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Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Locally Advanced Rectal Cancer Treated with Neoadjuvant Chemoradiotherapy

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Background: Increasing evidence suggests that cancer-associated inflammation is associated with poorer outcomes. The neutrophil-to-lymphocyte ratio (NLR), considered as a systemic inflammation marker, is thought to predict prognoses in colorectal cancer. In this study, we explored the association between the NLR and prognoses following neoadjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC).

Material/Methods: From February 2002 to December 2012, a group of 202 patients diagnosed with LARC and receiving neoadjuvant CRT followed by radical surgery was included in our retrospective study. The associations between the pre-CRT NLR and clinicopathological characteristics, as well as the predictive value of pre-CRT NLR against survival outcomes, were analyzed.

Results: The average NLR was 2.7±1.5 (median 2.4, range 0.6–12.8). There were 63 (31.2%) patients with NLR ≥3.0, and 139 (68.8%) patients with NLR <3.0. Correlation analyses showed that no clinicopathological characteristics except age were associated with NLR. We did not find an association between NLR and survival outcomes. In multivariate Cox model analyses, the R1/R2 resection, lymph node ratio ≥0.1, and perineural/lymphovascular invasion were independently associated with worse disease-free survival and overall survival.

Conclusions: In our cohort, the NLR did not correlate with survival outcomes in LARC patients undergoing neoadjuvant CRT. The prognostic value of NLR should be validated in large-scale prospective studies.

MeSH Keywords: Chemoradiotherapy • Neutrophils • Prognosis

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Background

Along with colon cancer, rectal cancer is the second leading cause of cancer-associated deaths in the U.S. with about 40,000 newly diagnosed cases in 2014 [1]. Despite the high percentage (approximately 25%) of metastatic cases at diagnosis, the 5-year survival rate has improved in recent years, mainly due to the development of systemic therapeutic strategies such as neoadjuvant chemoradiotherapy (CRT) [2,3]. Neoadjuvant CRT has been developed as a standard strategy, especially for the management of locally advanced rectal cancer (LARC) [4]. With the advent of neoadjuvant CRT, the survival rates of patients with LARC has significantly improved [5,6]. However, patients who do not reach a pathologically complete response (pCR) from neoadjuvant CRT could more easily suffer local or distant recurrence at any time with poorer outcomes. The 5-year disease-free survival (DFS) was 83% for patients with pCR and 66% for those without pCR [7]. Hence, it is still necessary to find specific biomarkers to improve the selection of patients who will most benefit from neoadjuvant CRT and therefore achieve a better outcome. This could help to prevent unnecessary radiation therapy and surgery delays [8,9]. Therefore, identifying appropriate biomarkers has become a topic of investigation.

Increasing evidence suggests that cancer-associated inflammation is associated with poorer outcomes of cancers, including rectal cancer [10]. Immune cells produce cytokines, chemokines, and inflammatory mediators to cause an inflammatory response leading to changes in circulating white blood cell levels [11,12]. Various markers have been studied in solid tumors, including the neutrophil-to-lymphocyte ratio (NLR). Meta-analyses have indicated that NLR is a useful predictive factor in several cancers, such as esophageal cancer [13], gastric cancer [14], hepatocellular carcinoma [15], and non-small cell lung cancer [16].

However, the role of NLR in rectal cancer remains controversial [17,18]. Hence, our study further explored the associations between the baseline NLR and prognosis following neoadjuvant CRT for LARC. The role of NLR as a predictor for pCR after neoadjuvant CRT in LARC was also assessed.

Material and Methods

Patients

In total, 202 patients diagnosed with LARC (cT3-4 and/or cN1-2) and receiving neoadjuvant CRT followed by radical surgery at Zhejiang Cancer Hospital from February 2002 to December 2012 were included in this retrospective study. All patients had histologically confirmed rectal adenocarcinoma within 15 cm from the anal verge, and patients with distant metastasis were excluded from this study. All patients signed informed consent, and underwent pelvic radiation (range 45–55 Gy) with concurrent 5-fluorouracil-based chemotherapy (FOLFIRI or FOLFOX) before surgery. Radiation was given according to the institutional protocols.

