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Platelet to lymphocyte ratio is a predictive marker of prognosis and therapeutic effect of postoperative chemotherapy in non-metastatic esophageal squamous cell carcinoma

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ABSTRACT

Increasing evidence has indicated that inflammatory biomarkers, including the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and prognostic nutritional index (PNI), can be used as prognostic indicators in esophageal squamous cell carcinoma (ESCC). However, the best predictor for prognosis in ESCC remains controversial. Few studies have focused on the association between inflammatory biomarkers and postoperative chemotherapy. A cohort of 515 non-metastatic ESCC patients was retrospectively reviewed. Harrell's concordance index (c-index) was used to identify the optimal cut-off values of the inflammatory markers, and their prognostic value was compared. Cox multivariate analysis indicated that, among these inflammatory biomarkers, PLR (≥133 vs. < 133) was the only independent prognostic factor for poor OS [hazard ratio = 1.370, 95% confidence intervals = 1.076–1.745, $p = .011$]. The c-index values of PLR were higher compared with NLR and PNI. For patients with PLR < 133, the surgery plus chemotherapy group had significantly longer OS than the surgery group alone ($p = .004$), but the significant difference of OS between these two groups was not observed in patients with PLR ≥ 133 ($p = .624$). PLR is a predictive marker of prognosis and therapeutic effect of postoperative chemotherapy in non-metastatic ESCC.

1. Introduction

Esophageal cancer (EC) is one of the most common malignant tumors worldwide and is characterized by demanding surgical therapy and poor prognosis [1]. Esophageal squamous cell carcinoma (ESCC) is a major type of EC in China [2]. Recently, some clinicopathological factors, such as tumor differentiation and TNM stage, have been widely regarded as predictors of prognosis for patients with ESCC. However, the clinical outcome varies widely even in patients with the same clinicopathological factors. Therefore, a new and accurate prognostic biomarker for ESCC patients is required to identify high-risk patients with poor outcomes and even guide the treatment.

A growing body of evidence has reported the tumor progression and prognosis are determined not only by the features of the tumor but also a host of microenvironments, including inflammation and the immune response [3–5]. The inflammation and immune response involves acute-phase proteins (including albumin), lymphocytes, neutrophils and platelets in the peripheral blood. Indeed, the inflammatory biomarkers, including the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have been reported to be significantly associated with the prognosis of the cancers [6–8], including ESCC [9–12]. However, controversy exists about which is the best inflammatory biomarkers for the prognostic prediction in ESCC. To the best of our knowledge, few studies have focused on the association between inflammatory biomarkers and postoperative chemotherapy. In addition, controversies about the optimal cut-off values for these inflammatory biomarkers in predicting prognosis still exist.

Abbreviations: CI, confidence interval; c-index, Harrell's concordance index; EC, Esophageal cancer; ESCC, esophageal squamous cell carcinoma; FP, 5-FU plus platinum; HR, hazard ratio; IR, irregular regimen; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; TP, paclitaxel plus platinum

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Table 1
Associations of clinicopathological features with NLR, PLR and PNI in ESCC.

