Prognostic Value of Lymphocyte-to-Monocyte Ratio in Locally Advanced and Metastatic Esophageal Cancer

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Abstract:
Objective: To explore the prognostic value of pre-treatment lymphocyte-to-monocyte ratio (LMR) in peripheral blood for patients with locally advanced and metastatic esophageal cancer.
Methods: A retrospective analysis was conducted on the clinical data of 155 patients with locally advanced or metastatic esophageal cancer who received chemoradiotherapy or chemotherapy alone at the Cancer Hospital of Shantou University Medical College from January 2008 to December 2012. The optimal cutoff value for LMR was determined using receiver operating characteristic (ROC) curves. Survival curves were plotted using the Kaplan-Meier method, and univariate analysis was performed using the Log-rank test. Multivariate analysis was carried out using the Cox proportional hazards regression model, and stratified analyses were also conducted.
Results: The optimal cutoff value for LMR was 3.06, with a sensitivity of 69.2% and a specificity of 62.9% in predicting overall survival. In the low-LMR group (<3.06), the median overall survival was 11.0 months, significantly shorter than the 17.0 months observed in the high-LMR group (⩾3.06) (P<0.001). Multivariate analysis revealed that LMR, tumor location, and TNM stage were independent prognostic factors for esophageal cancer patients (P<0.001). Stratified analysis showed that, across various subgroups defined by tumor stage, histological type, tumor location, and treatment regimen, the low-LMR group consistently had significantly poorer outcomes compared to the high-LMR group (P<0.05).
Conclusion: Pre-treatment peripheral blood LMR is an effective indicator for assessing the prognosis of patients with locally advanced and metastatic esophageal cancer; a low LMR suggests a poorer prognosis.

Keywords: Lymphocyte-to-monocyte ratio; Esophageal cancer; Prognosis; Inflammation; Immunity

1. Introduction

Esophageal cancer is a common gastrointestinal malignancy worldwide, ranking 11th in incidence and 7th in mortality among all cancers, imposing a heavy disease burden [1]. In China, esophageal cancer is predominantly squamous cell carcinoma, with most cases occurring in the

middle thoracic segment. Although surgical resection remains the standard curative treatment, even after radical surgery, long-term survival rates remain low. Postoperative recurrence and distant metastasis are the primary factors contributing to poor prognosis. Currently, the prognosis assessment for esophageal cancer relies mainly on the traditional TNM staging system, which has limited predictive power and insufficient precision in risk stratification. Therefore, it is of great significance to explore new, effective prognostic biomarkers.

Inflammation and immune responses in the tumor microenvironment play a crucial role in tumor initiation and progression [2,3]. In recent years, peripheral blood indicators reflecting inflammatory and immune status [4,5], such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have attracted considerable attention due to their ease of acquisition, low cost, and convenience for dynamic monitoring. Among these, LMR was first demonstrated to have prognostic value in hematologic malignancies; subsequently, numerous studies have shown that a low LMR is associated with poor prognosis in various solid tumors, including lung cancer, breast cancer, and colorectal cancer [6-8].

Currently, there are relatively few studies on the prognostic value of LMR in esophageal cancer, and most of these studies have focused on patients who underwent surgery. However, more than 60% of esophageal cancer patients are diagnosed at a locally advanced stage or with distant metastasis, thereby losing the opportunity for surgical intervention. For such patients, concurrent chemoradiotherapy or palliative chemotherapy represents the primary treatment approach. Given this context, the present study retrospectively analyzed clinical data from 155 patients with locally advanced or metastatic esophageal cancer who received either chemoradiotherapy or chemotherapy alone, aiming to explore the correlation between pre-treatment peripheral blood LMR levels and prognosis in esophageal cancer patients undergoing palliative treatment.

2. Materials and Methods

2.1 Study Subjects

We retrospectively collected clinical data from 155 patients with locally advanced and metastatic (stages II, III, and IV) esophageal cancer who were hospitalized at the Cancer Hospital of Shantou University Medical College from January 2008 to December 2012. All patients had been pathologically confirmed and had undergone either chemotherapy or chemoradiotherapy. Staging was performed according to the seventh edition (2009) of the International Staging System for Esophageal Cancer.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Pathology confirmed diagnosis of esophageal squamous cell carcinoma or adenocarcinoma; (2) Complete clinical data, including gender, age, tumor location, TNM stage, and pre-treatment peripheral blood lymphocyte and monocyte counts; (3) TNM stage II, III, or IV, with non-surgical treatment as the primary approach; (4) Undergoing chemotherapy or chemoradiotherapy; (5) ECOG performance status 0–1, with no contraindications to radiotherapy or chemotherapy.