Pretreatment assessment

The pretreatment assessment included a detailed medical history and physical examination, digital rectal examination, endoscopy, biopsy, endorectal ultrasonography, abdominal and pelvic computed tomography (CT), chest X-ray/CT, and pelvic magnetic resonance imaging (MRI). Laboratory examination included whole blood cell count, as well as liver and kidney function tests. Cardiac function was assessed by electrocardiography and echocardiography. All patients had baseline blood samples obtained within 1 week before CRT. The routine blood test was performed in our hospital. The NLR was calculated as the neutrophil count divided by the lymphocyte count.

Histopathological evaluation of response to chemoradiation

All patients underwent diagnostic rectal biopsy before the start of CRT. Pathological evaluation was performed after surgery. The pCR was defined as an absence of all malignant cells. The degree of primary tumor regression was determined by the amount of viable malignancy versus the amount of fibrosis as described by Dworak et al. [19]. Tumor regression Grade 0 (TRG0) was defined as no regression; TRG1 as minor regression (dominant tumor with fibrosis in 25% of the tumor mass); TRG2 as moderate regression (dominant tumor with fibrosis in 26–50% of the tumor mass); TRG3 as good regression (>50% tumor regression); and TRG4 as total regression (no viable tumor cells).

Statistical analysis

Statistical analysis was performed using SPSS Statistics software, version 20.0 (IBM, Armonk, NY, USA). Continuous variables are expressed as the mean ± standard deviation and/or median (range). Categorical data are expressed as percentages. Receiver operating characteristic (ROC) analysis was used to determine the cut-off value of the NLR. In this analysis, we established the cut-off value of the NLR with maximum sensitivity and specificity in predicting 3-year overall survival (OS) and 3-year DFS. The correlation analysis between the NLR and the clinicopathological characteristics was performed using chi-squared tests. Survival analysis was performed using the Kaplan-Meier method with the log-rank test and the Cox's proportional hazard regression test. A multivariate analysis was performed for the variables with P value less than

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Table 1. Clinicopathological characteristics.

Variables	N	%	NLR <3	%	NLR ≥3	%	P
Sum	202		139		63		
Gender							0.129
Male	143	70.8	103	72.0	40	28.0	
Female	59	29.2	36	61.0	23	39.0	
Age							0.017
<60 y	156	77.2	101	64.7	55	35.3	
≥60 y	46	22.8	38	82.6	8	17.4	
Tumor location							0.464
Low (≤5 cm)	123	60.9	87	70.7	36	29.3	
Mid/upper (>5 cm)	79	39.1	52	65.8	27	34.2	
Clinical T before CRT							0.895
cT3	82	40.6	56	68.3	26	31.7	
cT4	120	59.4	83	69.2	37	30.8	
Clinical N before CRT							0.459
cN–	98	48.5	65	66.3	33	33.7	
cN+	104	51.5	74	71.2	30	28.8	
CEA before CRT							0.435
<5 ng/ml	104	51.5	69	66.3	35	33.7	
≥5 ng/ml	98	48.5	70	71.4	28	28.6	
Sphincter-preserving							0.323
Yes	103	51.0	68	66.0	35	34.0	
No	98	48.5	71	72.4	27	27.6	
Unknown	1	0.5	0	0.0	1	100.0	
Surgical margin							0.296
R0	190	94.1	133	70.0	57	30.0	
R1/R2	11	5.4	6	54.5	5	45.5	
Unknown	1	0.5	0	0.0	1	100.0	
pCR							
Yes	38	18.8	25	65.8	13	34.2	0.674
No	163	80.7	113	69.3	50	30.7	
Unknown	1	0.5	1	100.0	0	0.0	
T-downstaging							
Yes	125	61.9	87	69.6	38	30.4	0.813
No	75	37.1	51	68.0	24	32.0	
Unknown	2	1.0	1	50.0	1	50.0	

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Table 1 continued. Clinicopathological characteristics.

