis, 2010). In addition, PNI has been recognized as a worthy prognostic biomarker in certain cancers, including EC (Okada et al., 2017; Sun, Chen, Xu, Li, & He, 2014). However, the associations between PNI and prognosis of patients are still inconsistent (Chen, Yang, & Feng, 2016; Feng and Chen, 2013; Han et al., 2016; Hirahara et al., 2017; Kubo et al., 2018; Migita et al., 2018; Miyazaki et al., 2016; Okadome et al., 2018; Sun et al., 2013; Wang et al., 2018; Yang & Xu et al., 2018; Zhang et al., 2018). Therefore, we conducted this meta-analysis to clarify the association between PNI level and clinicopathological features along with the outcome of EC.

2 MATERIALS AND METHODS

An exhaustive search was conducted in Pubmed, Embase, and Cochrane databases for eligible studies based on "PRISMA" guideline, up to December 3rd, 2018 (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). And, there were no language restrictions. The following items were applied to research: ("esophageal neoplasm", "cancer of esophagus", or "esophageal cancer") and ("prognostic nutritional index" or "PNI"). Moreover, the references lists in additional papers were also manually screened for potentially associated studies. A flow diagram of the studies selection process was showed in Figure 1.

2.1 Inclusion and exclusion criteria

The inclusive studies had to meet the following criteria: (a) the EC was identified by pathological examination, (b) PNI was measured before clinical treatments. The researches with one of these criteria were excluded: (a) no available data were present in articles, (b) PNI was measured after clinical treatments, and (c) studies were nonoriginal researches. In addition, if studies shared the same patients’ population, only the most recent, or most complete, articles were included.

2.2 Data extraction

Two independent investigators (YBX and XZ) extracted relevant data from eligible studies, respectively. Another author (LX) examined extracted data again. The following items were extracted: first author, year of publication, country of patients' population, sex, recruitment period, age, follow-up period, number of patients, clinical treatments, pathology, tumor stage, PNI cut-off value and outcome of patients, covering hazard ratios (HR) with 95% confidence interval (CI) of overall survival (OS), and cancer-specific survival (CSS). Furthermore, we adopted Newcastle-Ottawa-Scale to evaluate the quality of the included studies.

2.3 Statistical analysis

Stata software (version 12.0; Stata Corp LP, College Station, TX) was applied to this meta-analysis. The pooled odds ratio (OR) along with 95% CI was used to evaluate the associations between PNI level and clinicopathological features, such as sex of cases, age, and tumor stage. For the prognostic role of PNI, HR with 95% CI of OS and CSS were applied to assess the relationships between PNI and outcomes of patients. When multivariable and univariable outcome analyses were provided simultaneously, we selected the former. If papers did not directly report HR and 95% CI but offered Kaplan–Meier curves, HR with 95% CI were extrapolated by the data directly acquired from the curves. We applied the $\chi^2$ and $I^2$ tests to assessing the heterogeneity across the studies. If significant heterogeneity was observed, $p < 0.10$ or $I^2 > 50\%$, the random-effects model was used to estimate the pooled ORs/HRs. Moreover, the fixed-effects model was used with $p > 0.10$ and $I^2 < 50\%$. Meanwhile, we also conducted a sensitivity analysis to check the stability of the results by sequentially omitting each inclusive study. Furthermore, the Begg test and a funnel plot were performed to assess the publication bias between the researches. Two-tailed $p$ values of statistical tests less than 0.05 were regarded as statistically significant.
**TABLE 1** Detailed characteristics of the studies included in this meta-analysis