	NLR			PLR			PNI		
Variable	< 1.2	≥1.2	*p*	< 133	≥133	*p*	< 57	≥57	*p*
Age (y)			0.171			0.668			0.062
< 60	27(55.1)	209(44.9)		142(46.6)	94(47.8)		143(42.8)	93(51.4)	
≥60	22(44.9)	257(55.2)		163(53.4)	116(55.2)		191(57.2)	88(48.6)	
Gender			0.003			0.429			0.163
Male	32(65.3)	386(82.8)		251(82.3)	167(79.5)		277(82.9)	141(77.9)	
Female	17(34.7)	80(17.2)		54(17.7)	43(20.5)		57(17.1)	40(22.1)	
Tumor length (cm)			0.002			0.010			0.050
< 4	29(59.2)	172(36.9)		133(43.6)	68(32.4)		120(35.9)	81(44.8)	
≥4	20(40.8)	294(63.1)		172(56.4)	142(67.6)		214(64.1)	100(55.2)	
Tumor location			0.942			0.802			0.865
Upper	4(8.2)	33(7.10)		20(6.6)	17(8.1)		23(6.9)	14(7.7)	
Middle	30(61.2)	282(55.3)		186(61.0)	126(60.0)		205(61.4)	107(59.1)	
Lower	15(30.6)	151(32.4)		99(32.5)	67(31.9)		106(31.7)	60(33.1)	
Diffrentiation			0.030			0.826			0.403
Well - moderate	34(69.4)	383(82.2)		246(80.7)	171(81.4)		274(82.0)	143(79.0)	
Poor - undifferentiated	15(30.6)	83(17.8)		59(19.3)	39(18.6)		60(18.0)	38(21.0)	
pT category			0.005			0.353			0.008
T1	3(6.1)	23(4.9)		17(5.6)	9(4.3)		14(4.2)	12(6.6)	
T2	20(40.8)	97(20.8)		76(24.9)	41(19.5)		62(18.6)	55(30.4)	
T3	10(20.4)	81(17.4)		49(16.1)	42(20.0)		63(18.9)	28(15.5)	
T4	16(32.7)	265(56.9)		163(53.4)	118(56.2)		195(58.4)	86(47.5)	
pN category			0.773			0.769			0.807
pN0	30(61.2)	248(53.3)		167(54.8)	111(53.1)		184(55.3)	94(51.9)	
pN1	14(28.6)	160(34.4)		102(33.4)	72(34.4)		111(33.3)	63(34.8)	
pN2	3(6.1)	33(7.1)		19(6.2)	17(8.1)		21(6.3)	15(8.3)	
pN3	2(4.1)	24(5.2)		17(5.6)	9(4.3)		17(5.1)	9(5.0)	
TNM stage			0.001			0.494			0.010
I	1(2.0)	19(4.1)		13(4.3)	7(3.3)		13(3.9)	7(2.9)	
II	27(55.1)	135(29.0)		101(33.1)	61(29.0)		90(26.9)	72(39.8)	
III	21(42.9)	312(67.0)		191(62.6)	142(67.6)		231(69.2)	102(56.4)	
Postoperative chemotherapy			0.090			0.964			0.258
Yes	22(44.9)	268(57.5)		172(56.4)	118(56.2)		182(54.5)	108(59.7)	
No	27(55.1)	198(42.5)		133(43.6)	92(43.8)		152(45.5)	73(40.3)	
Postoperative radiotherapy			0.742			0.990			0.429
Yes	6(12.2)	65(13.9)		42(13.8)	29(13.8)		49(14.7)	22(12.2)	
No	43(87.8)	401(86.1)		263(86.2)	181(86.2)		285(85.3)	159(87.8)	

Abbreviations, ESCC: esophageal squamous cell carcinoma; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; PNI: prognostic nutritional index.

In our study, we explored the prognostic role and clinical use of these inflammatory biomarkers in patients with ESCC and compared their capacity to predict prognosis. Moreover, we also investigated the optimal cut-off values of these inflammatory biomarkers for predicting prognosis.

2. Material and methods

2.1. Patients

A cohort of non-metastatic ESCC patients who underwent resection at the Tianjin Medical University Cancer Institute and Hospital between May 2005 and December 2011 were reviewed. Patients who met the following criteria were selected: [1] ESCC was diagnosed by histopathology after surgery; [2] Routine blood and liver function tests were obtained before breakfast within two weeks of the operation. Patients who received neoadjuvant or anti-inflammatory treatment before surgery, or had long-term use of anticoagulant drugs, were excluded. Finally, a total of 515 patients with ESCC were included in our study. Patient clinical information, including age, sex and operation date, clinicopathological features (including tumor length, tumor differentiation and TNM stage), and preoperative laboratory data were collected from the medical records. The neutrophil, lymphocyte and platelet counts were collected using a routine blood test, and albumin level was collected using the hepatic function test. PNI was calculated as the 10 × albumin level (g/dl) + 0.005 × total lymphocyte count (per mm^3) [13]. The median follow-up was 35 months (range of 2–106). All cases of ESCC were staged based on the 7th edition of the AJCC/UICC TNM classification system.

2.2. Statistical analysis

STATA software version 12.0 and SPSS software version 20.0 were used to perform the statistical analyses in this study. A two-sided *p*-value of < 0.05 was considered statistically significant.

The association between inflammatory biomarkers and clinicopathological features was assessed by the chi-square test. The overall survival (OS) rate was analyzed using the Kaplan–Meier method and differences in variables were compared by the log-rank test. Prognostic factors were evaluated using univariate and multivariate analyses with the Cox proportional hazard regression model.

We evaluated the predictive ability of the different categories by measuring discrimination, which is the ability to distinguish between high-risk and low-risk patients. The discrimination and optimal cut-off values of inflammatory biomarkers were determined by the method of Harrell's concordance index (c-index) [14, 15]. The maximum c-index value of 1.0 indicates a model with perfect predictive prognostic capacity and a greater c-index indicates a better model for predicting prognosis.