Prognostic Value of Pretreatment Inflammatory Biomarkers in Primary Small Cell Carcinoma of the Esophagus

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DOI:
10.21203/rs.2.10549/v1

SUBJECT AREAS
Cancer Biology	Oncology
KEYWORDS

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, total lymphocyte counts, primary small-cell carcinoma of the esophagus, prognosis inflammatory biomarker
Abstract
Background: Growing evidence indicates that several inflammatory biomarkers may predict survival in patients with malignant tumors. The aim of this study is to evaluate the prognostic value of pretreatment biomarkers in patients with primary small-cell carcinoma of the esophagus (PSCCE).

Methods: There were 73 PSCCE patients enrolled between January 2009 and December 2017 at the Affiliated Cancer Hospital of Zhengzhou University. The total lymphocyte counts (TLC), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) prior to anticancer therapy were collected as inflammation biomarkers. The cut-off value was determined by Receiver operating characteristic (ROC). The Kaplan–Meier method was utilized to analysis overall survival (OS). Cox proportional hazards regression was used to identify univariate and multivariate prognostic factors.

Results: Univariate analysis showed that high NLR group (hazard ratio (HR) 1.685; 95% CI: 1.001–2.838; P=0.047) and high PLR group (hazard ratio (HR) 1.716; 95% CI: 1.039–2.834; P=0.033) were associated with poor OS, and TLC was not correlated with OS. On multivariate analysis, high PLR (hazard ratio (HR) 1.751; 95% CI: 1.042–2.945; P=0.035) was an independent prognostic factor of unfavorable OS. Conclusions: Pre-treatment PLR and NLR are correlated with OS. These biomarkers are easily accessible, cost effective, and can serve as a marker to identify high-risk patients for further designing personalized treatment and predicting treatment outcomes.

Background
Esophageal carcinoma is the sixth leading cause of cancer-related deaths worldwide and the third most common cancer in China [1, 2]. The common types of esophageal cancer are squamous cell carcinoma and adenocarcinoma and primary small cell carcinoma of the esophagus (PSCCE) is a relatively rare histological subtype, accounting for only 0.5-2.8% of all esophageal malignant tumors [3]. PSCCE is characterized by high aggression, early dissemination and poor prognosis [4-9]. Although the first case was noticed by McKeown in 1952, the lower incidence of PSCCE made it is difficult to establish a standard treatment [10]. Currently, different treatments including surgery, chemotherapy and radiotherapy have been performed alone or in combined strategies, the outcomes are really inconsistent [6, 7]. Therefore, it is critical to identify reliable biomarkers for predicting
prognosis and distinguishing patients with negative prognoses. Taking into account individual variability, using the prognostic biomarker to select eligible patients and administration specific treatments is a promising strategy in the era of precision medicine.

Previous studies have shown that systemic inflammatory response plays an important role in the tumorigenesis development, and metastasis [11, 12]. In the tumor microenvironment, inflammatory cells involved in angiogenesis, viability, mobility, and invasion [13, 14]. Numerous of evidences demonstrate that inflammatory biomarkers are correlated with the survivals of distinct types of cancers such as nasopharyngeal carcinoma[15], liver cancer[16], cervical cancer [17], lung cancer [18], and esophageal cancer [16, 19]. The patients outcomes can be effectively evaluated with pretreatment hematological biomarkers, including total lymphocyte count (TLC), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). In addition, the count of neutrophil, lymphocyte and platelet are easily available from the complete blood cell (CBC) counts in daily clinical practice and the cost of CBC is inexpensive. Nevertheless, there is seldom evidence of the relationship between these factors and the prognosis of PSCCE.

For the above reasons, we investigated whether the markers (TLC, NLR and PLR) have independent prognostic values in the patients with PSCCE.

Methods

Patients

We performed a retrospective analysis on hematologic and clinicopathological data of PSCCE patients from January 2009 to December 2017. This study was approved by the ethical board of the Affiliated Cancer Hospital of Zhengzhou University. Inclusion criteria were: (1) PSCCE proven by histopathology, (2) blood samples prior to anticancer therapy were available, (3) complete medical records. Exclusion criteria including :(1) non-primary esophageal carcinoma (2) pathologically confirmed or combined with squamous cell carcinoma, adenocarcinoma and other neuroendocrine carcinoma, (3) received any other treatment before blood samples were collected, (4) incomplete medical records.

A total of 73 patients were screened in the analysis, pathological diagnosis was confirmed PSCCE via endoscopic biopsy. Detailed physical and laboratory examination were performed after patients were
administered to the hospital. The tumor stage was classified according to the 6th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Informed Consent was obtained from all individuals prior to treatment.

