Impact of Platelets to Lymphocytes Ratio and Lymphocytes during Radical Concurrent Radiotherapy and Chemotherapy on Patients with Nonmetastatic Esophageal Squamous Cell Carcinoma

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Purpose. This study examined the importance of hematological parameters as prognostic markers for people with esophageal cancer receiving radical concurrent chemoradiation.

Methods. 106 patients with esophageal cancer are included in this study. Cox regression analysis, Kaplan-Meier method, and chi-square test were used to analyze our data.

Results. The median follow-up time for patients was 15.5 months (3-55). Univariate and multivariate analyses showed that age, the change of platelet-to-lymphocyte ratio ($\Delta$PLR), and the change rate of circulating lymphocyte count ($\Delta$CLC%) were independent influencing factors of OS and DFS. The patients were grouped according to the median of $\Delta$PLR and $\Delta$CLC%, and analysis showed that a higher $\Delta$PLR and a higher $\Delta$CLC% was related to poor OS and DFS ($P < 0.001$, $P < 0.001$, and $P < 0.001$).

Conclusion. $\Delta$PLR and $\Delta$CLC% are independent factors of OS and DFS, and a lower $\Delta$PLR and $\Delta$CLC% are associated with a better OS and DFS.

1. Introduction

China is one of the countries with an high risk in esophageal carcinoma, and esophageal squamous cell carcinoma (ESCC) accounts for 90% of the national cases [1]. Recently, there are many factors influence clinical outcomes. Among them, TNM stage is more influential and more acceptable [2]. However, the value of TNM stage is unclear. Patients with same TNM stage have various outcomes. Therefore, the new biomarker should be found to predict more precise outcomes for people with ESCC.

Above 70% of esophageal carcinoma patients have malnutrition [3], malnutrition is associated with poor survival, and it increases complications [4]. Studies shown that malnutrition can increase blood system toxicity [5]. Many studies have shown that tumor-related factors including inflammatory factors and nutritional status are also related to the prognosis of tumor patients [6–20]. Evidence has shown that monocytes/lymphocytes ratio (MLR) maybe an effective prognostic indicator of tumors [21, 22]. The study by Xiao et al. [23] also found that the low NLR before neoadjuvant chemoradiation for esophageal cancer...
was significantly associated with postoperative pCR, and the lower PLR after neoadjuvant chemoradiation was also associated with pCR. In addition to NLR, treatment-related lymphopenia is a powerful factor in the poor prognosis of esophageal [14, 15, 24]. Severe lymphopenia during neoadjuvant concurrent radiotherapy and chemotherapy is associated with adverse pathological reactions and recurrence of cancer [25, 26]. These markers are cheap and easy to obtain, so they are expected to act as clinical prognostic factors of cancer.

Now, the relationship between changes of inflammatory factors during CCRT of esophageal cancer and prognosis has rarely been shown. What our study wants to research is to determine the influence of inflammatory factors on the prognosis of patients with esophageal cancer undergoing radical concurrent radiotherapy and chemotherapy.

### 2. Materials and Methods

#### 2.1. Patients

106 newly diagnosed patients with ESCC, who received radical concurrent radiotherapy and chemotherapy (CCT) between January 2016 and December 2017, were included in this study (Figure 1). The 8th edition of AJCC system was used to stage the patient [2]. Patients should have at least two routine blood tests, one should be within 2 weeks before radiotherapy, and the other should be within 1 month after radiotherapy. If patient has undergone surgery and has concomitant diseases that may affect the count of white blood cells, neutrophils, lymphocytes, platelets, etc., including inflammation, autoimmune diseases, history of blood transfusion, liver cirrhosis, spleen disease, and severe hypertension will be excluded. The ethics committee of Liaoning Cancer Hospital permitted this study. We have got the consent.