Variables	N	%	NLR <3	%	NLR ≥3	%	P
Pathologic response*							
Good	119	58.9	79	66.4	40	33.6	0.359
Poor	80	39.6	58	72.5	22	27.5	
Unknown	3	1.5	2	66.7	1	33.3	
Lymph node ratio							
<0.1	148	73.3	101	68.2	47	31.8	0.695
≥0.1	52	25.7	37	71.2	15	28.8	
Unknown	2	1.0	1	50.0	1	50.0	
Histologic differentiation							
Well/moderate	127	62.9	88	69.3	39	30.7	0.907
Poorly/mucinous/signet	73	36.1	50	68.5	23	31.5	
Unknown	2	1.0	1	50.0	1	50.0	
PNI and/or LNI							
No	153	75.7	103	67.3	50	32.7	0.566
Yes	36	17.8	26	72.2	10	27.8	
Unknown	13	6.4	10	76.9	3	23.1	
RT dose							
≥50 Gy	117	57.9	82	70.1	35	29.9	0.647
<50 Gy	85	42.1	57	67.1	28	32.9	
Adjuvant chemotherapy							
Yes	108	53.5	74	68.5	34	31.5	0.914
No	91	45.0	63	69.2	28	30.8	
Unknown	3	1.5	2	66.7	1	33.3	

* Good pathological response, TRG 3-4; poor pathologic response; TRG 0-2. NLR – neutrophil-to-lymphocyte ratio; CRT – chemoradiotherapy; CEA – carcinoembryonic antigen; pCR – pathologic complete response; PNI – perineural invasion; LNI – lymphovascular invasion; RT – radiotherapy.

0.10 by univariate analysis. A 2-sided P value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

The patients' clinical characteristics are summarized in Table 1. The median age was 51 years (range, 23–76 years) and 70.8% of the patients were male. Of these patients, 190 (94.1%) had R0 resection, and 103 (51.0%) received sphincter-preserving operations. Pathological results showed that the pCR rate was 18.8%, and the T-downstaging percentage was 61.9%. The median number of examined lymph nodes was 13 (range, 2–51). The lymph node ratio (LNR) of 52 (25.7%) patients was ≥0.1. Poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma were totally present in 73 (36.1%) patients. Thirty-six (17.8%) patients presented with perineural invasion (PNI) and/or lymphovascular invasion (LNI). Of the patients, 108 (53.5%) received adjuvant chemotherapy. The median follow-up was 45 months, with a range of 3–162 months. At the last follow-up, 116 (57.4%) patients were alive, 82 (40.6%) had disease progression, 18 (8.9%) had

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Table 2. Risk factors associated with overall survival.

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender			0.857			
Male	1					
Female	1.043	0.658–1.653				
Age			0.152			
<60 y	1					
≥60 y	0.669	0.383–1.168				
Tumor location			0.482			
Low (≤5 cm)	1					
Mid/upper (>5 cm)	1.165	0.759–1.789				
Clinical T before CRT			0.182			
cT3	1					
cT4	1.348	0.865–2.101				
Clinical N before CRT			0.282			
cN–	1					
cN+	1.261	0.824–1.932				
CEA before CRT			0.095			0.633
<5 ng/ml	1			1		
≥5 ng/ml	1.431	0.935–2.189		1.130	0.684–1.866	
Sphincter-preserving			0.257			
Yes	1					
No	1.277	0.833–1.957				
Surgical Margin			0.000			0.000
R0	1			1		
R1/R2	8.329	4.168–16.643		6.769	3.127–14.653	
pCR			0.000			0.239
Yes	1			1		
No	5.025	2.033–12.500		1.838	0.668–5.051	
T-downstaging			0.001			0.087
Yes	1			1		
No	2.049	1.344–3.115		1.531	0.940–2.494	
Pathologic response			0.041			0.457
Good	1			1		
Poor	1.555	1.011–2.392		1.221	0.722–2.062	

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Table 2 continued. Risk factors associated with overall survival.

