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Research Article

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Prognostic Value of Hematologic Markers in Esophageal Squamous Cell Carcinoma Treated by Curative Esophagectomy

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Abstract Objective: To investigate the prognostic values of hematologic markers, consisting of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR), in patients with esophageal squamous cell carcinoma (ESCC) by curative esophagectomy.

Methods : A total of 227 patients with ESCC receiving standard curative esophagectomy from 2010 to 2012 were retrospectively analyzed. These patients were grouped for further analysis according to the median values of NLR, PLR and MLR. Kaplan–Meier method was adopted to calculate and compare the progression-free survival (PFS) with these parameters. The Cox proportional hazards model was used to carry out univariate and multivariate analyses.

Results: In univariate analysis, the following factors were significantly associated with poor PFS: N stage, TNM stage, NLR, PLR and MLR (all $p<0.05$). Furthermore, multivariate Cox regression analysis showed that NLR ($P = 0.012$) and N stage ($P = 0.035$) were independent prognostic factors for PFS.

Conclusion: This study demonstrated that NLR was promising as predictive marker for predicting clinical outcomes in patients with ESCC receiving surgery.

Keywords Esophageal cancer, Surgery, Hematological markers, Prognosis

Introduction

Esophageal cancer (EC) is the eighth common malignancy and the fifth common cause of cancer death all over the world [1]. China accounts for about half of the world's total cases of EC, and the number of newly diagnosed EC is about 250,000 and dramatically increasing each year in China [2]. Esophageal squamous cell carcinoma (ESCC) is the most lethal pathological type in China [3], in contrast to the predominance of adenocarcinoma in the Western countries [4]. Although the progress in the multi-disciplinary therapy, surgical resection remains the best curative method for non-metastatic patients. Nevertheless, most of the patients developed local relapse or distant metastasis after esophagectomy, so the 5-year overall survival (OS) rate is still low, and only ranges from 26.2% to 49.4% [5]. Therefore, it is critical to search biomarkers for distinguishing patients who are likely to develop recurrence following surgery from other ones.

It is generally recognized that the survival of cancer patient is determined not only by tumor itself, but also by host-related inflammatory status. Some trials reported a close relationship between systemic hematological markers and prognosis in human malignancies, including EC [6-10], and the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte–monocyte ratio (LMR) have been studied in variety of malignancies [11-16]. These markers, which can be measured easily and inexpensively, are widely used in clinical practice and may contribute to predict an unfavorable prognosis in patients with EC [17-18]. This

correlation has been well documented in other types of human malignancies, but the hematological markers have rarely been studied in ESCC patients. Therefore, The purpose of this study was to investigate the prognostic value of these markers, including NLR, PLR and MLR.

Materials and Methods

Patients

Between January 2010 and December 2012, a total of 227 esophageal carcinoma patients who underwent esophagectomy at the Department of Thoracic Surgery, Affiliated Taixing People's Hospital of Yangzhou University, were enrolled in this retrospective study. The inclusion criteria were as follows: (1) curative esophagectomy with R0 resection and no presence of preoperative adjuvant therapy. (2) histologically proven ESCC (3) normal liver and renal function, without severe dysfunction of important organs, and overall performance status of 0 or 1; (4) complete record of pretreatment hematological variables; (5) no presence of distant metastasis, (6) without second primary cancers before or at diagnosis. (7) The patients with complete follow-up time, The hematological and laboratory parameters were routinely examined in all patients within 1 week prior to surgery. All patients were staged according to the American Joint Committee on Cancer staging manual (seventh edition, 2010) [19].

Hematological parameters calculation and follow up

The following pretreatment hematological parameters were collected within 1 week prior to the initial treatment: neutrophil count, lymphocyte count, monocyte count, and platelet count. The NLR, PLR, and MLR were calculated by division of the absolute values of the corresponding hematological parameters.

After the completion of treatment, all patients were asked to return to the hospital for examination every 3 months for the first years, every 6 months for the next 2 years, and then annually. The duration of follow-up was calculated from the day of treatment to the day of death or May 2017.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Science (SPSS for Windows, version 17.0, SPSS Inc.,Chicago, IL) program. NLR, PLR and MLR were divided into high/low group by corresponding median value. PFS was defined as the length of time after surgery during which the patient survived with no sign of tumor recurrence.The Kaplan–Meier method and log-rank tests were used for 5-year PFSanalyses. Univariate and multivariate analyses of Cox regression proportional hazard model were used to evaluate the influence of each variable on PFS with the enter method. Hazard ratio (HR) with 95% confidence interval (CI) was used to quantify the strength of the association between predictors and survival. A 2-tailed p-value ≤ 0.05 was considered statistically significant.