| Characteristics | Patients (%) | N = 106 |
|-----------------|-------------|---------|
| Sex             |             |         |
| Male            | 102 (96.2)  |         |
| Female          | 4 (3.7)     |         |
| Age (years)     |             |         |
| ≥65             | 32 (30.2)   |         |
| <65             | 74 (69.8)   |         |
| Tumor T stage   |             |         |
| 1               | 2 (1.9)     |         |
| 2               | 35 (33)     |         |
| 3               | 35 (33)     |         |
| 4               | 34 (32.1)   |         |
| Tumor N stage   |             |         |
| 0               | 14 (13.2)   |         |
| 1               | 69 (65.1)   |         |
| 2               | 23 (21.7)   |         |
| Tumor TNM stage |             |         |
| 1               | 6 (5.7)     |         |
| 2               | 54 (50.9)   |         |
| 3               | 46 (43.4)   |         |
| Alcohol consumption |       |         |
| Yes             | 78 (73.6)   |         |
| No              | 28 (26.4)   |         |
| Smoking         |             |         |
| Yes             | 89 (84)     |         |
| No              | 17 (16)     |         |
| Treatment       |             |         |
| Concurrent CRT  | 106 (100)   |         |

**Figure 1:** Overall study flow chart. Abbreviations: OS: overall survival; DFS: disease-free survival; PLR: platelet-to-lymphocyte ratio; CLC: circulating lymphocyte count.
2.2. Radiation. IMRT with 6 megavoltage (MV) photons was given to total patients. The prescribed doses were defined as follows: 60-64 Gy for CTV. Each dose was divided into 30-32 fractions.

2.3. CCT. CCT was cisplatin (75 mg/m$^2$, days 1-3) and fluorouracil (750-1000 mg/m$^2$, CIV24h, d1-4) which was given to all patients. All patients received two cycles of chemotherapy during radiotherapy.

2.4. Inflammatory Factors. Eight parameters are the inflammatory factors, namely, changes during CCRT in the neutrophil-to-lymphocyte ratio ($\Delta$NLR), the PLR ($\Delta$PLR), the platelet ($\Delta$PLT), the circulating lymphocyte count ($\Delta$CLC), change rates during CCRT in the NLR ($\Delta$NLR%), the PLR ($\Delta$PLR%), the platelet ($\Delta$PLT%), the circulating platelet count ($\Delta$CPC%), and the circulating lymphocyte count ($\Delta$CLC%).

NLR1, PLT1, PLR1, and CLC1 are the count before radiotherapy. NLR2, PLT2, PLR2, and CLC2 are the count after radiotherapy (NLR2): $\Delta$NLR = NLR1 – NLR2, $\Delta$NLR% = (NLR1 – NLR2)/NLR1, $\Delta$PLR = PLR1 – PLR2, $\Delta$PLR% = (PLR1 – PLR2)/PLR1, $\Delta$CLC = CLC1 – CLC2, and $\Delta$CLC% = (CLC1 – CLC2)/CLC1.

2.5. Statistics. The Cox proportional hazard regression model was used to analyze the prognostic factors affecting disease-free survival (DFS) and overall survival (OS). Variables with $P < 0.05$ were included in a multivariate analysis. Subgroup analyses were performed using Chi-square test. The rates of DFS and OS were estimated with the Kaplan–Meier method and compared with the log-rank test. All data were analyzed using SPSS 22.0 software package (IBM Corporation, Armonk, NY, USA).

3. Result and Discussion

3.1. Patient Characteristics. 106 patients with ESCC were included in the study, including 102 males (96.2%) and 4
females (3.8%), and received radical concurrent radiotherapy and chemotherapy (CCRT) (Table 1).