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Lymph node ratio			0.000			0.001
<0.1	1			1		
≥0.1	2.800	1.808–4.335		2.467	1.448–4.203	
Histologic differentiation			0.068			0.252
Well/moderate	1			1		
Poorly/mucinous/signet	1.484	0.967–2.273		1.330	0.816–2.169	
PNI and/or LNI			0.000			0.027
No	1			1		
Yes	2.614	1.619–4.222		1.876	1.076–3.271	
RT dose			0.094			0.170
≥ 50 Gy	1			1		
<50 Gy	1.443	0.935–2.227		1.418	0.861–2.336	
Adjuvant chemotherapy			0.089			0.134
Yes	1			1		
No	1.451	0.940–2.237		1.462	0.890–2.404	
NLR			0.779			
<3.0	1					
≥3.0	1.066	0.681–1.668				

HR – hazard ratio; CI – confidence interval; CRT – chemoradiotherapy; CEA – carcinoembryonic antigen; pCR – pathological complete response; PNI – perineural invasion; LNI – lymphovascular invasion; NLR – neutrophil-to-lymphocyte ratio; RT – radiotherapy.

local recurrence, 76 (37.6%) had distant metastasis, and 9 patients (4.5%) were lost to follow-up.

The association between clinicopathological characteristics and NLR

The average NLR was 2.7±1.5 (median, 2.4; range, 0.6–12.8). In the ROC analysis, we failed to identify an appropriate cut-off value because the area under the curve for NLR was 0.555 [95% confidence interval (CI), 0.467–0.642; P=0.223] for the 3-year OS and 0.558 (95% CI, 0.477–0.638; P=0.159) for the 3-year DFS. Finally, an NLR ≥3.0 was considered as elevated NLR on the basis of previous studies [20,21]. There were 63 (31.2%) patients with NLR ≥3.0 and 139 (68.8%) patients with NLR <3.0. We compared the difference in clinicopathological characteristics between the NLR ≥3.0 group and the NLR <3.0 group (Table 1). The results showed that elevated NLR were more common in patients ages <60 years (P=0.017). No other clinicopathological characteristics were found to be associated with the NLR. It is worth noting that there were no differences in the pCR rate or the T-downstaging rate between the 2 NLR groups.

Survival analysis

The correlations between OS and various clinicopathological characteristics are shown in Table 2. Surgical margin status [hazard ratio (HR), 8.329; 95% CI, 4.168–16.643; P=0.000], pCR (HR, 5.025; 95% CI, 2.033–12.500; P=0.000), T-downstaging (HR, 2.049; 95% CI, 1.344–3.115; P=0.001), pathological response (HR, 1.555; 95% CI, 1.011–2.392; P=0.041), LNR (HR, 2.800; 95% CI, 1.808–4.335; P=0.000), and perineural and/or lymphovascular invasion (HR, 2.614; 95% CI, 1.619–4.222; P=0.000) were significantly associated with OS on univariate analysis. In the multivariate analysis, R1/R2 resection (HR, 6.769; 95% CI, 3.127–14.653; P=0.000), LNR ≥0.1 (HR, 2.467; 95% CI, 1.448–4.203; P=0.001), and perineural and/or lymphovascular invasion (HR, 1.876; 95% CI, 1.076–3.271;

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Table 3. Risk factors associated with disease-free survival.

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Gender			0.770			
Male	1					
Female	1.072	0.669–1.715				
Age			0.025			0.074
<60 y	1			1		
≥60 y	0.504	0.273–0.931		0.555	0.291–1.060	
Tumor location			0.892			
Low (≤5 cm)	1					
Mid/upper (>5 cm)	0.970	0.620–1.516				
Clinical T before CRT			0.411			
cT3	1					
cT4	1.204	0.771–1.882				
Clinical N before CRT			0.049			0.892
cN–	1			1		
cN+	1.548	0.995–2.409		1.033	0.646–1.651	
CEA before CRT			0.263			
<5 ng/ml	1					
≥5 ng/ml	1.279	0.828–1.974				
Sphincter-preserving			0.115			
Yes	1					
No	1.414	0.915–2.188				
Surgical margin			0.000			0.000
R0	1			1		
R1/R2	6.389	3.012–13.551		5.708	2.548–12.790	
pCR			0.004			0.408
Yes	1			1		
No	2.801	1.348–5.814		1.408	0.626–3.165	
T-downstaging			0.036			0.795
Yes	1			1		
No	1.742	1.133–2.681		3.922	2.045–16.667	

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Table 3 continued. Risk factors associated with disease-free survival.