| First author | Year | Country | Sex | Recruitment period | Age (Year) (mean/median) | Follow-up (month) (mean/median) | No. pts | Treatment | Pathology | Tumor stage | PNI cut-off value | Outcome | NOS |
|-------------|------|---------|-----|-------------------|--------------------------|-------------------------------|--------|-----------|-----------|-------------|------------------|----------|-----|
| Sun P       | 2013 | China   | Male and female | 2007–2008 | 59 | 30 | 502 | NR | SCC | I–IV | 50 | OS | 7 |
| Han L       | 2015 | China   | Male and female | 2007–2008 | 60 | 39.5 | 206 | Surgery | SCC | I–IV | 45.5 | OS | 6 |
| Miyazaki T  | 2016 | Japan   | Male and female | 2004–2014 | 65.8 | 26.5 | 192 | Surgery | SCC | I–IV | 47.7 | OS | 6 |
| Hirahara N  | 2017 | Japan   | Male and female | 2006–2015 | NR | NR | 169 | Surgery | SCC | I–III | 49.2 | OS | 7 |
| Zhang H     | 2018 | China   | Male and female | 2005–2013 | 61 | NR | 655 | Surgery | SCC | 0–III | 52.28 | OS | 8 |
| Feng JF†    | 2018 | China   | Male and female | 2006–2008 | 59 | NR | 375 | Surgery | SCC+ADC+others | T1–T4/N0–N+ | 42 | CSS | 7 |
| Wang J      | 2018 | China   | Male and female | NR | NR | 24 | 97 | CRT | SCC+ADC+others | I–IV | 45 | OS | 7 |
| Okadome K   | 2018 | Japan   | Male and female | 2005–2014 | 65.9 | 60 | 337 | Surgery | SCC+ADC+others | I–IV | 45 | OS | 9 |
| Migita K    | 2018 | Japan   | Male and female | 2004–2015 | NR | NR | 137 | Surgery, neoCRT | SCC | T1–T4/N0–N+ | 47 | OS | 7 |
| Kubo N      | 2018 | Japan   | Male and female | 2000–2012 | 63.4 | NR | 240 | Surgery, neoCRT, CRT | SCC | I–IV | 44 | OS | 7 |
| Yang Y      | 2018 | China   | Male and female | 2005–2011 | 61 | 35 | 515 | Surgery, CRT | SCC | I–III | 57 | OS | 7 |

Note. ADC: adenocarcinoma; CI: confidence interval; CRT: chemoradiotherapy; CSS: cancer-specific survival; HR: hazard ratio; M: multivariate analysis; neoCRT: neoadjuvant chemoradiotherapy; No. pts: number of patients; NOS: Newcastle-Ottawa Scale; NR: not report; OS: overall survival; PNI: prognostic nutritional index; SC: survival curves; SCC: squamous cell carcinoma.

†Two studies shared this patients population. Only HR and 95% CI of CSS were extracted from one study.
### RESULTS

#### Study characteristics

A total of 11 eligible studies, 3,425 EC patients, were included in the present meta-analysis for a future evaluation, all of which were retrospective and published between 2013 and 2018. Most studies only contained esophageal SCC (Chen et al., 2016; Feng and Chen, 2013; Han et al., 2016; Hirahara et al., 2017; Kubo et al., 2018; Migita et al., 2018; Miyazaki et al., 2016; Sun et al., 2013; Yang & Xu et al., 2018; Zhang et al., 2018), and two studies consisting of 434 patients included SCC, ADC, and other pathological types (Okadome et al., 2018; Wang et al., 2018). PNI was calculated before clinical treatments in all included studies, cut-off values ranging from 42 to 57, seven of which calculated PNI preoperatively (Feng and Chen, 2013; Han et al., 2016; Hirahara et al., 2017; Migita et al., 2018; Miyazaki et al., 2016; Sun et al., 2013; Yang & Xu et al., 2018; Zhang et al., 2018), and two studies consisting of 434 patients included SCC, ADC, and other pathological types (Okadome et al., 2018; Wang et al., 2018). PNI was calculated before clinical treatments in all included studies, cut-off values ranging from 42 to 57, seven of which calculated PNI preoperatively (Feng and Chen, 2013; Han et al., 2016; Hirahara et al., 2017; Migita et al., 2018; Miyazaki et al., 2016; Sun et al., 2013; Yang & Xu et al., 2018; Zhang et al., 2018). Detailed characteristics of included studies were summarized in Table 1.

#### Clinicopathological characteristics and PNI

Male patients, advanced age and higher tumor stage were associated with reduced PNI level (OR = 1.40, 95% CI: 1.10–1.79; OR = 1.35, 95% CI: 1.10–1.66; OR = 2.37, 95% CI: 1.91–2.94; Table 2). In addition, there was low heterogeneity existing in these polled ORs ($I^2 = 0.0\%$, $p = 0.936$; $I^2 = 0.0\%$, $p = 0.922$; $I^2 = 11.6\%$, $p = 0.341$; Table 2). However, no significant difference was observed between PNI and tumor grade along with distant metastases (OR = 1.24, 95% CI: 0.79–1.95; OR = 1.27, 95% CI: 0.59–2.72; Table 2).

The association between lymph node metastases (LNM) and PNI was evaluated in six of the studies, 2,112 cases included. And, the pooled OR demonstrated that patients with lower PNI took more possibility to suffer LNM (OR = 1.63, 95% CI: 1.04–2.56, $I^2 = 79.5\%$, $p = 0.000$; Figure 2a). As high heterogeneity was shown in the studies, a subgroup analysis according to the cut-off value of PNI was conducted. When cut-off value of PNI was <46, there was a significant difference in the association between PNI and LNM (OR = 3.67, 95% CI: 2.33–5.78, $I^2 = 0.0\%$, $p = 0.975$; Figure 2b).

