

# Perioperative changes of inflammation-based biomarker for predicting the prognosis in colorectal cancer patients: a retrospective analysis

Xie Ya<sup>1</sup>, Fan Wenbin<sup>2</sup>, Yan Wenfeng<sup>3</sup>, Wu Gang<sup>3</sup>, Ren Ke<sup>3</sup>, Zhou Yang<sup>3</sup>, Tao Yong<sup>4</sup>

<sup>1</sup>Department of Gastrointestinal Surgery, Henan Provincial People's Hospital, School of Clinical Medicine, Henan University, Zhengzhou, Henan, China

<sup>2</sup>Department of Colorectal Surgery, Chengdu Traditional Chinese Medical University, Chengdu, China

<sup>3</sup>Department of Gastrointestinal Surgery, Henan Provincial People's Hospital, Zhengzhou, Henan, China

<sup>4</sup>Department of Colorectal Surgery, Ningbo First Hospital and Zhejiang Chinese Medicine University, Affiliated No. 3 Hangzhou Hospital, Ningbo, China

Gastroenterology Rev 2019; 14 (4): 258–267  
DOI: <https://doi.org/10.5114/pg.2019.90252>

**Key words:** neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, colorectal cancer.

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**Address for correspondence:** Tao Yong MD, PhD, Department of Colorectal Surgery, Ningbo First Hospital and Zhejiang Chinese Medicine University Affiliated No. 3 Hangzhou Hospital, Ningbo, China, phone: +86 15858148782, e-mail: [doctortaoyong@163.com](mailto:doctortaoyong@163.com)

## Abstract

**Introduction:** Perioperative inflammatory markers, including the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), are associated with oncological prognosis. However, their changes in colorectal cancer surgery for predicting the prognosis are rarely investigated.

**Aim:** To compare perioperative changes to evaluate the prognostic significance of patients' survival.

**Material and methods:** Retrospective clinical data and baseline laboratory parameters of 183 colorectal cancer (CRC) patients who underwent curative surgery were collected between January 2007 and January 2013. The clinicopathological characteristics were compared. Statistical analysis was used to identify the predictive changes of perioperative NLR and PLR associated with survival prognosis.

**Results:** ROC analysis indicated that perioperative NLR/PLR showed higher predictive accuracy for prognosis, and the optimal cut-off values of pre-NLR, post-NLR, pre-PLR, and post-PLR were 2.94, 4.32, 184.29, and 212.37, respectively. Kaplan-Meier analysis suggested that the four groups stratified by perioperative changes had significantly different recurrence-free survival and overall survival ( $p < 0.05$ ). Univariate and multivariable analysis revealed that patients with higher cancer stage, lymph node metastasis, and perioperative change of NLR/PLR (HH, LH) had significant association with poor prognosis of RFS and OS (all  $p < 0.05$ ).

**Conclusions:** Perioperative NLR and PLR might be good predictors for prognosis in CRC patients who have undergone curative surgery, which could guide the customised therapeutic strategy. Furthermore, their assessment could contribute to accurately predicting oncologic outcomes and provide an in-depth understanding of the patients, which could guide the operational strategy.

## Introduction

Colorectal cancer (CRC) is regarded as the third most frequent malignant tumour worldwide, and its rate of mortality has increased over the past several decades due to recurrence and metastasis [1]. Despite advances in cancer treatments and management of CRC, prognostic biomarkers remain a promising way to predict the outcome of cancer [2]. Currently, some prognostic factors, such as tumour TNM stage, cell differentiation grade, and vascular invasion, have been widely utilised

as the most accurate predictors of tumour recurrence and prognosis [3]. However, the survival outcome varies widely even in patients with the same TNM stage and tumour differentiation grade. Therefore, to estimate more specific oncological outcomes, novel prognostic markers are also required.

