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Preoperative neutrophil-to-lymphocyte ratio is a more valuable prognostic factor than platelet-to-lymphocyte ratio for nonmetastatic rectal cancer

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ABSTRACT

Several combinations of inflammatory factors, including neutrophil-to- lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been reported to be prognostic factors in various malignant tumors, including colorectal cancer (CRC). The aim of this study was to evaluate the prognostic value of NLR and PLR for patients with rectal cancer (RC) who underwent curative surgery. Data from patients who underwent curative resection for RC were retrospectively reviewed. The cutoff for NLR and PLR was defined as 2.3 and 144 by receiver operating characteristic (ROC) curve. Overall survival (OS) and disease-free survival (DFS) were assessed using Kaplan-Meier method. Multivariable Cox regression model was used to evaluate the independent prognostic significance of variables. A total of 140 patients were eligible in the study. High NLR (>2.3) and high PLR (>144) both predicted lower OS and DFS according to Kaplan-Meier method. But in the multivariable Cox regression model, only the high NLR retained significance for reduced OS and DFS. According to Chi-square test, patients with higher NLR had larger tumor size and higher pN-stage. While PLR was only associated with the pN-stage. High preoperative NLR was shown to be a negative independent prognostic factor in patients undergoing resection for nonmetastatic RC. It may be helpful as a factor to guide the postoperative therapies.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer with an estimated 376,000 new cases diagnosed in 2015 in China and it is one of the most common causes of cancer-related death for Chinese people [1]. Rectal cancer (RC) is defined as carcinoma originating from the area between the inferior margin of sigmoid colon and the dentate line. Surgical resection is the cornerstone of therapy for RC and the survival of patients with unresectable RC is very poor [2]. Several risk evaluation tools used for predicting survival of patients with RC have been accepted, such as histological subtype and the TNM stage. Although the TNM stage according to the Union for International Cancer Control (UICC) is very important and widely accepted as a predictor for prognosis, it is well known that sometimes it is unreliable, even if the patients are in the same stage [3]. Therefore, we need to find out a new way to predict the prognosis more precisely.

Increasing evidences show that cancer progression is related not only to the tumor itself, but also the systemic inflammation response [4]. An elevated systemic inflammatory response is associated with a poor survival [5]. The blood NLR and PLR, indicators of systemic inflammation response, have been associated with poor outcome in several tumors, including gastric [6], renal [7] and ovarian cancers [8]. Cumulating evidences in CRC suggest that a high NLR/PLR might represent an independent adverse prognostic factor [9–11]. Compared with the previous studies, the primary purpose of the present study focus on two points. Firstly, the study could provide more information from a different clinical center to further confirm the progonostic value of preoperative NLR/PLR. Secondly, although both categorized into CRC, the RC has many differences compared to colon cancer, owing to its special physiological and pathological features. However, a limited number of studies have examined both the NLR and PLR of patients with RC alone. On this premise, the aim of this study was to determine the preoperative NLR and PLR as prognostic markers in RC with respect to long-term oncologic outcomes.

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2. Materials and methods

2.1. Information of cases

The medical records of patients who underwent surgical resection for rectal adenocarcinoma between January 1, 2008 and July 30, 2010 at the Department of General Surgery in the Affiliated Hospital of Xuzhou Medical College, China were retrospectively reviewed. A total of 161 cases were identified. We excluded patients with metastatic disease (n = 11), synchronous malignancy (n = 1), or inflammatory conditions (n = 4). We also excluded patients who received neoadjuvant therapy (n = 5), because the chemoradiation therapy may affect the counts of blood neutrophils and lymphocytes. The 140 patients remained with non-metastatic RC were included into our study. The variables analyzed included age at diagnosis, gender, tumor site, tumor T stage, tumor N stage, tumor differentiation, and preoperative blood neutrophil, platelet and lymphocyte count. Staging was performed according to the TNM classification of the UICC. Preoperative blood values which were used to calculate the NLR and PLR were obtained within one week before surgical operation. NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count.