Results

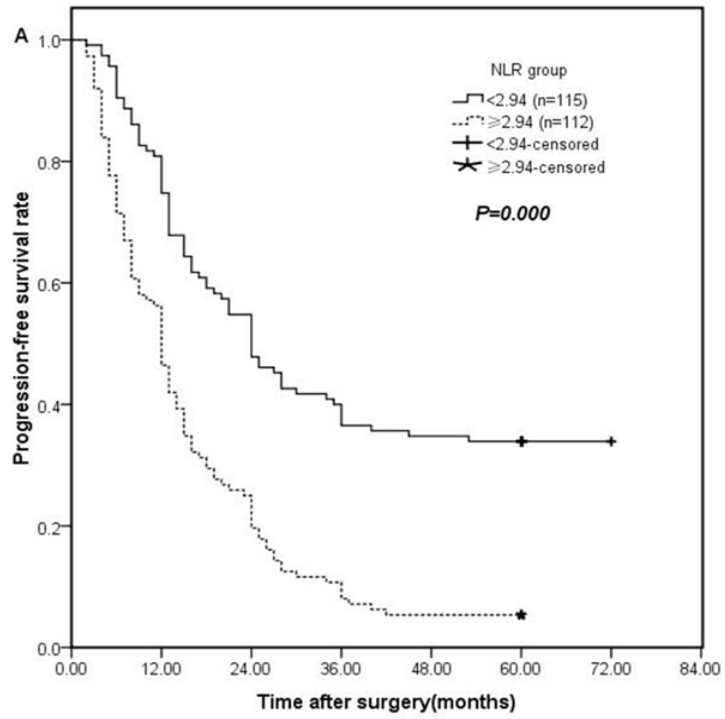
Clinicopathological characteristics of patients

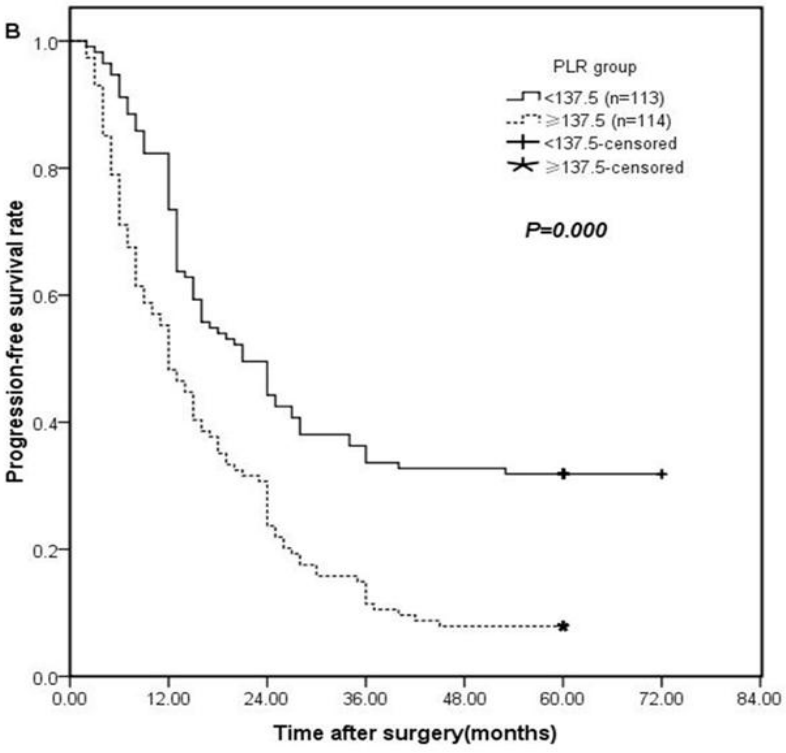
Among the 227 patients, 54 (24%) were female and 173 (76%) were male. The median age prior to surgery was 62 years (range 40–82 years). The location of the tumors mostly occurred in the middle third (149/227, 65%) and the lower third (69/227, 30%) of the esophagus. In stage III or lymph node-positive stage II–III ESCC patients receiving postoperative chemoradiation; According to this criteria, in our cohort, 61 (27%) underwent esophagectomy alone, 166 (73%) received postoperative chemotherapy or radiotherapy. None of these patients received neoadjuvant therapy before surgery. The median follow-up period was 37 months (range 6–72 months). During the follow-up time, 159 (70%) occurred in tumor recurrences, (30 cases with surgical anastomosis recurrences, 79 cases with locally regional lymph node metastasis, and 50 cases with distant metastasis).