Strong evidence has confirmed that systemic inflammatory response is known to play a vital role in human cancer development and progression [4]. Tumours are closely related to inflammation. Inflammation is an essential component of the tumour microenvironment,

and the changes in inflammatory cells might influence tumour progression, such as neoplastic cell proliferation, migration, invasion, collapse of anti-tumour immunity, metastasis, and so forth [5, 6]. Accumulating evidence shows that the peripheral neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been widely proposed as prognostic factors for many malignancies such as gastric cancer [7], nasopharyngeal carcinoma [8], liver cancer [9], and especially colorectal cancer [10]. Moreover, it is likely that the tumour microenvironment as well as systemic inflammatory response might be changed because of surgery [11]. However, only a few studies have assessed the relationship between dynamic changes of these perioperative inflammatory markers and survival prognosis in such patients.

## Aim

In the present study, we hypothesised that both predictors are associated with prognostic survival in CRC patients who have undergone curative surgery. Furthermore, we compared perioperative changes to evaluate the prognostic significance of patients' survival.

## Material and methods

This study was conducted according to the Declaration of Helsinki and was approved by our Hospital. Written, informed consent was obtained from all individual participants included in the study.

### Patient selection

A total of 183 CRC patients treated with curative surgery at the Department of Colorectal Surgery in our hospital from January 2007 to January 2013 were reviewed. Patients are excluded if they suffered from infection, haematological diseases, hyperpyrexia, renal dysfunction, diabetes mellitus, and other acute or chronic diseases, or if they had received previous chemotherapy, radiotherapy, or other targeted therapy. Postoperative follow-ups were generally performed by letter and by telephone interview every 3–6 months until death or 5 years and were ended after January 1, 2018.

### Perioperative model of NLR and PLR

Preoperative blood samples were obtained prior to the surgical operation. The median interval between pre- and postoperative blood tests was 14 days. For the calculation of the NLR and PLR, NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and PLR was also conducted in the same way. The cut-off value for haematological profiles was

determined using the receiver operating characteristic (ROC) curve analysis. According to the cut-off value, all patients were divided into four groups: HH, patients with both high preoperative and postoperative values; HL, patients with high preoperative and low postoperative values; LH, patients with low preoperative and high postoperative values; and LL, both low preoperative and postoperative values. Medical records were assimilated with respect to the patients' age, sex, and clinicopathological characteristics (such as location, size, histological type, TNM stage, invasion, and lymph node).

### Statistical analysis

The end points of this study were recurrence-free survival (RFS), which was defined as the time from the first day of palliative operation to the disease progression or recurrence, and overall survival (OS), which was defined as the time from the first day of palliative operation to death by any cause or to the last follow-up. ROC analysis determined the optimal cut-off value as a predictive marker for OS and RFS. The association between the clinicopathological characteristics and perioperative change of the four groups were compared using the  $\chi^2$  test or Fisher's exact probability test. The survival curves were generated using the Kaplan-Meier method, and the differences were compared using the log-rank test. The univariate analysis assessed the prognostic factors, and multivariate analysis (Cox's proportional-hazards regression model) evaluated the independent factors for survival prognosis. *P*-values < 0.05 were considered statistically significant. The statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patient demographics and clinicopathological characteristics

Table I shows the clinicopathological characteristics of the 183 patients in the study. The female-to-male ratio was 85:98, and the median age was 69 years, ranging from 45 to 79 years. Patients predominantly suffered from rectal cancer (64.48%), and 58.47% of patients presented tumour size  $\geq 3$  cm. The clinical TNM stage revealed the pathological diagnoses as follows: 37 patients with stage I, 67 patients with stage II, 49 patients with stage III, and 30 patients with stage IV. Moreover, the histological grade revealed 121 patients in G1-2 and 62 patients in G3-4. In terms of cancer invasion, high grades (T1-2) constituted 94 patients, and the other grades (T3-4) constituted 99 patients. A total of 71 patients presented lymph node with negative tumour (N0), while 112 patients were positive, and 109