Exclusion criteria: (1) No complete blood count performed within 1 week prior to treatment, or incomplete data; (2) Presence of factors that may affect the complete blood count results, such as acute infection, pregnancy, hematological disorders, or autoimmune diseases; (3) Coexisting other malignancies; (4) Coexisting severe organ dysfunction; (5) Missing follow-up data.

2.3 Follow-up

Telephone follow-up was used, and overall survival (OS) was defined as the time from diagnosis to death or the date of the last follow-up. The follow-up cutoff date was December 31, 2015. A total of 132 cases (85.2%) had died, while 23 cases (14.8%) were still alive, resulting in a 100% follow-up rate.

2.4 Statistical Analysis

Statistical analyses were performed using SPSS 25.0 software. The optimal cutoff value for LMR was determined by means of the ROC curve. Chi-square test was used to compare categorical variables across groups. Survival analysis was conducted using the Kaplan-Meier method and Log-rank test, while multivariate analysis was carried out using the Cox proportional hazards model. A P-value less than 0.05 was considered statistically significant.

3.Results

3.1 Clinical and Pathological Characteristics of Patients

Among the 155 patients, 136 were male (87.7%) and 19 were female (12.2%); the median age was 58 years. There were 112 cases of squamous cell carcinoma (72.3%) and 43 cases of adenocarcinoma (27.7%). Stage II accounted for 11 cases (7.1%), stage III for 31 cases (20.0%), and stage IV for 113 cases (72.9%). Of these patients, 130 (83.9%) received chemotherapy alone, while 25 (16.1%) underwent chemoradiotherapy.

3.2 Optimal Cutoff Value for LMR

The ROC curve analysis (Figure 1) showed that the area under the curve (AUC) for LMR in predicting overall survival was 0.678 (95% CI: 0.577–0.778). Based on the Youden index, the optimal cutoff value for LMR was determined to be 3.06, with a sensitivity of 69.2% and a specificity of 62.9%. There were 88 patients in the low-LMR group (<3.06) and 67 patients in the high-LMR group (⩾3.06).

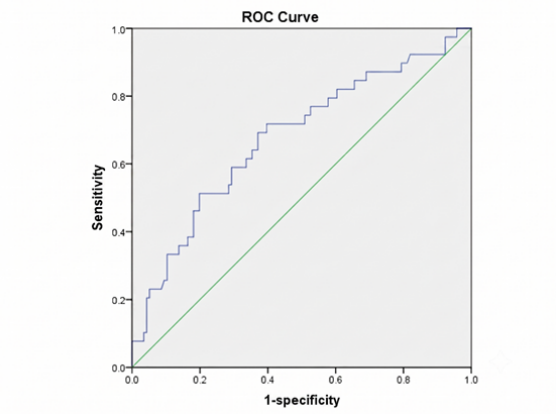

Figure 1: ROC curve for OS was plotted to verify the optimum cut-off value for LMR.

3.3 Relationship between LMR and Clinical Pathological Features

There were no statistically significant differences between the low-LMR group and the high-LMR group in terms of gender, age, tumor location, treatment regimen, or pathological type. However, there was a significant difference in TNM staging (P=0.022), with the low-LMR group having more advanced tumor stages.

3.4 Univariate and Multivariate Survival Analysis

In the low LMR group, the median OS was 11.0 months (95% CI: 9.62–12.38), whereas in the high LMR group it was 17.0 months (95% CI: 13.74–20.26) (Figure 2). The difference was statistically significant (P < 0.001). The 1-year, 2-year, and 3-year cumulative survival rates in the low LMR group were 43.2%, 4.5%, and 0%, respectively, while in the high LMR group they were 79.1%, 22.4%, and 3.0%, respectively (P < 0.001).

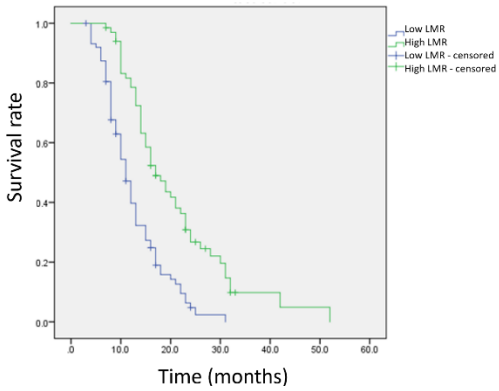

Figure 2: Kaplan-Meier survival curve stratified by LMR.