PFS according to NLR, PLR and MLR

For all patients, the median PFS time was 15 months (CI: 11.924-18.076); The PFS rates at the 1-, 3- and 5-year period were 60.8%, 33.9% and 19.8%, respectively; As is shown in Figure 1, in the NLR < 2.94 group, the 1-, 3-

, and 5-year PFS rates were 74.8%, 36.5% and 8.0% separately, while in the NLR ≥ 2.94 group, the PFS rates were 46.4%, 19.6% and 5.4% respectively(see Figure 1A. χ^2=39.709, *P*=0.000). In the PLR < 137.5 group, the 1-, 3-, and 5-year PFS rates were 73.5%, 33.6% and 31.9%, and in the PLR ≥ 137.5 group, the PFS rates were 48.2%, 11.4% and 7.9% (see Figure 1B. χ^2=23.819, *P*=0.000). In the MLR < 0.27 group, the 1-, 3-, and 5-year PFS rates were 71.4%, 34.8% and 32.1%, while in the MLR ≥ 0.27 group, the PFS rates were 50.4%, 10.4% and 7.8% (see Figure 1C. χ^2=10.978, *P*=0.001).





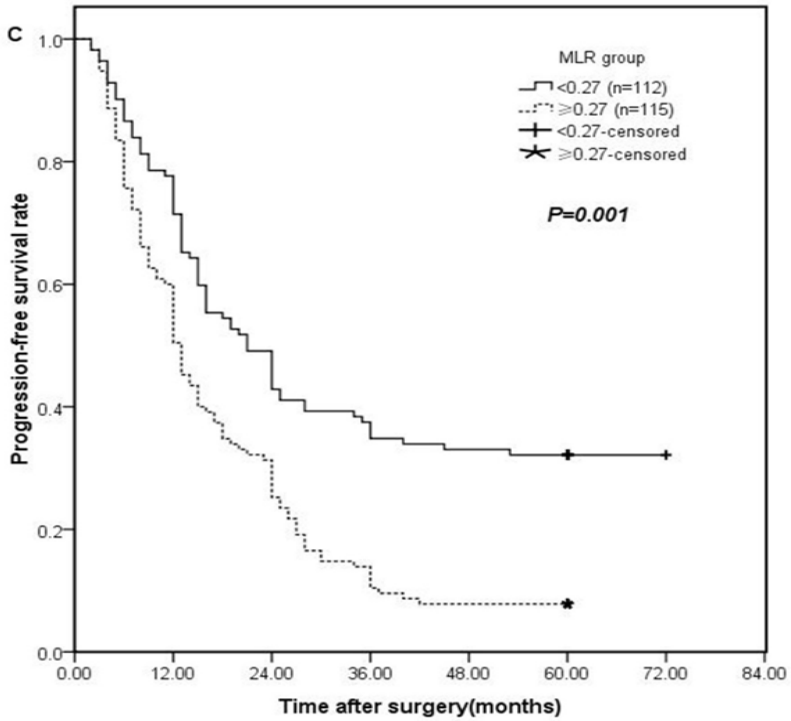


Figure 1: Kaplan–Meier survival curves for progression-free survival (PFS) in patients with ESCC after surgery. (A) 1-, 3-, and 5-year PFS of patients with NLR <2.94 were longer than those with NLR ≥ 2.94. (P= 0.000, log-rank). (B) 1-, 3-, and 5-year PFS of patients with PLR <137.50 were obvious different from those with PLR ≥ 137.50. (P = 0.006, log-rank). (C) 1-, 3-, and 5-year PFS of patients with MLR<0.27 were longer than those with MLR.≥0.27 (P = 0.001, log-rank).