**Table I.** Comparison between groups stratified by perioperative changes and patients' clinicopathological

Characteristics	Total N = 183	NLR				P-value	PLR				P-value
		LL-NLR	LH-NLR	HL-NLR	HH-NLR		LL-PLR	LH-PLR	HL-PLR	HH-PLR	
Age [years]:		35	42	50	56	0.365	46	43	40	54	0.837
< 65	74	16	18	15	25		21	16	15	22	
≥ 65	109	19	24	35	31		25	27	25	32	
Sex:						0.125					0.622
Female	85	12	16	28	29		22	22	15	26	
Male	98	23	26	22	27		24	21	25	28	
Location:						0.095					0.114
Colon	65	12	19	21	13		12	17	11	25	
Rectal	118	23	23	29	43		34	26	29	29	
Tumour size [cm]:						0.409					0.639
< 3	76	18	17	22	19		20	21	14	21	
≥ 3	107	17	25	28	37		22	26	26	33	
Cancer stage:						0.005					0.012
I-II	104	27	24	21	22		32	29	21	22	
III-IV	79	8	18	19	34		14	14	19	32	
Cancer grade:						0.034					0.008
G1-2	121	28	29	35	29		35	32	27	26	
G3-4	62	7	13	15	27		10	11	13	28	
Tumour invasion:						0.007					0.001
T1-2	94	22	23	23	16		32	21	15	16	
T3-4	99	13	19	27	40		14	22	25	38	
Lymph node:						0.004					0.039
N0	71	21	19	18	13		22	21	15	13	
N+	112	14	23	32	43		24	22	25	41	
Adjuvant chemotherapy:						0.240					0.239
No	74	9	19	23	23		14	16	17	27	
Yes	109	26	23	27	33		32	27	23	27	

NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, LL-NLR/PLR – low pre- + low post-NLR/PLR, LH-NLR/PLR – low pre- + high post-NLR/PLR, HL-NLR/PLR – high pre- + low post-NLR/PLR, HH-NLR/PLR – high pre- + high post-NLR/PLR.

patients received postoperative adjuvant chemotherapy. ROC analysis could calculate the sensitivity and specificity levels of NLR and PLR as survival estimation predictors, as shown in Figure 1. For RFS, pre- and post- NLR showed a larger AUC than pre- or post- NLR. Moreover, the predictor of PLR showed similar results. Regarding OS, pre- and post-NLR/PLR was superior to

the pre- or post-NLR/PLR. The optimal cut-off values of perioperative NLR and PLR were pre-2.94, post-4.32 and pre-184.29, post-212.37, respectively. Furthermore, we divided the patients into four groups according to these perioperative cut-off values. Table I also shows the distribution of patients in these four groups. Patients with higher cancer stage, poorer differentiation, and greater