Variables	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Pathologic response			0.151			
Good	1					
Poor	1.376	0.887–2.132				
Lymph node ratio			0.000			0.001
<0.1	1			1		
≥0.1	2.621	1.680–4.088		2.376	1.419–3.978	
Histologic differentiation			0.119			
Well/moderate	1					
Poorly/mucinous/signet	1.412	0.911–2.188				
PNI and/or LNI			0.000			0.031
No	1			1		
Yes	2.661	1.634–4.334		1.762	1.054–2.943	
RT dose			0.325			
≥50 Gy	1					
<50 Gy	1.244	0.803–1.927				
Adjuvant chemotherapy			0.299			
Yes	1					
No	1.259	0.812–1.953				
NLR			0.542			
<3.0	1					
≥3.0	0.863	0.536–1.390				

HR – hazard ratio; CI – confidence interval; CRT – chemoradiotherapy; CEA – carcinoembryonic antigen; pCR – pathological complete response; PNI – perineural invasion; LNI – lymphovascular invasion; NLR – neutrophil-to-lymphocyte ratio; RT – radiotherapy.

P=0.027) were independently associated with worse OS. The correlations between DFS and various clinicopathological characteristics are shown in Table 3. Age (HR, 0.504; 95% CI, 0.273–0.931; P=0.025), clinical N stage before CRT (HR, 1.548; 95% CI, 0.995–2.409; P=0.049), surgical margin status (HR, 6.389; 95% CI, 3.012–13.551; P=0.000), pCR (HR, 2.801; 95% CI, 1.348–5.814; P=0.004), T-downstaging (HR, 1.742; 95% CI, 1.133–2.681; P=0.036), LNR (HR, 2.621; 95% CI, 1.680–4.088; P=0.000), and perineural and/or lymphovascular invasion (HR, 2.661; 95% CI, 1.634–4.334; P=0.000) were significantly associated with DFS on univariate analysis. In the multivariate analysis, R1/R2 resection (HR, 5.708; 95% CI, 2.548–12.790; P=0.000), LNR ≥0.1 (HR, 2.376; 95% CI, 1.419–3.978; P=0.001), and perineural and/or lymphovascular invasion (HR, 1.762; 95% CI, 1.054–2.943; P=0.031) were independently associated with worse DFS. We did not find an association of NLR with OS (HR, 1.066; 95% CI, 0.681–1.668; P=0.779) or DFS (HR, 0.863; 95% CI, 0.536–1.390; P=0.542) using 3.0 as a cut-off value (Figures 1, 2). Furthermore, we repeated survival analyses using different cut-off values (2.0 [21] and 4.0 [22]) and again did not find an association between NLR and survival outcomes.

Discussion

The tumor node metastasis (TNM) staging and Dukes' staging system are the basis for subdividing colorectal cancer, but even patients with the same stage may turn out to have different clinical characteristics and outcomes. It is necessary in clinical practice to generate a personalized treatment strategy.

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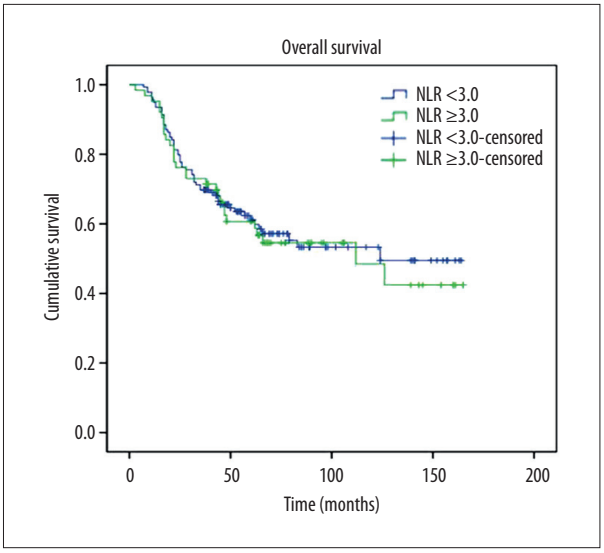

Figure 1. Overall survival stratified by neutrophil-to-lymphocyte ratio (NLR).