**Data collection**

Clinical data including patient characteristics, laboratory outcomes, tumor location and stage, treatment, and pathological results were extracted from medical records. Because the levels of hematological parameters might be influenced by antitumor treatments, such as chemotherapy, radiotherapy, or nutritional support, the blood samples were collected within 14 days prior to treatment. The neutrophil count, lymphocyte count, and platelet count were obtained from the pretreatment complete blood count. NLR was defined as the total neutrophil count divided by the total lymphocyte count. PLR was defined as the total platelet count divided by the total lymphocyte count. The optimal cut-off values of TLC, NLR, and PLR were calculated based on receiver operating curve. Patients were stratified according to the cut-off points. Other clinical characteristics were divided into different groups, including age (<60 or ≥60 years), gender male or female, alcohol abuse (yes or no), tobacco abuse (yes or no), locations (upper, middle or lower), length of tumor lesion ≤6 or ≥6 cm, TNM stage (I, II, III, IV) and treatment modalities surgery alone vs. chemoradiotherapy vs. surgery combined with chemoradiotherapy.

**Statistical analysis**

OS was served as the primary endpoint, and was calculated from the date of diagnosis by histopathology to the date of death from any cause or the time of last follow-up. The connections between TLC, NLR, PLR and clinicopathological factors were analyzed by chi-square test. The Kaplan-Meier method was used to conduct univariate analysis of survival. The variable with p-value was less than 0.05 in univariate analysis were evaluated by multivariate logistic regression analysis. Cox proportional hazards regression was used to identify univariate and multivariate prognostic factors. All statistical analyses were conducted using SPSS version 22.0 (IBM Software Group, Chicago, USA). Differences were considered statistically significant at p<0.05.

**Results**
**Patient characteristics**

The clinicopathological characteristics of included PSCCE patients are illustrated in Table 1. There are contained 51 (69.9%) men and 22 (30.1%) women. The median age was 60 year, ranging from 37 to 77 year. The percent of primary tumor located in the middle, upper and lower thoracic esophagus were 67.1% (n=49), 2.7% (n=2) and 30.1% (n=22) respectively. The mean diameter of the tumor lesion was 5cm (ranging from 1cm to 11cm). According to the 6th edition of the AJCC Cancer Staging Manual, 6 patients had stage I PSCCE (8.2%), 32 individuals had stage II PSCCE (43.8%), 12 people belong to stage III PSCCE (16.4%), and the remained 23 persons had stage IV PSCCE (31.5%). Among the eligible individuals, 10 patients was treated by surgical resection (13.7%); 30 of the patients underwent surgery and chemoradiotherapy (41.1%); and the rest 33 persons have received chemoradiotherapy. The outcomes revealed that NLR and PLR were insignificantly associated with clinicopathological variables. In addition, significant correlations were observed between the TLC and alcohol and tobacco abuse, and there was no significant relationship between TLC and other features.

**Survival analyses**

The median follow-up time was 26.5 months, ranging from 1 to 116 months. At the end of follow-up, 69 patients died (94.5%). The median survival time was 22.0 months. The 1-, 3-, and 5-year OS rates were 83.5%, 24.6%, and 6.8%, respectively. On univariate analysis, seven clinicopathologic features including tumor location, lesion length, TNM stage, treatment, pre-treatment NLR and pre-treatment PLR were found to be associated with OS (Table 2).

**Relationships between inflammation biomarkers and OS**

In the study, we determined cut-off points for TLC, NLR, and PLR to be 1.8, 2.37 and 145 respectively. According to the cut-off points patients were divided into two groups separately (TLC³1.8×10⁹ as high TLC group; TLC<1.8×10⁹ as low TLC group; NLR³2.37 as high NLR group, NLR<2.37 as low NLR group; PLR³145 as high PLR group, PLR<145 as low PLR group). Patients in the high NLR group had expressively poorer OS than those in the low NLR group (hazard ratio (HR) 1.685; 95% CI: 1.001–2.838; P=0.047, Figure 1). The patients in the high PLR group had significantly worse OS than those in the low PLR group (hazard ratio (HR) 1.716; 95% CI: 1.039–2.834; P=0.033, Figure 2). Meanwhile, no
statistical difference was observed in patients with different TLC (Figure 3). Furthermore, the multivariate analysis showed that low pretreatment PLR (hazard ratio (HR) $\hat{1.751}$; 95% CI: 1.042–2.945; $P \leq 0.035$) was an independent predictor of superior survival in PSCCE. Treatment strategies (hazard ratio (HR) $\hat{1.563}$; 95% CI: 1.081–2.262; $P \leq 0.018$) and tumor location (hazard ratio (HR) $\hat{1.788}$; 95% CI: 1.037–3.083; $P \leq 0.036$) were significantly correlated with survival; And there is no significant relationship between low pre-treatment NLR and OS (Table 2).