3.2. Follow-Up and Hematological Parameters. The median OS of the patients was 15.5 months (3-55 months), the median DFS was 10 months (1-55 months) in our study. By analyzing the relationship between hematological parameters and OS and DFS, we found that there was a significant correlation between ΔPLR and ΔCLC% and OS and DFS. After Cox regression univariate analysis, ΔPLR, ΔPLR%, ΔNLR, ΔNLR%, ΔCLC, and ΔCLC% were the independent factors of OS and DFS, ΔPLR, ΔPLR%, and age are the independent factors of OS (Table 2).

| Factor                  | ΔPLR ≥ 290 (n = 53) | ΔPLR < 290 (n = 53) | P value |
|-------------------------|---------------------|---------------------|---------|
| Sex                     |                     |                     |         |
| Male                    | 50 (94.3%)          | 52 (98.1%)          | 0.618   |
| Female                  | 3 (5.7%)            | 1 (1.9%)            |         |
| Age (years)             |                     |                     |         |
| ≥61                     | 16 (30.2%)          | 16 (30.2%)          | 1       |
| <61                     | 37 (69.8%)          | 37 (69.8%)          |         |
| Tumor T stage           |                     |                     | 0.982   |
| 1                       | 1 (1.9%)            | 1 (1.9%)            |         |
| 2                       | 18 (34%)            | 17 (32.1%)          |         |
| 3                       | 18 (34%)            | 17 (32.1%)          |         |
| 4                       | 16 (30.1%)          | 18 (34%)            |         |
| Tumor N stage           |                     |                     | 0.461   |
| 0                       | 5 (9.4%)            | 9 (17%)             |         |
| 1                       | 37 (69.8%)          | 32 (60.4%)          |         |
| 2                       | 11 (20.8%)          | 12 (22.6%)          |         |
| Tumor TNM stage         |                     |                     | 0.923   |
| 1                       | 3 (5.7%)            | 3 (5.7%)            |         |
| 2                       | 26 (49.1%)          | 28 (52.8%)          |         |
| 3                       | 24 (45.3%)          | 22 (41.5%)          |         |
| Alcohol consumption     |                     |                     | 1       |
| Yes                     | 39 (73.6%)          | 39 (73.6%)          |         |
| No                      | 14 (26.4%)          | 14 (26.4%)          |         |
| Smoking                 |                     |                     | 0.791   |
| Yes                     | 45 (84.9%)          | 44 (83%)            |         |
| No                      | 8 (15.1%)           | 9 (17%)             |         |
| Pre-CLC                 | 1.697 ± 0.688       | 1.854 ± 0.654       | 0.228   |
| Pre-PLT                 | 264 ± 90.731        | 237 ± 74.592        | 0.109   |
| Radiation pneumonia     |                     |                     | 0.027   |
| 0–1                     | 28                  | 42                  |         |
| 2–3                     | 25                  | 11                  |         |
| Radiation esophagitis   |                     |                     | 0.407   |
| 1                       | 27                  | 30                  |         |
| 2                       | 15                  | 18                  |         |
| 3                       | 8                   | 3                   |         |
| 4                       | 3                   | 2                   |         |

All factors such as age, ΔPLR, ΔPLR%, ΔNLR, ΔNLR%, ΔCLC, and ΔCLC% are used into multivariate analysis. Age and ΔPLR were the independent factors of OS (P = 0.028, HR = 0.961; P = 0.030, HR = 0.998), and ΔCLC% was an independent influence factor of DFS (P = 0.024, HR = 1.044) (Table 3). The median was used as the cut-off value for grouping. The high ΔPLR group refer to the absolute value of ΔPLR ≥ 290.72, and the low ΔPLR group was the absolute value of ΔPLR < 290.72. Comparing the clinical characteristics (Table 4) and OS and DFS between the two groups, the OS in the low ΔPLR group was better than the high ΔPLR group (95% CI: 12.838-17.162, P < 0.001) (Figure 2(a)), and the DFS was also better than the high ΔPLR group (95% CI:
The radiation pneumonitis of the low ΔPLR group was better than that of the high ΔPLR group ($P = 0.027$), but there was no significant difference in gender, age, tumor TNM stage, smoking history, drinking history, and radiation esophagitis. The high ΔCLC% group was defined as $Δ\text{CLC}\% \geq 75.51$, and the low ΔCLC% group was defined as $Δ\text{CLC}\% < 75.51$.