#### Table 2

| Clinical parameters | Number of studies (number of patients) | OR (95% CI) | Model | Heterogeneity | Significance (p) |
|---------------------|---------------------------------------|-------------|-------|---------------|-----------------|
| Sex (male vs female) | 7 (2,449)                             | 1.40 (1.10–1.79) | Fixed | 0.0 | 0.936 | 0.007 |
| Age (old vs young)   | 4 (1,751)                             | 1.35 (1.10–1.66) | Fixed | 0.0 | 0.922 | 0.004 |
| T stage (T3-T4 vs T1-T2) | 6 (2,112)                          | 2.37 (1.91–2.94) | Fixed | 11.6 | 0.341 | 0.000 |
| Grade (G3 vs G2-G1)  | 3 (1,545)                             | 1.24 (0.79–1.95) | Random | 62.9 | 0.068 | 0.350 |
| Distant metastases (present vs absent) | 3 (735)                       | 1.27 (0.59–2.72) | Fixed | 44.0 | 0.168 | 0.542 |

Note. CI: confidence interval; OR: odds ratio; PNI: prognostic nutritional index.

†Cut-off value of age included 60 and 61 years old.
3.3 | Long-term outcomes and PNI

Overall, decreased PNI EC cases retained a worse CSS compared with patients with higher PNI (HR = 2.53, 95% CI: 1.15-5.57, \( I^2 = 65.5\% \), \( p = 0.089 \)), whose HR were all calculated by multivariate analysis adjusting for TNM stage (Figure 3a). Meanwhile, our meta-analysis also suggested that the EC patients with decreased PNI held a worse OS compared with those who carried a higher PNI using a random-effects model after 11 studies were synthesized (HR = 1.29, 95% CI: 1.10-1.50, \( I^2 = 69.8\% \), \( p = 0.000 \); Figure 3b). Low-PNI was confirmed as an independent poor predictive factor for OS when 10 studies whose HR of OS was calculated by multivariate analysis adjusting for TNM stage were synthesized (HR = 1.26, 95% CI: 1.08-1.48, \( I^2 = 70.6\% \), \( p = 0.000 \)) (Figure 3c). Stratified analysis of country of patients' population depicted that both Chinese and Japanese patients with lower PNI, suffered a significantly declined OS (HR = 1.06, 95% CI: 1.04-1.08, \( I^2 = 20.0\% \), \( p = 0.283 \); HR = 1.86, 95% CI: 1.50-2.32, \( I^2 = 0.0\% \), \( p = 0.856 \); Figure 3d).

3.4 | Sensitivity and publication analysis

The sensitivity analysis was implemented to evaluate the contribution of every study to the polled estimation. One individual research was omitted, and the pooled OR/HR was reevaluated based on the remaining studies. And, low heterogeneity across the inclusive studies was again depicted by the sensitivity analysis. We assessed the publication bias among the studies by the Begg funnel plot, and there was no publication bias found in the funnel plots (Figure 4). Accordingly, this showed that the outcomes of meta-analysis were statistically robust.

4 | DISCUSSION

Patients with cancers, especially upper digestive tract tumors, are more vulnerable to malnutrition since metabolic requirements growing, oral intake decreasing and dyspepsia lead to nutrition losing (Mariette, Botton, & Piessen, 2012). Meanwhile, multimodality therapy, including...
surgery beside neoadjuvant and adjuvant chemoradiotherapy, is routinely conducted to treat EC patients (Ajani et al., 2015). Lately, more intensive elements, such as docetaxel, cisplatin, and 5-fluorouracil constituting the combination chemotherapy have been tried as a neoadjuvant chemotherapy (NAC; Hara et al., 2013; Watanabe et al., 2014). Although NAC takes the advantage of shrinking the tumor bulk and reducing micrometastasis preoperatively, patients treated by intensive NAC are more likely to worsen nutritional status on account of side effects triggering by chemotherapy (Motoor, et al., 2012; Reisinger et al., 2015).

In addition, even though complications and mortality of esophagectomy have decreased during the past decade, esophagectomy is still one of the most invasive gastrointestinal cancer surgeries (Paul & Altorki, 2014). Two or three regions including thorax, abdomen, and neck may be involved in a surgical site of esophagectomy, which would accompany with the extensive wound and more blood loss, undoubtedly increasing nutrition demand (Takagi et al., 2001).