**Discussion**

The currently study demonstrated that the pre-treatment PLR is an independent prognostic factor for OS. Moreover, patients diagnosed as PSCCE with the low PLR may have superior OS than those with the high PLR. NLR was also correlated with OS and TLC, NLR, as well as PLR were uncorrelated with other clinicopathologic factors. As far as we know, this is the first study to analysis the pre-treatment TLC, NLR and PLR in the prediction of OS in patients with PSCCE.

Recently, the systemic inflammation involved in the process of tumorigenesis [20]. Chronic inflammation trigger molecular cascades in tumor cells, which promote tumor invasion and immune cell evasion [21]. The cancer-related inflammation recruiting T lymphocytes and activating chemokines, forming a immunosuppressive microenvironment, results in the inhibited antitumor immunity followed by which promoting tumor growth and metastasis [20, 22]. Theoretically, after inflammatory cytokines release, the blood cells including neutrophil, lymphocyte, platelet and so on proliferate and differentiate on the instant[23]. It is well known that Neutrophils produce angiogenic cytokines and induce angiogenesis in tumor cells. Neutrophilia is frequently found in cancer patients and is associated with a poor prognosis [24]. In antitumor immune reactions, lymphocytes induce tumor cell apoptosis and suppress tumor cell proliferation and metastasis [25]. Platelet contributes a lot in tumor growth, infiltration and dissemination [26]. The activation of platelets can lead to the release of angiogenic growth factors. Also, their adherence to tumor micro-vessels may enhance the vascular permeability [27]. Many studies have reported that cancer produce interleukin-1, and interleukin-6, granulocyte colony-stimulating factor, as well as tumor necrosis factor-alpha, which may cause neutrophilia. The neutrophilia and thrombocytosis always symbolize a nonspecific
response to the cancer-related inflammation [22, 28]. Above all, systemically inflammatory biomarkers such as the TLC, NLR, and PLR are expected to predict tumor prognosis. Systemic chemotherapy, radiotherapy or post-operative stress response will inevitably influence the count of hematological components. Thus, we assess the potential prognostic value of TLC, NLR and PLR in patients with PSCCE who are newly diagnose.

In previous studies, the utility of inflammation biomarkers as a prognostic factor was investigated in various types of solid tumors. Chen and K. Raghav et al demonstrated high NLR was an independent poor prognostic marker in colorectal cancer [29]. Suzuki R et al identified low TLC and high NLR was associated with inferior survival in the extensive-stage small-cell lung cancer [30]. Luo et al indicated high PLR was an independent prognostic indicator of short OS in patients of early stage non-small cell lung cancer who received SABR [31]. Ye et al reported that both high NLR and PLR were correlated with poor survival in patients of nasopharyngeal carcinoma [32]. A meta-analysis by H. Yodying et al showed elevated pretreatment NLR and PLR were remarkably associated with unfavorable OS of Esophageal Cancer [33]. In patients undergoing surgery for esophageal squamous cell cancer, PLR was revealed as an independent prognostic factor, moreover, a significant different survival was found between patients with high NLR group and low NLR group [34]. The results were similar to our analysis. Likewise, Feng et al suggested that PLR should be superior to NLR as a predictive factor in esophageal squamous cell cancer [35]. In addition, others reported that NLR was regarded as an independent prognostic factor for patients with PSCCE [36]. This is mainly because of different inclusion criteria and a various cutoff value of NLR. In the current study, the patients who underwent surgery preceded by neoadjuvant therapy or only accepted chemoradiotherapy and the patients who diagnosed as distant metastasis were included in the analysis. Wang and Liu et al suggested the cut-off value to be 2.97 by the ROC analysis and the area under the curve was 0.702, with the same methods, the cut-off value of this study was calculated as 2.37 and the area under the curve was 0.713. To date, there is no recognizably optimal cut off point of inflammatory biomarkers. Future researches are needed.

Such limitations that retrospective study, a small sample size and the date from a single institution
must be taken into consideration in our study. In addition, other biomarkers of the systemic inflammatory response, for example C-reactive protein, fibrinogens, albumin were not included in the analysis. Therefore, large, prospective, multi-center and randomized controlled trials are required to confirm our results.

Conclusions
In conclusion, our study suggested that pretreatment inflammatory biomarkers containing NLR, PLR have a relationship with the survival of patients with PSCCE. The PLR could be deemed as a valuable independent prognostic factor of PSCCE. PLR can be considered as a supplement in distinguishing higher risk group of PSCCE, predicting treatment outcomes and tailoring treatment based on risk stratification. Future multi-center and large clinical trials should be carried out to find optimal cut-off values of inflammatory biomarkers, after which, the further exploration of the independent prognosis value of these inflammatory biomarkers could be performed.