The basic clinical characteristics (Table 5) and OS and DFS of the two groups were compared. The basic clinical characteristics in two groups have no difference. The OS with the low ΔCLC% group was better than the high one (95% CI: 12.838, 17.162, $P < 0.001$) (Figure 2(c)), and DFS was also significantly better than high group (95% CI: 8.340, 13.660, <0.001) (Figure 2(d)).

### Subgroup Analysis

We make patients into different subgroups by the T stage (T1-2, T3, and T4), N stage (N0-2 and N3), and age ($\geq 61$ and <61). TNM staging is closely related to the prognosis, and age in this study was an independent prognostic factor of OS.

For age, the OS and DFS were better in the low group than those in the high group (Figure 3).

For patients with T1-4, the OS in the low ΔPLR group were better than the high ΔPLR group ($P = 0.03$, $P < 0.001$, and $P = 0.001$) (Figures 4(a), 4(c), and 4(e)). For patients with N2-3, the OS were better than the high ΔPLR group, too ($P < 0.001$ and $P = 0.008$) (Figures 5(a), 5(c), and 5(e)). For patients with T3-4N1-2, the DFS in the low ΔPLR group were better than in the high ΔPLR group ($P < 0.001$, $P = 0.016$ and $P < 0.001$, $P = 0.022$) (Figures 4(b), 4(d), 4(f), 5(b), 5(d), and 5(f); Table 6).

For patients with T1-4N0-2, the OS in the low ΔCLC% group were better than the high ΔCLC% group ($P = 0.01$, $P < 0.001$, $P < 0.002$, $P = 0.012$, $P < 0.001$, and $P = 0.024$) (Figures 6(a), 6(c), 6(e), 7(a), 7(c), and 7(e)). For patients with T1-4N1-2, the DFS were better in the low ΔCLC%
Radiotherapy is the indispensable treatment methods of esophageal cancer [27]. In our study, we studied 106 patients with ESCC who received radical concurrent radiotherapy and chemotherapy. ∆PLR and ∆CLC% during treatment are related to survival. During radiotherapy, the more ∆PLR and ∆CLC% fluctuate, the poorer patients survive. We included the patient’s age, ∆PLR, ∆PLR%, ∆NLR, ∆NLR%, ∆CLC, ∆CLC%, and other factors into the Cox analysis. ∆PLR and ∆CLC% are, respectively, related to OS and DFS. Grouped by median, the prognosis of the low ∆PLR group and the low ∆CLC% group were better, and the difference between these two groups was obvious. Bone marrow suppression was a common side effect of concurrent radiotherapy and chemotherapy for esophageal cancer. When bone marrow suppression occurs, hematopoietic stem cells cannot produce adequate number of blood cells who have normal function, resulting in complications such as anemia, infection, and bleeding; these complications lower the survival of the patient severely. Several studies show that inflammation factors in the blood (for example, NLR, Table 5: Comparison of clinical baseline data between ∆CLC% ≥ 75 and ∆CLC% < 75.