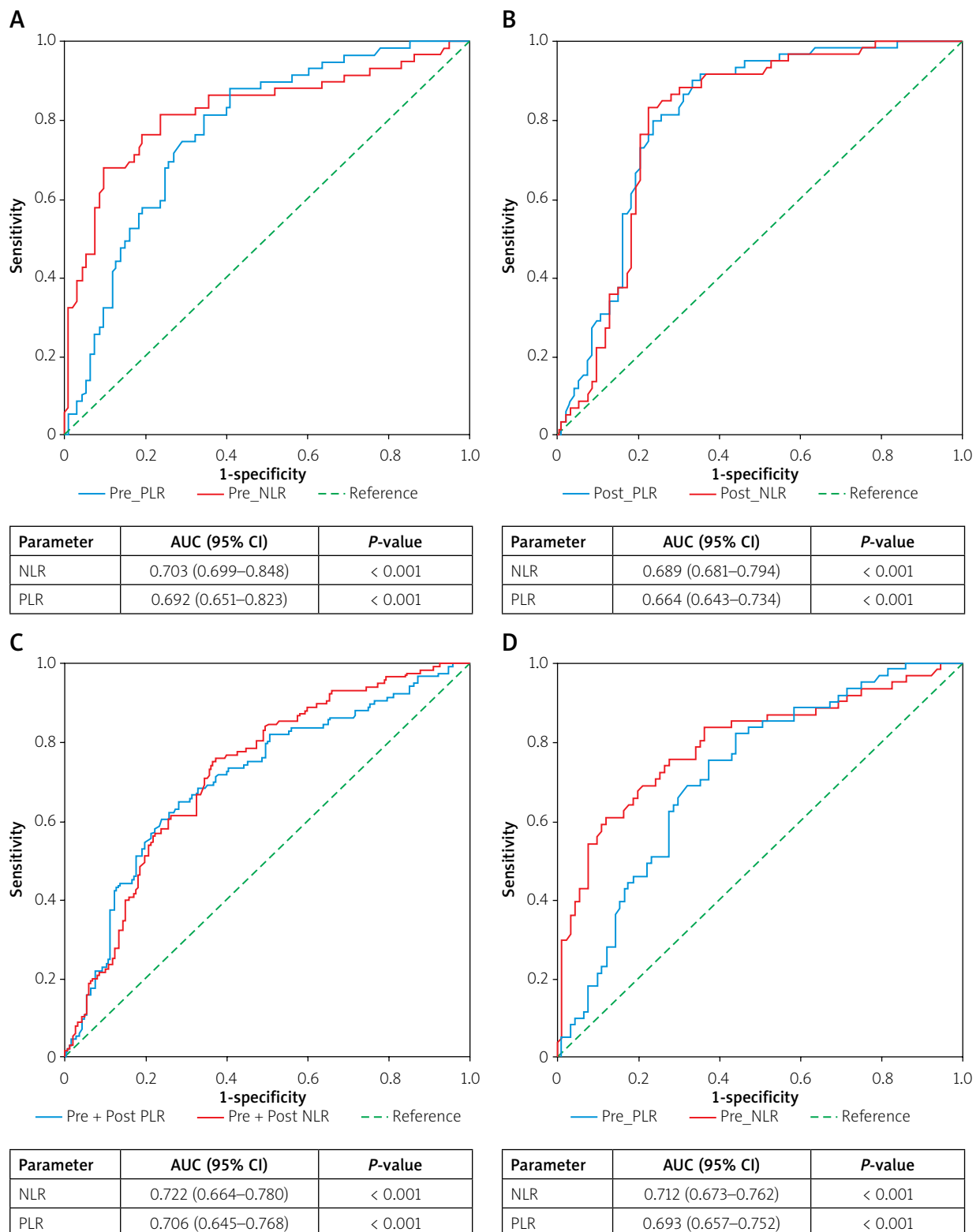


Figure 1. Comparison of area under ROC curves between NLR and PLR for RFS and OS. A–C – RFS, D – OS