2.2. Follow-up

Patients were recommended to reexamine every 3 months for the first 2 years postoperatively, every 6 months for the next 3 years, and every year thereafter. Physical examinations and a serum tumor marker assay, such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9, were performed at each reexamination. Chest X-ray, abdominopelvic computed tomography (CT) scan and colonoscopy were performed annually, or when there is a suspicion of recurrence. Recurrence was detected by the imaging tests and the serum tumor marker level, then was confirmed by pathologic examinations. OS was measured from date of surgery to date of death. DFS was measured from date of surgery to date of recurrence or date of non-tumor related death. After the latest follow-up, if patients are still alive or lost, the cases were identified as censored. The study was approved by the local ethical committee of the Xuzhou Medical College.

2.3. Statistics

The cutoffs of NLR and PLR were determined by testing all possible cutoffs by ROC. Chi-square test was used to examine differences between low and high NLR/PLR groups. Continuous data were analyzed as dichotomous variables according to approximate optimal cutoff value. Kaplan-Meier analyses were used to estimate the OS and DFS for rectal cancer, and differences between survival curves were analyzed by using the log-rank test. Univariable and multivariable Cox analyses were used to identify the variable-independent influence on OS and DFS. Multivariable models were built using stepwise enter selection. Statistical analysis was performed with SPSS software, using 2-sided testing with a significance level of 0.05.

3. Results

3.1. Clinicopathological characteristics

A total of 140 patients were finally included in the study. The characteristics of these patients were shown in Table 1. There were 81 (57.9%) men and 59 (42.1%) women in the 140 patients, their median age at diagnosis was 60 (range 25 to 88) years. The patients were divided into two groups by the tumor size, ≤4 cm was 110 (78.6%), and >4 cm was 30 (21.4%). Of 140 patients, there were a total of 34 recurrences with a median time to recurrence of 15 (range 3 to 52) months with a median follow-up of 42 (range 2 to 92) months.

Table 1
Clinicopathological characteristics of patients.

Features		Value
Age(years)	Mean ± SD	60.00 ± 13.001
	Median	60
	Range	25–88
No. gender(%)	Male	81 (57.9)
	Female	59 (42.1)
	Third quartile	2.87
Tumor size(%)	≤4 cm	110(78.6)
	>4 cm	30(21.4)
pT stage(%)	T1	17 (12.1)
	T2	38 (27.1)
	T3	59 (42.1)
	T4	26 (18.6)
pN stage(%)	N0	93(66.4)
	N1	42(30.0)
	N2	5(3.6)
Neutrophils	Mean ± SD	3923 ± 1617
	Median	3540
	Range	1620–13510
Lymphocytes	Mean ± SD	1724 ± 524
	Median	1700
	Range	700–3200
Platelets	Mean ± SD	254 ± 63
	Media	247
	Range	104–442
NLR	Mean ± SD	2.44 ± 1.16
	Median	2.29
	Range	0.87–8.50
	First quartile	1.67
	Third quartile	2.29
PLR	Mean ± SD	158 ± 57
	Median	147
	Range	55–350
	First quartile	118
	Third quartile	185

According to the ROC curve, we determined 2.3 and 144 as the optimum for NLR and PLR to estimate the patients' survival, respectively. The NLR was significantly correlated with tumor size (P = 0.028) and pN stage (P = 0.037). The PLR was only correlated with pN stage (P = 0.020). However, no significant correlations were found between NLR/PLR and any other factors (Tables 2 and 3).

Table 2
The relationship between patients' preoperative NLR and other factors.

Variables	Preoperative NLR		Total	χ2	P[a]
	≤2.3 (%)	≤2.3 (%)			
All cases	71(50.7%)	69(49.3%)	140		
Age at diagnosis(years)					
≤60	40(55.6%)	32(44.4%)	72	1.130	0.238
>60	31(45.6%)	37(54.4%)	68		
Gender					
Male	38(46.9%)	43(53.1%)	81	1.111	0.292
Female	33(55.9%)	26(44.1%)	59		
Tumor size					
≤4.5 cm	42(60.0%)	28(40.0%)	70	4.830	0.028
>4.5 cm	29(41.4%)	41(58.6%)	70		
Pathological grading					
I + I − II + II	51(54.8%)	42(45.2%)	93	1.885	0.170
II – III + III	20(42.6%)	27(57.4%)	47		
pN stage					
N0	53(57.%)	40(40.0%)	93	4.364	0.037
N1–N2	18(38.3%)	29(61.7%)	47		
pT stage					
T1–T2	32(58.2%)	23(41.8%)	55	2.021	0.155
T3–T4	39(45.9%)	46(54.1%)	85		

[a] Two sided Fisher's exact tests.