Univariate and multivariate survival analyses

The results of univariate analysis of the factors related to PFS were shown in Table 1. In univariate analysis, the following factors were significantly associated with poor PFS: N stage, TNM stage, NLR, PLR and LMR(all *P*<0.05). Table 2 showed the results of multivariate Cox regression analysis of the factors related to PFS. This analysis showed that NLR (HR = 1.823; 95% CI 1.263-2.632; *P* = 0.012)and N stage (HR =1.350; 95% CI 1.121-1.696; *P* = 0.035) were independent prognostic factors for PFS in patients with ESCC after surgery.

Table 1: Univariate analysis of survival of esophageal squamous cell carcinoma treated by surgery (n=227)

Factors	**Progression-free survival**		
	HR	***95%CI***	***P-value***
Age(<62/≥62)	0.854	0.636-1.146	0.293
Sex(male/female)	1.291	0.909-1.835	0.154
Location(middle/lower)	1.143	0.834-1.566	0.405
Differential grade (Well +middle/poor)	0.816	0.591-1.125	0.214
T stage(T1+T2/T3+T4)	1.179	0.876-1.587	0.278
N stage(N0/N1+N2)	1.418	1.016-1.763	0.035
TNM stage(I+II/ III+IV)	1.468	1.101-1.845	0.041
NLR(< 2.6/≥2.6)	2.482	1.838-3.352	0.000
PLR(< 143.1/≥143.1)	2.019	1.501-2.716	0.002
LMR(<3.48/≥3.48)	1.943	1.442-2.618	0.018

Table 2: Multivariate analysis of survival of esophageal squamous cell carcinoma treated by surgery (n=227)

Factors	Progression-free survival		
	HR	***95%CI***	***P-value***
TNM stage	0.994	0.727-1.359	0.971
N stage	1.350	1.121-1.697	0.035
NLR	1.823	1.263-2.632	0.012
PLR	1.402	0.990-1.980	0.057
MLR	1.005	0.684-1.477	0.978

Discussion

Systemic inflammatory response is common in many cancers and is associated with tumor progression. In this clinical study, we investigated the significance for the survival prognosis of pre-treatment NLR, PLR and MLR in patients with ESCC treated with surgery. This study indicated that NLR and N stage were independent risk factors for PFS.

In the case of hematologic markers, a high NLR was significantly associated with poor PFS in our ESCC patients receiving curative esophagectomy with R0 resection. Since the pathologist Rudolf Virchow first discovered leukocytes in malignant tissue specimens about 150 years ago [20], the prognostic values of pre-treatment hematologic markers have been highlighted. Currently, compelling evidences suggested that there were statistically significant difference in the survival rates grouped by NLR, PLR and LMR levels for several types of malignancies [11-16], including ESCC[17-18]. A previous study suggested that pretreatment elevated NLR were independent factors for poor prognosis in SCLC patients. High PLR was associated with poor PFS, but it was not an independent prognostic factor for PFS and OS [21]. Another study indicated that systemic inflammation represented by NLR and PLR predicted the OS of patients with advanced biliary tract cancer who received palliative chemotherapy [22]. However, the current study also showed that hematologic parameters were controversial in the prediction of prognosis in esophagus carcinoma. Duan et al [23] reported that preoperative serum NLR is a useful prognostic marker to complement TNM staging for operable ESCC patients, particularly in patients with stage IIIA disease; On the contrary, Rashid et al [24] found that NLR did not prove to be a significant predictor of number of involved lymph nodes, disease recurrence or death. Furthermore, survival time was not significantly different between patients with high (≥ 3.5) or low (< 3.5) NLR ($p = 0.49$). In our present study, the results indicate that pre-treatment NLR is an independent prognostic factor for PFS in ESCC following surgery, nevertheless, there are no prognostic associations found for PLR and MLR in multivariate analyses; This controversy might result from the particular characteristics of the cohort in terms of tumor pathological type; It is generally accepted that ESCC is the most lethal pathological type in China [3], in contrast to the predominance of adenocarcinoma in the Western countries [4].

The limitations of this study are as follows: First, not all hematologic markers of inflammation were used in the analysis, because some biomarkers were not routinely examined, such as C-reactive protein [25-26] and fibrinogen [27] Second, it was a single-institution, retrospective study. Third, 227 patients with ESCC were enrolled in this study and the sample size is relatively small and may be insufficient to strengthen our results.

In conclusion, this study demonstrated that NLR was promising as a predictive marker for predicting clinical outcomes in patients with ESCC receiving surgery. However, considering the retrospective nature of this study, large-scaled prospective trials are still warranted to verify our results.

Conflicts of Interest

The authors declare no competing financial interests.

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