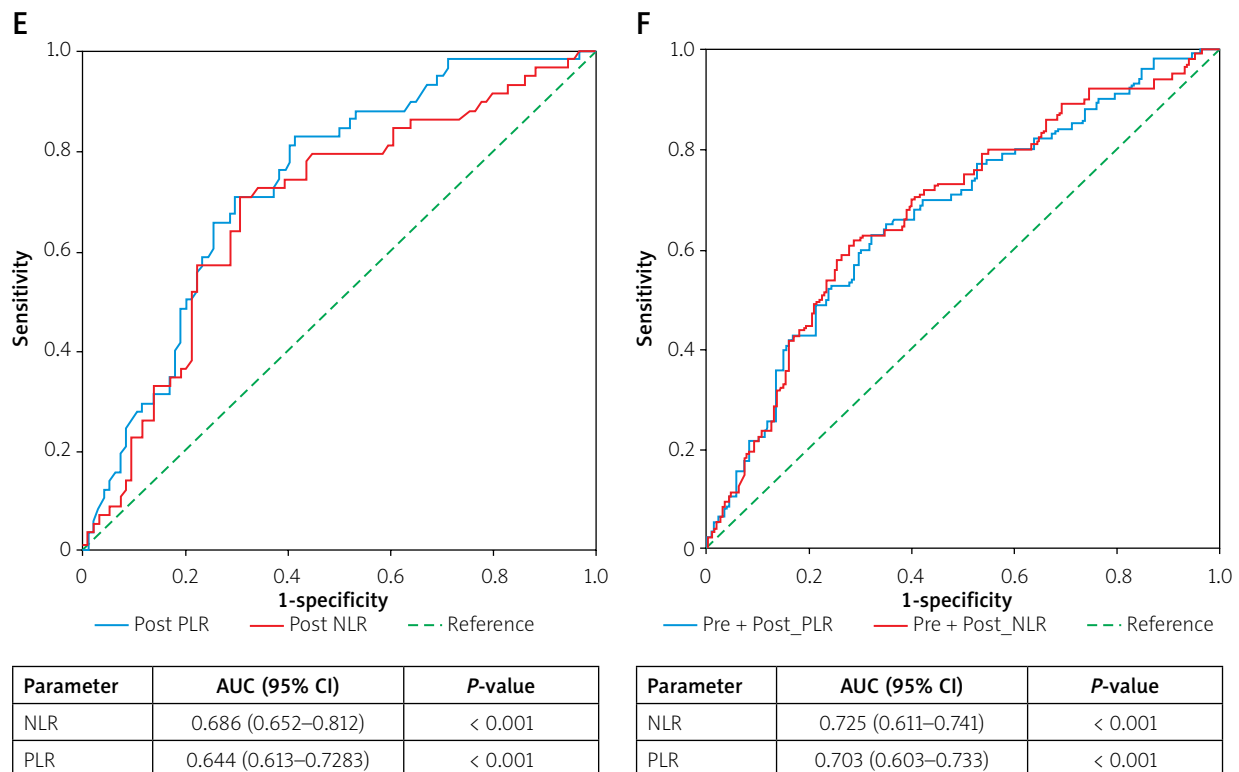


Figure 1. Cont. E, F – OS

lymph node metastasis were significantly associated with perioperative NLR or PLR (all  $p < 0.05$ ). Conversely, no difference was observed in age, gender, tumour location, size, and adjuvant chemotherapy (all  $p > 0.05$ ).

### Comparison between survival prognosis and perioperative changes

According to the follow-up period, 61 (33.33%) patients had recurrence: 22 patients presented local recurrence and 39 patients developed distant metastasis. Seventy-six (41.53%) patients died: 33 patients from tumour recurrence, one from chemotherapeutic toxicity, and the other patients due to unknown reasons. For prognosis of patients according to the Kaplan-Meier curve and log-rank test, the four groups (LL, LH, HL, and HH) stratified by perioperative changes had significantly different RFS and OS, as shown in Figure 2 (all  $p < 0.05$ ). Thus, perioperative changes of NLR and PLR could effectively predict the prognostic survival of CRC patients in the present study.