| Factor              | ∆CLC% ≥ 75 (n = 52) | ∆CLC% < 75 (n = 54) | P value |
|---------------------|---------------------|---------------------|---------|
| Sex                 |                     |                     | 0.672   |
| Male                | 51 (96.2%)          | 51 (96.2%)          |         |
| Female              | 2 (3.8%)            | 2 (3.8%)            |         |
| Age                 |                     |                     | 0.768   |
| ≥65                 | 15 (28.3%)          | 17 (32.1%)          |         |
| <65                 | 37 (71.7%)          | 37 (67.9%)          |         |
| Tumor T stage       |                     |                     | 0.420   |
| 1                   | 2 (3.8%)            | 0 (0%)              |         |
| 2                   | 15 (28.8%)          | 20 (37%)            |         |
| 3                   | 17 (32.7%)          | 18 (33.3%)          |         |
| 4                   | 18 (34.6%)          | 16 (29.6%)          |         |
| Tumor N stage       |                     |                     | 0.258   |
| 0                   | 4 (7.7%)            | 9 (18.5%)           |         |
| 1                   | 36 (69.2%)          | 32 (61.1%)          |         |
| 2                   | 12 (23.1%)          | 12 (20.4%)          |         |
| Tumor TNM stage     |                     |                     | 0.674   |
| 1                   | 2 (3.8%)            | 4 (7.4%)            |         |
| 2                   | 26 (50%)            | 28 (51.9%)          |         |
| 3                   | 24 (46.2%)          | 22 (40.7%)          |         |
| Alcohol consumption |                     |                     | 0.768   |
| Yes                 | 38 (73.6%)          | 40 (73.6%)          |         |
| No                  | 14 (26.4%)          | 14 (26.4%)          |         |
| Smoking             |                     |                     | 0.763   |
| Yes                 | 44 (84.9%)          | 45 (83%)            |         |
| No                  | 8 (15.1%)           | 9 (17%)             |         |
| Radiation pneumonia |                     |                     | 0.370   |
| 0                   | 1                   | 0                   |         |
| 1                   | 30                  | 39                  |         |
| 2                   | 18                  | 13                  |         |
| 3                   | 3                   | 2                   |         |
| Radiation esophagitis|                    |                     | 0.315   |
| 1                   | 24                  | 33                  |         |
| 2                   | 18                  | 15                  |         |
| 3                   | 6                   | 5                   |         |
| 4                   | 4                   | 1                   |         |

4. Discussion

Radiotherapy is the indispensable treatment methods of esophageal cancer [27]. In our study, we studied 106 patients with ESCC who received radical concurrent radiotherapy and chemotherapy. ∆PLR and ∆CLC% during treatment are related to survival. During radiotherapy, the more ∆PLR and ∆CLC% fluctuate, the poorer patients survive. We included the patient’s age, ∆PLR, ∆PLR%, ∆NLR, ∆NLR%, ∆CLC, ∆CLC%, and other factors into the Cox analysis. ∆PLR and ∆CLC% are, respectively, related to OS and DFS. Grouped by median, the prognosis of the low ∆PLR group and the low ∆CLC% group were better, and the difference between these two groups was obvious. Bone marrow suppression was a common side effect of concurrent radiotherapy and chemotherapy for esophageal cancer. When bone marrow suppression occurs, hematopoietic stem cells cannot produce adequate number of blood cells who have normal function, resulting in complications such as anemia, infection, and bleeding; these complications lower the survival of the patient severely. Several studies show that inflammation factors in the blood (for example, NLR,
lymphocyte count, and neutrophil count) can predict the prognosis of patients with a variety of tumors [28–31]. Lymphocytes are related to host immunity. Lymphopenia has a negative impact on cellular immunity [32]. Increasing evidence shows that lymphopenia during CCRT in cancer patients is related to tumor prognosis and pathological reactions [33–35]. In all kinds of cancers (including EC), treatment-induced lymphopenia has a close connection with adverse outcomes [14, 36–40].

Platelets contribute to inflammation and immunomodulatory processes. It is reported that the platelet count in cancer patients will increases by about 10–57% [41]. Platelets by serving as a barrier to immune escape promote development of tumor, which can lead to abnormal vasculature and release the secreted factors [1, 42, 43].

Our study believes that age and ΔPLR are independent influencing factors of OS, and the OS in the low ΔPLR group is better than the high one (95% CI: 12.838–17.162, P < 0.001); and ΔCLC% is an independent influencing factor of DFS; the low ΔCLC% group had better DFS (95% CI: 8.340–13.66, P < 0.001). The study of Liang et al. is consistent with ours, in ESCC patients receiving radiotherapy or chemoradiation, NLR, ALC before treatment, NLR and ΔNLR after treatment are all significant for the short-term survival of patients [44]. Research on limited-stage small-cell lung cancer by Yu et al. also showed that CLC and PLR are related to prognosis, and higher NLR and PLR are related to decreased survival rate [31]. Research included patients with esophageal and junctional adenocarcinoma (OJA) treated with neoadjuvant chemotherapy shows that PLR is related to poor OS and DFS [45]. A 2015 study that includes 86 esophageal cancer patients who have CRT have the same idea with our study. The high PLR and NLR are related to inferior survival [46].