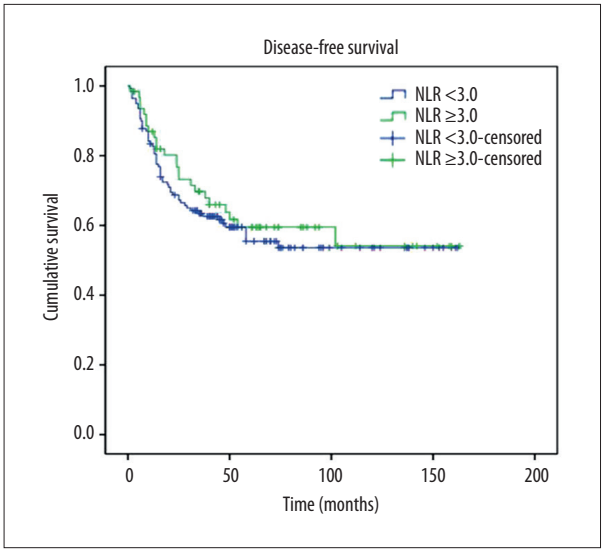

Figure 2. Disease-free survivals stratified by neutrophil-to-lymphocyte ratio (NLR).

Hence, supplementary methods, such as the laboratory index, added to the TNM staging and Dukes' staging system, may have an important role in the determination of personalized treatment strategy [23]. However, the choice of the most appropriate laboratory marker is a serious issue.

The relationship between inflammation and tumors is well established. Inflammation can increase the risk of cancer and promote carcinogenesis, including colorectal cancer [24]. Data also showed that patients who used regular non-steroidal anti-inflammatory drugs had decreased risk of colorectal cancer [25]. Clinical studies and pool analyses have shown that several markers of systematic inflammatory reactions, such as C-reactive protein, modified Glasgow score, and NLR, show prognostic value in patients with cancer [26]. Among the laboratory markers, NLR has some advantages, such as low cost and wide availability.

A meta-analysis of 7 studies involving 959 patients suggested that elevated NLR was related to worse OS, DFS, and recurrent-free survival [27]. Interestingly, all the studies included in the meta-analysis obtained "positive" results. However, some recent studies reported negative results. Leonardo et al. reviewed a cohort of 175 patients, and analyzed the association between NLR and survival outcomes using different cut-off values (2.0, 2.5, 3.0, 4.0, and 5.0). The results did not show differences in disease-specific survival, recurrent-free survival, or pCR [21]. In our present study, we also found no association of the NLR with either OS or DFS.

One explanation for these contradictory results could be the clinical heterogeneity of the patients enrolled in the different studies. In our cohort, a higher proportion (59.4%) of patients had clinical stage T4, compared with other clinical studies of rectal cancer [28,29]. In our previous study, we found that tumor burden, which is regarded as an important prognostic factor, was the most pivotal factor influencing systemic inflammation before treatment in colorectal cancer patients [30]. We speculate that NLR, as a type of systemic inflammatory marker, may predict the prognosis by distinguishing patients with different tumor burdens. If a group of patients had a wide spectrum of tumor burdens, NLR would be an effective predictor of outcomes. In contrast, if patients enrolled in a certain study had a narrow spectrum of tumor burdens, the predictive power of the NLR would be weakened. However, this hypothesis requires further research for validation. In addition, when interpreting the contradictory results in different studies, other possible reasons need to be taken into account, such as random error caused by small sample and variability of treatment in different centers.

In addition to finding no association between the NLR and survival outcomes, we also found no association between the NLR and short-term effects indicators of CRT (e.g., pCR, downstaging, and pathological response), for which previous studies have yielded conflicting results [20,31]. However, there is no convincing explanation of the mechanism by which systemic inflammatory factors affect the short-term actions of CRT. In the present study, we found that younger patients were associated with higher NLR, while previous studies have not found this correlation [31,32]. The most probable reason for this disagreement is the randomly caused uneven distribution of baseline characteristics in different age groups.

Caution is required when interpreting our results because of the limitations in our study. First, this was a retrospective study, and some comorbidity that may affect the level of NLR had not been included in our analysis. Second, nearly 3/5 of

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the patients in our cohort were cT4, and the percentage was higher when compared with that of other studies. Finally, the heterogeneity of the tumor burden in different studies may affect the predictive power of the NLR.

Conclusions

In our cohort, the NLR did not correlate with survival outcomes in LARC patients undergoing neoadjuvant CRT. The prognostic value of NLR should be validated in future large-scale prospective studies.

Statement

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