### Prognostic variables for RFS and OS

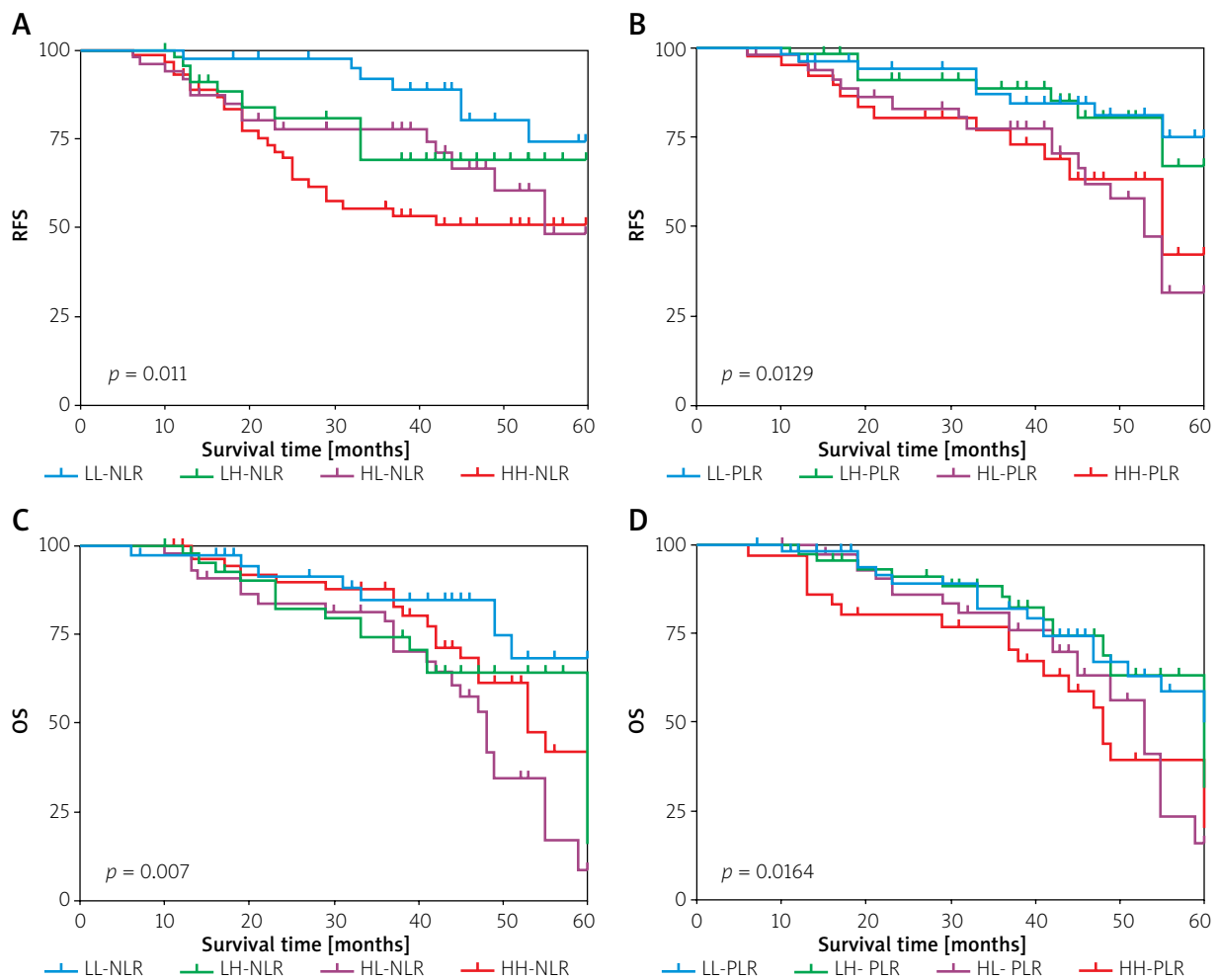
With respect to all prognostic factors, Tables II and III showed the results of univariate and multivariate analysis of various parameters in terms of RFS and OS. Univariate analysis revealed that patients with high

cancer stage, poorer differentiation grade, severer invasion and lymph node metastasis, no adjuvant chemotherapy, and greater perioperative change of NLR/PLR (HH, LH) were obviously associated with worse RFS and OS (all  $p < 0.05$ ). Although tumour location was significantly associated with poor OS ( $p < 0.05$ ), it was not related to RFS. Factors with  $p < 0.05$  in univariate analysis were conducted for further multivariate analysis. Patients with higher cancer stage, lymph node metastasis, and perioperative change of NLR/PLR (HH, LH) had significant association with poor prognosis of OS and RFS (all  $p < 0.05$ ). Simultaneously, it suggested that LH-NLR/PLR is a protective factor for survival (HR < 1).

### Discussion

To our knowledge, this is the first study to evaluate the associations between perioperative changes of NLR and PLR and the postoperative outcome in patients with CRC, who underwent palliative resection of the primary tumour. Our results indicate that perioperative changes of NLR and PLR as biomarkers to predict prognosis would help to elucidate the survival rates in such patients.