**Figure 3:** Kaplan-Meier plots of OS (a) and PFS (b) among patients whose age ≥ 61 stratified by ΔPLR and OS (c) and PFS (d) among patients whose age < 61 stratified by ΔPLR.
Figure 4: Kaplan-Meier plots of OS (a) and PFS (b) among patients with T1-2, OS (c) and PFS (d) among patients with T3, and OS (e) and OS (f) with T4 stratified by ΔPLR.

Figure 5: Kaplan-Meier plots of OS (a) and PFS (b) among patients with N0, OS (c) and PFS (d) among patients with N1, and OS (e) and OS (f) with N2 stratified by ΔPLR.
In our study, we also found that ΔPLR is related to the pulmonary side effects of patients after CCRT. In the high ΔPLR group, there were 25 patients with radiation pneumonitis 2 and above after CCRT, while the low ΔPLR group had 11 patients; the high ΔPLR patients were more possibly to develop radiation pneumonitis ($P = 0.027$) (Table 4). We temporarily do not found research on the relationship between radiation pneumonitis and PLR. A study by Dong et al.

| Factor | ΔPLR ≥ 290 (n = 53) | ΔPLR < 290 (n = 53) | $\chi^2$ | $P$ value | ΔPLR ≥ 290 (n = 53) | ΔPLR < 290 (n = 53) | $\chi^2$ | $P$ value |
|--------|----------------------|----------------------|----------|-----------|----------------------|----------------------|----------|-----------|
| Age ≥61 | 27                   | 27                   | 23.3     | <0.001    | 27                   | 27                   | 21.244   | <0.001    |
| <61    | 26                   | 26                   | 25.637   | <0.001    | 26                   | 26                   | 8.895    | 0.003     |
| Tumor T stage 1–2 | 19                   | 18                   | 9.001    | 0.003     | 19                   | 18                   | 0.091    |           |
| 3      | 18                   | 17                   | 24.484   | <0.001    | 18                   | 17                   | 29.506   | <0.001    |
| 4      | 16                   | 18                   | 11.893   | 0.001     | 16                   | 18                   | 5.858    | 0.016     |
| Tumor N stage 0 | 5                    | 9                    | 1.847    | 0.174     | 5                    | 9                    | 0.318    | 0.573     |
| 1      | 37                   | 31                   | 27.019   | <0.001    | 37                   | 31                   | 22.935   | <0.001    |
| 2      | 11                   | 12                   | 7.111    | 0.008     | 11                   | 12                   | 5.209    | 0.022     |

Figure 6: Kaplan-Meier plots of OS (a) and PFS (b) among patients with T1-2, OS (c) and PFS (d) among patients with T3, and OS (e) and OS (f) with T4 stratified by ΔCLC%.
believes that PLT is related to the occurrence of esophageal fistula during CCRT. Patients with PLT > 153 are more likely to develop fistula than those with PLT ≤ 153 (P < 0.001); the study included 379 patients with esophageal cancer; analyzed the relationship between NLR, PLR, MLR, and esophageal fistula; and finally found that PLR is an independent predictor of EC patients receiving CCRT [47]. Unfortunately, this study did not find a correlation between other inflammatory indicators and radiation esophagitis. It may be related to the fact that fewer patients were included in this study.
5. Conclusion

Our study found that age and ΔPLR are independent factors of OS in patients with ESCC treated with CCRT, and ΔCLC% is an independent factor of DFS. And we compared the DFS and OS with ΔPLR and ΔCLC% and found that lower ΔPLR and ΔCLC% is associated with a better survival. And T3-4N1-2 patients in the low ΔPLR group and low ΔCLC% group have greater survival benefit. Nevertheless, these results are preliminary and need to be validated. The large-scale prospective clinical trials are needed to verify the result.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interests.

Authors’ Contributions

Yaotian Zhang and Ning Han contributed equally to this work.

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