It was shown that 60–80% of the EC cases suffered nutritional deficiency (Andreyev, Norman, Oates, & Cunningham, 1998). Increasing researches have demonstrated that nutritional status is related to postoperative morbidities, the response rate to clinical treatments, prognosis, and quality of life (Andreyev et al., 1998; Mariette et al., 2012; Migita et al., 2013; Migita et al., 2016). Albumin is recognized as a biomarker of nutrition status widely, and its level is identified to be associated with comorbidity and prognosis in certain cancers (Gupta & Lis, 2010). Lymphocyte belongs to the fundamental elements of cell-mediated immunity, which can inhibit the proliferation and invasion of cancer cells in virtue of cytokine-mediated cytotoxicity (Gupta & Lis, 2010; Ray-Coquard, Cropet, Glabbeke, Sebban, & Blay, 2009). Cancer cells escaping from host immune surveillance due to decreased lymphocyte count and a weak function of lymphocyte leads to a worse outcome of cancer patients (Gupta & Lis, 2010). PNI is calculated by serum albumin and lymphocyte count in peripheral blood (Onodera et al., 1984). Therefore, it quantifies the nutritional and immunological status of EC patients.

Our meta-analysis demonstrated that male patients, advanced age, higher tumor stage, and LNM were associated with reduced PNI level. Moreover, lower PNI EC patients held a worse oncological prognosis compared with higher PNI cases. Particularly, low-PNI was confirmed as independent poor predictive factors for OS and CSS, when studies whose HR of OS/CSS was calculated by multivariate analysis adjusting for TNM stage were synthesized. As mentioned above, decreased PNI, representing low albumin/lymphocyte count, was a symbol of malnutrition and dysfunction of antitumor immunity. In addition, Okadome et al. (2018) demonstrated that PNI was significantly relevant to tumor-infiltrating lymphocytes (TILs) status and CD8+ cell count. Meanwhile, there was also a significant difference existing in the relationship between lymphocyte count in peripheral blood and TILs. And, certain studies have shown that increased TILs are related to lower tumor stage and a better outcome than patients with few TILs (Gooden, De Bock, Leffers, Daemen, & Nijman, 2011; Ruiter, Ooft, Devriese, & Willems, 2017). So, PNI may affect the prognosis of EC patients by the tumor local immune response. Therefore, the EC cells become more aggressive with low PNI, such as higher tumor stage, LNM, and worse prognosis. What is more, because patients with advanced age are in the period of declining in physical functions, they are more likely to suffer low PNI during the progression of cancer. Moreover, females carry favorable prognosis in certain tumors, such as gastric carcinoma and colorectal cancer. The differences of sex in genetic, hormonal, immunological, and environmental factors account for this phenomenon (Yang &
Wang et al., 2017). Consequently, male EC patients taking lower PNI may also be ascribed to these differences in sex.

Because PNI is easily measured routinely and can be measured before treatment, PNI can assist to predict the prognosis and guide the treatment of EC patients in advance of pathologic results. On the other hand, PNI can reflect the nutrition status and antitumor immunity of cancer patients. So, it is essential to improve the PNI level of patients for better tolerance of chemoradiotherapy and surgery.

Admittedly, there were some limitations in this meta-analysis. First, present meta-analysis only included 11 studies and clinical studies with higher quality and large sample size are needed to support our conclusions. Second, HR and 95% CI, estimated according to Kaplan–Meier curves and the method proposed by Tierney, Stewart, Ghersi, Burdett, and Sydes (2007) and Williamson, Smith, Hutton, and Marson (2002) are not that accurate as reported by the authors.

5 CONCLUSION

Our meta-analysis suggested that male patients, advanced age and higher tumor stage were associated with reduced PNI level in EC. Meanwhile, PNI level was an independent prognostic factor in EC, and patients with lower PNI held worse CCS and OS.

AUTHOR CONTRIBUTIONS

Y. X. took part in the data extracted, statistical analysis, and drafting of the manuscript. X. Z. and L. X. helped to recheck the results and revised the manuscript. J. L. designed the study program and took responsibility for the integrity of the data and the accuracy of the data analysis. R. Z. participated in data extracted.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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**How to cite this article:** Xue Y, Zhou X, Xue L, Zhou R, Luo J. The role of pretreatment prognostic nutritional index in esophageal cancer: A meta-analysis. *J Cell Physiol*. 2019;234:19655–19662. [https://doi.org/10.1002/jcp.28565](https://doi.org/10.1002/jcp.28565)