Univariate analysis showed that LMR, tumor location, TNM stage, and whether radiotherapy was administered were all associated with median OS in patients (P < 0.05). Multivariate Cox regression analysis (Table 1) revealed that LMR (HR = 0.379, 95% CI: 0.251 – 0.572, P < 0.001), tumor location (HR = 0.243, 95% CI: 0.123–0.480, P < 0.001), and TNM stage (HR = 9.394, 95% CI: 2.678–32.956, P < 0.001) were independent prognostic factors for esophageal cancer patients.

Table 1: Multivariate analyses of OS in esophageal cancer patients.

Prognostic Factor	HR (95%CI)	P value
Tumor location	0.243(0.123-0.480)	<0.001
Radiotherapy (yes vs. no)	1.421(0.843-2.397)	0.188
Chemotherapy Regimen	0.807(0.483-1.349)	0.414
TNM stage	9.394(2.678-32.956)	<0.001
LMR	0.379(0.251-0.572)	<0.001

3.5 Stratified Analysis

Stratified analysis revealed that, in subgroups defined by different tumor stages (stage II/III vs. stage IV), different histological types (squamous cell carcinoma vs. adenocarcinoma), mid- and lower-esophageal cancers, different chemotherapy regimens (platinum-containing vs. platinum-free), and whether or not radiotherapy was combined, patients in the low LMR group had significantly shorter mean survival times than those in the high LMR group (P < 0.05). In the subgroup of upper-esophageal cancer, there was no statistically significant difference between the two groups (P = 0.327), which may be attributable to the small sample size (only 16 cases).

4. Discussion

Esophageal cancer is a common malignant tumor in China, and most patients are diagnosed at an advanced stage, resulting in a poor prognosis. The TNM staging system is an important predictor

of prognosis for esophageal cancer; however, it still has certain limitations. In recent years, indicators reflecting inflammatory and immune status have shown great potential in the assessment of tumor prognosis.

This study included 155 patients with locally advanced and metastatic esophageal cancer who received non-surgical treatment. We found that the pre-treatment peripheral blood LMR was an independent prognostic factor. The median OS in the low-LMR group was significantly shorter than that in the high-LMR group (11.0 months vs. 17.0 months, P<0.001). Stratified analysis further confirmed that, regardless of tumor stage, histological type, tumor location, or treatment regimen, a low LMR consistently indicated a poorer prognosis. These findings are consistent with numerous previous studies. Huang et al. [9] were the first to report that preoperative LMR in esophageal cancer is associated with prognosis; similarly, studies by Han et al. [10] and Hirahara et al. [11] also reached comparable conclusions.

From a biological perspective, lymphocytes are the core effector cells of the body's anti-tumor immune response. CD8+ cytotoxic T cells, CD4+ helper T cells, and NK cells play crucial roles in recognizing and eliminating tumor cells. A reduction in peripheral blood lymphocytes may reflect a weakened anti-tumor immune response and is associated with poor prognosis in various malignancies [12,13]. Monocytes and their differentiated counterparts, tumor-associated macrophages (TAMs), on the other hand, exert pro-angiogenic, immunosuppressive, and prometastatic effects within tumor microenvironment [14]. Shibutani et al. [15] found that peripheral blood monocyte count is closely associated with the density of TAM infiltration in tumor tissues. Therefore, the LMR comprehensively reflects the balance between lymphocyte-mediated antitumor immunity and monocyte-mediated immunosuppression; a low LMR suggests a predominance of immunosuppression and is associated with a poorer prognosis.

This study has certain limitations: it is a retrospective, single-center study conducted on a relatively small sample size; the follow-up indicators do not include progression-free survival; and tumor tissues were not examined for TILs and TAMs to validate the correlation between peripheral blood markers and the tumor microenvironment status. Nevertheless, the findings of this study provide supporting evidence for the prognostic value of LMR in patients with locally advanced or metastatic esophageal cancer.

5. Conclusion

(1) Among patients with locally advanced or metastatic esophageal cancer who received non-surgical treatment, a low LMR (<3.06) before treatment was associated with shorter overall survival. LMR is an independent prognostic factor for patients with esophageal cancer.

(2) In subgroups defined by different tumor stages, pathological types, mid-to-lower esophageal cancer, and various treatment regimens, the low-LMR group consistently showed significantly poorer prognosis than the high-LMR group.

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