Declarations

Compliance with ethical standards

Funding
This work was supported by the National Natural Science Foundation of China [grant no 81372436, 81773230]. The technology open and cooperation program of Henan [grant no 182106000062].

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Affiliate Cancer Hospital of Zhengzhou University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables
## Table 1. Patient characteristics

|                | NLR ≤ 2.37 (n=44, 60.3%) | NLR > 2.37 (n=29, 39.7%) | P Value | PLR ≤ 136.5 (n=38, 52.1%) | PLR > 136.5 (n=35, 47.9%) | P Value |
|----------------|--------------------------|--------------------------|---------|---------------------------|---------------------------|---------|
| **Age (year)** |                          |                          |         |                           |                           |         |
| 60             | 24                       | 15                       | 0.813   | 22                        | 17                        | 0.425   |
| ≥60            | 20                       | 14                       |         | 16                        | 18                        |         |
| **Gender**     |                          |                          |         |                           |                           |         |
| Male           | 31                       | 20                       | 0.892   | 29                        | 22                        | 0.211   |
| Female         | 13                       | 9                        |         | 9                         | 13                        |         |
| **Alcohol abuse** |                      |                          |         |                           |                           |         |
| Yes            | 10                       | 12                       | 0.089   | 12                        | 10                        | 0.78    |
| No             | 34                       | 17                       |         | 26                        | 25                        |         |
| **Tobacco abuse** |                      |                          |         |                           |                           |         |
| Yes            | 23                       | 18                       | 0.409   | 23                        | 18                        | 0.434   |
| No             | 21                       | 11                       |         | 15                        | 17                        |         |
| **Location**   |                          |                          |         |                           |                           |         |
| Upper          | 1                        | 1                        | 0.458   | 0                         | 2                         | 0.206   |
| Middle         | 32                       | 17                       |         | 27                        | 22                        |         |
| Lower          | 11                       | 11                       |         | 11                        | 11                        |         |
| **Length (cm)**|                          |                          |         |                           |                           |         |
| ≤6             | 30                       | 17                       | 0.404   | 28                        | 19                        | 0.084   |
| 6              | 14                       | 12                       |         | 10                        | 16                        |         |
| **TNM stage**  |                          |                          |         |                           |                           |         |
| I              | 4                        | 2                        | 0.233   | 4                         | 2                         | 0.261   |
| II             | 21                       | 11                       |         | 20                        | 12                        |         |
| III            | 4                        | 8                        |         | 5                         | 7                         |         |
| IV             | 15                       | 8                        |         | 9                         | 14                        |         |
| **Treatment modalities** |                |                          |         |                           |                           |         |
| S              | 5                        | 5                        | 0.756   | 6                         | 4                         | 0.083   |
| S+CRT          | 19                       | 11                       |         | 19                        | 11                        |         |
| CRT            | 20                       | 13                       |         | 12                        | 21                        |         |
Table 2 Univariate analysis of prognosis factors of overall survival

| Variable               | Hazard Ratio | 95% CI       |
|------------------------|--------------|--------------|
| Age (year)             | 1.105        | 0.682-1.789  |
| Gender                 | 1.081        | 0.639-1.826  |
| Alcohol abuse          | 0.89         | 0.530-1.493  |
| Tobacco abuse          | 1.134        | 0.701-1.835  |
| Location               | 1.764        | 1.035-3.007  |
| Length(cm)             | 1.672        | 1.004-2.785  |
| AJCC                   | 1.601        | 1.220-2.100  |
| Treatment modalities   | 1.723        | 1.194-2.487  |
| NLR                    | 1.685        | 1.001-2.838  |
| PLR                    | 1.716        | 1.039-2.834  |
| TLC                    | 0.798        | 0.488-1.305  |

Table 3 Multivariate analysis for potential prognostic factors of overall survival

| Variable                | Hazard Ratio | 95% CI       |
|-------------------------|--------------|--------------|
| Treatment modalities    | 1.563        | 1.081-2.261  |
| PLR                     | 1.751        | 1.042-2.945  |
| Location                | 1.788        | 1.037-3.083  |
| Length(cm)              | 1.604        | 0.935-2.750  |

Figures
Figure 1

Kaplan-Meier analysis of NLR for overall survival in patents with PSCCE.
Kaplan–Meier analysis of PLR for overall survival in patents with PSCCE.
Figure 3

Kaplan-Meier analysis of TLC for overall survival in patients with PSCCE.