Various studies have indicated that changes in immune cellular components in peripheral venous blood could reflect the inflammation status of the tumour,



**Figure 2.** Kaplan-Meier curves showing RFS and OS. **A, B** – Patients with higher perioperative change of NLR and PLR tended to have worse recurrence-free survival (all  $p < 0.05$ ). **C, D** – Patients with higher perioperative change of NLR and PLR tended to have worse overall survival (all  $p < 0.05$ )

which is valuable in predicting survival prognosis [12, 13]. It is increasingly speculated that the inflammation and tumour are correlated, resulting in the establishment of novel biomarkers of cancer for the evaluation of the prognostic significance [14]. Reportedly, neutrophils reflect the status of the systematic inflammation and accelerate the remodelling of the extracellular matrix [15]. This, in turn, stimulates the tumour-cell proliferation, migration, and metastasis via the enzymatic actions, such as the release of reactive oxygen species (ROS), nitric oxide (NO), and anginas [16]. Moreover, neutrophilia activates the inflammatory response to promote the tumour growth by pro-angiogenic and growth factors [17]. Another study showed the lymphocyte infiltration response to the tumour. Increased lymphocytic reactions have been associated with a better outcome [18]. In addition, platelets could secrete cellular growth factors such as platelet-derived growth

factor, vascular endothelial growth factor, transforming growth factor  $\beta$ , and platelet factor 4, followed by the stimulation of tumour angiogenesis and growth [19, 20]. Therefore, NLR and PLR represent the tumour-inflammatory response, which indicates the degree of tumour progression and contributes to the prediction of survival prognosis.

However, there is a great deal of risk and bias in using only one index for detection. For more comprehensive assessment of prognosis in this study, we use the combined preoperative and post-operative changes of both biomarkers to increase the predictive accuracy for survival compared with preoperative or postoperative ones alone. ROC analysis indicated that pre- and post-NLR/PLR were superior to the pre- or post-NLR/PLR for RFS and OS, respectively. The change of tumour status and surgical stress may affect systemic inflammation as well as oncological outcome [21]. It

**Table II.** Univariate and multivariate analysis of factors associated with recurrence-free survival

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age [years]:						
< 65	Reference					
≥ 65	1.211	0.911–2.126	0.450			
Sex:						
Female	Reference					
Male	0.806	0.454–1.432	0.464			
Location:						
Colon	Reference					
Rectal	0.577	0.325–1.024	0.060			
Tumour size [cm]:						
< 3	Reference			Reference		
≥ 3	1.379	0.969–1.853	0.012	0.811	0.312–1.642	0.311
Cancer stage:						
I–II	Reference			Reference		
III–IV	3.096	1.318–5.899	< 0.001	3.104	1.291–5.916	0.001
Cancer grade:						
G1–2	Reference			Reference		
G3–4	1.798	1.007–3.209	0.012	1.484	0.972–2.134	0.079
Tumour invasion:						
T1–2	Reference			Reference		
T3–4	2.277	1.100–4.715	0.006	1.970	1.129–3.571	0.081
Lymph node:						
N0	Reference			Reference		
N+	2.371	1.633–4.912	0.002	2.164	1.472–4.529	0.011
Adjuvant chemotherapy:						
No	Reference			Reference		
Yes	1.896	1.341–3.722	0.007	1.687	1.276–3.572	0.018
NLR:						
LL-NLR	Reference			Reference		
LH-NLR	1.976	1.311–2.512	0.031	1.822	1.137–2.714	0.045
HL-NLR	1.791	1.019–2.352	0.022	0.892	0.522–1.876	0.245
HH-NLR	2.768	1.422–5.016	0.001	2.648	1.376–4.763	0.005
PLR:						
LL-PLR	Reference			Reference		
LH-PLR	1.867	1.112–3.422	0.024	1.648	0.973–2.544	0.079
HL-PLR	1.822	1.221–2.936	0.015	0.762	0.589–1.866	0.326
HH-PLR	2.399	1.578–4.971	0.002	2.011	1.422–4.372	0.021

**Table III.** Univariate and multivariate analysis of factors associated with overall survival

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age [years]:						
< 65	Reference					
≥ 65	1.065	0.657–1.727	0.279			
Sex:						
Female	Reference					
Male	0.836	0.520–1.343	0.458			
Location:						
Colon	Reference			Reference		
Rectal	0.599	0.372–0.966	0.035	0.664	0.386–1.143	0.140
Tumour size [cm]:						
< 3	Reference			Reference		
≥ 3	0.520	0.322–1.839	0.007	0.616	0.368–1.030	0.072
Cancer stage:						
I–II	Reference			Reference		
III–IV	3.488	1.305–5.879	<0.001	3.112	1.194–5.682	0.001
Cancer grade:						
G1–2	Reference			Reference		
G3–4	1.212	0.746–3.029	0.009	1.048	0.672–2.876	0.026
Tumour invasion:						
T1–2	Reference			Reference		
T3–4	2.467	1.391–4.377	0.002	2.242	1.421–4.979	0.014
Lymph node:						
N0	Reference			Reference		
N+	2.302	1.386–3.822	0.001	2.065	1.168–3.279	0.012
Adjuvant chemotherapy:						
No	Reference			Reference		
Yes	2.146	1.244–3.561	0.005	1.884	1.071–3.624	0.027
NLR:						
LL-NLR	Reference			Reference		
LH-NLR	1.071	0.781–2.896	0.012	1.027	0.637–2.544	0.036
HL-NLR	1.791	1.224–2.786	0.018	1.884	1.522–2.941	0.121
HH-NLR	2.894	1.236–5.412	<0.001	3.048	1.271–5.664	0.002
PLR:						
LL-PLR	Reference			Reference		
LH-PLR	1.276	0.972–3.524	0.015	1.451	0.867–2.832	0.225
HL-PLR	1.443	1.021–3.514	0.036	1.662	1.188–2.866	0.175
HH-PLR	2.678	1.172–4.861	0.001	2.477	1.321–4.372	0.015



is conceivable that significant tumour reduction after surgery may lead to improvement of systemic inflammation as well as immunological response [22]. It is reported that the surgery itself promotes the release of tumour emboli and induces immunosuppression that favours the survival and progression of cancer [23]. We also found that the change in perioperative NLR/PLR was independently associated with elevated risk for RFS and OS. Simultaneously, it indicated that LH-NLR/PLR seems to be a protective factor for survival (HR < 1). Although this stratification requires external validation, it may enable us to identify patients with risk or protective factors.

Besides perioperative NLR/PLR factors, cancer stage, lymph node, and adjuvant chemotherapy were also identified as robust prognostic indicators in the univariate and multivariate analysis, which is consistent with the results of previous studies [24, 25]. However, our study showed that tumour invasion and cancer grade were associated with poor prognosis in the univariate analysis but not in the multivariate analysis. Compared with previous prognostic indicators, this inflammatory biomarker has the advantage of being simple, easily available, economical, objective, and reproducible, and it could be measured at the beginning of chemotherapy treatment and monitored throughout the entire therapy period [26].

Nevertheless, our study has some limitations that should be mentioned. First, it is a retrospective investigation; thus, a potential bias in the selection of patients is inevitable. Second, surgery was performed by several surgeons, which possibly influenced oncological outcome. Finally, the current study lacked any evaluation of tumour-associated neutrophils and lymphocytes, which could cause different immune responses.

## Conclusions

The current study suggests that perioperative NLR/PLR might be a good predictor for prognosis in CRC patients undergoing curative surgery. It is recommended as a practical tool to assess the prognosis of RFS and OS. Thus, these findings provided an in-depth understanding of the patients, which could help guide a customised therapeutic strategy.

## Acknowledgments

The authors thank the members of Zhejiang Chinese Medicine University Affiliated No.3 Hangzhou Hospital for the follow-up of colorectal cancer and collecting the clinical data.

## Conflict of interest

The authors declare no conflict of interest.

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**Received:** 16.02.2019

**Accepted:** 26.02.2019